Practicing oncology between continents

Reintroduction of irinotecan and oxaliplatin as a combination (IROX regimen) in heavily pretreated colorectal cancer patients

Cancer Pain: Global awareness and guideline recommendation

Hormonotherapy: present and future in ER+ breast cancer

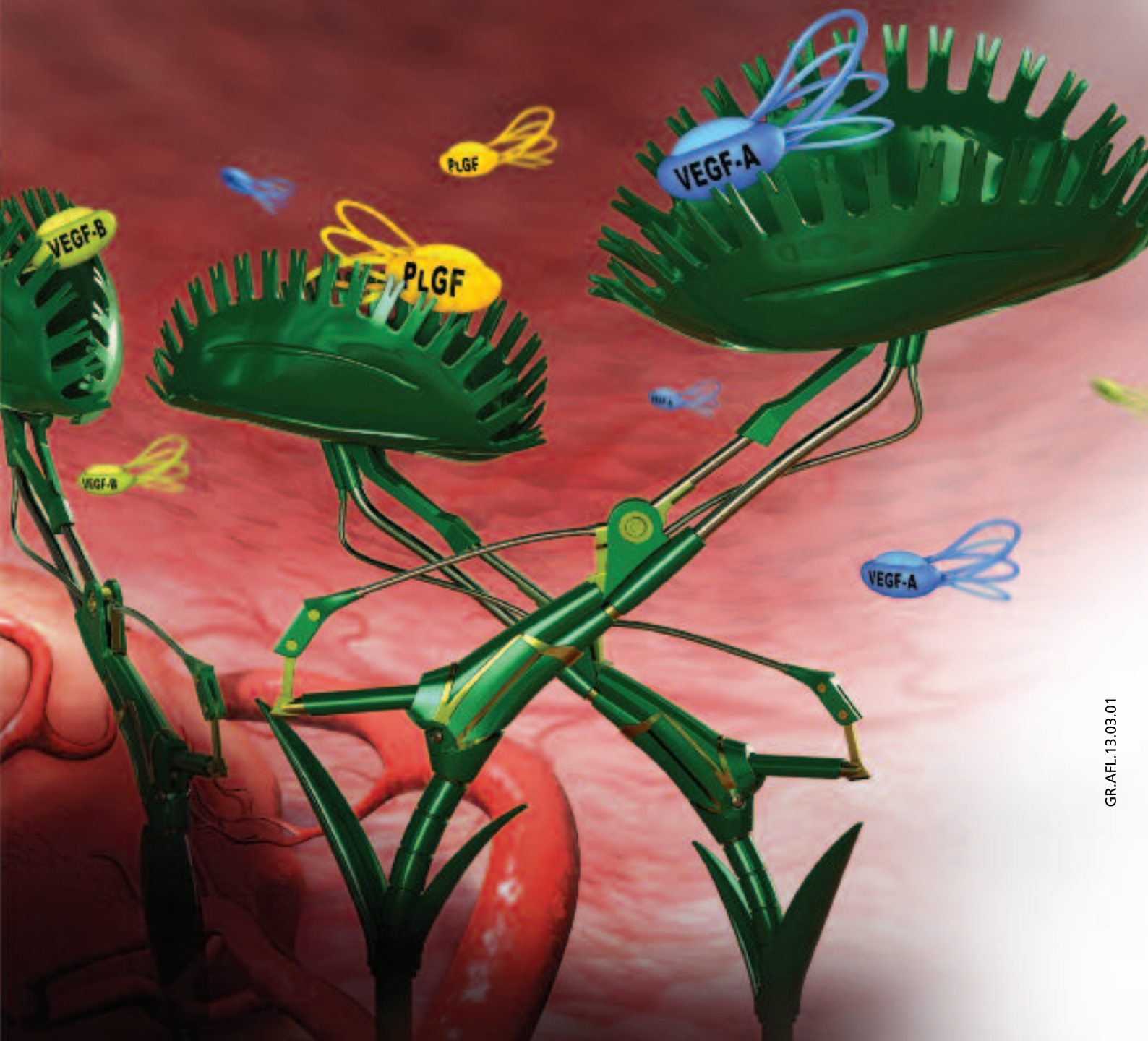**Incidence of EGFR and KRAS mutations in Greece**

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It has been over six decades since Sidney Farber was feverishly searching for a cure for leukaemia, while at the same time struggling to secure the funds necessary to finance the fight against cancer.

Numerous and important breakthroughs have since been achieved; in terms of discovering new drugs, understanding tumour biology, palliative treatment; also, important breakthroughs have been accomplished as far as research organisation and funding are concerned. The results of this progress are palpable. Many people suffering from some form of cancer may now be cured; numerous others live longer than they would in the past; and even more are relieved from their symptoms. Progress is indeed observable, but it is far from enough.

In the decades to come, more and faster steps need to be taken. Cancer has been attacked but is not yet defeated. Each year, society mourns countless victims.

"Oncopolicy", as was defined in the recent ECC 2013 conference in Amsterdam, includes all legislative, regulatory and political decisions and projects that are of direct interest to patients and their caregivers.

Technological advancements, combined with the demands of patients and their families, are running at a very fast pace; far too fast for the already fragmented healthcare services to follow, which is why we, at a European level, need coordinated actions and activities that will include the ensemble of all procedures necessary to combat cancer. That is to say, basic and translational research; institutional framework for clinical trials; drug accessibility and safety; and the overall management of cancer patients and their families.

Only an amalgamated voice combined with joint action and inclusion of all procedures in a single framework, *«All for one and one for all»* may give us hope that all necessary actions shall be undertaken in a timely and appropriate manner.

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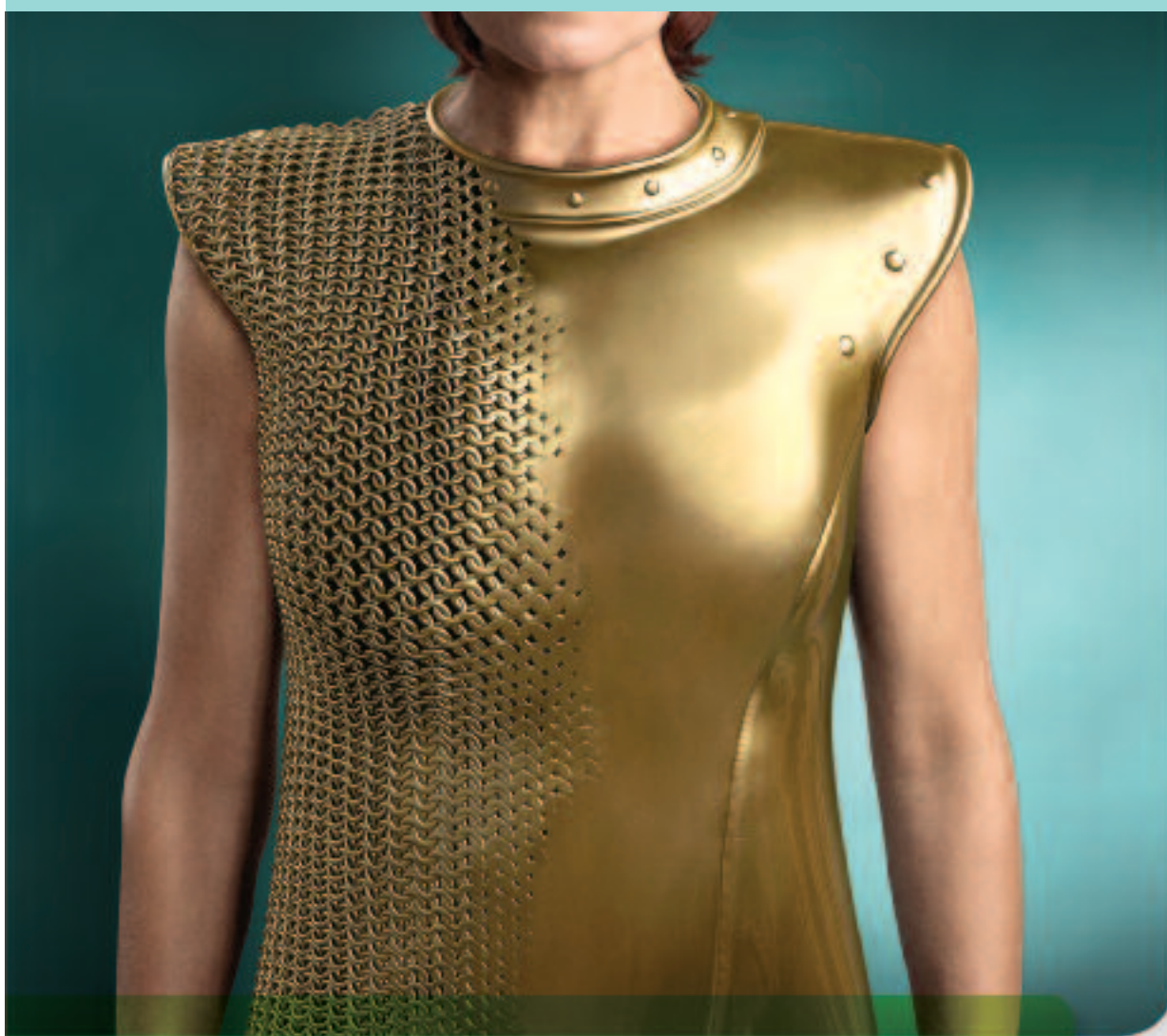
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Practicing oncology between continents

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Going away to study or to further train in medicine can be a very easy decision. Twenty years ago, my medical school reality was dominated by US elements. Many of the textbooks were translations of famous American textbooks; many of the advances in medicine came from the United States, while many of my role model professors were trained in the US. So, I came to the US for medical studies.

Training in Oncology requires complete training in Internal Medicine first, which usually takes 3 years. Oncology and Hematology are subspecialties of Internal Medicine. Many training programs are combined Heme/Onc programs and training in both subspecialties takes an additional 3 years. Certification for each specialty and subspecialty requires separate written exams. In addition, physicians are required to re-certify their competence in each specialty and subspecialty through a complicated and expensive process of ongoing education and recertification. This includes written exams every 10 years, as well as a rather long list of things, among which is the evaluation of the physician by at least 20 patients as well as peer physicians, and additional interview with questions and case discussions. Specific information and literature on all of the above can be found at the website of the American Board of Internal Medicine, (http://www.abim.org/certification/default.aspx).

For various reasons, another Greek colleague oncologist and I, decided to share a practice in the US and in Thessaloniki. So, I now spend a few months in the US practicing Hematology, Oncology and some Internal Medicine and then a few months in Greece, practicing oncology. I then return back to the US, while the other oncologist is doing the inverse. This correspondence concerns my experience practicing oncology between continents.

Since 2004, the year that I started practicing Oncology in Thessaloniki, the field of Oncology in Greece grew tremendously and the quality of practice of Oncology rose proportionately. Complicated chemotherapy regimens requiring significant support and engagement by the treating physician gradually became well-known and more frequently used. The patients also learned their rights and accordingly there was a rise in the demands to their treating physicians with requests for more information on diagnosis, personalized treatment and prognosis. Most striking, however, even today, remains the process of Informed Consent for participation in clinical trials. The US National Cancer Institute has extensive guidelines on this issue: (http://www.cancer.gov/cancertopics/pdq/supportivecare/communication/healthprofessional/page1/AllPages).

In the US, it is illegal to have the informed consent signed by the patient's family when the patient is competent to make decisions, yet is unaware even of the diagnosis of cancer, let alone of the investigational nature of the treatment he will receive. This was a common situation in Greece in 2004 and is now increasingly rare. It is also now increasingly common in Greece to discuss in full disclosure diagnosis and prognosis with the patient [1, 2, 3].

In the US, full disclosure of a cancer diagnosis and prognosis is a mandate and considered a duty of the oncologist. While in the past this was part of the first encounter with the oncologist, now it is not uncommon for the oncologist to answer patient's pertinent questions without necessarily leading to a full disclosure of prognosis if he/she feels that the patient is not (yet) interested in this or the patient does not ask for this information specifically [4].

In other aspects of care, in the years since 2004 we saw the differences between practice settings in the US and Greece diminish. Some still remain and are obvious, like for example the exemplary layout of facilities of hospitals or private institutions; the professional environment in most medical practices in the US; the very widespread application of technology and equipment; and the extensive use of readily available laboratory and imaging studies, in order to objectively support clinical impressions. Equally important is the very strong, rigorous and supportive/motivating educational environment for everyone involved in medical care, not simply residents or fellows.

In the US, most routine chemotherapy regimens are administered as outpatient with the patient sitting on a comfortable lounge chair that can recline and has its own television set. There are many state-of-the-art private oncology practices that administer outpatient chemotherapy with immediately available on-premises laboratory and radiology support. This type of private oncology practice is rare in Greece.

On the other hand, inpatient oncology care in the US is mostly reserved for patients who are very ill, or are receiving complicated chemotherapy regimens that require intensive support.

I will further focus on some points as I see them in 2013.

The economic crisis in Greece has created many difficulties in the delivery of medical care, with efforts to cut cost, sometimes so extreme that certain drugs would be impossible to use (cetuximab being unavailable due to company policy, trastuzumab and bevacizumab unavailable in Thessaloniki for long periods in summer 2012). In the US, on the other hand, a serious effort to decrease the cost of medical care started from as early as 2007. This involved a push for electronic health records, paperless medical practice, development of guidelines for practicing oncology (these are also in part used for authorization of use of specific chemo drugs by insurance companies) and finally the change of the goals of healthcare, where outcomes are very closely monitored in regards to their quality and cost-effectiveness; all these based on outcomes research. For example, the cost of care I give to a 45 year-old female with Stage IV breast cancer is compared to the average cost of a medical oncology practice throughout the US. To reach this average cost, a large number of oncology practices are surveyed and the statistics are thus formed. So, if I exceed the average national cost of care for my breast cancer patient by far, I am in a potentially difficult position where I may need to justify my treatment strategy to the patient's insurance company or agency. What percentage of my patients had complete documentation of their vital signs; an updated medication list; an updated status of their vaccinations; were given educational material concerning their disease; have an updated medical problem list; had medical notes communicated to the other consulting physicians of the same patient? All these are elements that physicians are evaluated and graded on, deficiencies leading to poor grading published on the Internet - but also to denial of payment by insurance companies.

Hospitals are evaluated for outcomes also. A classic current example for oncology departments is the number of central catheter-related infections over a period of 18 months. Although it may appear difficult to believe, zero central catheter-related infections are now a common achievement of which many hospitals are proud. Zero is a true number and not as some may think a statistical manipulation, and is based on strict criteria outlined by the Joint Commission of Hospital Accreditation of the USA (JCAHO). Another meas-

ure is the number of patients who can and do receive prophylaxis for deep venous thrombosis when admitted to the hospital for any reason, or should be immunized for flu and pneumonia and indeed did receive those prior to hospital discharge.

As part of a free market economy in the US, even under Obama's Medical Care Act, there are many different insurance policies to choose from. Depending on the cost of the insurance policy, services covered are unfortunately often commensurate with the savings, as patients may find that they do not have coverage for specific medications; or participate at a rate of 20% for medical treatment costs; or have $50 as minimum co-pay for brand name drugs even when a generic does not exist. In a free market economy the "fine print" in the contract is unfortunately an important issue.

In Greece, leaving cost issues aside, it was extremely difficult to know what each insurance company would allow for its patients until the implementation of a common policy by the National Organization for Health Care Provision (EOPYY). Even so, currently at the Interbalkan Medical Center in Thessaloniki, some chemotherapy drugs are given to the patient by a central public hospital pharmacy, others by the patient's local pharmacy, yet others by the private hospital pharmacy where chemo is administered.

In the US, all of the above regulations and outcomes measures require an easy system with which every aspect of care can be accounted for, and challenged in terms of its validity, evidence base, and quality. The electronic health record (EHR) can provide this. The EHR existed even 15 years ago but it would not be capable of transmitting orders and other important information in real time to all sectors of medical care involved. Whether in the hospital or in the office, every single move, decision, order, comment, is documented by physicians and nurses in the electronic record of each patient. I write an order and it immediately is communicated via e-mail notification to the nurse who has a computer terminal near the patient. It's no longer a problem reading a doctor's handwriting, and because you can usually select an order from a pre-specified menu for medications, diagnosis or labs/tests, the possibility of a wrong interpretation of what you said on the phone or wrote on paper, as well as other mistakes, is minimized. Medication administration orders are easily screened and double-checked by the pharmacy, the electronic record is easily accessible to any person that is involved with the care of the specific patient. Moreover, the insurance companies and government can use the data for research and outcomes evaluation [5, 6].

The downside to this is that the programs used cannot be considered user-friendly. For all the information to be entered into the patient's chart a significant amount of time is required. No government policy took this into consideration and now doctors are wasting a substantial amount of time entering this information. Since the amount of

money reimbursed for each patient has also been tangibly decreased, it is impossible to hire a person to do the work of entering data. As a result, most doctors in the US complain that they see a patient for 10 minutes but have computer work to do for the patient for another 20 minutes. Below is a brief example why.

A few years ago we used to dictate the initial history and physical of a patient. This took only a few minutes. Now, the doctor has to type all the information in by him/herself, electronically select the list of diagnoses of the patient with a corresponding ICD-9 or ICD-10 code (this is the number through which computers can work since they are not capable of recognizing verbal diagnoses, at least not yet). The doctor needs to place orders for the patient's care: Labs, radiology studies, pathology slides to be reviewed, to name but a few. Previously, these could be quickly written down on a piece of paper. You then have to select a treatment regimen from a list of allowed treatments for the specific diagnosis of the patient and e-mail that order to the specific person at our institution that deals with getting approval for this treatment from the patient's insurance. All these require separate clicks and menus to be downloaded selected and processed. And computers are not lightning-fast despite the fact that modern technology wants to make us think they are.

Philosophically, it is sad that one of the most important characteristics that differentiates man from animals, *λόγος (logos)*, is abolished: When we want to give a special type of chemotherapy for a particular cancer, and need authorization by the patient's insurance, we are unfortunately not talking to a person but rather the information goes to someone that only knows how to match diagnoses by ICD-9 code number to a list of allowed chemotherapy regimens on a computer screen. We do not talk to that person. And even when the ICD-9 code matches the chemotherapy regimen we request, there is still more to come. As an extreme example -albeit a real one- we could not have TCH chemotherapy [7] authorized for a breast cancer patient unless Herceptin was administered weekly and not every 3 weeks (the submitted schedule showed Herceptin to be administered together with Taxotere and Carboplatin every 3 wks), which would have been much more convenient for the patient. The reason for this is that the original BCIRG 006 publication was using weekly Herceptin. The menu list of the insurance only allowed the particular combination with the particular weekly Herceptin schedule of administration. This is how far "evidence-based medicine" can sometimes be (mis)interpreted.

Already in 2007, justification of all treatment plans to insurance companies was a requirement in the US. This did not simply involve approval of individual drugs separately but of the drug combination and the particular stage of disease for which the drug combination was to be used. Everything has to be clearly stated. (First-line or second-line treatment, adjuvant or metastatic?) So, when the insurance authorities in Greece recently started to move towards this type of questioning, it was neither a novelty nor surprise for me.

