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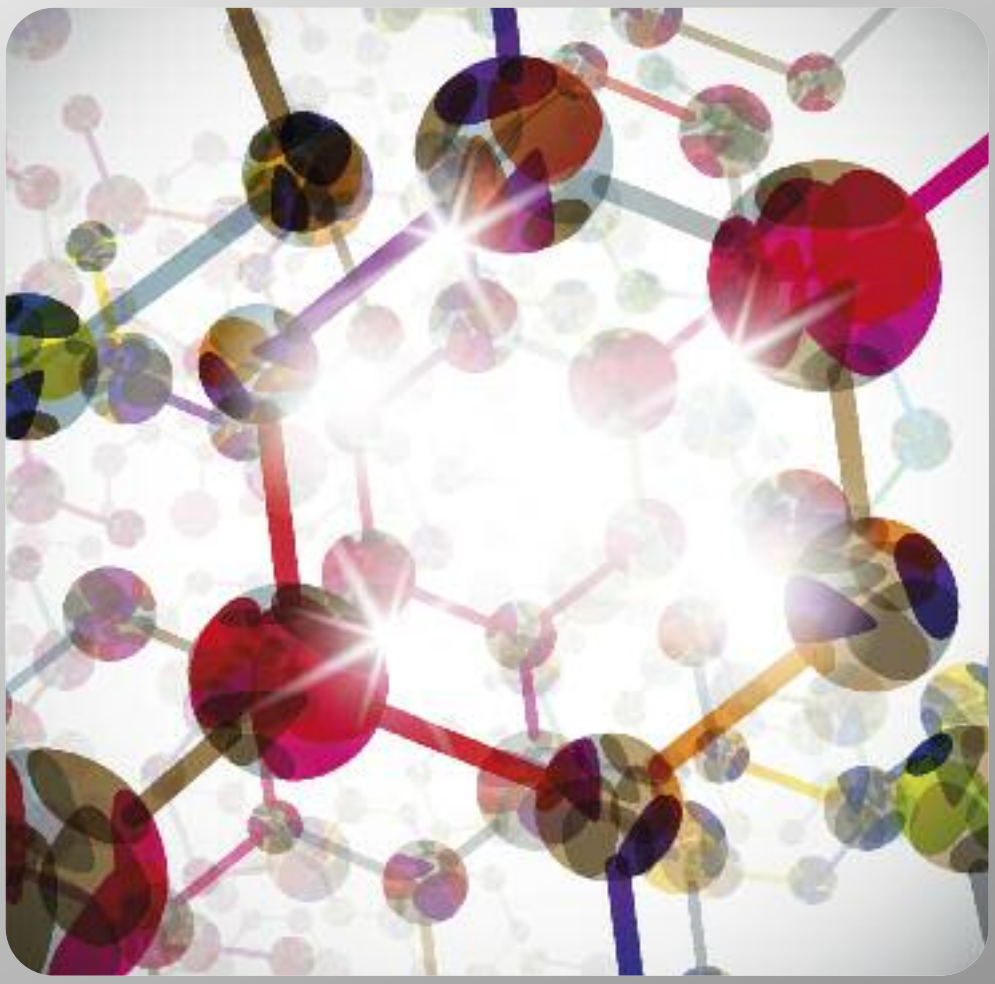

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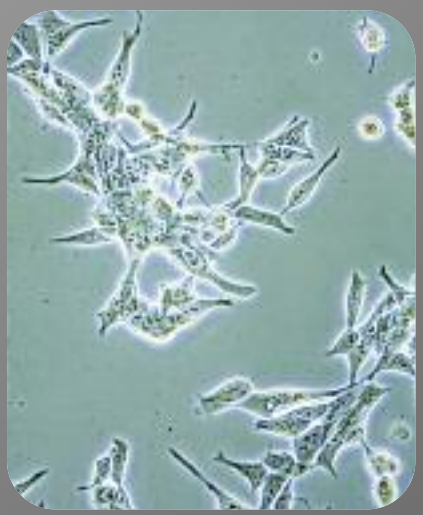

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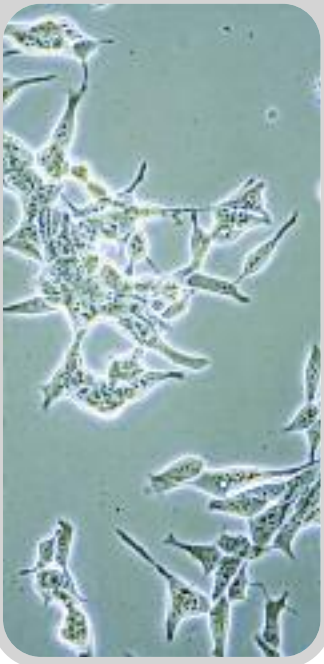

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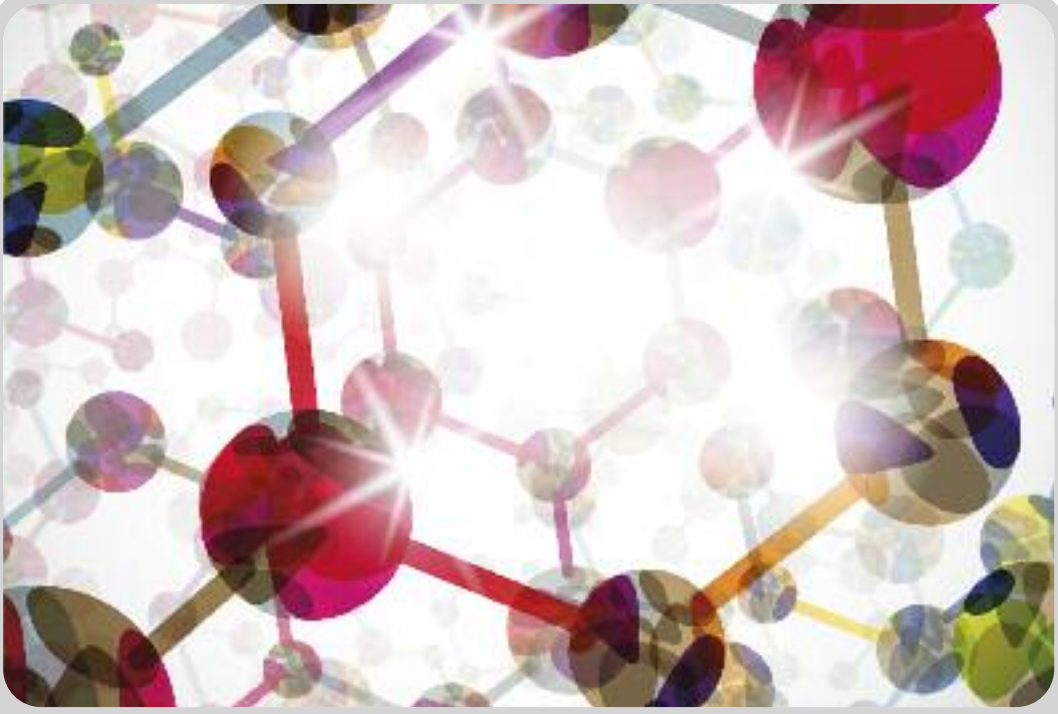

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Editorial

Vassilios Barbounis

Predictions are ominous: in the next 20 years the victims of cancer will triple, and unfortunately, so will the deaths from that cause compared to the incidence and mortality rates at the beginning of our century.

All the interested parties, society, academic community, industry and health professionals should join their forces to rapidly discover effective solutions to overcome the tidal wave of cancer consequences in areas such as disease prevention, early diagnosis, but essentially, treatment with innovative but low cost medicines, the last one being an absolute necessity.

George Fountzilas, Professor of Oncology in the Aristotle University of Thessaloniki and President of the Hellenic Cooperative Oncology Group, tries to describe the pressing responsibilities, actions and areas of activity for everyone involved in the fight against cancer.

Common denominator for all the efforts mentioned above is research. The article *"Clinical trials: Research and innovation at the service of patients and society"*, FCO 2012 June; 3(2):11-17, alludes to the rules, methodology, motives of all of us and also to the obstacles they might encounter.

A significant part of the article refers to the Greek contribution to the research against cancer within the European Union as well as the difficulties and future prospects; proposals for the improvement of the current situation are also put forward.

The author's arguments –although based on theory stated 30 years ago– are in accordance with contemporary reality and future projections, and provide a framework, for research against cancer to advance in the next decades, while commenting accountabilities and initiatives of all involved in this struggle.

One more reason why we should treat unresectable gliomas

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Gliomas and particularly glioblastoma multiforme (GBM) are tumors with grave prognosis and profound consequences for the patients' quality of life. Few agents have shown activity so far, though many targeted molecules have been tested with or without pre-existing biological rationale. Most targeted agents have been tested on all-comers and thus, if a small subgroup were to derive a significant benefit, such benefit would be diluted and, therefore, missed [1, 2]. This seems to be the story, almost universally, (in all tumors) with bevacizumab [3] and in GBM with all targeted agents [4].

Granted, there have been strong scientific reports [5, 6] that demonstrate the plurality of mutations in GBM and, therefore, the redundancy of growth signals and resilience of the cell. However, a more systematic approach to the study of new agents could lead to a better understanding of tumor biology and to the identification of the processes that drive each glioma -if not to the identification of a constitutional mutation.

It was previously proposed by Tim Cloughes at the American Society of Clinical Oncology annual meeting in 2009 that there should be a standardized biopsy-treat-rebiopsy approach to the study of such agents in GBM. This approach would first ensure that the agent actually reaches the tumor and achieves measurable levels in it. Subsequently, molecular biology and proteomic studies should test whether the agent causes changes in some core biological processes. Furthermore, this approach would allow us to determine the characteristics of cells that respond versus those that don't and subsequently identify the "targets" of the agent being tested. Such an approach would also allow clinicians to avoid the use of very expensive, potentially dangerous agents in patients who are unlikely to benefit. Using a targeted agent in a non-targeted fashion is, after all, very unlikely to be an acceptable way of doing things in the era of cost containment.

In this issue of FCO we include an article on the utility of GBM therapy in the setting of unresectability [7]. This is a retrospective study that includes patients that were treated after biopsy or debulking surgery. The definition of the latter is not given. Additionally, it includes patients who received radiotherapy only without Temozolomide. The retrospective and non-randomized nature of the study forbids us from drawing firm conclusions. Additionally, the study conclusion is derived indirectly through the comparison of the 2 radiotherapy only arms with the "biopsy only-chemoradiotherapy" arm. Besides arguing the obvious benefits that have been previously demonstrated in patients with some cytoreduction [8, 9], it would be useful to consider the aforementioned rationale for therapy in the setting of a clinical trial with targeted agents. This could be followed by a secondary resection in cases that respond to the agent under trial. We have previously published such a trial which, at least, demonstrates proof of principle of this approach [10].

It is intuitively obvious that we should make a point of learning from our successes and failures and use them to guide us in a more rational design of future studies. Clearly, there are patients who derive no benefit, ones that derive a very modest benefit and ones that derive a very large benefit from chemotherapy. Shouldn't therefore our society insist on more methodical approaches to the study of GBM, so that such expensive and potentially toxic agents can be used only on those who have a higher likelihood to benefit?

The study of Hany Eldeeb *et al.* makes a valid point [7]. Every therapeutic approach, even ones that are included in guidelines, should be re-evaluated for their cost/benefit ratio and for their ethics and utility for the patient. In fact, the patient should, at the very least, be offered a "no treatment" option. However, if we are forced by limited resources to adopt a universal "no treatment" approach on all unresectable gliomas, we might be doing many current and future patients a great disservice.

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Clinical trials: Research and innovation at the service of patients and society

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Cancer is already a global health problem with gigantic social, political and financial repercussions. According to data from the International Agency for Research on Cancer [1] it is estimated that in 2030 there will be a worldwide recording of 20-25 million new cancer cases and 13-16 million deaths as a result of the disease. Comparing some of these numbers with the 10.4 million new cancer cases and 6.5 million deaths recorded in the year 2000, one may deduce that this is in fact an "explosive" outburst of cancer instances worldwide.

Modern lifestyle with changes in dietary habits, lack of exercise, obesity, smoking and longer life expectancy are but a few visible reasons for this problem and it is quite clear that enormous investments will be required in disease prevention, cancer patient treatment, as well as research. The latter includes both basic research for the discovery of new, effective anti-cancer drugs at the preclinical level, as well as clinical research for the development of said drugs in patients.

In this text we shall allude to: 1) the motives and rules that must govern clinical research in Oncology from the point of view of the researcher, the pharmaceutical industry and the patient; 2) how Greece ranks in cancer-related research in the European Union; 3) the obstacles that, in my opinion, hinder the progress of clinical research in our country; and 4) proposals for improving the current situation.

Clinical trials are a very important part of clinical research. There are many advantages in conducting clinical trials, the most significant of which include patient access to new drugs; educating young doctors through both clinical trials and the translational research that usually accompanies them; enhancing basic research; and improving technological infrastructure through the influx of research funds. For my part, patient access to new treatments -especially in Oncology- is what matters the most.

It is obvious that clinical research must be regulated by rules aiming at protecting patients and guaranteeing that clinical trials are conducted properly. Instead of referring to Good Clinical Practice rules, I preferred to list the seven rules, best known as Freireich's Laws, after one of the founding fathers of modern Medical Oncology (Table) [2]. Though formulated 30 years ago, they are currently timelier than ever, given the progress in fields of Oncology such as transplantations, supportive treatment with the use of growth factors, translational research, focused treatment, etc.

FREIREICH'S LAW #1 (Clinical Investigator's Creed)

"The primary beneficiary of clinical research is the patient participating in that research."

According to the first law, the primary concern of every clinical researcher -their "credo", as it were- must always be caring for the health and well-being of each and every individual patient. Any aims and ethical commitments to future patients, the academic community, the Institute or society in general, should come second. Every patient must feel that their doctor's first and foremost interest lies in their own medical problems and secondarily in those of other patients.

FREIREICH'S LAW #2 (Optimist's Creed)

"Always be prepared for success. Failure creates few problems."

Most of us believe that we must always prepare for a potential failure. When we are young, we buy life insurance to prepare for death or car insurance to prepare for a possible accident. So, in cancer patient treatment clinical trials, most of us are prepared for a negative outcome and very few are prepared for the opposite. The question is who will be an optimist inside the Health System from the onset, if not researchers? The history of Oncology includes several very important treatment-related accomplishments, achieved by optimistic researchers. It is precisely this optimism that we must pass on to our patients, so that they may feel that the new drug (undergoing testing on them)

Table.
Freireich's Seven Laws on Clinical Research.

LAW # 1	Clinical Investigator's Creed	The primary beneficiary of clinical research is the patient participating in that research.
LAW # 2	Optimist's Creed	Always be prepared for success. Failure creates few problems.
LAW # 3	The Academic Question	If we must experiment on patients to obtain medical information, then we had best do without that information.
LAW # 4	Statistician's Creed	The best therapeutic research gives the best results.
LAW # 5	Physician's Creed	"Primum Non" to do the possible and the necessary.
LAW # 6	Health Service Delivery Creed	The best patient care (service) is clinical research. Alternate form: The best clinical research offers the patient the best possible care.
LAW # 7	Regulator's Creed	The general solution to a specific problem will soon become a specific problem requiring a general solution.

offers positive prospects for a dramatic improvement of their condition.

FREIREICH'S LAW #3
(The Academic Question)

"If we must experiment on patients to obtain medical information, then we had best do without that information."

According to the third law, clinical research does not necessitate negative results as a prerequisite for clinical trials to be successful. As researchers, we must be satisfied in knowing that our research results are better than anticipated and that they will be corroborated by future trials. We must not offer our patients treatments with limited chances of success. Research questions must be addressed exclusively *in vitro*, rather than on patients.

FREIREICH'S LAW #4
(Statistician's Creed)

"The best therapeutic research gives the best results."

A condition *sine qua non* for a proper clinical trial is to be accompanied by adequate statistical analysis. We must keep in mind that a brilliantly designed clinical trial is not one that yields the highest *p* value or the greatest statistical significance; it is the one that gives the best therapeutic results. When I was younger, I had no intention of succumbing to what researchers refer to as "the statistics tyranny"; over the years, however, I came to realise how important statistical design and proper data analysis is for a successful clinical trial. So, instead of opposing them, I decided to work with them.

FREIREICH'S LAW #5
(Physician's Creed)

"'Primum Non' fail to do the possible and the necessary."

Unfortunately, Hippocrates' phrase "primum non nocere" (to do good or to do no harm) is not always applicable in Medicine -and Oncology in particular, where we must very often act curatively and urgently at that. Perhaps in everyday medical practice (and medical research) we should paraphrase the fifth Law into "Do for patients whatever may be done -or at least do what is deemed necessary".

FREIREICH'S LAW #6
(Regulator's Creed)

"The general solution to a specific problem will soon become a specific problem requiring a general solution."

It is a well-known fact that all clinical trials require their protocol to have been approved by the host Institution's competent Committee, by the National Ethics Committee, and that researchers need to obtain written consent from patients.

In all probability, the latter is the single most stress-inducing document ever to be placed before a person, describing in such detail all potential risks involved in a clinical trial.

To generalise based on an exception is indeed a great human weakness. Researchers know all too well that the best solution to a specific problem is a specific one. So, it should be perfectly clear to all of us that legal procedures like the two that I described above (i.e. the clinical trial approval process and the written consent form) have been created so as to protect rather than impede proper clinical research and, by extension, research for new, effective treatments.

FREIREICH'S LAW #7
(Health Service Delivery Creed)

"The best patient care (service) is clinical research."
Alternate form: "The best clinical research offers the patient the best possible care."

Relevant studies report that patients participating in clinical trials have a better prognosis than respective patients

treated according to established practices. This different outcome may be attributed to the higher scientific profile of physicians involved in clinical trials or the Health Institutions participating in similar studies; closer observation or increased care enjoyed by protocol patients; modern treatments or experimental drugs administered within protocol frameworks; or other, currently unknown factors. This means that treatment practice improves as well -albeit indirectly- through both clinical trials and the knowledge produced therein.

As an example, I would like to cite the results of a HeCOG meta-analysis of >2,000 patients with metastatic breast carcinoma (Figure 1) [3]. Within the framework of clinical trials conducted by the Group, the average survival of these patients (which was 15.6 months in the 1991-1994 period), increased progressively and practically doubled in the 2003-2006 period. This achievement was due not only to the improvement of hospitalization conditions and support treatment, but also to a great extent to the use of new anti-cancer drugs, such as taxanes and monoclonal antibodies. However, despite the obvious benefits, the proportion of cancer patients participating in clinical trials -even in advanced countries- is <3%. Insufficient information, lack of trust and overwhelming red tape are but a few of the reasons that account for this unacceptably low rate.

Naturally, clinical trials are not a one-way street to success. Especially in Oncology, there is a very high percentage of failed Phase III trials (i.e. randomised studies comparing the effectiveness as to survival of a new treatment with an existing, approved one). According to specialists, as was expressed in a JCO article [4], it appears that anti-cancer drug development projects, and Phase III trials in particular, are more often than not designed in a way that aims solely at a successful Phase III study. No particular emphasis is placed in understanding biological mechanisms of the disease or identifying patient groups with the greatest chances to benefit from the treatment in order to include only those in Phase III trials. Pressure on behalf of pharmaceutical companies and researchers for fast starting trials is often great. Such pressure usually stems from:

1) high expectations for a positive outcome of Phase III trials that would entail an increase in stock prices and consequently huge profits for shareholders;
2) personal scientific ambitions of the researchers involved, aiming at a prompt academic advancement;
3) financial benefits enjoyed by all parties involved in clinical research. These are some of the reasons why certain clinical trials are designed in a superficial way, resulting -of course- in a failed outcome with negative repercussions for patients.

According to the aforementioned article author [4], the close involvement of Wall Street in Oncology (in the form of direct pecuniary compensation to researchers in exchange for advice etc.) does not herald positive developments pertaining to the objectivity and independence of clinical trials. For all these reasons, it is imperative that clinical trial funding is accessible to the wider public.

The example of a trial, the results of which were published in the New England Journal of Medicine [5], and which was financed by a tobacco industry unbeknownst to the editor, should be a sad exception -rather than the rule.

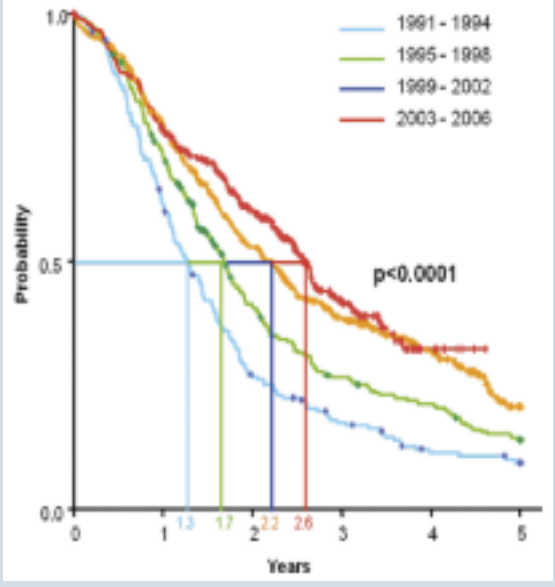
There are obviously no magic solutions to such problems. A large part of the responsibility falls on our shoulders, i.e. the Oncology Community. We should be more cautious regarding our participation in clinical trials which are not based on convincing data. Increased objectivity on behalf of the researchers will result in greater balance between the increased risk of failure of such a trial and the scientifically substantiated process of developing new anti-cancer drugs.

After describing the clinical research-related motives and obligations of researchers and the pharmaceutical industry, let us now focus on cancer patients. Why should they take part in a clinical trial of a new treatment?

In a Journal of Clinical Oncology [6] publication, a multifactorial study showed that the most significant incentive for patients to participate in a clinical trial is the prospect for personal benefit from the treatment. Also, other relevant studies showed that the majority of breast cancer patients are willing to receive a particularly toxic treatment provided that the researcher will somehow guarantee them that this

Figure 1.

Triennial overall survival of patients with advanced breast cancer, having participated in clinical trials by the Hellenic Cooperative Oncology Group (HeCOG).



new treatment has a 1% better possibility of increasing survival as compared to the standard one.

I would now like to briefly describe the position of Greece in the European Union, in terms of Oncology research.

A study published in the European Journal of Cancer [7] mentioned that the in the EU15, Greece, Portugal and Ireland had the largest average annual rates of increase regarding cancer-related publications between 2000 and 2006.

In this period of time, the number of Greek researcher publications amounted to 776. The journal impact factor for Greece was higher than for the other two aforementioned countries.

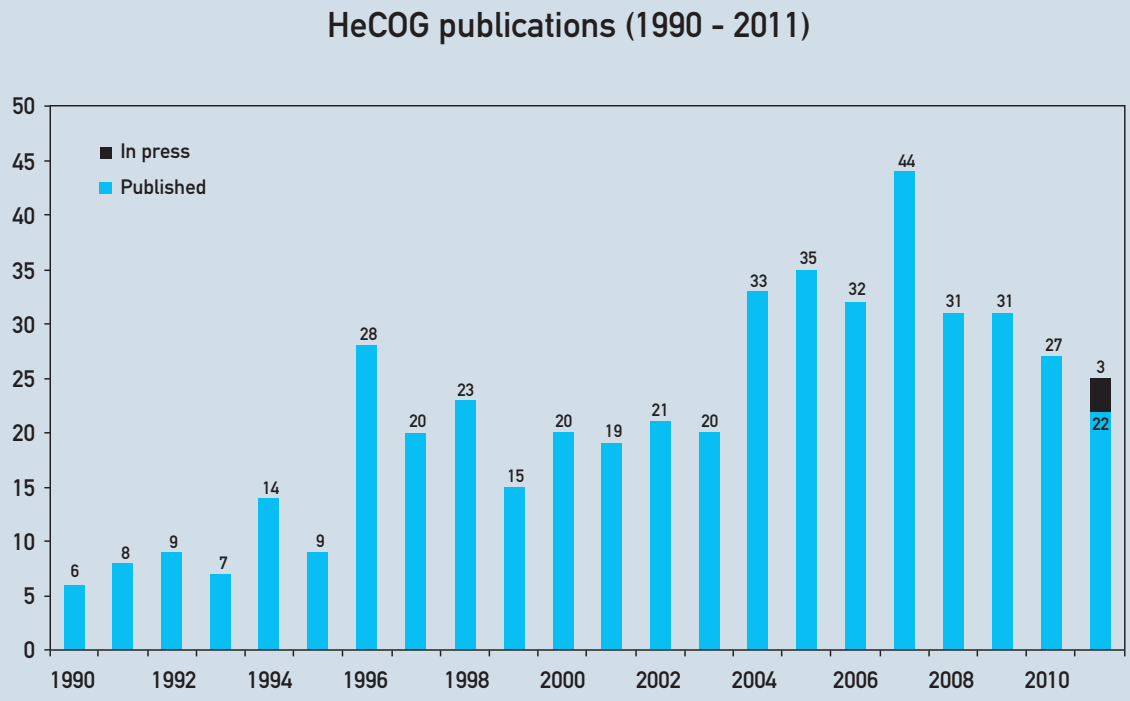
If one compares the number of publications for every country per million inhabitants and according to its GNP (expressed in millions of US dollars), one can easily see that Greece has 69.8 publications, clearly more than Portugal and less than Sweden, both countries of comparable populations. Another interesting fact is that the number of publications per billion US dollars of GNP is 3.2 for Greece, 2.3 for Belgium and 1.0 for Portugal.

Since the beginning of the recent financial crisis in Greece, academic researcher earnings have suffered a 20% cut and university research funds have been reduced by 50%. In the general climate of pessimism and disappointment, a most recent publication in the Nature journal gives credit to our country for ranking particularly well in the participations of Greek researchers in European Union research projects from 1984 to 2009 [8]. Based on the classification of countries presented in the article, Greece ranks eighth among the 27 EU member-states, well above countries such as Sweden, Austria and Finland. Apart from the five largest economies (Germany, the UK, France, Italy and Spain), only the Netherlands and Belgium outranked Greece. Despite all this, the article is entitled "Greek science on the brink", in an attempt to stress that although Greek researchers are doing well, how many will finally make the jump over the valley of death? In researcher jargon, "the valley of death" is the distance -or gap- between a research finding and its practical application. So, the issue is also to turn research results into something applicable.

This is the reason why one of the main priorities of the new Law on higher education is the connection between Universities (where nearly 80% of research is carried out) and the market. It is within the same framework that the Greek Prime Minister invited the Israeli Chairman of the YOZMA Group to visit Greece. The YOZMA Group is the evolution of a state project to attract investment capital for

Figure 2.

Number of Hellenic Cooperative Oncology Group (HeCOG) publications in international scientific journals during the 1990-2011 period.



innovation, which started off in Israel and is now active worldwide.

What also seems promising is the bill aiming at restructuring the country's research network. According to the final deliberation document, the fragmentation of research centres, the inability to utilise infrastructures, inadequate collaboration among researchers and the existence of institutes with far too few researchers (over 20 such facilities have up to 5 researchers), are considered the most serious weaknesses of our research network.

This evidence suggests that, despite the tragic lack of funds in our country, Oncology-related research activity is at quite respectable levels, obviously due to the superhuman efforts and zeal of Greek researchers.

This effort includes the Hellenic Cooperative Oncology Group, which is a non-profit research group established in 1990, currently involving 17 Oncology Clinics from the whole of Greece and Cyprus.

Main goals of the Group are the promotion of clinical and basic research in Oncology in Greece; improving the training of physicians or other related scientists; as well as the study of new cancer treatment methods.

The Group has always been prolific in its research and writing endeavours, resulting in the publication of a noteworthy amount of papers in approved foreign journals.

In the Group's 21 years of existence, a total of 477 papers have been published in foreign medical media, while the number of citations for these papers exceeds 6,000 (Figure 2). The overall impact factor of the journals in which said papers appeared is 1,735 (Figure 3).

