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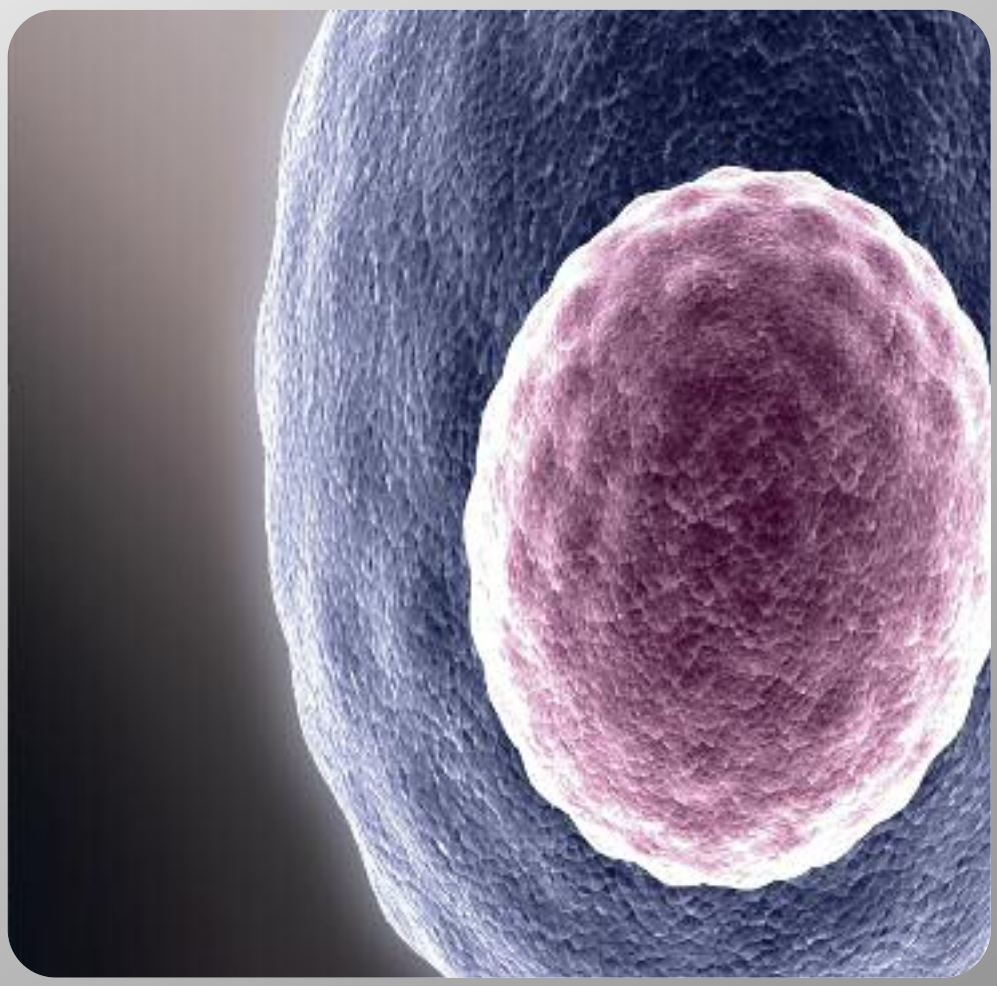

How much cancer treatment evolution can we afford?

PATHOS Survey - Treatment of advanced pancreatic adenocarcinoma

Current role of chemotherapy in the management of PDNECs

Biosimilars: Facing the incoming challenge

Osteonecrosis of the jaw in a patient with chronic myelogenous leukemia

Lepto-meningeal metastasis from esophageal carcinoma

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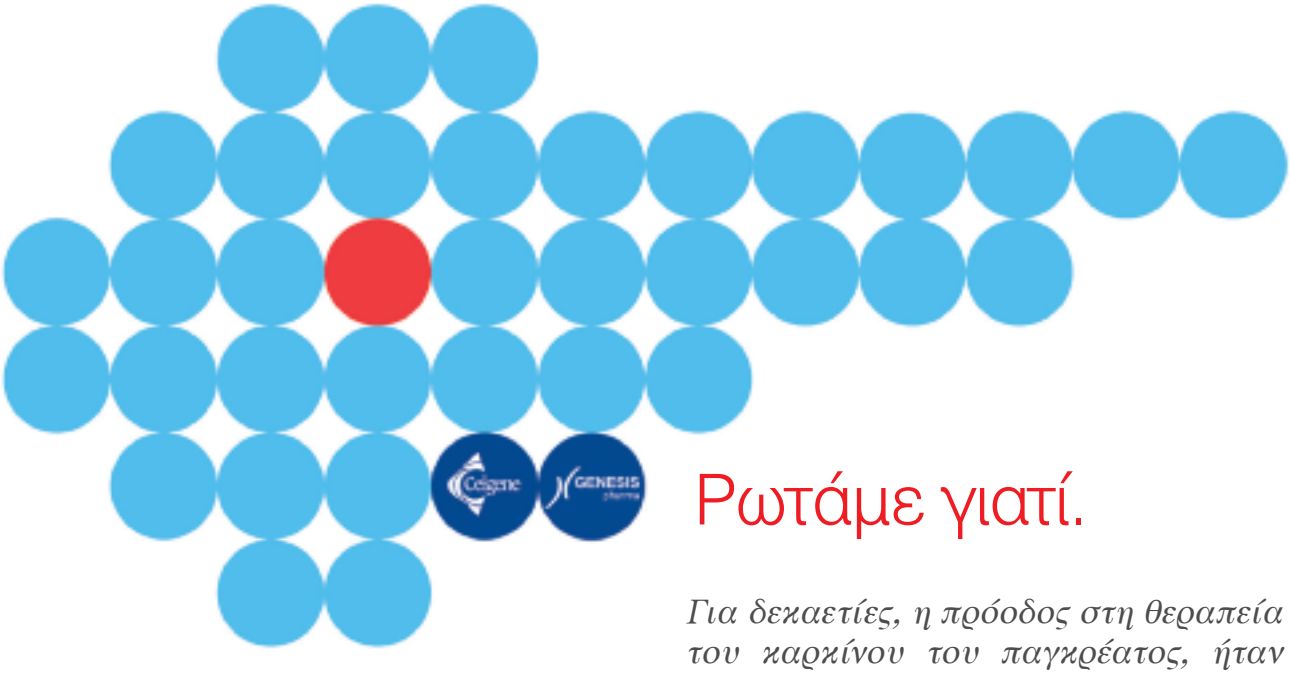

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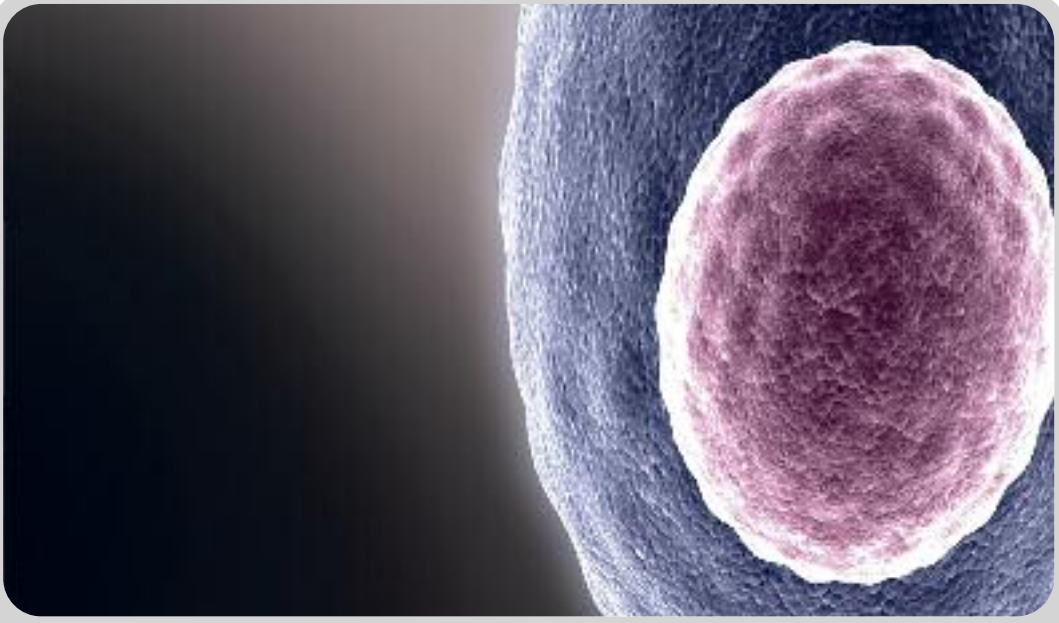

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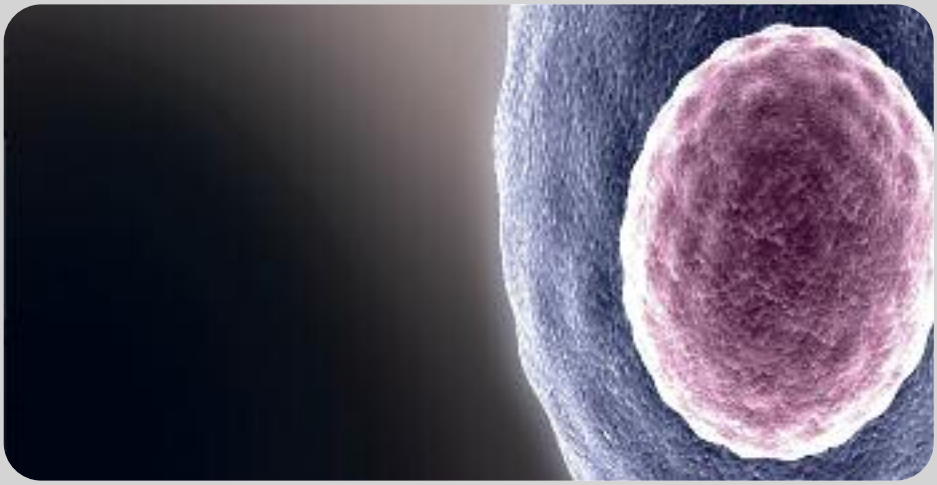

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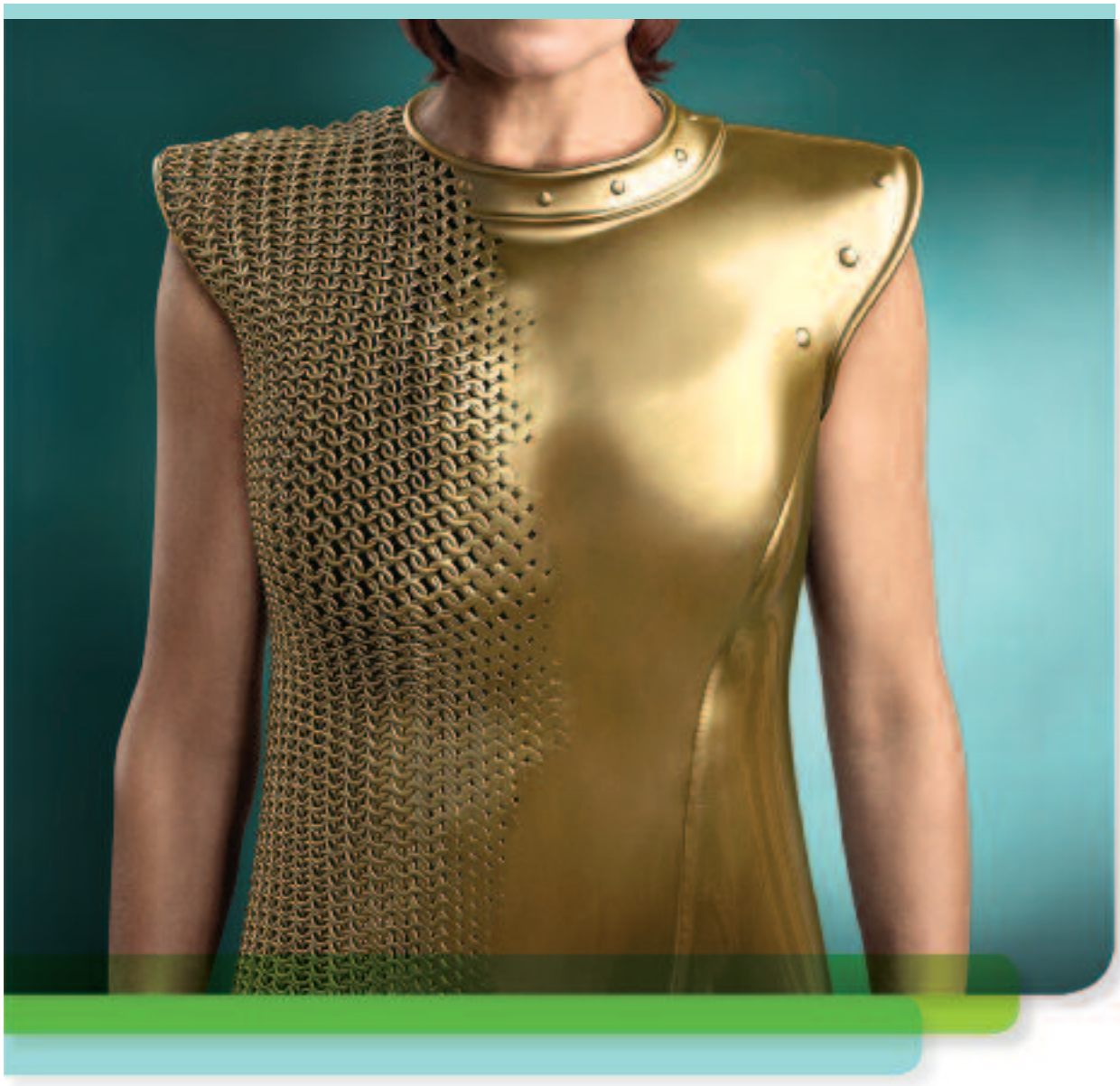

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Health is wealth, but wealth is limited: is health limited?

Editorial

Vassilios Barbounis

Cancer is the second cause of death worldwide. Over the past years, cancer mortality appears to be subsiding, despite the fact that more people are being diagnosed with cancer. Population ageing inevitably results is a larger number of cancer patients, which, in turn, contributes to an increase in healthcare expenditure the world over.

Moreover, as Dr Kosmidis correctly points out in the current issue's Position Article *(FCO, Vol. 4, Issue 4, p. 9)*, the cost of anti-cancer drugs in Europe doubled between the years 2004 and 2008. Similar phenomena were recorded across the Atlantic as well.

Although the dramatic increase in cost jeopardises insurance funds, it should also be noted that this increase has contributed to the increase of patient survival. So, the question now is to what extent society will avail resources for health, in order to benefit a specific group of citizens. For it is well-known that even though health is priceless, the available resources are limited. The cost of Health is twice the cost of Defence and Education combined.

Therefore, at least for Greece and other countries lacking such regulations, what is required is to reach a minimum consent on the cost of each quality-adjusted life-year gained. Specifically for our country, we need a special organisation charged with technologically assessing the value of a drug, as well as the capacity of administering it under the current conditions.

The use of biosimilar products -as is described by Mountzios and Boukovinas- may possibly contribute to a reduction in the prices of this category of very expensive drugs, thereby giving more patients the opportunity to benefit from their use, at a lower cost for their respective health systems *(FCO, Vol. 4, Issue 4, p. 26)*. Be that as it may, there still remain numerous unregulated issues concerning the use of biosimilars that still need addressing.

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How much cancer treatment evolution can we afford?

Paris A. Kosmidis

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Today, cancer is the number one cause of death in the USA and the number two (after cardiovascular diseases) in Europe. Each year, 10 million people are diagnosed with cancer in the world. Based on recent OECD data, cancer is responsible for 7.6 million deaths (13% of all deaths) and the number is expected to rise to over 13.1 million in 2030. In the OECD countries, cancer was responsible for 28% of all deaths for 2009. Since 1995, cancer mortality deaths have been dropping slightly in all OECD countries, except Greece, Portugal and Estonia, where the rates remained unchanging. Cancer appears with an increasing frequency in older people and it is estimated that 2/3 of patients are over 50 years old. Given that the average lifespan of people in the western civilisation is currently 80 years of age and is expected to rise further, it is concluded that the frequency of cancer cases shall also increase. The good news comes from the progress achieved over the past years in cancer prevention, diagnosis, as well as treatment. Seven in ten people live for over 5 years with an improved quality of life, while the number of patients diagnosed with cancer and living among us is well over 30 million the world over, as compared to a mere 10 million 35 years ago.

Pharmaceutical industry investments in the discovery and promotion of these new drugs are indeed very expensive. Consequently, the use of such drugs, since they are much more costly than their predecessors, results in a significant increase in insurance and welfare funds expenses in nearly all countries.

In Europe, the cost of administering anticancer drugs has doubled in the years between 2004 and 2008. In the States, the respective cost for cancer treatment amounted to 70 billion dollars. What is impressive, is that the percentage of per capita income spent on health each year increases dramatically. A large part of this percentage corresponds to pharmaceutical expenses. Projecting these costs in the future is nothing short of a nightmare, since cancer is expected to increase in frequency and anticancer drugs shall become even more expensive.

Thanks to these drugs, cancer mortality has decreased and survival has increased. Cancer patient survival is not the same in all countries. It depends on the amount of funds allotted by each country for health in general and fighting cancer in particular. According to recent statistics, the increase of expenses results in longer-term survival. In Europe, a breast cancer patient shall live (on average) more in Austria than she would if she were in a country such as Lithuania or Poland. Data shows that cancer patient survival is in direct relation to their country's per capita income. The distribution of resources per cancer patient also differs from country to country. So, the amount spent on the health of each patient corresponds to $6,000 in Luxembourg, $2,690 in Portugal, $2,551 in Slovenia and $818 in Romania. It is, therefore, very easy to explain the difference in the way cancer patients are treated, from early diagnosis to their supportive treatment. Of course, the question that lingers is just "how much cancer" can a society, an economy or a state afford? The truth is that each state is held hostage by the evolution and progress in the field of oncology at various levels. The more organised and well-prepared the state for the oncoming cancer epidemic, the fewer the repercussions for its finances; and we do have such examples. In some countries, the rendering of services depends on the clinical cost of treatment. In others, in hinges on the cost/benefit ratio and in others on the approved budget for health. At any rate, there is always an agreement between the state and healthcare providers.