Seeing how this has evolved over the years in the US, many express their concern that as insurance carriers follow the various guidelines for oncology practice (Pittsburgh, NCCN) so strictly, physicians may be forced to think less and less and adopt a guidelines-only cookbook approach to oncology.

The actual practice of oncology has seen convergence between the US and the EU, first with NCCN use in both continents and then with separate -but to a large extent similar- guidelines developed in the EU. There are some differences in practice; however, these are few. More importantly, the availability of certain drugs is evident as a difference between continents. Some examples include the fact that using bevacizumab for breast cancer is practically impossible in most US settings; abiraterone is not yet approved in the EU for use immediately after failure of hormonal therapy, as is the case in the US and some drugs like enzalutamide and bendamustine, although approved in the EU, are not readily available in Greece. Moreover, sipuleucel-T (Provenge) for prostate cancer, Zelboraf (vemurafenib) and Yervoy (ipilimumab) for metastatic melanoma are commonly used in the US, but rather difficult to obtain in Greece. Cabozantinib was recently approved by the US FDA for metastatic medullary thyroid cancer. When it comes to breast cancer, ixabepilone and eribulin are two chemotherapy drugs available in the US; that may offer additional mileage for some patients with metastatic disease but are not yet approved in the EU. The above are only a few examples and are not meant to be a comprehensive list.

With some effort, I have been able to obtain some of the above agents for treatment of patients in Greece and I am certainly not the only one to have done so.

This is a limited account of some of the differences I see practicing in the US and Greece. It would be a cliché to say that we can do better with Oncology in Greece. More importantly, I would like to emphasize that we can learn from the problems that other countries considered to be "ahead" of Greece in oncology are now experiencing. Still, I find it remarkable and I am proud of it, that despite the current issues Greece is facing today, I am able to offer good oncology care to my patients in Greece. And talking to many of my oncology colleagues throughout Greece, it is clear that despite the shortcomings, they too are doing the same.

Conflict of interest statement

The author declares no conflict of interest.

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Reintroduction of irinotecan and oxaliplatin as a combination (IROX regimen) in heavily pretreated colorectal cancer patients - A single-center experience

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ABSTRACT

Introduction: The aim of this retrospective, observational study was to assess the efficacy of the reintroduction of irinotecan and oxaliplatin as a combination (IROX regimen) in heavily pretreated colorectal cancer patients.

Patients & Methods: Patients were eligible for the study if they had already been treated with oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if K-RAS wild type or unknown status). Starting doses of irinotecan and oxaliplatin were 180 mg/m^2 and 85 mg/m^2 respectively, every 2 weeks but in case of poor performance status or a history of side-effects from previous chemotherapy regimens, lower doses were given and at longer intervals. Assessment was done every 5 to 6 cycles. Control disease rate (CDR), progression free survival (PFS) and median overall survival (OS) were calculated.

Results: Twenty five patients with a median number of 3 previous chemotherapy regimens were included in the study. The median number of metastatic sites per patient was 2. Seventy six percent of the patients received treatment at reduced doses. Neutropenia (16%), diarrhea (12%) and fatigue (8%) were the more common severe (grade 3 and 4) side-effects. One patient had partial response of his disease (4%) and 7 patients showed stabilization of their disease (28%) (CDR: 32%). Control of the disease was noticed in 27% of patients with refractory disease to both irinotecan and oxaliplatin. Median PFS and median OS were 3 (95% confidence interval 2.3-3.7) and 7 (95% confidence interval 6.2-7.8) months respectively.

Conclusions: Reintroduction of IROX chemotherapy every two weeks produces a 32% CDR and a 7-month median OS with acceptable toxicity in heavily pretreated colorectal cancer patients.

Key words: metastatic colorectal cancer, reintroduction, oxaliplatin, irinotecan, IROX.

INTRODUCTION

Irinotecan and oxaliplatin are among the most active drugs for patients with colorectal cancer. Irinotecan is a topoisomerase 1 inhibitor and oxaliplatin a platinum-based drug that blocks DNA replication. Tests in colorectal cancer cell lines have shown the synergism of the two drugs [1, 2] while phase II studies have confirmed the activity of the combination (IROX regimen) in patients with colorectal cancer either untreated in the past [3] or previously treated with 5-fluorouracil [4]. The IROX combination has been also examined in the setting of phase III studies in either untreated or previously treated patients with 5-fluorouracil and its activity was proven [5-7].

However, as other combinations have been proven more active than IROX, it was abandoned from the first-line setting.

Most often, patients with metastatic colorectal cancer are currently treated from the onset with a combination of chemotherapy drugs and targeted agents which includes either irinotecan or oxaliplatin; and upon progression with a combination of drugs which includes the other, hitherto not used drug. Yet, most of these pretreated with irinotecan and oxaliplatin patients will ultimately progress and oncologists dealing with them are often faced with the dilemma of how to treat them further, especially if they have received all the currently available targeted agents, as well as

Table 1.
Patient baseline characteristics.

Characteristic	Patients (n =25), No (%)
Age (years)	
Range	39-82
Median	68
Gender	
Male	16 (64)
Female	9 (36)
ECOG performance status*	
0-1	23 (92)
2	2 (8)
Primary site	
Colon	16 (64)
Rectum	9 (36)
Time from the diagnosis of metastatic disease until 1st cycle of IROX (months)	
Range	5-74
Median	25
Metastatic sites per patient (number)	
Range	1-3
Median	2
Most common metastatic sites	
Liver	17 (68)
Lungs	17 (68)
Liver only disease	2 (8)
CEA value at baseline (ng/ml) †	
Range	3-3940
Mean	372

Eastern Cooperative Oncology Group, † Carcinoembryonic antigen

Table 2.
Patient treatment history.

Characteristic	Patients (n =25), No (%)
Adjuvant chemotherapy	
Yes	9 (36)
No	16 (64)
Chemotherapy regimens for stage IV disease (number)	
Range	2-7
Median	3
Treatment with bevacizumab	
Yes	22 (88)
No	3 (12)
Treatment with EGFR* inhibitor	
Yes	16 (64)
No	9 (36)
Interval from previous irinotecan exposure (months)	
Range	1-29
Mean	9
Refractory disease† to irinotecan	
Yes	21 (84)
No	4 (16)
Interval from previous oxaliplatin exposure (months)	
Range	1-26
Mean	7
Refractory disease† to oxaliplatin	
Yes	21 (84)
No	4 (16)

Epidermal Growth Factor Receptor, † Disease progressing during treatment with the specific drug or within three months from discontinuation of the drug (or within six months in case the drug was given as adjuvant therapy)

mitomycin C, and whether novel therapeutic options are not available. Reintroduction of oxaliplatin or irinotecan, either within the same combination of drugs that patients had in the past or within a different combination, might be justified in some of them [8].

In our hospital we have used in the past, based on the above strategy of reintroduction, the IROX regimen in patients with metastatic colorectal cancer already exposed to irinotecan and oxaliplatin. We sought to review its efficacy in heavily pretreated patients and results are presented herein.

PATIENTS AND METHODS

This was a retrospective, observational study of the medical records of patients with metastatic colorectal cancer treated at the 3rd Department of Medical Oncology at "Agii Anargiri"

Cancer Hospital with the IROX regimen. A patient treated with IROX was eligible for the current analysis if they had already been treated with oxaliplatin as well as with irinotecan. Previous treatment at least once with a fluoropyrimidine (5-fluorouracil or capecitabine) and the targeted agents bevaci-zumab and cetuximab or panitumumab (in case of patients with tumors with KRAS wild type or unknown mutational status) was mandatory. Additional eligibility criteria included normal renal and liver function as well as adequate bone marrow function. Their general condition needed to be good [Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2]. They also had to have measurable disease by the revised RECIST criteria [9].

Treatment was administered every two weeks. Irinotecan was administered at a dose of 180 mg/m^2 and oxaliplatin at a dose of 85 mg/m^2, although patients with performance

status 2 or with a history of side-effects on previous chemo-therapy regimens could be treated with 75% of the afore-mentioned doses (irinotecan 135 mg/m^2 and oxaliplatin 65 mg/m^2) or receive treatment at a three-week interval. Antiemetics were administered prophylactically and, in case of toxicity, doses were reduced as per generally acceptable guidelines. Assessment was performed every 5 or 6 cycles of chemotherapy using the revised RECIST criteria [9].

We calculated response rate with this regimen; disease control rate (CDR); median progression-free survival (PFS); and median overall survival (OS). We correlated tumor control rate with interval from previous exposure to irino-tecan and oxaliplatin as well as with refractory disease either to irinotecan or to oxaliplatin or both. Refractory disease was defined as disease progressing during treatment with the specific drug or within three months from discontinuation thereof (six months, in case treatment was administered as adjuvant). We also correlated response to treatment with changes in values of the carcinoembryonic antigen (CEA) tumor marker after two months of treatment.

PFS was measured from the time of first cycle of chemothe-rapy delivery to progression or death (in case death occurred prior to documented progression) and OS from the first dose of chemotherapy until death. Where required, statistical comparisons were carried out using the Chi-square and Fisher's exact test. Kaplan-Meier analysis was used to calculate progression-free and overall survival curves [10]. Version 15.0 of the SPSS statistical package was used and a 5% value was assumed for significance for all comparisons.

Toxicity of the regimen was assessed using the 4th version of the Common Terminology Criteria for Adverse Events published by the US Department of Health and Human Services, the NIH and the NCI [11].

RESULTS

Twenty-five patients were included in the current analysis. As shown in Table 1, almost all of them (92%) had an ECOG performance status 0 to 1. The median number of metastatic sites was 2 and the organs most frequently involved with metastases were the liver and the lungs (Table 1).

Patients included in our analysis were heavily pretreated (median number of previous lines of chemotherapy was 3) and the vast majority of them had disease that was refractory to irinotecan as well as to oxaliplatin (Table 2). 88% and 64% of them had received bevacizumab and an EGFR inhibitor, respectively (Table 2).

As can be seen in Table 3, the median number of chemothe-rapy cycles administered was 4. For the majority of patients (76%), the starting doses of irinotecan and oxaliplatin were reduced by 25% compared to the planned doses, although most of them received treatment every two weeks (80%).

Treatment, at the doses and interval administered, was well tolerated. The most common severe (grade 3 or 4) clinical adverse events were diarrhea (12%) and fatigue (8%), while

Table 3.
Treatment characteristics and response to therapy.

Treatment Characteristic	Patients (n =25), No (%)
Cycles of IROX administered (number)	
Range	1 - 11
Median	4
Dose of IROX administered per patient	
Full dose	6 (24)
Reduced dose	19 (76)
Interval between chemotherapy cycles	
IROX cycles administered every 2 weeks	20 (80)
IROX cycles administered at longer intervals	5 (20)
Response to therapy	
Partial response	1 (4)
Stable disease	7 (28)
Progressive disease	13 (52)
Not evaluable	4 (20)

the most common laboratory severe side-effect was neutropenia (16%) (Table 4). Only two patients had to be admitted for the management of side-effects caused by chemotherapy. One admission was due to vomiting and the other due to diarrhea.

One patient succeeded partial response of his disease and 7 had stabilization of their disease (Table 3). The patient with partial response was a male with metachronous meta-stases to the lungs and mediastinum from rectal cancer; DCR with IROX was 32%. As can be seen in Table 5, appro-ximately 25% of patients with refractory disease either to irinotecan or to oxaliplatin or to both drugs achieved control of their disease with IROX. Also, the interval from previous chemotherapy with irinotecan or oxaliplatin was longer for patients who had control of disease with IROX, as compared to patients without control of disease, but without statistical significance. Control of disease was not correlated with decrease or rise of less than 20% in the values of CEA after two months of treatment.

At the time of the current analysis, 4 patients were still alive. Median PFS and median OS were 3 (95% confidence interval 2.3-3.7) and 7 (95% confidence interval 6.2-7.8) months, respectively.

DISCUSSION

Our analysis showed that in patients with metastatic colorectal cancer, heavily pretreated (the median number of previous lines of chemotherapy for our patients was 3) IROX chemotherapy every two weeks produces a CDR of 32% and a median OS of 7 months, with minimal toxicity. Of interest

Table 4.

Most common treatment toxicities (n =25).

Toxicity	All grades toxicity		Mild toxicity (grade 1 or 2)		Severe toxicity (grade 3 or 4)	
	Number of patients	%	Number of patients	%	Number of patients	%
Hematological						
Anemia	14	56	13	52	1	4
Neutropenia	7	28	3	12	4	16
Thrombocytopenia	3	12	2	8	1	4
Non-hematological						
Alopecia	13	52	13	52	--	--
Diarrhea	12	48	9	36	3	12
Fatigue	12	48	10	40	2	8
Neurotoxicity	10	40	9	36	1	4
Vomiting	8	32	7	28	1	4
Allergy to Oxaliplatin	3	12	2	8	1	4

Table 5.

Correlation of refractory disease* either to previous irinotecan-based therapy or oxaliplatin-based therapy or both with DCR[†] with IROX regimen.

Refractory disease		DCR with IROX			
		Yes		No – Not applicable	
	Number of patients	Number of pts	%	Number of pts	%
To irinotecan	21	6	29	15	71
To oxaliplatin	21	5	24	16	76
Both to irinotecan and oxaliplatin	15	4	27	11	73

*Disease progressing during treatment with the specific drug or within three months from discontinuation of the drug (or within six months in case the drug was administered as adjuvant therapy), [†] Complete response, partial response or stable disease

is the fact that control of disease was detected in approximately one in four patients with refractory disease both to irinotecan and oxaliplatin. Of course, we must underline that these results are retrospective and based on a relatively small number of patients, so they have to be interpreted with caution.

One important issue regarding IROX regimen in patients with metastatic colorectal cancer is how often to administer it and at which dose. And that is because IROX has been used in the past with various schedules and doses in colorectal cancer patients. In two phase III studies from the USA, each cycle was administered every three weeks with the doses of oxaliplatin and irinotecan being 85 mg/m^2 and 200 mg/m^2, respectively [5, 7]. Fischer von Weikersthal et al. have administered the IROX (which they called mIROX) at a different schedule, which was oxaliplatin fortnightly at a dose of 85 mg/m^2 and irinotecan at a dose of 80 mg/m^2 weekly for 6 times every 7 weeks [6]. Finally, the regimen has been also administered every two weeks at doses of 85 mg/m^2 and 175 mg/m^2 for oxaliplatin and irinotecan, respectively [3]. Based on the fact that the data in question is based on administering the IROX every two weeks, we opted to use this version, as we considered that it would be more convenient for patients (compared to a weekly schedule of

irinotecan) and less toxic compared to the 'every three weeks' schedule.

And indeed that was the case. As an example in the previously mentioned phase III studies with the regimen being administered every three weeks, the rates of severe diarrhea varied between 22% and 28%, while in our study it was only 3%; the rate of severe vomiting ranged between 15% and 22%, while in ours it was 1%; and the rate of febrile neutropenia episodes was around 10%, while in ours we had no episodes of febrile neutropenia. Of course, we have to mention that approximately 75% of our patients received treatment at a reduced dose (oxaliplatin at a dose of 65 mg/m^2 and irinotecan at a dose of 135 mg/m^2) due to the fact they had experienced toxicities from previous regimens. Similarly, in the study of Scheithauer et al. [3], when patients received treatment at the planned dose of irinotecan of 175 mg/m^2 and oxaliplatin of 85 mg/m^2 every two weeks, the rate of severe toxicities was high (diarrhea grade 3/4 in 35% and nausea/vomiting grade 3/4 in 30%) but when the dose of irinotecan was reduced to 150 mg/m^2 while the dose of oxaliplatin was unchanged, patients had fewer severe side-effects. So, in our opinion regarding the schedule of IROX in colorectal cancer patients and minimal toxicity, the fortnightly schedule with the irinotecan dose being between 135 and 150 mg/m^2 and the oxaliplatin dose being between 65 and 85 mg/m^2 seems to be the best available option.

As far as different schedules of IROX delivery and their efficacy in metastatic colorectal cancer are concerned, it is difficult to draw any conclusion based on the results of our analysis, as the patients of our study were heavily pre-treated. But from the data existing in the literature, the efficacy seems to be similar no matter which schedule is chosen to be administered. In chemo-naïve patients, the response rate when treatment is administered every three weeks is 35%; when administered fortnightly it is 43.5%; while, with the weekly schedule of irinotecan, the response rate is 41% [3, 5, 6]. Although a formal comparison regarding the efficacy of various schedules has not been performed, the fortnightly schedule produces slightly higher response rates.

In our analysis, patients with heavily pretreated colorectal cancer were treated with IROX and were thus rechallenged both with oxaliplatin and irinotecan. Although, as already mentioned, rechallenge seems to be an option for some of these patients [8], not much data exists in the literature. Townsend et al. showed that the rechallenge of patients with metastatic colorectal cancer with an oxaliplatin - fluoropyrimidine combination produces a 65% control of disease with a median survival of 7.8 months [12]. The rate of disease control in that study was double compared to the rate in our analysis but in that Australian study the median number of previous lines of chemotherapy was two (compared to three in our study), only 20% had received prior bevacizumab treatment (compared to 88% in ours) and it was not clear from the data given how many patients had been administered irinotecan in the past. Fornaro et al. rechallenged patients who had received in the first-line setting the triplet 5-fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX regimen) with FOLFIRINOX or chemotherapy doublets which included either oxaliplatin and 5-fluorouracil or irinotecan and a fluoropyrimidine or single-agent chemotherapy which was irinotecan in a few of them [13]. Response with the chemotherapy triplets or doublets was 38% and 28%, respectively. These figures are much better compared to ours, however (again, as in the Australian study), patients in the Italian study were not as much pretreated as in ours. Regarding the subgroup of patients in the study of Fornaro et al., who received only one chemotherapy drug, results seem similar to the ones we had with the IROX regimen in our analysis (PFS 3 and OS 8.7 months in the Italian study compared to 3 and 7 months, respectively in our study).

In the aforementioned study of Fornaro et al., one chemo-therapy regimen that was used in the group of patients not receiving one of the chemotherapy triplet or doublet combinations based on oxaliplatin or irinotecan, was mitomycin C with a fluoropyrimidine. Compared to this combination, which is commonly used in the setting of heavily pretreated colorectal cancer patients, the IROX regimen seems to have at least the same efficacy. To the best of our knowledge, there are in the literature four studies in which the combination of mitomycin C with a fluoro-pyrimidine is tested for colorectal cancer patients already treated with both oxaliplatin and irinotecan combinations [14-17]. In these four studies the CDR varied from 23.8% to 36.6%, while the median PFS varied from 2.5 to 6 months. The figures mentioned above seem very similar to the results we have achieved by giving our patients rechallenge chemotherapy with IROX regimen. As far as toxicity is concerned, it seems that the combinations of mitomycin C with a fluoropyrimidine, at least at the dose level and schedule used are tolerated as well as IROX given fortnightly.