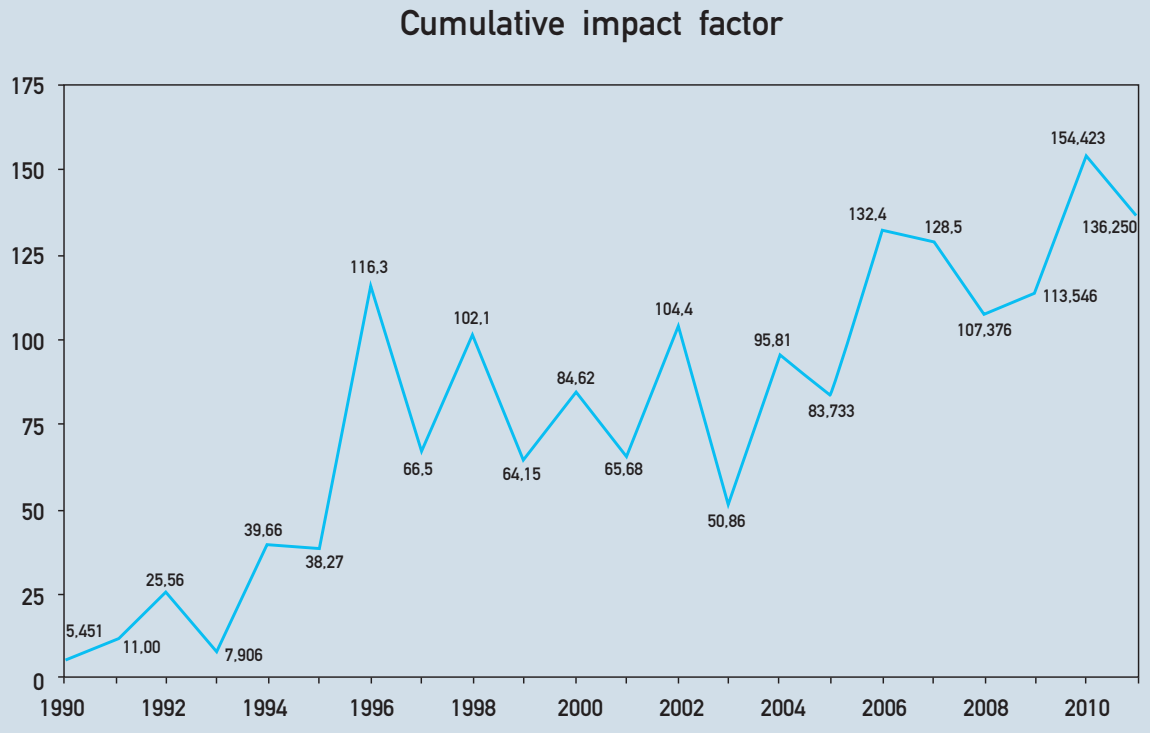
This research effort of ours received recognition in Greece, as our Group was awarded an honorary distinction by the Academy of Athens, the top scholarly institution of our country, in December 2002 for its important scientific work in the fight against cancer; and received an award by the Hellenic Society of Medical Oncology in March 2009.

Apart from the number of publications, what mainly interests us is for our papers to be characterised by scientific integrity and excellent quality data. These are the two elements in which we pay particular attention and we spare no effort or expense in our attempt to achieve the best possible results.

These obvious prerequisites that should characterise each and every research effort appear to no longer be that much "required" or "obvious". Instances of result falsification are becoming increasingly common. Peer pressure on young researchers for publications, as a requirement for their own

Figure 3.

Cumulative impact factor of Hellenic Cooperative Oncology Group (HeCOG) publications in international scientific journals.



scientific progress; increasing needs for research project funding; and the lack of education are but a few of the reasons for the steep increase of cases of scientific fraud internationally.

It is my firm belief that measures must be taken in our country by the political leadership, assisted by the National Organization for Medicines (NOM) and other bodies of similar orientation. At the same time, however, all administrative and scholar leaderships of Academic Institutions must also assume their responsibilities and immediately crush this union-like cover-up mentality prevalent over the past years in Universities, threatening to tear down the last few bastions of honest, free and truly independent research.

Keeping all this in mind, I consider it a most fortuitous event that after 2004 the Greek Legislation was harmonised with the respective European one, pertaining to clinical trials of drugs intended for use on humans. I must, however, reiterate that without substantial reinforcement by the NOM and other regulating bodies, as well as support by the scientific community, we shall not manage to be successful in our efforts. If we want to gain and maintain Public Opinion trust as regards patient participation in clinical trials and relinquishing biological material for translational research, we must convince the public that our research activities are characterised by transparency and integrity.

On the other hand, this European Union Directive, despite its undoubtedly positive aspects, entails a clear and present danger: due to the enormous bureaucratic, operational and financial burden imposed on research sponsors, it is nearly impossible to conduct trials in Research Institutes, Cooperating Groups, Universities, etc., thus rendering research the exclusive privilege of Pharmaceutical Companies.

This new emerging trend is of great concern to competent authorities all over Europe. At a recent forum held in Brussels [9], it was noted that the increasing requirements by auditing and regulating bodies led to a 30% rise in the cost of clinical trials between 2005-2007. Consequently, the number of clinical protocols submitted for approval in the 2007-2010 period in Europe was reduced by 20%. Therefore, it becomes clear that Europe has ceased being an attractive venue for conducting clinical research.

At the same time, at the European Union member-state national level, research appears ineffective, given that although multicentred-multinational clinical trials (usually funded by the pharmaceutical industry) amount to only 20% of the total, they attract 70% of participating patients. Multicentred trials are not only larger in size, they are also more effective in terms of patient inclusion, given that pharmaceutical companies, with their massive financial resources and tremendous organisation, do not face any significant problems when conducting clinical trials -particularly Phase III. Nonetheless, this abolishes in action independent academic research, forcing it to be industry-guided -with all implied implications.

It is not by coincidence or chance that countries such as Belgium, Ireland or Germany have already amended their legislation so as to support academic research; at the same time, a pan-European effort is currently underway aimed at homogenising procedures through a common European platform, on the one hand allowing the expediting of necessary authorisations and on the other further protecting patients and ensuring the credibility of research results [9]. It is our belief that our country must follow the same path. From as early as last summer, we have already submitted pertinent proposals to the NOM and are ready for a productive collaboration.

It is a known fact that within a few years technological advances will allow for personalised prognosis and treatment, as well as for determining the risk factor of healthy individuals developing cancer or cancer patients relapsing. The prospects look promising, yet basic research intensification is required on behalf of the entire scientific community -including our country's. Of course, all this stipulates that Basic Research funding increases substantially. However, allotting approximately 0.5% of the country's GNP for research, especially when compared to 2.7% for the US, 3.3% for Japan or the European Union 3% target for the following years, does not leave much room for optimism at present. We must all intensify our efforts so as to make the political leadership realise how tremendously important is to change the policy in the field in question. It is unthinkable to keep trailing behind when Research -and consequently Technology- keeps making leaps forward in the USA and the other advanced countries.

In conclusion of this short perambulation in the field of Clinical Research, I should like to make some suggestions for improving the current situation in this field. My suggestions happen to largely coincide with those of the Hellenic Society of Medical Oncology for the development of Clinical Research in our country:

1) A drastic decrease in bureaucracy. Approvals by such committees as the Regional Health Directorates, Hospital Boards of Directors, etc., not stipulated by the EU Directive, are counterproductive and add nothing to the procedure apart from unacceptable delays. It should be noted that, since August 2010, considerable progress has been made in cutting down times required for a clinical trial receiving approval from the NOM and the National Ethics Committee -but there is still much room for improvement.

It is already known that the time presently required for a drug to be approved by the European Medicines Agency (EMEA) is unacceptably long as compared to the American FDA. For instance, in the 2003-2010 period, the average time of approval of new oncology drugs by the EMEA and the FDA was 350 and 184 days, respectively [10]. Moreover, the time necessary to develop new anticancer drugs is particularly long, mainly due to methodological weaknesses and research effort fragmentation. This is mainly the reason why the European Commission intends to attract funds from the

Pharmaceutical Industry, in order to create a research project, the priorities of which shall be defined by the industry itself. The first steps in that direction include the initial funding of said project with €2 billion for the years 2008-2017. 50% of the funds shall be made available by the European Commission and the remaining 50% by the Pharmaceutical Industry. The aim of this project is to find ways to shorten and facilitate new drugs development procedures (what is aptly described as the bottleneck effect), as well as to implement new methodologies to be jointly applied by all pharmaceutical companies and timely describe the necessity for, as well as the safety and effectiveness of new drugs before the start of large clinical trials on patients. As is usually the case, this very promising effort has numerous supporters and an equal number of critics, so final assessment will have to be based on its results.

2) A generous increase in national funds for basic and translational research, to be used for the improvement of technological infrastructures and the financing of research projects. It goes without saying that, at least in Oncology, there can be no serious attempt at clinical research nowadays without the previous two.
3) The establishment of a National Archive of Neoplasias; it is a disgrace for Greece to be one of the last 2-3 European Union countries without one. There can be no proper National Strategy for cancer without a reliable National Archive of Neoplasias.
4) As already mentioned, another requirement is the meaningful support of regulating bodies (such as the NOM) and the full computerisation of all Health Services, which is expected to greatly facilitate and improve the credibility of research in our country.
5) Greece must, at long last, directly link financial support with productivity. Both material and moral incentives must be offered in order to attract young scientists to research.

It is my firm belief that we do have all the necessary, high-quality scientific personnel; what we lack is the political will to move forward in this most significant field of Clinical Research. Our patients need it; our younger colleagues desire it; and society demands it.

Professor of Medicine, Director of the Department of Medical Oncology, Chairman of the Hellenic Cooperative Oncology Group (HeCOG), Director of the Hellenic Foundation for Cancer Research (HeFCR)

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A phase I-II and pharmacokinetic study of imatinib mesylate in combination with irinotecan in patients with relapsed or refractory small-cell lung cancer

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ABSTRACT

Background: The purpose of this study was to determine the maximum tolerated doses (MTDs); the dose limiting toxicities (DLTs); the possible pharmacokinetic (PK) interactions; and to evaluate the clinical activity of the imatinib plus irinotecan combination in pre-treated patients with extensive stage SCLC.

Patients & Methods: Patients with refractory/relapsed SCLC were eligible. During the phase I part of the study, escalated doses of imatinib were administered daily in combination with irinotecan every 14 days. DLT and pharmacokinetic parameters of both drugs were determined during the first treatment cycle. During the phase II part of the study, the determined MTDs of the drugs were used to treat eligible patients.

Results: During the phase I part of the study (n=11 patients), the MTDs for imatinib and irinotecan were defined at 400 mg/day and 150 mg/m^2 every 2 weeks, respectively. Grade 4 neutropenia and treatment delay due to grade 3 neutropenia were the DLTs. PK analysis for imatinib, irinotecan and their major metabolites revealed no statistically significant drug interactions. Among the 28 patients treated in the context of the phase II study, one complete and two partial responses (overall response rate=8.8%; 95% CI; 0-18.4%) were observed. c-kit expression on tumour cells, which was detected by immunohistochemistry in 17 (71%) of the 24 patients with available tissue material, was not correlated with response to treatment. The median overall survival was 4.8 months (range, 0.8-14.4 months) and the median time to tumour progression 2.2 months (range, 0.5-10.6 months). Grade 3-4 neutropenia and grade 2-3 diarrhoea occurred in 10 (29.4%) patients each. There were no episodes of febrile neutropenia or treatment-related deaths.

Conclusions: The MTDs of the imatinib plus irinotecan combination were 400 mg once daily and 150 mg/m^2 every 2 weeks, respectively. The regimen has modest antitumour activity even in patients whose tumours expressing the c-kit receptor. A better understanding of the biology of the c-kit expression in SCLC and the resistance mechanisms of imatinib is warranted.

Key words: imatinib; irinotecan; phase I-II; pharmacokinetic; SCLC.

INTRODUCTION

Small-cell lung cancer (SCLC) is one of the most aggressive and lethal cancers in humans constituting approximately 15%-25% of all primary lung cancer cases [1]. Although standard combination of cytotoxic agents (etoposide and cisplatin) has shown antitumour activity in 70%-90% of patients with both limited and extensive stages of SCLC, most patients present with disease progression and die from generalized disease [2]. Therefore, there is an unmet need for additional effective therapies for these patients.

Imatinib mesylate is a small molecule and a selective inhibitor of the chimeric Bcr-Abl fusion protein, the platelet-derived growth factor receptors alpha and beta (PDGFRs) and the c-kit tyrosine kinase receptor [3]. Imatinib has shown significant antitumour activity in patients with chronic myeloid leukaemia (CML), where the consistent molecular abnormality is the Bcr-Abl fusion gene [4]. Imatinib

produces complete haematological and cytogenetic responses in 24% and 17% of CML patients in chronic phase, respectively [5]. Furthermore, imatinib is effective against relapsed or unresectable gastrointestinal stromal tumours (GIST) [6, 7], which harbour activating mutations of the c-kit tyrosine kinase gene and is currently the treatment of choice in both the metastatic and adjuvant settings [8-10].

Autocrine and paracrine growth mechanisms are involved in the proliferation of SCLC tumour cells [11-12]. The study of the c-kit autocrine loop in SCLC has shown an interaction with other SCLC autocrine loops and it seems to confer a tumour survival advantage in SCLC tumour cells [12]. Interestingly, *in vitro* treatment of H526 SCLC cells, which express c-kit and produce stem cell factor (SCF), with inhibitors of c-kit tyrosine kinase reversed apoptosis resistance to growth factor deprivation [13]. Furthermore, the activation of c-kit by SCF in the same cell line led to a hypoxia-induced-factor (HIF)-1α-mediated enhancement of vascular endothelial growth factor (VEGF) expression resulting in imatinib-mediated inhibition of tumour angiogenesis [14]. Previous reports have shown that about 70% of SCLCs express the c-kit receptor and/or its ligand SCF [15-18].

Imatinib has been shown to inhibit the proliferation of SCLC cells in association with the c-kit expression [19]. The efficacy of single-agent imatinib in SCLC was evaluated in four phase II studies which failed to demonstrate objective tumour regressions [20-23]. However, imatinib may affect tumour response when combined with traditional cytotoxic agents by preventing tumour re-growth between the cycles of treatment [24]; in addition, imatinib may also prevent resistance to irinotecan by inhibiting the ABCG2 transporter or increasing topoisomerase I activity [25-27]. Furthermore, there are potential pharmacokinetic interactions between imatinib and chemotherapy. Indeed, imatinib is principally metabolized by CYP3A4 to *N*-demethyl derivative, whereas the other cytochrome p450 enzymes are less involved in its metabolism [28]. Imatinib is also a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 and its co-administration with agents that are metabolized by cytochrome 450 enzymes may result in increased exposure to imatinib levels [28].

Irinotecan (CPT-11) is a camptothecin derivative with significant activity in various types of tumours including small-cell lung cancer [29-33]. Irinotecan is a pro-drug which is converted by carboxylesterase enzymes to the more active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38); SN-38 is a specific inhibitor of topoisomerase I, resulting in DNA damage and cell death. SN-38 is conjugated further in the liver and is then excreted in the bile and urine; in addition, irinotecan undergoes oxidation mediated by CYP3A4/5 to various metabolites with different degrees of activity [29-30]. Given that imatinib shares a common metabolic pathway with irinotecan, combination therapy with these agents may lead to increased irinotecan or imatinib exposure and toxicity. In a previous phase I study in patients with untreated extensive stage SCLC, it was shown that the combination of imatinib, irinotecan and cisplatin given every 3 weeks, with granulocyte-colony-stimulating factor support, is feasible and well-tolerated; however, the pharmacokinetic analysis revealed that the co-administration of imatinib led to a 36% decreased clearance of irinotecan, which resulted in an increased exposure to and toxicity of the drug [24]. In another phase II study, the combination of imatinib, irinotecan and carboplatin in previously untreated patients with extensive stage SCLC resulted in an objective response rate of 66%; although 86% of the patients had tumours expressing c-kit, there was no correlation with treatment efficacy. Moreover, the regimen was associated with increased toxicity, mainly neutropenia, nausea, diarrhoea, fatigue and oedema [34].

Since there was no published pharmacokinetic and clinical data for the combination of imatinib and irinotecan at the time this study was designed, a phase I-II study was conducted in order to determine the maximum tolerated doses (MTDs), the dose limiting toxicities (DLTs) and the possible pharmacokinetic interactions of the combination and to investigate its activity in pre-treated patients with extensive stage SCLC.

PATIENTS & METHODS

Eligibility criteria

Patients >18 years old with a histologically or cytologically confirmed SCLC and an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0–2 were eligible. Patients also had to have relapsed or refractory extensive disease after at least one prior chemotherapy regimen and bidimensionally measurable disease (only for those enrolled in the phase II part of the study). Disease was considered refractory for patients who either did not respond to first-line chemotherapy or responded initially but relapsed within 90 days of completion of their primary therapy [35]. Other inclusion criteria were: adequate bone marrow (absolute neutrophil count ≥1500/dL, haemoglobin >10 g/dL and platelets >100.000/dL); renal (serum creatinine <2 mg/ml) and liver (total bilirubin <1.5 mg/ml; and alanine aminotransferase/aspartate aminotransferase <3x upper normal limit) function; life expectancy of at least 3 months; absence of severe congestive heart failure or unstable angina pectoris, active infection, severe malnutrition as well as absence of any psychological or social condition potentially hampering compliance with the study protocol. Prior radiotherapy (to <25% of marrow-containing bones) was allowed provided that the radiotherapy-free interval was at least 4 weeks. CNS metastases were allowed provided that they were clinically stable after radiotherapy. Prior treatment with imatinib was not allowed. All patients signed a written informed consent and the study was approved by the Ethics and Scientific Committees of participating Institutions as well as by the National Drug Administration (EOF) of Greece.

Treatment schedule

During the phase I part of the study, irinotecan (Pfizer, USA) was administered at the fixed dose of 180 mg/m^2 as a 90 min intravenous (iv) infusion on days 1 and 14 every 28 days after pre-medication with ondansetron and atropine. Imatinib mesylate (Novartis Pharmaceuticals, Switzerland) was administered orally every day at escalated doses starting from 400 mg/day in 50 mg/day increments. On the days of irinotecan administration, imatinib was given 2 ½ hours prior to infusion. No prophylactic administration of growth factors was allowed. The DLT was assessed during the first cycle of treatment and was defined as the occurrence of any of the following: (i) grade 4 neutropenia or thrombocytopenia; (ii) febrile neutropenia; (iii) grade 3/4 non-haematological toxicity; and (iv) any treatment delay for more than 3 days because of unresolved toxicity. Dose escalation was discontinued and the DLT dose level was reached if at least 50% of the patients treated at that dose level developed a DLT (e.g. at least two of three, or three of six patients). The doses of the previous to the DLT dose level were defined as Maximum Tolerated Doses (MTDs) [imatinib 400 mg/day p.o. and irinotecan 150 mg/m^2 q 2 weeks], and were used for the subsequent phase II part of the study. Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent.

Dose modifications

In case of grade 2-4 neutropenia or thrombocytopenia or febrile neutropenia or grade 3-4 diarrhoea, both drugs were withheld until toxicity was resolved to ≤grade 1; treatment was re-started with CPT-11 and imatinib doses reduced by 20% and 25%, respectively. In case of treatment interruption because of sustained grade ≥1 diarrhoea for ≥14 days, further administration of CPT-11 was discontinued. In addition, in case of re-appearance of grade 3-4 haematological toxicity upon imatinib re-treatment, the drug was withheld. No dose reductions were performed for anaemia. In case of ≥grade 2 non-haematological toxicity, imatinib was withheld until the toxicity was resolved to grade ≤1 and then was resumed at a dose reduced by 25%; if grade >2 toxicity recurred again, imatinib was stopped. Granulocyte colony-stimulating factor in combination with i.v. antibiotics were used in cases of grade 4 neutropenia and fever ≥38° C.

Concomitant medication with drugs known to interact with the same CYP450 isoenzymes were used with caution and patients were carefully monitored for potentiation of toxicity. In this context, therapeutic anticoagulation with warfarin was not allowed and was substituted by low-molecular weight heparin.

Patient evaluation

Baseline evaluation had to be completed within 7 days before study registration and included: patient history and physical examination, complete blood cell count with differential and platelet count, serum chemistry, electrocardiogram (ECG), chest X-rays, thoracic and abdominal computed tomography (CT) scans. Additional imaging studies were performed if indicated. Complete blood cell counts with differential and platelet counts were performed weekly and daily until recovery in the case of grade 3/4 neutropenia, thrombocytopenia or febrile neutropenia. Physical examination, detailed toxicity questionnaire, complete blood cell count with differential and platelets and blood chemistry were performed before each cycle. Disease was assessed every 2 cycles (2 months) by the same methods used in the baseline evaluation or earlier in case of clinical evidence of disease progression. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria [36] and evaluation of response was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [37]. All patients receiving at least one cycle of treatment were evaluable for toxicity and patients with bi-dimensionally measurable disease receiving at least two cycles were evaluable for response.

Immunohistochemistry for c-kit expression

Paraffin blocks, of the patients studied, were retrieved from the archives of the Pathology Department of the University General Hospital of Heraklion, Crete, Greece. Four μm-thick tissue sections were stained, after deparaffinisation, with the polyclonal rabbit anti-Human antibody c-kit (CD 117, DAKO, Danemark; code no. A4502). Tissue sections were treated with 0.01 mol/L (pH 6.0) citrate buffer in a microwave oven three times for 5 min at 500W. Immunohistochemical staining was carried out manually according to the APAAP complex technique (DAKO PATTS). Briefly, slides were treated with normal rabbit serum for 20 min and were incubated for 60 min at room temperature for the primary antibody. The working dilution was 1/50 (v/v). After rinsing, the sections were incubated with rabbit anti-mouse Ig (Z259; DAKO) for 30 min and, then, with APAAP mouse MoAb (D651; DAKO) for 30 min at room temperature. The same procedure was repeated with a 15 min incubation time. The substrate chromogen used was K699, a Fast-Red system (DAKO PATTS). Slides were counter-stained with haematoxylin and, subsequently, were mounted with Glycergel. Positive and negative controls were used.

For the evaluation of c-kit staining the percentage of stained cells (< or >10%); the staining pattern (cytoplasmic or membranous); and the intensity of the stain (0=absent, 1=weak, 2=moderate and 3=strong) were taken into account. Cases with >10% cells with strong or moderate/weak membranous staining were considered strongly or weakly positive, respectively. Cytoplasmic staining was also observed in all the positive cases. The cases showing cytoplasmic but not membrane staining in <10% stained cells were considered as negative [38-39].

Pharmacokinetic study

Pharmacokinetic analysis was conducted in nine patients

receiving imatinib (at the dose of 400 mg/day) followed by irinotecan (at the dose of 150 mg/m^2) 2.5 h later. Heparinised blood samples (5 ml) for imatinib pharmacokinetics were obtained at the following time points: 0h, 1h, 2h, 3h, 4h, 4.5h, 5h, 6h and 24h. For irinotecan pharmacokinetics, blood samples (5 ml) were collected into heparinised Vacutainer, at the following time points: i) before the beginning of CPT-11 infusion; ii) 45 min after the beginning of infusion; iii) at the end of infusion; iv) at 30 min and 1h, 2h, 4h and 6 h after the end of CPT-11 infusion. Blood samples were centrifuged immediately at 1200xg for 10 min and 1 ml aliquots of plasma were frozen at -70° C until analysis. Plasma concentrations of imatinib and its main metabolite (CGP74588) were performed at the Department of Pharmacology (Bordeaux University Hospital, Bordeaux, France) using the previously described LC-MS/MS assay [40].

CPT-11 and its metabolite SN-38 levels were determined using a reverse phase high-performance liquid chromatography (HPLC) method with fluorescence detection as previously described [41]. Briefly, 250 µl of plasma were mixed with an internal standard solution (camptothecin) in acidified acetonitrile to precipitate plasma proteins which were incubated for 15 min at 40° C. The samples were then buffered with 0.025 M triethylamine buffer (pH 4.2), centrifuged and an aliquot of the supernatant (60 µl) was analyzed by HPLC. A separate plasma sample (250 µl) was incubated with b-glucuronidase at 40° C for 30 min before precipitation and the same procedure was repeated. SN-38G concentrations were estimated as the difference of SN-38 concentrations before and after glucuronidase hydrolysis. Chromatographic conditions involved a Zorbax – C8 column (5 µm, 4.6 x 250 mm) (Agilent Technologies Inc., Santa Clara, Ca, USA) and a mobile phase consisting of a 25:75 (v/v) acetonitrile:triethylamine buffer 25 mM (pH 4.2). Fluorescent detection was monitored at an excitation wavelength of 372 nm and at emission wavelength of 425 nm and 535 nm for CPT-11 and SN-38, respectively. CPT-11 and SN-38 were assayed on a LC-10A/10Avp Shimadzu chromatographic system equipped with an RF-10Axl fluorescence detector and an SPD-M10Avp ultraviolet detector (Shimadzu Deutschland GmbH, Duisburg, Germany). CPT-11 and SN-38 were kindly provided from Pfizer.

All the pharmacokinetic parameters were evaluated by non-compartmental analysis (WinNonlin™ standard version 2.1, Pharsight Corp., Palo Alto, CA). The following parameters were calculated from the plasma concentration-time profiles of imatinib, irinotecan and their metabolites: time of maximum observed plasma concentration (t_{max}), plasma concentration corresponding to t_{max} (C_{max}), terminal elimination phase constant (Lambda_z), terminal half-life ($t_{1/2}$ or $t_{1/2\_Lambda\_z}$), area under the concentration-time curve from the time of dosing to the time of the last observation (AUC_{all}) or to infinity (AUC_{inf}), total body clearance (imatinib & CGP74588: Cl/F; for CPT-11 & metabolites: Cl) and volume of distribution (imatinib & CGP74588: V_z/F; for CPT-11 & metabolites: V_z).

Statistical analysis

This was a phase I-II clinical trial. The number of patients required for the phase I part of the study was dependent on the encountered toxicity. At least three patients were enrolled at each dose level. No intra-patient dose escalation was allowed. If a dose limiting toxicity (DLT) was observed in one of the first three patients, then three additional patients were enrolled at the same dose level. The primary endpoint of the phase II part of the study was progression-free survival (PFS); secondary endpoints were response rates, overall survival and toxicity assessment. Considering an alpha error of 5% and a power of 80% a total of 35 patients were required in order to detect a 3-month prolongation of PFS (from 3 months from historical controls to 6 months).

Analysis was performed on an intent-to-treat basis. Duration of tumour response was measured from the date of the first objective response was documented to the first date of

Table 1.
Patient characteristics (n=34).

	Frequency	%
Median age (years, range)	57 (42-80)	
Sex		
Male	30	88
Female	4	12
Stage at diagnosis		
Limited	15	44
Extended	19	56
Performance status		
0-1	29	85
2	5	15
Line of chemotherapy		
2nd	11	32
≥2nd	23	68
Chemotherapy-free interval		
>90 days	6	18
≤90 days	28	82
Prior radiotherapy		
Curative	21	62
Palliative	2	6
Disease localization		
Lung	21	87.5
Lymph Nodes	7	29.2
Liver	6	25.0
CNS	7	29.2
Bones	2	8.3
Other	19	55.6
Organs involved		
1	8	23.5
2	11	32.3
≥3	5	14.7

tumour progression or death from any cause. The PFS was measured from study entry until the day of the first evidence of disease progression or death and OS from the date of study entry to death or last contact. The probability of survival was calculated by the method of Kaplan-Meier [42] and tested for differences by using the log-rank test. All tests were two-sided and were considered significant when the resulting p-value was ≤0.05.

RESULTS

Patients

From July 2002 to September 2005, 34 patients with pretreated SCLC were enrolled onto the study. Twelve and 22 patients were enrolled in the phase I and phase II parts of the study, respectively. Patient characteristics are shown in Table 1. The patients' median age was 57 years (range, 42-80), 88% were males (88%) and most of them (85%) had a PS of 0-1. Nineteen (56%) patients had extended stage disease and nine (27%) brain metastases. Twenty-three (68%) patients had received at least 2 prior chemotherapy regimens while 21 (62%) had received prior curative radiotherapy. The vast majority of patients had either relapsed or refractory disease, with only 6 (18%) patients receiving treatment as second-line for platinum-sensitive disease.

Dose-limiting toxicities

Since the MTD was observed at the first dose-level, the dose of irinotecan was reduced to 150 mg/m^2; no further dose escalation of imatinib was evaluated since the drug was given at the standard daily dose (400 mg/day p.o.). Table 2 demonstrates the number of patients enrolled at each dose-level and the observed DLT events which were: grade 4 neutropenia (n=2 patients) and treatment delay due to grade 3 neutropenia (n=2 patients). At the 1st dose-level, three out of six patients developed DLTs. At the level with reduced doses one out of six patients developed a dose- limiting event (grade 4 neutropenia) and, therefore, the starting dose level was considered as the DLT level and the MTDs, which correspond to the doses administered in the consecutive phase II part of the study were irinotecan 150 mg/m^2 every 2 weeks and imatinib 400 mg daily.