The state legislates and health providers with physicians have to operate within the legal and wider institutional framework put in place by the state. Their sincere cooperation is the sole prerequisite so that both the current and the next generation of cancer patients shall continue to enjoy the achievements and progress of oncology. It is the duty of the state

to distribute its available resources in an efficient and fair manner, so as to ensure that everyone has access. For such a thing to happen, though, it takes planning; prevention, early diagnosis and treatment programmes; utilisation of experience coming from other countries; and the ability to predict. At the same time, oncologists, alongside all other oncological service providers must work together in order to achieve the common goal.

Pancreatic Adenocarcinoma Treatment Hellenic Oncology Survey 'PATHOS': Frequency and current treatment modalities of advanced pancreatic adenocarcinoma in Greece

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ABSTRACT

Background: Advanced pancreatic adenocarcinoma (APA) remains a difficult to manage disease with a high mortality rate. Limited data is available from the Greek Cancer Registry on patients with pancreatic cancer.

Patients & Methods: The PATHOS multicenter survey aimed at capturing real-world data on pancreatic cancer disease status in Greece. A standardized questionnaire administered to ten interviewed physicians specialized in pancreatic cancer, captured data from patient medical records as well as the physicians' opinion about limitations of the most common treatment modalities for APA and the likelihood of using nab-paclitaxel in the metastatic APA population.

Results: During 2011, 187 patients with APA, 63.6% of whom had been diagnosed with metastatic (Stage IV) disease, were treated by the participating physicians. Surgery had been performed in 39.7% of patients with locally advanced and in 8.4% of those with metastatic APA. Overall, 62/68 patients with locally advanced disease received chemotherapy (31 adjuvant/neoadjuvant). Of 119 patients with metastatic disease, 101 received chemotherapy (7 adjuvant; 94 palliative). As part of standard practice, 89% of patients with metastatic APA had received first-line therapy, mainly with gemcitabine, gemcitabine +erlotinib or FOLFIRINOX. However, various limitations were reported for gemcitabine +erlotinib and FOLIFIRINOX, underscoring the need for new treatments. Of the physicians, 80% reported that they were highly likely to use the combination of nab-paclitaxel/gemcitabine for metastatic APA in the future.

Conclusions: The survey demonstrated that APA in Greece is mostly diagnosed in the metastatic state and underscored the importance of adding new treatment modalities to the current therapeutic armamentarium.

Key words: pancreatic cancer; metastatic pancreatic adenocarcinoma; management; treatment; frequency; *nab*-paclitaxel; survey.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the Western world (1, 2). Notably, despite declines in the mortality rates of most types of cancer, the pancreatic cancer mortality rate is rising. For 2013, the mortality rates were projected to be 8/100,000 for men and 5.5/100,000 for women (2). The majority of pancreatic cancer patients are diagnosed with advanced pancreatic adenocarcinomas (APA), including the locally advanced (stages IIB-III) or metastatic (stage IV) disease stages (1). Pancreatic cancer is characterized by a lack of symptomatology at diagnosis and rapid disease progression, both of which contribute to diagnosis at an advanced stage and subsequently to unresectable disease that cannot be cured with available treatments (3, 4). The 5-year overall survival rates have been estimated to be 5%, 3% and 1% for patients with disease stages IIB, III and IV, respectively (5, 6).

For patients with locally advanced or metastatic APA, surgery is not curative in nature as R0 resection cannot be achieved. Improvements in surgical techniques and periope-

rative management have allowed surgery to be performed in patients previously thought to be unresectable (7). Guidelines for establishing tumor resectability have been set forth by the National Comprehensive Cancer Network (NCCN) (8). The term 'borderline resectable' or 'marginally operable' is now commonly used to describe tumors that cannot easily be clearly classified as resectable or as locally advanced (7). Neoadjuvant treatment is often employed prior to surgery with the goal of achieving tumor regression that will allow R0 resection (7, 8). Following resection, adjuvant chemotherapy (CTx) with or without radiotherapy (RTx) is used due to the fact that APA is characterized by a high recurrence rate (9). Adjuvant CTx may be combined with RTx, but the benefits remain controversial (10).

For patients with locally advanced disease, CTx is the most common treatment modality, with gemcitabine (GEM) being the recommended agent (12). Treatment aims at prolonging survival and at the palliation of symptoms related to the disease. Chemoradiation may improve survival for patients with locally advanced APA (13), but this finding is not consistently supported by available studies (14, 15).

For patients with metastatic disease, CTx is used to decrease the size of the tumor and offer relief from disease symptoms, but also to control growth of metastases (4, 16). Among CTx therapies available for patients with metastatic disease, GEM was the standard choice for years, offering a median survival of 6.2 months and a 1-year survival rate of 20% (17). Although there is some controversy, GEM combined with platinum analogues or with capecitabine seems to confer a survival benefit over GEM monotherapy (17–20). However, a trial with FOLFIRINOX (the combination of 5-FU, leucovorin, irinotecan and oxaliplatin) demonstrated a median survival of 11.1 months vs. 6.8 months for the GEM arm, thus establishing superiority of FOLFIRINOX for patients with metastatic APA. Based on this data, and despite the fact that FOLFIRINOX appears to have a worse safety profile than that of GEM, FOLFIRINOX is now considered the first choice for patients with metastatic APA, especially when they have a good performance status (21).

Despite some progress, further improvements in the therapeutic options for patients with advanced pancreatic cancer are needed, and thus enrollment of patients with APA in clinical trials is encouraged. Several agents with various mechanisms of action are currently being explored for patients with APA (22 25). However, for some agents that have entered early phase clinical trials, results have not met expectations (22, 23). Positive efficacy results have been reported in a phase III trial of GEM in combination with nanoparticle albumin-bound *(nab)*®-paclitaxel, while this combination also demonstrated a favorable toxicity profile compared to FOLFIRINOX (24) and preliminary evidence suggests that it is effective even in heavily pretreated patients, as second- or further line of treatment (25).

Combining recent data on *nab*-paclitaxel with the fact that data on patients with APA from the Greek Cancer Registry is scarce, the present survey aimed at capturing real-practice data on the incidence and management patterns of patients with APA in Greece as well as the opinion of Greek physicians about a promising new treatment modality, i.e. *nab*-paclitaxel for metastatic APA patients.

METHODS

Study design

PATHOS was a multicenter survey about advanced pancreatic cancer (APC) conducted between April and December 2012 via an interpersonal standardized questionnaire administered to the interviewed physicians. Ten physicians, all of whom were oncologists practicing in the hospital sector in various regions across Greece, participated in the present survey. The medical oncologists were selected on the basis of their clinical and research interest in pancreatic cancer, in accordance with their participation in clinical trials and their publications in the specific field.

The questionnaire was divided into three parts. For the first part, physicians were asked to answer questions relating to their practice and to patients with cancer attending their hospital-based clinics between February 2011 and January 2012. This first part aimed at ascertaining the frequency of APC occurrence in Greece and in identifying among patients with APC those with APA, who would constitute the population for whom disease characteristics and treatment modalities would be captured in the second part of the questionnaire. In the second part of the questionnaire, APA patients were divided into two groups based on whether they had locally advanced (stages IIB-III) or metastatic disease (stage IV), in order to evaluate differences in the treatment modalities used for the two groups. Treatment modalities used as part of standard care as well as in clinical trials were recorded.

The third part of the questionnaire aimed at capturing the physicians' opinion about limitations of the most common treatment modalities of APA and the likelihood of using *nab*-paclitaxel in metastatic APA patients.

Survey objectives

The survey had three objectives corresponding to the three parts of the standardized questionnaire. The first objective was the assessment of the frequency of APC occurrence in 10 representative centres, (according to geographical regions, type of hospitals and population coverage) in Greece. The second objective was the assessment of the treatment modalities used for patients with locally advanced and metastatic APA as part of the standard clinical practice, as well as in clinical trials. Lastly, the survey aimed at ascertaining physician's opinion on the currently available treatment modalities, as well as on using *nab*-paclitaxel for the metastatic APA patient population.

Statistical analysis

Descriptive statistical analysis has been performed for all

study data and mainly epidemiological methods were applied. Continuous variables are presented as number of observations, mean and standard deviation, as well as median and range where applicable, while categorical variables are presented as N, %.

RESULTS

Physician characteristics

Of the 10 participating physicians, 4 practiced at hospitals located inside Attica, while the remaining 6 practiced at hospitals outside of Attica. In terms of hospital type, 4 physicians were practicing in public hospitals, 4 in university hospitals, 1 in a military hospital and 1 in a private hospital. In addition to APA, all physicians had treated patients with breast, lung and ovarian cancer, as well as with soft tissue sarcoma. Of the physicians, 90% (9/10) had treated patients with melanoma and 20% (2/10) with osteosarcoma.

Table 1.

Characteristics of patients with advanced pancreatic adenocarcinoma (N=187).

	N	%
Newly diagnosed pancreatic adenocarcinoma	164	87.7
Distribution based on potential for surgical management		
Unresectable, metastatic	119	**63.6**
Unresectable, locally advanced	49	26.2
Resectable	10	5.3
Marginally operable	9	4.8
Distribution based on tumor location*		
Head	117	62.6
Body	41	21.9
Tail	28	15.0

**One patient with missing data*

Frequency of APC and APC patient characteristics

In order to estimate the frequency of APC occurrence, the physicians were asked to indicate the total number of patients that had been admitted to their hospital clinic between February 2011 and January 2012. Of 10 physicians, 8 were able to provide the total number of patients they had seen in addition to the specific number of patients with APC they had treated. The respective numbers were 5794 and 171. Thus, the frequency of APC based on data available from 8 hospitals was estimated at 3.0% (171/5794).

In terms of clinic capacity, during the year before the interview, the mean number of patients that had been seen at the clinics of the 8 physicians for whom data was available, was 724±423 patients.

The total number of patients with confirmed APC from the 10 clinics was 191. Of these, 53 had presented in hospitals located in Attica; 52 in hospitals of Thessaloniki; while the remaining 86 had presented in hospitals located in other areas of Greece. The median number of patients with APC that presented at the participating hospitals was 20, with a range of 6-32.

Of the APC patients, 167 (87.4%) were newly diagnosed, while 24 (12.6%) had been diagnosed with APC more than 3 months before they were first seen by the physician. Of the 191 patients with APC who had been treated by the participating physicians during the 12 months prior to the interview, 187 (97.9%) had APA and 4 (2.1%) neuroendocrine tumors of the pancreas (pNET). The characteristics of the patients constituting the population of interest of the present survey, i.e. those with APA (N=187) are presented in Table 1.

Among 187 patients with advanced pancreatic adenocarcinoma, 68 had locally advanced and 119 metastatic disease. In terms of their distribution according to their Eastern Cooperative Oncology Group (ECOG) status, the majority (92.6%) of patients with locally advanced, as well as those with metastatic disease (73.1%), had ECOG performance Status 0-1 (Figure 1).

Figure 1.

Distribution of patients with APA according to their ECOG performance status.

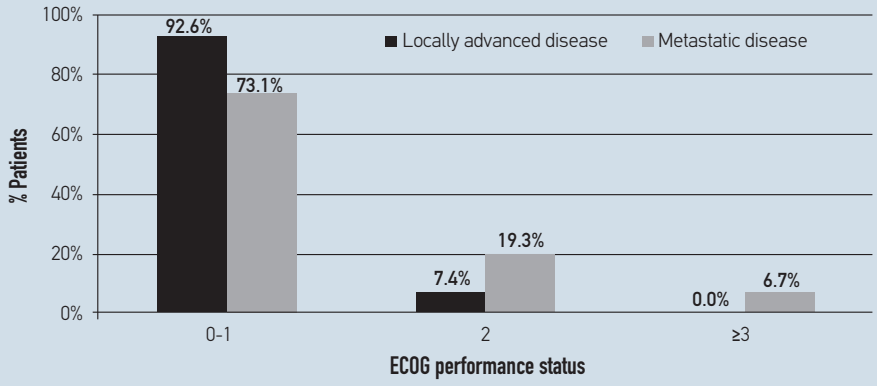
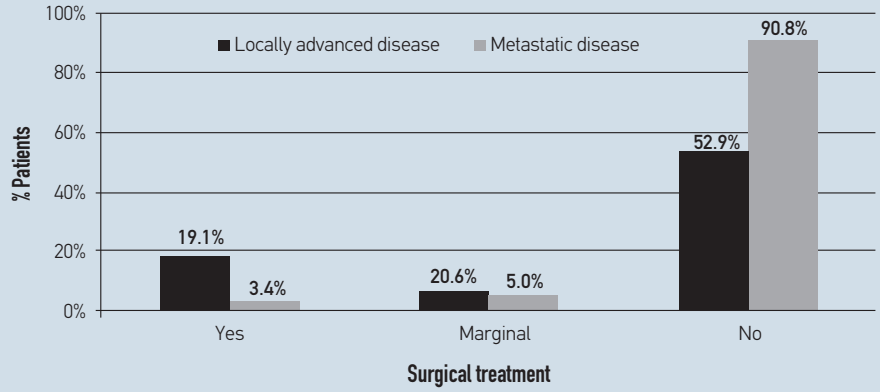


Figure 2.

Distribution of patients according to their surgical management.



Therapeutic management of patients with APA

Of the 68 patients with locally advanced disease, surgery was performed on 27 (39.7%) patients (13 were classified as resectable and 14 as "marginally operable") (Figure 2). Of the 14 patients who were classified as "marginally operable", 5 had undergone a whipple procedure, 4 bypass surgery, while for the remaining 5 patients data about the type of surgical intervention was not available. Of the patients with metastatic disease, surgery was performed on 8.4%. Of the 6 patients with metastatic disease who were classified as "marginally operable" 4 had undergone bypass surgery, 1 a Whipple procedure and 1 had missing data pertaining to the type of surgery.

According to the available data, a total of 163 patients received CTx. Of the 68 patients with locally advanced disease, 62 (60 with ECOG status 0-1 and 2 with ECOG status 2) had received CTx, while data was missing for the remaining 6 patients. Of patients with ECOG status 0-1 (n =60) receiving CTx, 29 (48.3%) had received adjuvant therapy (Figure 3).

As regards the 119 patients with metastatic disease, 101 received CTx (81 with ECOG status 0-1, 16 with ECOG status 2 and 4 with ECOG status ≥3), of whom only 7 received adjuvant therapy (Figure 4). Data on receiving CTx treatment was not available for 5 patients with metastatic APA, while 13 did neither receive nor were they scheduled to receive CTx.

Seven patients with locally advanced (stage IIB-III) and 28 patients with metastatic disease (stage IV) were treated with CTx within the framework of a clinical trial. All patients who were treated with CTx within the context of a clinical trial received first-line CTx. Of the 10 participating physicians, 6 had administered CTx as part of a clinical trial. The most commonly administered schemes were combinations of GEM. Specifically, 2 physicians reported the combination GEM + temsirolimus, 2 reported GEM + lipoplatin, 1 the

Figure 3.

Chemotherapy in patients with locally advanced disease.

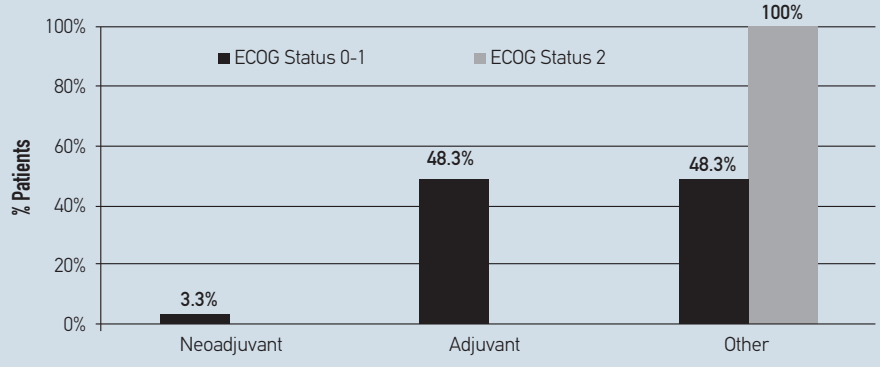
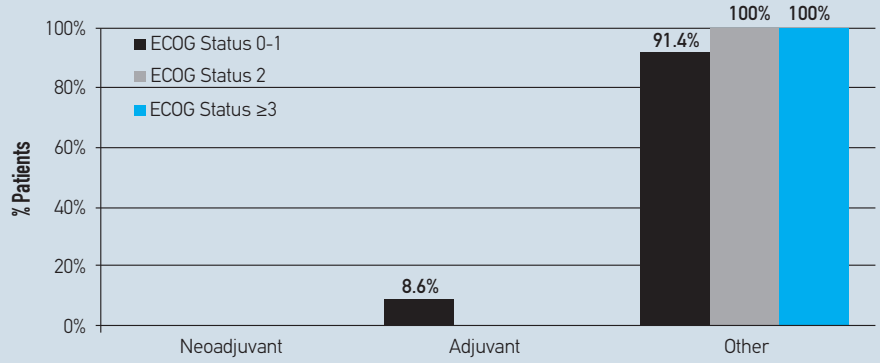


Figure 4.

Chemotherapy in patients with metastatic disease.



combination GEM + oxaliplatin + irinotecan and 1 the combination GEM + AMG479 as the most common schemes.

Of the 55 patients with locally advanced (stage IIB-III) disease who received CTx as standard care (i.e. not in the context of a clinical trial), 58.2% received adjuvant and 41.8% palliative CTx. GEM monotherapy was received by 61.8%, combination CTx by 23.7%, while 9.1% received CTx in combination with erlotinib targeted therapy (TT) and 5.5% CTx in combination with radiotherapy (RTx) and only as palliative treatment (Table 2).

Of the metastatic patients (N =73) who received CTx outside of a clinical trial setting, 65 (89%) received first-line treatment, 27 (37.0%) second-line and 2 (2.7%) third-line treatment. Four patients (5.5%) received adjuvant therapy, while data was not available for 4 patients. Of the 65 patients who received first-line treatment, 46.2% received monotherapy and 27.7% combination CTx regimens. The most common first-line treatment modality was GEM monotherapy (Table 3). In terms of second-line treatments for the metastatic APA population, the three most common second-line treatments were FOLFOX (29.6% of the patients), capecitabine (14.8% of the patients) and FOLFIRINOX (14.8% of the patients).

Limitations on current treatment modalities and physicians' opinion about *nab*-paclitaxel

Physicians were asked to choose limitations among prespecified options, on the most common currently administered treatment modalities for patients with APA, relating and not relating to the patients.

The list of limitations not relating to the patients included the choices: "high cost", "without marketing authorization by the National Organization for Medicines (EOF)", "not part of the positive list of reimbursed medicines/ not available in pharmacies", "insufficient scientific data", "other reasons, specify" and "there are no limitations". Non-patient related

Table 2.