Another treatment option for these heavily pretreated patients is regorafenib, which is already licensed for use in some countries such as the USA. This oral inhibitor of multiple protein kinases including kinases of tumor angiogenesis, oncogenesis and tumor microenvironment, has been found to prolong survival compared to placebo in a multinational study published in 2012 [18]. In this study, 760 patients with similar treatment history as the ones of our analysis received regorafenib 160 mg daily for three weeks every four weeks. The control of the disease with the new drug was 41%, median PFS was 1.9 months and median OS was 6.4 months. The figures are very close to the ones we present with IROX, bearing though in mind that data from the regorafenib study is much more solid as it comes from a randomized prospective study involving a large number of patients.

In conclusion, our study, with the weaknesses of being

retrospective, showed that for patients with colorectal cancer already treated with oxaliplatin and irinotecan in the past, IROX rechallenge chemotherapy every two weeks could be a valid option for approximately 30% of them. IROX could be potentially one more option with acceptable toxicity in the oncologist's armamentarium for the treatment of colorectal cancer patients.

Conflict of interest statement: The authors declare no conflict of interest.

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Cancer Pain: Global awareness and guideline recommendation

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ABSTRACT

Background: Although pain is a common event during cancer treatment, its assessment and management remains suboptimal on daily practice. A possible cause for this phenomenon might be a low level of cancer pain awareness and web guideline recommendations among health providers. The aim of this study was to scrutinize global on-line cancer-pain guideline recommendations among anesthesiology and oncology societies.

Patients & Methods: Systematical web identification of anesthesiology and oncology societies. International variations on cancer pain guideline recommendations were analyzed.

Results: Among 181,200 web pages scrutinized, 370 eligible societies were identified. Only 18 societies provided recommendations on cancer pain (12 for physicians). The level of global awareness of cancer pain was extremely poor, independently of nation and continent analyzed. Different society categories showed differences in cancer pain guideline recommendations (p = 0.0045). The highest rate of societies recommending guidelines on cancer pain was found among pain-related medical societies (27%). Anesthesiology and oncology societies did not pass 3% and 9%, respectively, in any sub-setting considered. Half the recommendations regarding cancer pain management were outdated and only half of these supported their statements with level I evidence in their references.

Key words: cancer pain; global awareness; guideline recommendations; web; medical societies; medical providers; oncology; anesthesiology.

INTRODUCTION

Cancer pain is a common event during treatment of cancer patients. Its prevalence was documented to be 64% among patients with advanced metastatic or terminal phases of the disease, 59% among patients on anti-cancer treatment and 33% among patients following curative treatment [1]. However, in spite of its frequency and its negative impact on patient quality of life, pain assessment and management remain suboptimal in daily clinical practice. Less than half of cancer patients receive adequate pain treatment [2-4], a proportion which may even reach 82.3% in some settings [3]. This lack of management of cancer-related pain is even more prominent if we consider that six out of ten patients under analgesics experience breakthrough pain; 7 out of 10 report pain-related difficulties with everyday activities; while eventually half of the patients believe that their quality of life is not considered a priority in their overall care by their health care professional [4].

Taking into account that clinical practice guidelines are important for translating evidence in medical decision-making and clinical practice applications, reducing undesirable practices and encouraging services of proven efficacy [5], we hypothesized that one of the possible causes of current medical mismanagement of cancer pain might stem from a low level of cancer pain awareness and low number of web guideline recommendations among oncology educational and policymaker societies/institutions.

Therefore, we set to examine the global intercontinental coverage of cancer pain guidelines produced by professional societies and caregivers. Since different levels of development and economy might largely influence clinical daily practice and priorities in guideline recommendations, we further separately scrutinized differences in cancer pain guideline recommendations among the ten most highly developed countries [6].

Table 1.

Distribution of the scrutinized societies and caregivers organization by location, type (anesthesiology, oncology, pain); eligibility, accessibility and relative guideline recommendations.

	Eligible N = 370	Accessible N = 346	English language N=276	Any guideline N=120	Any guideline p.	Cancer Pain guideline N=18	Own vs. (link)	Cancer Pain p.
CONTINENT								
INTERCONTINENTAL	57	52	51	17		2	1 (1)	
NORTH AMERICA	71[#]	71[#]	71[#]	71[#]		7	7	
SOUTH AMERICA	7	6	2	3		1	1	
EUROPE	35	31	30	15		1	1	
AFRICA	11	10	10	4		1	1	
ASIA	5	4	4	0		0	-	
OCEANIA	2	2	2	1	p=0.3996	0	-	p=0.6367
TOP 10 DEVELOPED COUNTRIES*								
NORWAY	4	4	4	0		0	-	
AUSTRALIA	16	16	16	8		0	-	
NEW ZEALAND	7	7	7	3		0	-	
USA	54	54	54	24		6	6	
IRELAND	10	7	7	2		0	-	
LIECHTENSTEIN	0	0	0	0		0	-	
NETHERLANDS	9	9	1	0		0	-	
CANADA	17	17	17	7		1	1	
SWEDEN	4	4	2	1		0	-	
GERMANY	10	10	2	0	p=0.0223[†]	0	-	p=0.5422
OTHER COUNTRIES								
JAPAN	13	12	10	2		0	-	
UNITED KINGDOM	18	17	17	11		3	3	
ITALY	11	11	6	3		2	2	
SWITZERLAND	14	14	8	3		0	-	
SPAIN	14	14	5	6		1	(1)	
BELGIUM	9	8	4	3		0	-	
DENMARK	7	5	2	1		0	-	
FRANCE	12	12	6	4		0	-	
CHINA	14	11	7	1		0	-	
AUSTRIA	10	9	2	1	p=0.0359[†]	0	-	p=0.1339
ANY COUNTRY ANALYSED					p=0.0060[†]			p=0.3127
SOCIETY CATEGORY								
ANESTHESIA	79	73	55	28		2	2	
ONCOLOGY	271	253	203	75		11	10(1)	
PAIN	15	15	14	14		4	3(1)	
OTHER	5	5	4	3	p< 0.0001[†]	1	1	p=0.0003[†]

Table 1. (suite)

SOCIETY SUBTYPE	Eligible N = 370	Accessible N = 346	English language N=276	Any guideline N=120	Any guideline p.	Cancer Pain guideline N=18	Own vs. (link)	Cancer Pain p.
ANESTHESIA RESEARCH	4	4	4	0		0	-	
ANESTHESIA COMPREHEN.	45	42	31	19		1	1	
ANESTHESIA OTHER	30	27	20	9		1	1	
PAIN	15	15	14	14		4	3(1)	
CANCER RESEARCH	50	49	47	10		1	1	
RADIATION ONCOLOGY	36	30	21	11		0	-	
MEDICAL ONCOLOGY	25	23	13	8		2	2	
SURGICAL ONCOLOGY	15	13	8	5		0	-	
SUPPORTIVE ONCOLOGY	11	11	9	5		1	1	
CA. MGM** COMPR.	77	73	58	25		7	6(1)	
OTHER SOCIETIES	62	59	51	14	p< 0.0001[†]	1	1	p=0.0045[†]

*Countries were selected from the top 10 countries from the human development index; ** COMPR. CA. MGM = Comprehensive Cancer Management*

[#] *= North American guidelines were obtained by the addiction of USA & Canada societies/organizations*

[†] *= Statistical significant difference at 95% CI, RCTs = Inclusion of Randomized Controlled Trials in references.*

METHODS

Identification of pertinent societies and caregivers

We constructed a database of anesthesiology, oncology and pain societies/organizations (educational, professional, health policymakers, caregivers) that might provide guidelines for cancer pain. We considered societies and organizations that were intercontinental (with a global outlook); continental (including two or more countries in the same continent); or national belonging to one of the top 10 countries with the highest development index [6]. Countries with a long-lasting tradition in medical oncology but not included in the top 10 high developed countries, were further included in the online searches [Table 1]. (Based on our previous meta-analyses, we considered as countries with a long-lasting tradition in medical oncology, those in which the largest number of chemo/hormonal therapy randomized trials for advanced malignancies was performed [7-10]).

We conducted online searches (the last being in June 2011) involving possible combinations of 11 subject matters ("anesthesiology", "anesthetics, "cancer", "oncology", "medical oncology", "clinical oncology", "radiation oncology", "radiotherapy", "surgical oncology", "cancer research", "supportive oncology"); 3 terms for educational and policymaker societies ("society" or "association" or "organization"); and 30 terms of geographic identifiers (10 pertaining to continents: "Asian", "American", "North American", "South American", "America Latina", "African", "European", "Australian", 'Oceanian"; "International"; 10 pertaining to eligible countries by

highest development index [6]: "Norway", "Australia", "New Zealand", "USA", "Ireland", "Liechtenstein", "Netherlands", "Canada", "Sweden", "Germany"; and 10 pertaining to countries with a long-lasting tradition in oncology but not included in the top 10 high developed countries: "Austria", "Belgium", "China", "Denmark", "France", "Japan", "Italy", "UK", "Spain", "Switzerland"). Due to notable economic and development differences between South and North American countries, the continental entities were separately searched and analyzed for North and South America [6].

The first 100 results for each online search were scrutinized. We included both societies with accessible web pages, as well as those whose presence was mentioned in some URL but did not have a webpage or their link was not functional (under construction or not working). The study methodology has been previously described [10, 11].

Data extraction from eligible websites

For each pertinent anesthesiology / oncology / pain society and caregiver website we recorded its name; URL; continent and/or country; sub-specialty setting (anesthesia research, comprehensive anesthesia managing, pain, supportive oncology, medical oncology, surgical oncology, radiation oncology, cancer research); and whether they provided any guidelines on any subject matter (any setting) and on cancer pain-related guideline (last update June 2011). Whenever there was availability to perform an electronic search within

the website, we used the terms "guidelines" or "recommendations" or "position statements" in English. For non-English websites, we translated these terms into the language used in the website. We were able to do this in all languages except for 7 Chinese, 3 Japanese, 5 Danish and 8 Dutch organizations.

Whenever any eligible guidelines were available, we recorded whether recommendations were freely accessible through the website and whether they provided separate information developed by the society/organization itself or a link to another society/organization's guidelines.

For each cancer pain guideline retrieved, we further examined whether it was recommended for patient or for physicians and whether it pertained to cancer pain assessment or treatment setting. In order to evaluate guideline consistency, we further extracted whether any references were provided to support guideline statements, and whether the evidence from randomized controlled trials and/or meta-analyses was provided to support the guideline statements.

Analyses

We evaluated whether the proportion of associations/organizations present intercontinental and international variations and the possible role played by the society type and subtype in guideline recommendations. Group comparisons for categorical variables used Chi-square and Fisher's exact test.

RESULTS

Eligible societies and organizations

We scrutinized 181,200 web pages during online searches and we identified 370 anesthesiology, oncology, and pain societies / organizations covering a large array of settings (educational / clinical / research / policymaker) [Appendix 1]. Among these, 118 were international (58 intercontinental and 60 continental: African, American, Asian, European, Oceanian); 130 belonged to the top 10 countries with the highest development index [6]; and 122 pertained to countries with a long-lasting tradition in medical oncology but not included in the top 10 high developed countries [Table 1]. US societies/organizations (n = 53) accounted for 21% of all societies analyzed. For the remaining 19 countries, the number of societies analyzed per each nation did not exceed 18, and each country thereafter did not contribute with more than 7% of the overall number of societies analyzed.

Searches for North America did not lead to comprehensive (US + Canada) North American societies/organizations and only societies for each separate country were retrieved and scrutinized [Table 1]. Thereafter, in estimating intercontinental variation for cancer pain guideline implementation, data for North American was provided by the combination of US and Canada societies/organizations [Table 1]. As a result, the vast majority of international societies/organization analyzed were intercontinental (31%), North American (37%) and European

(19%). African, Asian, South American and Oceanian societies together, accounted for the remaining 13% [Table 1].

When the society/institution type was considered, most societies were devoted to comprehensive cancer management (n = 77), cancer research (n = 50), anesthesia comprehensive management (n = 45) and radiation oncology (n = 32); while only a minority pertained to pain (n = 15), surgical oncology (n =15), supportive oncology (n = 11), and anesthesia research (n = 4) [Table 1].

Twenty four societies were not eligible for analysis: 12 of these did not have an accessible webpage, 9 had no functional webpage and 3 web pages were under construction [Appendix 2]. Thereafter, 346 anesthesiology, oncology, pain societies and organizations websites could be accessed for the presence of guidelines. Most of them (n = 276) had a webpage in English [Table 1].

Overall guideline recommendations

Among the 370 anesthesiology, oncology, and pain societies and organizations identified, 120 (32%) provided guidelines (any setting considered). No continental variation was observed in the proportion of societies recommending guideline for any setting (p = 0.3997) [Table 1].

When national variations were scrutinized, we noted remarkable differences in the probability to deliver guidelines (any setting considered) from single medical societies/organizations (p = 0.0060). High rate of guideline recommendations (42-50%) were found among Australian, Irish, New Zealand, Spanish, USA societies, and particularly high (61%) among UK societies. These national variations were evident even when countries were separately analyzed for the top 10 highest development index countries (p = 0.02233) [6], or the 10 countries with a long-lasting tradition in oncology but were not included in the top 10 most highly-developed countries (p = 0.0359) [Table 1].

An impressive proportion of pain societies/organizations (93%) was found to give recommendations (any setting considered) in their URL, while only 35% and 28% of anesthesiology and oncology societies, respectively, did so (p < 0.0001). This difference was maintained (p < 0.0001) even when subtypes of anesthesiology and oncology societies were analyzed [Table 1].

Implementation of cancer pain guidelines

Only 4.9% of scrutinized societies (18/370) [12-29] provided recommendations on cancer pain: 12 societies (3.2%) were providing guidelines for physicians [12-23], and only 8 (2.2%) for patients [22-29] (two societies were providing guidelines both for patients and physicians [22, 23].

No continental variation was observed in the proportion of societies providing web guidelines for cancer pain (p = 0.6367) [Table 1].

Cancer pain guideline recommendations were almost zero across each single country. No web recommendation for

Figure 1.

Study flowchart diagram for the selection of anesthesiology, oncology and pain societies / organizations, and their relative guideline production for cancer pain.
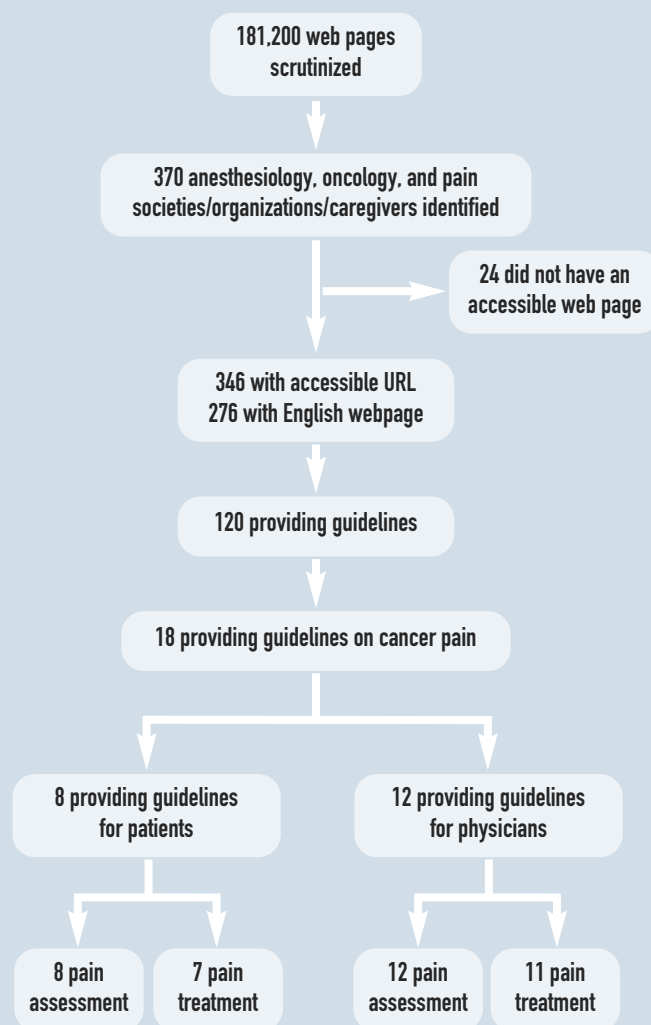
cancer pain was found among societies of 15 nations [Table 1]. Only thirteen societies belonging to 5 of the 20 analyzed nations implemented guidelines on cancer pain [12, 13, 19-29]. The highest proportion of cancer pain recommendations was reported among the Italian (18%), UK (17%) and US (11%) societies; however, this was not enough to document any statistically significant difference in the national variation of cancer pain guideline recommendations [Table 1].

No differences were reported even in case we separately analyzed the top 10 highest development index countries, and the 10 countries with a long-lasting tradition in oncology not included in the top 10 most highly developed countries [Table 1].

The proportion of pain societies providing web guidelines for cancer pain was low (27%) but was statistically higher than that retrieved for anesthesiology (3%) and oncology (4%) societies (p = 0.0003) [Table 1]. Statistical difference was maintained even when the anesthesiology and oncology society subtypes were scrutinized (p = 0.0045). Indeed, the proportion of societies of medical oncology, supportive oncology and comprehensive oncology providing guidelines was only 8%, 9% and 9%, respectively. The proportion of anesthesiology societies recommending guidelines on the web for cancer pain did not amount to more than 3% in any subcategory (comprehensive / general anesthesia, anesthesia research and other anesthesiology settings) [Table 1].

Use of references and guideline updating

Cancer pain guidelines for physicians: Overall, only 12 societies (3.2%) gave guidelines for physicians on cancer pain [12-23],

Table 2.

Physician oriented guidelines recommendation for cancer pain assessment and treatment; time of guidelines delivery and quality of references used.

PHYSICIAN ORIENTED GUIDELINES	Pain ASSESSMENT# N=12	Ref. N=7	year	Pain TREATMENT N=11	Ref. N=9	RCT/MET N=4/2	year
CONTINENT & COUNTRY							
INTERCONTINENTAL	2	1	2005, 2009	2	2	1 RCT	2005, 2009
SOUTH AMERICA	1	1	2005	1	1	-	2005
EUROPE	1	1	2011	1	1	1 RCT+MET	2011
AFRICA	1	-	2006	1	1	-	2006
TOP DEV. COUNTRIES*							
USA*	3	1	1996, 2002, 2011	3	1	1 RCT	1996, 2002, 2011
OTHER COUNTRIES							
UNITED KINGDOM	1	1	2010	1	1	1 RCT+MET	2010
ITALY	2	1	2003, 2009	1	1	1 RCT	2003
SPAIN	1	1	2011	1	1	1 RCT	2011
SOCIETY CATEGORY							
ANESTHESIA	2	1	1996, 2003	2	1	1 RCT	1996, 2003
ONCOLOGY	7	4	2005, 2006 2x2009 3x2011	6	6	3 RCT 1RCT+MET	2005, 2006 2009, 3x2011
PAIN *	3	2	2002, 2005 2010	3	2	1RCT+MET	2002, 2005 2010
SOCIETY SUBTYPE							
ANESTHESIA COMPR	1	-	1996	1	-	-	1996
ANESTHESIA OTHER	1	1	2003	1	1	1 RCT	2003
PAIN*	3	2	2002, 2005 2010	3	2	1RCT+MET	2002, 2005 2010
MED. ONCOLOGY	2	1	2009, 2011	1	1	1RCT+MET	2011
SUPP. ONCOLOGY	1	1	2005	1	1	-	2005
CA. COMPR.	4	2	2006, 2009 2x2011	4	4	3 RCT	2006, 2009 2x2011

 # No guidelines reported randomized controlled trials or meta-analyses (RCT/MET, N=0) in their references to support their recommended evidence,
*Ref = number of guidelines with references, year = year of last recommendation review; * = one site was of restricted access (only for subscribers).*

[Table 2]. All of these were reporting guidelines for cancer pain assessment [12-23], and 11 for cancer pain treatment [12, 20, 22, 23]; however, one website was of restricted access and was accessible only to subscribers [19] [Table 2]. When the 10 accessible guidelines for *cancer pain treatment* were scrutinized, all [13-20, 22, 23] but one [12] guideline for physicians reported references to support the evidence of their proposals; six of them supported their statements with level I evidence (4 reporting randomized controlled trials [13, 16, 22, 23], and two reporting both randomized controlled trials and meta-analyses [15, 20]. Guideline updating proved discouraging; indeed, less than half of the guidelines (5/11) [15, 16, 20, 22, 23] were updated within three years (with only 3 of these being updated within one year [15, 22, 23]). Six recommendations were to be considered outdated since they had to be discontinued over 5 years ago [12-14, 17-19] [Table 2].