Pharmacokinetics

The pharmacokinetic parameters for imatinib both for the parent drug and its metabolite determined by non-compartmental analysis are presented in Table 3. After daily oral administration of imatinib, the C_{max} of both the parent drug and the CGP74588 slightly changed from 3124.8 and 475.0 ng/ml on day-1 to 2602.4 and 436.8 ng/ml on day-2 (17% and 8% decrease, respectively). The t_{max} as well as the $t_{1/2}$ for imatinib and CGP74588 were found to be increased on day-2 (terminal half-life: 10.5 to 15.2 h for the parent drug, and 10.3 to 21.2 h for the metabolite); the observed total body clearance (Cl/F) of the two compounds was decreased from day-1 to day-2, but this could not reach statistical significance. Finally, AUC_{all} and volume of distribution (V_z/F) of both compounds were the same on day-1 and day-2, as well as the conversion ratio of imatinib to CGP74588 (Table 3).

Table 4 lists the mean values of the pharmacokinetic parameters for irinotecan and its metabolites SN-38 and SN-38G. Peak concentrations for CPT-11 and SN-38 were observed at the end of infusion (t_{max}=1.81 and 1.64 hours after the beginning of 90 min infusion); as it was expected, the t_{max} for SN-38G was longer (t_{max}=2.28 h). The plasma exposure to the active metabolite SN-38 was approximately 3% of the parent drug and for the glucuronide was almost 5-6 times more (AUC all ratios, Table 4, Figure). The elimination rate for the metabolites was longer than for the parent drug as well as the respective values for clearance (Table 4).

Treatment administration

A total number of 188 chemotherapy cycles were administered during the phase II part of the study with a median of 4 cycles/patient (range, 1-15). There were 24 (12.8%) cycles delayed for more than 3 days with a median of 7 days (range, 4-31). Ten (42%) of the delayed cycles were due to haematological toxicity and 4 (17%) to non-haematological toxicity; the rest of cycles were delayed for reasons unrelated to treatment (pending imaging studies for disease assessment, late admission or personal reasons). For the 28 patients who were included in the phase I and II parts of the study receiving the MTD doses, the median dose

Table 2.
Phase I dose levels, number of patients enrolled and DLTs during the first cycle.

Dose level	Irinotecan mg/m^2	Imatinib mg/day	No. of patients	DLT (no. of patients)
1	180	400	6	Treatment delay due to grade 3 neutropenia (n=2), grade 4 neutropenia (n=1)
2	150	400	6	Grade 4 neutropenia (n=1)

intensity for irinotecan was 70.3 mg/m^2/week (corresponding to 78.1% of the planned protocol dose); similarly, the median dose intensity for imatinib was 400 mg/day (100% of the protocol planned dose).

c-kit expression, treatment efficacy and clinical outcome

Tumour tissue from 24 patients was available for the assessment of c-kit expression and 17 (71%) of them were characterized as positive. One complete and two partial responses were achieved in both phase I and II parts of the study for an overall response rate of 8.8% (95% CI; 0-18.4%); in addition, eight (23.5%) patients had stable disease while 16 (47%) had disease progression. Among the responding patients, two had strong c-kit receptor expression on their

Table 3.

PK parameters of imatinib and CGP74588.

imatinib	**day-1**	**day-2**	**P**
tmax * (h)	2.6 (2.0-6.0)	3.8 (2.0-6.0)	-
Cmax (ng/ml)	3124.8 ± 1612.2	2602.4 ± 1127.0	0.464
Lambda_z (/h)	0.073 ± 0.025	0.051 ± 0.043	0.239
t1/2 (h)	10.5 ± 3.2	15.2 ± 9.9	0.240
AUCall (ng.h/ml)	13188.1 ± 8038.5	12858.6 ± 6425.7	0.929
Cl/F (L/h)	23.2 ± 20.4	10.9 ± 16.5	0.220
Vz/F (L)	152.1 ± 91.6	160.6 ± 86.4	0.857
CGP74588	**day-1**	**day-2**	**P**
tmax * (h)	3.6 (2.0–5.0)	3.9 (2.0-6.0)	-
Cmax (ng/ml)	475.0 ± 304.9	436.8 ± 224.1	0.779
Lambda_z (/h)	0.110 ± 0.080	0.060 ± 0.050	0.258
t1/2 (h)	10.3 ± 7.2	21.2 ± 18.5	0.159
AUCall (ng.h/ml)	2019.8 ± 1371.1	2099.7 ± 1373.5	0.909
Cl/F (L/h)	120.8 ± 90.6	61.1 ± 62.8	0.214
Vz/F (L)	1133.1 ± 798.6	854.4 ± 329.6	0.464
AUCall ratio **	15.3	16.2	-

** median (range); all unflagged values are: means ± SD.*

*** conversion ratio of imatinib to CGP74588 (in %).*

Table 4.

PK parameters of CPT-11 and its major metabolites (SN-38 and SN-38G).

A	**CPT-11**	**SN-38**	**SN-38G**
tmax * (h)	1.81 (0.75-3.5)	1.64 (0.75-2.0)	2.28 (1.5-3.5)
Cmax (µg/ml)	1355.9 ± 429.2	31.9 ± 11.9	162.5 ± 69.0
Lambda_z (/h)	0.218 ± 0.064	0.197 ± 0.088	0.166 ± 0.052
t1/2 (h)	3.45 ± 0.94	4.30 ± 1.88	4.67 ± 1.67
AUCall (µg.h/ml)	5382.6 ± 1546.3	142.3 ± 57.1	784.3 ± 412.8
AUCinf (µg.h/ml)	7581.1 ± 2325.3	223.7 ± 93.2	1314.0 ± 866.2
Cl (L/h/m^2)	0.022 ± 0.007	0.869 ± 0.571	0.153 ± 0.075
Vz (L/m^2)	0.104 ± 0.030	4.683 ± 2.167	0.924 ± 0.334
B		**AUCall ratio (%)**	
SN-38/CPT-11		2.6	
SN-38G/CPT-11		14.6	
SN-38G/SN-38		550.9	

A: Day 1; B: AUC ratio (% values) for irinotecan and its metabolites

** median (range); all unflagged values are: means ± SD.*

tumour cells; the patient who achieved complete response had c-kit receptor-expressing tumour and had received front-line irinotecan plus cisplatin with compete response and 2nd line docetaxel plus gemcitabine with a new complete response. One of the patients who experienced a partial response was c-kit positive and had been previously treated with carboplatin plus etoposide with partial response. The third partially responding patient had previously received front-line concurrent radiotherapy and cisplatin/etoposide followed by paclitaxel plus cisplatin post-radiotherapy; a partial response and 2nd line irinotecan plus gemcitabine was administered at the time of disease progression with a new partial response; unfortunately, there was no tumour sample available for the assessment of c-kit expression for this patient.

The duration of response for the three responding patients was 2.8, 3.9 and 4.2 months, respectively. The median time to progression (TTP) was 2.2 months (range, 1-10.6) while the median overall survival was 4.8 months (range 0.8-14.4). The 1-year survival rate was 13.1%.

Toxicity

Table 5 shows the grade 2-4 haematological toxicity observed in all chemotherapy cycles for both phase I and II parts of the study. Four (11.7%) and six (17.6%) patients developed grade 3 and 4 neutropenia, respectively; in addition, three (8.8%) and one (2.9%) patients experienced grade 2 and 3 thrombocytopenia, respectively, while three (8.8%) patients grade 2 anaemia. There was no episode of febrile neutropenia or toxic death. Grade 2 and 3 diarrhoea was the most common non-haematological toxicity occurring in nine (26.4%) and one (2.9%) patients, respectively. Grade 2 and 3 asthenia was also a common toxicity observed in seven (20%) and two (5.8%) patients, respectively. Grade 2 nausea was rarely seen and no other grade 3 or 4 toxicity was observed. Table 6 shows the grade 2-4 non-haematological toxicity observed in all chemotherapy cycles for both phase I and II parts of the study.

DISCUSSION

The current study demonstrates that imatinib mesylate in combination with irinotecan, has a modest activity in pretreated patients with SCLC; in addition the combination was associated with substantial haematological and non-haematological toxicity. Indeed, the overall response rate of 8.8% was inferior to that reported in previous phase II studies with irinotecan monotherapy in refractory or relapsed SCLC patients [31-32]. This could probably be attributed to worse patient characteristics, since the majority (68%) of the patients enrolled in the current study were heavily pretreated and had already received 2 or more chemotherapy regimens. It is well recognised that SCLC, although

Figure.
Representative patient plasma concentration versus time for irinotecan and its metabolites.

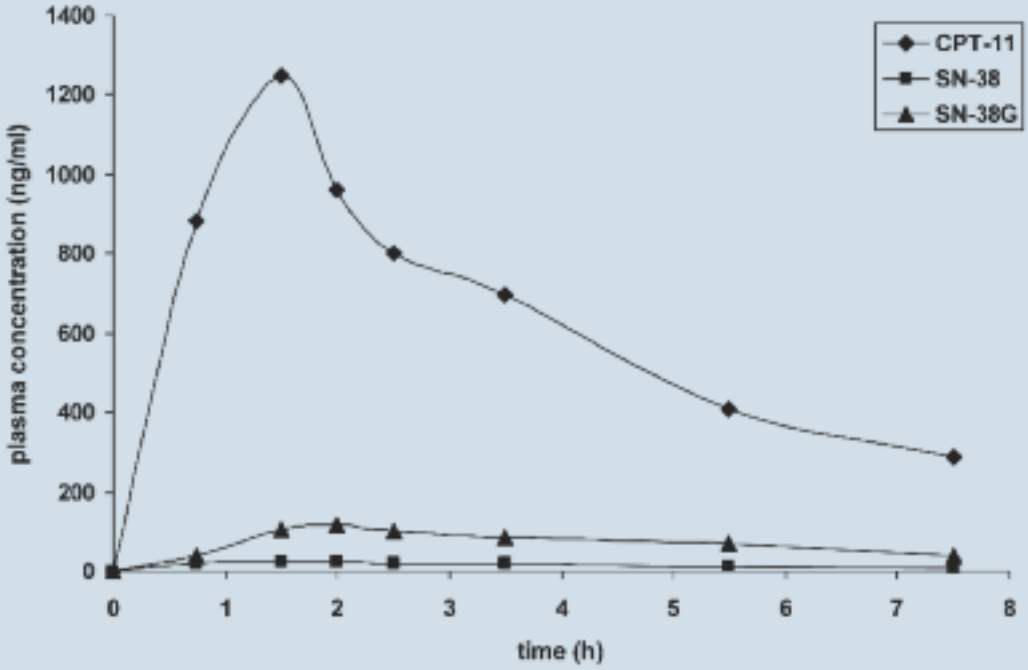

Table 5.
Haematological toxicity (WHO grade 2-4) in all cycles by dose level.

Level	No of patients	Neutropenia			Anaemia	Thrombocytopenia	
		Grade 2 n	Grade 3 n	Grade 4 n	Grade 2 n	Grade 2	Grade 3
1	6	2 (33.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	-
2	28	3 (10.7%)	2 (7.1%)	5 (17.9%)	2 (7.1%)	1 (3.6%)	1 (3.6%)
Total	34	5 (14.7%)	4 (11.7%)	6 (17.6%)	3 (8.8%)	3 (8.8%)	1 (2.9%)

Table 6.
Non-haematological toxicity in all cycles by dose level.

Level	No of patients	Nausea	Diarrhoea		Asthenia		Other
		Grade 2	Grade 2	Grade 3	Grade 2	Grade 3	Grade 2
1	6	-	2 (33.3%)	-	-	1 (16.1%)	4 (66.7%)
2	28	3 (10.7%)	7 (25%)	1 (3.6%)	7 (25%)	1 (3.6%)	4 (14.2%)
Total	34	3 (8.8%)	9 (26.4%)	1 (2.9%)	7 (20%)	2 (5.8%)	8 (23.5%)

considered to be a highly chemosensitive disease in the first line setting, soon becomes chemo-resistant to subsequent chemotherapy treatment. Furthermore, the required dose reduction of irinotecan, attributed probably to the toxicity of the drug combination, may have also contributed to the limited activity of the regimen.

In our study, tumour material was available from 24 patients for immunohistochemical analysis, and 17 (71%) among them were considered positive for c-kit expression, which is in accordance with previous reports showing that 38-92% of SCLC cases express the c-kit receptor [11, 15-18, 20, 21, 23]. Two out of three responding patients were positive for c-kit, while the c-kit status was unknown for the third one. This observation makes difficult any correlation between the expression of c-kit and response to imatinib/CPT-11.

The rationale for combining the two agents was based on the efficacy of imatinib in other c-kit expressing neoplasms and in preclinical data concerning the effect of imatinib in SCLC cell lines. Indeed, imatinib has shown astonishing activity in the treatment of neoplasms in which the targeted receptor-associated tyrosine kinase is activated by chromosomal translocation (Abl kinase in chronic myeloid leukaemia) or genomic mutation (c-kit in GIST) [4, 43-44]. However, the efficacy of imatinib, when the c-kit receptor is present but its activation status is unknown, remains questionable. In previous phase II studies, imatinib given as single agent failed to show any activity both in patients with chemo-naïve or sensitive relapse [21, 23] and resistant recurrent and refractory [22] SCLC. This observation may be due to the fact that c-kit is not essential for the survival and growth of SCLC tumour cells. Alternatively, we cannot exclude that the time elapsed from the initial diagnosis and the storage conditions, may account for the immunohistochemistry results. Indeed, it has been reported that up to 50% of SCLC cases that were c-kit positive at diagnosis were found to be c-kit negative in the post-chemotherapy tumour specimen [45].

Preclinical data support a possible synergistic effect of the combination of imatinib with camptothecins [25]. This hypothesis could not be supported from the data of the current study. On the contrary, an unexpected unfavourable toxicity profile was observed during the phase I part of the study requiring a dose de-escalation of the irinotecan from 180 mg/m^2 which is the dose used in biweekly chemotherapy regimens [46]. Based on this observation, further escalation of the imatinib dose in combination with the reduced dose of irinotecan was not attempted for safety reasons. Instead, it was decided to proceed with the phase II part of the study using the already established MTDs for the combination. Therefore, the scheduled escalation of the imatinib dose was not really performed in the present study and, therefore, it remains unknown whether that could have led to a more active regimen.

In a previous phase I study of the combination of imatinib with cisplatin and irinotecan in patients with SCLC [24], the chronic exposure to imatinib led to an increased half-life and AUC of irinotecan perhaps due to inhibition of the CYP3A4 oxidative pathway of irinotecan by imatinib; this pharmacokinetic interaction was associated with an increased incidence of neutropenia and diarrhoea. Furthermore, increased

neutropenia, nausea, diarrhoea, fatigue and dyspnoea were also reported when imatinib was given in combination with irinotecan and carboplatin [34]. In our study, neutropenia was the DLT and the most frequent haematological toxicity, while diarrhoea and asthenia were the most frequent non-haematological toxicities. However, the pharmacokinetic data reported in the current study, did not reveal any significant interaction between imatinib and irinotecan since all studied PK parameters for imatinib and its major metabolite were unchanged between day-1 and day-2 (Table 3); conversely, PK levels of CPT-11 as well as of its metabolites (Table 4) were found to be in accordance with other published reports [47-48]. Additionally, the metabolic ratios of product to substrate (Table 4) are in agreement with already published data [41, 49]. Nevertheless sampling for irinotecan (i.e. before imatinib administration during cycles 2 and 3) would have given more data to assess for possible PK interactions, as already has been reported by Johnson *et al.* [24]. Considering the importance of PK levels of CGP74588 in a study examining possible interactions of imatinib with other co-administered drugs [50], a noticeable day-1 to day-2 difference for CGP74588 but also for the parent drug, was determined regarding the elimination time and clearance, but these changes were not statistically significant (Table 3). Another interesting finding for imatinib came from the fact that the C_{max} of both the parent drug and the CGP74588 were found to be lower on day-2 than on day-1 in 2 and 3 patients, respectively (data not shown); however, the two mean values were not significantly different (p=0.464 and 0.779, respectively). Moreover, the AUC_{all} mean values seemed to be equal on day-1 and day-2 (Table 5). Limitations associated with the number of patients or/and the sampling time (up to 6 hours after drug administration) could also account for the failure to demonstrate statistically significant differences. Finally, the conversion ratio of imatinib to CGP74588 as well as the mean ratio of imatinib and its metabolite's concentrations are in accordance with other reports (15-17%) [50-51].

To our knowledge, this is the first study published to date evaluating the imatinib plus irinotecan combination in SCLC patients. Like previous reports of imatinib alone or in combination with other cytotoxic agents, this study also failed to show adequate efficacy for the experimental combination. The regimen was associated with an unfavourable toxicity profile, probably due to an increased exposure to irinotecan and its active metabolites when given in combination with imatinib; although our PK data does not clearly indicate a drug-to-drug interaction we cannot exclude an interaction since both agents share the same metabolic pathways. The addition of haematopoietic growth factor support could allow the tolerance of higher doses of imatinib and irinotecan. However, given the lack of activating mutations in c-kit positive SCLC [52-53], the role of imatinib in the treatment of SCLC is probably limited. Therefore, based on the results of the present study as well as those of the literature, we do not recommend any further study of the imatinib and irinotecan combination in SCLC.

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Do we need to treat patients with Glioblastoma Multiforme with radical chemoradiotherapy if they had biopsy alone? Northampton Experience

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ABSTRACT

Background: Concomitant and adjuvant chemoradiotherapy with Temozolomide (TMZ) has become the standard treatment for newly diagnosed Glioblastoma Multiforme (GBM). The aim of this retrospective trial is to assess the survival benefit of radical treatment given to patients with GBM treated at our centre and to assess various prognostic factors with emphasis on the value of addition of TMZ to patients who had biopsy alone.

Patients & Methods: We retrospectively analyzed the medical records of seventy three patients with pathologically proven GBM included in this analysis. 49 patients underwent surgical debulking, while 24 patients were only biopsied; 37 patients received postoperative radiotherapy, while 36 patients received concurrent chemoradiotherapy and adjuvant chemotherapy.

Results: Patients who underwent debulking and received adjuvant CRT had longer median overall survival of 19.8 months (95% CI, 13.9-25.7) versus 9 months (95% CI, 7.8-10.2) for those who underwent just biopsy and also received adjuvant CRT (p=0.001). The survival of those treated with biopsy and concurrent CRT was not statistically significant when compared to those who had debulking or biopsy with radiotherapy (p>0.05). In the multivariate analysis, age, sex, extent of surgery, and adjuvant treatment were statistically significant factors in predicting prognosis.

Conclusion: Offering radical concomitant chemoradiotherapy to patients with GBM who only had biopsy should be thoroughly discussed as its benefit is very small -if any. A prospective randomized trial is recommended to define the benefit of said approach for this group of patients.

Key words: glioblastoma multiforme; chemoradiotherapy; surgery.

INTRODUCTION

Primary tumors of the central nervous system are classified according to the World Health Organization (WHO) guidelines, which were updated in 2007 [1]. Glioblastoma Multiforme WHO grade IV (GBM) is one of the most aggressive human malignant diseases and the most frequent primary tumor of the central nervous system with an incidence of 4-5 per 100,000 inhabitants per year in industrialized countries like Europe and the US [2].

Despite the progress recorded in the identification of these tumors' complex biology, prognosis has not improved substantially over the past three decades [3].

Postoperative radiotherapy (RT) has been recognized as standard GBM therapy for a long time [4]. The role of chemotherapy based on alkylating agents had been controversial until the results of trial EORTC 26981 came out. The results showed that Temozolomide (TMZ) provided a statistically significant and clinically meaningful survival benefit, producing an increase in the median survival time from 12.1 to 14.6 months and in the two-year survival rate from 10 to 26% [5].

Recently, concomitant and adjuvant chemoradiotherapy (CRT) with TMZ has become the standard treatment for newly diagnosed glioblastoma. Despite multimodal aggressive treatment, the median survival time after diagnosis is still in the range of just 12 months [6].

Even when receiving the same treatments, the clinical outcome of patients with GBM varies significantly. It is important for us to

Table 1.
Patient characteristics.

Patient characteristics		N	%
		73	100
Gender			
	Male	48	65.5%
	Female	25	34.2%
WHO PS	0	11	15.1%
	1	57	78.1%
	2	5	6.8%
Extent of surgery			
	Debulking	49	67.1%
	biopsy	24	32.9%
Adjuvant treatment			
	RT	36	49.3%
	CRT	37	50.7%

PS=performance status

understand the factors that contribute positively or negatively to the prognosis of patients, which may guide treatment paradigms and therapeutic strategies aimed at prolonging survival [7].

Several clinical and therapeutic factors as well as tumor characteristics have been reported as significant to survival. A more efficient determination of the prognostic factors is required to optimize individual therapeutic management [8].

The aim of this retrospective trial is to evaluate the outcome of patients with GBM treated with radical intent at our center and assess various prognostic factors with emphasis in the value of adding TMZ to patients who had biopsy alone.

PATIENTS & METHODS

We retrospectively examined the medical records of all patients with GBM treated with radical intent at the Northampton Oncology Centre, Northampton General Hospital between January 2005 and December 2010.

Data collected included age, sex, performance status (PS), treatment details and patient outcome.

Seventy three patients with pathologically proven GBM were included in this analysis; 49 patients underwent surgical debulking, while 24 patients were only biopsied. 37 patients received postoperative radiotherapy alone, while 36 patients received concurrent chemoradiotherapy and adjuvant chemotherapy.

Treatment

Radiotherapy consisted of localized fractionated radiotherapy for a total dose of 60 Gy (2 Gy per fraction once daily, five days per week) over a period of 6 weeks. Radiotherapy was delivered to planning target volume that was grown from a 2.5cm gross tumor volume. Radiotherapy was planned on a conformal three-dimensional planning system. Treatment was delivered using a 6 MV Linear accelerator.

Concomitant chemotherapy consisted of Temozolomide at a dose of 75 mg/m^2 given daily from the first until the last day of radiotherapy. Adjuvant chemotherapy started 4-6 weeks after the end of the concurrent course. Patients received up to six cycles of adjuvant Temozolomide 200 mg/m^2 for 5 days, to be repeated every 28 days.

Follow-up

The baseline examination included Magnetic Resonance Imaging (MRI), full blood counts, blood chemistry tests as well as physical examination.

Patients were reviewed weekly during radiotherapy and in every cycle during the adjuvant chemotherapy period. An MRI scan was performed after 2, 4 & 6 cycles of the adjuvant TMZ.

Statistical methods

Mean, median, standard deviation and frequency were used to describe data. Life tables, log rank test, Cox regression and hazard ratio were used to test the effect of different risk factors on survival. Tests were run on an IBM compatible PC using an SPSS for windows statistical package version 17 (SPSS Inc., Chicago, IL).

RESULTS

This study is a retrospective analysis of 73 patients. Patient and tumor characteristics are presented in Table 1.

The mean received radiotherapy dose was 49 Gy (range 10-60 Gy, ±SD 11.8), the mean number of fractions was 24.5 (range 5-30, ±SD 5.9). The mean time between patient seen and start radiotherapy was 24 days (range 5-61, ±SD 8.98). There was no significant difference between those who has been treated within three weeks from diagnosis or more (35 versus 38 patients; p=0.29).

The mean and median overall survival time (OS) for all patients was 12.4 months (range 1.73-43, ±SD 8.2) and 8.2 months (95% CI, 4.5-12.7), respectively. The best median overall survival (OS) for patients with PS 0 was 14 months (95% CI, 5-23.2), but the worst was for patients with PS 2 (4 months, 95% CI, 1.5-6.5) (p=0.03), while patients with PS 1 had a median overall survival of 10.8 months (95% CI, 7.52-14.07). It is to be noted that the number of patients with PS 0 or 2 was small (11 and 5, respectively).

Patients who underwent debulking surgery had a median OS of 13 months (95% CI, 9.5-16) versus 7.7 months (95% CI, 3.8-11.6) for those who underwent biopsy alone (p=0.02) (Figure 1). For patients treated with adjuvant RT, the median OS was 6.4 months (95% CI, 3.4-9.4), as compared to 14.5 months (95% CI, 9.5-19.4) for those treated with adjuvant CRT (p=0.001) (Figure 2).

Patients who underwent debulking and received adjuvant CRT had longer median overall survival of 19.8 months (95% CI, 13.9-25.7) versus 9 months (95% CI, 7.8-10.2) for those who underwent biopsy alone and also received adjuvant CRT, whereas patients who underwent debulking and received adjuvant RT alone had a median overall survival of 7.6 months (95% CI, 4.18-11.9) versus 5 months (95% CI, 3.39-6.80) for those who underwent just biopsy and received also adjuvant RT alone (Figure 3).

There was a statistically significant difference in median OS between patients who underwent debulking and received CRT (19.8 months, 95% CI, 13.9-25.7) versus those with debulking and RT only (7.6 months, 95% CI, 4.18-11.9) (p=0.001).

As regards the role of adjuvant chemotherapy in relation to biopsy, a non-significant difference in survival was found between patients who had biopsy and adjuvant CRT (9 months, 95% CI, 7.8-10.2) as compared to those who only had biopsy plus radiotherapy (5 months, 95% CI, 3.39-6.80) (p=0.13) or debulking and radiotherapy only (7.6 months, 95% CI, 4.18-11.9) (p=0.24).

Univariate analysis revealed that age (p=0.002); extent of resection (p=0.02); and adjuvant treatment (in favor of CRT) (p=0.001) were statistically significant factors (Table 2).

In the multivariate analysis, age, sex, extent of resection, and adjuvant treatment were statistically significant predicting factors in prognosis, where poorer prognosis was associated with greater age (p=0.01); male sex (p=0.03); extent of surgery (biopsy worse than debulking, p=0.007); and adjuvant treatment (adjuvant RT worse than adjuvant CRT, p=0.001) (Table 3).

DISCUSSION

Glioblastoma Multiforme is the most devastating primary brain tumor with dismal prognosis and furthermore is one of the most expensive cancers to be treated [9].

In our study, analysis of prognostic factors was performed regarding age, sex, performance status, extent of surgery, adjuvant treatment, radiotherapy dose and number of RT fractions, where age, sex, extent of surgery and adjuvant treatment (in favor of CRT) were found to affect survival significantly.

Nearly all trials showed a significant negative relationship between advancing age and postoperative survival [10, 11]. Similarly, we observed poorer prognosis with greater age in both univariate and multivariate analysis.

Many trials state that performance status had been one of the most well-documented predictors of survival [7, 12, 13]. However, in our results performance status was very near

Table 2.
Univariate analysis of factors predicting survival.

Model	Regression coefficient	Wald x^2	P value	*Hazard ratio	(95% CI) of hazard ratio
1. Age	0.37	9.14	0.002	1.45	(1.14-1.84)
2. Sex	-0.37	1.77	0.2	0.69	(0.41-1.18)
3. PS	0.54	3.01	0.08	1.72	(1.197-3.768
4. Extent of resection	0.64	5.65	0.02	1.89	(1.12-3.19)
5. Adjuvant treatment	0.88	11.73	0.001	2.42	(1.46-4.01)

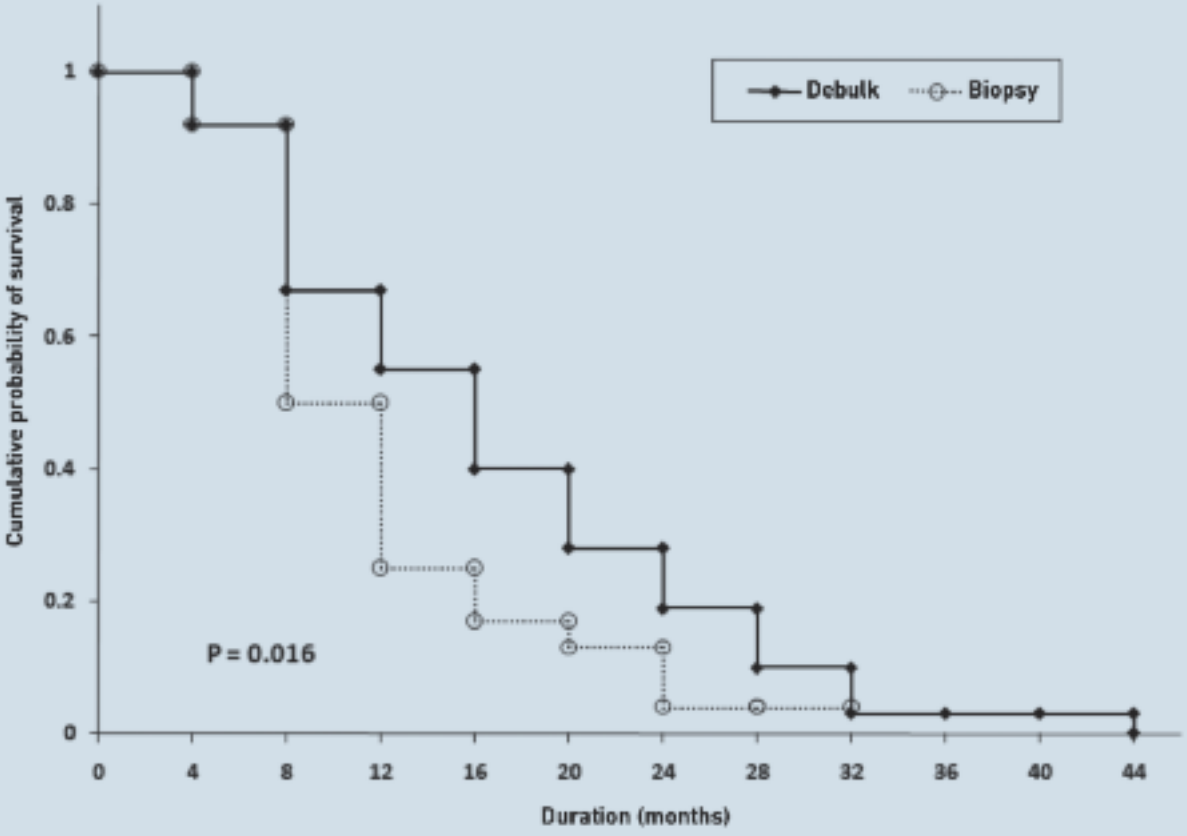
CI=confidence interval; x^2= Chi-square

Table 3.
Multivariate analysis of factors predicting survival.

