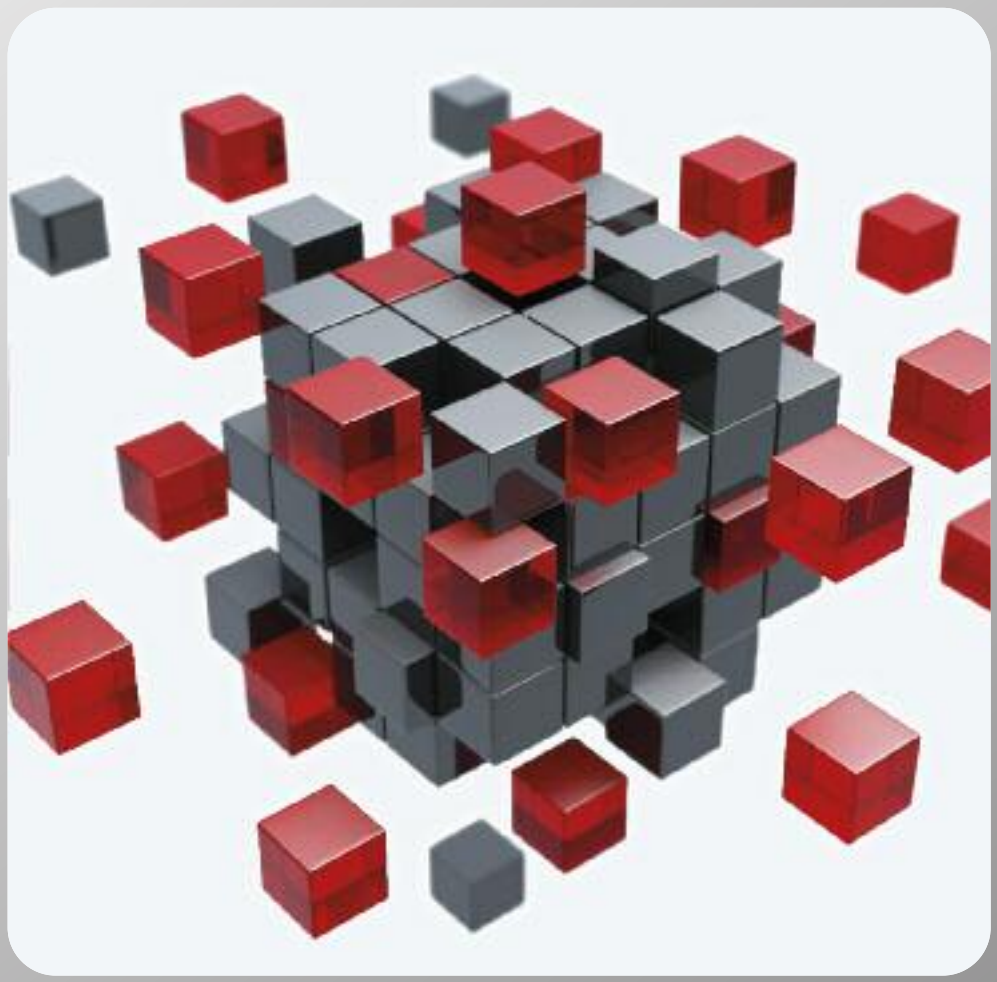
Issue 4 • Vol. 3

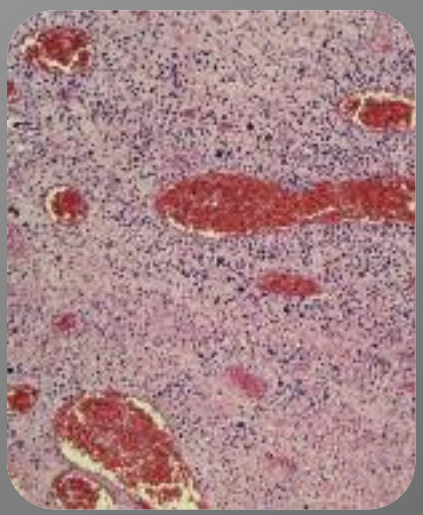
FCO
FORUM of CLINICAL ONCOLOGY

December 2012
www.forumclinicaloncology.org
(PRINTED VERSION)