Predominant regimens for patients with locally advanced APA who received chemotherapy as part of standard care (outside clinical trial) (N=55).

		Adjuvant	Palliative	Total
Monotherapy	GEM	40.0%	21.8%	61.8%
Combination CTx	GEM + Oxaliplatin	5.5%	3.6%	9.1%
	GEM + Cisplatin	5.5%	-	5.5%
	FOLFIRINOX	7.3%	1.8%	9.1%
CTx + TT	GEM + Erlotinib	-	9.1%	9.1%
CTx + RTx	5-FU + RTx	-	3.6%	3.6%
	GEM + 5-FU + RTx	-	1.8%	1.8%
Patient total		**32**	**23**	**55**

CTx: chemotherapy, TT: targeted therapy, RTx: radiotherapy

Table 3.
Predominant first line-therapies for patients with metastatic APA who received chemotherapy as part of standard care according to their ECOG performance status (N=65).

		ECOG Status 0–1	ECOG Status 2	ECOG Status ≥3	Total
Monotherapy	GEM	36.9%	7.7%	1.5%	46.2%
Combination	FOLFIRINOX	9.2%	-	-	9.2%
	GEM + Cisplatin	6.2%	1.5%	-	7.7%
	GEM + Oxaliplatin	6.2%	-	-	6.2%
	FOLFOX	3.1%	-	-	3.1%
	FOLFIRI	1.5%	-	-	1.5%
CTx+TT	GEM + Erlotinib	16.9%	3.1%	1.5%	21.5%
CTx+RTx	5-FU + RTx	-	-	1.5%	1.5%
	GEM + RTx	1.5%	-	-	1.5%
	Capecitabine + RTx	1.5%	-	-	1.5%
Patient total		**54**	**8**	**3**	**65**

limitations were reported by 50% of the physicians for the GEM + erlotinib combination, while none of the physicians reported non-patient relating limitations for GEM monotherapy and 5-FU/Folinic Acid (Table 4).

The list of limitations relating to the patients included "comorbid conditions", "limitations in quality of life", "adherence", "high ECOG performance status", "adverse events" "age restriction", "other reasons, specify" and "there are no limitations". According to the physicians there were no limitations relating to the patients about therapy with

Table 4.
Therapy limitations not related to the patients

	No limitations – Physicians, N		With limitations – Physicians, N / Type of limitation
GEM	10		-
5-FU/ Folinic acid	10		-
Capecitabine	9	1	Without marketing authorization by the National Organization for Medicines (EOF)
GEM + Cisplatin	9	1	Insufficient scientific data
GEM + Capecitabine	9		
FOLFOX	9		
FOLFIRI	9		
Oxaliplatin + Capecitabine	9		
5-FU + RTx	9	1	Problems of the Radiotherapy Department
GEM + RTx	9		
GEM + Oxaliplatin	8	2	1- Insufficient scientific data 1- Twice daily administration
FOLFIRINOX	8	2	1- High cost 1- Without marketing authorization by the National Organization for Medicines (EOF)
Capecitabine + Erlotinib	7	3	2- Insufficient scientific data 1- High cost
GEM + Erlotinib	5	5	4- High cost 1- Insufficient scientific data

Table 5.
Therapy limitations related to the patients.

	No limitations – Physicians, N	With limitations – Physicians, N	Type of limitation
GEM	10		-
5-FU/ Folinic acid	10		-
Capecitabine + Erlotinib	10		-
GEM + Erlotinib	10		-
Capecitabine	9	1	Comorbid conditions
GEM + Capecitabine	9	1	Adverse events
FOLFOX	9	1	Age restriction
FOLFIRI	8	2	1- Adverse events/ 1- Age restriction
Oxaliplatin + Capecitabine	8	2	1- Comorbid conditions 1- Age restriction
5-FU + RTx	8	2	2- Only for patients that have undergone surgery
GEM + RTx	8	2	2- Only for patients that have undergone surgery
GEM + Cisplatin	8	2	1- High ECOG performance status 1- Neurotoxicity
GEM + Oxaliplatin	6	4	2- Adverse events 1- Neurotoxicity 1- Difficulty of administration
FOLFIRINOX	2	8	5- Adverse events 1- High ECOG performance status 1- Comorbid conditions 1- Neutropenia

GEM, 5-FU/ Folinic acid, capecitabine + erlotinib or GEM + erlotinib. Most limitations were reported for FOLFIRINOX. Specifically, 8 physicians reported patient-related limitations for FOLFIRINOX, including "adverse events" by 5 physicians and the choices "high ECOG performance status", "comorbid conditions" and "neutropenia" by 1 physician each (Table 5). All physicians had knowledge of the data pertaining to the use of *nab*-paclitaxel for metastatic breast cancer and had used it for this disease. In addition, 30% reported being aware of the data regarding use of *nab*-paclitaxel/GEM for patients with metastatic APA, but none had used it.

The physicians were given a list summarizing the efficacy and safety findings from the phase I/II study of *nab*-paclitaxel/GEM in patients with metastatic APA (24) and were asked to rate the importance and positivity of these findings using a scale from 0 to 10. The results are shown in Table 6. Overall, the physicians rated efficacy results, specifically the overall response rate (ORR) and the mean progression-free survival (PFS) positively (medians of 10 and 9.5, respectively). Positive ratings were also given for infusion duration and treatment preparation. The lowest scores given by the physicians were 1 and 4 and were related to the safety and dosage regimen, respectively. Neutropenia and neuropathy were the most common physician-reported safety concerns. Notably, 80% of the physicians reported that it was highly likely (score of 10) to use *nab*-paclitaxel/GEM for patients with metastatic APA, while 10% each gave a score of 8 and 7 (on a 0 to 10 scale).

DISCUSSION

Surveys are powerful tools for capturing information about a population of interest. Although surveys cannot establish a cause-effect relationship, they are useful in providing data about disease incidence and real-life management patterns during the time period under study. As data from the Greek Cancer Registry about the incidence and treatment modalities of patients with APA, a patient population whose mortality continues to rise and for which current therapies are mainly palliative in nature, was not available, the present survey aimed at filling this gap.

According to the present survey, between February 2011 and January 2012, APC accounted for about 3% of the cases presenting with cancer at the participating centers in Greece with available data. The vast majority of APC patients (97.9%) had been diagnosed with APA.

Most patients with locally advanced APA (62/68) had received CTx. Seven of these patients had received CTx in the framework of a clinical trial while all others as part of standard practice. Of the patients with locally advanced (stage IIB-III) disease who received CTx as standard care, 58.2% received adjuvant CTx. Adjuvant therapy is commonly used in this patient population to avoid recurrence (7-9). In

Table 6.
Physicians' opinion of clinical efficacy and safety of nab-paclitaxel in patients with metastatic pancreatic adenocarcinoma according to the results of the phase I/II trial.

	Positivity of the findings (scale 0 to 10, very poor to very good)			Importance of findings (scale 0 to 10, not important to very important)		
	Median	Minimum	Maximum	Median	Minimum	Maximum
Overall Response Rate (ORR)	10	7	10	10	7	10
Mean Progression Free Survival (PFS)	9.5	5	10	10	5	10
Safety	8	1	10	9	7	10
Dosage regimen	8.5	4	9	8.5	4	9
Infusion duration	9.5	8	10	9.5	7	10
Treatment preparation	9.5	9	10	9	7	10

accordance with the proposed regimens from the literature, most patients with locally advanced disease who had received CTx, either adjuvant or palliative, received GEM monotherapy (12).

The population of patients diagnosed with metastatic APA was larger than those diagnosed with locally advanced disease (119 vs. 68 patients). The metastatic APA population was mostly managed with CTx (n =101). Many of these patients (n =28) received CTx in the context of a clinical trial. For those not participating in a clinical trial (n =73) physicians favored the literature recommended treatments, i.e. GEM monotherapy and FOLFIRINOX (17-21). It is notable that FOLIFIRINOX was only administered to patients with ECOG status 0-1, which is in accordance with the recommendations for using this treatment modality only in patients with a good performance status (21). In terms of second-line treatments for the metastatic APA population, the three most common second-line treatments were FOLFOX, capecitabine and FOLFIRINOX.

However, limitations were reported for common treatments (especially GEM combinations and FOLFIRINOX) used for patients with metastatic APA. This finding, combined with the fact that a significant percentage of metastatic APA patients participated in clinical trials, underscores the need for new treatment modalities.

Nab-paclitaxel has shown promise for the metastatic APA patient population, demonstrating increased ORR, PFS, prolongation of overall survival and a good toxicity profile (23, 24). *Nab*-paclitaxel is an albumin bound formulation of paclitaxel nanoparticles that constitutes a trademark of Celgene Corporation. This formulation appears to be better tolerated than soluble paclitaxel (25, 26). *Nab*-paclitaxel is currently approved for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline-containing therapy is not indicated (27). Preliminary reports suggest efficacy of *nab*-paclitaxel as monotherapy in a post-first-line setting for the heavily pretreated pancreatic cancer population (28). Participating physicians valued the results of the clinical trial with *nab*-paclitaxel (24) and were aware of efficacy data for this agent in metastatic breast cancer. The majority of the participating physicians were highly likely to use *nab*-paclitaxel/GEM for the treatment of metastatic APA.

As with all surveys, the results of the present study are limited by the fact that the data is as complete and as accurate as the medical records from which the data was abstracted. Furthermore, the population of interest was drawn from 10 hospitals, with considerable heterogeneity in the size of primary care practices and the number of patients seen by each physician, thus the conclusions drawn in terms of treatment management practices are not equally weighted among the physicians. However, the selection of the participating hospitals ensured the results reflected the broad Greek situation and not that limited to the large hospital centers of Attica and Thessaloniki. In addition, as regards the limitations of available treatments for the metastatic APA population, the survey captured the perceptions of the participating physicians and may not be generalizable to the entire Greek healthcare oncology community of physicians.

Despite these limitations, the survey provided much needed information about management patterns and illustrated an unmet need that exists for the management of APA patients. Strengths of the survey lie in the fact that it provided an easy and cost-effective method to study a population of patients for whom no data was available in existing databases. Furthermore, the survey results are representative of the 'real world', given that the participants were not 'selected' based on inclusion/ exclusion criteria, as they would have been in case of a clinical trial.

In conclusion, the present survey demonstrated that the majority of patients with APC in Greece are diagnosed at the metastatic stage for which novel treatment modalities are

needed. The physicians agreed that *nab*-paclitaxel shows promise for this patient population and that they may use this formulation in the future.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Current concepts of the role of chemotherapy in the management of poorly differentiated gastrointestinal neuroendocrine carcinomas

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ABSTRACT

Poorly differentiated neuroendocrine tumors constitute a heterogeneous group of tumors that are increasingly being diagnosed due to improved awareness and identification of specific immunohistochemical markers. Recent evidence suggests that, although the overall prognosis of these tumors is worse than that of the most commonly encountered well differentiated tumors, there is considerable variation between them in terms of response to treatment and survival rate. Systemic chemotherapy with cisplatin and etoposide remains the main therapeutic modality but the objective response rate differs by primary site of origin, Ki67 labeling index and other clinical prognostic parameters such as patient performance status. Although patients with poorly differentiated neuroendocrine carcinoma may respond optimally to chemotherapy, their median survival still remains relatively poor. This renders imperative the need for better understanding of the biology of these malignancies and the development of new treatments.

Key words: poorly differentiated neuroendocrine tumors; neuroendocrine tumors; chemotherapy; mTOR inhibitors.

INTRODUCTION

Poorly differentiated neuroendocrine carcinomas (PDNECs) represent a heterogeneous group of small-cell, large-cell and mixed tumors (small- and large-cell) that may occur in any organ, although in 30% of cases no primary site can be identified (1). PDNEC are characterized by a high mitotic rate and a Ki67 labeling index (LI) ranging from 20 to 100% (2). According to the latest WHO classification, PDNECs are defined as grade 3 tumors and have a Ki67 LI of above 20% that may increase to above 75% in certain small-cell subtypes (2, 3). Initially extrapulmonary PDNECs were considered to be similar to small-cell lung cancer (SCLC). Although some have questioned this rationale, as there are many differences between pulmonary and extrapulmonary PDNECs (4, 5), up to now it has not been possible to design clinical trials for extrapulmonary PDNECs and therefore SCLC treatment guidelines have been adopted (6). Recently, several retrospective studies have appeared demonstrating the heterogeneity of these tumors and their difference from SCLC (7-9). This review attempts to present current data regarding the epidemiology, as well as recent and potentially evolving therapeutic modalities.

EPIDEMIOLOGY & CLASSIFICATION OF PDNECs

As extrapulmonary PDNECs are rare, there are relatively few epidemiological studies, mainly describing the most common small-cell subtype. One large study including 1618 patients with small-cell subtype showed that the most commonly involved systems were the gastrointestinal (GI, 33%) and the genitourinary (20%), whereas the commonest involved primary organs were the esophagus (18%) and the breast (10%) (10). There was an overall 15-fold difference in the incidence of extrapulmonary and SCLCs, whereas the median 3-year survival was 19% and 5%, respectively (10). In the same study it was shown that among all extrapulmonary PDNEC patients, those with breast disease had the best prognosis with a 3-year survival of 60%, whereas those with GI-PDNEC had the worst, with a 3-year survival of 7% (10).

Although the incidence of extrapulmonary GI-PDNEC is increasing due to better understanding of their histopathology, it still remains a rare cancer, representing 0.2 % of all digestive cancers (11). Initially, it was thought that the neuroendocrine cells that give rise to various neuroendocrine tumors (NETs) migrating from the neural crest to the gut endoderm, but it is now apparent that enteropancreatic neuroendocrine cells originate from pluripotent stem cells of endodermal origin, that also give rise to other epithelial cells (12). Nevertheless, although the molecular fingerprint of small- and large-cell pancreatic PDNECs seems to be relatively similar, it is quite different compared to well- and moderately differentiated NETs or adenocarcinomas regarding p53, Rb/p16 and bcl-2 gene expression (13). Additionally, in a large cohort of 305 patients, it was shown that within the GI-PDNEC group there is large clinical variability even among tumors originating from the same primary that justifies distinction of PDNECs into further subgroups (7).

The earlier classification used for extrapulmonary PDNEC was a 2-stage system derived from the Veterans' Affairs Lung Study Group classification for SCLC (14). According to this classification system, if the disease was confined to the primary site, with or without regional lymph node involvement, it was defined as "limited"; and if it was spread beyond locoregional boundaries, it was considered as "extensive" (14).

Computed tomography scan and magnetic resonance imaging are used to delineate tumor extension, particularly in the liver and bones (5). With respect to somatostatin receptor scintigraphy, either with ^{111}Indium labeled-octreotide or more recently with ^{68}Gallium-DOTATE/TOC, this is useful in a small number of PDNECs, as most lack SSTR expression (5, 15). Most frequently, these tumors present an intense metabolic activity that also relates to their high proliferative rate. For these tumors, employing 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) may provide more information for baseline staging and for the monitoring of treatment response (5, 15). This may specifically hold true for PDNECs with relatively Ki67 LI closer to 100%, rather than to the lower end of the spectrum. Nevertheless, the use of both imaging procedures may identify tumor heterogeneity and may add to the information obtained from the histopathological study of a tumor sample (16). Additionally, 18F FDG PET may represent an imaging method of choice in particular cases, such as those of unknown primary site (17).

The role of biomarkers is not well defined, as the value of the currently used universal marker Chromogranin A (CgA) has been questioned, whereas other markers, such as neuron specific enolase (NSE) or progastrin may be more appropriate (18). This has been shown by a number of studies and is probably related to the de-differentiation of these tumors that most commonly express NSE (19). Nevertheless, in the Nordic study, 2/3 of 188 patients had an elevation of CgA, while NSE was not tested (7). It has been suggested that both CgA and NSE could be used for the initial evaluation of the tumor and when found abnormal their serial assessment could be valuable for the monitoring of the disease and response to treatment (19).

The median survival of untreated patients with metastatic PDNEC disease is very low and in the Nordic study, including 53 patients, it was reported as being 1 month (7, 20). In the National Cancer Registry of Spain, the median survival of 85 PDNEC patients, regardless of stage or treatment, was 1.7 years (7, 20). As the rarity and heterogeneity of GI-PDNECs have hampered the introduction of specific relevant clinical trials, such patients are usually treated with established combination chemotherapy previously tested in clinical trials for SCLC. Current clinical guidelines support the use of a platinum-based agent, cisplatin or carboplatin and etoposide (5). According to the latest European Society of Medical Oncology guidelines, all patients with metastatic PDNECs should be offered treatment with cisplatin and etoposide at an early stage (19). Although not curative, chemotherapy increases the median survival to 11-15 months (7, 9). Prognosis of the majority of these patients is largely dependent on the stage and anatomical primary (6, 7, 10, 11). All these findings urge for the development of more effective diagnostic, prognostic and therapeutic approaches.

TREATMENT OF PATIENTS WITH LIMITED GI-PDNECS

Poorly differentiated neuroendocrine carcinomas are rarely diagnosed at limited stage but even so they have a high tendency for metastatic dissemination. It has been shown that most patients treated with surgery alone eventually develop recurrent disease (5, 21). A recent retrospective study including 57 patients with grade 1 and grade 2 malignant pancreatic NETs (pNETs) supports the use of adjuvant therapy in selected patients with resected tumors and positive lymph nodes (22). Similar studies on PDNEC are lacking but a retrospective study including 93 patients with localized small-cell carcinomas of the esophagus showed that the use of adjuvant systemic treatment made a statistically significant difference on survival compared to those treated with surgery alone (median survival, 5 vs. 20 months, respectively) (23). Another retrospective study of extrapulmonary PDNEC showed that the best chance for cure in patients with limited stage disease is aggressive multimodality treatment including chemotherapy, radiotherapy and surgery (4). Although there are no prospective studies evaluating the benefit gained by adjuvant treatment, even in an apparently complete surgical resection, adjuvant treatment with radiotherapy and/or chemotherapy should be considered to eradicate any residual disease as well as in cases where the risk of local recurrence is high (4, 5, 24, 25). Prophylactic whole-brain radiotherapy is not recommended, since brain metastases rarely occur in patients with extra-pulmonary PDNECs in contrast to what happens in patients with SCLC (4, 26, 27).