	Partial regression coefficient	Wald x^2	P value	*Hazard ratio	(95% CI) of hazard ratio
Sex	-0.64	4.58	0.03	0.529	(0.295-0.948)
Adjuvant treatment	0.89	11.13	0.001	2.403	(1.436-4.023)
Extent of resection	0.79	7.12	0.007	2.198	(1.237-3.904)
Age	0.30	6.52	0.01	1.354	(1.073-1.709)

*The hazard ratio was calculated for values between brackets.
CI=confidence interval, x^2=Chi-square

Figure 1.
Effect of extent of surgery on survival.



to statistical significance levels (p=0.08). This may be explained by the fact that most of our patients had a good PS (57 patients with PS 1; 11 patients with PS 0; and only 5 patients with PS 2) and that they were unevenly distributed among the 3 available categories with accumulation of most patients in PS 1.

Debulking surgery can relieve patient symptoms and provides conclusive pathological diagnosis. Our results demonstrated statistically significant benefit in patients who underwent debulking surgery versus biopsy in both univariate and multivariate analysis. This finding was in accordance with previous results [14, 15].

In patients with GBM that were either unfit for or declined radiotherapy, management with best supportive care after biopsy resulted in a median survival time of 3 months versus 6-7 months, a median survival in a historical series of radiotherapy. This analysis included 26 patients treated between 1998 and 2003 [16].

Over the past several years, therapeutic strategy in the treatment of glioblastoma has changed and survival was increased by concomitant chemoradiotherapy with Temozolomide. Temozolomide (TMZ) has been shown to provide a statistically significant and clinically meaningful survival benefit, producing an increase in the median survival time from 12.1 to 14.6 months and in the two-year survival rate from 10% to 26% [5]. Several studies confirmed the influence of concomitant chemoradiotherapy with Temozolomide [7, 17, 18, 19].

Our study demonstrated statistically significant better survival for patients treated with adjuvant chemoradiotherapy; 14.5 months (95% CI, 9.5-19.4) versus 6.4 months for those treated with adjuvant radiotherapy alone (95% CI, 3.4-9.4), p=0.001.

Another important observation is that patients who underwent debulking and postoperative chemoradiotherapy had a longer median overall survival of 19.8 months (95% CI, 13.9-25.7), versus 9 months (95% CI, 7.8-10.2) for those who underwent biopsy alone and also received adjuvant chemoradiotherapy.

There was a statistically significant difference in median OS between patients who underwent debulking and received CRT (19.8 months, 95% CI, 13.9-25.7) versus those with debulking and RT alone (7.6 months, 95% CI, 4.18-11.9) (p=0.001). The lower survival of patients who received adjuvant radiotherapy alone may be due to the selection bias

Figure 2.
Effect of adjuvant RT VS adjuvant CRT with TMZ on survival.

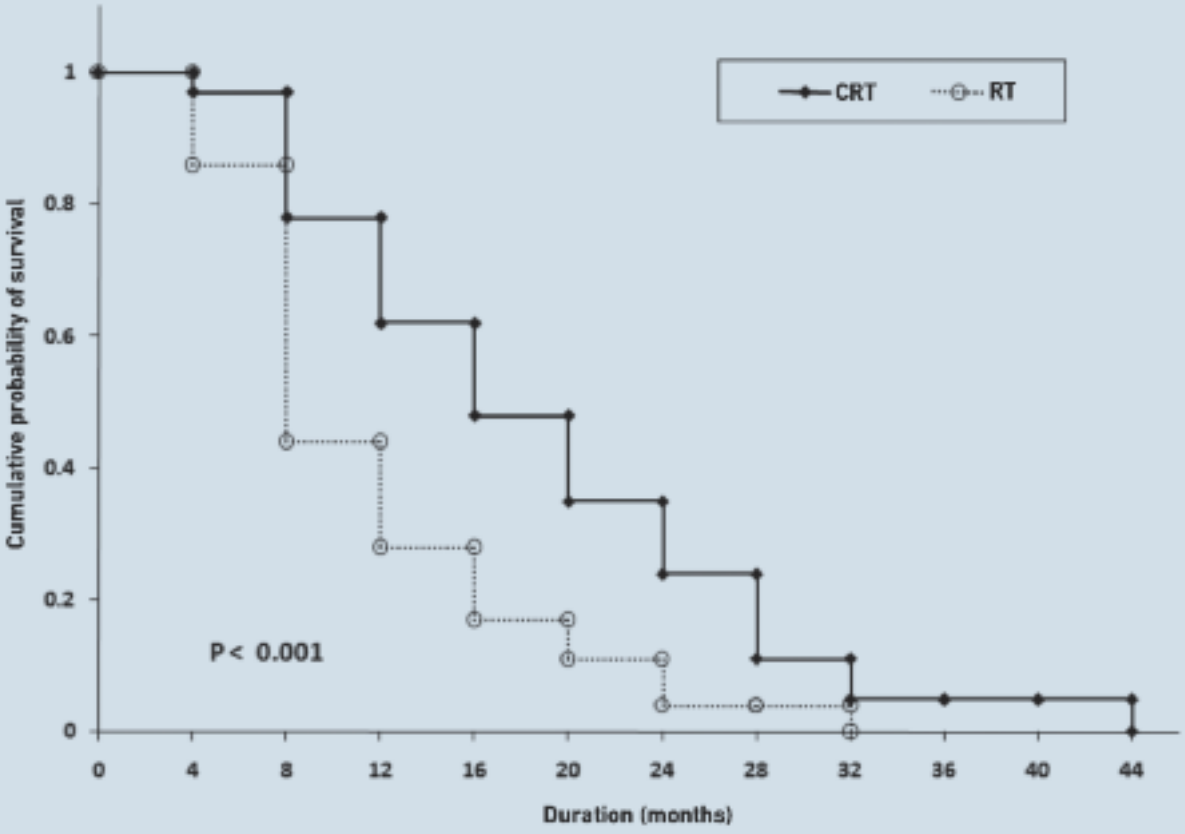
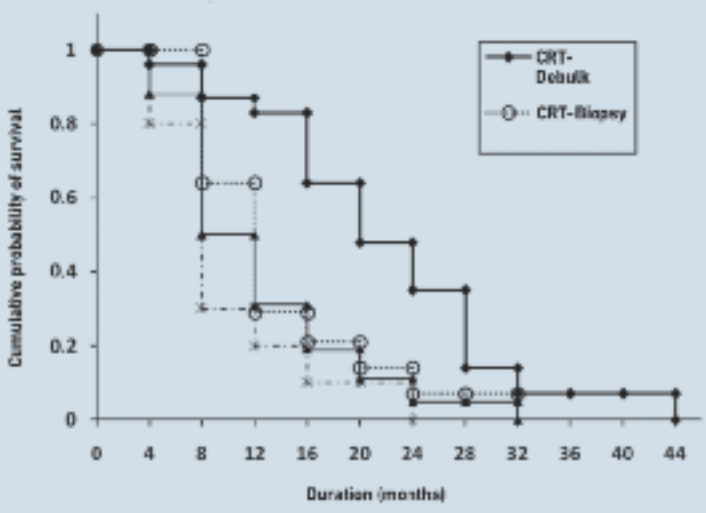


Figure 3.
Effect of Temozolomide and extent of surgery.



of patients who were chosen on the basis of poor PS, which negatively affected survival.

As regards the role of adjuvant chemotherapy in relation to biopsy, non-significant difference in survival was found between patients who had biopsy and adjuvant CRT (9 months, 95% CI, 7.8-10.2) and those who had biopsy plus radiotherapy alone (5 months, 95% CI, 3.39-6.80) (p=0.13), meaning that CRT did not affect survival in patients who had biopsy alone, and which may give a satisfactory answer to our question.

The important finding is that, unless patients have optimal debulking followed by concurrent chemoradiotherapy, their survival will remain poor and that inadequate surgery cannot be compensated simply by adding Temozolomide.

The same finding was demonstrated by a previous study conducted by Stupp *et al.* who reported unfavorable median survival of 5 months as historical data for patients who underwent biopsy alone and received postoperative chemo-radiotherapy with Temozolomide [20]. Another large trial conducted by the European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) with 573 patients included 16% with biopsy alone. The median survival was 7.9 months after radiotherapy alone and 9.4 months after radiotherapy plus Temozolomide. The difference was not statistically significant [5]. In addition, it was reported by Combs *et al.* that median survival for those patients who had biopsy alone and received postoperative chemoradiotherapy with Temozolomide was 10 months [21]. Furthermore, it was confirmed that the most important prognostic factors were type of surgery and application of adjuvant Temozolomide for at least 4 cycles [22].

Since GBM is characterized by vascular proliferation and produces high levels of vascular endothelial growth factor (VEGF), attempts to better control the disease with targeted anti-angiogenesis therapies are currently underway. Seventy five patients with newly diagnosed glioblastoma were enrolled on this phase II trial that investigated the addition of Bevacizumab to standard radiation therapy and daily Temozolomide followed by the addition of Bevacizumab and Irinotecan to adjuvant Temozolomide. The median overall survival was 21.2 months (95% CI, 17.2-25.4), and the median progression-free survival was 14.2 months (95% CI, 12-16). Results from phase III trials are required before the role of Bevacizumab for newly diagnosed glioblastoma is established [23].

CONCLUSION

Despite the limitations of this retrospective study, offering radical concomitant CRT for patients with GBM who only had biopsy should be thoroughly discussed as it does not seem to produce significant survival benefit. More prospective randomized trials are needed to define the benefit of adjuvant CRT in this group of patients.

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Testicular cancer: The experience of the 2nd Oncology Department of Metropolitan Hospital and a brief review of the literature

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ABSTRACT

Background: Testicular cancer (TC) is the most common malignancy in males throughout their second and third decade of life. TC is considered as a highly curable cancer. Since 1960 numerous chemotherapeutic regiments have been studied for their effectiveness and toxicity on different stages of male germ cell tumor. Accordingly, the aim of this study is to present the experience of the Second Oncology Department of Metropolitan Hospital, to briefly review the history of TC therapy and to remind the current recommended treatment approach.

Patients & Methods: We retrospectively reviewed the data from a non-selected population of 86 men diagnosed with TC from 2000 until 2011. Twenty-seven patients with seminoma and fifty-nine patients with non-seminoma were included in this study. We evaluated patients according to the well-known TNM system and to IGCCCG risk factors. The patients were treated as usual according to the everyday practice of our clinic. None of them had received prior chemotherapy.

Results: No unexpected toxicities were observed. Most of the treatment-related adverse events were of grade I or II and generally reversible. The most common adverse reactions of patients under treatment, who had received two cycles of carboplatin 6AUC, were gastrointestinal symptoms (nausea/vomiting), hiccups and fatigue. Nausea, vomiting and alopecia were most frequent in the group of patients with non-seminoma who were treated with bleomycin, etoposide and cisplatin (BEP). One male with low risk advanced non-seminoma died due to lung and hematological toxicity. All others are still alive.

Conclusions: The treatment of TC is a story of success in oncology. The vast majority of patients are being cured. Nevertheless, treatment toxicities remain a problem that doctors still need to overcome. There is a necessity, especially for patients with poor risk metastatic non-seminoma, to specify the responsible molecular mechanism and to invent effective drugs. Our improved understanding of the biology and molecular mechanisms of TC will lead to novel, less toxic therapies.

Key words: testicular cancer; seminoma; non-seminoma; bleomycin; etoposide; cisplatin.

Acronyms

TC:	Testicular Cancer
BEP:	Bleomycin-Etoposide-Cisplatin
CARBO:	Carboplatin
IBEP:	Ifosfamide-Bleomycin-Etoposide-Cisplatin
M-VIP:	Methotrexate-Etoposide-Ifosfamide-Cisplatin
αFP:	α-Fetoprotein
βHCG:	β-Human Chorionic Gonadotrophin
RECIST:	Response Evaluation Criteria in Solid Tumors
PFS:	Progression Free Survival
OS:	Overall Survival
IGCCCG:	International Germ Cell Cancer Collaborative Group
NCCN:	National Comprehensive Cancer Network

INTRODUCTION

Regardless of the fact that testicular cancer (TC) accounts for only 1% of all cancers in males, it is the most common malignancy throughout the second and third decade of men's life [1, 2]. The incidence of non-seminomatous tumor is higher in men between 15-35 years old, but the occurrence of seminoma is presenting a decade later [3]. Over the past thirty years, the frequency of TC has increased, especially in industrialized countries of Europe, North America and Australia [1]. Fortunately, TC is considered as a highly curable malignancy after the addition of cisplatin in the therapeutic regimen [4]. Indeed, the relative survival rate 5 and 10 years after diagnosis of the malignancy is more than 97% [5].

TC is not so common in the black race in comparison with the Caucasian race [3]. Furthermore, within the same race TC shows different incidence between various countries. For instance, the incidence in Scandinavian countries is higher than in the Mediterranean [3, 6]. This observation suggests a genetic background for the tumor, which is still unknown. As a matter of fact, brothers of patients with TC have a 6 to10 times higher possibility to develop germ cell tumor [7]. Certain environmental and epidemiological factors such as cryptorchidism; low birth weight; exposure of the mother to exogenous estrogen during pregnancy; increased body weight of the mother; testicular cancer in first-grade relatives; and contralateral tumor have been accused as risk factors for germ line tumor in men [6, 8]. On the other hand, acne in puberty seems to protect men against TC [8].

During the past 50 years TC has changed from a fatal disease to a highly curable one. New chemotherapeutic agents and novel drug combinations have been established to act effectively. But still, the problem of toxicity remains a main issue. That is the reason why it is necessary for oncologists to be aware of expected toxicities.

Nowadays, the therapeutic approach of TC is a model of multidisciplinary care; this includes surgery, chemotherapy and radiotherapy. The aim of this study is to present our experience regarding the safety and effectiveness of various chemotherapeutic combinations.

PATIENTS & METHODS

We retrospectively reviewed data from a non-selected population of 86 men histologically diagnosed with TC from 2000 until 2011. The patients were classified into groups according to the TNM staging system, and clinically independent adverse factors, as presented in Table 1 [29]. The patients were treated as applicable in the everyday practice of our department. It is important to notice that the therapeutic directions have changed over the past 20 years. Therefore, our patients of the same TC stage received different regimens. All patients in this study received adjuvant treatment for stage I seminoma and non-seminoma or 1st line treatment for metastatic TC. None of them had received prior chemotherapy. We noticed recurrences in some of them but do not further investigate salvage therapy in this study.

Staging included abdomen CT scan, chest X-ray, renal clearance measurement, liver function tests and measurement of serum α-fetoprotein (αFP) and β-human chorionic gonadotrophin (βHCG) levels. Radiographic response and serum tumor markers were evaluated as indicated. Res-

Table 1.
Prognostic-based staging system for metastatic TC according to IGCCCG criteria [6].

Good prognosis group	
Non-seminoma (56% of cases)	All of the following criteria:
5-yr PFS 89%	Testis/retroperitoneal primary
5-yr survival 92%	Pulmonary visceral metastases
	AFP <1000 ng/ml
	hCG <5000 IU/l (1000ng/ml)
	LDH <1.5 x ULN
Seminoma (90% of cases)	All of the following criteria:
5-yr PFS 82%	Any primary site
5-yr survival 86%	Pulmonary visceral metastases
	Normal AFP
	Any hCG
	Any LDH
Intermediate prognosis group	
Non-seminoma (28% of cases)	All of the following criteria:
5-yr PFS 75%	Testis/retroperitoneal primary
5-yr survival 80%	Pulmonary visceral metastases
	AFP 1000-10,000 ng/ml, or
	hCG 5000-50,000 IU/l, or
	LDH 1.5-10 x ULN
Seminoma (10% of cases)	Any of the following criteria:
5-yr PFS 67%	Any primary site
5-yr survival 72%	Non-pulmonary visceral metastases
	Normal AFP
	Any hCG
Poor prognosis group	
Non-seminoma (16% of cases)	Any of the following criteria:
5-yr PFS 41%	Mediastinal primary
5-yr survival 48%	Non-pulmonary visceral metastases
	AFP >10,000 ng/ml, or
	hCG >50,000 IU/l (10,000 ng/ml), or
	LDH >10 x ULN
Seminoma	
No patients classified as poor prognosis	

Abbreviations: PFS=progression free survival; AFP=a-fetoprotein; hCG=human chorionic gonadotrophin; LDH=lactate dehydrogenase; ULN=upper limit of normal range.

ponse was assessed using Response Evaluation Criteria in Solid Tumors (RECIST). Adverse events were graded using NCI Common Toxicity Criteria version 3.0 at baseline, every course of therapy and in the follow-up.

Before 2008, bleomycin and cisplatin were administered in patients with seminoma or non-seminoma of stage I or II-IV intravenously, according to the protocol of the Hellenic Cooperative Oncology Group (HeCOG). The protocol dictated: bleomycin 15 mg (days 1-3, 8 hour-infusion) and cisplatin 40 mg/m^2 or 50 mg/m^2 (days 1-2, diluted in one liter of normal saline and given for more than 2 hours). Intravenous hydration started 12 hours prior to the first dose of cisplatin and was maintained throughout each cycle. Etoposide was given 120 mg/m^2 intravenously on days 1-3. After 2008, according to NCCN guidelines, the above schedule was administered only in patients with seminoma or non-seminoma stage I. On stage II-IV BEP was administered as follows: bleomycin 30 mg (days 1, 8, 15), etoposide 165 mg/m^2 (days 1-3) and cisplatin 50 mg/m^2 (days 1-2) or bleomycin 30 mg (days 1, 8, 15), etoposide 100 mg/m^2 (days 1-5) and cisplatin 20 mg/m^2 (days 1-5). The cycles were given every 3 weeks, unless delayed for one week due to toxicity.

Five patients with high risk disseminated non-seminoma were treated taking four cycles of IBEP. This schedule was administered as follows: ifosfamide 1.2 g/m^2 (days 1-5), bleomycin 15 mg (days 1, 3 and 5), etoposide 80 mg/m^2 (days

Table 2.

Baseline characteristics of the 27 men with seminoma, the number of relapses and their 5-yr overall survival (OS).

SEMINOMA STAGE I			
CHARACTERISTICS		**No of patients (%)**	
SEMINOMA Stage I		21	
Age at diagnosis			
Median		33	
Range		23-44	
Primary tumor site-Testis			
Right		9 (43%)	
Left		12 (57%)	
Treatment		**Relapse**	**5-yr OS**
Carboplatin 6AUC x 2 cycles	11 (52%)	1	11 (100%)
Surveillance	6 (29%)	0	6 (100%)
B_{45} E_{360} P_{80} x 2 cycles	3 (14%)	0	3 (100%)
E_{360} P_{80} x 2 cycles	1 (5%)	0	1 (100%)

SEMINOMA STAGE II-IV			
CHARACTERISTICS		**No of patients**	
SEMINOMA Stage II-IV		6	
Age at diagnosis			
Median		35	
Range		23-44	
Primary tumor site-Testis			
Right		3 (50%)	
Left		3 (50%)	
Sites of metastasis			
Lymph nodes		6 (100%)	
Lung		3 (50%)	
Lymph nodes and lung		2 (33%)	
Treatment		**Relapse**	**5-yr OS**
B_{45} E_{360} P_{80} x 2 cycles	1 (17%)	0	1 (100%)
B_{45} E_{360} P_{80} x 5 cycles	1 (17%)	0	1 (100%)
B_{45} E_{360} P_{80} x 4 cycles	4 (66%)	1	4 (100%)

Table 3.

Baseline characteristics of the 59 men with non-seminoma, the number of relapses and their 5-yr overall survival (OS).

NON-SEMINOMA STAGE I			
CHARACTERISTICS		**No of patients**	
NON-SEMINOMA Stage I		34	
Age at diagnosis			
Median		27	
Range		16-46	
Primary tumor site-Testis			
Right		16 (47%)	
Left		18 (53%)	
IGCCG Classification			
Low Risk		15 (44%)	
High Risk		19 (56%)	
Treatment		**Relapse**	**5-yr OS**
B_{45} E_{360} P_{80} x 2 cycles	26 (76%)	1	26 (100%)
B_{45} E_{360} P_{100} x 2 cycles	3 (9%)	0	3 (100%)
Surveillance	4 (12%)	0	4 (100%)
B_{45} E_{360} P_{80} x 4 cycles	1 (3%)	0	1 (100%)

NON-SEMINOMA STAGE II-IV			
CHARACTERISTICS		**No of patients**	
NON-SEMINOMA Stage II-IV		25	
Age at diagnosis			
Median		25	
Range		16-48	
Primary tumor site-Testis			
Right		14 (56%)	
Left		11 (44%)	
IGCCG Classification			
Low Risk		19 (72%)	
High Risk		7 (28%)	
Sites of metastasis			
Lymph nodes		25 (100%)	
Lung		7 (28%)	
Liver		2 (8%)	
Treatment		**Relapse**	**5-yr OS**
B_{45} E_{360} P_{80} x 4 cycles	10	0	10 (100%)
I_{6000} B_{45} E_{340} P_{100} x 4 cycles	5	0	5 (100%)
B_{45} E_{360} P_{80} x 2 cycles	1	0	1 (100%)
B_{90} E_{500} P_{100} 5-days schedule	4	1	4 (100%)
B_{90} E_{495} P_{100} 3-days schedule	2	1	1 (50%)
E_{498} P_{100} x 4 cycles	1	0	1 (100%)
M-VIP x 6 cycles	1	0	1 (100%)
B_{45} E_{360} P_{40} x 6 cycles	1	0	1 (100%)

1-5) and cisplatin 20 mg/m^2 (days 1-5). All five patients received standard G-CSF on the 1st and the 7th day because of the myelotoxic effect of this regimen.

One patient with high grade disseminated non-seminoma was treated with six cycles of M-VIP according to the Athanassiou *et al.* study [45] as follows: methotrexate 250 mg/m^2 on day 1, etoposide 100 mg/m^2 (days 2-4), cisplatin 100 mg/m^2 on day 2 and ifosfamide 5 g/m^2 on the 1st day.

RESULTS

Between June 2000 and December 2011, twenty-seven patients with seminoma and fifty-nine patients with non-seminoma were enrolled on this study. All of them had histological evidence of their disease. Baseline characteristics of the population included in this study are presented in Tables 4 and 5. The mean age of all patients with seminoma and non-seminoma was 33 and 26 years, respectively. The primary tumor site of all studied population was the left or right testis.

Furthermore, Tables 2 and 3 present patient treatment management, recurrence and 5-years OS. As mentioned above, the diversity of chemotherapeutic regimens demonstrates

Table 4.
Adverse events: seminoma.

ADVERSE EVENTS	Carboplatin 6AUC x 2	B_{15} E_{120} P_{40} x 2	B_{15} E_{120} P_{40} x 4
No of patients	11	4	4
Nausea/Vomiting	2 (18%)	1 (25%)	3 (75%)
Fatigue	1 (9%)	0	1 (25%)
Neutropenia	0	1 (25%)	1 (25%)
Thrombopenia	0	0	2 (50%)
Alopecia	0	0	1 (25%)
Neurotoxicity	0	0	2 (50%)
Ototoxicity	0	0	1 (25%)
Stomatitis	0	0	1 (25%)
Hiccups	1 (9%)	1 (25%)	1 (25%)
Glomerulonephritis	0	0	1 (25%)
Diarrhea	0	0	1 (25%)
Rash	0	0	1 (25%)

Table 5.
Adverse events: non-seminoma.

ADVERSE EVENTS	B_{15} E_{120} P_{50} x 4 cycles	B_{90} E_{495} P_{100} 3-days	B_{90} E_{500} P_{100} 5-days	IBEP
No of patients	10	2	4	5
Nausea/Vomiting	4 (40%)	2 (100%)	2 (50%)	1 (20%)
Fatigue	0	1 (50%)	1 (25%)	0
Neutropenia	1 (10%)	2 (100%)	0	1 (20%)
Thrombopenia	0	1 (50%)		1 (20%)
Alopecia	4 (40%)	0	1 (25%)	1 (20%)
Neurotoxicity	2 (20%)	0	0	0
Ototoxicity	0	1 (50%)	0	0
Fever	1 (10%)	1 (50%)	1 (25%)	1 (20%)
Hiccups	4 (40%)	0	1 (25%)	0
Rash	1 (10%)	0	0	1 (20%)
Epigastralgia	1 (10%)	0	0	0
Lung toxicity	0	1 (50%)	0	0

Table 6.
Highlights in the progression of TC treatment.

1960	The combination of actinomycin D, chlorambucil and methotrexate was used in advanced TC by Li *et al.* [10].
1970	Mithramycin and vinblastine were introduced for the treatment of advanced TC [11, 12].
1973	The combination of the Japanese antitumor antibiotic Bleomycin with vinblastine seems to be silver lining [13, 14].
1974	PVD was first used at Indiana University [15].
1978	Cisplatin plus etoposide: The first time in the oncology history when an adult solid tumor was cured with second-line chemotherapy [16].
1984	BEP, having less toxicity and better survival comparing with PVD, established as 1st line treatment in disseminated TC [9].

the different therapeutic approaches for males with TC during the past 20 years.

Three of our patients with stage I seminoma became fathers two, seven and ten years after the end of their treatment receiving two cycles of carboplatin 6AUC. One of them had his offspring with *in vitro* fertilization. A 33-year-old patient with seminoma disease stage I presented contralateral TC 1 year after first diagnosis. One patient with seminoma stage IV presented relapsing liver lesions after receiving two cycles of BEP.

Relapse was also observed in one patient of high risk grade I non-seminoma on his left subclavian lymph nodes after receiving two cycles of BEP. Two of our high risk stage I non-seminoma patients had their offspring 6 and 8 years after completion of two cycles of BEP. In low-grade metastatic non-seminoma, we observed two relapsed cases 1 and 10 years post treatment and one of these patients had his child 10 years after been treated with four cycles of BEP. It is important to mention that on either seminoma or non-seminoma, subsequent treatment after relapse was taxane-based. All of these patients have achieved progression-free survival until now. In our population, only one patient died due to drug toxicity, as described later. Thus, the 5-years OS for the remaining patients is 100%. The median follow-up for seminoma stage I is 55 months and for stage II-IV 71 months. According to non-seminoma, the median follow-up is 72 months for stage I and 63 months for stage II-IV.

Toxicity evaluation

No unexpected toxicities were observed. Most of the treatment-related adverse events were of grade I or II and generally reversible (Tables 4 and 5).

The most common adverse reactions, for patients under therapy taking two cycles of carboplatin 6AUC, were gastrointestinal (nausea/vomiting), hiccups and fatigue. Indeed, when giving four cycles of BEP to patients with seminoma, the treatment was more toxic than administering two cycles of BEP. Thrombopenia, neurotoxicity, ototoxicity, stomatitis, glomerulonefritis, diarrhea and rash appeared to patients who received four cycles of BEP but not to those who received two cycles of the therapy. Of note is that those four cycles were administered to 4 patients with advanced disease and two cycles to 3 patients with stage I seminoma and to 1 patient with low risk advanced seminoma. All toxicity events were as expected and definitely reversible.

For the non-seminoma patients, fatigue, nausea, vomiting and alopecia were the most frequent adverse events (Table 5). Five patients treated with IBEP did not seem to present excessive toxicity. But given that only 5 patients were treated with IBEP, we cannot compare their toxicity levels with the incidence of adverse events of the other 14 patients treated with four cycles of BEP.