Quarterly official publication of the Hellenic Society of Medical Oncology

ISSN: 1792-345X





1985

MINDWORK
BUSINESS SOLUTIONS LTD.
15, M. Botsari Street,
GR-14561 – Kifissia,
Athens, Greece

ΠΛΗΡΩΜΕΝΟ ΤΕΛΟΣ
PORT PAYÉ
Κ.Ε.Μ.Π.Α.
Αρ. Αδ. 4025
ΕΛΛΑΣ - HELLAS
B

ΕΛΤΑ
Hellenic Post

Abraxane®

paclitaxel albumin

GENESIS pharma
Λ. Κηφισίας 274, 152 32 Χαλάνδρι
Τηλ.: 210 8771500, Fax: 210 6896619
e-mail: info@genesispharma.com
www.genesispharma.com

Celgene

Publisher

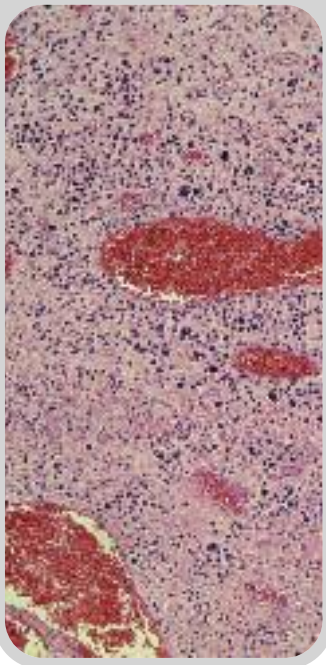
1985

Hellenic Society of Medical Oncology
105, Alexandras Avenue,
GR-11475 – Athens, Greece
tel./ fax: 0030 210 6457971
e-mail: hesmo@otenet.gr

Publication coordinator

Mindwork Business Solutions Ltd.
15, M. Botsari Street,
GR-14561 – Kifissia,
Athens, Greece
tel.: 0030 210 6231305
fax: 0030 210 6233809
e-mail:
info@forumclinicaloncology.org
website:
www.forumclinicaloncology.org

Printer: Lithoprint
I. Skourias Ltd.