When the 12 guidelines for *cancer pain assessment* were scrutinized [12-23], only six guidelines [13, 17, 18, 20, 22, 23] reported references to support the evidence of their proposals and no recommendation was supported by randomized evidence or meta-analysis in the references (probably reflecting the lack of level 1 evidence in this setting). Guideline updating was also disappointing and overlapping with that of the guidelines for pain treatment [Table 2], with half of the guidelines (6/12) being considered as outdated [12-14, 17-19] [Table 2].

Cancer pain guidelines for patients: Overall, only eight societies gave patient oriented guidelines for cancer pain [22-29]; all of these were reporting recommendations for cancer pain assessment [22-29], and seven for cancer pain treatment [22-28] [Table 3]. Overall, only two societies (2/8) used references to support their sentences for pain assessment [28, 29], and two societies (2/7) for pain treatment [22, 28]. No level I evidence was included in these references, regardless of whether pain assessment or pain treatment guidelines were considered. Recommendation updating was encouraging in the patients-oriented setting, with only one (1/8) guideline for pain assessment being outdated [29], and no outdated guidelines for pain treatment. This last detail, however, was not enough to compensate for the unpleasantly low level of awareness on cancer pain that is characterized by a heavy scarcity of society/organizations implementing web guidelines.

Table 3.

Patient oriented guidelines recommendation for cancer pain assessment and treatment; time of guidelines delivery and quality of references used in recommended guidelines.

PATIENT ORIENTED GUIDELINES	Pain ASSESSMENT# N=8	Ref. N=2	year	Pain TREATMENT N=7	Ref. N=2	year
CONTINENT & COUNTRY						
TOP DEV. COUNTRIES*						
USA	4	2	2003, 2009, 2X2011	3	1	2009, 2X2011
CANADA	1	-	2010	1	-	2010
OTHER COUNTRIES						
UNITED KINGDOM	2	-	2009, 2010	2	-	2009, 2010
SPAIN	1	-	2011	1	1	2011
SOCIETY CATEGORY						
ONCOLOGY	6	1	2003, 2009 2x2010 2x2011	5	1	2009 2x2010 2x2011
PAIN	1	1	2011	1	1	2011
OTHER	1	-	2009	1	-	2009
SOCIETY SUBTYPE						
PAIN	1	1	2011	1	1	2011
CANCER RESEARCH	1	-	2010	1	-	2010
CA. COMPR.	5	1	2003, 2009 2010, 2x2011	4	1	2009, 2010, 2x2011
OTHER SOCIETIES	1	-	2009	1	-	2009

No guidelines reported randomized controlled trials or meta-analyses (RCT/MET, N=0) in their references to support their recommended evidence,
Ref = number of guidelines with references, year = year of last recommendation review.

DISCUSSION

Our analysis provides strong evidence regarding the lack of guidelines for the management of cancer-related pain among anesthesiology and oncology societies. However, can this deficiency in guideline recommendations change medical thought as regards decision-making and result in shortcomings in cancer pain assessment / management in daily practice?

We, therefore, hypothesized that pain management was unlikely to be considered a priority on daily practice by caring physicians. This hypothesis was reinforced by a recent pan-European survey, in which 50% of cancer patients believed that their quality of life was not considered a priority in their overall care by their health care professional [4].

As a matter of fact, clinical practice guidelines are important for translating evidence in medical decision-making and clinical practice applications, reducing undesirable practices and encouraging services of proven efficacy [5]. Furthermore, medical guideline / recommendation availability in websites has been documented as being of extreme importance, since it improves patient safety; it reduces complications and shortens the length of stay among Medicare beneficiaries [30]. Consequently, it appears that the provision of guidelines may substantially affect patient management, given that it helps physicians put evidence into practice and eventually result in a uniform evidence-based treatment of specific patient categories.

Therefore, the documented severe lack in cancer pain guideline recommendations appears to justify patient belief that their quality of life might not be considered as a priority in their overall care by their health care professional.

The crucial question is why this low level of priority in cancer pain management exists, especially when the prevalence of cancer-related pain appears to be very high [1] and given that its assessment and management are frequently less than satisfactory in daily oncology practice [2-4].

As was shown in our analysis, an impressive number of medical, anesthesiology, pain and cancer societies have developed over time, offering a general picture of flourishing professional and scientific activity. Many of these organi-

zations have a very extensive membership and organize large meetings; furthermore, a third of these societies provide guidelines, recommendations and position statements within their websites that have substantial influence on their members, subscribers, and website visitors [31-34]. So, why do these societies not prioritize guideline recommendations for so common a problem (cancer pain) in daily clinical practice? Probably, the exuberance of medical society high professional activity might not always be interpreted into a substantial benefit for patients. The new question to answer is what motivates a determined medical society to establish guidelines on a certain subject? This manuscript underscores that many a time the prevalence of a specific problem and patient expectancies from physicians might be different from the priorities of physicians and medical professional societies. Subsequently, how to resolve this divergence and positively impact the medical decision-making to develop or not determined clinical practice guidelines and make them available on the web could represent a new challenging filed for future research.

In summary, our study outlined that overall web guidelines coverage for cancer pain was absolutely not satisfactory and totally inadequate, in any setting considered.

The study presents some limitations: firstly, for 24 societies /organizations we could not find access to a website; however, they only account for 6.5% of all entities included in our study and it is not very likely that these entities would have guidelines.

The Spanish society of medical oncology (SEOM) [35], and the European Association for Palliative Care (EAPC) [36] have issued new evidence-based guidelines to aid clinicians across Europe in providing treatment for cancer pain; however, these guidelines were published in 2012, after the date of our study cut-off for web survey searches. Furthermore, there are no established validated searches for locating professional societies and organizations and some of them may have been missed by our searches. However, given the multiple layers of our search, it is unlikely that any prominent entities were, in fact, missed.

Conflict of interest statement: The authors declare no conflict of interest.

Appendix 1.
List of analyzed societies

- ACORN CRO
- Africa Oxford Cancer Consortium
- African Cancer Organization
- African Organisation for Research and Training in Cancer
- African Radiation Oncology Group
- African Women's Cancer Awareness Association
- Age Anaesthesia Association

- Alles Over Cemotherapie
- Alliance mondiale contre le cancer
- American Academy of Pain Management
- American Anti-Cancer Society
- American Association for Cancer Education
- American Association for Cancer Research
- American Brachytherapy Society

- American Cancer Society
- American College of Oncology Administrators
- American College of Radiation Oncology
- American Institute for Cancer Research
- American Pain Foundation
- American Pain Society
- American Society for Therapeutic Radiology and Oncology
- American Society of Anesthesiologists
- American Society of Clinical Oncology
- American Society of Preventive Oncology
- American Society of Regional Anesthesia and Pain Medicine
- American-Italian Cancer Foundation
- Anaesthesia Patient Safety Foundation
- Anaesthetic Research Society
- Arbeitsgemeinschaft Internistische Onkologie
- Asia- Oceania Clinical Oncological Society
- Asian American Network for Cancer Awareness
- Asian Clinical Oncology Society
- Asian Federation of Organizations for Cancer Research and Control
- Asian Fund for Cancer Research
- Asian Pacific Organization of Cancer Prevention
- Association for Directors of Radiation Oncology Programs
- Association for International Cancer Research
- Association for Research on Treatment against Cancer
- Association for the International Development of Anesthesia
- Association Latin American for Therapeutic Radiation Oncology (ALATRO)
- Association of Physician Assistants in Oncology
- Association of American Cancer Institutes
- Association of Anesthesia Clinical Directors
- Association of Burns and Reconstructive Anaestheists (formerly Plastic Surgical & Burns Anaesthetists)
- Association of Cancer Executives
- Association of Cancer Online Resources
- Association of Community Cancer Centers
- Association of European Cancer Leagues
- Association of Freestanding Radiation Oncology Centers
- Association of Integrative Oncology and Chinese Medicine
- Association of Residents in Radiation Oncology
- Association of University Anesthesiologists
- Associazione Anestesisti Rianimatori Ospedalieri Italiani
- Australasian Society of Anaesthesia Paramedical Officers
- Australian Cancer Research Foundation
- Australian Society of Anaesthetists
- Austrian Cancer Aid Society
- Austrian Cancer Association
- Austrian Society of Anaesthesiology, Resuscitation and Intensive Care
- Austrian Society of Hematology and Oncology
- Austrian Society of Oncology
- Austrian Society of Oncology Pharmacy
- Austrian Society of Radiation Oncology
- Austrian Society of Surgical Oncology

- Belgian Association for Cancer Research
- Belgian Association for Radiotherapy and Oncology
- Belgian Federation Against Cancer
- Belgian Pain Society
- Belgian Society of Medical Oncology
- Belgian Society of Surgical Oncology
- Berufsverband Deutscher Anaesthesisten
- British Accelerator Science and Radiation Oncology Consortium
- British Anaesthetic & Recovery Nurses Association
- British Association of Cancer Research
- British Association of Cancer United Patients
- British Association of Surgical Oncology
- British Oncological Association
- British Oncology Pharmacy Association
- Canadian Association of General Practitioners in Oncology
- Canadian Association of Medical Oncologists
- Canadian Association of Nurses in Oncology
- Canadian Association of Pharmacy in Oncology
- Canadian Association of Provincial Cancer Agencies
- Canadian Association of Radiation Oncologists
- Canadian Cancer Action Network
- Canadian Cancer Advocacy Network
- Canadian Cancer Research Alliance
- Canadian Cancer Society / National Cancer Institute of Canada
- Canadian Oncology Societies
- Canadian Partnership Against Cancer
- Canadian Society for Surgical Oncology
- Cancer Advocacy Coalition of Canada
- Cancer assistance network
- Cancer Association of South Africa
- Cancer Australia
- Cancer care,Inc.
- Cancer Control New Zealand
- Cancer Council Australia
- Cancer Cure Foundation
- Cancer Federation Inc.
- Cancer Foundation of China (formerly Chinese Cancer Research Foundation)
- Cancer Hope Network
- Cancer Net in Spanish
- Cancer Patients Foundation
- Cancer Project
- Cancer research foundation of America
- Cancer Research Initiative of South Africa
- Cancer Research Institute
- Cancer Research Society of Canada
- Cancer Research UK
- Cancer Society of New Zealand
- Cancer Support Association of Western Australia
- Cancer Support France
- Cancer Trials New Zealand

- Cancérologues Sans Frontières" / "Oncologists Without Borders
- Canteen Ireland
- Central European Cooperation Oncology Group
- China East Radiation Oncology Group
- Chinese American Society of Anesthesiology
- Chinese Anti-Cancer Association
- Chinese Center for Disease Control and Prevention
- Chinese Medical Association
- Chinese Medical Association Society of Oncology
- Chinese Oncology Society (Taiwan)
- Chinese Preventive Medicine Association
- Chinese Society of Anesthesiologists
- Chinese Society of Clinical Oncology
- Chinese Society of Therapeutic Radiology and Oncology / Chinese Society of Radiation Oncology
- Clinical Cancer Research Center
- Clinical Oncology Society of Australia
- Coc Member Organization Cancer Care Initiatives
- Community oncology alliance
- Complementary and Alternative Medicine for Cancer
- Confederación Latinoamericana de Sociedades de Anestesiología
- Confederation of European National Societies of Anaesthesiologists
- Conseils pour la chimiothérapie
- Cris Foundation for Cancer Research
- Cure Cancer Australia Foundation
- Danish Anaesthesiological Organisation
- Danish Cancer Society
- Danish Research School in Molecular Cancer Research
- Danish Society of Intensive Care Therapy
- Danish Society of Anaesthesiology and Intensive Care Medicine
- Danish Society of Medical Oncology
- Dansk Selskab for Cancerforskning
- Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin
- Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin
- Dutch Association of Medical Oncology
- Dutch Association of Oncology Nurses
- Dutch Belgian Hemato-Oncology Cooperative Group
- Dutch Cancer Society
- Dutch Society for Radiotherapy and Oncology
- Dutch Society of Oncology
- Dutch Society of Surgical Oncology
- Eastern Cooperative Oncology Group
- European (Spain) Website of Anaesthesia, Intensive Care and Pain Medicine
- European Academy of Anaesthesiology
- European Association for Cancer Education
- European Association for Cancer Research
- European Cancer Organisation
- European cancer prevention organization
- European Masters Program in Radiation Sciences for Oncology
- European organization for palliative care

- European Organization for Research and Treatment of Cancer
- European Palliative Care Research Collaborative
- European School of Oncology
- European Society for Hyperthermic Oncology
- European Society for Intravenous Anaesthesia
- European Society for Medical Oncology
- European Society for Therapeutic Radiology and Oncology
- European Society of Anesthesiology
- European Society of Cancer Immunology and Immunotherapy
- European Society of Intensive Care Medicine
- European Society of Oncology Pharmacy
- European Society of Surgical Oncology
- Federación Panamericana e Ibérica de Sociedades de Medicina Crítica y Terapia Intensiva
- Fédération Nationale des Centres de Lutte Contre le Cancer
- Federation of Spanish Cancer Societies
- Fight Cancer Foundation
- Foundation Cancer Research Switzerland
- Foundation for Anaesthesia Education and Research
- Foundation for European Education in Anaesthesiology
- Foundation of Geriatric Oncology Netherlands
- Freesia Group for Cancer Charities Spain
- French National Institute of Cancer
- French Society of Radiation Oncology
- French Society of Surgical Oncology
- German Cancer Aid
- German Cancer Research Center
- German Cancer Society
- German Society for Hematology and Oncology
- German Society of Radiation Oncology
- Ialian Association of Cancer Patients
- Intercultural Cancer Council
- Intercultural Cancer Council Caucus
- International Agency for Research on Cancer
- International Anesthesia Research Society
- International Association for the Study of Pain
- International Cancer Biomarker Consortium
- International Cancer Microenvironment Society
- International Cancer Rehabilitation Association
- International Network for Cancer Treatment and Research
- International Organization for Cancer Prevention and Researc
- International Society for Biological Therapy of Cancer
- International Society for Cell and Gene Therapy of Cancer
- International Society for Oncology and Biomarkers
- International Society for Preventive Oncology
- International Society of Cellular Oncology
- International Society of Chemotherapy (ISC) for Infection and Cancer
- International Society of Intraoperative Radiation Therapy
- International Society of Oncology Pharmacy Practitioners
- International Society of radiation oncology
- International Union Against Cancer

- Ireland Cooperative Oncology Research Group
- Irish Association for Cancer Research
- Irish Association for Nurses in Oncology
- Irish Cancer Data Association
- Irish Cancer Society
- Irish Institute of Radiography and Radiation Therapy
- Irish Society of Medical Oncology
- Irish Society of Surgical Oncology
- Israel Cancer Association
- Italian Association for Cancer Research
- Italian Association for Radiation Oncology
- Italian Cancer Society
- Italian Foundation for Cancer Research
- Italian Institute for Cancer Rasearch and treatment
- Italian Institute of Medical Oncology
- Italian League Against Cancer
- Italian Society for Surgical Oncology
- Japan Clinical Cancer Research Organization
- Japan Society of Clinical Oncology
- Japan Society of Therapeutic Radiology and Oncology
- Japanese Cancer Association
- Japanese Foundation for Cancer Research
- Japanese Organization of Radiotherapy Quality Management
- Japanese Society of Anesthesiologists
- Japanese Society of Hyperthemic Oncology
- Japanese Society of Medical Oncology
- La Ligue Nationale contre le Cancer
- La Sociedad Española del Dolor
- La Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor
- l'Association Ensemble contre la douleur
- L'Association pour la Recherche sur le Cancer (ARC)
- Latin American and Caribbean Society of Medical Oncology
- Latin American Association for Palliative Care
- Latin American Cancer Research Coalition
- Latin-American Group of Oncologic. Radiotherapy /Grupo Latino-Americano de Curieterapia y Radioterapia Oncologica
- Macmillan Cancer Support
- Medical Oncology Group of Australia
- Mediterranean School of Oncology
- Multinational Association of Supportive Care in Cancer
- National Association of Professional Cancer Coaches
- National Cancer Institute
- National Cancer Registrars Association
- National Cancer Research Institute
- National Cancer Research Network
- National Coalition for Cancer Survivorship
- National Comprehensive Cancer Network
- National Foundation for Cancer Research
- National Health and Medical Research Council
- National Institute of Health and Excellence

- Navy Anesthesia Society
- Nederlandse Vereniging voor Anesthesiologie
- New Zealand Society for Oncology
- New Zealand Society of Anaesthetists
- Nordic Cancer Union
- Norwegian Cancer Society
- Norwegian Group on Inherited Cancer
- Norwegian Society of Anaesthesiology
- Oncology Nutrition Dietetic Group
- Organisation of European Cancer Institutes
- Organization for Oncology and Translational Research
- Österreichische Gesellschaft für Internistische und Allgemeine Intensivmedizin
- Peripheral Regional Anesthesia
- Physician Assistants in Anesthesia
- Prevent Cancer Foundation
- Radiation Therapy Oncology Group
- Royal Australian & New Zealand College of Radiologists
- Royal College of Anaesthetists
- Schweizerische Gesellschaft für Intensivmedizin-Société Suisse de Médecine Intensive
- Scientific Association of Swiss Radiation Oncology
- Scottish Intercollegiate Guidelines Network
- Sino-American Network for Therapeutic Radiology and Oncology
- Sociedad Española de Enfermería Oncológica
- Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias
- Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva
- Societé de Réanimation de Langue Francaise
- Société Française d'Anesthésie et de Réanimation
- Societe Francaise du cancer
- Société suisse d'anesthésiologie et de réanimation/Schweizerische Gesellschaft für Anästhesiologie und Reanimation
- Society for Ambulatory Anesthesia
- Society for Anesthesia and Resuscitation of Belgium
- Society for Education in Anesthesia
- Society for Education in Anesthesia
- Society for Integrative Oncology
- Society for the Advancement of Geriatric Anesthesia
- Society of Academic Anesthesiology Associations
- Society of Neurosurgical Anesthesia and Critical Care
- Society of Radiation Oncology Administrations
- Society of Surgical Oncology
- South African Oncology Consortium
- South African Society of Clinical and Radiation Oncology
- South African Society of Medical Oncology
- South East Asian Radiation Oncology Group (SEAROG)
- Southeast Anesthesiology Consultants
- Spanish Association Against Cancer
- Spanish Association for Cancer Research
- Spanish Association of Radiotherapy and Oncology
- Spanish Society of Chemotherapy