Several treatment schedules are recommended by the National Comprehensive Cancer Network (NCCN) and the European Neuroendocrine Tumor Society (ENETS), the most

common being etoposide 100 mg/m^2 for 3 days and cisplatin at a dose of 45 mg/m^2/day on days 2 and 3, every four weeks (28). An alternative regimen that does not require hospitalization replaces carboplatin with cisplatin. Although 4-6 cycles have been administered, there is no data evaluating whether the administration of six is superior to four cycles (5)

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TREATMENT OF PATIENTS WITH EXTENSIVE GI-PDNEC

First-Line Therapy

Similarly to adjuvant chemotherapy, the combination of a platinum agent and etoposide are most often used in metastatic GI-PDNEC. Originally, two prospective studies, an American and a French one, evaluated the efficacy of two different regimens containing cisplatin and etoposide in patients with GI-PDNEC. In the first study, 18 patients with metastatic PDNEC were treated with etoposide 130 mg/m^2/day, days 1-3 and cisplatin 45 mg/m^2/day on days 2 and 3, achieving a response rate (RR) of 67% lasting for 8 months and obtaining a median survival of 19 months (29). In the second study, 53 patients (41 with PDNEC, among whom 20 with GI-PDNEC) were treated with a more toxic regimen including etoposide 100 mg/m^2/day on days 1-3 and cisplatin 100 mg/m^2 on day 1, achieving a RR of 42% with response duration of 9 months and a median survival of 15 months (30). Although both of these studies included a small number of patients, several other retrospective studies have validated the efficacy of this regimen in GI-PDNEC. Recent data has also shown that the combination of cisplatin and irinotecan in patients with extra-pulmonary PDNEC of various primaries obtained a high RR of 64-75% and a progression-free survival (PFS) of 7.3-7.6 months (31, 32).

Combinations of three agents have not found a place as first-line treatment, as they produce similar clinical responses but with a far greater toxicity. A phase II study of 78 PDNEC patients treated with paclitaxel, carboplatin and etoposide, resulted in an overall objective RR in 41 patients [52%; 12 complete response (CR), 29 partial response (PR)] counterbalanced by a high, grade 3-4 toxicity (33). A study that employed a scheme including carboplatin, vincristine and etoposide capsules in 31 previously untreated patients with PDNEC obtained a 52% RR and a PFS of 6.6 months (34). The toxicity in this trial was reported as low, most probably because of the oral intake of etoposide that is less toxic compared to intravenous administration, and vincristine that has a lower hematological toxicity.

A report from the Nordic Neuroendocrine Treatment Group, the largest retrospective study performed up to date that included 305 patients with GI-PDNEC, revealed that survival and RR were not different between the various platinum chemotherapy schedules (cisplatin-based vs. carboplatin-based) employed (7). However, patients with Ki67 LI <55% were less responsive to platinum-based chemotherapy, but had a longer survival than patients with a higher Ki67 LI. This feature demonstrated the heterogeneity of grade 3 NEC as there seem to be subsets of patients with different growth patterns responding differently to chemotherapy and obtaining different survival rates. Although Ki67 LI seems to distinguish some of these tumors, further indicators are needed to identify different patient subgroups.

Second-Line therapy

Following the initial response to chemotherapy, a significant number of patients will develop progressive disease (PD) requiring second-line treatment. Given the lack of studies evaluating the efficacy of second-line chemotherapy in GI-PDNEC, information is extrapolated from studies in relapsed SCLC that usually achieve a RR of 0-20% (5). It is not uncommon for patients to develop recurrences 3-6 months following initial platinum-based treatment, and if so they may be rechallenged with a platinum compound and etoposide or irinotecan (5, 32). Another therapeutic option is oral topotecan that has been shown to improve the median survival of patients with SCLC by 3 months (35). This approach may be valuable in patients with GI-PDNEC, particularly those who have a borderline performance status (PS) instead of using intravenous regimens. Other agents derived from experience in SCLC are paclitaxel, docetaxel, vinorelbine and gemcitabine (5, 26). Currently, there is limited information in the literature regarding re-challenging patients with progressive disease with a platinum agent, and administration of second- or third-line agent. Data derived for the Nordic study showed that 26 evaluable patients who experienced progression and were retreated with a platinum agent and etoposide achieved a 15% PR and 27% stable disease (SD) (7). In the same study, 84 evaluable patients who received mainly temozolomide or docetaxel as second-line therapy achieved an 18% RR (2 CR, 13 PR), 33% SD and 49% PD (7). Additionally, following third-line therapy, 29 evaluable patients had a RR of 7% (2 PR), SD of 34% and PD of 59% (7).

Based on the initial experience of temozolomide activity in advanced malignant NETs (36), several studies have been conducted to further investigate its role in these patients (8, 9, 34, 37, 38). A study testing temozolomide with capecitabine as first-line treatment in patients with well- and moderately differentiated metastatic pNETs produced a high RR (70%) with acceptable toxicity (37). This approach of using temozolomide either alone or in combination with capecitabine or bevacizumab as second-line following failure to platinum/etoposide therapy was tested in 25 patients with PDNEC most of whom had GI-PDNEC (8). The overall RR obtained was 33% (1 CR, 7 PR, 9 SD) and the median PFS and OS were 6 and 22 months, respectively (8). However, definite conclusions about the beneficial effect produced by the addition of capecitabine and bevacizumab to temozolomide cannot be drawn as the number of patients treated was small (8). The authors noted that patients with Ki67 LI of <60%, positive immunohistochemistry for CgA, positive somatostatin receptor scintigraphy, and lack of response to

first-line therapy with cisplatin/etoposide responded better to temozolomide (8). Another phase II study evaluating temozolomide and bevacizumab in patients with advanced NETs included 3 patients with PDNEC, none of whom responded to treatment (38). A further single centre retrospective study of 16 evaluable PDNEC patients receiving temozolomide as second- and third-line treatment revealed SD in 6 patients, PD in 10 patients and an overall median PFS of 2.4 months (34). The authors in the latter study indicated that a PS = 0-1, a Ki67 LI < 50% and a pancreatic origin of the tumor were associated with a better response to temozolomide treatment (34).

From the study by Welin et al., it became apparent that patients with Ki67 LI > 60 did not respond to temozolomide, whereas most responding patients (12/25) had a Ki67 LI of 20-30% (8). Based on similar results from other studies indicating that temozolomide may have a role in NETs with not excessively high Ki67 LI (7, 34, 37, 38), it can be hypothesized that temozolomide is a more active treatment in patients with well-moderate differentiated tumors. Temozolomide could also be used in poorly differentiated carcinomas with relatively low (<60%) Ki67 LI that are probably not good candidates for treatment with cisplatin and etoposide (7, 34, 37, 38).

PROGNOSTIC AND PREDICTIVE VARIABLES

In an early study including 101 patients with extrapulmonary SCC, the prognostic variables identified in the multivariate analysis were abnormal white blood cell count, PS and extensive disease (39). A few more recent and mainly retrospective studies from national and multinational databases have revealed the distinctive features of extrapulmonary PDNEC and have identified parameters that may predict response to treatment and survival.

From the largest multinational multicentre retrospective study of 305 patients with GI-PDNEC, it became evident that there was some heterogeneity of the responses obtained based on the primary location and proliferation rate (7). Multivariate analyses of the clinical and pathological features of this patient cohort identified several variables associated with response to treatment (Ki67 LI and PS), and survival such as PS, platelet count, lactic dehydrogenase (LDH) levels and primary site of origin (7). PS is a factor commonly found influencing response to treatment and survival in several PDNEC studies, as it is the main factor affecting the decision of chemotherapy delivery, thus a patient with a borderline PS may not be treated optimally (7, 34, 39). With respect to lactic dehydrogenase, and particularly isoform 5, it has been shown to increase in hypoxia and highly angiogenic tumors such as PDNECs (7, 40). Apart from the Nordic study, the primary site has been found to be related to prognosis in several other studies as well (7, 10, 11).

Evaluation of O^6-methylguanidine-DNA methyltransferase (MGMT) expression, an enzyme that when present may predict poor response to temozolomide, did not seem to be necessary for predicting treatment efficacy, as it was positive only in 1/17 tested patients (8). The identification of clear predictive and prognostic markers in this disease is a task of the outmost difficulty, as it is nearly impossible to design prospective studies with enough power to validate them.

MOLECULAR BIOLOGY AND TARGETED THERAPIES

Poorly differentiated neuroendocrine tumors are characterized by genetic and epigenetic alterations. Loss of PTEN, an important molecule for physiological cell growth, apoptosis, cell adhesion and cell migration, is frequently found altered in PDNEC (41). A statistically significant loss of the adhesion molecules E-cadherin, alpha and beta catenin is found in GI-PDNEC compared to normal tissue (42). Other very interesting observations, mainly in pancreatic PDNECs, are mutations of the p53 tumor suppressor, loss of Rb/p16 expression and overexpression of the anti-apoptotic protein Bcl-2 (13). Based on the latter finding, a phase I study of navitoclax, a novel inhibitor of Bcl-2 family proteins, was conducted to evaluate safety, pharmacokinetics, and preliminary efficacy in patients with pulmonary PDNEC showing promising results (43).

Other studies in pulmonary PDNEC testing targeted therapies such as oblimersen, a Bcl-2 inhibitor (44); imatinib (45); mammalian target of rapamycin (mTOR) inhibitors (46); vascular endothelial growth factor receptor (VEGFR) inhibitors, including bevacizumab (47), sorafenib (48), and cediranib (49) have produced negative results. Several *in vitro* analyses of established NET cell lines support further efforts in the development and application of drugs acting at general-, such as inhibitors of DNA methyltransferase and histone deacetylation, as well as at more specific epigenetic alterations (50).

Other clinical trials currently underway in PDNEC are:

- A Phase II clinical study from Beijing, China, evaluating the sequential therapy of irinotecan combined with cisplatin (IP) and Octreotide LAR in the first-line treatment of metastatic or inoperable GI-PDNEC: the IPO-NEC Trial (http://clinicaltrials.gov/show/NCT01480986).
- A Phase II clinical study from MD Anderson, assessing the clinical activity of irinotecan and cisplatin in untreated patients with metastatic or unresectable high-grade GI-NEC (http://clinicaltrials.gov/show/NCT00353015).
- A French multicenter phase II open study coupled with a translational assessment of biomarkers predictive of response to sunitinib in patients with advanced/inoperable PDNEC (http://clinicaltrials.gov/show/NCT01215578).

CONCLUSIONS

Poorly differentiated NETs represent a heterogeneous group of tumors with poor prognosis mainly due to lack of understanding of the molecular pathways responsible for malignant transformation and to treatment modalities that

are efficient in the short run. It is important to support research for the identification of deregulated cellular pathways in these rare tumors. There is an urgent need to improve therapies and outcomes and, in order to achieve this, it is imperative to undertake a collaborative effort involving multiple sites, so as to collect biological material and include patients in clinical trials.

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Biosimilars: Facing the incoming challenge

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ABSTRACT

Biosimilars are medicinal products, biological in origin, which are similar to biological medicines that have already been authorized for use. Namely, biosimilars are an approved new version of an innovator biologic drug, after patent expiry which has undergone rigorous comparability tests. The evolution of this class of medicinal products implies certain assumptions and problems, the most significant among them being efficacy, which is expected to be similar to the one of the reference product. The safety profile is another issue of equal importance to efficacy. The manufacturing process, design and development of the biosimilar product is a very complex and challenging process without any similarity to the development of generic drugs. Thus, the legislation regarding these medicines in the US and the EU is quite different in comparison to the legislation on generics, which means that different –in fact, much higher- standards are implemented altogether to ensure the quality of these products, as well as their efficacy and safety. These products have been used safely in clinical practice for a decade now, and their market share has been growing. What we expect from these products is a less costly alternative to existing biological drugs.

Key words: biosimilars; biological drugs; substitution; generics; legislation.

THE BIOTECHNOLOGY

Recent advances in biotechnology have offered to both patients and the scientific community, the use of biological drugs against serious diseases such as cancer, multiple sclerosis, diabetes, rheumatoid arthritis and autoimmune diseases. The DNA recombinant techniques introduced as early as the 1980s were the cornerstone of these achievements. When this technology becomes widely available, many more similar biological medicinal products will be developed, with many of them being already available.

Biological drugs comprise a broad spectrum of molecules like proteins, enzymes, monoclonal antibodies, vaccines or genes. Among them are hormones, like growth hormone, insulin, low molecular weight heparins or blood cell growth factors like erythropoietin or granulocyte stimulating factors. Some of them are naturally produced in humans or consistent with advanced technology products.

In order to produce biological drugs, modern technology uses various living systems like plant or animal cells, bacteria, viruses and yeast. Genetically modified cells are very useful tools for this purpose; however, each manufacturer has their own unique biological productive systems and invests in their own manufacturing processes. These processes for biological medicines are very sensitive procedures, as they are expected to produce consistent results and products with acceptable efficacy and safety.

The major problem in the manufacturing line is the availability of high-level technical infrastructure and expertise. It is worth mentioning that production of a biological drug typically requires about 250 tests, as compared to only 50 tests approximately for a generic product. That is why there are very strict procedures and legislations in both the US and the EU for a biological medicinal product or a biosimilar drug to be granted a license.

THE DIFFERENCES BETWEEN GENERICS AND BIOSIMILARS

Generics are drugs consisting mainly of small molecules with low molecular weight and simple in their general structure. They can be analyzed, so as to yield their components. On the contrary, biosimilars differ to small molecule drugs in many ways; among them is the molecular weight and the complexity of the molecule, their stability under certain con-

ditions and, above all, the manufacturing process. This means that another difference lies in the fact that the generics are typically manufactured by means of chemical synthesis, whereas most biosimilars are made by living systems and it is absolutely necessary that their purification is achieved using a very complex manufacturing technique.

As a consequence, the characteristics of biosimilars possess an enormous variability, to such a degree that a biosimilar is actually considered a mixture of various isoforms of the same product wherein minor differences exist.

Another very important difference among generics and biosimilars is the immunogenicity of the latter. All biosimilars have the potential to exert an immune response that recognizes some substances as invaders and act against them. Nevertheless, sometimes, such an immune response is considered as an adverse reaction. These immune reactions can lead to differences among similar biological medicines.

LEGISLATION

Recently the EMA accepted the following new definition for "biosimilars": *"A similar biological medicinal product, also known as 'Biosimilar', is a product which is similar to a biological medicine that has already been authorized, the so-called 'reference medicinal product'. The active substance of a biosimilar medicine is a* ***known biological*** *active substance and similar to the one of the reference medicinal product. A similar biological medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile as generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. Medicinal products are expected to have the same safety and efficacy profile and are generally used to treat the same conditions."* (1).

Biosimilar drugs are biological medicinal products, and they are covered by the EU legislation on all biopharmaceuticals. A very interesting point is that a biosimilar is a biological drug similar to another biological drug which has already been granted a marketing authorization and is the drug to which the biosimilar is referred (2).

The reference product is usually already in the market and its patent is one step before expiry. There are very strict guidelines issued by the EMA regarding the regulatory process before granting marketing license. The guidelines are revised regularly.

There are two basic terms concerning the use of biosimilars. The first one is the comparability between the reference and the biosimilar, which describes the core principle of a biosimilar development (3).

The second one is "Biosimilarity". This is a regulatory term used to denote the comparability between a biosimilar and its reference drug. The core assumption is that the biosimilar product is based upon a regulatory assessment that the biosimilar in question has demonstrated its similarity to the reference drug, as this similarity has had already been described by the Committee for Medicinal Products for Human Use (CHMP)/EMA. The comparability implementation is divided into three major steps, namely the physicochemical and biological comparability; the comparative non-clinical studies; and the comparative clinical studies, mainly Phase II and III.

Other issues concerning biosimilars are the quality of studies, extrapolation of indications, traceability and immunogenicity. There is no need for large phase III trials aiming to show overall benefit or progression-free survival. What is needed is only a non-inferiority trial with primary endpoints the response rate and efficacy. The relevant population required in order to detect differences in both efficacy and safety, should be homogeneous to reduce variability, as in early-stage disease. Without extrapolation, the biosimilar concept is null. Extensive scientific justification for the extrapolated indication (rather than separate demonstration of equivalence) is made on a case-by-case basis and may not be possible in many cases. Because biosimilars are given the international non-proprietary name (INN) as the originator, additional information including the brand name should be used when prescribing in order to detect incidence of immunogenicity and other adverse events. Biosimilars are similar to the originator drugs, not identical, and there is currently no scientific basis to substitute different products. Therefore, automatic substitution by a pharmacist without the physician's consent should not be permitted.

The key issues for factors contributing to immunity are:

- **Host related**, as genetic predisposition (major histocompatibility complex alleles), concomitant therapy (e.g. interferon); immunesupression (cancer); activated immune system due to infection; ethnic sensitivity, and prior treatments;
- **Product related**, as structural properties; glycosylation; impurities; formulation; storage; aggregates;
- **Treatment related**, as route of administration; dose; length of treatment.

Immune reactions to biologic therapeutics may lead to altered efficacy or serious adverse events. The immunogenicity of monoclonal antibodies is complex; there are a number of often poorly understood factors that make it difficult to predict with any certainty whether a therapeutic or diagnostic monoclonal antibody is likely to provoke a clinically relevant immune response.

PHARMACOVIGILANCE AND RISK MANAGEMENT SYSTEM

It is absolutely necessary for the pharmaceutical companies involved in the production of biosimilar medications to establish two very important systems.

The system of pharmacovigilance aims at monitoring the safety of marketed products and detecting any not-previously described side-effects or different frequency (usually increased) of already described undesirable effects.

The risk management plan aims at organizing a system which the company will introduce for the medicine concerned, once the latter is marketed, in order to react properly against the emerging adverse reactions, like immunogenicity and others. The risk management plan for a biosimilar should take into account the already known safety profile of the reference product (4).

IMPACT ON THE ECONOMY

Biological drugs are generally more expensive than small molecule products, and their everyday use poses a difficult problem for the economies and health systems of numerous countries. Price reduction when generics are used -compared to the originator- reaches 80%. Similar numbers are not expected for biosimilars, as development costs are higher. Development time is 6-9 years, while for generics it is 3 years. Biosimilars require phase I and phase III trials, whereas generics only require bio-equivalence studies. Manufacturing costs are of 250-450 million dollars for complex biosimilars and post-approval pharmacovigilance programs are needed.

The budgetary implication of biosimilars is that they offer a less costly alternative to existing biologic drugs. Another important parameter is that they facilitate and enhance competition. Consequently, the availability of biosimilars may improve access to expensive biological drugs for large parts of the population and may contribute to the economic benefit of health systems.