Finally, one patient with advanced low risk non-seminoma died due to lung toxicity and myelotoxicity after receiving one cycle of BEP administered for three days. On the 10th day of the first cycle, the patient developed hemoptysis, dyspnea, fever, pancytopenia and finally vesicular hemorrhage; he was hospitalized in the intensive care unit and died a few days later. After this event we administer the 5-day schedule of BEP in patients with non-seminoma stage II-IV. Indeed, minor toxicity symptoms appeared in our four patients treated with 5-day BEP, as compared to two patients receiving BEP for 3 days (Table 5). Obviously, the number of patients is inadequate to add up to safety conclusions.

DISCUSSION AND A BRIEF REVIEW OF THE LITERATURE

TC treatment does not target either survival prolongation or palliation but the cure. As mentioned above, over the past 50 years the management of seminoma and non-seminoma has changed as new studies brought up more effective results (Table 6). Nowadays, the combination of bleomycin, etoposide and cisplatin (BEP) is considered as the standard of care for the treatment of disseminated TC [3]. Initially, BEP was administered to patients presenting relapse after radiotherapy. Meanwhile, the results from phase I/II studies were very promising and so, in 1984, BEP was established as a 1st line treatment for disseminated TC [9].

Since 1984, numerous chemotherapeutic regiments have been studied for their effectiveness and toxicity at different

stages of male germ cell tumor. BEP was studied in several groups of patients in order to determine the appropriate dosage for the best therapeutic profit, minimum toxicity and best quality of life [3, 9, 17-21]. Therefore, our investigated population received different therapeutic combinations during this period.

The major disadvantage of BEP therapy is that it causes significant side effects. Nausea, vomiting, alopecia, nephrotoxicity, fatigue, VIIIth nerve damage, peripheral neuropathy, neutropenia and sepsis are the common toxicity effects particularly due to cisplatin [22]. Bleomycin has been associated with chills, fever, swelling and lung toxicity. Indeed, researchers had shown that 0.5-1% of patients developed fatal pneumonitis [17, 23]. In our population one patient with low risk advanced non-seminoma disease died due to lung toxicity and myelotoxicity after the first administration of 3-day BEP. For this reason we decided to administer the 5-day BEP rather than the 3-day BEP in patients with seminoma or non-seminoma stage II-IV. We observed that when the BEP lasts longer, fewer toxicity problems appear, while patient benefit is equivalent. Pneumonitis is a serious side effect that should always be kept in mind, particularly in patients over 40 years old, who are smokers or have a history of pulmonary disease or impaired renal function [2].

Moreover, according to the literature, cardiovascular disease is another adverse event that occurs more frequently in patients with TC 5 years after their treatment. Genetic predisposition, lifestyle and the presence of cardiovascular risk factors, such as hypercholesterolemia, hypertension, overweight, and metabolic syndrome are risk factors in this population [41]. In our investigated population none of the patients developed cardiovascular disease.

Furthermore, even though skin pigmentation and nails changes may be present in patients receiving bleomycin, we did not notice skin toxicity. Etoposide administration may be associated with nausea, vomiting, reversible alopecia, fever, chills, hypotension and bronchospasm [24]. An important problem in patients treated with BEP is the long term toxicities. Raynaud's syndrome, damage to peripheral and auditory sensory nerves and a vascular necrosis of the hip might develop, in low incidence, 2-3 years after treatment [22, 25].

Another serious problem caused by combination chemotherapy is the reproductive deficiency of young patients. Azoospermia is a frequent adverse event, but is reversible in 70-80% of the cases. However, cisplatin and alkylating agents are responsible for the infertility of some patients [26]. According to our population, two of the twenty-seven patients with seminoma and two of the fifty-nine patients with non-seminoma became fathers. It is expected that this number will increase in the future, as patients will be in the mean age when having their children in Greece.

Over the past 25 years, the improvement of supportive drugs, such as antiemetics, has minimized the toxic effects of chemotherapy. Moreover, the amelioration of imaging methods and meta-analytic data has modulated current TC treatment approach. Other combinations such as Methotrexate-Etoposide-Ifosfamide-Cisplatin (MVIP) and Ifosfamide -Bleomycin-Etoposide-Cisplatin (IBEP) show effectiveness and safety in intermediate/poor risk advanced TC, but need further investigation [27, 28].

Table 7 presents TC treatment approach according to the European Association of Urology and NCCN Guidelines Version 2011 [6, 30]. It is remarkable that there is a 15-20% possibility for patients with seminoma stage I, who have been treated only with orchiectomy, to relapse. These patients usually have retroperitoneal metastatic disease [31]. On the other hand, for patients with non-seminoma stage I this possibility is as high as 30% [32]. To limit this possibility, patients can be classified within a high and a low risk group, according their histological examination. To be more specific, patients with vascular invasion are classified into the high risk group and have to be treated with adjuvant chemotherapy. On the other hand, the recommended management for patients with no vascular invasion (low risk group) is surveillance [33-35].

As far as metastatic TC is concerned, studies have shown that chemotherapy is the standard of care [6]. The only exception is the treatment approach of seminoma and non-seminoma stage IIA/IIB. In seminoma stage IIA/IIB either radiotherapy with a radiation dose of 36 Gy or four cycles of EP chemotherapy or three cycles of BEP have similar therapeutic effects [36-37]. For non-seminoma stage II, retroperitoneal lymph node resection is suggested, because of the suspicion of teratoma. If metastasis in lymph node mass is more than 2cm (pN2, pN3) according to the TNM system (7th edition, 2010), chemotherapy is required (Table 3) [38, 39].

In advanced metastatic disease, the treatment approach is the same for both seminoma and non-seminoma [6]. The standard of care is three cycles of BEP for patients with good prognostic factors and four cycles of BEP for patients with either intermediate or poor prognostic factors (Table 2). BEP dosage is: Bleomycin 30 mg (days 1, 8 and 15), Etoposide 100 mg/m^2 (days 1-5) and Cisplatin 20 mg/m^2 (days 1-5) in a cycle of 21 days. Studies showed that this chemotherapeutic combination can be administered in three days with the same effectiveness but with more toxic effects [40]. Furthermore, 4 cycles of EP are equivalent to three cycles of BEP [18]. Our vast majority of patients received different doses of BEP than the current standard of care, because the treatment approach has changed during the past decade. However, we cannot compare the efficacy of BEP different dosages, because our study population is neither sufficient nor homogeneous.

Another important step for the treatment of TC is the follow-up after therapy. The necessity thereof is dictated by: i) the early detection of a possible relapse and the initiation of salvage therapy; ii) the early detection of contralateral cancer or other secondary malignancy; iii) the identification and

Table 7.
The treatment approach of TC according to the European Association of Urology.

SEMINOMA	
STAGE I	**Surveillance** is the recommended treatment.
	Carboplatin 7AUC - 1 cycle can be recommended in patients at high risk.
	Radiotherapy is not recommended.
METASTATIC	
STAGE IIA/IIB	**Radiotherapy.**
	EP x 4 cycles or BEP x 3 cycles is equivalent to radiotherapy in stage IIB.
ADVANCED	**BEP x 3 cycles or EP x 4 cycles** in patients with good prognosis.
	BEP x 4 cycles in patients with intermediate prognosis.
NON-SEMINOMA	
STAGE I	**Surveillance** in patients at low risk.
	BEP x 2 cycles in patients at high risk.
	Retroperitoneal lymph node resection if conditions are against surveillance and chemotherapy.
METASTATIC	
STAGE IIA/IIB	**Retroperitoneal lymph node resection** if there is a stable or growing lesion with normal tumor markers.
	EP x 4 cycles or BEP x 3 cycles if there is a stable or growing lesion with lymph node mass more than 2 cm.
ADVANCED	**BEP x 3 cycles or EP x 4 cycles** in patients with good prognosis.
	BEP x 4 cycles in patients with intermediate and poor prognosis.

confrontation of long term toxicity effects; and iv) the support and guidance of possible infertility [2, 6]. Follow-up includes physical examination, measurement of tumor markers, chest X-ray and abdominopelvic CT.

For seminoma stage I, physical examination and measurement of tumor markers must be performed three times per year and chest X-ray and abdominopelvic CT twice per year for the first 2 years after completion of the chemotherapy. During the next 3 years this follow-up has to be carried out yearly [6, 30].

For low risk non-seminoma stage I, physical examination and measurement of tumor markers is recommended four times per year, chest X-ray and abdominopelvic CT twice per year for the first 2 years and annually thereafter, until the completion of 5 years following diagnosis. For high risk non-seminoma stage I disease, the recommended follow-up is the same as for the low risk non-seminoma stage I with one exception: the abdominopelvic CT must be performed annually from first diagnosis until the 5th year of observation [6, 30].

For advanced TC, physical examination, levels of tumor markers and chest X-ray have to be measured four times per year for the first 2 years, twice per year for the following 3 years and annually thereafter. Abdominopelvic CT has to be evaluated twice per year for the first 2 years and as indicated thereafter. If an abnormality is detected in the chest X-ray or if the patients present headaches, focal neurological findings or any central nervous system neurological symptom the oncologist has to add chest CT, brain CT and FDG emission tomography scanning to patient screening if available [6, 30].

Reducing toxicity and treatment duration is the goal for TC treatment, both seminoma and non-seminoma. The effective treatment for good prognosis-metastatic non-seminomatous germ cell tumors has been defined; however, the therapeutic approach of poor prognosis-metastatic non-seminoma has to be further investigated [2]. Better imaging methods, such as positron emission tomography, might be able to identify early the recurrence or appearance of a second malignancy [42]. In this highly curable disease, prevention and awareness of young men are the highlights for early diagnosis and rapid confrontation. For that reason, follow-up must be an important part of the treatment.

Another difficulty of TC is the increased risk of second malignant neoplasm. Lois B *et al.* in particular showed that 22.6% of men with testicular tumors would probably develop a second primary cancer within 30 years compared with 13.1% of men in the general population, which means an excess of about 10% [43]. The most common secondary malignancies are secondary leukemia, sarcoma and cancers of the lung, gastrointestinal tract, and other urogenital sites [44]. A possible explanation would be chemotherapy; radiation fields; genetic predisposition; immunodeficiency; common carcinogenic influences; diagnostic surveillance; risk factors unrelated to TC; or a combination of said factors [43]. In our

population, only one patient with seminoma disease stage I presented contralateral TC after 1 year from initial diagnosis.

A multidisciplinary team of medical oncologists, pathologists, urologists, and radiotherapists have to be involved in the management of such patients. There is a necessity, especially for patients with poor risk metastatic non-seminoma, in order to identify the responsible molecular mechanism and to invent effective targeting drugs [2]. Therefore, patients with poor prognosis should be encouraged to participate in ongoing prospective trials investigating dose-intensified or high-dose chemotherapy [6]. Our improved understanding of TC biology will lead to novel, less toxic therapies.

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The ERBB family of proteins in breast carcinomas – An alternative therapeutic proposal

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ABSTRACT

The epidermal growth factor (HER) receptor family represents a membrane protein group with cytoplasmic tyrosine kinase (TK) activity. There are four HER members 1-4 (ERBB1-4) and in order to be functional, ligands must be attached to the extracellular domain of the proteins. Afterwards, conformational change leads to dimerization and activation of their TK activity. HER-2 has no ligand and its activation depends on dimerization with the other members. A signaling cascade begins with several cellular outcomes. Proliferation, differentiation, apoptosis are some of HER functions, while they are implicated in the pathogenesis of various malignant tumors. Pharmaceutical agents against HER-2 have already been developed and currently used for breast cancer patients with HER-2 overexpression. The implication of HER-3 and its ligand heregulin in HER-2 signaling raises the possibility of combinational therapies and application of HER-2 targeting agents in HER-2 negative but HER-3 and heregulin positive breast cancer patients.

Key words: EGF receptors; HER-1; HER-2; HER-3; HER-4; breast cancer.

INTRODUCTION

The ERBB/HER receptors are type I growth factor receptors with tyrosine kinase activity corresponding to epidermal growth factor stimuli. Their main function is the flow of information from the extracellular environment to the cell nucleus. As indicated by their name, epidermal growth factor receptors promote proliferation when stimulated, providing those cells with a survival advantage.

The members of this family are four proteins that integrate the membrane; epidermal growth factor receptor 1 (also called EGFR, ERBB1 or HER-1), HER-2 (also called ERBB2 or Neu), HER-3 (also called ERBB3) and HER-4 (also called ERBB4). The ERBB receptors belong to the greater family of receptor tyrosine kinases (RTKs) and are cell surface allosteric enzymes. These enzymes consist of a transmembrane hydrophobic domain that separates an extracellular ligand-binding domain and an intracellular kinase domain [1].

In order to activate their TK activity, ligands that contain an EGF-like domain bind to ERBB receptors. Different EGF-like ligands activate different receptors of the ERBB family, except ERBB2 who has no identified ligand yet. Then, dimer formation between the four receptors occurs to activate the TK domain. Upon activation, ERBB receptors activate downstream intracellular pathways, including PI-3K/Akt, Ras/MAPK, PLCγ1/PKC, STAT and Par6-atypical PKC pathways [2]. These pathways are involved in different cellular functions such as apoptosis inhibition, proliferation progression, differentiation, angiogenesis, metastasis, epithelial-mesenchymal transition and cell motility [3]. Proper regulation of these signaling networks is a prerequisite for cell homeostasis. Deregulation and subsequent aberrant signaling due to mutation, amplification or presence of autocrine loops contributes to the development of carcinomas.

ACTIVATION OF ERBB RECEPTORS

There are multiple potential ligands for the HER receptors. The ectodomain of the HER proteins is highly conserved and ligand interaction promotes a conformational change. The extracellular domain in the "ligand-free" scenario obtains a close/"tethered" composition, masking the dimerization binding sites of the protein. The result of this alteration is receptors dimerization and activation of their TK domain. This extracellular region has four distinct domains, two of which are leucine-rich and are responsible for ligand binding. After ligand binding the conformational change results in open composition of the extracellular domain and exposure of dimerization inter-

faces and subsequent dimerization of the ERBB proteins [1].

The ligands that activate the HER receptors, except HER-2, are expressed as transmembrane precursors and contain a conserved structural region -the epidermal growth factor (EGF)-like domain. The ligand family of EGFs comprises 13 members, each of which binds a specific receptor and induce the homo- or hetero-dimerization of the HER receptors [4]. EGF, TGF*α*, betacellulin (BC), amphiregulin (AR), epiregulin (EPR), heparin-binding EGF-like ligand (HB-EGF) and epigen are HER-1 ligands. Neuregulin 1 and 2 (NRG1, NRG2) are HER-3 and HER-4 ligands while HER-4 has additionally neuregulins 3 and 4 (NRG3, NRG4) and share ligands BC, EPR, HB-EGF and epigen with HER-1 receptor [5]. HER-2 is a "ligand-free" receptor and can activate its TK domain through autophosphorylation after homo-dimerization or hetero-dimerization with other ERBB partners (Figure).

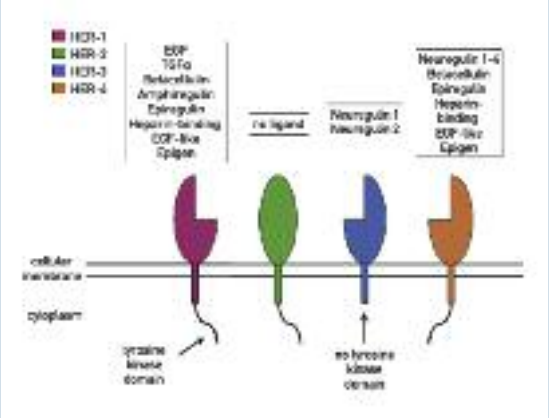
Homo-dimerization and/or hetero-dimerization of HER receptors is required for intracellular TK domain activation [5]. EGFR and HER-2 create both hetero-dimers and homo-dimers between all members of the HER family. HER-2/HER-3 dimer is the preferred hetero-dimer with the strongest proliferative downstream signals [6]. Exactly which dimers are assembled each time is dependent on the ligands available in the environment and their relative affinities for each receptor. After ligand binding the two receptor-proteins are interacting and the TK domain, localized at the cytoplasmic region, is activated through trans-phosphorylation. Thus, the C-terminal lobe of the first receptor tail contacts the N-lobe of the second receptor, which becomes allosterically activated and signaling cascades are further activated [7].

Between the four receptors, HER-1, HER-3 and HER-4 share the "close-open" composition of the extracellular domain, but HER-2 has no ligands and possesses an open composition at all times. Its activation depends on the homo- or hetero-dimerization process and acts as a co-receptor with high affinity for the other three receptors. On the other hand, HER-3 does not share an intracellular TK domain and also depends on hetero-dimerization to become functional and further activate its downstream signaling pathways. These two receptors have well-recognized molecular cross-reaction and form active dimers that trigger downstream signaling networks [1, 2].

NUCLEAR FUNCTION OF ERBB RECEPTORS

Although HER receptors are membrane proteins, there is increasing evidence of nuclear translocation and function [8]. All four receptors have been reported to be located in the nucleus of cancer and/or normal cells. Full length of nuclear HER-1 is implicated in transcriptional regulation, DNA replication and DNA repair [3, 9-11]. In several tumors, HER-1 has been found in cancer cell nucleus and these patients have a remarkable poor outcome [8]. In mouse type II epithelial cells, HER-1 and HER-2 have been shown to be mainly localized in the nucleus and to a lesser extent in the cytoplasm, while HER-3 was found almost exclusively in the nucleoli and HER-4 shuttled between the nucleolus and the cytoplasm [12].

Figure.
Molecular anatomy of HER-receptor protein family.



HER-3 has been found to be present in the nucleus of human mammary epithelial cells and when nuclear export inhibitor is used, accumulation of HER-3 to the nucleus occurs. Heregulin β1 stimulation can shift HER-3 from the nucleolus to the nucleus and then to the cytoplasm, demonstrating an additional role for HER-3 to the nucleolus [13].

EXPRESSION OF ERBB RECEPTORS IN NORMAL AND TUMOR BREAST TISSUES

Expression of all four HER receptors is necessary during normal development of mammary glands participating in several normal processes, such as growth regulation , differentiation, apoptosis and/or remodeling [14, 15]. During puberty HER-1 and HER-2 are expressed at high levels, while HER-3 and HER-4 are absent or at very low levels. The opposite expression pattern is observed during pregnancy. Finally, during involution HER-1, HER-2 and HER-3 are present and HER-4 is absent [15].

Breast cancer accounts for about 20% of female carcinomas. Expression of these receptors in breast carcinomas is very common. Polymorphism at amino acid codon 655 replacing isoleucine with valine of HER-2 gene is associated with increased risk in breast cancer patients. A subpopulation of HER-2 overexpressing breast cancer patients expresses a truncated active form, p95HER2, which lacks the extra-cellular domain. Cells carrying the truncated form of HER-2 protein are more prone to constant HER-2 homo-dimer activity and uncontrolled growth, division and avoidance of apoptosis. HER-2 overexpression is present in 20-30% of breast carcinomas and is associated with worst prognosis

[16, 17]. Estrogen receptor, progesterone receptor, and HER-2 expression still remain essential components of pathological examination of breast cancer specimens since they provide important clues for further treatment schedule [18].

HER-3 is expressed at low levels in embryonic mammary tissue and is elevated during postnatal maturation. During lactation and pregnancy high HER-3 levels are present along with HER-4. HER-3 is often overexpressed in human breast cancer cells due to higher protein expression or increased half-life of the receptor [19, 20]. HER-3 is detectable in 50-70% of human breast cancers and its increased expression in malignant mammary tissues compared with normal mammary tissue is present in 18-29% of the cases [21]. Different groups have also studied mRNA levels of HER-3 and high mRNA levels from two-fold to 100-fold variation were recorded. Increased mRNA levels or high protein levels detected with immunohistochemistry as a prognostic indicator had various results regarding its association with metastasis, tumor grade and recurrent rate [21].

HER4 is expressed in normal mammary glands and plays a critical role in their development and function. Highest expression is observed during pregnancy and low levels are detected during lactation and involution. Inactivation of HER-4 signaling in mouse mammary glands resulted in developmental abnormalities at mid-lactation and deficient lactation products [22]. Although not frequently overexpressed in breast cancer, HER-4 is correlated with good prognosis and seems to antagonize HER-2-related dismal clinical outcome [23]. Overexpression of both HER-3/HER-4 has also been associated with good prognosis [24].

NRGs ligands play an important role in normal mammary gland development and function. They contain an EGF-like domain and activate HER-3 and HER-4 receptors. The heregulin family consists of four genes and their different spliced mRNA products give many variant proteins. They are also studied together with HER receptors as they activate them and participate in the proliferation process. Heregulin 1 is a ligand for HER-3 and HER-4 receptors and activates HER-2 through the dimerization process with HER-3 and/or HER-4. They are also widely expressed in a variety of tumors and mainly in breast cancer. Overexpression of NRG1 has been reported in 24% of breast carcinomas, which are thought to have an aggressive physical history [25]. They play an important role in normal mammary gland development and function but their levels are usually increased in invasive breast carcinomas [26]. NRG1a; 2a; 2b have the highest immunohistochemical expression in breast cancers as compared to other HER ligands and have been correlated with worst overall survival [27]. In another study, mRNA transcripts for NRG2 were present in almost all breast tumor samples while NRG1 was present in 80% of the samples tested [28]. The presence of NRG ligands in breast cancer tissues is believed to represent a potential resistance mechanism in anti-HER-2 targeting agents as they can activate remnant-non-bound HER-2 receptors through HER-3 binding.

BREAST CANCER THERAPIES DIRECTED AGAINST ERBB RECEPTORS

Based on HER-2 overexpression at protein level or gene amplification, breast cancer patients follow treatment with anti-HER-2 agents (Table). Trastuzumab is an antibody against the extracellular domain of the HER-2 receptor preventing its activation. The exact mechanism of action is not yet fully understood but among potential mechanisms are prevention of HER-2 dimerization, increased endocytic destruction, inhibition of extracellular domain shedding and activation of immune response [17]. Pertuzumab, another novel HER-2 antibody, binds to the dimerization binding sites of the HER-2 receptor inhibiting more effectively its dimerization and neuregulin-induced activation through HER-3 [29]. Combinational therapy of HER-2 breast carcinomas with trastuzumab and pertuzumab is ongoing and phase II trials have shown positive clinical results in terms of efficacy without toxicity enhancement [30]. A recently published phase III study showed that the combination of trastuzumab and pertuzumab with docetaxel is more effective than trastuzumab alone and docetaxel alone as first-line treatment in HER-2 breast cancer patients [31]. Another anti-HER-2 agent that is evaluated in large clinical trials is the combination of trastuzumab with DM1, an anti-microtubule drug which is released into the cell after binding to the extracellular domain of the HER-2 receptor, thus having limited toxicity and more effective targeting of HER-2 overexpressing breast cancer cells [29].

Another mechanism for inhibiting HER signaling is by targeting the tyrosine kinase activity using small molecule tyrosine kinase inhibitors (TKIs). Lapatinib is a dual action TKI targeting HER-1 and HER-2 receptors [32]. In patients previously treated with trastuzumab and resistant to this therapy, lapatinib was more effective. An explanation for lapatinib effectiveness against trastuzumab is the presence of a truncated HER-2 form named p95 HER-2, which lacks the extracellular domain and is constitutively homo-dimerized and active [29]. In that vein, the combination of trastuzumab with lapatinib could confer a more effective therapy of breast cancer and is currently evaluated in a phase III clinical trial. Neratinib is a TKI with dual function on HER-1 and HER-2 receptors and has proven to be effective in untreated and trastuzumab-resistant breast cancer patients [33].

Heat Shock Proteins (HSPs) represent another potential valuable therapeutic target mechanism of HER-2 over-expressing breast cancer cells. HER-2 receptor is particularly sensitive in the presence of HSP90 as it is responsible for its proper folding and cellular localization [34]. There are four HSP90 chaperone inhibitors summarized in Table, which additionally target ATK, VEGFR and ERs.

So far it was believed that activation of HER-2 occurs only when HER-2 is overexpressed, amplified or in the presence of a truncated form. Many breast cancer patients present intrinsic or acquired resistance to anti-HER-2 directed therapies [35]. Growing evidence support the participation of

HER-3 and NRGs in HER-2 activation, regardless of it expression. Preliminary results show that HER-2 overexpression is not necessary and activation of HER-3/HER-4 by NRGs might be enough to subsequently activate HER-2 [36-38]. Patients with increased levels of NRGs but negative or low expression of HER-2 and low or high HER-3 expression, could benefit from treatment with anti-HER-2 agents [39]. In a study on 124 early-stage or metastatic breast cancer patients and MCF7 breast cancer cell line expressing NRG, trastuzumab was effective in mice transfected with the MCF7-NRGα2c cells and in patients with overexpression of NRG and low or normal HER-2 expression [36]. Another study in MCF7 cells overexpressing HRG, which are resistant to cisplatin, showed sensitivity to trastuzumab co-exposure [40]. In the same study active/phosphorylated HER-2 was present in 67% of the heregulin overexpressing and only 12% in the HER-2 overexpressing invasive breast carcinomas. Additionally, while 32% of the breast cancer patients were HER-2 positive, 52% of them were positive for the combinational analysis of HRG and phosphorylated HER-2 and could benefit from trastuzumab therapy [40].

CONCLUSIONS

The HER receptor family consists of tyrosine kinase proteins involved in numerous cellular processes like proliferation; angiogenesis; inhibition of apoptosis; differentiation; and cell motility. Their implication in breast carcinogenesis has been confirmed, thus increasing the necessity for better understanding of their biology and downstream pathways. The detailed function of each receptor is not fully unraveled as well as the function and activated pathways of each formed dimer.

In-depth elucidation of the dimerization pattern of HER receptors along with their ligands will facilitate basic and clinical researchers to untangle the skein of HER family function. In the case, whenever only one member of the HER family is overexpressed, its activated pathways should be investigated to reveal its role in cell proliferation and cancer progression. Also in the case of suppression of one of the receptors through pharmacological agents, the alternative activated pathways should be studied. It is becoming clear that the combination of anti-HER agents would be more effective than a single drug alone. The timing and best combination of such agents still remains a challenge.

Table.
HER-2 targeting agents in breast cancer therapeutics.

Agent	Target	Action
Antibodies		
Cetuximab	HER-1	Inhibition of HER-1 signaling
Panitumumab	HER-1	Inhibition of HER-1 signaling
Trastuzumab	HER-2	Inhibition of HER-2 signaling, recruitment of immunology cells
Trastuzumab-DM1	HER-2	Inhibition of HER-2 and potent anti-microtubule cytotoxic agent
Pertuzumab	HER-2	Inhibition of HER-2 dimerization sites, recruitment of immunology cells
Ertumaxomab	HER-2	Bispecific antibody and recruitment of immunology cells
MM-111	HER-2, HER-3	Bispecific antibody for both receptors
Tyrosine Kinase inhibitors		
Lapatinib	HER-1, HER-2	TKI
Neratinib/HKI-272	HER-1, HER-2	Irreversible TKI
Afatinib/BIBW-2992	HER-1, HER-2	Irreversible TKI
Canertinib/CI-1033	HER-1, HER-2	Irreversible TKI
ARRY-334543	HER-1, HER-2, HER-4	Reversible TKI
AEE788	HER-1, HER-2, VEGFR	Reversible TKI
Erlotinib	HER-1	Reversible TKI
Gefitinib	HER-1	Reversible TKI
Heat Shock protein inhibitors		
Tanespimycin/17-AAG	HSP90 chaperones	Ansamycin, targets HER-2, AKT, VEGFR, ER
Retaspimycin/IPI-504	HSP90 chaperones	Ansamycin, targets HER-2, AKT, VEGFR, ER
NVP-AUY922	HSP90 chaperones	Isoxazole resorcinol, targets HER-2, AKT, VEGFR, ER
BIIB021	HSP90 chaperones	Purine scaffold

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Pharmaceutical agents used for the treatment of cancer cachexia

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ABSTRACT

Cancer cachexia is a complex but very common syndrome observed in the majority of cancer patients during the course of their disease, especially at the later stages. This syndrome undoubtedly affects their quality of life and is often associated with worse prognosis. The complicated nature of cancer cachexia is mirrored at the difficulty to treat it effectively. Despite the numerous efforts to discover novel agents for the treatment of cancer cachexia, high quality evidence exists only for the progesterone analogue megestrol acetate and less so for other agents such as ghrelin, thalidomide or specific anti-cytokine molecules which require further examination and validation. More research on this very important for patients, families and physicians subject is needed and combinational therapeutic strategies might prove more successful. This overview presents the pathophysiological mechanisms of cancer cachexia syndrome and the current evidence-based data on its management. Finally, it aims to capture some of the potential agents that may play a role in future.