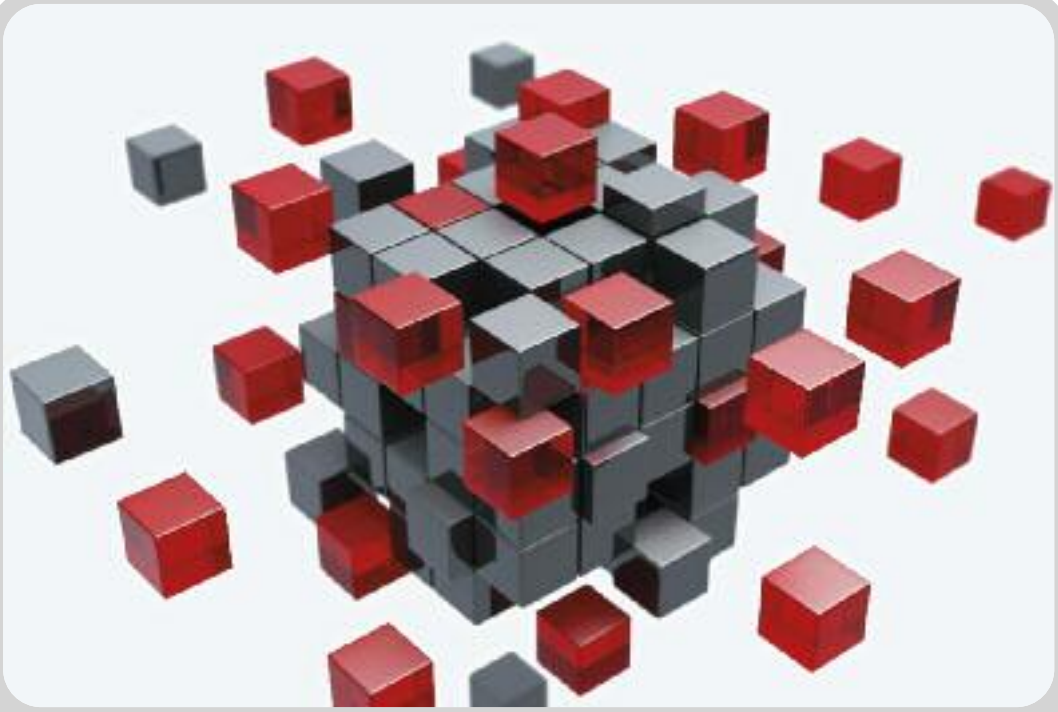


Issue 4 • Vol. 3

FCO
FORUM of CLINICAL ONCOLOGY

December 2012
www.forumclinicaloncology.org
(PRINTED VERSION)

Quarterly official publication of the Hellenic Society of Medical Oncology



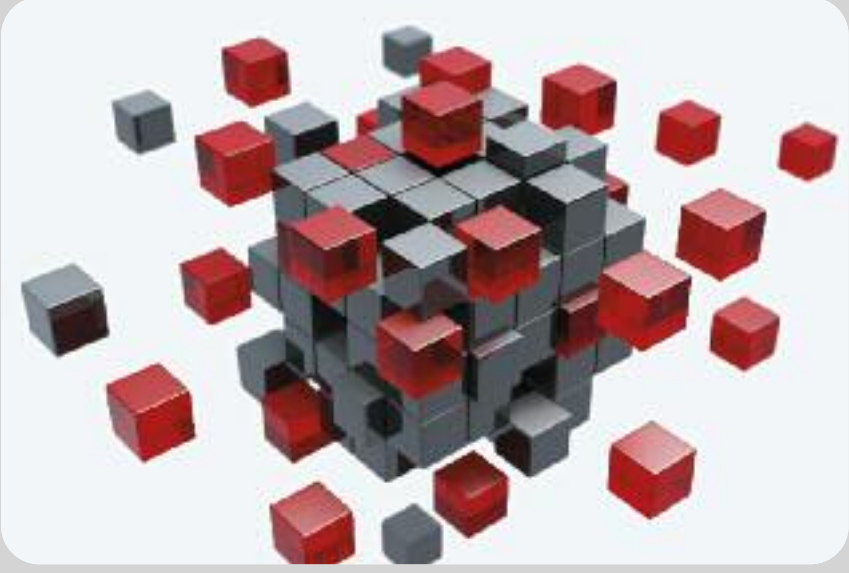
Contents

FCO FORUM of CLINICAL ONCOLOGY
Quarterly official publication of the Hellenic Society of Medical Oncology

Contents (suite)

Original Report

Case Reports



So far, so good

Editorial

Vassilios Barbounis

This last issue of 2012, a year of hardship, uncertainty, insecurity, and scarce funding, Forum of Clinical Oncology managed to maintain the goals set by its founders: to be the forum of a creative, small but dynamic oncological community, which strives for better results and greater output in spite of our times.

The past year, FCO published a number of very significant articles with regard to the global issues of today's Oncology as well as current pressing issues of our society as a whole; Questions such as: What is the framework of translational and clinical research today? What are the boundaries of bioethics? How should we manage critical information about patients or healthy subjects? And an even more complex question, in what way do we deal with information referring to serious future disease.