A point of concern is that the price differences between biosimilar products and their reference products have not been as clear as was the case in the market of generic drugs. A new system of market prices arrangement remains to be developed over the next few years. Recent market data shows that biosimilar products belong to a growing part of pharmaceuticals, decreasing the cost of treatment for a significant patient population.

The most serious issue regarding the use of a biosimilar product and its reference one is whether or not they are interchangeable. There is no clear answer as yet; however, regulatory authorities of the vast majority of European countries discourage doctors from making such substitutions, despite the lack of legal regulatory frameworks.

CONCLUSIONS

Overall, the use of biosimilar drugs is not as simple as that of small molecule generics. Many issues regarding their quality, efficacy and safety are as yet unresolved. The existing legislation is adequate for the safe production of this class of medicines; however, there is concern regarding many stages of their production or use. In general, biosimilars have no safety issues, and if they prove to be cheaper than the reference product, they will provide enormous help to health systems worldwide.

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4. A business process map in relation to the mandatory follow-up of information for the identification of suspected biological medicinal products is presented in Appendix 1 of the Guideline on Good Pharmacovigilance Practice (GVP).

Osteonecrosis of the jaw in a patient with chronic myelogenous leukemia receiving imatinib – A case report with clinical implications

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ABSTRACT

We present a case of osteonecrosis (2010) in a woman with chronic myelogenous leukemia (CML) receiving imatinib (2008-present). Four years earlier (2005-2006) the patient received chemotherapy and rituximab for non-Hodgkin's lymphoma as well as alendronate and one injection of zoledronate for osteoporosis. Osteonecrosis (ONJ) was associated with imatinib, combined with the previous bisphosphonates. ONJ was healed in 2011 and recurred in 2012 following an injection of denosumab for deteriorating osteoporosis. Today (September 2013), the patient remains asymptomatic, with ONJ at stage 1 and continues imatinib therapy. Clinical, radiological and histological similarities between imatinib- or other angiogenic inhibitor-related ONJ and ONJ related to antiresorptives, point to a common pathogenetic mechanism. With the increasing use of imatinib, often in combination with other ONJ-inducing agents, it is important to alert clinicians so they can follow these patients closely.

Key words: alendronate; chronic myelogenous leukemia; denosumab; imatinib; osteonecrosis of the jaw; zoledronic acid.

INTRODUCTION

Imatinib mesylate (Glivec®), an approved agent for the first-line treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) Chronic Myelogenous Leukemia (CML), is a potent tyrosine kinase inhibitor of the bcr/abl oncogene in CML, as well as the platelet-derived growth factor receptor (PDGFR) and the stem cell factor (c-kit), both important factors in angiogenesis (1). Different tyrosine kinase inhibitors, such as sunitinib or sorafenib, and anti-angiogenic drugs such as bevacizumab, administered as monotherapy or in combination with antiresorptives, have been related to the development of or increased risk for or deterioration of ONJ (2-12). We aim to present a case of ONJ related, at least partly, to imatinib and we discuss similarities between ONJ observed in patients receiving imatinib or other tyrosine kinase inhibitors and ONJ seen in patients receiving antiresorptives.

CASE REPORT

A 71 y.o. non-smoking female receiving imatinib (2008-present) for CML presented (2010) with pain on the left mandible. Two lower molars had been extracted (May and June 2010) because of pain, swelling, purulence, and tooth mobility. Clinically non-healing extraction sockets of more than 8 weeks duration, exposed necrotic bone, swelling and purulence as well as a radiolucency with radiopacities compatible with bone sequestrum seen in the panoramic radiograph (Figure 1) were consistent with ONJ stage 2 (13). Without imatinib being interrupted, amoxicillin 1 g x 3/day and metronidazole 500 mg x 3/day were prescribed for two weeks. Local antiseptic rinses and miconazole oral gel for topical use were introduced (14). ONJ regressed to stage 1. After cycles of remissions and recurrences treated with different antibiotics, the area of the necrotic bone was finally covered with oral mucosa and ONJ was considered healed (September 2011).

The patient had been diagnosed with CML in December 2008 during a regular follow up for a previously diagnosed non-Hodgkin's lymphoma (NHL), when blood counts revealed

Figure 1.
Panoramic radiograph, first event of osteonecrosis (August 2010). A large radiolucency with bone sequestrum formation can be observed (arrow).

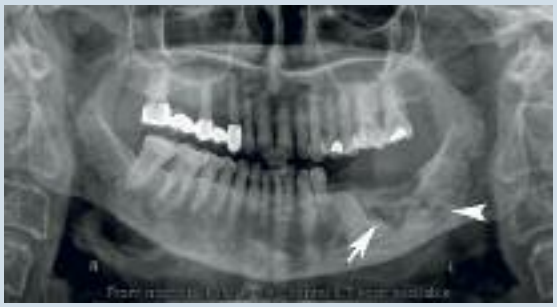
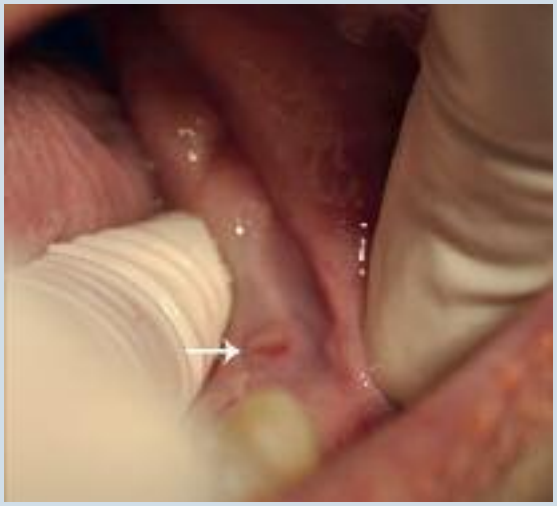


Figure 2.
Recurrence of osteonecrosis (October 2012). A fistula and soft tissue edema and inflammation can be observed on the mandible (arrow).



thrombocytosis (platelets at 950,000/ml) and leukocytosis with basophilia (absolute basophil number 1000/ml). Bone marrow biopsy and aspirate showed a chronic myeloproliferative picture, while bone marrow and peripheral blood were positive for the bcr-abl translocation. She was started on treatment with imatinib mesylate, 400 mg daily, with good hematological response. Due to anemia and fatigue imatinib was reduced to 300 mg daily.

In July 2005 the patient had received one cycle of rituximab and cyclophosphamide, vincristine, prednisone for the management of grade I follicular B cell CD 20+ lymphoma (NHL), stage II, with abdominal lymphadenopathy. Due to severe neurotoxicity vincristine was discontinued and patient received 7 additional cycles of rituximab, cyclophosphamide and prednisone. Complete radiographic remission was achieved and the patient received 4 doses of rituximab maintenance during 2006. At the same time (2005-2006) she received alendronate 70 mg/week, vitamin D and calcium supplements as well as a single dose of zoledronic acid (4 mg) to manage osteoporosis, in this dance teacher at high risk of fracture.

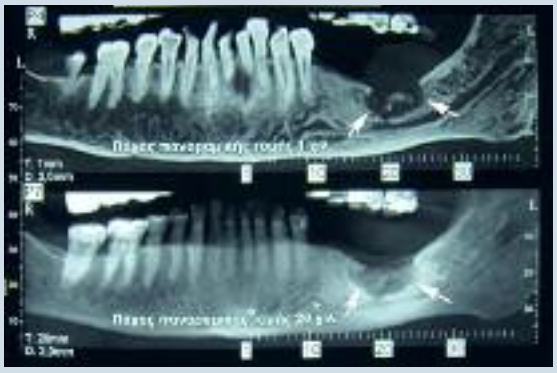
We hypothesized that ONJ was related to the antiangiogenic properties of imatinib, combined with the low preceding doses of bisphosphonates (BP).

A year later (October 2012) the patient presented, again, with pain, swelling and purulent secretion in the area of the previous ONJ lesion, one month after an injection of denosumab, (60 mg) because of deteriorating osteoporosis (Figure 2). Radiolucency, surrounding opacity, compatible with bone sequestrum, was observed on the cone beam computed tomography (CBCT) (Figure 3). A recurrence of the previous ONJ was diagnosed, possibly related to the potential synergistic effect of imatinib and denosumab. Amoxicillin 1 g x 3/day was prescribed and patient underwent surgical debridement of the bone sequestrum. Histopathological examination of the bone fragments disclosed necrotic bone, granulation tissue, inflammatory infiltrate, and bacterial aggregates (Figure 4). Amoxicillin 500 mg x 3/day alternating with clindamycin 300 mg x 2/day continued until January 2013, combined with weekly topical ozone oil applications (1, 16). Today (September 2013), the patient remains asymptomatic, with ONJ at stage 1 (Figure 5), on weekly ozone oil applications. She remains bcr-abl positive and continues imatinib, at 300 mg daily, as she has achieved hematological remission and tolerates this dose very well. She has also started subcutaneous injections with teriparatide because of deterioration of osteoporosis.

DISCUSSION

We presented a case of ONJ attributed, at least partly, to the chronic use of imatinib. Other tyrosine kinase angiogenesis inhibitors (TKIs), targeting PDGFR, c-kit and vascular endothelial growth factor receptor (VEGFR), such as sunitinib, sorafenib and bevacizumab have also been associated with the development or worsening or increased risk of ONJ (2-12). In our case, pretreatment of bone with BP, 4 years earlier, may have increased the risk for the development of ONJ. An additive effect of the antiangiogenic properties of BP and angiogenic inhibitors has also been reported, leading to a higher incidence or recurrence of BP-related ONJ (17). ONJ recurred in our patient following one injection of denosumab, suggesting a role for the combined effect of imatinib with the single dose of denosumab, which has also been related to ONJ (18). Denosumab is an inhibitor of the receptor activator of nuclear factor κ-B ligand (RANKL), and has no known antiangiogenic action.

Figure 3.
Cone Beam Computed Tomography (CBCT): Bone sequestrum is observed within the radiolucency (October 2012, arrow).



It has become apparent that ONJ is associated with drugs with antiresorptive and/or antiangiogenic properties. The pharmacological mechanisms of these drugs appear distinct, yet a common effect on bone, by shared mechanisms, may occur in susceptible hosts. Detrimental effects to macrophages have been proposed to play a central role in the development of ONJ, by increasing the risk of oral infection followed by local necrosis. Osteoclasts differentiate from the monocyte-macrophage lineage under the influence of cytokine growth factors, especially the macrophage colony-stimulating factor (M-CSF), RANKL and VEGF (19, 20). All those factors can be affected by the above antiresorptives or angiogenesis inhibitors. Oral/oropharyngeal epithelial damage/stomatitis, as the first line of defense, has to precede the macrophage-related host immune response and may represent another pathway targeted by drugs associated with ONJ. Sunitinib-associated stomatitis and painful episodes of mucosal infection have been associated with ONJ (3, 7). Stomatitis is common in sorafenib and bevacizumab use (21, 22). Oral mucosal toxicity from imatinib has been reported and has been hypothesized to be associated with the altered function of c-kit expressed in mast cells, melanocytes and keratinocytes (23, 24, 25). Esophagitis is a known adverse effect of exposure to oral BP, while a toxic effect of zoledronate on keratinocyte cell lines has been shown (26, 27). Thus, soft tissue injury and impaired host mechanisms and infection may be some of the initial steps in the chronic process of ONJ. Clinical, histological and imaging studies also suggest that an infectious process and a form of osteomyelitis precede the appearance of the exposed bone. Periapical infection or periodontal disease preceded dental extractions associated with ONJ, while histologically dead bone, with signs of inflammation and bacterial colonization was observed in all patients of one study, as in our case (28). In another study, radionuclide uptake showed that inflammation of bone preceded the development of ONJ (29). The reduced prevalence of BP-related ONJ reported with the implementation of preventive dental programs that control the dental/periodontal microbial load also point to an inflammatory process as an initial stage in the chronic pathology of ONJ (30-32).

Figure 4.
Histopathological examination: acellular, necrotic bone (thick arrows), granulation tissue with inflammatory infiltrates (thin arrows), and bacterial aggregates are observed (pins). Hematoxylin & eosin X 400.

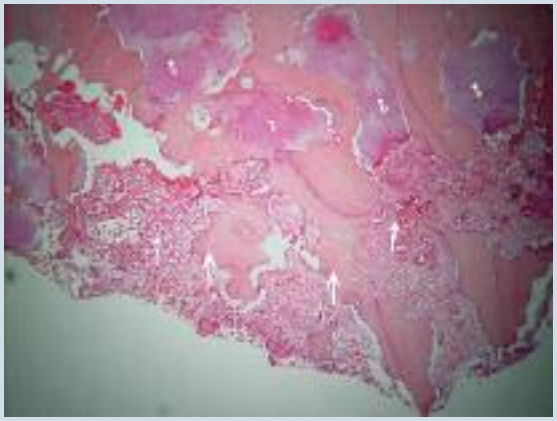
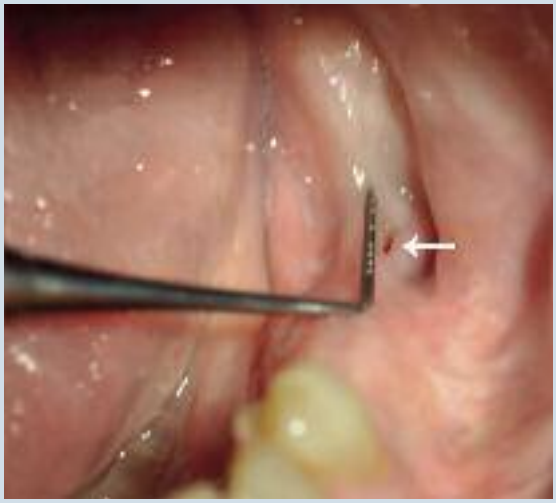


Figure 5.
June 2013: Clinical remission and partial mucosal coverage. A fistula is seen (arrow).



In our patient healing was achieved with conservative treatment, which is the standard treatment strategy for BP-related ONJ, while she remained on imatinib (13, 14). Antibiotics and minor surgery resulted to the stabilization of ONJ recurrence. We have no comments as to the effect of ozone oil therapy in the treatment of ONJ, except for the positive feedback from the patient on immediate pain relief, without notable toxicity. Ozone has been reported to have a beneficial effect on the clinical outcome of ONJ (15, 16). Ozone oil therapy might be a useful adjunctive therapy in the treatment of ONJ.

Similarities between antiresorptive-related ONJ and that related to angiogenesis inhibitors, such as (1) the history of dental extraction often following a periodontal or periapical abscess; (2) the clinical presentation of exposed, necrotic bone; (3) radiolucencies surrounding radiopacities; and (4) similar histology with necrotic bone, inflammation and bacterial colonies point to a common pathway targeted by different ONJ-related medications.

With the increasing use of imatinib, often following oral bisphosphonates or other antiresorptives used in the setting of osteoporosis, a detailed evaluation of the patient and the overall risk for ONJ becomes important.

Note: Patient permission was obtained. There was no funding.

Conflict of interest statement

Ourania Nicolatou-Galitis has received conference support from Novartis and Pfizer. Evangelia Razis has received conference support from Amgen, Roche and Novartis. Emmanouil Vardas has received conference support from Amgen. Stefanos Labropoulos has received conference support from Novartis. All remaining authors have declared no conflicts of interest.

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Leptomeningeal metastasis from gastroesophageal carcinoma

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ABSTRACT

Esophageal carcinoma (EC) rarely metastasizes to the CNS. In our center, among 21 cases of esophageal cancer registered for treatment during a 33-month (January 2011 - August 2013) period, leptomeningeal metastasis from esophageal carcinoma was detected in only one case, that relapsed with leptomeningeal metastasis with multi-level neurological affection in the form of cerebral involvement, cranial nerve palsy and spinal dysfunction after 21 months from primary diagnosis of the cancer. After diagnosis documentation by CSF examination and brain MRI, patient PS had deteriorated and he became comatose with response only to pain stimulation. We tried single injection of intrathecal methotrexate and hydrocortisone together with IV dexamethasone, but unfortunately he died 3 days after start of treatment. This case reflects the fatal outcome when there is delay in diagnosis.

Key words: gastroesophageal cancer; leptomeningeal metastasis; intrathecal chemotherapy.

INTRODUCTION

Leptomeningeal carcinomatosis (LMC) is a devastating complication of advanced cancer, and due to advances in neuroimaging and improved treatment outcomes, it is nowadays seen more frequently. The most common neoplasms metastasizing to the leptomeninges are carcinoma of the breast, lymphomas and leukemia. LMC caused by gastroesophageal cancer can present as part of the initial clinical presentation or during late metastatic disease. As the diagnosis is often difficult to establish, the presence of malignant cells in CSF is considered diagnostic. The incidence of LMC is 3-8% of all solid cancers (1). We report a case of early gastroesophageal cancer that presented with isolated LMC after successful treatment of the primary cancer.

CASE REPORT

A 49-year-old male patient presented with progressive dysphagia, vomiting with infrequent attacks of hematemesis and weight loss for about 6 months until he presented to King Abdullah Medical City (KAMC) on 17 November 2011 for further work-up. Upper GI endoscopy revealed a mass in the lower part of the esophagus measuring approximately 5 cm in length, promptly bleeding on touch. Mass biopsy revealed signet ring adenocarcinoma. Staging work-up was performed by neck, chest, abdomen and pelvis CTs, which revealed circumferential thickening in the distal part of the esophagus and the cardiac region of the stomach, measuring about 5.2 cm in length. There were multiple sub-centimeter sized lymph nodes at the hepatogastric ligament and celiac region (Figure 1). Bone scan was negative for osseous metastasis.

The patient was subsequently transferred to the surgical department where he underwent esophagogastrectomy and the pathology study (Figure 2) revealed:

- Signet ring cell adenocarcinoma of the lower esophagus.
- 3x2 cm-sized tumor invading through the *muscularis propria* into the periesophageal region.
- All surgical margins were negative.
- Lymphovascular invasion was positive.
- Regional lymph nodes were positive 6/12.

The post-op recovery period passed smoothly without complications, and then the patient was moved again to the oncology center, where he received adjuvant radiotherapy concomitant with capecitabine (45 Gy in 25 fra-

Figure 1.
Abdomen CT.