Key words: cancer cachexia; anorexia; progesterone analogues.

INTRODUCTION

Cancer Cachexia (CC), as recently defined by an international experts study group, is a multifactorial syndrome characterized by a continuous loss of muscle mass, with or without synchronous loss of fat mass, which cannot be fully reversed by conventional nutritional support and which can lead progressively to functional impairment [1]. Epidemiological data suggests that up to 80% of cancer patients might eventually develop CC during the terminal course of their disease [2]. The highest prevalence of weight loss has been observed in patients with upper gastrointestinal or lung cancer. On the contrary, the least weight loss has been described in patients diagnosed with breast cancer, sarcoma and Non-Hodgkin lymphoma [3]. The impact of CC is quite significant since it may represent the main cause of death in almost 20% of cancer patients and affect the quality of life in many more. Furthermore, weight loss has been a known poor prognostic factor in many solid tumors [4].

DIAGNOSIS AND CLINICAL FEATURES

The diagnostic criteria for CC according to a recent international consensus by experts in this field include: i. unintentional weight loss of more than 5% or weight loss greater than 2% in individuals already showing low Body Mass Index (below 20 for patients >65 years old and below 22 for those aged <65 years); ii. hypoalbuminemia (<3.5 g/dl); iii. low fat-free mass; and iv. often systemic inflammation or evidence of cytokine excess (e.g. elevated C-reactive protein) [1]. The severity of CC depends on the degree of energy stores depletion and body protein reduction in association with the level of ongoing weight loss. Reduced appetite and food intake, early satiety, weight loss with depletion and alteration of body compartments, anemia, edema and asthenia are some of the many clinical features of CC.

PATHOGENESIS OF CANCER CACHEXIA

The pathogenesis and pathophysiology of CC syndrome is rather complex and only partly understood. The whole process is described and summarized by a negative protein to energy balance, due to decreased food intake and altered metabolism. This protein-energy imbalance could be the result of primary causative factors such as anorexia, altered body metabolism and various humoral molecules secreted by the host or the tumor and/or due

to secondary nutritional deterioration as often observed in patients with alimentary system mechanical problems, adverse effects of current treatments etc. (Figure 1).

Firstly, anorexia, found in more than 50% of cancer patients, is the result of deranged central and peripheral signaling pathways that control food intake. In fact, excess of many cytokines such as interleukin 1β (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α) may cause an excessive negative feedback signaling from leptin, increased levels of the anorexigenic peptide-CRH (corticotrophin releasing hormone) or the inhibition of the neuropeptide Y [5]. Secondly, mechanical problems, such as malignancies of the gastrointestinal tract and large tumors or nodal masses exerting external pressure may also contribute and eventually lead to the development of secondary malnutrition. Thirdly, adverse events of current treatments e.g. anorexia or mucositis from chemotherapy and radiotherapy, bowel obstruction or short bowel from previous surgery, may also attribute to secondary malnutrition. Of equal importance is the role of altered metabolism such as the increased Resting Energy Expenditure (REE), which seems to vary widely, and the changed lipid metabolism. The latter consists of increased lipolysis, decreased lipogenesis (with a profound loss of adipose tissue up to 85%) and reduced levels of lipoprotein lipase which in turn leads to decreased clearance of triglycerides, hypertriglyceridemia and low levels of both high density (HDL) and low density lipoprotein (LDL) [4]. During the cancer cachexia state we observe an increase in muscle catabolism which is mostly the result of alterations and interactions of various molecules and pathways regulating muscle metabolism such as the upregulation of ubiquitin-proteasome pathway, increase of proteolysis inducing factor (PIF) and activation of NF-kB and of reactive oxygen species (ROS) and so on [6]. There is also preclinical evidence that upregulation of uncoupling proteins (UCP) results to increased thermogenesis and increased resting energy expenditure, thus contributing to cancer cachexia [7]. The role of these proteins in energy balance and lipid and muscle metabolism seems to be pivotal. There are three uncoupling proteins (UCP) which mediate the leakage of protons across the inner mitochondrial membrane, thus decreasing the level of respiration coupling to ADP phosphorylation [6].

These phenomena, along with a decrease in muscle protein synthesis and an increase in tumor protein- and liver protein synthesis, lead to changes in protein metabolism in general and eventually in skeletal muscle mass reduction. Similarly, changes in glucose homeostasis are also described with a significant increase in gluconeogenesis and glycolysis from the breakdown of muscle and fat tissues and an elevated production of lactate and of cycle of Cori activity [8].

Finally, the role of humoral factors secreted either by the host or the tumor in the pathogenesis of CC has been increasingly recognized and explored. The host-related secreted humoral factors include pro-cachectic cytokines [e.g. TNF-α, IL-1, IL-6, Leukemia inhibitor factor (LIF), ciliary neurotrophic factor (CNTF), IFN-γ] and anti-cachectic cytokines (e.g. IL-4, IL-10, IL-15, soluble receptor for TNF and IL-6) whereas the tumor-derived factors include the lipid mobilizing factor (LMF), proteolysis inducing factor (PIF), anemia inducing substance (AIS) and toxohormone-L, the activation of which lead to anorexia and metabolic alterations and eventually to CC [9, 10].

MANAGEMENT OF CANCER CACHEXIA

The treatment goals when dealing with the CC syndrome are mainly two. First, the reduction of anorexia which leads to a simultaneous increase in food intake; and second, the drug-induced regulation of the previously described metabolic disturbances, especially restoring normal metabolism of carbohydrates, lipids and liver proteins. There is no doubt that the pivotal and possibly most successful treatment of CC syndrome is management of the background cancer itself. An effective treatment of the neoplastic disease might significantly improve the accompanied disease-related problems and consequences, including CC, though the anticancer treatment itself might sometimes adversely affect body weight and musculature in various ways, such as by inducing gastrointestinal toxicity, increasing levels of cytokines and deteriorating existing sarcopenia [11].

Numerous pharmaceutical agents aiming at different molecular agents and levels of the pathogenesis of CC have been studied over the past few decades. A high number of phase III clinical studies have been conducted with differences in their design and primary endpoints (weight gain, quality of life, survival) all these years. As we note below, for such a complex medical problem as CC, multimodal approach, addressing nutritional consultation and support, exercise and combined pharmaceutical agents is likely the most promising strategy, according to recent published clinical studies [12]. The main categories of drugs tested in clinical practice include appetite stimulants, anabolic agents, anti-inflammatory agents, anti-cytokines and other novel approaches. Of all these agents, some have provided evidence of benefit and are used in clinical practice, some failed to show efficacy and some are still under investigation in clinical trials.

Appetite stimulants and orexigenic agents

A. Progesterone analogues: Of all therapeutic options available at present, high quality evidence exist for the progesterone analogues **megestrol acetate** (MA) and **medroxyprogesterone acetate** (MPA) [13-15]. In the first randomized, double-blind, placebo control study published by Simons *et al.* in 1998, 54 patients with advanced solid tumors and cancer cachexia received either medroxyprogesterone acetate (MPA) 500 mg or placebo for 12 weeks. The authors reported a significant increase in energy intake (p=0.003) and fat mass (p=0.009) in favor of MPA, and a non-significant increase in the fat-free mass and the REE (p=0.07) [13]. At

the same time, a randomized double-blind study on cancer patients with CC tested the efficacy of megestrol acetate (MA) on appetite, food intake, body weight, performance status, quality of life and other secondary parameters. Out of 42 patients recruited in the study, 33 were evaluable for efficacy (17 MA, 16 placebo). The authors reported a significant improvement of the appetite on the MA arm as compared to placebo (p=0.0064), whereas the other parameters did not change significantly [16]. Since then, numerous studies have explored the role of megestrol acetate on cancer cachexia, which were reviewed in a recent meta-analysis for the Cochrane Database of Systemic Reviews, and found that MA improves appetite and weight gain but with no effect on the quality of life [14]. Regarding the optimal dose of progesterone analogues in cancer cachexia, there is insufficient evidence (and therefore no absolute recommendation can be offered), but possibly 320 mg of megestrol acetate might be as effective as higher doses [17]. The most important studies of progesterone analogues and steroids tested in cancer cachexia are presented and listed in Table.

B. Steroids: There is some evidence suggesting benefit from the use of steroids in individuals with cancer cachexia [18]. For example, the use of dexamethasone along with chemotherapy in a small cohort of patients with lung cancer resulted in reduced loss of appetite and weight (but no increase from baseline), an effect not seen at the placebo plus chemotherapy group [19]. When compared to megestrol acetate in a randomized study, dexamethasone was found equal in terms of efficacy but with more toxicities observed in the dexamethasone arm (36% versus 25%, p=0.03) [20]. Considering the significant short- and long term adverse effects of steroids, such as hyperglycemia, hypertension, osteoporosis and, the hard to treat, steroid-induce myopathy, one has to be particularly wise in their use.

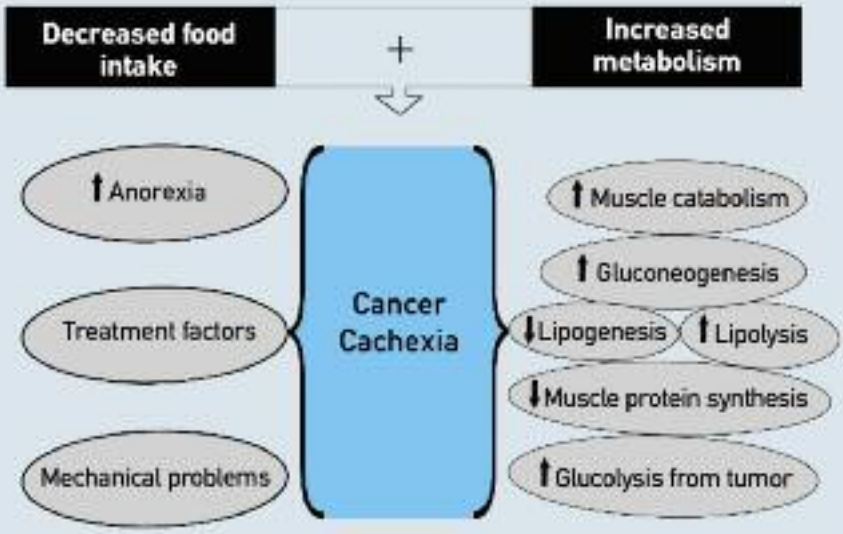
C. Cannabinoids: use of **9-tetrahydrocannabinol** (found in marijuana) or **cannabis extract** has been associated with weight gain and thus proposed as a treatment option of CC syndrome. Despite initial positive reports, randomized phase III studies have failed to show any meaningful improvement in patient appetite or quality of life [21, 22].

D. Ghrelin: **ghrelin** is a novel endogenous ligand (produced in gastric P/D1 cells, pancreatic E cells, pituitary gland and hypothalamus) which acts on its receptors, also known as growth hormone secretagogue receptor (GHS-R), causing secretion of growth hormone from the anterior pituitary and stimulating both appetite and food intake. Preclinical data on rats treated with continuous infusion of ghrelin showed some improvement in food intake, body weight and lean body mass. Nevertheless, data from early phase clinical studies have shown that though the agent is safe and well-tolerated, the efficacy results are equivocal [23, 24]. Therefore, larger studies are required and until then this agent has to be considered experimental.

Interestingly, the synthetic analogue RC-1291 (Anamorelin, Sapphire Therapeutics, Bridgewater, NJ) which is a small

Figure 1.

Pathophysiological basis of cancer cachexia. The syndrome is developed when reduced food intake (left) is combined with increasing catabolism (right), therefore an energy imbalance is taking place.



molecule GHS-R agonist was tested in a phase II placebo controlled clinical study and showed improvement in total body mass and trend to improvement in lean mass. The quality of life though between RC-1291 and placebo remained the same [25]. Similarly to ghrelin, this compound needs further prospective testing.

Anti-cytokine and anti-inflammatory agents

Since inflammation has been postulated to play a role in the development of CC, there are a few agents with anti-cytokine and anti-inflammatory properties tested in clinical trials. Although early trial results were encouraging, most of the agents failed to show a meaningful benefit in randomized phase III studies and have therefore not been granted approval from health authorities. It is important though to be aware of their therapeutic potential for future trials where combinational strategies might be adopted.

A. Eicosapentaenoic acid (EPA) or ω-3 fatty acids and N-3 fatty acids have been proposed to have specific anti-cachectic effects. In animals and *in vitro* models with CC, EPA administration was able to induce attenuation of the proteolysis inducing factor (PIF), a catabolic protein for skeletal muscle which is considered a key protein in CC pathogenesis [26]. Despite results from some clinical trials and one systematic review of published studies (including observational studies) that indicated some clinical benefit from single agent EPA or N-3 fatty acids in the treatment of CC, a Cochrane meta-analysis of randomized controlled studies failed to show superiority of EPA over placebo [27-29]. Similarly, in the most recent systematic review, by Ries *et al.*, on the role of fish oil, n-3-FA and EPA for the treatment of CC, the authors concluded that there is not enough or high quality evidence to support the use of these supplements in advanced cancer, therefore the level of recommendation is low [30]. One should admit the methodological problems that arise from the studies included in these systematic reviews and meta-analyses, as there are significant differences in the studied populations and patient characteristics (pancreatic and upper digestive tract cancer or all types of cancer, operated or not patients, different doses of active treatment, placebo or not arm etc.) along with the different endpoints (e.g. quality of life, performance status, weight, body composition) The research is ongoing and hopefully we will find a selected cancer patient subpopulation that may really benefit from this approach, either in the early or the advanced disease, as indicated in a study on patients with operable esophageal cancer [31].

B. Pentoxifylline is a methylxanthine with tumor necrosis factor (TNF) synthesis inhibitor properties. Based on preclinical evidence that it reduces cytokine induced toxicity, it was tested for the treatment of CC, but unfortunately despite an initial pilot clinical study that showed some improvement in the well-being of patients on this agent, the subsequent randomized placebo control study did not demonstrate any benefit of pentoxifylline over placebo [32, 33].

C. Thalidomide, an immunomodulatory, anti-inflammatory

Figure 2.

Treatment options based on pathogenetic alterations. Red arrows point at the molecules or biological phenomena targeted by various pharmaceutical agents.

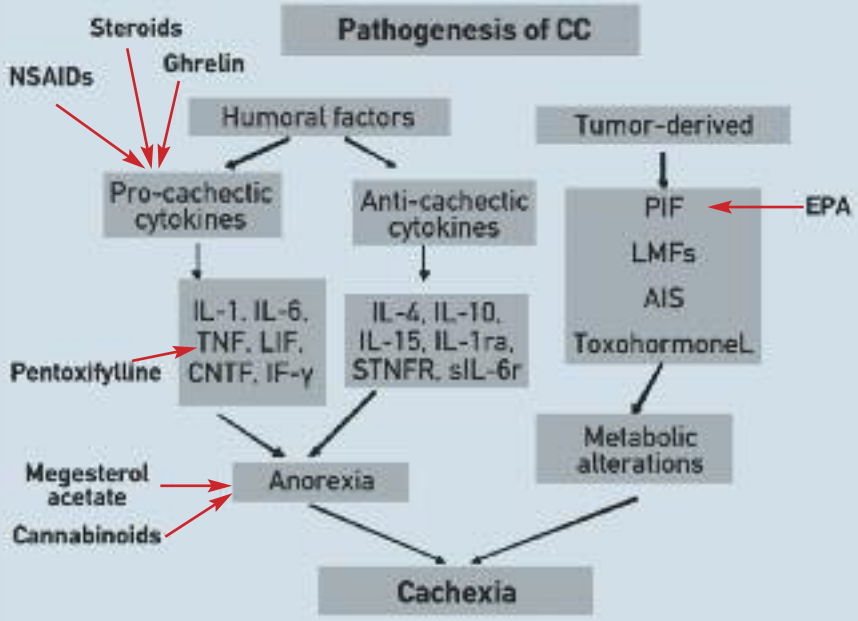


Table.

Clinical studies of progesterone analogues and steroids used in the treatment of cancer cachexia.

Author, Year and Study design	Total N of pts	Cancer type	Intervention arms (N)	Dose (mg)	Duration	Endpoints	Results 1. Weight 2. Appetite 3. Well-being / QoL / OS & other
Willox et al, 1984, RCT placebo crossover	41	Various	P (23) Placebo (18)	15 0	3 w	1. Weight 2. Appetite 3. Well being	1. No difference 2. Increased with P (p<0.001) 3. Increase (p<0.001)
Cuna et al, 1989, RCT	403	Various	M (203) Placebo (196)	125 0	8 w	QoL	Increase in QoL with M vs. Placebo (p<0.05)
Heckmayr et al, 1990, prospective non RCT	40	Lung	MA (20) MA (20)	160 480	3-4 m	1. Weight 2. Appetite 3. Well being	1. Increased in 80% of pts in group A and 50% of pts in group B 2. Increased in 80% of pts. Dose independent 3. 80% increased in both groups
Loprinzi et al, 1993, prospective RT	342	Various (GI+lung)	MA (88) MA (86) MA (85) MA (83)	160 480 800 1280		1. Weight 2. Appetite 3. Survival	1. Greater increase in group of 800 vs. 160, 480,1280 (p=NS) 2. Increased 3. No effect
Rowland et al, 1996, RCT	252	Lung (SCLC)	CT+MA (122) CT +placebo (121)	CT +800 CT+0	4 m	1. Weight 2. Appetite 3. Side effects	1. Weight gain with MA vs. Placebo (p=0,04) 2. Appetite increase with MA vs. Placebo (p=0.03) 3. More TE with MA vs. Placebo (p=0.01)
Gebbia et al, 1996, prospective RCT	122	Various	MA (62) MA (60)	160 320 Dose escalation: if no response	30 d	1. Weight 2. Appetite 3. PS 4. Survival 5. Toxicity	1. Increased (p=NS) 2. Increased (p=NS) 3. No change 4. No difference 5. No difference
Bruera et al, 1998, RCT crossover	84	Various (esp. lung)	MA (84) Placebo (84)	480 0	10 d	1. Weight 2. Appetite 3. Well being	1. No difference (p=NS) 2. Improved with MA vs. Pl (p=0.005) 3. Improved with MA vs. Pl (p=0.027)
Loprinzi et al, 1999, RCT	475	Lung or GI	MA (158) D (159) F (158)	800 3 20	4 w	1. Weight 2. Appetite 3. Side effects	1. Higher with MA vs. D vs. F (p=NS) 2. Increased with MA and D (p=NS), 3. Higher with D vs. MA except for DVT
Ulutin et al, 2002, RCT	119	Lung (NSCLC)	MA (59) MA (60)	160 320	12w	1. Weight 2. Appetite 3. PS 4. Survival	1. Improved with HD vs. LD (p=0.0380) 2. Improved (p=NS) 3. Improved (p=NS) 4. Not increased

Tomiska et al, 2003, RCT	22	Lung or GI	MA (11) MA (8)	840 480 with dose titration to 840 if no effect	8 w	1. Weight 2. Appetite 3. QoL	1. Improved (p=NS) 2. Improved (p=0.0001) 3. QoL improved in 63% of pts
Downer et al, 1992, RCT	60	Various (esp. lung)	MPA (30) Placebo (30)	300 mg 0	6 w	1. Weight 2. Appetite 3. PS	1. No change 2. Increase with MPA vs. Pl (p=0.015) 3. No change
Simons et al, 1996, RCT	201 134 (6 w) 99 (12 w)	Various (esp. lung)	MPA (103) Placebo (103)	1000 0	12 w	1. Weight 2. Appetite 3. QoL	1. Gain >2.0 kg with MPA vs. Pl (p=0.04) 2. Increased (p=NS) 3. No change

Abbreviations: CT, chemotherapy; d, days; D, dexamethasone; F, fluoxymesterone; GI, gastrointestinal; HD, high dose; LD, low dose; m, months; M, methylprednisolone; MA, megestrol acetate; MPA, medroxyprogesterone acetate; NSCLC, non small cell lung cancer ; Pts, patients; NS, non significant; P, prednisolone; PS, performance status; Pl, placebo; QoL, quality of life; RCT, randomised controlled trial; SCLC, small cell lung cancer; TE, thromboembolism; w, weeks

and anti-angiogenic agent, suppresses the production of TNF-α and IL-6 levels. A randomized placebo controlled study on pancreatic cancer patients has showed evidence of efficacy of thalidomide in cancer cachexia, in terms of attenuating loss of weight and arm muscle mass compared to placebo [34]. In another small study on patients with advanced esophageal cancer and cachexia, thalidomide reversed the weight loss and in fact increased it slightly [35]. More data is definitely needed regarding the actual benefit of thalidomide in cancer cachexia, to justify routine use of this agent, which may be associated with significant adverse effects.

Numerous other agents have been tested in cancer cachexia syndrome, as single therapies in most cases, such as non steroid anti-inflammatory drugs (NSAID) that inhibit cyclo-oxygenase-2 (COX-2 inhibitors, e.g. celecoxib), drugs that inhibit nitric oxide, TNF-α (infliximab) or proteasome (bortezomib), peptide-nucleic acids (OHR118), insulin, olanzapine and mirtazapine. For few of them (celecoxib, insulin, antidepressants, OHR118) [36-40] the preliminary results are encouraging, while others have failed when tested prospectively (bortezomib, infliximab) [41, 42]. In any case, confirmatory testing on larger well-designed trials is required to provide conclusive answers.

Experimental agents and future directions

Potential future therapeutic strategies are already under development and include a wide variety of agents like chimeric or monoclonal antibodies against inflammatory cytokines, therapeutic cytokines (IL-15), anti-myostatin antibodies, ubiquitin ligase and specific inhibitors of proteolysis inducing factor (PIF), lipid mobilizing factor (LMF) and insulin growth factor-1 (IGF-1) and selective androgen receptor modulators (SARMs).

Targeting a sole molecule or specific abnormal pathway of cancer cachexia pathogenesis seems unlikely to produce the desired results. More promising effects are observed by combinational approaches where more than one drugs are tested together against various targets at once. For example, a recent randomized phase III study of five different arms comparing progesterone analogue (arm 1) with pharmaco-nutritional support containing EPA (arm 2), L-carnitine (arm 3), thalidomide (arm 4) and the combination of all (arm 5), showed that the combinational approach was the most effective. In fact, the combination regimen increased significantly, compared to other treatment arms, all endpoints which included lean body weight and appetite while reduced resting energy expenditure and fatigue [43]. In a similar context, combination of oral supplements (EPA and essential amino acids) with celecoxib and resistance training produced favorable results in terms of anabolic skeletal muscle effect in lung cancer patients with cancer cachexia [44]. Another interesting approach in the treatment of CC is the combination of EPA with melatonin and aerobic exercise, the efficacy of which might confirm the hypothesis that CC requires a multimodal management (details for this ongoing study can be found online, http://clinicaltrials.gov).

Many more trials testing various combinations are in progress at present and the results might shed more light as to which is the best way of tackling this common and devastating syndrome.

CONCLUSION

It seems from the aforementioned data that little progress has been made in the management of a very common problem such as CC, despite the advances in understanding its pathophysiology. The lack of headway is not surprising, since the phenomenon of CC is based on very complex

mechanisms and one should not expect improvements using single agents or targeting single pathways. Another possible explanation for the fact that most of the promising agents tested in clinical trials failed to produce positive results in systematic reviews or meta-analysis of randomized studies, is methodological insufficiencies including the differences in endpoints and doses used, the heterogeneity of the studied populations as well as the fact that CC is directly related to the background neoplasia, which ultimately affects the outcomes of the disease-associated problems. Therefore, in the future, a combination of appetite-improving agents with others that reduce metabolic disorders and inflammation and possibly with cancer-directed treatment is more likely to produce positive results. Until then, researchers and clinicians have to work together in order to encourage patients to participate in experimental treatments, as no standard intervention exists at present, with the exception of progesterone analogues.

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Informal carers: A focus on the real caregivers of people with cancer

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ABSTRACT

Background: Those who become active caregivers out of their simple need to be included in their loved ones' experience may act as a force in the support and sustenance of the person with cancer. Apart from family members, individuals "considered as family" by the patient may actively participate in the patient's cancer journey. The purpose of this clinical review is to raise clinician awareness on the multiple responsibilities assumed and the impact of active caregiving experienced by informal carers of patients with cancer, also offering a number of practical suggestions to promote person-centred support.

Patients & Methods: An electronic search for original and review articles published between January 1990 and July 2011 in three research and evidence databases (MedLine, CINAHL, EMBASE) was carried out using the terms "caregiver" and "cancer".

Results: Informal caregivers are often required to assume numerous roles and make changes in their lives until they find themselves striving to balance a host of responsibilities. By being practically and emotionally involved, however, caregivers' own lives can be affected, sometimes overwhelmingly. The physical, emotional, social, and financial stress that caregivers can face in this role may result in the neglect of their own needs, adversely affecting their quality of life.

Conclusions: Research-driven support interventions such as peer support groups or psychological/emotional therapy, as well as honest, open and personalised communication with health care professionals and ongoing assessment of their needs can be of utmost importance in supporting those who contribute the most to the patients' cancer journey.

Key words: informal carer; cancer; caregiver roles; caregiving impact; burden; caregiver support.

INTRODUCTION

People diagnosed with a curable cancer may have a transitory care requirement, often before, during and immediately after treatment, whereas those for whom prognosis is less favourable may require long-term palliative care. Whatever the case may be, in their majority people with cancer will rely on families and friends for help and support [1], perhaps over an extended period of time. Regardless of its nature, support provided by persons considered by the patient as significant -often recognised by health professionals as their "informal caregivers"- has been found to be equally or more beneficial than support derived from other sources [2, 3]. Those who become active caregivers out of their simple need to be included in their loved ones' experience [4] may act as a force in the support and survival of the person with cancer. This can be a potentially rewarding experience for the caregiver [5], but mainly a meaningful action to the patient. By providing actual and ongoing care for essential daily tasks to be undertaken and for an acceptable quality of life to be achieved [1], these key holders can play an important part in a patient's ability to respond to and cope with the challenges of living with cancer [2].

From the health system's perspective, the expectation and prevalence of caregiving in significant others is also high. As social welfare costs rise in many nations and medical management of cancer becomes more complex, there are increasing obligations placed on individuals close to the ill person to undertake caregiving responsibilities [6] and deal with extensive coordination of care [7]. Moreover, recent changes in health policy [8] such as shifting the balance of care from hospitals to

the community, coupled with a shortage of health care providers [9] and a reduction in the length of hospital stay [10] have further impacted on the roles and responsibilities of these persons in providing primary and ongoing care at home [11-13]. In fact, the use of outpatient-based cancer treatment means that it is often family members, partners, or friends who provide daily support to the person with cancer, rather than healthcare professionals [14]. According to reports from several organisations for caregivers, over 100 million people in Europe, Australia, and the United States provide care on an unpaid basis for a relative, friend or neighbour in need of support due to old age, disability, frailty or illness [15-20]. By providing approximately 80% of care hours [17], informal caregivers save the world's economy at least €500 billion a year [15, 18-20], and economic considerations form a key element in government policy to support such individuals [15].

Current policy encourages health care professionals to work in partnership with informal caregivers [8]. In order for this cooperation to be effective, an understanding of the significance of the roles caregivers fulfil is required along with recognition of the impact said roles can have on their lives. Therefore, the purpose of this clinical review was to raise clinician awareness on the multiple responsibilities assumed and the impact of active caregiving experienced by informal carers of patients with cancer, also offering a number of practical suggestions to promote person-centred support.

BALANCING A HOST OF ROLES AND TASKS

What the existing literature signals is that *what caregivers do* as individuals and/or as part of caregiver networks can make an essential contribution to the patient's "care package" and that patients' well-being can be profoundly affected by the quality of the informal care they receive [21]. This implies that caregivers can be construed as the "co-caregivers" of formal health care providers [21]. However, Thomas & Morris [21] pose a core question: 'what is the informal caregiver role and how does it contribute to the care of the patient with cancer?' Current knowledge or understanding about what informal caregiving actually involves in cancer contexts, and about the difference that this makes to the overall health care endeavour is based on limited information derived from a few studies. In general, care may be organised into numerous dimensions each possibly consisting of several specific tasks and processes as outlined in the Figure [4, 22-29]. Moreover, it has been suggested that informal caregiving roles and responsibilities:

- may occur in relation to the health transition experienced by the ill person during treatment [22];
- may not necessarily be linear through predictable stages of development; rather they may be fluid and ever changing [22];
- deserve a wider rather than an individualistic focus as care is an area in which *both* the ill person *and* the caregiver participate [22];
- may be novel and never before undertaken [26];
- may be interchangeable, negotiated and adopted as necessary [4, 30]; and
- may depend on the specific moment, setting or patient need [22].