- Spanish Society of Medical Oncology:
- Spanish Society of Surgical Oncology
- Supportive and Rehabilitation Oncology
- Swedish Cancer Society
- Swedish Society for Anaesthesiology and Intensive Care
- Swedish Society of Oncology
- Swedish Surgical Society
- Swiss Bridge Foundation
- Swiss Cancer League, Swiss League Against Cancer
- Swiss Federation Against Cancer
- Swiss Group of Clinical Cancer Research
- Swiss Institute for Experimental Cancer Research
- Swiss Radiation Oncology Centers
- Swiss Society for Oncology
- Swiss Society of Medical Oncology
- Swiss Society of Surgery
- Taiwan Clinical Oncology Society
- The American Academy of Pain Medicine
- The American Board of Anesthesiology
- The American Chronic Pain Association
- The American College of Surgeons Oncology Group (ACOSOG)
- The American Academy of Anesthesiologist Assistants
- The Anaesthesia Research Trust
- The Anesthesia Foundation
- The Association of Anaesthetists of Great Britain and Ireland
- The Association of Anesthesia Clinical Directors
- The Australian Organisation for Young People Living with Cancer
- The Australian Society of Post Anaesthesia and Anaesthesia Nurses
- The Australian Pain Society
- The Australian Patient Safety Foundation

- The Austrian Cancer League
- The Belgian Society of Intensive Care Medicine
- The British Medical Acupuncture Society
- The British Pain Society
- The Canadian Anesthesiologists' Society
- The Cancer Information and Support Society
- The European Cancer Patient Coalition
- The European Oncology Nursing Society
- The European Society of Digestive Oncology
- The European Society of Regional Anesthesia and Pain Therapy
- The Global Regional Anesthesia website
- The Intensive Care Society of Ireland
- The International Society for Anesthetic Pharmacology
- The International Spine Intervention Society
- The Japan Cancer Society
- The Japanese Association for Molecular Target Therapy of Cancer
- The National Board of Anesthesiology
- The Neuroanaesthesia Society of Great Britain and Ireland
- The New Zealand Association of Cancer Specialists
- The Royal College of Radiologists
- The Society of Anaesthetists of Hong Kong
- The South African Society of Anaesthesiologists
- The South Asian Association for Regional Cooperation
- The UK Society for Intravenous Society
- Trans-Tasman Radiation Oncology Group
- World Anesthesia Society
- World Cancer Research Fund International
- World Federation of Surgical Oncology Societies
- World Federation Societies of Anaesthesiologists
- World Institute of Pain

Appendix 2.
Twenty four societies not eligible for cancer pain analyses

Twelve of these did not have an accessible web page:
1. International Society of Radiation Oncology
2. International Cancer Rehabilitation Association
3. Asia-Oceania Clinical Oncological Society
4. Confederation of European National Societies of Anaesthesiologists
5. Dutch Belgian Hemato-Oncology Cooperative Group
6. African Radiation Oncology Group
7. Asian Clinical Oncology Society
8. Irish Society of Medical Oncology
9. Irish Society of Surgical Oncology
10. Danish Anaesthesiological Organization
11. Chinese Medical Association Society of Oncology
12. China East Radiation Oncology Group

Nine had no functional web page:
1. World Federation of Surgical Oncology Societies
2. Latin-American Group of Oncologic. Radiotherapy /Grupo Latino-Americano de Curieterapia y Radioterapia Oncologica
3. European Master's Program in Radiation Sciences for Oncology
4. Danish Research School in Molecular Cancer Research
5. Irish Cancer Data Association
6. Age Anaesthesia Association
7. European Academy of Anaesthesiology
8. The Belgian Society of Intensive Care Medicine
9. Japanese Society of Hyperthemic Oncology

3 web pages were under construction:
1. Chinese Society of Therapeutic Radiology and Oncology / Chinese Society of Radiation Oncology
2. British Oncological Association
3. Österreichische Gesellschaft für Internistische und Allgemeine Intensivmedizin

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Hormonotherapy: present and future in ER+ breast cancer

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ABSTRACT

Endocrine therapy is a fundamental component of the therapeutic armamentarium for the management of early and metastatic, hormone receptor-positive breast cancer. Inevitably, tumors develop resistance to endocrine therapy and, therefore, overcoming said resistance is a key motivator of research in this field.

Relevant references for hormonal therapy in breast cancer including guidelines for clinical use were identified by PubMed search and from the annual meeting proceedings of the European and American Societies of Clinical Oncology and the San Antonio Breast Cancer Symposia. This review summarizes the current status of endocrine therapy for the treatment of both early and metastatic ER+ breast cancer. Current therapeutic strategies that could potentially reverse endocrine resistance and future perspectives are also presented.

Combinations of endocrine therapy with HER2 targeting agents and/or compounds interfering with PI3K/Akt/mTOR signaling pathway are two promising strategies for delaying or overcoming endocrine resistance. Due to increased costs and the burden of toxicity associated with these combination therapies, the importance of establishing predictive biomarkers cannot be emphasized.

Key words: breast cancer, tamoxifen, aromatase inhibitors, endocrine resistance, everolimus.

INTRODUCTION

Breast cancer mortality has been declining constantly in the recent years [1]. This decline is due to earlier diagnosis, as a direct effect of the widespread use of mammographic screening, as well as to improvements in surgical and adjuvant treatment (radiotherapy, chemotherapy, endocrine therapy and biologically targeted therapy) [2]. An increased armamentarium of effective anticancer medications has also a positive impact on the prognosis of patients with metastatic disease [3].

Overall, about 80% of breast cancers express estrogen receptors (ER) and/or progesterone receptors (PgR). In patients with hormone receptor-positive breast cancer, endocrine therapy is a fundamental component of the therapeutic strategy. Recent progress in the research of endocrine therapy has produced a significant number of novel active compounds that are available for clinical use mostly in the metastatic setting.

This review will briefly summarize the current endocrine therapeutic options for both premenopausal and postmenopausal women with hormone receptor-positive early and advanced breast cancer. We focus primarily on the most recent results from randomized trials evaluating pharmacological strategies to overcome endocrine resistance.

HORMONAL THERAPY FOR EARLY-STAGE BREAST CANCER

Endocrine therapy is critical for reducing the risk of recurrence and promoting survival in women with hormone receptor-positive early breast cancer. Overall, the risk of disease recurrence is reduced by approximately 40% with adjuvant endocrine therapy [4]. Given this substantial effect and the high prevalence of hormone receptor-positive breast cancer, it is reasonable to conclude that adjuvant endocrine therapy had the greatest impact on reducing cancer mortality compared to other anticancer medical therapies. In addition to distant disease recurrence prevention, adjuvant endocrine therapy reduces the risk of locoregional recurrences and lowers the risk of contralateral breast cancer by approximately 50% [4]. Based on these benefits, adjuvant

Table 1.

Prognostic factors in hormone receptor-positive breast cancer.

- Tumor size (T)
- Nodal status (N)
- Tumor grade
- Quantitative levels of hormone receptor expression
- HER2 expression status
- Lymphovascular invasion
- Multigene prognostic signatures, such as the 21-gene recurrence score (Oncotype DX assay, Genomic Health Inc, Redwood City, CA, USA)

endocrine therapy is recommended for nearly all patients with hormone receptor–positive breast cancer irrespective of tumor size or nodal status [5-7].

Tumor expression of ER and/or PgR has both a prognostic as well as a predictive impact on adjuvant endocrine therapy. In the absence of ER and/or PgR adjuvant endocrine therapy is of limited or no benefit [8]. This observation leads to the recommendation for routinely hormone receptor expression testing for all newly diagnosed breast cancers [9]. Besides the expression of hormone receptors, a variety of other prognostic factors have been associated with an increased recurrence risk of ER-positive breast cancer (Table 1). Taken together, these biomarkers can help physicians to estimate the likelihood of tumor recurrence and the expected absolute treatment benefit. However, no other biomarker other than the hormone receptor expression is currently available for identifying patients who are likely to derive benefit from adjuvant hormonal manipulations. Moreover, no biomarker exists that can identify which endocrine treatment is optimal for each individual patient.

Estrogen receptor-positive breast cancers have a different pattern of tumor recurrence from other types of breast cancer. Patients who did not receive adjuvant endocrine therapy have the highest risk of recurrence in years 2 through 5 and then a steady persistent risk of recurrence through at least 20 years after diagnosis [10]. However, if adjuvant endocrine therapy is administered, the risk of recurrence is reduced dramatically during the first 10 years after diagnosis [11]. There is also a carryover effect, such as in patients who had 5 years of endocrine therapy continue to experience a lower risk of recurrence for at least 15 years after breast cancer diagnosis. Despite these positive effects, patients receiving adjuvant endocrine therapy need long-term follow-up for the detection of second primary breast cancers and non-breast cancer morbidity both of which contribute a large percentage of events in studies of adjuvant endocrine therapy.

Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive early breast cancer

Tamoxifen, which is effective irrespective of menopausal status, remains the standard adjuvant endocrine therapy for pre- or perimenopausal women with ER-positive breast cancer [12]. The Early Breast Cancer Trialists' Collaborative Group analyzed numerous prospective, randomized, clinical trials of adjuvant tamoxifen and concluded that five years of tamoxifen therapy lowers the risk of breast cancer recurrence by approximately 40% and the risk of breast cancer mortality by approximately 20% [4]. The benefits of tamoxifen were seen regardless of patient age or menopausal status. The optimal duration of tamoxifen treatment seemed to be 5 years in total. However, the recent publication of the results from the ATLAS trial raised a new question regarding this common practice. In the ATLAS trial a 2.8% absolute reduction in breast cancer-specific mortality has been shown for women who received tamoxifen for 10 years compared to those who were treated for 5 years [13]. Since only 10% of patients enrolled in this trial were premenopausal, at present, 5 years of tamoxifen remains the standard of care for premenopausal women. Nevertheless, the results of the ATLAS trial certainly should be discussed with the patient during the decision making process.

The side-effects of tamoxifen have been well-recognized (Table 2). Menopausal symptoms, such as hot flashes and night sweats, and in premenopausal women, menstrual irregularities are the most commonly seen. Tamoxifen is associated with a low, yet increased risk of uterine cancer and deep venous thrombosis, particularly in postmenopausal women. Quality-of-life studies suggest that most women receiving tamoxifen have a well-preserved quality of life in all functional domains and that most of them remain committed to their treatment.

Although some young women who receive adjuvant chemotherapy may experience treatment-induced amenorrhea, the role of ovarian suppression in addition to tamoxifen is a seminal issue in the management of premenopausal women with early-stage breast cancer. Ovarian suppression, mainly through the administration of gonadotropin-releasing hormone analogues, is an effective adjuvant treatment for women with ER-positive breast cancer [4]. However, its role in the modern management of ER+ early breast cancer remains unclear because of the confounding effects of chemotherapy-induced amenorrhea in younger women treated with adjuvant chemotherapy. Uncertainty also exists regarding the relevant benefits since the design of major clinical studies in the 1990s did not analyze the impact of ovarian suppression in addition to tamoxifen, but rather as an alternative to chemotherapy or tamoxifen. Thus, the relative value of ovarian suppression in addition to tamoxifen for pre- or perimenopausal patients is still a matter of debate [14].

Several lines of indirect data suggest that patients with ER-positive breast cancer may benefit from ovarian suppres-

Table 2.
Side-effects of adjuvant endocrine therapy.

	Tamoxifen	Aromatase Inhibitors	Ovarian Suppression
Gynecological	Vaginal discharge or dryness/atrophy	Vaginal dryness/atrophy	Vaginal dryness/atrophy
	Increased risk of vaginal bleeding and uterine cancer		
Menstrual Function	Irregular menstrual cycles or amenorrhea	Not applicable	Amenorrhea
Menopausal symptoms	Hot flashes, night sweats	Hot flashes, night sweats	Hot flashes, night sweats
Musculoskeletal health	Mixed effects on bone density	Osteopenia, osteoporotic fractures	Osteopenia
		Musculoskeletal (arthralgia) syndrome	
Cardiovascular health	Increased risk of deep vein thrombosis	Increased risk of hypercholesterolemia, hypertension	Unknown

sion in addition to tamoxifen. First, the addition of ovarian suppression to tamoxifen improves outcomes in young women compared with chemotherapy alone [15]. Second, women who receive both chemotherapy and tamoxifen and who experience treatment-induced amenorrhea have a superior outcome compared with women who do not go into menopause with therapy [16]. Finally, a meta-analysis of ovarian suppression trials suggests that gonadotropin-releasing hormone analogues might reduce the risk of cancer recurrence [17]. This collective work supports the hypothesis that ovarian suppression in addition to tamoxifen might further lower the risk of breast cancer recurrence in premenopausal women. However, definitive data is still lacking. The Suppression of Ovarian Function Trial (SOFT), a randomized study run by the International Breast Cancer Study Group (BIG), that compares tamoxifen alone versus tamoxifen plus ovarian suppression versus an aromatase inhibitor (AI) plus ovarian suppression, will answer this question. Women who experience ovarian suppression as part of a program of adjuvant therapy seem to suffer more intensive menopausal side-effects than women receiving tamoxifen alone. This includes greater severity of hot flashes, night sweats, and other climacteric symptoms as well as osteoporosis [16].

Adjuvant endocrine therapy for postmenopausal women with hormone receptor–positive early breast cancer

The introduction of aromatase inhibitors (AIs) has defined a new era in the adjuvant endocrine treatment of postmenopausal women with hormone receptor–positive breast cancer. Aromatase inhibitors block the conversion of androgens to estrogens by the aromatase enzyme and lead to depletion of circulating estrogen levels by 90% from baseline [18, 19]. Presumably, the resultant estrogen deprivation is responsible for the antineoplastic effects of AI therapy. Since premenopausal women have residual ovarian function and retain the capacity to up-regulate aroma-

tase expression in the ovarian tissue in response to estrogen deprivation, AIs are contraindicated in this patient population.

Aromatase inhibitors have been studied in several contexts as adjuvant endocrine treatment for postmenopausal women. Most of the major adjuvant trials have compared AI-based treatment with the historical standard of 5 years tamoxifen. The development of AIs as adjuvant treatment included studies of upfront endocrine therapy, which used AIs as initial treatment instead of tamoxifen; sequential endocrine therapy, which integrated AIs as adjuvant treatment after several (typically 2 to 3) years of tamoxifen; and extended adjuvant therapy, which explored AI-based treatment after 5 years of adjuvant tamoxifen. The major adjuvant trials that have been reported in the past decade on the role of AIs in the adjuvant setting are summarized in Table 3. These trials demonstrated that AIs are an important component of adjuvant endocrine treatment for postmenopausal women with early breast cancer. Incorporating an AI during the first 5 years of adjuvant endocrine treatment, or as extended therapy after 5 years of tamoxifen, is associated with a 15% to 20% reduction in the risk of breast cancer recurrence compared with tamoxifen. The absolute difference in breast cancer events associated with AI-based therapy compared with tamoxifen is only 2% to 3% but this is mostly due to the generally favorable prognosis for most postmenopausal women with early-stage breast cancer. The improvement in breast cancer outcome includes reduction in the risk of distant recurrence as well as reduction in locoregional events and contralateral breast cancer [20]. These modest gains are noted when comparing upfront use of an AI versus tamoxifen or tamoxifen alone versus a sequence of tamoxifen followed by an AI [21]. Regarding overall survival, no study has reported a significant survival advantage for initial use of an AI compared with a sequential treatment strategy incorporating tamoxifen followed by an AI. However, compared with tamoxifen treatment alone, sequential use of an AI may confer a modest survival advantage. It seems that different treatment strategies yield similar

Table 3.

Major trials of AI therapy as adjuvant treatment in early-stage, hormone receptor–positive breast cancer.

	Study	Schema	Duration (yr)	AI	Ref
Primary endocrine therapy	ATAC	TAM versus AI versus TAM + AI	5	ANA	31,32
	BIG 1-98	TAM → AI versus AI → TAM versus TAM versus AI	5	LET	33,34
	ABCSG 12	TAM versus AI (premenopausal at diagnosis; all patients receive ovarian suppression)	5	ANA	35
	TEAM	AI versus TAM /AI	5	EXE	36
Sequential endocrine therapy (after 2–3 years of TAM)	IES	TAM versus TAM /AI	5	EXE	37
	ARNO 95 ABSCG 8	TAM versus TAM /AI	5	ANA	38-39
Extended endocrine therapy (after 5 years of TAM)	MA 17	AI versus placebo	10	LET	40
	ABCSG 6a	AI versus placebo	7	ANA	41
	NSABP B-22	AI versus placebo	10	EXE	42

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ANA, anastrozole; ARNO 95, Arimidex-Nolvadex; EXE, exemestane; IES, Intergroup Exemestane Study; LET, letrozole; NSABP, National Surgical Adjuvant Breast and Bowel Project; TAM, tamoxifen

outcomes, provided that an AI is incorporated in the therapeutic plan at some point. Direct comparisons of results between initial use of an AI and sequential treatment with tamoxifen followed by an AI showed equivalent rates of tumor recurrence in the BIG 1-98 and the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trials. When an AI (anastrozole) was combined with tamoxifen, the outcome was not superior to tamoxifen alone in the Arimidex, Tamoxifen Alone or in Combination (ATAC) study. Therefore, a recommendation for consideration of an AI at some point during adjuvant endocrine treatment in postmenopausal women is supported by these findings [22].

Open questions remain about the optimal timing of AI therapy compared with tamoxifen and whether or not a treatment prolongation, accomplished by extended therapy with tamoxifen followed by an AI, would be different than initial use of an AI. Another open question is the optimal duration of AI treatment. Whether or not longer use of an AI in excess of 5 years' total duration is more effective and still safe is a matter of ongoing clinical research. No studies reported to date have directly compared one AI versus another in the adjuvant setting. In broad terms, the findings with all the commercially available AIs (anastrozole, exemestane, and letrozole) seem qualitatively similar. Thus, it seems likely that the benefit seen with AI treatment represents a class effect. Ongoing clinical trials are comparing directly one AI versus another.

Patients taking AIs are at greater risk for musculoskeletal health problems, including accelerated bone loss and fractures, than women taking tamoxifen [23]. Bisphospho-

nate therapy seems to ameliorate AI-associated bone loss [24-25]. Additionally, AIs are associated with a unique arthralgia syndrome, characterized by muscle and joint pain and stiffness, which is common -although usually of modest intensity [26]. They are also associated with a slightly greater risk of hypertension and hypercholesterolemia but whether these adverse effects have any long-term cardiac consequences is not yet well characterized [27]. The side-effects of treatment with AIs are summarized in Table 2.