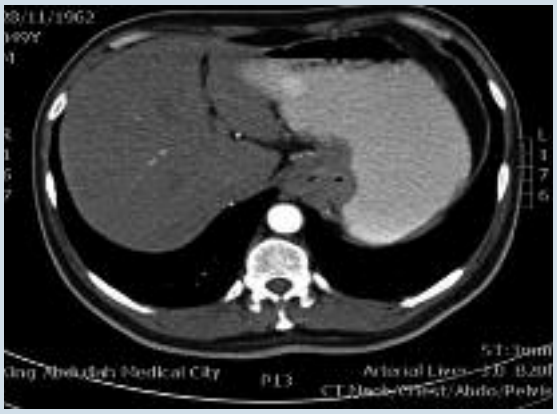
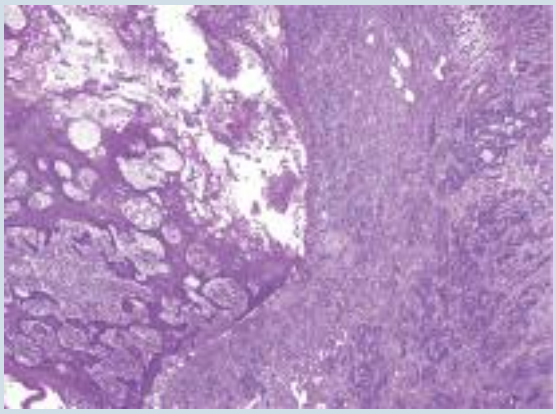


Figure 2.
Esophagus H & E stain.



ctions over 5 weeks with capecitabine 650 mg/m^2 twice daily along with radiation therapy).

Since then, the patient was followed-up at the oncology clinic on a regular basis with no evidence of recurrence or distant metastasis, until 30 August 2013, when he presented to the ER complaining of numbness in the perineum and paraparesis for about 3 months, which progressed to complete loss of sensation in these areas; then autonomic dysfunction occurred in the form of constipation and urine retention.

Clinically, the patient was conscious and well-oriented; vital signs were stable with hypotonia and hyporeflexia in both lower limbs.

The following investigations were requested:

- Chest & abdomen CT: No evidence of local recurrence or distant metastasis.
- Brain CT: No evidence of metastasis.
- Pelvis MRI: normal.
- Lumbar spine MRI: bilateral spondylosis with minimal anterior displacement of L5 over S1.
- EMG: findings are suggestive of mild axonal neuropathy at the level of the L5 nerve root and below, that are proximal to sensory ganglion.

On the 2nd day there was marked deterioration of his general condition in the form of complete paraplegia, double-sphincter incontinence, slurred speech and Cranial nerves VI, VII, IX and X being affected. Brain & whole spine MRI were performed and revealed evidence of leptomeningeal disease, mostly metastatic (Figures 3a, 3b). CSF examination was also positive for malignant cells and the IHC was weakly positive for CK AE1/AE3 and negative for CD68 (Figures 4a, 4b).

The strategy plan was to start the patient on intrathecal methotrexate and hydrocortisone biweekly with IV dexamethasone daily. He received only one injection with rapid deterioration on the level of consciousness, drifted into a deep coma and died of severe respiratory distress 3 days later.

DISCUSSION

LMC is a severe complication that occurs usually in cancer patients with advanced disease. Giglio et al. reported the frequency of LMC occurrence from gastro-esophageal cancer as being 0.19% and Lee et al. reported a prevalence of 0.17% in a review of 11,335 cases with gastroesophageal cancers (2).

There are different proposed mechanisms of tumor spread into the leptomeninges. Tumor cells may reach the leptomeninges by hematogenous spread to the vessels of the arachnoid or choroid plexus, direct extension from parenchymal, dural and bone-based metastases and/or via the perineural route along the cranial nerves to finally enter the subarachnoid space (3). Neurological symptoms and clinical signs are frequently the result of the relatively acute onset of debilitating neurological deficits affecting various motor or sensory functions and possibly cognitive function (4).

They usually manifest clinically as multi-level neurological dysfunction in the form of cerebral involvement, cranial nerve palsy or spinal affection. Most of these cases have multiple metastatic lesions outside the nervous system, including the liver, lungs and bone (5). Our patient had isolated leptomeningeal metastasis with no signs of extra-neural metastasis.

In most of the reported cases, the time interval between initial diagnosis of cancer and established diagnosis of LMC presenting with heavy neurological symptoms is approximately 12 months (6). However, in our case, the interval between primary diagnosis of cancer and development of metastasis was about 21 months.

Figure 3A.
Brain MRI.

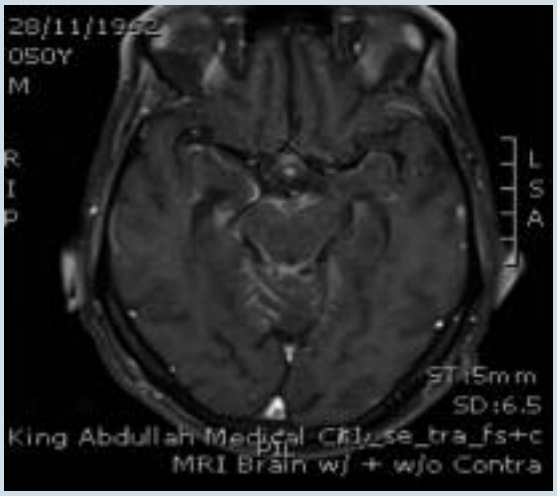
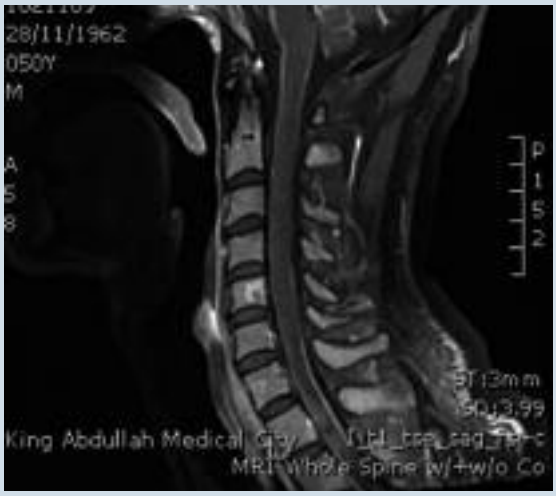


Figure 3B.
Spine MRI; cervical part.



Early diagnosis of LMC is important since fixed neurological signs do not resolve with therapy (5). In a series published by Kim et al., they reported a prognostic significance for cytologically negative conversion of CSF by IT chemotherapy for survival; however, due to the small sample size and inherent selection bias of the retrospective design of their study, drawing any conclusions on the outcomes of treatment is somewhat difficult (7). Unfortunately, in our case, when the LMC diagnosis was established, there were already fixed neurological deficits, such as complete paraplegia, autonomic dysfunction and multiple cranial nerve palsies, which gravely affected patient prognosis.

CONCLUSION

In patients with gastroesophageal cancers presenting with neurological manifestations, the dissemination to the CNS and leptomeningeal involvement should be suspected. Early CNS assessment should be performed so as to rule out metastasis, since early treatment intervention may reverse the symptoms and improve prognosis, as any delay may be fatal.

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

Figure 4A.
CSF with DQ stain.

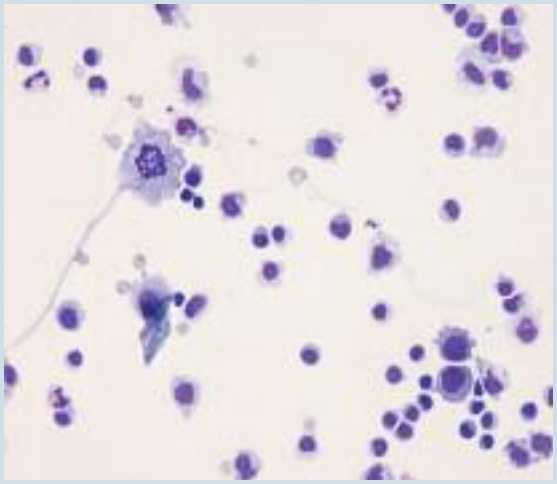
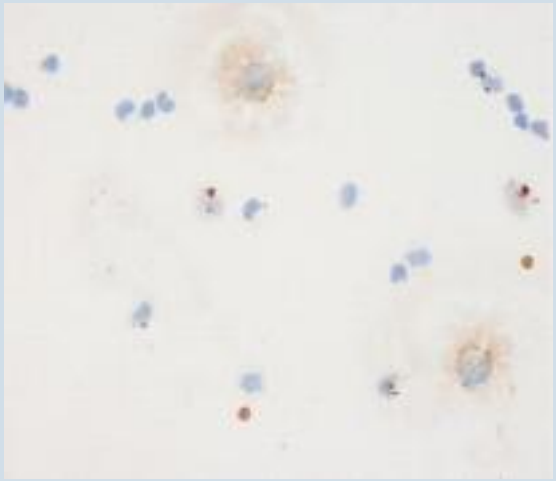


Figure 4B.
CSF IHC +ve CK AE1/AE3.



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Οφθαλμικές διαταραχές	Αυξημένη δακρύρροια		
Καρδιακές διαταραχές		Δυσλειτουργία αριστερής κοιλίας † (συμπεριλαμβανομένης της συμφορητικής καρδιακής ανεπάρκειας)	
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωράκιου	Δύσπνοια † Βήχας†	Πλευριτική εξιδρωματική συλλογή	Διάμεση πνευμονοπάθεια
Διαταραχές του γαστρεντερικού	Διάρροια † Έμετος † Στοματίτιδα Ναυτία † Δυσκοιλιότητα † Δυσπεψία		
Διαταραχές του δέρματος και του υποδόριου ιστού	Αλωπεκία Εξάνθημα † Διαταραχές των ονύχων Κνησμός Ξηροδερμία		
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	Μυαλγία Αρθραλγία		
Κατηγορία/οργανικό σύστημα	***Πολύ συχνές***	***Συχνές***	***Όχι συχνές***
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	Βλεννογονίτιδα/φλεγμονή του βλεννογόνου Άλγος † Οίδημα † Πυρεξία Κόπωση † Εξασθένιση †	Ρίγη	