Nonetheless, evidence regarding caregiving roles is confined in terms of generalisability and is inconsistent with regard to type of cancer, stage of disease, phase in the cancer experience, or setting. For instance, it is unclear whether differences in roles assumed are influenced more by the type or stage of the disease, or by who the caregiver might be (family versus non-family member; spouse versus child), whether caregiving tasks are driven more by patient need (caregiving "on demand") or by caregiver attitude towards provision of care, or how (or if) they develop across time, cultures, or socioeconomic status. In that sense, evidence is largely inconclusive and the wide variation in the expression of caregiving tasks remains to be captured. Whereas caregiving might become more significant during periods when patients are in receipt of medical treatments and/or are at later critical moments in the cancer experience [24], what tasks might be involved in different phases have not been explored. Similarly, due to the cross-sectional nature of most studies, a description of transformations or fluctuations in the caregiving tasks across time or across health transitions is practically inexistent. Wagner *et al.* [26] aimed at exploring caregiving responsibilities of husbands of women with breast cancer during active treatment and one year later. Between time points, comparisons indicated relatively stable levels of assistance with daily living activities, despite opposite expectations. Sadly, the specific reasons for this trend were not inquired or explored, thus only hypotheses can be made including the potential impact of disease stage or treatment on women's functioning one year after treatment. However, additional latent reasons may remain unexplained.

On the other hand, the aforementioned broad role categorisation, albeit basically useful, seems too simplistic to depict the array of caregiving tasks, and might imply that caregiving roles are confined only to those that happen to fall into these specific categories, or should be similar in every individual case. One explanation of this wide array of care tasks might be that the majority of patients were more physically impaired and in greater need of support. It can be hypothesized that in the case of patients who might rely more on self-care, caregiving roles might be more limited or even focused on some areas rather than others. Yet, this remains to be established. According to some findings, husbands of women with breast cancer might provide less assistance with more intimate activities such as bathing, toileting, or eating [26]. Still, whether this is a purely gender- or age-related behaviour needs to be confirmed. An important association implied is that caregiving tasks might fluctuate according to the amount of shared involvement of patient and caregiver in the former's care [22]. In other words, what might be important is not only the possible

Figure.
Roles and tasks potentially undertaken by individuals providing informal care for people with cancer.

range of caregiving tasks, but how these tasks fit in each patient-caregiver situation, depending on patients' varying needs and abilities in different time-points, as well as caregivers' capacity to respond to these needs. Studies involving dyads of patients and caregivers can be of particular importance in characterising the dynamics of such interactive processes.

Given the diversity of the caregiving demands, it is equally reasonable to claim that caregivers themselves will possess different skills, capabilities and preferences when performing the different caregiving tasks [1], which to a great extent are influenced or mediated by several endogenous (individual-related) and exogenous (environment-related) factors. In addition, it should be recognized that not all people assume a supportive role in the event of a cancer diagnosis among their loved ones. Becoming a caregiver has been described as an equally demanding process as providing actual care [23], and it has been described as *role tuning* involving engagement, negotiation, and settling of roles between caregiver and care recipient [31]. Age, gender, cultural background, societal beliefs, ethnicity, socioeconomic status, educational level, type of personality, coping style, personal health, as well as family dynamics, quality of relationships, and over time adjustment to cancer diagnosis and illness stage [6, 32-36] may work together as integral factors in predicting a person's involvement in caregiving, the extent of associated tasks, and finally their *reaction* to this demanding role. Along these lines, Fletcher *et al.* [37] urged the need for development and research in areas such as caregiver physical health, culture, and socioeconomic status to enhance conceptualisation of caregiving in the context of cancer.

"I AM ONLY HUMAN": SUFFERING DURING CAREGIVING

It is now recognised that patients' illness experiences cannot be understood as individualised phenomena [35, 38]. A serious illness carries with it a host of physical, psychological and social consequences for everyone close to the ill

person [21]; especially those individuals who assume the short- or long-term role of the caregiver are impacted the most. When cancer becomes a reality, spouses, partners, other family members and friends may actively participate in shaping the cancer experience, and also *share* this experience. However, the practical and emotional involvement in patients' cancer journeys often affects caregivers' own lives [39]. Among others, caregivers may be forced to make changes in their own lives, take on new roles and responsibilities, or give up past activities [26]. These life changes can be viewed as commonalities or *stressors*, which can create burden and strain, especially when extremely high physical and emotional demands are placed on caregivers [11]. It is generally agreed that the concept of caregiver burden has both objective and subjective dimensions [6]. *Objective burden* can be seen as the effort required to attend to the needs of an ill person. Thus, it may include the amount of time spent in caregiving, the type of caregiving services provided, and financial resources expended on behalf of the "dependent" person [34, 40, 41], which can have economic implications, as well as a personal and social impact [42]. On the other hand, *subjective burden* consists of the beliefs, assumptions, and feelings with regard to the caregiver role. Studies in the context of cancer care have included such elements as the extent to which caregiving causes strain with regard to work productivity, finances, physical well-being, family relationships and social life, or emotional distress associated with caregiving [6, 35, 43-45].

The physical, emotional, social, and financial stress that caregivers can face in this role may result in the neglect of their individual needs [15, 42, 45], whereas a diminished immune response may increase their susceptibility to physical illness and infection. Where caregiving is intense, providing round-the-clock care can also leave a caregiver feeling exhausted with little opportunity to socialise and engage in social pursuits [36]. This may not only create social stress as caregivers fail to meet other obligations beyond the patient, such as work and other family responsibilities, but also a sense of isolation. Often informal caregivers face continual and concurrent challenges: apart from caring for the ill person, they at the same time have to meet family responsibilities, work commitments, and household duties [36]. A feeling that care is never enough might emerge, whereas daily priorities may be continually juggled within narrow time limits [15].

Caregivers may be more likely to report anxiety, depression, loss of confidence and self-esteem than non-caregivers [46]. Current hypotheses suggest that patients with cancer and their informal caregivers react to cancer as a single emotional system [47, 48]. Based on this assumption there may be a significant reciprocal relationship between each person's response to the illness, with caregivers often reporting similar [49, 50] or greater [51] emotional distress, anxiety, or depression than patients do. The risk of psychological distress may increase both with the intensity and the duration of caregiving [15]. Some studies report that caregivers' psychological distress reduces over time after diagnosis [52], but others suggest it increases and becomes prolonged [7, 53, 54]. The latter might be the case for caregivers who disregard their own problems in order to focus exclusively on fulfilling patients' needs; however, this is only one of several possible explanations. Distress, anxiety and anger may be experienced while patients' symptoms manifest; appearance changes; and functioning declines [36]. The ongoing emotional distress may be part of a cascading process that may lead caregivers to disheartenment and exhaustion [55]. Along these lines, caregivers may be less likely than patients to disclose their concerns and worries, and up to only half of those with serious psychological problems may actively seek help [33]. Similarly, caregivers' family and social well-being might become affected, especially in relation to talking about the illness; dealing with deficits in sexual well-being; changing roles and assuming new responsibilities; as well as maintaining support systems [9]. Difficulty communicating their feelings and negotiating their roles can hinder patients' and caregivers' ability to support one another and decrease intimacy within the dyad [56]. In addition, cultural and societal beliefs about cancer may pose additional burdens on both patients and caregivers [42, 57]. Belief in the inevitability of death once cancer is diagnosed can lead to an early withdrawal from life. This fatalistic or deterministic view of cancer can lead to inactivity [42]. As a result, anger and resentment may arise when, despite the caregiver's efforts, the patient is giving up.

Caregivers of patients with cancer may also experience a decline in their physical well-being [9, 58]. Notably, caregivers may be more than twice as likely to suffer from poor health compared to people without caring responsibilities [16]. Although caregivers' health status is initially similar to that of the normal population, they often report more problems with fatigue, sleep disturbances, and impaired cognitive function than non-caregivers [49]. Over time, as caregiver burden and strain increase, caregivers' physical well-being might be at stake including -while not limited to- possible reasons such as little time to rest; engagement in fewer self-care behaviours (e.g. physical activity); poor dietary habits; or failure to seek medical care for themselves when sick [9, 45, 53]. Indeed, relevant research suggests that, as a direct result to new caregiving tasks, an increase in alcohol consumption and smoking; sleep deprivation; lack of exercise; and infrequent use of preventive health services may be noted [45, 59]. A considerable proportion of informal caregivers have chronic health problems of their own, such as excessive body weight, heart disease, hypertension, and arthritis [9], and these health problems can be exacerbated by the stress of caregiving [34]. Presence or worsening of pre-existing symptoms, as well as the development of new ones may interfere with caregivers' ability to assume roles and/or fulfill those already assumed. Furthermore, adjustments caregivers may be forced to make in their way of life

[60] can result in added strain on their physical well-being. Eventually, both unrelieved symptoms and ongoing demands of caregiving may adversely affect both their functional status and quality of life [7].

Is this evidence enough to exhaustively describe the impact caregiving has on persons in caregiving roles? Given the methodological limitations of studies conducted thus far, the most probable answer is no, which subsequently renders additional questions unavoidable. What precipitating (e.g. blood relationship, hours of caregiving, number of roles, cohabitation etc.) or protective (e.g. coping strategies, relationship quality etc.) factors predict or mediate prediction of levels of perceived burden? For instance, what is the impact of cultural caregiving demands on caregiver burden? And then, how closely inter-related patient-specific and caregiver-specific factors affect caregiver burden? Moreover, how do predictors of caregiver burden change over time as changes occur in a patient's condition or as caregivers adapt or become fatigued? On the other hand, what are the differences in levels of caregiver burden in different caregiving situations as determined by type or stage of cancer; setting of care provision (hospital or home); treatment modality; or changes in stereotypically assumed roles? Notably, what is the inter-related impact of increased burden on caregiver and patient health variables over time and across joint transitions? Studies implementing a dyadic approach [37], drawing on a multiple-measures design across major transitions, using an adequate sampling methodology to recruit representative samples of our multi-cultural, multi-caregiving society, and assessing multiple facets of burden could prove to be helpful towards clarification of these issues.

IMPLICATIONS FOR CLINICAL PRACTICE

Nowadays, caregivers are not only legitimised as persons affected by cancer in profound ways, but also construed as actual or potential "co-users" of health services in addition to being "co-caregivers" [21]. Key cancer service policy documents [61, 62] reflect this acceptance, acknowledging the presence of these 'significant others' and legitimising their interests as service users alongside patients: "Patients, families and carers need access to support from the time that the cancer is first suspected through to death and into bereavement" (p. 62) [62]. In practice, however, health care professionals only rarely pay attention to the situation of informal caregivers, to the extent that they may feel neglected by the health care system [63]. Although informal caregivers constitute a vulnerable population, often their needs may not be adequately addressed, and resources to assist them may be extremely limited and fragmented [42].

There is a need for informal caregivers to be recognised as "care recipients" in their own right, and their right to having their own support acknowledged [36, 42]. Given their documented general lack of preparation to respond to the demands of providing informal care [64], more and better resources and emotional support for caregivers are of the utmost importance. Availability of sufficient resources, acknowledgement of their burden, and active engagement in social roles can lead to more positive perspectives on caregiving [42]. Within hospital clinics, participation in small informal groups can offer caregivers the opportunity to discuss and validate their experiences and feelings with similarly affected individuals [36]. Moreover, education sessions and individualised training for family and friends could very well assist those caring for a person with cancer to develop their skills, enhance their self-efficacy, and increase their understanding of the situation they are in [36, 65]. In the home setting, provision of non-clinical social support services [66] or clinical community nursing services [36], or participation in computer-mediated interactive social support groups [67] may be beneficial towards caregiver reassurance and emotional and practical support. Informal family conferences can offer the opportunity for caregivers to assess their responsibilities and jointly plan their actions [68]. When palliative and end-of-life care is required, dyadic emotional and psychological interventions [69], as well as the support services of a hospice may be vital in relieving caregivers from their physically demanding and emotionally exhausting responsibilities [36, 70].

Even individually, health care professionals can make a significant difference in caregivers' lives by being present and by actively engaging in caregiver support [36, 70, 71]. With caregivers being in a constant pursuit for information across all stages of their indirect illness experience, honest, open and personalised communication is the cornerstone of a supportive relationship [36, 72]. Health care professionals should always consider the needs of informal caregivers as they develop and change. Careful evaluation and re-evaluation of caregiver experiences is vital in ensuring that mounting burden is assessed and interventions are provided in a timely manner. For instance, in many cultures caregivers may be reluctant to seek help or accept assistance provided by health care services outside the family [36]. Caregiver willingness to reach out and accept help from others may be a significant factor to mediate caregiver experiences [73]. Health care professionals are expected to show respect and support such choices, but also encourage caregivers to request assistance from "support persons" such as other family members or friends, or from health care services whenever they feel overwhelmed in their roles [72].

A holistic understanding of the caregiver's unique situation, views, and desired outcomes can enable limited resources to be targeted appropriately [42]. Caregivers may suffer in silence. Some may have difficulty accepting the diagnosis of cancer, whereas others may feel guilt or being punished, or even question their purpose in life in the face of a life-threatening illness in their loved one [74, 75]. Strategies caregivers of people with cancer may employ to help them cope in their role can predict their ability to survive the challenges they face. Positive coping styles such as problem-solving deserve reinforcement; whereas negative

strategies such as avoidance or denial require attention and intervention to avoid interference with caregivers' psychological well-being [13]. For a significant part of informal caregivers, being present with the patient can be seen as an irreplaceable means towards fulfilling their role, or achieving a personal connection that will help us cope with the anticipatory grief they experience [36, 70, 76]. Especially in the hospital setting, those who are denied this "healing presence" may perceive it as a sense of personal failure, which can add to their emotional burden. Informal caregivers rely on what they perceive as "meaningful actions" to endure potentially distressing experiences in this role. If this motivation source is depleted, caregivers may question their contribution and become frustrated or withdraw. Ongoing assessment and consideration of psychological and cognitive interventions can be useful in supporting individuals in need [36, 77]. Apart from being aware of and open to such reactions or beliefs, health care professionals should also act towards making time and space for informal caregivers to accompany patients, and find a meaningful way to share in the patients' cancer journey.

Finally, significant transitions in the caregiving experience need to be addressed and evaluated in a rigorous prospective manner. Caregiver transitions encompass not only the patient's phases of illness, but also the daily adjustments made by significant others in response to the patient's needs [42]. During transitional times, the presence of health care professionals can encourage and support caregivers to continue functioning [36], thus supporting the whole patient-caregiver dyad. Seen in the context of a whole-systems framework that allows interpersonal relationships to be understood [12], caregiver experiences can be addressed in conjunction to the patients' responses to their joint illness journey. In that sense, implementation of a dyadic approach, where both the patient and the caregiver are seen as the core of one unit in which they share the same challenges, can lead to improving supportive interventions for those affected by cancer.

CONCLUSIONS

Be they spouses, partners, siblings, children, or friends, informal caregivers not only unconditionally invest an immeasurable amount of energy in caring for their loved ones with cancer [36], but also greatly contribute to the sustainability of the health care system in general. When, however, caregivers feel overwhelmed in their roles, both their and patients' needs may become hampered, and their well-being as a dyad may be threatened. The least health care professionals can offer in turn to this "caregiving force" is acknowledgement of their rights and needs, adequate assistance in their tasks, and effective, tailored support and respite services when -but preferably before- their experiences become difficult to handle.

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On the role of clinical practice guidelines in oncology

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Dr. Kappas has written a very thoughtful overview of the importance of clinical practice guidelines (CPG), including the methodology of CPG developments, accompanied by an update, potential pitfalls and benefits, as well as drawbacks of CPG application.

Looking at the etymology of the word "guidelines", it becomes obvious that CPGs are meant to assist (guide) clinical decision making, not substitute it. This immediately implies that clinical judgment is, of course, included in the process of treatment planning.

Therefore, guidelines are neither restrictive of nor a substitute for good clinicians. However, guidelines are meant to be considered in all decisions and should serve as the framework within which one acts, usually after confirming that such therapeutic action is appropriate for the patient in question. And because of how they are developed, they should apply to most cases, so that deviation should be necessary as an exception, rather than as a rule; that is to say, if deviation is routinely necessary, then there is either a problem with the guideline itself or a problem with the particular physician and/or his patient population, the latter being different than that of the guidelines in one or more ways (i.e. culturally, reli-giously, financially, etc.).

In other words, guidelines are meant to "guide" clinicians in their decisions and should apply in most cases, but also allow for occasional, clinically appropriate deviations.

The other significant role of guidelines is to serve as a measure for quality control. If at such a quality evaluation, a clinician discovers frequent deviations from guidelines, he or she should consider it a reason for re-evaluation of his/her practice habits.

In summary, the debate regarding CPGs is false. In clinical practice, there will -by definition- be deviations from CPGs and that is why they are called "guidelines" instead of "laws" or "rules". However, evaluations of the frequency and quality of CPG deviations should serve as a measure of the quality of the services provided to patients. For this purpose, the acceptable threshold of deviations (in % of clinical decisions) should be defined, and the parameters (age, comorbidity, patient wishes, etc.) that may necessitate such deviations should also be accounted for.