Considerable interest remains in the efforts to tailor specific adjuvant endocrine treatment options for each individual patient based on tumor characteristics, biomarkers or pharmacogenomics. Unfortunately, there is only retrospective data on these topics and the results remain inconclusive. At present, there does not seem to be sufficient data to support CYP2D6 genotyping for predicting whether tamoxifen is a suitable treatment option for a specific woman [28]. A variety of pathologic and other biomarker studies confirm prognostic markers for patients treated with AIs [29-30]. However, this data lacks sufficient power for predicting which treatment strategy (tamoxifen alone, AI alone, or a sequence of tamoxifen and an AI) would be best for a particular woman. At present, the recommendation for selecting the initial endocrine treatment should be based on available data of efficacy, side-effects, and patient preference.

HORMONAL THERAPY FOR METASTATIC BREAST CANCER

Historically, endocrine therapy represents the first form of

Table 4.

Randomized studies comparing third-generation aromatase inhibitors with tamoxifen in the first-line treatment of hormone receptor-positive, metastatic breast cancer.

Treatment	Patients (N)	ORR (%)	PFS (months)	OS (months)	Ref
Letrozole 2.5 mg	458	32*	9.4*	34	55
Tamoxifen 20 mg	458	21	6.0	30	
Anastrozole 1 mg	340	33	8.2	NR	56
Tamoxifen 20 mg	328	33	8.3	NR	
Letrozole 2.5 mg	171	21	11.1*		57
Tamoxifen 20 mg	182	17	5.6		
Exemestane 25 mg	182	46*	9.9*	37.2	58
Tamoxifen 20 mg	189	31	5.8	43.3	

ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; NR: not reported

*Statistically significant difference

medical therapy for metastatic breast cancer patients discovered by an empirical observation made in women submitted to surgical oophorectomy [43]. In the years that followed, several forms of endocrine manipulations were tested, including estrogens, progestins, androgens or anti-androgens [44]. These treatments led to some antitumor activity in patients that, at the time, were not selected according to the hormone receptor status of the tumor. Indeed, the discovery of the ER and its correlation with tumor endocrine response occurred decades after initial observation [45].

When cytotoxic chemotherapy was introduced for the treatment of breast cancer, growing enthusiasm for this form of therapy generated a dichotomy that persisted until recently in the mind of oncologists. This dictated that chemotherapy was preferable in younger patients with visceral disease, whereas endocrine therapy -supposedly less active- was restricted to older patients, who were unsuitable for chemotherapy or who had indolent metastatic disease [46]. Randomized studies conducted to explore a possible superiority of chemotherapy compared to endocrine treatment, showed better response rates for chemotherapy, but no difference in overall survival [47]. Nowadays, this comparison is no longer therapeutically relevant; chemotherapy is still recommended upfront for patients with life-threatening disease, while endocrine therapy is considered to be a better option for patients with endocrine-responsive visceral or non-visceral disease [48]. International guidelines emphasize the role of first-, second- and even third-line endocrine therapy for patients who are selected on the basis of hormone receptor positivity and potential endocrine-responsiveness [48].

Most of the data reviewed here refer to postmenopausal women, where absence of ovarian function is a prerequisite for the effectiveness of aromatase inhibitors and the selective ER down-modulator fulvestrant. However, several studies have shown that these compounds may also be active in premenopausal metastatic breast cancer patients if concomitant therapeutic ovarian function suppression is achieved [44, 45].

Aromatase Inhibitors

For several years the cornerstone of endocrine therapy in metastatic breast cancer has been tamoxifen [12]. Its success was due to its higher efficacy and better tolerability compared to previously used compounds such as progestins [49]. Continuing efforts to discover different strategies for treating tamoxifen-resistant breast cancer led to the development of aromatase inhibitors (AIs). The initial compounds of this class had significant toxicity with non-specific action. However, these limitations have been overcome with the third generation non-steroidal AIs anastrozole and letrozole as well as the steroidal AI exemestane [50]. A number of randomized trials compared AIs with megestrol acetate (MA) and with tamoxifen in patients with tamoxifen-resistant and potentially hormonal-sensitive advanced breast cancer, respectively [51-58]. Overall, AIs compared favorably to MA in terms of clinical efficacy and tolerability.

In the setting of potentially tamoxifen-sensitive patients, the results of randomized trials are summarized in Table 4. AIs became the first-line option of choice in women with hormone receptor-positive metastatic breast cancer. Therefore, any new endocrine compound should henceforth be compared with them. Currently, there is no solid evidence indicating that a particular AI is preferable to another. In the second-line setting, letrozole showed a slight superiority in terms of response rate compared to exemestane with no difference in time-to-progression [59]. Another randomized

Table 5.

Randomized studies of fulvestrant in postmenopausal women with hormone receptor-positive, metastatic breast cancer.

Treatment	Patients (N)	ORR (%)	PFS (months)	OS (months)	Ref
Fulvestrant 250 mg	428	19.2	5.5	27.4	62
Anastrozole 1 mg	423	16.5	4.1	27.7	
Fulvestrant 250 mg	313	31.6	6.8	36.9	63
Tamoxifen 20 mg/d	274	33.9	8.3	38.7	
Fulvestrant 250 mg	351	7.4	3.7	NR	66
Exemestane 25 mg	342	6.7	3.7	NR	
Fulvestrant 250 mg	362	9.1	6.5*	25.1	69
Fulvestrant 500 mg	374	10.2	5.5	22.8	
Fulvestrant 250 mg	102	23.8	23.4*	NR	70
Anastrozole 1 mg	103	21.1	13.1	NR	

ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; NR: not reported

*Statistically significant difference

phase II study failed to show any significant difference between anastrozole and exemestane [60].

Fulvestrant

Fulvestrant competes with estradiol for the ER and therefore is a selective estrogen receptor modulator (SERM). Upon binding, fulvestrant induces estrogen-receptor down-regulation and degradation [61]. Unlike other endocrine therapies (tamoxifen and AIs), fulvestrant is administered intramuscularly and showed encouraging activity in tamoxifen- and AIs-resistant preclinical models.

Fulvestrant was approved for the treatment of postmeno-pausal women with hormone receptor-positive metastatic breast cancer based on the results of two randomized trials comparing this compound with anastrozole [62]. In another randomized, placebo-controlled study, fulvestrant admini-stered at the dose of 250 mg, was compared to tamoxifen as first-line treatment of metastatic breast cancer [63]. Ful-vestrant had a similar efficacy with tamoxifen in the sub-group of patients with hormone receptor-positive tumors, although the study was not designed to show non-inferiority. In fact, disease control rate was higher with tamoxifen than with fulvestrant. This difference in early activity was explained by the fact that, when administered at the conventional monthly schedule and dose, it takes 3-6 months for fulvestrant to reach its steady state concentration [64]. This finding provided the rationale to refine the dose and schedule of administration in order to achieve the drug's steady-state concentration sooner. This goal was achieved by doubling the first dose of fulvestrant to 500 mg and led to a steady state in just a few weeks, rather than months [65]. This schedule of administration (500 mg on day 0; 250 mg on days 14 and 28; followed by 250 mg monthly) was compared to exemestane in the Evaluation of Faslodex versus Exe-mestane Clinical Trial (EFECT) [66]. The control arm of this study was selected to reflect the common practice of using exemestane after a non-steroidal AI failure. This strategy was based only on nonrandomized trials or case series, suggesting non-cross-resistance between the two molecular classes of AIs [67, 68]. However, despite the loading dose, fulvestrant and exemestane showed similar clinical activity in this patient population.

Increasing the dose to 500 mg per administration by two intramuscular injections was the next step in the optimiza-tion of fulvestrant treatment. When compared to the classical monthly schedule of 250 mg per injection, 500 mg resulted in progression-free survival (PFS) prolongation with compa-rable tolerability [69]. Finally, fulvestrant 500 mg was com-pared with anastrozole as first-line treatment of hormone-sensitive metastatic breast cancer in the Fulvestrant First-Line Study (FIRST) [70]. Although best overall response and clinical benefit rates were similar between the two groups, fulvestrant resulted in a 34% reduction in the risk of progression [median PFS 23.4 months versus 13.1 months; Hazard Ratio (HR) = 0.66; 95% Confidence Interval (CI): 0.47-0.92; p = 0.01]. Based on these observations, fulvestrant administered at a dose of 500 mg is approved for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. The aforementioned trials of fulvestrant are summarized in Table 5.

STRATEGIES TO OVERCOME ENDOCRINE RESISTANCE

Although endocrine therapy is the mainstay of treatment for

a substantial proportion of metastatic breast cancer patients, the vast majority of them will eventually develop resistance. This clinical problem has been the focus of extensive preclinical research in an effort to understand both primary and acquired resistance, and to develop strategies to overcome them [71]. Much of this valuable preclinical research has been generated in hormone receptor-positive breast cancer cell lines and showed that, not only the ER is persistently expressed in most endocrine resistance models, but it also becomes instrumental to resistance and can still be stimulated by its physiological ligand [71]. The ER is, in fact, part of an adaptive network that enables cancer cells to escape simple manipulations like those represented by the currently available endocrine therapies. For example, molecular cross-talk between the ER and tyrosine kinase receptors belonging to the family of the epidermal growth factor receptor (EGFR), in particular, the specific member, HER2, has been invoked as a mediator of resistance to endocrine therapy [72]. Another interaction that seems to be crucial in mediating resistance to endocrine therapy involves the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, a ubiquitous signal transduction pathway also interconnected with other tyrosine kinase receptors, including, but not limited to EGFR family [71, 73-74]. These observations have provided the rationale for designing clinical trials evaluating combinations of endocrine agents with drugs targeting other interconnected pathways.

Combination of endocrine agents and HER2 targeted therapies

The HER2 oncogene is amplified and/or overexpressed in 15-20% of human breast cancers. HER2 is well characterized, both as a prognostic factor and as a predictive factor of biological therapy [75]. About half of HER2-positive tumors also co-express the hormone receptor. Given that HER2 positivity is associated with resistance to both tamoxifen and AIs, the combination of endocrine therapy and anti-HER2 agents has a strong therapeutic rationale [71]. This rationale has been tested in three randomized trials that have been fully published [76-78]. The combination of anastrozole and trastuzumab was compared with anastrozole monotherapy, as first-line treatment for patients with HER2- and hormone receptor-positive advanced breast cancer in the 'Trastuzumab and Anastrozole Directed against ER-Positive HER2-Positive Mammary Carcinoma' (TanDEM) trial [76]. Patients who received the combination of trastuzumab and anastrozole experienced a doubling in median PFS (4.8 vs. 2.4 months; p = 0.016) and a significant increase in the overall response rate (20.3% vs. 6.8%; p = 0.018), compared to those who received anastrozole alone. Furthermore, these improvements were achieved at the cost of a modest increase in some side-effects like fatigue, diarrhea, vomiting, arthralgia and pyrexia, which were mostly of grade 1 and 2 in severity. No difference in median overall survival was noted but it is noteworthy that 70% of the patients in the

anastrozole arm who experienced progressive disease subsequently received a trastuzumab-containing regimen. The same design, but with a different AI, was studied in the 'Efficacy and Safety of Letrozole Combined with Trastuzumab in Patients with Metastatic Breast Cancer' (eLEcTRA) study [77]. Similarly to the TanDEM findings, the addition of trastuzumab to letrozole was associated with improved PFS and clinical benefit rate but the results did not reach statistical significance since the trial closed prematurely due to slow accrual. Finally, the combination of letrozole and lapatinib, a dual HER1/HER2 tyrosine kinase inhibitor, as compared with letrozole monotherapy, resulted in a doubling of the response rate and time-to-progression, in the 'EGF30008' trial. This large, double blind, randomized trial conducted in 1286 women with hormone receptor-positive breast cancer who were not selected on the basis of HER2 status [77, 78]. As expected, patients with centrally confirmed HER2-negative tumors (n = 952) had no improvement in PFS. However, the addition of lapatinib to letrozole was accompanied by an increase in those side-effects that are commonly associated with the dual tyrosine kinase inhibitor. Although, overall, grade 3 and 4 events were rare in both arms, diarrhea, cutaneous rash, nausea, vomiting, hot flushes, pruritus and alopecia were significantly more common in the lapatinib arm.

In these three trials, women treated with endocrine therapy alone experienced response rates 7-15% and median time-to-progression 2.4-3.3 months, supporting the relative resistance to hormonal treatment of HER2-positive breast cancers. These results demonstrated that combined targeted strategy may overcome the HER2-associated endocrine resistance, and represents a reasonable therapeutic option for patients with hormone receptor- and HER2-positive disease.

Combination of endocrine agents and EGFR targeted therapies

Similarly to what has been described for HER2, the overexpression of EGFR has been associated with resistance to endocrine therapies [72]. Inhibition of EGFR activity may overcome endocrine resistance as suggested by preclinical models [72]. Unlike HER2, the EGFR is a much more elusive target in breast cancer, since its overexpression is restricted to 'basal-like' tumors, which do not express hormone receptors, or HER2 [80]. The data of both EGFR inhibition and endocrine therapy in metastatic breast cancer patients is limited, with the majority of the studies not preselecting patients on the basis of EGFR status. Instead, investigators have attempted to stratify the patients by clinical characteristics that could suggest endocrine sensitivity or endocrine resistance. We have already reported that the addition of the dual EGFR and HER2 inhibitor lapatinib to letrozole did not offer any PFS benefit in HER2-negative patients in the 'EGF30008' trial [79]. Interestingly, 'tamoxifen-resistant' patients (who relapsed or progressed during, or within 6

Table 6.

Randomized studies of everolimus in postmenopausal women with hormone receptor-positive breast cancer.

Treatment	Patients (N)	ORR (%)	PFS (months)	OS (months)	Ref
Everolimus + Letrozole	132	68.1*	NR	NR	90
Letrozole + Placebo (neoadjuvant study)	138	59.1	NR	NR	
Everolimus + Tamoxifen	54	61*^	8.6*	31*	91
Tamoxifen	57	42	4.5	16	
Everolimus + Exemestane	485	9.5*	11*	NR	92
Exemestane (refractory to anastrozole/letrozole)	239	0.4	4.1	NR	

ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; NR: not reported

*Statistically significant difference; ^ Clinical benefit rate

months from, the completion of adjuvant tamoxifen treatment) experienced a trend towards a meaningful improvement in PFS by the addition of lapatinib. In particular, the magnitude of benefit was in the same range with that observed in HER2-positive patients.

Gefitinib, a pure EGFR tyrosine kinase inhibitor, was added to tamoxifen in patients with hormone receptor-positive advanced breast cancer in the context of a phase II randomized trial [80]. Patients were stratified according to clinical criteria of endocrine responsiveness or resistance. In women with newly-diagnosed metastases or those who had recurred at least one year after the completion of adjuvant tamoxifen, gefitinib in addition to tamoxifen resulted in median PFS improvement (10.9 versus 8.8 months; HR = 0.84; 95% CI, 0.59-1.18) that met the protocol's criteria to warrant further investigation of this strategy. To the contrary, the group of patients defined as being resistant to AIs, derived no benefit from the addition of gefitinib to tamoxifen.

A third randomized trial studied anastrozole with or without gefitinib in patients defined as tamoxifen-resistant [82]. A marked advantage in median PFS in patients treated with the combination compared with those treated with anastrozole and placebo (14.7 versus 8.4 months; HR = 0.55; 95% CI, 0.32-0.94] was found. The authors concluded that endocrine therapy resistance might be delayed by the inhibition of growth factor signaling. The clinical impact of this study is unfortunately limited by the fact that enrollment was prematurely discontinued because of slow accrual. The enrichment of the study population with patients sharing EGFR activation as a mechanism of adaptation to tamoxifen inhibition may explain the observed benefit of EGFR targeting. Interestingly, in one neoadjuvant study conducted in patients who had been preselected on the basis of EGFR overexpression, gefitinib alone or in combination with anastrozole showed inhibition of tumor-cell proliferation as measured by the Ki67 antigen labeling index [83].

Combination of different endocrine agents

Several models of endocrine resistance are characterized by a fully functional estrogen receptor with the ability to circumvent tamoxifen inhibition or long-term estrogen deprivation. The combination of fulvestrant and an aromatase inhibitor, compared with either agent alone, delays the development of resistance by down-regulation of several signaling molecules involved in the development of resistance [84, 85]. There are three randomized trials exploring the combination of fulvestrant with an aromatase inhibitor that showed overall an unclear benefit for the combination. The addition of anastrozole to fulvestrant versus anastrozole alone was studied in the FACT trial [86]. Both postmenopausal and premenopausal women receiving a gonadotropin-releasing hormone agonist (GnRH) were eligible for this study. Patients had to be sensitive to AIs, defined as either no prior exposure, or relapse occurring at least 1 year after the completion of adjuvant endocrine therapy. There was no difference between the two arms with regards to time-to-progression that was the primary study endpoint, as well as clinical benefit rate and overall survival.

The same question, whether the combination of anastrozole and fulvestrant would be superior to anastrozole alone as first-line therapy, was evaluated in the SWOG S226 trial [87]. The design included stratification by prior tamoxifen exposure. Overall, the study was positive in terms of its primary endpoint, with a small, but statistically significant 1.5-month increase in median progression-free survival (15 vs. 13,5 months; HR = 0.8; 95% CI: 0.68-0.94).

In the third study, patients with resistant disease to non-steroidal AIs were randomized to fulvestrant plus anastrozole, fulvestrant plus placebo or exemestane [88]. Similarly to the previous studies, the combination of fulvestrant and anastrozole fared equally to the other arms in terms of PFS that was the primary end point as well as, response rate, clinical benefit rate and overall survival.

We sould underline that, in all these studies, fulvestrant was administered at a monthly dose of 250mg, which has been shown to be inferior to the currently accepted high-dose regimen of the CONFIRM trial. Whether the combination of high-dose fulvestrant (500 mg per month) in combination with anastrozole is superior to anastrozole alone should be addressed in future trials.

Combination with mTOR inhibitors

Alterations of the PI3K/Akt/mTOR signaling pathway are common in hormone receptor-positive breast cancer, and have been associated with resistance to endocrine therapy [74, 89]. The mTOR inhibitors have been shown to be clinically effective and well-tolerated in various cancers [89]. Everolimus, a rapamycin derivative inhibitor of the mTOR pathway, was evaluated in a randomized phase II study. Postmenopausal women with operable, hormone receptor-positive, HER2-negative breast cancer were randomized to neoadjuvant letrozole (2.5 mg/day) plus everolimus (10 mg/day) or letrozole plus placebo for 4 months before surgery [90]. The study required tumor biopsies both at baseline and after 15 days of treatment for evaluation of PI3K mutations, Ki67, phospho-S6 (a downstream target of mTOR), Cyclin D1 and the PgR. The addition of everolimus to letrozole was associated with an increased objective response rate, a higher rate of Ki67 response, together with down-regulation of phospho-S6, Cyclin D1 and PgR.