Our editorial board draws emphasis on the multicultural origin of contributors to the journal. It is with great pleasure that the editorial board published articles by authors from countries neighbouring or far-away from Greece. The fact that we receive requests for reprints or use and citation of FCO's articles by scientists worldwide is evidence that our efforts are embraced and acknowledged. It is worth mentioning that FCO has agreements with international publishers for inclusion of selected articles in their respective databases & websites.

Moreover, the supplements published on the occasion of important scientific meetings or written symposia on key issues contribute to the training of oncologists and offer easily accessible advanced knowledge.

Our efforts aim even further; our strategic goal is to include FCO in PubMed, a fact that will add prestige and larger scientific scope.

We trust that within the coming year, with hard work and dedication to quality and ethics, many of the goals of the Forum of Clinical Oncology will be realized.

GR.CAB.12.01.01

SANOFI ONCOLOGY

Sanofi-aventis A.E.B.E. Λεωφ. Συγγρού 348, Κτήριο Α', 176 74 Καλλιθέα
Τηλ.: 210 90 01 600, Fax: 210 92 49 088 www.sanofi.gr

JEVTANA®
(cabazitaxel)

Thoughts for the therapeutic treatment of neuroendocrine tumors (NETs) after the 9th ENETS conference

Adamantia Nikolaidi[1], Gregory Kaltsas[2]

[1]Medical Oncologist, Oncology Department, Mitera Hospital
[2]Associate Professor, Endocrinology Unit Head, Department of Pathophysiology, Laikon Hospital, School of Medicine, National and Kapodistrian University of Athens

Correspondence:
Adamantia Nikolaidi,
Medical Oncologist,
Oncology Department, Mitera Hospital,
e-mail: jfil@otenet.gr

Key words: molecular therapies; neuroendocrine tumors; NET; TAE.

Recently, the 9th annual conference of the European Neuroendocrine Tumors Society (ENETS) was organized in Copenhagen. Approximately 1,540 delegates attended the conference that included 3 satellite symposia, 1 postgraduate course, which set a record by doubling its attendance from the previous year to 400 participants, a symposium for nurses and one "Meet the Professor" session. The participants were clinicians that covered a wide range of specialties such as endocrinologists, oncologists, surgeons, pathologists, nuclear physicians, gastroenterologists and nurses.

Although no significantly novel clinical data were presented in this meeting, it was a chance to go through an in-depth analysis of the data announced in ESMO 2010, concerning the evolving role of the new molecular targeted therapies in NETs. An in-depth discussion of the data was developed, based on a series of clinical cases and the clinical trials' updates were assessed.

Moreover, the recently revised (2011) ENETS guidelines were presented. The improvement on the diagnosis and therapeutic approach of patients with NETs is based on the new classification systems of these neoplasms that have incorporated four major different parameters: differentiation, grading, staging and location of the primary tumor site.

Regarding the treatment of NETs, surgery remains the primary therapeutic approach, with an ultimate goal to completely remove the primary tumor where possible, or alternatively, to reduce metastatic load mainly to the liver. However, for the majority of patients who present with stage IV disease surgery alone may not suffice and other cytoreductive techniques such as TAE (transcatheter arterial embolisation) or percutaneous RFA may be required. For patients who are not amenable to such techniques and/or in whom there is disease progression further medical treatment directed against tumor growth is needed. This is a typical example of the complexity of these tumors and highlights the importance of the multidisciplinary approach of GEP-NETs.

Available treatment options including chemotherapy, SSA, PRRT, and the new molecular targeted treatments were presented through discussion and debate around real case studies. According to the revised ENETs treatment guidelines, chemotherapy is now recommended for selected pNET patients, as well for patients with poorly differentiated neuroendocrine carcinomas (G3/small cell). However, chemotherapy has no place in the treatment of patients with well differentiated NETs of gastro-intestinal (GI) origin.