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ΣΥΝΟΠΤΙΚΗ ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ. 1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση. **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:** Κάθε ml πυκνού διαλύματος περιέχει 5 mg ipilimumab. Ένα φιαλίδιο των 10 ml περιέχει 50 mg ipilimumab. Ένα φιαλίδιο των 40 ml περιέχει 200 mg ipilimumab. Το ipilimumab είναι ένα πλήρως ανθρώπινο αντι CTLA4 μονοκλωνικό αντίσωμα (IgG1κ) που παράγεται σε κύτταρα ωοθηκών κινεζικού κρικητού με τεχνολογία ανασυνδυασμένου DNA. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις:** Το YERVOY ενδείκνυται για τη θεραπεία του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος σε ενηλίκους που έχουν λάβει προηγούμενη θεραπεία. **4.3 Αντενδείξεις:** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα. **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Το YERVOY σχετίζεται με φλεγμονώδεις ανεπιθύμητες αντιδράσεις που προκύπτουν από αυξημένη ή εκτεταμένη δραστηριότητα του ανοσοποιητικού (ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό) και πιθανόν σχετίζονται με το μηχανισμό δράσης του. Ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό που μπορεί να είναι σοβαρές ή απειλητικές για τη ζωή, είναι πιθανό να συμπεριλαμβάνουν γαστρεντερικές, ηπατικές, δερματικές, νευρολογικές, ενδοκρινολογικές ή άλλων οργανικών συστημάτων. Ενώ οι περισσότερες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό εμφανίστηκαν κατά την περίοδο επαγωγής έχει επίσης αναφερθεί εκδήλωση μήνες μετά από την τελευταία δόση του YERVOY. Εκτός αν προσδιοριστεί διαφορετική αιτιολογία, η διάρροια, η αυξημένη συχνότητα κενώσεων, το αίμα στα κόπρανα, οι αυξήσεις LFT, το έξανθημα και η ενδοκρινοπάθεια πρέπει να θεωρηθούν φλεγμονώδεις και να συνδέονται με το YERVOY. Η πρώιμη διάγνωση και η κατάλληλη διαχείριση είναι απαραίτητες για την ελαχιστοποίηση απειλητικών για τη ζωή επιπλοκών. Συστηματική εισαγωγή υψηλών δόσεων κορτικοστεροειδών με ή χωρίς επιπρόσθετη ανοσοκατασταλτική θεραπεία είναι πιθανό να απαιτηθεί για την αντιμετώπιση σοβαρών ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό. Ειδικές για το YERVOY κατευθυντήριες γραμμές για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό περιγράφονται παρακάτω. Γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρα περιστατικά λόγω διάτρησης του γαστρεντερικού σωλήνα έχουν αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg σε μια μελέτη προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος Φάσης 3 (MDX01020, βλέπε παράγραφο 5.1) ο διάμεσος χρόνος έως την εκδήλωση σοβαρών ή θανατηφόρων (Βαθμού 35) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (εύρος 5 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, η υποχώρηση (ορίζεται ως βελτίωση σε ήπια [Βαθμού 1] ή λιγότερο ή στη σοβαρότητα κατά την έναρξη) εμφανίστηκε στις περισσότερες περιπτώσεις (90%) σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 4 εβδομάδες (εύρος 0,6 έως 22 εβδομάδες). Οι ασθενείς πρέπει να παρακολουθούνται για γαστρεντερικά σημεία και συμπτώματα που είναι πιθανό να υποδεικνύουν κολίτιδα σχετιζόμενη με το ανοσοποιητικό ή διάτρηση του γαστρεντερικού σωλήνα. Στην κλινική εικόνα είναι πιθανό να συμπεριλαμβάνεται διάρροια, αυξημένη συχνότητα εντερικών κινήσεων, κοιλιακό άλγος ή αιματοχεσία, με ή χωρίς πυρετό. Διάρροια ή κολίτιδα που εμφανίζεται μετά από την έναρξη του YERVOY πρέπει να αξιολογείται έγκαιρα για τον αποκλεισμό λοιμώδους ή άλλης εναλλακτικής αιτιολογίας. Σε κλινικές δοκιμές, κολίτιδα σχετιζόμενη με το ανοσοποιητικό συσχετίστηκε με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξελκώσεις και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Συστάσεις για την αντιμετώπιση της διάρροιας ή της κολίτιδας βασίζονται στην βαρύτητα των συμπτωμάτων (σύμφωνα με την ταξινόμηση της βαθμολόγησης της βαρύτητας κατά NCICTCAE v3). Ασθενείς με ήπια έως μέτρια (Βαθμού 1 ή 2) διάρροια (αύξηση έως 6 κενώσεις την ημέρα) ή πιθανολογούμενη ήπια έως μέτρια κολίτιδα (π.χ. κοιλιακό άλγος ή αίμα στα κόπρανα), είναι πιθανό να παραμείνουν στο YERVOY. Συνιστάται συμπτωματική θεραπεία (π.χ. λοπεραμίδη, υποκατάσταση υγρών) και προσεκτική παρακολούθηση. Εάν τα ήπια έως μέτρια συμπτώματα υποτροπιάσουν ή επιμείνουν για 57 ημέρες, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλείπεται και θα πρέπει να ξεκινήσει θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg από το στόμα άπαξ ημερησίως ή ισοδύναμο). Εάν παρουσιαστεί υποχώρηση σε Βαθμό 01 ή επιστροφή στην έναρξη, το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) διάρροια ή κολίτιδα (βλέπε παράγραφο 4.2),και πρέπει να ξεκινήσει αμέσως υψηλής δόσης ενδοφλέβια θεραπεία με κορτικοστεροειδή. (Σε κλινικές δοκιμές έχει χρησιμοποιηθεί μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελέγχεται η διάρροια και άλλα συμπτώματα, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται σε κλινική απόφαση. Σε κλινικές δοκιμές, η ταχεία βαθμιαία μείωση και διακοπή (σε διαστήματα < 1 μήνα) οδήγησε στην υποτροπή της διάρροιας ή της κολίτιδας σε ορισμένους ασθενείς. Οι ασθενείς πρέπει να αξιολογούνται για στοιχεία διάτρησης του γαστρεντερικού σωλήνα ή περιτονίτιδας. Η εμπειρία από κλινικές δοκιμές σχετικά με την αντιμετώπιση διάρροιας ανθεκτικής σε κορτικοστεροειδή ή κολίτιδας είναι περιορισμένη. Ωστόσο, είναι δυνατόν να ληφθεί υπόψη η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, προστέθηκε εφάπαξ δόση infliximab 5 mg/kg, εκτός εάν ήταν αντένδειξη. Δεν πρέπει να χρησιμοποιείται infliximab εάν πιθανολογείται διάτρηση του γαστρεντερικού σωλήνα ή σηψαιμία (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για το infliximab). Ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρή ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό. Θανατηφόρος ηπατική ανεπάρκεια έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 25) ηπατοτοξικότητας που συνδέεται με το ανοσοποιητικό κυμάνθηκε από 3 έως 9 εβδομάδες από την έναρξη της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμάνθηκε από 0,7 έως 2 εβδομάδες. Οι ηπατικές τρανσαμινάσες και η χολερυθρίνη πρέπει να αξιολογούνται πριν από κάθε δόση του YERVOY, καθώς πρώιμες εργαστηριακές μεταβολές μπορεί να υποδεικνύουν ανακύπτουσα ηπατίτιδα σχετιζόμενη με το ανοσοποιητικό (βλέπε παράγραφο 4.2). Αυξήσεις σε LFT είναι πιθανό να αναπτυχθούν απουσία κλινικών συμπτωμάτων. Πρέπει να αξιολογούνται αυξήσεις της AST και της ALT ή της ολικής χολερυθρίνης προς αποκλεισμό λοιπών αιτίων κάκωσης του ήπατος, συμπεριλαμβανομένων λοιμώξεων, εξέλιξης της νόσου ή φαρμακευτικών προϊόντων και να παρακολουθούνται έως την υποχώρησή τους. Βιοψίες ήπατος από ασθενείς που είχαν ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό, κατέδειξαν στοιχεία οξείας φλεγμονής (ουδετερόφιλα, λεμφοκύτταρα και μακροφάγα). Για ασθενείς με αυξημένη AST ή ALT στο εύρος των > 5-≤ 8 x ULN ή ολική χολερυθρίνη στο εύρος των > 3-≤ 5 x ULN που πιθανολογείται ότι σχετίζεται με το YERVOY, πρέπει να παραλείπεται η προγραμματισμένη δόση του YERVOY και πρέπει να παρακολουθούνται οι LFT έως την υποχώρηση. Όταν βελτιωθούν τα επίπεδα LFT (AST και ALT ≤ 5 x ULN και ολική χολερυθρίνη ≤ 3 x ULN), το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Για ασθενείς με αυξήσεις της AST ή της ALT > 8 x ULN που πιθανολογείται ότι σχετίζονται με το YERVOY, η θεραπεία πρέπει να διακόπτεται οριστικά (βλέπε παράγραφο 4.2) και πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με κορτικοστεροειδή υψηλής δόσης (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg ημερησίως ή ισοδύναμο). Σε αυτούς τους ασθενείς, πρέπει να παρακολουθούνται οι LFT έως την ομαλοποίηση. Όταν υποχωρούν τα συμπτώματα και ομαλοποιηθούν οι αυξήσεις των LFT, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Αυξήσεις των LFTs κατά τη βαθμιαία μείωση και διακοπή είναι δυνατόν να αντιμετωπιστούν με αύξηση της δόσης του κορτικοστεροειδούς και βραδύτερη βαθμιαία μείωση και διακοπή. Για ασθενείς με σημαντικές αυξήσεις των LFT που είναι ανθεκτικοί σε θεραπεία με κορτικοστεροειδή, είναι δυνατόν να εξεταστεί η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, χρησιμοποιήθηκε μυκοφαινολική μοφετίλη σε ασθενείς χωρίς ανταπόκριση σε θεραπεία με κορτικοστεροειδή ή που παρουσίασαν αύξηση του LFT κατά την βαθμιαία μείωση και διακοπή κορτικοστεροειδών που δεν ανταποκρινόταν σε αύξηση της δόσης των κορτικοστεροειδών (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για τη μυκοφαινολική μοφετίλη). Δερματικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντιδράσεις που μπορεί να συνδέονται με το ανοσοποιητικό. Θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Εξάνθημα και κνησμός επαγόμενα από YERVOY ήταν κυρίως ήπια ή μέτρια (Βαθμού 1 ή 2) και ανταποκρίνονταν σε συμπτωματική θεραπεία. Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως σοβαρών ή θανατηφόρων (Βαθμού 25) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες (εύρος 0,9 έως 16 εβδομάδες) από την έναρξη της θεραπείας. Με ειδικές για το πρωτόκολλο κατευθυντήριες γραμμές για την αντιμετώπιση, παρουσιάστηκε υποχώρηση στις περισσότερες περιπτώσεις (87%), σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (εύρος 0,6 έως 29 εβδομάδες). Εξάνθημα και κνησμός επαγόμενα από YERVOY πρέπει να αντιμετωπίζεται με βάση τη σοβαρότητα. Ασθενείς με μια ήπια έως μέτρια (Βαθμού 1 έως 2) δερματική ανεπιθύμητη αντίδραση μπορούν να παραμείνουν σε θεραπεία με YERVOY με συμπτωματική θεραπεία (π.χ. αντισταμινικά). Για ήπιο έως μέτριο εξάνθημα ή κνησμό που εμμένει για 1 έως 2 εβδομάδες και δεν βελτιώνεται με τοπικά κορτικοστεροειδή, πρέπει να ξεκινήσει η από του στόματος θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg άπαξ ημερησίως ή ισοδύναμο). Για ασθενείς με μια σοβαρή (βαθμού 3) δερματική ανεπιθύμητη αντίδραση, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί. Εάν βελτιωθούν τα αρχικά συμπτώματα σε ήπια (Βαθμού 1) ή υποχωρήσουν, η θεραπεία με YERVOY μπορεί να συνεχιστεί και πάλι στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με ένα πολύ σοβαρό (Βαθμού 4) εξάνθημα ή σοβαρό (Βαθμού 3) κνησμό (βλέπε παράγραφο 4.2) και θα πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με υψηλές δόσεις κορτικοστεροειδών (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελεγχθεί το εξάνθημα ή ο κνησμός, η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρο σύνδρομο Guillain-Barré έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Έχουν επίσης αναφερθεί συμπτώματα ομοιάζοντα με μυασθένεια gravis. Οι ασθενείς μπορεί να παρουσιάσουν μυϊκή αδυναμία. Μπορεί ακόμη να παρουσιαστεί αισθητική νευροπάθεια. Ανεξήγητη κινητική νευροπάθεια, μυϊκή αδυναμία ή αισθητική νευροπάθεια που διαρκεί > 4 ημέρες πρέπει να αξιολογείται και θα πρέπει να αποκλειστούν μη φλεγμονώδη αίτια, όπως εξέλιξη της νόσου, λοιμώξεις, μεταβολικά σύνδρομα και φαρμακευτικά προϊόντα. Για ασθενείς με μέτρια (Βαθμού 2) νευροπάθεια (κινητική με ή χωρίς αισθητική) που πιθανόν σχετίζεται με το YERVOY, θα πρέπει να παραλείπεται η προγραμματισμένη δόση. Εάν τα νευρολογικά συμπτώματα υποχωρήσουν στην έναρξη, ο ασθενής μπορεί να ξαναρχίσει το YERVOY στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) αισθητική νευροπάθεια που πιθανολογείται ότι συνδέεται με το YERVOY (βλέπε παράγραφο 4.2). Οι ασθενείς πρέπει να αντιμετωπίζονται σύμφωνα με τις κατευθυντήριες γραμμές του ιδρύματος για την διαχείριση αισθητικής νευθροπάθειας και πρέπει να ξεκινήσουν αμέσως ενδοφλέβια θεραπεία με κορτικοστεροειδή (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Προοδευτικά σημάδια κινητικής νευροπάθειας θα πρέπει να θεωρείται ότι σχετίζονται με το ανοσοποιητικό και να αντιμετωπίζονται ανάλογα. Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) κινητική νευροπάθεια ανεξαρτήτως αιτιολογίας (βλέπε παράγραφο 4.2). Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό: Το YERVOY μπορεί να προκαλέσει φλεγμονή των οργάνων του ενδοκρινικού συστήματος, συγκεκριμένα υποφυσίτιδα, υποϋποφυσισμό, επινεφριδιακή ανεπάρκεια και υποθυρεοειδισμό και οι ασθενείς μπορεί να παρουσιάσουν μη ειδικά συμπτώματα, τα οποία μπορεί να μοιάζουν με άλλα αίτια, όπως μετάσταση στον εγκέφαλο ή υποκείμενη νόσο. Στη συχνότερη κλινική εικόνα συμπεριλαμβάνεται η κεφαλαλγία και η κόπωση. Στα συμπτώματα μπορεί να συμπεριλαμβάνονται ελλείμματα του οπτικού πεδίου, αλλαγές της συμπεριφοράς, διαταραχές των ηλεκτρολυτών και υπόταση. Επινεφριδιακή κρίση ως αίτιο των συμπτωμάτων του ασθενούς πρέπει να αποκλείεται. Η κλινική εμπειρία με ενδοκρινοπάθεια σχετιζόμενη με το YERVOY είναι περιορισμένη. Για ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 24) ενδοκρινοπάθειας σχετιζόμενης με το ανοσοποιητικό κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την έναρξη της θεραπείας. Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με ανοσοκατασταλτική θεραπεία και θεραπεία υποκατάστασης ορμονών. Εάν υπάρχουν οποιαδήποτε σημεία επινεφριδιακής κρίσης, όπως σοβαρή αφυδάτωση, υπόταση ή καταπληξία, συνιστάται άμεση χορήγηση ενδοφλέβιων κορτικοστεροειδών με αλατοκορτικοειδική δράση και ο ασθενής θα πρέπει να αξιολογηθεί για την παρουσία σηψαιμίας ή λοιμώξεων. Εάν υπάρχουν σημεία επινεφριδιακής ανεπάρκειας, αλλά ο ασθενής δεν βρίσκεται σε επινεφριδιακή κρίση, πρέπει να εξεταστούν περαιτέρω παρακλινικές εξετάσεις στις οποίες συμπεριλαμβάνεται η αξιολόγηση εργαστηριακών και απεικονιστικών ελέγχων. Η αξιολόγηση των αποτελεσμάτων των εργαστηριακών ελέγχων για την έλεγχο της ενδοκρινούς λειτουργίας πρέπει να πραγματοποιείται πριν από την έναρξη θεραπείας με κορτικοστεροειδή. Εάν οι απεικονιστικοί έλεγχοι της υπόφυσης ή εργαστηριακοί έλεγχοι της ενδοκρινούς λειτουργίας είναι μη φυσιολογικοί, συνιστάται βραχύ σχήμα θεραπείας με υψηλές δόσεις κορτικοστεροειδών (π.χ. δεξαμεθαζόνη 4 mg ανά 6 ώρες ή ισοδύναμο) ώστε να αντιμετωπιστεί η φλεγμονή του προσβεβλημένου αδένα και η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί (βλέπε παράγραφο 4.2). Αυτή τη στιγμή είναι άγνωστο εάν η θεραπεία με κορτικοστεροειδή αναστρέφει την αδενική δυσλειτουργία. Θα πρέπει επίσης να ξεκινήσει κατάλληλη υποκατάσταση ορμονών. Είναι πιθανό να είναι απαραίτητη μακροχρόνια θεραπεία με υποκατάσταση ορμονών. Όταν τεθούν υπό έλεγχο τα συμπτώματα ή οι μη φυσιολογικές εργαστηριακές τιμές και είναι εμφανής η βελτίωση του ασθενούς συνολικά, μπορεί να συνεχιστεί η θεραπεία με YERVOY και η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν πεπτιδικό εμβόλιο με YERVOY 3 mg/kg + gp100 στην MDX01020 (βλέπε παράγραφο 4.8). Αν οι αντιδράσεις είναι σοβαρές (Βαθμού 3 ή 4) είναι πιθανό να απαιτηθεί άμεσα θεραπεία με υψηλές δόσεις κορτικοστεροειδών και διακοπή του YERVOY (βλέπε παράγραφο 4.2). Για ραγοειδίτιδα, ιρίτιδα ή επισκληρίτιδα που συνδέεται με το YERVOY, θα πρέπει να εξετάζεται η χρήση τοπικών κορτικοστεροειδών στη μορφή των οφθαλμικών σταγόνων όπως ενδείκνυται ιατρικά. Ειδικοί πληθυσμοί: Ασθενείς με οφθαλμικό μελάνωμα, πρωτοπαθές μελάνωμα του ΚΝΣ και ενεργές μεταστάσεις του εγκεφάλου δεν συμπεριελήφθησαν στην πιλοτική κλινική δοκιμή (βλέπε παράγραφο 5.1). Αντίδραση στην έγχυση: Υπήρχαν μεμονωμένες αναφορές σοβαρών αντιδράσεων στην έγχυση σε κλινικές δοκιμές. Σε περίπτωση σοβαρής αντίδρασης στην έγχυση, η έγχυση YERVOY πρέπει να διακόπτεται και να χορηγείται κατάλληλη ιατρική θεραπεία. Ασθενείς με ήπια ή μέτρια αντίδραση στην έγχυση, μπορούν να λάβουν YERVOY με προσεκτική παρακολούθηση. Μπορεί να ληφθεί υπόψη η προφαρμακευτική αγωγή με αντιπυρετικό και αντισταμινικό. Ασθενείς με αυτοάνοση νόσο: Ασθενείς με ιστορικό αυτοάνοσης νόσου (εκτός από λεύκη και επαρκώς ελεγχόμενη ανεπάρκεια ενδοκρίνης, όπως υποθυρεοειδισμός), συμπεριλαμβανομένων αυτών για τους οποίους απαιτείται συστηματική ανοσοκατασταλτική θεραπεία για προϋπάρχουσα ενεργό αυτοάνοση νόσο ή για διατήρηση μοσχεύματος μετά από μεταμόσχευση οργάνου, δεν αξιολογήθηκαν σε κλινικές δοκιμές. Το ipilimumab είναι ενισχυτής των Τκυττάρων που καθιστά δυνατή την ανοσολογική ανταπόκριση (βλέπε παράγραφο 5.1) και είναι πιθανό να παρέμβει στην ανοσοκατασταλτική θεραπεία, γεγονός που οδηγεί σε παροξυσμό της υποκείμενης νόσου ή αυξημένο κίνδυνο απόρριψης του μοσχεύματος. Το YERVOY πρέπει να αποφεύγεται σε ασθενείς με σοβαρή ενεργό αυτοάνοση νόσο, σε περιπτώσεις στις οποίες περαιτέρω ενεργοποίηση του ανοσοποιητικού είναι ενδεχομένως άμεσα απειλητική για τη ζωή και χρησιμοποιείται με προσοχή σε άλλους ασθενείς με ιστορικό αυτοάνοσης νόσου, μετά από προσεκτική εξέταση του ενδεχόμενου κινδύνου-οφέλους σε ατομική βάση. Ασθενείς που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. Κάθε ml αυτού του φαρμακευτικού προϊόντος περιέχει 0,1 mmol (ή 2,30 mg) νατρίου. Θα πρέπει να λαμβάνεται υπόψη κατά την θεραπεία ασθενών που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. **4.8 Ανεπιθύμητες ενέργειες: Περίληψη του προφίλ ασφάλειας:** Το YERVOY έχει χορηγηθεί σε > 3.000 ασθενείς σε ένα κλινικό πρόγραμμα το οποίο αξιολόγησε τη χρήση του με διάφορες δόσεις και τύπους όγκων. Εκτός εάν ορίζεται διαφορετικά, τα δεδομένα παρακάτω αποτυπώνουν την έκθεση σε YERVOY στα 3 mg/kg σε κλινικές δοκιμές μελανώματος. Στη μελέτη Φάσης 3 MDX01020, (βλέπε παράγραφο 5.1), οι ασθενείς έλαβαν ένα διάμεσο 4 δόσεων (εύρος 14). Το YERVOY σχετίζεται πολύ συχνά με ανεπιθύμητες ενέργειες που προκύπτουν από αυξημένη ή εντεταμένη δράση του ανοσοποιητικού. Οι περισσότερες από αυτές, στις οποίες συμπεριλαμβάνονται σοβαρές αντιδράσεις, υποχώρησαν μετά από την έναρξη κατάλληλης ιατρικής θεραπείας ή τη διακοπή του YERVOY (βλέπε παράγραφο 4.4 για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, οι ανεπιθύμητες ενέργειες που αναφέρθηκαν συχνότερα (≥ 10% των ασθενών), ήταν διάρροια, εξάνθημα, κνησμός, κόπωση, ναυτία, έμετος, μειωμένη όρεξη και κοιλιακό άλγος. Στην πλειονότητά τους ήταν ήπιες έως μέτριες (Βαθμού 1 ή 2). Η θεραπεία με YERVOY διακόπηκε λόγω ανεπιθύμητων ενεργειών στο 10% των ασθενών. Κατάλογος ανεπιθύμητων ενεργειών σε πίνακα: Ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ασθενείς με προχωρημένο μελάνωμα, οι οποίοι έλαβαν YERVOY 3 mg/kg σε κλινικές δοκιμές (n = 767), παρουσιάζονται στον Πίνακα 2. Αυτές οι αντιδράσεις παρουσιάζονται ανά κατηγορία συστήματος οργάνων σύμφωνα με την συχνότητα. Η συχνότητα ορίζεται ως εξής: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000). Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες εμφανίζονται κατά φθίνουσα σειρά σοβαρότητας. Τα ποσοστά ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό σε HLAA2*0201 θετικούς ασθενείς οι οποίοι έλαβαν YERVOY στην MDX01020, ήταν παρόμοια με εκείνα που παρατηρήθηκαν στο κλινικό πρόγραμμα συνολικά.

Πίνακας 2: Ανεπιθύμητες ενέργειες σε ασθενείς με προχωρημένο μελάνωμα που έλαβαν YERVOY 3 mg/kg (n = 767)[α]

Λοιμώξεις και παρασιτώσεις	
Όχι συχνές	σηψαιμία[β], σηπτική καταπληξία[β], μηνιγγίτιδα, γαστρεντερίτιδα, εκκολπωματίτιδα, ουρολοίμωξη, λοίμωξη του ανώτερου αναπνευστικού συστήματος, λοίμωξη του κατώτερου αναπνευστικού συστήματος
Νεοπλάσματα καλοήθη, κακοήθη και μη καθορισμένα (περιλαμβάνονται κύστεις και πολύποδες)	
Συχνές	πόνος από όγκο
Όχι συχνές	παρανεοπλασματικό σύνδρομο
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	
Συχνές	αναιμία, λεμφοπενία
Όχι συχνές	αιμολυτική αναιμία[β], θρομβοπενία, ηωσινοφιλία, ουδετεροπενία
Διαταραχές του ανοσοποιητικού συστήματος	
Όχι συχνές	υπερευαισθησία
Διαταραχές του ενδοκρινικού συστήματος	
Συχνές	υποϋποφυσισμός (συμπεριλαμβάνεται η υποφυσίτιδα)[γ], υποθυρεοειδισμός[γ]
Όχι συχνές	επινεφριδιακή ανεπάρκεια[γ], υπερθυρεοειδισμός[γ], υπογοναδισμός
Διαταραχές του μεταβολισμού και της θρέψης	
Πολύ συχνές	μειωμένη όρεξη
Συχνές	αφυδάτωση, υποκαλιαιμία
Όχι συχνές	υπονατριαιμία, αλκάλωση, υποφωσφοραιμία, σύνδρομο λύσης όγκου
Ψυχιατρικές διαταραχές	
Συχνές	συγχυτική κατάσταση
Όχι συχνές	μεταβολές της νοητικής κατάστασης, κατάθλιψη, μειωμένη γενετήσια ορμή
Διαταραχές του νευρικού συστήματος	
Συχνές	περιφερική αισθητική νευροπάθεια, ζάλη, κεφαλαλγία, λήθαργος
Όχι συχνές	σύνδρομο Guillain-Barré[β,γ], συγκοπή, κρανιακή νευροπάθεια, εγκεφαλικό οίδημα, περιφερική νευροπάθεια, αταξία, τρόμος, μυόκλωνος, δυσαρθρία
Οφθαλμικές διαταραχές	
Συχνές	θαμπή όραση, πόνος του οφθαλμού
Όχι συχνές	ραγοειδίτιδα[γ], αιμορραγία του υαλοειδούς σώματος, ιρίτιδα[γ], μειωμένη οπτική οξύτητα, αίσθημα ξένου σώματος στους οφθαλμούς, επιπεφυκίτιδα
Καρδιακές διαταραχές	
Όχι συχνές	αρρυθμία, κολπική μαρμαρυγή
Αγγειακές διαταραχές	
Συχνές	υπόταση, έξαψη
Όχι συχνές	αγγειίτιδα, αγγειοπάθεια[β], περιφερική ισχαιμία, ορθοστατική υπόταση
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου	
Συχνές	δύσπνοια, βήχας
Όχι συχνές	αναπνευστική ανεπάρκεια, σύνδρομο οξείας αναπνευστικής δυσχέρειας[β], διήθηση πνεύμονα, πνευμονικό οίδημα, πνευμονίτιδα, αλλεργική ρινίτιδα
Διαταραχές του γαστρεντερικού	
Πολύ συχνές	διάρροια[γ], έμετος, ναυτία
Συχνές	γαστρεντερική αιμορραγία, κολίτιδα[β,γ], δυσκοιλιότητα, γαστροοισοφαγική παλινδρόμηση, κοιλιακό άλγος
Όχι συχνές	διάτρηση του γαστρεντερικού σωλήνα[β,γ], διάτρηση του παχέος εντέρου[β,γ], διάτρηση του εντέρου[β,γ], περιτονίτιδα[β], παγκρεατίτιδα, εντεροκολίτιδα, γαστρικό έλκος, έλκος του παχέος εντέρου, οισοφαγίτιδα, ειλεός[δ]
Διαταραχές του ήπατος και των χοληφόρων	
Συχνές	μη φυσιολογική ηπατική λειτουργία
Όχι συχνές	ηπατική ανεπάρκεια[β,γ], ηπατίτιδα, ηπατομεγαλία, ίκτερος
Διαταραχές του δέρματος και του υποδόριου ιστού	
Πολύ συχνές	εξάνθημα[γ], κνησμός[γ]
Συχνές	δερματίτιδα, ερύθημα, λεύκη, κνίδωση, αλωπεκία, νυκτερινοί ιδρώτες, ξηροδερμία
Όχι συχνές	τοξική επιδερμική νεκρόλυση[β,γ], λευκοκυτταροκλαστική αγγειίτιδα, αποφολίδωση δέρματος
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	
Συχνές	αρθραλγία, μυαλγία, μυοσκελετικός πόνος, μυϊκοί σπασμοί
Όχι συχνές	ρευματική πολυμυαλγία, αρθρίτιδα-
Διαταραχές των νεφρών και των ουροφόρων οδών	
Όχι συχνές	νεφρική ανεπάρκεια[β], σπειραματονεφρίτιδα[γ], νεφρική σωληναριακή οξέωση
Διαταραχές του αναπαραγωγικού συστήματος και του μαστού	
Όχι συχνές	αμηνόρροια
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	
Πολύ συχνές	κόπωση, αντίδραση της θέσης ένεσης, πυρεξία
Συχνές	ρίγη, εξασθένιση, οίδημα, άλγος
Όχι συχνές	πολυοργανική ανεπάρκεια[β,γ], σχετιζόμενη με την έγχυση αντίδραση
Παρακλινικές εξετάσεις	
Συχνές	αυξημένη αμινοτρανσφεράση της αλανίνης[γ], αυξημένη ασπαρτική αμινοτρανσφεράση[γ], αυξημένη χολερυθρίνη αίματος, μειωμένο σωματικό βάρος
Όχι συχνές	μη φυσιολογικές δοκιμασίες ηπατικής λειτουργίας, αυξημένη κρεατινίνη αίματος, αυξημένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη κορτιζόλη αίματος, μειωμένη κορτικοτροφίνη αίματος, αυξημένη λιπάση[γ], αυξημένη αμυλάση αίματος[γ], μειωμένη τεστοστερόνη αίματος

α Οι συχνότητες βασίζονται σε συγκεντρωτικά στοιχεία από 9 κλινικές δοκιμές που εξέτασαν το YERVOY 3 mg/kg δόση σε μελάνωμα.
β Συμπεριλαμβάνεται η θανατηφόρος έκβαση.
γ Πρόσθετες πληροφορίες σχετικά με αυτές τις πιθανώς φλεγμονώδεις ανεπιθύμητες ενέργειες παρέχονται στην «Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών» και την παράγραφο 4.4. Τα δεδομένα που παρουσιάζονται σε αυτές τις παραγράφους αποτυπώνουν κυρίως την εμπειρία από μια μελέτη Φάσης 3, την MDX01020.
δ Αναφέρονται σε πρόσφατες μελέτες εκτός των ολοκληρωμένων κλινικών δοκιμών στο μελάνωμα.

Πρόσθετες ανεπιθύμητες ενέργειες που δεν αναφέρονται στον Πίνακα 2 έχουν αναφερθεί σε ασθενείς που έλαβαν άλλες δόσεις (είτε < ή > 3 mg/kg) YERVOY σε κλινικές δοκιμές μελανώματος. Αυτές οι πρόσθετες αντιδράσεις παρουσιάστηκαν όλες σε συχνότητα < 1%: μηνιγγισμός, μυοκαρδίτιδα, καρδιομυοπάθεια, αυτοάνοση ηπατίτιδα, πολύμορφο ερύθημα, αυτοάνοση νεφρίτιδα, συμπτώματα ομοιάζοντα με μυασθένεια gravis, αυτοάνοση θυρεοειδίτιδα, υπερυποφυσισμός, δευτεροπαθής ανεπάρκεια του φλοιού των επινεφριδίων, υποπαραθυρεοειδισμός, θυρεοειδίτιδα, επισκληρίτιδα, βλεφαρίτιδα, οίδημα του οφθαλμού, σκληρίτιδα, κροταφική αρτηρίτιδα, φαινόμενο Raynaud, πρωκτίτιδα, σύνδρομο παλαμοπελματιαίας ερυθροδυσαισθησίας, ψωρίαση, αιματουρία, πρωτεϊνουρία, μειωμένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη γοναδοτροφίνη αίματος, μειωμένη θυροξίνη, λευκοπενία και πολυκυτταραιμία. Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών: Με εξαίρεση τις περιπτώσεις στις οποίες επισημαίνεται, τα δεδομένα για τις παρακάτω επιλεγμένες ανεπιθύμητες ενέργειες βασίζονται σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg (n = 131) ή YERVOY 3 mg/kg σε συνδυασμό με gp100 (n = 380) σε μια μελέτη Φάσης 3 του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος (MDX01020, βλέπε παράγραφο 5.1). Οι κατευθυντήριες γραμμές για την αντιμετώπιση αυτών των ανεπιθύμητων ενεργειών περιγράφονται στην παράγραφο 4.4. Γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρα περιστατικά λόγω διάτρησης του γαστρεντερικού σωλήνα έχουν αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με gp100. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε διάρροια και κολίτιδα οποιασδήποτε βαρύτητας στο 27% και το 8% αντίστοιχα. Η συχνότητα σοβαρής (Βαθμού 3 ή 4) διάρροιας και σοβαρής (Βαθμού 3 ή 4) κολίτιδας ήταν 5% για το καθένα. Ο διάμεσος χρόνος έως την εκδήλωση σοβαρών ή θανατηφόρων (Βαθμού 3 έως 5) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (εύρος 5 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο η υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (90%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση (ορίζεται ως βελτίωση σε ήπια [Βαθμού 1] ή λιγότερο ή στη σοβαρότητα κατά την έναρξη) 4 εβδομάδες (εύρος 0,6 έως 22 εβδομάδες). Σε κλινικές δοκιμές η κολίτιδα που συνδέεται με το ανοσοποιητικό συσχετίστηκε με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξελκώσεις και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρή ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό. Θανατηφόρος ηπατική ανεπάρκεια έχει αναφερθεί σε < 1% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg. Αυξήσεις της AST και της ALT οποιασδήποτε βαρύτητας αναφέρθηκαν στο 1% και το 2% των ασθενών αντίστοιχα. Δεν υπήρχαν αναφορές σοβαρής (Βαθμού 3 ή 4) αύξησης της AST ή της ALT. Ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 2 έως 5) ηπατοτοξικότητας που συνδέεται με το ανοσοποιητικό κυμάνθηκε από 3 έως 9 εβδομάδες από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμάνθηκε από 0,7 έως 2 εβδομάδες. Σε κλινικές δοκιμές, βιοψίες ήπατος από ασθενείς που είχαν ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό, εμφάνισαν στοιχεία οξείας φλεγμονής (ουδετερόφιλα, λεμφοκύτταρα και μακροφάγα). Δερματικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντιδράσεις που μπορεί να συνδέονται με το ανοσοποιητικό. Θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY σε συνδυασμό με gp100 (βλέπε παράγραφο 5.1). Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε εξάνθημα και κνησμός διαφορετικής βαρύτητας, το καθένα στο 27% των ασθενών. Εξάνθημα και κνησμός επαγόμενο από YERVOY ήταν κυρίως ήπια (Βαθμού 1) ή μέτρια (Βαθμού 2) και ανταποκρίνονταν σε συμπτωματική θεραπεία. Ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως σοβαρών ή θανατηφόρων (Βαθμού 2 έως 5) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες από την αρχή της θεραπείας (εύρος 0,9 έως 16 εβδομάδες). Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (87%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (εύρος 0,6 έως 29 εβδομάδες). Νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές νευρολογικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρο σύνδρομο Guillain-Barré έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με gp100. Συμπτώματα ομοιάζοντα με μυασθένεια gravis έχουν επίσης αναφερθεί σε < 1% των ασθενών που έλαβαν υψηλότερες δόσεις YERVOY σε κλινικές δοκιμές. Ενδοκρινοπάθεια που συνδέονται με το ανοσοποιητικό. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, υποϋποφυσισμός οποιασδήποτε βαρύτητας αναφέρθηκε στο 4% των ασθενών. Επινεφριδιακή ανεπάρκεια, υπερθυρεοειδισμός και υποθυρεοειδισμός οποιασδήποτε βαρύτητας αναφέρθηκε το καθένα στο 2% των ασθενών. Η συχνότητα σοβαρού (Βαθμού 3 ή 4) υποϋποφυσισμού αναφέρθηκε στο 3% των ασθενών. Δεν υπήρχαν αναφορές σοβαρής ή πολύ σοβαρής (Βαθμού 3 ή 4) επινεφριδιακής ανεπάρκειας, υπερθυρεοειδισμού ή υποθυρεοειδισμού. Ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 2 έως 4) σχετιζόμενης με το ανοσοποιητικό ενδοκρινοπάθειας κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την αρχή της θεραπείας. Ενδοκρινοπάθεια σχετιζόμενη με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με θεραπεία υποκατάστασης ορμονών. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε < 2% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με πεπτιδικό εμβόλιο gp100. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυάλινο) x 10 ml με ενδεικτική Νοσοκομειακή τιμή 3.887,16 €, και ενδεικτική Χονδρική τιμή τιμή 4.468,00 €. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυάλινο) x 40 ml με ενδεικτική Νοσοκομειακή τιμή 15.548,65 €, και ενδεικτική Χονδρική τιμή τιμή 17.872,01 €.

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Bristol-Myers Squibb

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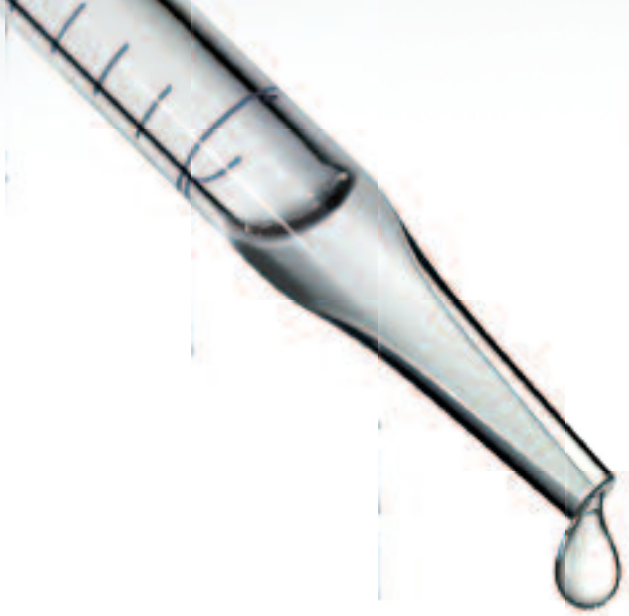

ΚΑΙ ΤΩΡΑ ΕΓΚΕΚΡΙΜΕΝΟ

Το YERVOY™ (ipilimumab) ενδείκνυται για τη θεραπεία του προχωρημένου (ανεγχείρητου ή μεταστατικού) μελανώματος σε ενηλίκους που έχουν λάβει προηγούμενη θεραπεία.[1]

ΠΡΟΟΔΟΣ ΤΗΣ ΕΠΙΣΤΗΜΗΣ
ΣΤΟ ΜΕΤΑΣΤΑΤΙΚΟ ΜΕΛΑΝΩΜΑ

Η δύναμη του ανοσοποιητικού συστήματος

Η σπουδαιότητα της παρατεταμένης επιβίωσης

- **YERVOY™: Ο πρώτος εγκεκριμένος παράγοντας που παρατείνει σημαντικά τη συνολική επιβίωση σε ασθενείς με προχωρημένο μελάνωμα*[2]**
- **YERVOY™: Μια νέα θεραπεία ενίσχυσης των Τ-κυττάρων που ενεργοποιεί το ανοσοποιητικό σύστημα ώστε αυτό να καταστρέφει τους καρκινικούς όγκους.[1]**

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YERVOY™ (ipilimumab)
πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση

*Σε μια τυχαιοποιημένη, ελεγχόμενη δοκιμή φάσης 3.

1. Περίληψη Χαρακτηριστικών Προϊόντος του YERVOY™. 2. Hodi FS *et al. N Engl J Med.* 2010;363(8):711-723.