*Περιλαμβάνει ανεπιθύμητες αντιδράσεις με θανατηφόρο έκβαση.
† Εξαιρουμένης της εμπύρετης ουδετεροπενίας, της ουδετεροπενίας, της λευκοπενίας, της αυξημένης δακρύρροιας, της διάμεσης πνευμονοπάθειας, της παρωνυχίας και της αλωπεκίας, όλα τα συμβάντα σε αυτόν τον πίνακα αναφέρθηκαν επίσης σε τουλάχιστον 1% των ασθενών που συμμετείχαν στις μελέτες μονοθεραπείας του Perjeta, παρόλο που δεν θεωρήθηκε απαραιτήτως ότι σχετίζονται αιτιατά με το Perjeta κατά τον ερευνητή. Τα πολύ συχνά συμβάντα (αναφέρθηκαν σε ≥10% των ασθενών υπό θεραπεία με Perjeta ως μονοθεραπεία) σημειώνονται στον Πίνακα με ένα †.
° Η υπερευαισθησία/αναφυλακτική αντίδραση βασίζεται σε μία ομάδα όρων.
°° Η σχετιζόμενη με την έγχυση αντίδραση/σύνδρομο απελευθέρωσης κυτοκινών περιλαμβάνει ένα εύρος διαφορετικών όρων σε ένα χρονικό πλαίσιο, βλ. «Περιγραφή επιλεγμένων ανεπιθύμητων αντιδράσεων» στη συνέχεια.
Ανεπιθύμητες αντιδράσεις φαρμάκου που αναφέρθηκαν σε ασθενείς που έλαβαν Perjeta και τραστουζουμάμπη μετά από τη διακοπή της δοσεταξέλης: Στη βασική δοκιμή CLEOPATRA, ανεπιθύμητες αντιδράσεις φαρμάκου αναφέρθηκαν λιγότερο συχνά μετά από τη διακοπή της θεραπείας με δοσεταξέλη. Μετά από τη διακοπή της δοσεταξέλης, όλες οι ανεπιθύμητες αντιδράσεις φαρμάκου στην ομάδα υπό θεραπεία με Perjeta και τραστουζουμάμπη σημειώθηκαν σε < 10% των ασθενών, εξαιρουμένης της διάρροιας (19,1%), της λοίμωξης του ανώτερου αναπνευστικού συστήματος (12,8%), του εξανθήματος (11,7%), της κεφαλαλγίας (11,4%) και της κόπωσης (11,1%). *Περιγραφή επιλεγμένων ανεπιθύμητων αντιδράσεων:* Αντιδράσεις στην έγχυση, αντιδράσεις υπερευαισθησίας/αναφυλαξίας: Η αντίδραση στην έγχυση ορίστηκε στη βασική δοκιμή ως οποιοδήποτε συμβάν (ανεξαρτήτως αιτιότητας) περιγράφεται ως υπερευαισθησία, αναφυλακτική αντίδραση, οξεία αντίδραση στην έγχυση ή σύνδρομο απελευθέρωσης κυτοκινών, το οποίο εμφανίζεται κατά τη διάρκεια της έγχυσης ή την ίδια μέρα με την έγχυση. Στη βασική δοκιμή CLEOPATRA, η αρχική δόση του Perjeta χορηγήθηκε την ημέρα πριν από τη χορήγηση της τραστουζουμάμπης και της δοσεταξέλης για να επιτραπεί η εξέταση των σχετιζόμενων με το Perjeta αντιδράσεων. Κατά την πρώτη ημέρα που χορηγήθηκε μόνο το Perjeta, η συνολική συχνότητα των αντιδράσεων στην έγχυση ήταν 9,8% στην ομάδα υπό θεραπεία με εικονικό φάρμακο και 13,0% στην ομάδα υπό θεραπεία με Perjeta, με την πλειοψηφία των αντιδράσεων στην έγχυση να είναι ήπιες ή μέτριες. Οι συνηθέστερες αντιδράσεις στην έγχυση (> 1,0%) στην ομάδα υπό θεραπεία με Perjeta ήταν πυρεξία, ρίγη, κόπωση, κεφαλαλγία, εξασθένιση, υπερευαισθησία και έμετος. Κατά τη διάρκεια του δεύτερου κύκλου, όταν όλα τα φαρμακευτικά προϊόντα χορηγήθηκαν την ίδια ημέρα, οι πιο συχνές αντιδράσεις στην έγχυση στην ομάδα υπό θεραπεία με Perjeta (> 1,0%) ήταν κόπωση, δυσγευσία, υπερευαισθησία, μυαλγία και έμετος. Στη βασική δοκιμή CLEOPATRA, η συνολική συχνότητα των συμβάντων υπερευαισθησίας/αναφυλαξίας (μη συμπεριλαμβανομένων των οξέων αντιδράσεων στην έγχυση/συνδρόμου απελευθέρωσης κυτοκινών) κατά τη διάρκεια ολόκληρης της περιόδου θεραπείας ήταν 9,1% στην ομάδα υπό θεραπεία με εικονικό φάρμακο και 10,8% στην ομάδα υπό θεραπεία με Perjeta, εκ του οποίου το 2,5% και το 2% ήταν 3ου-4ου βαθμού κατά NCI-CTCAE, αντίστοιχα. Συνολικά, 2 ασθενείς στην ομάδα υπό θεραπεία με εικονικό φάρμακο και 4 ασθενείς στην ομάδα υπό θεραπεία με Perjeta εμφάνισαν συμβάντα, τα οποία περιγράφηκαν ως αναφυλαξία από τον ερευνητή (βλ. παρ. Ειδικές προφυλάξεις). Συνολικά, η πλειοψηφία των αντιδράσεων υπερευαισθησίας ήταν ήπιες ή μέτριες σε σοβαρότητα και υποχώρησαν κατά τη θεραπεία. Βάσει των τροποποιήσεων που έγιναν στη θεραπεία της μελέτης, οι περισσότερες αντιδράσεις εκτιμήθηκαν ως δευτερεύουσες στις εγχύσεις δοσεταξέλης. ***Εμπύρετη ουδετεροπενία:*** Στη βασική δοκιμή CLEOPATRA, η πλειοψηφία των ασθενών και στις δύο ομάδες θεραπείες εμφάνισε τουλάχιστον ένα συμβάν λευκοπενίας (62,4% των ασθενών στην ομάδα υπό θεραπεία με Perjeta και 58,2% των ασθενών στην ομάδα υπό θεραπεία με εικονικό φάρμακο), εκ των οποίων η πλειοψηφία ήταν συμβάντα ουδετεροπενίας. Παρατηρήθηκε εμπύρετη ουδετεροπενία στο 13,8% των ασθενών υπό θεραπεία με Perjeta και στο 7,6% των ασθενών υπό θεραπεία με εικονικό φάρμακο. Και στις δύο ομάδες θεραπείας, το ποσοστό των ασθενών που εμφάνισε εμπύρετη ουδετεροπενία ήταν το υψηλότερο στον πρώτο κύκλο της θεραπείας και μειώθηκε σταδιακά στη συνέχεια. Αυξημένη επίπτωση εμπύρετης ουδετεροπενίας παρατηρήθηκε στους Ασιάτες ασθενείς και στις δύο ομάδες θεραπείας συγκριτικά με τους ασθενείς από άλλες φυλές και άλλες γεωγραφικές περιοχές. Μεταξύ των Ασιατών ασθενών, η επίπτωση της εμπύρετης ουδετεροπενίας ήταν υψηλότερη στην ομάδα υπό θεραπεία με Perjeta (26%) συγκριτικά με την ομάδα υπό θεραπεία με εικονικό φάρμακο (12%). *Διάρροια:* Στη βασική κλινική δοκιμή CLEOPATRA, διάρροια σημειώθηκε στο 66,8% των ασθενών υπό θεραπεία με Perjeta και στο 46,3% των ασθενών υπό θεραπεία με εικονικό φάρμακο. Τα περισσότερα συμβάντα ήταν ήπια-μέτρια σε σοβαρότητα και σημειώθηκαν μόλις στους πρώτους κύκλους της θεραπείας. Η επίπτωση της διάρροιας 3ου-4ου βαθμού κατά NCI-CTCAE ήταν 7,9% στους ασθενείς υπό θεραπεία με Perjeta έναντι 5,0% στους ασθενείς υπό θεραπεία με εικονικό φάρμακο. Η διάμεση διάρκεια του μεγαλύτερου επεισοδίου ήταν 17 ημέρες στους ασθενείς υπό θεραπεία με Perjeta και 8 ημέρες στους ασθενείς υπό θεραπεία με εικονικό φάρμακο. Τα διαρροϊκά συμβάντα ανταποκρίθηκαν καλά στην προδραστική διαχείριση με αντιδιαρροϊκούς παράγοντες. *Εξάνθημα:* Παρατηρήθηκε εξάνθημα στο 45,2% των ασθενών υπό θεραπεία με Perjeta συγκριτικά με το 36,0% των ασθενών υπό θεραπεία με εικονικό φάρμακο. Τα περισσότερα συμβάντα ήταν 1ου ή 2ου βαθμού σε σοβαρότητα, σημειώθηκαν στους πρώτους δύο κύκλους, και ανταποκρίθηκαν στις καθιερωμένες θεραπείες, όπως είναι η τοπική ή η από του στόματος θεραπεία για την ακμή. Μη φυσιολογικές εργαστηριακές εξετάσεις: Η επίπτωση της ουδετεροπενίας 3ου-4ου βαθμού κατά NCI-CTCAE (έκδοση 3) ήταν ισορροπημένη στις δύο ομάδες θεραπείας (85,9% των ασθενών υπό θεραπεία με Perjeta και 86,6% των ασθενών υπό θεραπεία με εικονικό φάρμακο, συμπεριλαμβανομένου του 61,0% και 64,3% με ουδετεροπενία 4ου βαθμού, αντίστοιχα). **Ημερομηνία αναθεώρησης του κειμένου:** 17 Ιουνίου 2013
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ΣΥΝΟΠΤΙΚΗ ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ. 1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση. **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:** Κάθε ml πυκνού διαλύματος περιέχει 5 mg ipilimumab. Ένα φιαλίδιο των 10 ml περιέχει 50 mg ipilimumab. Ένα φιαλίδιο των 40 ml περιέχει 200 mg ipilimumab. Το ipilimumab είναι ένα πλήρως ανθρώπινο αντι CTLA4 μονοκλωνικό αντίσωμα (IgG1κ) που παράγεται σε κύτταρα ωοθηκών κινεζικού κρικητού με τεχνολογία ανασυνδυασμένου DNA. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις:** Το YERVOY ενδείκνυται για τη θεραπεία του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος σε ενηλίκους που έχουν λάβει προηγούμενη θεραπεία. **4.3 Αντενδείξεις:** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα. **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Το YERVOY σχετίζεται με φλεγμονώδεις ανεπιθύμητες αντιδράσεις που προκύπτουν από αυξημένη ή εκτεταμένη δραστηριότητα του ανοσοποιητικού (ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό) και πιθανόν σχετίζονται με το μηχανισμό δράσης του. Ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό που μπορεί να είναι σοβαρές ή απειλητικές για τη ζωή, είναι πιθανό να συμπεριλαμβάνουν γαστρεντερικές, ηπατικές, δερματικές, νευρολογικές, ενδοκρινολογικές ή άλλων οργανικών συστημάτων. Ενώ οι περισσότερες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό εμφανίστηκαν κατά την περίοδο επαγωγής έχει επίσης αναφερθεί εκδήλωση μήνες μετά από την τελευταία δόση του YERVOY. Εκτός αν προσδιοριστεί διαφορετική αιτιολογία, η διάρροια, η αυξημένη συχνότητα κενώσεων, το αίμα στα κόπρανα, οι αυξήσεις LFT, το έξάνθημα και η ενδοκρινοπάθεια πρέπει να θεωρηθούν φλεγμονώδεις και να συνδέονται με το YERVOY. Η πρώιμη διάγνωση και η κατάλληλη διαχείριση είναι απαραίτητες για την ελαχιστοποίηση απειλητικών για τη ζωή επιπλοκών. Συστηματική εισαγωγή υψηλών δόσεων κορτικοστεροειδών με ή χωρίς επιπρόσθετη ανοσοκατασταλτική θεραπεία είναι πιθανό να απαιτηθεί για την αντιμετώπιση σοβαρών ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό. Ειδικές για το YERVOY κατευθυντήριες γραμμές για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό περιγράφονται παρακάτω. Γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρα περιστατικά λόγω διάτρησης του γαστρεντερικού σωλήνα έχουν αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg σε μια μελέτη προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος Φάσης 3 (MDX01020, βλέπε παράγραφο 5.1) ο διάμεσος χρόνος έως την εκδήλωση σοβαρών ή θανατηφόρων (Βαθμού 35) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (εύρος 5 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, η υποχώρηση (ορίζεται ως βελτίωση σε ήπια [Βαθμού 1] ή λιγότερο ή στη σοβαρότητα κατά την έναρξη) εμφανίστηκε στις περισσότερες περιπτώσεις (90%) σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 4 εβδομάδες (εύρος 0,6 έως 22 εβδομάδες). Οι ασθενείς πρέπει να παρακολουθούνται για γαστρεντερικά σημεία και συμπτώματα που είναι πιθανό να υποδεικνύουν κολίτιδα σχετιζόμενη με το ανοσοποιητικό ή διάτρηση του γαστρεντερικού σωλήνα. Στην κλινική εικόνα είναι πιθανό να συμπεριλαμβάνεται διάρροια, αυξημένη συχνότητα εντερικών κινήσεων, κοιλιακό άλγος ή αιματοχεσία, με ή χωρίς πυρετό. Διάρροια ή κολίτιδα που εμφανίζεται μετά από την έναρξη του YERVOY πρέπει να αξιολογείται έγκαιρα για τον αποκλεισμό λοιμώδους ή άλλης εναλλακτικής αιτιολογίας. Σε κλινικές δοκιμές, κολίτιδα σχετιζόμενη με το ανοσοποιητικό συσχετίστηκε με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξελκώσεις και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Συστάσεις για την αντιμετώπιση της διάρροιας ή της κολίτιδας βασίζονται στην βαρύτητα των συμπτωμάτων (σύμφωνα με την ταξινόμηση της βαθμολόγησης της βαρύτητας κατά NCICTCAE v3). Ασθενείς με ήπια έως μέτρια (Βαθμού 1 ή 2) διάρροια (αύξηση έως 6 κενώσεις την ημέρα) ή πιθανολογούμενη ήπια έως μέτρια κολίτιδα (π.χ. κοιλιακό άλγος ή αίμα στα κόπρανα), είναι πιθανό να παραμείνουν στο YERVOY. Συνιστάται συμπτωματική θεραπεία (π.χ. λοπεραμίδη, υποκατάσταση υγρών) και προσεκτική παρακολούθηση. Εάν τα ήπια έως μέτρια συμπτώματα υποτροπιάσουν ή επιμείνουν για 57 ημέρες, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλείπεται και θα πρέπει να ξεκινήσει θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg από το στόμα άπαξ ημερησίως ή ισοδύναμο). Εάν παρουσιαστεί υποχώρηση σε Βαθμό 01 ή επιστροφή στην έναρξη, το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) διάρροια ή κολίτιδα (βλέπε παράγραφο 4.2),και πρέπει να ξεκινήσει αμέσως υψηλής δόσης ενδοφλέβια θεραπεία με κορτικοστεροειδή. (Σε κλινικές δοκιμές έχει χρησιμοποιηθεί μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελέγχεται η διάρροια και άλλα συμπτώματα, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται σε κλινική απόφαση. Σε κλινικές δοκιμές, η ταχεία βαθμιαία μείωση και διακοπή (σε διαστήματα < 1 μήνα) οδήγησε στην υποτροπή της διάρροιας ή της κολίτιδας σε ορισμένους ασθενείς. Οι ασθενείς πρέπει να αξιολογούνται για στοιχεία διάτρησης του γαστρεντερικού σωλήνα ή περιτονίτιδας. Η εμπειρία από κλινικές δοκιμές σχετικά με την αντιμετώπιση διάρροιας ανθεκτικής σε κορτικοστεροειδή ή κολίτιδας είναι περιορισμένη. Ωστόσο, είναι δυνατόν να ληφθεί υπόψη η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, προστέθηκε εφάπαξ δόση infliximab 5 mg/kg, εκτός εάν ήταν αντένδειξη. Δεν πρέπει να χρησιμοποιείται infliximab εάν πιθανολογείται διάτρηση του γαστρεντερικού σωλήνα ή σηψαιμία (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για το infliximab). Ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρή ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό. Θανατηφόρος ηπατική ανεπάρκεια έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 25) ηπατοτοξικότητας που συνδέεται με το ανοσοποιητικό κυμάνθηκε από 3 έως 9 εβδομάδες από την έναρξη της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμάνθηκε από 0,7 έως 2 εβδομάδες. Οι ηπατικές τρανσαμινάσες και η χολερυθρίνη πρέπει να αξιολογούνται πριν από κάθε δόση του YERVOY, καθώς πρόωρες εργαστηριακές μεταβολές μπορεί να υποδεικνύουν ανακύπτουσα ηπατίτιδα σχετιζόμενη με το ανοσοποιητικό (βλέπε παράγραφο 4.2). Αυξήσεις σε LFT είναι πιθανό να αναπτυχθούν απουσία κλινικών συμπτωμάτων. Πρέπει να αξιολογούνται αυξήσεις της AST και της ALT ή της ολικής χολερυθρίνης προς αποκλεισμό λοιπών αιτίων κάκωσης του ήπατος, συμπεριλαμβανομένων λοιμώξεων, εξέλιξης της νόσου ή φαρμακευτικών προϊόντων και να παρακολουθούνται έως την υποχώρησή τους. Βιοψίες ήπατος από ασθενείς που είχαν ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό, κατέδειξαν στοιχεία οξείας φλεγμονής (ουδετερόφιλα, λεμφοκύτταρα και μακροφάγα). Για ασθενείς με αυξημένη AST ή ALT στο εύρος των > 5-≤ 8 x ULN ή ολική χολερυθρίνη στο εύρος των > 3-≤ 5 x ULN που πιθανολογείται ότι σχετίζεται με το YERVOY, πρέπει να παραλείπεται η προγραμματισμένη δόση του YERVOY και πρέπει να παρακολουθούνται οι LFT έως την υποχώρηση. Όταν βελτιωθούν τα επίπεδα LFT (AST και ALT ≤ 5 x ULN και ολική χολερυθρίνη ≤ 3 x ULN), το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Για ασθενείς με αυξήσεις της AST ή της ALT > 8 x ULN που πιθανολογείται ότι σχετίζονται με το YERVOY, η θεραπεία πρέπει να διακόπτεται οριστικά (βλέπε παράγραφο 4.2) και πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με κορτικοστεροειδή υψηλής δόσης (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg ημερησίως ή ισοδύναμο). Σε αυτούς τους ασθενείς, πρέπει να παρακολουθούνται οι LFT έως την ομαλοποίηση. Όταν υποχωρούν τα συμπτώματα και ομαλοποιηθούν οι αυξήσεις των LFT, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Αυξήσεις των LFTs κατά τη βαθμιαία μείωση και διακοπή είναι δυνατόν να αντιμετωπιστούν με αύξηση της δόσης του κορτικοστεροειδούς και βραδύτερη βαθμιαία μείωση και διακοπή. Για ασθενείς με σημαντικές αυξήσεις των LFT που είναι ανθεκτικοί σε θεραπεία με κορτικοστεροειδή, είναι δυνατόν να εξεταστεί η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, χρησιμοποιήθηκε μυκοφαινολική μοφετίλη σε ασθενείς χωρίς ανταπόκριση σε θεραπεία με κορτικοστεροειδή ή που παρουσίασαν αύξηση του LFT κατά την βαθμιαία μείωση και διακοπή κορτικοστεροειδών που δεν ανταποκρινόταν σε αύξηση της δόσης των κορτικοστεροειδών (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για τη μυκοφαινολική μοφετίλη). Δερματικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντιδράσεις που μπορεί να συνδέονται με το ανοσοποιητικό. Θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Εξάνθημα και κνησμός επαγόμενα από YERVOY ήταν κυρίως ήπια ή μέτρια (Βαθμού 1 ή 2) και ανταποκρίνονταν σε συμπτωματική θεραπεία. Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως σοβαρών ή θανατηφόρων (Βαθμού 25) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες (εύρος 0,9 έως 16 εβδομάδες) από την έναρξη της θεραπείας. Με ειδικές για το πρωτόκολλο κατευθυντήριες γραμμές για την αντιμετώπιση, παρουσιάστηκε υποχώρηση στις περισσότερες περιπτώσεις (87%), σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (εύρος 0,6 έως 29 εβδομάδες). Εξάνθημα και κνησμός επαγόμενα από YERVOY πρέπει να αντιμετωπίζεται με βάση τη σοβαρότητα. Ασθενείς με μια ήπια έως μέτρια (Βαθμού 1 έως 2) δερματική ανεπιθύμητη αντίδραση μπορούν να παραμείνουν σε θεραπεία με YERVOY με συμπτωματική θεραπεία (π.χ. αντισταμινικά). Για ήπιο έως μέτριο εξάνθημα ή κνησμό που εμμένει για 1 έως 2 εβδομάδες και δεν βελτιώνεται με τοπικά κορτικοστεροειδή, πρέπει να ξεκινήσει η από του στόματος θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg άπαξ ημερησίως ή ισοδύναμο). Για ασθενείς με μια σοβαρή (βαθμού 3) δερματική ανεπιθύμητη αντίδραση, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί. Εάν βελτιωθούν τα αρχικά συμπτώματα σε ήπια (Βαθμού 1) ή υποχωρήσουν, η θεραπεία με YERVOY μπορεί να συνεχιστεί και πάλι στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με ένα πολύ σοβαρό (Βαθμού 4) εξάνθημα ή σοβαρό (Βαθμού 3) κνησμό (βλέπε παράγραφο 4.2) και θα πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με υψηλές δόσεις κορτικοστεροειδών (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελεγχθεί το εξάνθημα ή ο κνησμός, η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρο σύνδρομο Guillain-Barré έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Έχουν επίσης αναφερθεί συμπτώματα ομοιάζοντα με μυασθένεια gravis. Οι ασθενείς μπορεί να παρουσιάσουν μυϊκή αδυναμία. Μπορεί ακόμη να παρουσιαστεί αισθητική νευροπάθεια. Ανεξήγητη κινητική νευροπάθεια, μυϊκή αδυναμία ή αισθητική νευροπάθεια που διαρκεί > 4 ημέρες πρέπει να αξιολογείται και θα πρέπει να αποκλειστούν μη φλεγμονώδη αίτια, όπως εξέλιξη της νόσου, λοιμώξεις, μεταβολικά σύνδρομα και φαρμακευτικά προϊόντα. Για ασθενείς με μέτρια (Βαθμού 2) νευροπάθεια (κινητική με ή χωρίς αισθητική) που πιθανόν σχετίζεται με το YERVOY, θα πρέπει να παραλείπεται η προγραμματισμένη δόση. Εάν τα νευρολογικά συμπτώματα υποχωρήσουν στην έναρξη, ο ασθενής μπορεί να ξαναρχίσει το YERVOY στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) αισθητική νευροπάθεια που πιθανολογείται ότι συνδέεται με το YERVOY (βλέπε παράγραφο 4.2). Οι ασθενείς πρέπει να αντιμετωπίζονται σύμφωνα με τις κατευθυντήριες γραμμές του ιδρύματος για την διαχείρηση αισθητικής νευθροπάθειας και πρέπει να ξεκινήσουν αμέσως ενδοφλέβια θεραπεία με κορτικοστεροειδή (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Προοδευτικά σημάδια κινητικής νευροπάθειας θα πρέπει να θεωρείται ότι σχετίζονται με το ανοσοποιητικό και να αντιμετωπίζονται ανάλογα. Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) κινητική νευροπάθεια ανεξαρτήτως αιτιολογίας (βλέπε παράγραφο 4.2). Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό: Το YERVOY μπορεί να προκαλέσει φλεγμονή των οργάνων του ενδοκρινικού συστήματος, συγκεκριμένα υποφυσίτιδα, υποϋποφυσισμό, επινεφριδιακή ανεπάρκεια και υποθυρεοειδισμό και οι ασθενείς μπορεί να παρουσιάσουν μη ειδικά συμπτώματα, τα οποία μπορεί να μοιάζουν με άλλα αίτια, όπως μετάσταση στον εγκέφαλο ή υποκείμενη νόσο. Στη συχνότερη κλινική εικόνα συμπεριλαμβάνεται η κεφαλαλγία και η κόπωση. Στα συμπτώματα μπορεί να συμπεριλαμβάνονται ελλείμματα του οπτικού πεδίου, αλλαγές της συμπεριφοράς, διαταραχές των ηλεκτρολυτών και υπόταση. Επινεφριδιακή κρίση ως αίτιο των συμπτωμάτων του ασθενούς πρέπει να αποκλείεται. Η κλινική εμπειρία με ενδοκρινοπάθεια σχετιζόμενη με το YERVOY είναι περιορισμένη. Για ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 24) ενδοκρινοπάθειας σχετιζόμενης με το ανοσοποιητικό κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την έναρξη της θεραπείας. Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με ανοσοκατασταλτική θεραπεία και θεραπεία υποκατάστασης ορμονών. Εάν υπάρχουν οποιαδήποτε σημεία επινεφριδιακής κρίσης, όπως σοβαρή αφυδάτωση, υπόταση ή καταπληξία, συνιστάται άμεση χορήγηση ενδοφλέβιων κορτικοστεροειδών με αλατοκορτικοειδική δράση και ο ασθενής θα πρέπει να αξιολογηθεί για την παρουσία σηψαιμίας ή λοιμώξεων. Εάν υπάρχουν σημεία επινεφριδιακής ανεπάρκειας, αλλά ο ασθενής δεν βρίσκεται σε επινεφριδιακή κρίση, πρέπει να εξεταστούν περαιτέρω παρακλινικές εξετάσεις στις οποίες συμπεριλαμβάνεται η αξιολόγηση εργαστηριακών και απεικονιστικών ελέγχων. Η αξιολόγηση των αποτελεσμάτων των εργαστηριακών ελέγχων για την έλεγχο της ενδοκρινούς λειτουργίας πρέπει να πραγματοποιείται πριν από την έναρξη θεραπείας με κορτικοστεροειδή. Εάν οι απεικονιστικοί έλεγχοι της υπόφυσης ή εργαστηριακοί έλεγχοι της ενδοκρινούς λειτουργίας είναι μη φυσιολογικοί, συνιστάται βραχύ σχήμα θεραπείας με υψηλές δόσεις κορτικοστεροειδών (π.χ. δεξαμεθαζόνη 4 mg ανά 6 ώρες ή ισοδύναμο) ώστε να αντιμετωπιστεί η φλεγμονή του προσβεβλημένου αδένα και η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί (βλέπε παράγραφο 4.2). Αυτή τη στιγμή είναι άγνωστο εάν η θεραπεία με κορτικοστεροειδή αναστρέφει την αδενική δυσλειτουργία. Θα πρέπει επίσης να ξεκινήσει κατάλληλη υποκατάσταση ορμονών. Είναι πιθανό να είναι απαραίτητη μακροχρόνια θεραπεία με υποκατάσταση ορμονών. Όταν τεθούν υπό έλεγχο τα συμπτώματα ή οι μη φυσιολογικές εργαστηριακές τιμές και είναι εμφανής η βελτίωση του ασθενούς συνολικά, μπορεί να συνεχιστεί η θεραπεία με YERVOY και η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν πεπτιδικό εμβόλιο με YERVOY 3 mg/kg + gp100 στην MDX01020 (βλέπε παράγραφο 4.8). Αν οι αντιδράσεις είναι σοβαρές (Βαθμού 3 ή 4) είναι πιθανό να απαιτηθεί άμεσα θεραπεία με υψηλές δόσεις κορτικοστεροειδών και διακοπή του YERVOY (βλέπε παράγραφο 4.2). Για ραγοειδίτιδα, ιρίτιδα ή επισκληρίτιδα που συνδέεται με το YERVOY, θα πρέπει να εξετάζεται η χρήση τοπικών κορτικοστεροειδών στη μορφή των οφθαλμικών σταγόνων όπως ενδείκνυται ιατρικά. Ειδικοί πληθυσμοί: Ασθενείς με οφθαλμικό μελάνωμα, πρωτοπαθές μελάνωμα του ΚΝΣ και ενεργές μεταστάσεις του εγκεφάλου δεν συμπεριελήφθησαν στην πιλοτική κλινική δοκιμή (βλέπε παράγραφο 5.1). Αντίδραση στην έγχυση: Υπήρχαν μεμονωμένες αναφορές σοβαρών αντιδράσεων στην έγχυση σε κλινικές δοκιμές. Σε περίπτωση σοβαρής αντίδρασης στην έγχυση, η έγχυση YERVOY πρέπει να διακόπτεται και να χορηγείται κατάλληλη ιατρική θεραπεία. Ασθενείς με ήπια ή μέτρια αντίδραση στην έγχυση, μπορούν να λάβουν YERVOY με προσεκτική παρακολούθηση. Μπορεί να ληφθεί υπόψη η προφαρμακευτική αγωγή με αντιπυρετικό και αντισταμινικό. Ασθενείς με αυτοάνοση νόσο: Ασθενείς με ιστορικό αυτοάνοσης νόσου (εκτός από λεύκη και επαρκώς ελεγχόμενη ανεπάρκεια ενδοκρίνης, όπως υποθυρεοειδισμός), συμπεριλαμβανομένων αυτών για τους οποίους απαιτείται συστηματική ανοσοκατασταλτική θεραπεία για προϋπάρχουσα ενεργό αυτοάνοση νόσο ή για διατήρηση μοσχεύματος μετά από μεταμόσχευση οργάνου, δεν αξιολογήθηκαν σε κλινικές δοκιμές. Το ipilimumab είναι ενισχυτής των Τκυττάρων που καθιστά δυνατή την ανοσολογική ανταπόκριση (βλέπε παράγραφο 5.1) και είναι πιθανό να παρέμβει στην ανοσοκατασταλτική θεραπεία, γεγονός που οδηγεί σε παροξυσμό της υποκείμενης νόσου ή αυξημένο κίνδυνο απόρριψης του μοσχεύματος. Το YERVOY πρέπει να αποφεύγεται σε ασθενείς με σοβαρή ενεργό αυτοάνοση νόσο, σε περιπτώσεις στις οποίες περαιτέρω ενεργοποίηση του ανοσοποιητικού είναι ενδεχομένως άμεσα απειλητική για τη ζωή και χρησιμοποιείται με προσοχή σε άλλους ασθενείς με ιστορικό αυτοάνοσης νόσου, μετά από προσεκτική εξέταση του ενδεχόμενου κινδύνου-οφέλους σε ατομική βάση. Ασθενείς που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. Κάθε ml αυτού του φαρμακευτικού προϊόντος περιέχει 0,1 mmol (ή 2,30 mg) νατρίου. Θα πρέπει να λαμβάνεται υπόψη κατά την θεραπεία ασθενών που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. **4.8 Ανεπιθύμητες ενέργειες: Περίληψη του προφίλ ασφάλειας:** Το YERVOY έχει χορηγηθεί σε > 3.000 ασθενείς σε ένα κλινικό πρόγραμμα το οποίο αξιολόγησε τη χρήση του με διάφορες δόσεις και τύπους όγκων. Εκτός εάν ορίζεται διαφορετικά, τα δεδομένα παρακάτω αποτυπώνουν την έκθεση σε YERVOY στα 3 mg/kg σε κλινικές δοκιμές μελανώματος. Στη μελέτη Φάσης 3 MDX01020, (βλέπε παράγραφο 5.1), οι ασθενείς έλαβαν ένα διάμεσο 4 δόσεων (εύρος 14). Το YERVOY σχετίζεται πολύ συχνά με ανεπιθύμητες ενέργειες που προκύπτουν από αυξημένη ή εντεταμένη δράση του ανοσοποιητικού. Οι περισσότερες από αυτές, στις οποίες συμπεριλαμβάνονται σοβαρές αντιδράσεις, υποχώρησαν μετά από την έναρξη κατάλληλης ιατρικής θεραπείας ή τη διακοπή του YERVOY (βλέπε παράγραφο 4.4 για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, οι ανεπιθύμητες ενέργειες που αναφέρθηκαν συχνότερα (≥ 10% των ασθενών), ήταν διάρροια, εξάνθημα, κνησμός, κόπωση, ναυτία, έμετος, μειωμένη όρεξη και κοιλιακό άλγος. Στην πλειονότητά τους ήταν ήπιες έως μέτριες (Βαθμού 1 ή 2). Η θεραπεία με YERVOY διακόπηκε λόγω ανεπιθύμητων ενεργειών στο 10% των ασθενών. Κατάλογος ανεπιθύμητων ενεργειών σε πίνακα: Ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ασθενείς με προχωρημένο μελάνωμα, οι οποίοι έλαβαν YERVOY 3 mg/kg σε κλινικές δοκιμές (n = 767), παρουσιάζονται στον Πίνακα 2. Αυτές οι αντιδράσεις παρουσιάζονται ανά κατηγορία συστήματος οργάνων σύμφωνα με την συχνότητα. Η συχνότητα ορίζεται ως εξής: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000). Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες εμφανίζονται κατά φθίνουσα σειρά σοβαρότητας. Τα ποσοστά ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό σε HLAA2*0201 θετικούς ασθενείς οι οποίοι έλαβαν YERVOY στην MDX01020, ήταν παρόμοια με εκείνα που παρατηρήθηκαν στο κλινικό πρόγραμμα συνολικά.