In detail, chemotherapy is recommended for patients with metastatic pNET, non pancreatic foregut G2 NETs and G3 NECs regardless of the primary tumor site. Combination chemotherapy using streptozocin with doxorubicin or 5FU is recommended for G1-G3 unresectable or/and metastatic pNET patients with disease progression. In the case of high grade G3 NECs, combination chemotherapy using cisplatin/etoposide is recommended, regardless of the primary tumor site.

SSA analogues are considered first line treatment of choice, for the relief of symptoms associated with carcinoid syndrome in functioning NETs, independently of the tumor site. Somatostatin analogues are effective for carcinoid syndrome control in up to 70-90% of the cases.

Octreotide LAR is also recommended as first-line treatment for functioning and non-functioning, unresectable or/and metastatic midgut tumors, especially G1, based on the results of the PROMID trial. SSA treatment is not recommended for G3 tumors, or as adjuvant therapy.

Targeted molecular therapies are currently an evolving treatment for NETs. Everolimus can be considered as a therapeutic choice for patients with advanced GI and lung carcinoid tumors, when other indicated therapeutic options have failed, based on the results of the RADIANT-2 trial. There is currently no published data on sunitinib in non-pancreatic neuroendocrine tumors.

Everolimus is recommended after failure of chemotherapy or as first line treatment for patients with advanced, pancreatic NETs, based on the results of the RADIANT-3 study. Sunitinib is indicated as second or third line treatment for advanced pNET patients, or as first-line treatment, when other therapeutic options are not available.

The use of PRRT is considered as an alternative therapeutic option for functioning and non functioning NETs, independently of the tumor location. It can be used to reduce the metastatic load of G1/G2 NET with ^{90}Y-and/or ^{177}Lu-DOTATOC or DOTATATE. It should be noted however, that there are no phase III data available for this form of treatment and that results from prospective, randomized clinical trials are pending.

Complete surgical resection of the tumor, remains the fist-line therapeutic approach for NET patients with localized disease. When surgery is not possible, or the disease is progressing, recommendations based on the ENETS consensus are as follows, depending on the location of the tumor.

A. Anti-proliferative treatments for stomach and duodenum NET include SSA and PRRT

Specifically for G1 NET, the recommended treatment is SSAs, whilst G3 NETs should be treated with systemic chemotherapy (cisplatin/etoposide).

The upfront combination of IFN and SSA for anti-proliferative purposes is not recommended for these tumors.

B. NET of primary tumor origin the colon and the rectum are not usually presenting with symptoms related to the carcinoid syndrome. Thus, experience from the use of IFN and SSA is limited. PRRT could be a choice for patients with metastatic disease and positive octreoscan.

C. For **non functioning** G1 NET **midgut tumors**, octreotide is considered as first line therapy (as also recommended by the recently updated NCCN guidelines). Based on the results of the PROMID trial, octreotide LAR is recommended, even for newly-diagnosed, metastatic patients without prior documented disease progression.

Everolimus use can be considered for the treatment of advanced, progressive midgut NETs, after failure of SSA. PRRT is not recommended as first line therapy, but only after failure of all other available treatment options. Positive octreoscan is a prerequisite.

D. Functional pNET

Gastrinomas

PPIs and H2 blockers are considered first line treatment for symptom relief.

Insulinomas

SSA may control hypoglycemia syndrome in patients that over-express the sst2 receptor. In some cases of malignant insulinomas, everolimus reduces insulin secretion with subsequent glucose control. SSAs are effective in the treatment of clinical symptoms related to rare pNET tumors secreting hormones such as Vasoactive Intestinal Peptide (VIPoma), Growth hormone Releasing Hormone (GRHoma), glugagon (glucagonoma) and some cases of somatostatinoma.

Other medical treatments aiming at tumor growth control are similar to non-functioning NETs.