Two studies evaluated the addition of everolimus to endocrine therapy in the metastatic setting [91, 92]. In the Tamoxifen plus Everolimus (TAMRAD) trial, 111 postmenopausal women with hormone receptor-positive, HER2-negtive advanced breast cancer who had been previously exposed to an AI, were randomized to receive tamoxifen with or without everolimus [91]. Everolimus significantly prolonged both PFS and overall survival (OS) in the overall patient population. Trial design included stratification according to type of resistance to previous treatment with AIs. Disease recurrence within 6 months from the completion of adjuvant therapy with an AI, or progression within 6 months from the initiation of an AI to treat metastatic disease was defined as primary resistance. All the other patients were defined as having secondary endocrine resistance. Everolimus was highly beneficial in women with secondary endocrine-resistant tumors while no effect was seen in patients with primary endocrine-resistant tumors.

Finally, and most importantly, everolimus in combination with exemestane was evaluated in the randomized BOLERO-2 study [92]. Seven-hundred twenty four postmenopausal women, who had recurrence or progression while receiving therapy with a non-steroidal AI (adjuvant or metastatic setting), were randomized in a 2:1 ratio to exemestane plus everolimus or exemestane plus placebo. About 60% of patients in both arms had also previously received an anti-estrogen (tamoxifen or fulvestrant). Everolimus led to a statistically significant increase in progression-free survival, which was the primary study end point, along with a significant increase of response rate (10.6 vs. 4.1 months; HR = 0.36, 95% CI; 0.27-0.47, p < 0.001 and 9.5% vs. 0.4 p < 0.001, respectively). A more recent update of BOLERO-2 results also showed a trend towards a numerical reduction in deaths in the combination arm (25.4% in the everolimus vs. 32.2% in the placebo arm), although analysis of survival was not mature enough to reach final conclusions on the survival end point [93].

In all three cited studies, the addition of everolimus was associated with a modest increase in toxicity. Fatigue, stomatitis, rash, anorexia and diarrhea were, in fact, more frequent in the combination arms. In the BOLERO-2 trial, for example, the rate of serious adverse events in the combination arm was almost twice than in the placebo arm (23% vs. 11%). Furthermore, more patients discontinued everolimus in the combination arm due to adverse events (19% vs. 4%), or consented withdrawal (5% vs. 2%). Similarly, a higher percentage of patients also discontinued exemestane in the combination arm than in the control arm. Beyond these potentially serious adverse events, the addition of everolimus to exemestane in the BOLERO-2 trial was associated with an increase in the incidence of those side-effects that can also be associated with exemestane alone, like stomatitis, diarrhea and appetite loss. Although mostly grade 1 and 2 in severity, these toxicities are likely to have an impact on treatment feasibility in some patients in the clinical practice.

CONCLUSIONS AND FUTURE PERSPECTIVES

Adjuvant endocrine treatment is an essential component of treatment for patients with hormone receptor–positive early breast cancer. For postmenopausal women with early disease, tamoxifen, AIs, or a sequence of these agents are the available options. It seems that incorporating an AI at some point improves outcome compared with tamoxifen alone. Tamoxifen and AIs have distinct side-effect profiles that clinicians should take into account. Among premenopausal women, tamoxifen remains the standard treatment. The role of ovarian suppression in addition to tamoxifen is still under investigation. Indirect data suggests that there may be a role for ovarian suppression, but this is not yet a standard treatment option. Questions about the duration of adjuvant endocrine therapy, the use of biomarkers for treatment selection and prognosis, and the management of side-effects of adjuvant endocrine therapy remain key areas of ongoing investigation.

In the metastatic setting, postmenopausal women can derive disease control via different lines of endocrine therapy. Either an aromatase inhibitor or fulvestrant can be considered as optimal first-line treatments. For patients who experience disease progression during treatment with one of these compounds, switching to the other (i.e., failure with AI, switch to fulvestrant or vice versa) or, for patients starting with an AI, a switch to an AI of a different molecular class

(i.e., failure with letrozole, switch to exemestane) are reasonable treatment strategies. A third possibility could be tamoxifen in those patients who had never been exposed to this compound, or that fulfill the criteria for potential tamoxifen sensitivity or progestins.

The issue of clinical resistance to endocrine therapy is a key motivator of clinical research in this setting. We believe that the two most promising strategies are the combination of endocrine agents with HER2-targeting agents in hormone receptor-positive/HER2-positive tumors, and interference with the PI3K/Akt/mTOR axis. Regarding mTOR inhibition in particular, the BOLERO-2 data is practice-changing, and likely to open an exciting new field of research. One common problem with these strategies is that improvements in outcome are accompanied by an increase in toxicity. Efforts should be concentrated on defining predictive markers of efficacy and toxicity for the different therapeutic strategies, rather than defining eligibility based on clinical surrogates of endocrine resistance or sensitivity. In the era of personalized medicine, both the cost-effectiveness and the toxicity to benefit ratio have to be optimized by better patients' selection for each therapeutic strategy.

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Detection of *EGFR* and *KRAS* mutations in NSCLC patients of Greek origin in daily clinical practice

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ABSTRACT

Background: Owing to novel therapeutic strategies in patients with epidermal growth factor receptor *(EGFR)* mutations, molecular analysis of the *EGFR* gene has become crucial for routine diagnostics. Moreover *KRAS* mutation status is considered in clinical trials designs. The aim of this study was to evaluate the frequency of *EGFR* and *KRAS* mutations in a population of Greek patients with non-small-cell lung cancer (NSCLC).

Patients & Methods: A total of 639 specimens (tissue or cytological material of primary and metastatic lung carcinomas) from Greek advanced NSCLC patients were analyzed for *EGFR* (exons 18-21) and *KRAS* (exon 2) somatic mutations by Sanger sequencing, and their associations with clinicopathological characteristics (including gender, smoking habit, histological subtype and tumor location) were examined.

Results: The incidence of patients with *EGFR* and *KRAS* mutations was 15.7% and 20.8%, respectively. Classical *EGFR* mutations were observed in 51 (8%) patients including 31 women whereas "other" *EGFR* variants were detected in 49 (7.7%) patients, including 8 women. Three point mutations have not previously been described, while 9 patients harbored compound *EGFR* mutations. Despite the conventional understanding of mutual exclusivity of *EGFR* and *KRAS* mutations, we identified ten dual mutations, including 9 with "other" *EGFR* variants. Classical *EGFR* mutations were more frequently observed in females (p < 0.001), non-smokers (p < 0.001) and adenocarcinomas (p = 0.007). *KRAS* mutations (20.8%) were more frequent in adenocarcinomas (p = 0.008) and were associated with smoking habits (p = 0.005).

Conclusions: The incidence of *EGFR* and *KRAS* mutations is similar in our cohort compared with the one reported for European cancer patients and are present in both men and women as well as in smokers and never-smokers.

Key words: *EGFR*, *KRAS*, Mutations, NSCLC, Greek patients.

INTRODUCTION

Lung cancer is the main cause of cancer-related death worldwide, with over one million deaths per year [1]. Non-small-cell lung cancer (NSCLC) accounts for about 80% of lung cancer cases and can be further divided into three major subclasses: adenocarcinoma (ADC); squamous cell carcinoma (SCC) and large-cell carcinoma (LCC). In Greece, lung cancer ranked first in males and third in females, with an incidence of 26.3% and 7%, respectively [2]. Despite advances in molecular pathology and improvement in screening programs, patient prognosis remains poor. Most patients with NSCLC are diagnosed in the advanced or metastatic stage with a median survival of about 4-5 months while the 1-year survival rate is less than 10%, if left untreated [3].

Epidermal growth factor receptor *(EGFR)* is critically involved in NSCLC pathogenesis and has recently emerged as an important target for molecular therapeutics. Previous studies have shown that activating mutations in the tyrosine kinase domain of the *EGFR* are significantly associated with sensitivity to tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib [4-6]. Several clinicopathological factors have been identified as related to *EGFR* mutations, including adenocarcinoma histology, female gender, non-smoking status, and

East Asian ethnicity [5, 6]. However, the frequency of *EGFR* mutations varies from 27 to 60% in Asians, 8 to 13% in Europeans and 12 to 16% in African and White Americans [7, 8].

Approximately 90% of the *EGFR* mutations involved in-frame deletions in exon 19 and a missense mutation resulting in the substitution of leucine 858 for arginine (p.L858R) in exon 21 [6]; these mutations are associated with *EGFR* TKI-mediated clinical responses and are characterized as "classical" activating mutations [9-12]. However, in tumor specimens "other" *EGFR* variants were also described, the clinical significance of which is still poorly understood [13]. Moreover, there were cases of complex mutation patterns, whereby two or more concurrent *EGFR* mutations were identified within a single tumor specimen [11, 14, 15].

Patients harboring *KRAS* activating mutations do not respond to treatment with TKIs [16-18]. *KRAS* mutations are found in 15 to 25% of NSCLC and approximately 97% of them occur in codons 12 and 13 [19, 20]. In Caucasians, 20 to 30% of lung adenocarcinomas have *KRAS* mutations as compared to 5 to 20% of lung adenocarcinomas in Asians [21]. Interestingly, somatic *EGFR* and *KRAS* mutations are almost always mutually exclusive [22].

The purpose of this study was to evaluate the incidence of *EGFR* and *KRAS* mutations in a cohort of Greek patients with NSCLC and to assess the association between these mutations and clinicopathological characteristics.

PATIENTS AND METHODS

Patients

The study population consisted of Greek patients with histologically confirmed NSCLC (stage IIIa-IV), who were being considered for TKI treatment and underwent EGFR testing in the context of routine daily practice. Cytological or histological specimens of patients were consecutively collected at the Laboratory of Cancer Cell Biology, Medical School of University of Crete, from 2005 to 2011. The samples were assessed by pathologists (A.K., L.G and E.L.) prior to testing. A total of 639 patients were recruited for this study.

Patient smoking history was obtained at baseline, and patients were categorized as having never smoked (<100 lifetime cigarettes); former smokers (≥1 year since cessation); or current smokers (still smoking, or <1 year since cessation).

All patients gave their informed consent for testing, and the protocol was approved by the local Institutional Review Board.

DNA extraction and mutation analysis

The majority of tumor samples were formalin-fixed paraffin-embedded tissues (FFPE). Representative sections were stained with hematoxylin-eosin and the neoplastic cell content was verified by an experienced pathologist (A.K.). Subsequently, tissue samples from at least 3 serial sections were microdissected (Eppendorf Piezo-Power Microdissector, Germany) to ensure that specimens contained at least 80% neoplastic cells. In some cases, the only available material for mutational analysis was the cytology specimen. Genomic DNA was extracted using the QIAamp DNA FFPE Tissue Kit (QIAGEN GmbH, Munich, Germany) according to the manufacturer's instructions. Exons 18, 19, 20 and 21 of *EGFR* and exon 2 of *KRAS* were sequentially amplified by two rounds of polymerase chain reaction (PCR) and subjected to direct sequencing as previously described [23]. Description of genetic sequence variants of *EGFR* and *KRAS* was performed based on GenBank Accession Numbers NM_005228.3 and NM_004985.3, respectively, according to the standard nomenclature recommendations of the HGVS (http://www.HGVS.org/mutnomen/). All test results were manually reviewed by two molecular scientists (A.V. and A.K.). All sequence variations were confirmed by sequencing in both directions and by an independent PCR amplification when sufficient material was available.

Statistical Analysis

Descriptive analysis was performed to provide a profile of the patient population. Variables were summarized by arithmetic means and standard deviation, whereas group categories were expressed in percentages. Differences in mutation rates between groups were examined using the χ^2 test, with statistical significance determined as $p < 0.05$. Logistic regression was performed to determine patient characteristics (sex, age, histology and smoking status) that predict the presence of *EGFR* and *KRAS* mutation. Data analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics

Six hundred thirty-nine patients of Greek origin and documented NSCLC were referred for evaluation to our laboratory in order to be screened for *EGFR* and *KRAS* mutations for therapeutic purposes. Patient clinical and pathological characteristics are shown in Table 1. There were 463 men (72.5%) and 176 women (27.5%), with a median age of 62 years (range 33 to 89 years); specimens were represented by 532 (83.3%) primary tumors and 107 (16.7%) biopsies obtained from metastatic lesions. Cytology material for the molecular analysis was used in 33 (5.2%) patients. The majority of patients had adenocarcinoma (65.6%) and 53.1% of them were smokers.

Types and Frequencies of *EGFR* and *KRAS* Mutations

EGFR mutation analysis was successfully performed in 634 patients. A total of 109 *EGFR* mutations were detected in 100 patients (Table 2). All mutations were distributed in exons 18-21 of the *EGFR* and involve 21 (19.2%) point mutations in exon 18; 49 (44.9%) deletions or point mutations in exon 19;

8 (7.3%) point mutations in exon 20; and 31 (28.4%) in exon 21. The most common mutation types were in-frame deletions around codons 746-750. (del 19; n = 38; 34.8%) and the substitution of leucine for arginine on codon 858 (p.L858R; n =12; 11%) which, along with the less prevalent p.G719D, constitute the "classical" *EGFR* activating mutations associated with benefit to *EGFR* TKIs. Classical *EGFR* mutations were observed in 51 (8%) patients while 43 "other" *EGFR* variants of unknown clinical impact were detected in 49 (7.7%) patients. Nine (9%) patients harbored compound *EGFR* mutations; in three of them, the p.L858R was detected with another variant of unknown significance (Table 3). Classical and "other" *EGFR* variants were found in 9% and 8% of surgical specimens; in 6% and 7% of biopsies; and in 15% and 6% of cytological specimens, respectively. Twenty five (49%) of the classical and 23 (47%) of the "other" variants were detected in surgical specimens. Four (8%) classical and 6 (14%) "other" *EGFR* variants (p.A698T, p.G733S, p.L798P, p.L838P, p.D837N, p.K860G) were detected in metastases. Three (7%) "other" variants (p.E762V, p.C781P, p.M793V) have not been previously reported in clinical specimens.

There was available material for *KRAS* mutational analysis only in 399 cases. Overall, *KRAS* mutations on codons 12 and 13 were identified in 83 (20.8%) patients; seventy-nine (95%) mutations were found on codon 12 and only four (5%) on codon 13. The most common *KRAS* amino acid substitutions observed on codon 12 was p.G12D (c.35G>A) in 26 cases (31.3%), p.G12V (c.35G>T) in 20 cases (24.1%) and p.G12C (c.34G>T) in 14 cases (16.8%).

Co-occurrence of *EGFR* and *KRAS* mutations

EGFR and *KRAS* mutation status was determined in 395 patients. Ten patients (2.5 %) harbored combined *EGFR* and *KRAS* mutations; the majority of them were males, smokers with adenocarcinoma histology. One male patient harbored an in-frame deletion in exon 19 of *EGFR* combined with the *KRAS* p.G12C mutation; the remaining patients harbored "other" (non-classical) *EGFR* variants combined with *KRAS* mutations (four with p.G12D, two with p.G13C, one with p.G12V, one with p.G12A and one with p.G12S).

Association of *EGFR* and *KRAS* mutations with clinicopathological variables

Patient clinicopathological characteristics and their association with *EGFR* or *KRAS* mutations are shown in Table 4. Classical *EGFR* mutations were detected more frequently in adenocarcinomas (10.3% versus 3.4%, p = 0.007) and primary tumors (9% versus 4%, p = 0.06) whereas the incidence of "other" *EGFR* variants is similar in adeno-carcinomas and non-adenocarcinomas (7.4% versus 8.7%, p = 0.77), primary tumors and metastases (8% versus 5.6%, p = 0.31). Additionally, classical *EGFR* mutations were detected more frequently in females (p < 0.001), never smokers (p <

Table 1.
Patient clinicopathological characteristics.

Characteristics	Patients (n = 639)	
	No.	%
Median age (years)	62	
Range	33 - 89	
Gender		
Male	463	72.5
Female	176	27.5
Histological type		
Adenocarcinoma	419	65.6
Squamous Cell Carcinoma	103	9.8
Mixed	26	4.1
Large Cell Carcinoma	31	4.9
Undifferentiated	14	2.2
No data	46	7.2
Smoking status		
Current smoker	211	33.0
Former smoker	72	11.2
Never smoker	114	17.8
No data	242	37.9
Type of specimen		
FFPE histologic specimens	606	94.8
Surgical samples	277	43.3
Biopsies	329	51.5
Cytological specimens	33	5.2
Sample origin		
Primary tumor	532	83.3
Metastasis	107	16.7

FFPE, formalin-fixed paraffin-embedded

0.001), while "other" *EGFR* variants were found more often in males (p = 0.16) with smoking history (p = 0.62) (Table 4).

KRAS mutations were detected more frequently in males (p = 0.64) with smoking history (p = 0.005) and adenocarcinoma histology (p = 0.008; Table 4). Notably, *KRAS* mutations were found more frequently in metastases than in primary tumors with a statistically significant difference (32.6% versus 19%, p = 0.02; Table 4).

DISCUSSION

In the present study we report the incidence of *EGFR* and *KRAS* mutations in patients of Greek origin with NSCLC who were tested in the context of daily clinical practice for

Table 2.
"Other" *EGFR* variants detected in advanced NSCLC patients.

Exon	Nucleotide substitution	Amino acid substitution	Incidence	Remarks
18	c.2071C>T	p.P691S‡	1	Reported [11]
	c.2075T>C	p.L692P	4	Reported [23]
	c.2092G>A	p.A698T‡	1	Reported [49]
	c.2104G>A	p.A702T	1	Reported A702S [50]
	c.2107C>T / 2108T>C	p.L703F‡/P	2	Reported [11, 50]
	c.2125G>A	p.E709K	1	Reported [51]
	c.2129C>A	p.T710N	1	Reported T710A [52]
	c.2131G>A	p.E711K	1	Reported [11]
	c.2171 G>C	p.G724D‡	4	Reported [53]
	c.2176G>A	p.V726M	1	Reported [11]
	c.2179T>C	p.Y727H‡	3	Reported [54]
19	c.2185G>A	p.G729R	1	Reported [11]
	c.2197C>T	p.P733S	1	Reported [55]
	c.2203G>A	p.G735W‡	1	Reported G735S [56]
	c.2221C>T	p.P741S	1	Reported P741L [57]
	c.2228C>T	p.A743V‡	2	ReportedA743T [58]
	c.2237A>T	p.E746V	1	Reported [11, 59]
	c.2240T>C	p.L747S	1	Reported [60]
	c.2247A>C	p.E749D	1	Reported E749G [49]
	c.2251A>G	p.T751A	1	reported T751I [56]
	c.2263G>A	p.A755T‡	1	Reported A755D [61]
20	**c.2285 A>T**	**p.E762V**	1	--
	c.2315C>T	p.P772L	1	Reported P772H [62]
	c.2341T>G	**p.C781P**	1	--
	c.2377A>G	**p.M793V**	1	--
	c.2390T>A	p.C797R	1	Reported C797Y [32]
	c.2392T>C	p.L798P	1	Reported L798F [56]
	c.2404G>A	p.V802I	1	Reported [63]
	c.2417A>G	p.K806R	1	Reported K806E [14]
	c.2434C>T	p.Q812stop	1	Reported Q812R [64]
21	c.2513T>C	p.L838P	1	Reported [14]
	c.2509G>A	p.D837N	1	Reported D837G [49]
	c.2516C>A	p.A839E	1	Reported A839V [65]
	c.2527G>A	p.V843I	2	Reported [66]
	c.2539A>G	p.T847A	1	Reported T847I [56]
	c.2566T>C	p.F856S	1	Reported [67]
	c.2570G>A	p.G857E	1	Reported [11]
	c.2575G>A	p.A859R	1	Reported A859T [51]
	c.2578A>G	p.K860G	1	Reported K860I [36]
	c.2582T>C	p.L861P/Q	2	Reported [4]
	c.2587G>A	p.G863S‡	4	Reported [68]
	c.2611G>A	p.A871T	1	Reported A871G [66, 69]
	c.2620G>A	p.G874S	1	Reported [11, 67]

Mutations in bold are not previously described. ‡Coexistence with KRAS mutation

Table 3.
Summary of patients harboring two *EGFR* mutations.