Πίνακας 2: Ανεπιθύμητες ενέργειες σε ασθενείς με προχωρημένο μελάνωμα που έλαβαν YERVOY 3 mg/kg (n = 767)[α]	
Λοιμώξεις και παρασιτώσεις	
Όχι συχνές	σηψαιμία[β], σηπτική καταπληξία[β], μηνιγγίτιδα, γαστρεντερίτιδα, εκκολπωματίτιδα, ουρολοίμωξη, λοίμωξη του ανώτερου αναπνευστικού συστήματος, λοίμωξη του κατώτερου αναπνευστικού συστήματος
Νεοπλάσματα καλοήθη, κακοήθη και μη καθορισμένα (περιλαμβάνονται κύστεις και πολύποδες)	
Συχνές	πόνος από όγκο
Όχι συχνές	παρανεοπλασματικό σύνδρομο
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	
Συχνές	αναιμία, λεμφοπενία
Όχι συχνές	αιμολυτική αναιμία[β], θρομβοπενία, ηωσινοφιλία, ουδετεροπενία
Διαταραχές του ανοσοποιητικού συστήματος	
Όχι συχνές	υπερευαισθησία
Διαταραχές του ενδοκρινικού συστήματος	
Συχνές	υποϋποφυσισμός (συμπεριλαμβάνεται η υποφυσίτιδα)[γ], υποθυρεοειδισμός[γ]
Όχι συχνές	επινεφριδιακή ανεπάρκεια[γ], υπερθυρεοειδισμός[γ], υπογοναδισμός
Διαταραχές του μεταβολισμού και της θρέψης	
Πολύ συχνές	μειωμένη όρεξη
Συχνές	αφυδάτωση, υποκαλιαιμία
Όχι συχνές	υπονατριαιμία, αλκάλωση, υποφωσφοραιμία, σύνδρομο λύσης όγκου
Ψυχιατρικές διαταραχές	
Συχνές	συγχυτική κατάσταση
Όχι συχνές	μεταβολές της νοητικής κατάστασης, κατάθλιψη, μειωμένη γενετήσια ορμή
Διαταραχές του νευρικού συστήματος	
Συχνές	περιφερική αισθητική νευροπάθεια, ζάλη, κεφαλαλγία, λήθαργος
Όχι συχνές	σύνδρομο Guillain-Barré[β,γ], συγκοπή, κρανιακή νευροπάθεια, εγκεφαλικό οίδημα, περιφερική νευροπάθεια, αταξία, τρόμος, μυόκλωνος, δυσαρθρία
Οφθαλμικές διαταραχές	
Συχνές	θαμπή όραση, πόνος του οφθαλμού
Όχι συχνές	ραγοειδίτιδα[γ], αιμορραγία του υαλοειδούς σώματος, ιρίτιδα[γ], μειωμένη οπτική οξύτητα, αίσθημα ξένου σώματος στους οφθαλμούς, επιπεφυκίτιδα
Καρδιακές διαταραχές	
Όχι συχνές	αρρυθμία, κολπική μαρμαρυγή
Αγγειακές διαταραχές	
Συχνές	υπόταση, έξαψη
Όχι συχνές	αγγειίτιδα, αγγειοπάθεια[β], περιφερική ισχαιμία, ορθοστατική υπόταση
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου	
Συχνές	δύσπνοια, βήχας
Όχι συχνές	αναπνευστική ανεπάρκεια, σύνδρομο οξείας αναπνευστικής δυσχέρειας[β], διήθηση πνεύμονα, πνευμονικό οίδημα, πνευμονίτιδα, αλλεργική ρινίτιδα
Διαταραχές του γαστρεντερικού	
Πολύ συχνές	διάρροια[γ], έμετος, ναυτία
Συχνές	γαστρεντερική αιμορραγία, κολίτιδα[β,γ], δυσκοιλιότητα, γαστροοισοφαγική παλινδρόμηση, κοιλιακό άλγος
Όχι συχνές	διάτρηση του γαστρεντερικού σωλήνα[β,γ], διάτρηση του παχέος εντέρου[β,γ], διάτρηση του εντέρου[β,γ], περιτονίτιδα[β], παγκρεατίτιδα, εντεροκολίτιδα, γαστρικό έλκος, έλκος του παχέος εντέρου, οισοφαγίτιδα, ειλεός[δ]
Διαταραχές του ήπατος και των χοληφόρων	
Συχνές	μη φυσιολογική ηπατική λειτουργία
Όχι συχνές	ηπατική ανεπάρκεια[β,γ], ηπατίτιδα, ηπατομεγαλία, ίκτερος
Διαταραχές του δέρματος και του υποδόριου ιστού	
Πολύ συχνές	εξάνθημα[γ], κνησμός[γ]
Συχνές	δερματίτιδα, ερύθημα, λεύκη, κνίδωση, αλωπεκία, νυκτερινοί ιδρώτες, ξηροδερμία
Όχι συχνές	τοξική επιδερμική νεκρόλυση[β,γ], λευκοκυτταροκλαστική αγγειίτιδα, αποφολίδωση δέρματος
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	
Συχνές	αρθραλγία, μυαλγία, μυοσκελετικός πόνος, μυϊκοί σπασμοί
Όχι συχνές	ρευματική πολυμυαλγία, αρθρίτιδα-
Διαταραχές των νεφρών και των ουροφόρων οδών	
Όχι συχνές	νεφρική ανεπάρκεια[β], σπειραματονεφρίτιδα[γ], νεφρική σωληναριακή οξέωση
Διαταραχές του αναπαραγωγικού συστήματος και του μαστού	
Όχι συχνές	αμηνόρροια
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	
Πολύ συχνές	κόπωση, αντίδραση της θέσης ένεσης, πυρεξία
Συχνές	ρίγη, εξασθένιση, οίδημα, άλγος
Όχι συχνές	πολυοργανική ανεπάρκεια[β,γ], σχετιζόμενη με την έγχυση αντίδραση
Παρακλινικές εξετάσεις	
Συχνές	αυξημένη αμινοτρανσφεράση της αλανίνης[γ], αυξημένη ασπαρτική αμινοτρανσφεράση[γ], αυξημένη χολερυθρίνη αίματος, μειωμένο σωματικό βάρος
Όχι συχνές	μη φυσιολογικές δοκιμασίες ηπατικής λειτουργίας, αυξημένη κρεατινίνη αίματος, αυξημένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη κορτιζόλη αίματος, μειωμένη κορτικοτροφίνη αίματος, αυξημένη λιπάση[γ], αυξημένη αμυλάση αίματος[γ], μειωμένη τεστοστερόνη αίματος

α Οι συχνότητες βασίζονται σε συγκεντρωτικά στοιχεία από 9 κλινικές δοκιμές που εξέτασαν το YERVOY 3 mg/kg δόση σε μελάνωμα.

β Συμπεριλαμβάνεται η θανατηφόρος έκβαση.

γ Πρόσθετες πληροφορίες σχετικά με αυτές τις πιθανώς φλεγμονώδεις ανεπιθύμητες ενέργειες παρέχονται στην «Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών» και την παράγραφο 4.4. Τα δεδομένα που παρουσιάζονται σε αυτές τις παραγράφους αποτυπώνουν κυρίως την εμπειρία από μια μελέτη Φάσης 3, την MDX01020.

δ Αναφέρονται σε πρόσφατες μελέτες εκτός των ολοκληρωμένων κλινικών δοκιμών στο μελάνωμα.

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

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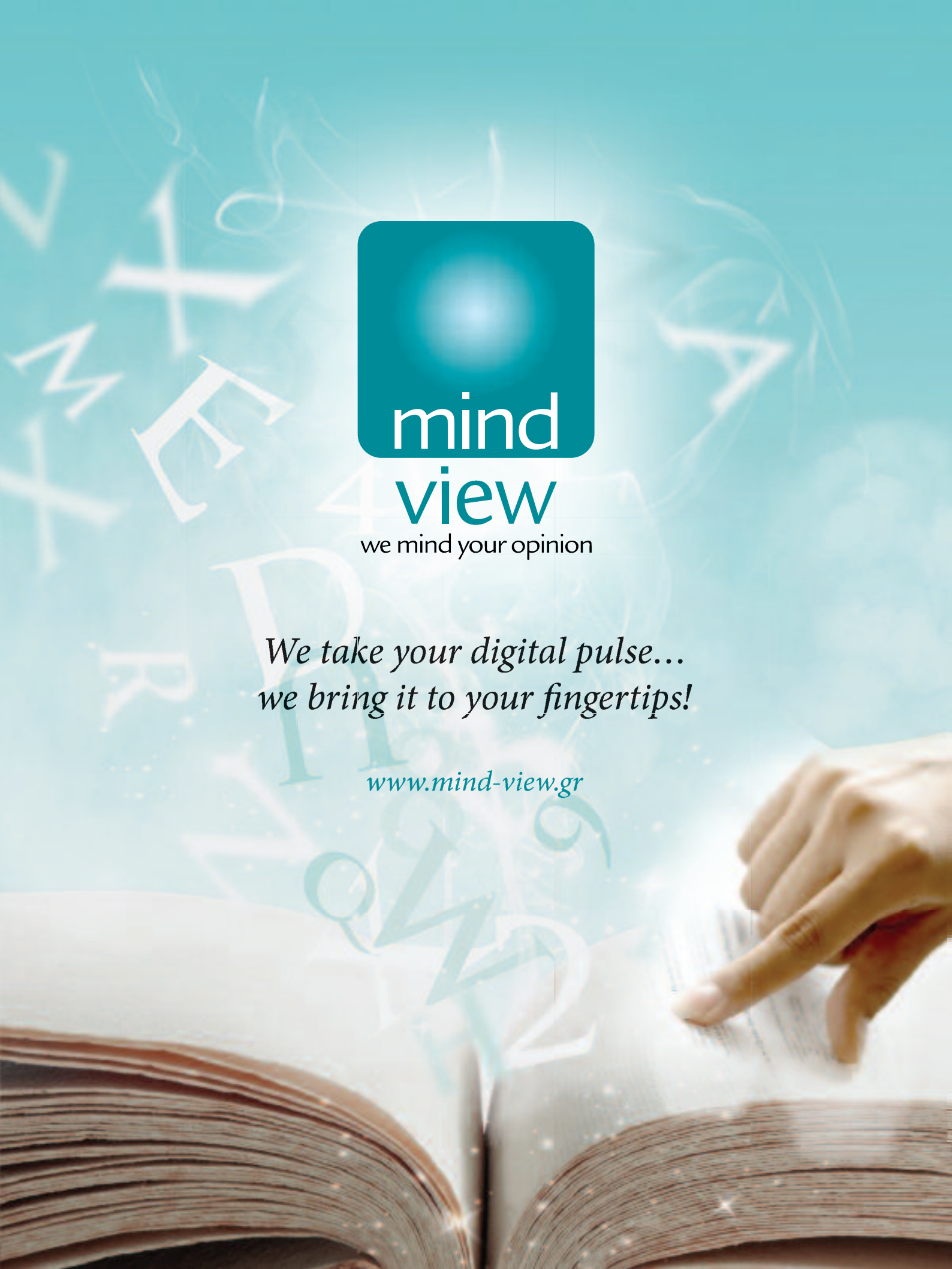

ΚΑΙ ΤΩΡΑ ΕΓΚΕΚΡΙΜΕΝΟ

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

ΠΡΟΟΔΟΣ ΤΗΣ ΕΠΙΣΤΗΜΗΣ
ΣΤΟ ΜΕΤΑΣΤΑΤΙΚΟ ΜΕΛΑΝΩΜΑ

Η δύναμη του ανοσοποιητικού συστήματος

Η σπουδαιότητα της παρατεταμένης επιβίωσης

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

Για σημαντικές πληροφορίες ασφάλειας, ανατρέξτε στην Περίληψη Χαρακτηριστικών Προϊόντος του YERVOY™

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

*Σε μια τυχαιοποιημένη, ελεγχόμενη δοκιμή φάσης 3.

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