Case	Age	Gender	Histology	Smoking status	Mutation	Exon
1	60	M	LCC	Active	p.L861P, p.L858R	21
2	52	F	MIXED	Active	p.Val843I, p.L858R	21
3	43	F	UN	Prior	p.E709K, p.L858R	18, 21
4	77	M	ADC	Never	p.C797R, p.A871T	20, 21
5	61	M	ADC	Active	p.T847A, p.G863S	21
6	61	M	SCC	Never	p.Q812stop, p.V843I	21
7	77	M	SCC	Active	p.L692P, p.F856S	18, 21
8	64	M	ADC	Active	p.L703F, p.G863S‡	18, 21
9	76	M	MIXED	Prior	p.G724D, p.A743V‡	18, 19

LCC; large cell carcinoma, MIXED; adenosquamous, ADC; adenocarcinoma, SCC; squamous cell carcinoma, UN; unknown histology; ‡ Coexistence with KRAS mutation

therapeutic decision making. The incidence of *EGFR* mutations (15.7%) observed in this patient population was higher than that described for Europeans (8-13%) and close to the rate observed in Americans (10-16%). However, the incidence of "classical" *EGFR* mutations (8%) was practically similar to the frequency observed in Europeans (8-13%).

The most frequently detected *EGFR* mutations were in-frame deletions around codons 746-750 (34.8%) followed by a L858R substitution in exon 21 (11%); these findings are in agreement with data previously reported by others investigators [5, 24-27]. Additionally, 43 "other" *EGFR* variants of unknown clinical impact were detected in 49 (7.7%) patients; all of these variants have been described before [11, 28-30], except for the p.E762V, p.C781P and p.M793V mutations.

Previous studies suggested that patients harboring classical *EGFR* mutations had the greatest benefit from *EGFR* TKIs therapy. Distinguishing novel *EGFR* mutations that are clinically relevant from those that are functionally silent or artifacts is clearly important, particularly as diverse responses to *EGFR* TKI therapy have been recently reported in patients with tumors harboring "other" *EGFR* mutations [11, 31-35]. The creation of a database containing outcomes of patients harboring these "other" *EGFR* variants will be helpful in understanding possible clinical significance.

The incidence of double mutations in our study was 8.1%; this is in agreement with a study reported that double mutations accounted for 6% of *EGFR* mutations, with approximately half of these occurring in five amino acids (E709, G719, S768, T790 and L861) [36].

The finding that classical *EGFR* mutations were more prevalent (10.3%) in Greek NSCLC patients with adenocarcinomas than in those with other histological subtypes is in agreement with other studies [27, 37, 38]. Since in advanced NSCLC diagnosis is mainly made through a biopsy or cytology, where histology determination is not accurate, all NSCLCs and not only adenocarcinomas should be tested for *EGFR* mutations.

Previous studies have shown that a never-smoking status was associated with higher rates of *EGFR* mutations [7, 27, 38]. Greek and other ethnicities display similar *EGFR* mutation rates regarding gender and smoking status [37, 39, 40]. An earlier study in Greek patients with operable stage I-IIIa NSCLC reported that *EGFR* mutations were more common in women and never smokers but these differences did not reach statistical significance, due to small patient numbers.

In this study, we investigated mutations in 106 and 528 specimens obtained from metastatic sites and primary tumors, respectively; classical *EGFR* mutations were detected in 4% of metastases and 9% of primary tumors. The lower rate of *EGFR* mutations in metastases is consistent with the findings of previous studies demonstrating a significant discordance of *EGFR* mutation status between primary tumors and metastases [23, 41, 42]. Accordingly, *EGFR* mutations should be tested, if feasible, in both primary tumors and metastases.

The incidence of *KRAS* mutations (20.8%) in our study is higher than the 2-9% reported for East Asia [43]; whereas it is similar to the 20-30% reported for Caucasians [44]. Indeed, a meta-analysis of 22 studies, including Asian and White populations, by Mao et al. reported that *KRAS* mutations were detected in 231 of the 1470 analyzed patients (16%) [45]. Concerning the association of *KRAS* mutations with different clinicopathological variables, it was observed that smokers and adenocarcinoma histology have a higher incidence of *KRAS* mutations than never-smokers and non-adenocarcinoma histology. Although this finding is consistent with other studies in different ethnicity populations [38, 40], we were unable to detect any significant differences concerning

Table 4.

Incidence of *EGFR* and *KRAS* mutations according to patients' clinicopathological characteristics.

| | Mutation status | | | | |
| | EGFR | | | KRAS | |
Characteristics	Classic mutations (%)	"Other" variants (%)	Wild type (%)	Mutations (%)	Wild type (%)
Gender					
Male	20 (39)	41 (84)	399 (75)	62 (75)	228 (72)
Female	31 (61)	8 (16)	135 (25)	21 (25)	88 (28)
p-value	<0.001[a]	0.16[a]		0.64[a]	
Histology subtype					
Adenocarcinoma	43 (88)	31 (67)	343 (70)	65 (86)	214 (70)
Squamous cell carcinoma	2 (4)	9 (20)	91 (18)	5 (7)	50 (16)
Mixed	2 (4)	3 (7)	21 (4)	2 (3)	13 (4)
Large cell carcinoma	1 (2)	3 (7)	27 (6)	2 (3)	13 (4)
Undifferentiated	1 (2)	---	12 (2)	1 (1)	8 (3)
p-value	0.007a	0.77a		0.008a	
Smoking status					
Current smoker	9 (28)	24 (59)	177 (55)	43 (65)	113 (48)
Former smoker	4 (13)	5 (12)	63 (20)	13 (20)	46 (19)
Never smoker	19 (59)	12 (29)	83 (26)	10 (15)	78 (33)
p-value	<0.001[a]	0.62[a]		0.005[a]	
Type of specimen					
Surgical	25 (49)	23 (47)	227 (43)	41 (49)	161 (51)
Biopsy	21 (41)	24 (49)	281 (53)	38 (46)	143 (45)
Cytology	5 (10)	2 (4)	26 (4)	4 (5)	12 (4)
p-value	0.15[a]	0.81[a]		0.90[a]	
Sample origin					
Primary tumor	47 (92)	43 (88)	438 (82)	66 (80)	281 (89)
Metastasis	4 (8)	6 (12)	96 (18)	17 (20)	35 (11)
p-value	0.06[a]	0.31[a]		0.02[a]	

[a] *The p values (x^2 test) represent the comparisons of the incidence of EGFR or KRAS mutations between men and women; between adenocarcinoma and non-adenocarcinomas; between smokers (included former smokers) and never-smokers; and between FFPE histological and cytological specimens, respectively.*

the incidence of *KRAS* mutation according to patient gender. Simultaneous presence of *EGFR* and *KRAS* mutations in NSCLC patients is relatively rare and their appearance is believed to be mutually exclusive. In this study, we observed 10 patients with tumors harboring dual *EGFR* and *KRAS* mutations, of which only one patient harbored a classical *EGFR* mutation combined with a *KRAS* mutation. This rare association of a classical *EGFR* mutation and *KRAS* mutations has already been described [11, 23, 46, 47].

A limitation of the present study is the low sensitivity (15-20%) of sequencing with Sanger chemistry; specimens with low neoplastic cell content are at risk of reporting false-negative *EGFR* mutations. However, isolating a more pure population of neoplastic cells, by using microdissection, resulted in increased sensitivity as we were able to detect mutations from specimens with low neoplastic cell content. Nevertheless, when using FFPE DNA, identification of rare *EGFR* mutations may sometimes be due to PCR artifact [48].

Another limitation is the fact that mutational analyses were requested by the treating physician; this introduces a selection bias towards patients who would potentially benefit from treatment with TKIs. However, this corresponds to daily clinical practice and makes the data relevant.

In conclusion, the incidence of classical *EGFR* and *KRAS* mutations in a Greek cohort of patients with advanced NSCLC is similar to those previously reported in other European patients. In the current study "other" *EGFR* variants of unknown clinical significance were detected in smokers with non-adenocarcinoma histology. Functional and clinical studies are required in order to determine the clinical relevance of the "other" *EGFR* variants which will support individualized treatment according to the mutation type.

Conflict of interest statement: The authors declare no conflict of interest.

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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 συνδέονται με το ανοσοποιητικό και πιθανόν σχετίζονται με το μηχανισμό δράσης του. Ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό και 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 προσδιορίστει διαφορετική αιτιολογία, η διάρροια, η αυξημένη συχνότητα κενώσεων, το αίμα στα κόπρανα, οι αυξήσεις LFT, το εξάνθημα και η ενδοκρινοπάθεια πρέπει να θεωρούνται ως 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 (MDX010 20), 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 ωαστρεντερικά 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 αιματοχεζία, με ή χωρίς πυρετό. Διάρροια ή κολίτιδα που εμφανίζεται μετά από την έναρξη του YERVOY πρέπει να αξιολογείται έγκαιρα για τον αποκλεισμό λοιμώξεων ή άλλων εναλλακτικών αιτιολογιών. Σε κλινικές δοκιμές, η 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 βαρύτητας κατά NCICTCAE v3). Ασθενείς με ήπια έως μέτρια (Βαθμού 1 ή 2) διάρροια (αύξηση έως 6 κενώσεις την ημέρα) ή πιθανολογούμενη ήπια ή μέτρια κολίτιδα (π.χ. κοιλιακό άλγος ή αίμα στα κόπρανα), είναι πιθανό να παραμείνουν σε 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 Βαθμού 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 υψηλή δόση ενδοφλέβια θεραπεία με κορτικοστεροειδή. (Σε κλινικές δοκιμές έχει χρησιμοποιηθεί μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελεγχθεί 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 παράγοντος 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. Θανατηφόρα ηπατική ανεπάρκεια έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX010 20, ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 35) 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 ενδεικνύουν αναδυόμενη 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 αιτιών 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 (ουδετεροφιλία, 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 σχετίζονται με το YERVOY, πρέπει να παραλείπεται η προγραμματισμένη δόση του YERVOY και 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 ή ολική χολερυθρίνη > 5 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 ημερησίως ή ισοδύναμο). Σε αυτούς τους ασθενείς, πρέπει να παρακολουθείται οι LFT έως την υποχώρηση. 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 σε 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 σημαντική αύξηση των LFT που είναι ανθεκτικοί σε θεραπεία με κορτικοστεροειδή, είναι δυνατόν να εξεταστεί η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντος στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, χρησιμοποιήθηκε μυκοφαινολάτη μοφετίλη σε ασθενείς χωρίς αντανάκρισης σε θεραπεία με κορτικοστεροειδή ή που παρουσίασαν αύξηση των LFT κατά τη βαθμιαία μείωση και διακοπή κορτικοστεροειδούς που δεν αντανακρισινόταν 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). Θανατηφόρος φαρμακευτικό εξάνθημα με ηωσινοφιλία και συστηματικά συμπτώματα (DRESS) έχει επίσης αναφερθεί στο πλαίσιο χρήσης YERVOY. 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 MDX010 20, ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως πολύ 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 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 τοπική 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 ανεπιθύμητων αντιδράσεων, 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 υποχωρήσει 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 ή εξαναρχίσει το YERVOY 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) 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 τη διαχείριση αισθητικής νευροπάθειας και πρέπει να ξεκινήσουν αμέσως ενδοφλέβια θεραπεία με κορτικοστεροειδή (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Προοδευτικά σημάδια κινητικής νευροπάθειας 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). Ενδοκρινοπάθειες που συνδέονται 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 αποκλειστεί. Η κλινική εμπειρία με ενδοκρινοπάθεια σχετιζόμενη με το YERVOY είναι περιορισμένη. Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX010 20, 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 γενικά ελεγχόμενη με ανοσοκατασταλτική θεραπεία υποκατάστασης ορμονών. Εάν υπάρχουν οποιαδήποτε σημεία επινεφριδιακής κρίσης, όπως σοβαρή αφυδάτωση, υπόταση ή καταπληξία, συνιστάται άμεση χορήγηση ενδοφλέβιων κορτικοστεροειδών με αλατοκορτικοειδή δράση και ο ασθενής να 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 ενδοκρινικής λειτουργίας πρέπει να πραγματοποιείται πριν από την έναρξη θεραπείας με κορτικοστεροειδή. Εάν οι απεικονιστικοί έλεγχοι της υπόφυσης ή εργαστηριακοί έλεγχοι της ενδοκρινικής 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 προσβληθέντος αδένα και η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλείπεται (βλέπε παράγραφο 4.2). Αυτή τη στιγμή είναι άγνωστο εάν η θεραπεία με κορτικοστεροειδή αναστρέφει τη αδενική δυσλειτουργία. Θα πρέπει επίσης να ξεκινήσει κατάλληλη υποκατάσταση ορμονών. Είναι πιθανό να είναι απαραίτητη μακροπρόθεσμη θεραπεία υποκατάστασης ορμονών. Όταν τεθούν υπό έλεγχο τα συμπτώματα ή οι μη φυσιολογικοί εργαστηριακοί τιμές και είναι εμφανής η βελτίωση του ασθενούς ολικευθεί, 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 MDX010 20: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξημένη αμυλάση, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν πεπτιδίου εμβόλιο με YERVOY 3 mg/kg + gp100 στην MDX010 20 (βλέπε παράγραφο 4.8). Αν οι αντιδράσεις είναι σοβαρές (Βαθμού 3 ή 4) είναι πιθανό να απαιτηθεί άμεση θεραπεία με υψηλές δόσεις κορτικοστεροειδών και διακοπή του YERVOY (Βλέπε παράγραφο 4.2). Για ραγοειδίτιδα, ιρίτιδα ή επισκληρίτιδα που συνδέεται με το YERVOY, 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 αντιπυρετικά και αντισταμινικά. Ασθενείς με αυτοάνοσο νόσο: Ασθενείς με ιστορικό αυτοάνοσης νόσου (εκτός από λεύκη και επαρκώς ελεγχόμενη ανεπάρκεια ενδοκρινικής όπως υποθυρεοειδισμός), συμπεριλαμβανομένων αυτών για τους οποίους απαιτείται συστηματική ανοσοκατασταλτική για προϋπάρχουσα ενεργό αυτοάνοση νόσο ή για διατήρηση μοσχεύματος μετά από μεταμόσχευση οργάνων, 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 παρόξυνση 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 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 η,1 mmol (ή 2,30 mg) νατρίου. Αυτό πρέπει να λαμβάνεται υπόψη για ασθενείς 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 σε διάφορες δόσεις και τύπους όγκων. Εκτός εάν ορίζεται διαφορετικά, τα παρακάτω δεδομένα αποτυπώνουν την έκθεση σε YERVOY στα 3 mg/kg σε κλινικές δοκιμές μελανώματος. Στη μελέτη Φάσης 3 MDX010 20, (βλέπε παράγραφο 5.1), οι ασθενείς έλαβαν ένα διάμεσο 4 δόσεων (εύρος 14). Το YERVOY σχετίζεται πολύ συχνά με ανεπιθύμητες ενέργειες που προκύπτουν από ανοσολογική ή την αυξημένη ανοσολογική δράση. Οι περισσότερες από αυτές, στις οποίες συμπεριλαμβάνονται σοβαρές αντιδράσεις, υποχώρησαν μετά από την έναρξη κατάλληλης ιατρικής 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 MDX010 20, οι αντιδράσεις που αναφέρθηκαν συχνότερα (≥ 10% των ασθενών), ήταν διάρροια, εξάνθημα, κνησμός, κόπωση, ναυτία, έμετος, μειωμένη όρεξη και κοιλιακό άλγος. Στην πλειονότητα τους αυτές οι ενέργειες 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. Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες εμφανίζονται κατά φθίνουσα σειρά σοβαρότητας. 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). Η ποσοστά ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό σε ασθενείς HLAA2*0201 θετικούς ασθενείς οι οποίοι έλαβαν YERVOY στην MDX010 20, ήταν παρόμοια με αυτές που παρατηρήθηκαν σε ολόκληρο το κλινικό πρόγραμμα συνολικά.

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

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 κύστες 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[β]
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 κορτικοτροπίνη αίματος, αυξημένη λιπάση[γ], αυξημένη αμυλάση αίματος[γ], μειωμένη τεστοστερόνη αίματος

[a] 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 MDX010 20.
[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%: μηνιγγίτιδα, εγκεφαλίτιδα, καρδιομυοπάθεια, αυτοάνοση ηπατίτιδα, πολυμορφο ερύθημα, αυτοάνοση νεφρίτιδα, συμπτώματα ομοιάζοντα με μυασθένεια gravis, αυτοάνοση θυρεοειδίτιδα, υπερυποφυσισμός, δευτεροπαθής ανεπάρκεια του φλοιού των επινεφριδίων, υποπαραθυρεοειδισμός, επισκληρίτιδα, βλεφαρίτιδα, οίδημα του οφθαλμού, σκληρίτιδα, κροταφική αρτηρίτιδα, φαινόμενο Raynaud, πρωκτίτιδα, αιμορραγικό παλαιμοπεληματώδης ερυθροδυσαισθησία, ψωρίαση, αιματοχεζία, πρωτεϊνουρία, μειωμένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη οπτική οξύτητα, αισθήματα έντασης, 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 και gp100 (n = 380) σε μια μελέτη Φάσης 3 του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος (MDX010 20, βλέπε παράγραφο 5.1). Οι κατευθυντήριες γραμμές για την αντιμετώπιση αυτών των ανεπιθύμητων ενεργειών περιγράφονται στην παράγραφο 4.4. Γαστρεντερικές ανεπιθύμητες ενέργειες 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 μονοθεραπείας με YERVOY 3 mg/kg, αναφέρθηκε διάρροια 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% και 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 (οριζόμενη 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. Θανατηφόρα 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 (ουδετεροφίλα, 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 επαγόμενα 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, παρουσιάστηκε υποχώρηση 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 συνδέεται 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 σοβαρής (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) ενδοκρινοπάθειας σχετιζόμενης με το ανοσοποιητικό κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την αρχή της θεραπείας. Ενδοκρινοπάθεια σχετιζόμενη με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικά ελεγχόμενη με θεραπεία υποκατάστασης ορμονών. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, αναφέρθηκαν 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 εμβόλιο gp100. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυαλιού) x 10 ml σε ενδεικτική Νοσοκομειακή τιμή 3.887,16€, και ενδεικτική Χονδρική τιμή 4.468,00 €. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυαλιού) x 40 ml σε ενδεικτική Νοσοκομειακή τιμή 15.548,65€, και ενδεικτική Χονδρική τιμή 17.872,01€.