E. Non functional G1/G2 **pNET**

Patients that are candidates for resection of liver metastases should be assessed based on the following parameters: absence of extra-abdominal disease, presence of low proliferative Ki-67 index (G1-G2) and the expression of somatostatin receptors for potential subsequent delivery of radio-labeled SSAs. In the case of synchronous unilobar liver metastases, the therapeutic approach includes primary tumor resection and hepatectomy. In the case of bilobar hepatic tumor load, treatment strategy includes two-step hepatectomy and/or RFA. For metachronous hepatic metastases or hepatic recurrence, hepatectomy or/and RFA are suggested for resectable metastases, whereas, for unresectable cases, the treatment approach should include systemic therapy regimens, RFA or (chemo)embolisation, in order to reduce the metastatic tumor load.

Everolimus and sunitinib are indicated for the treatment of advanced, unresectable or metastatic pNETs with progressive disease or upon progression, respectively.

Based on the results of the RADIANT 3 trial, everolimus can be considered as first line therapy in selected patients (as the study included 42% therapy naive patients).

Sunitinib is indicated as second or third line treatment for advanced pNET patients, or as first-line treatment, when other therapeutic options are not available.

As already mentioned, the use of PRRT is considered as an alternative therapeutic option for functioning and non functioning pNET, as well. It can be used to reduce the metastatic load of G1/G2 NET with ^{90}Y-and/or ^{177}Lu-DOTATOC or DOTATATE. It should be noted however, that there are no phase III data available and that results from prospective, randomized clinical trials are pending.

When more than one options are available according to the above guidelines, the criteria for the selection of 1st line therapy of stage IV NETs are as follows:

a. SSAs are recommended for functional G1 midgut tumors with positive somatostatin receptors and low tumor load.

b. The combination of STZ+5FU is recommended for advanced, G1 and G2 functional and non functional pancreatic tumors, progressive disease or/and high tumor load. Alternatively, in cases where the use of STZ+ 5-FU is

contra-indicated, the use of temozolamide and capecitabine is suggested, but with relevant available documentation only for G2 tumors.

c. Everolimus and sunitinib are recommended for G1-G2 functioning and non-functioning pancreatic NET, when systemic chemotherapy is contra-indicated. Especially in the case of metastatic insulinomas, everolimus is recommended as the standard treatment of choice.

d. PRRT is recommended for patients with G1-G2 tumors of any primary tumor site, positive sst2 receptors, advanced disease or extra-hepatic disease (with low liver tumor burden), or with limited disease that could lead to surgery after down staging.

e. The combination of cisplatin-etoposide is recommended for all poorly differentiated G3 tumors, independently of the primary tumor site.

In many European countries NETs are referred for treatment in centers of excellence for such tumors. The constitution of such centers is highly supported by ENETS, which provides "ENETS Centers of Excellence" certification based on the Society's standards. It is of great interest to note, that median survival of patients with metastatic carcinoids treated at "centres of excellence" has been recorded to be more than 3 times higher than the median survival of patients with NETs in the SEER database.

The diagnosis and therapeutic treatment of NETs does not depend only on the work of one clinician. The collaboration of a radiologist, gastroenterologist, surgeon, pathologist, endocrinologist and oncologist in the context of a multidisciplinary team is a necessity and is something that can be achieved only in well organized centers of excellence.

In our country, there is no qualified center of excellence for neuroendocrine tumors. However, patients could benefit from the constitution of a collaborative network between different specialists across the country hospitals that would offer them a broader view of their disease status and treatment possibilities, as well as access to advanced and individualized therapy.

REFERENCES

1. Delle Fave, et al. ENETS consensus guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology 2012; 95:74-87.

2. Caplin, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: Colorectal neuroendocrine neoplasms. Neuroendocrinology 2012; 95:88-97.

3. Jensen, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: Functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012; 95:98-119.

4. Falconi, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: Well-differentiated pancreatin non-functional tumors. Neuroendocrinology 2012; 95:120-134.

5. Pape, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012; 95:135-156.

6. Pavel, et al. ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hingut and unknown primary. Neuroendocrinology 2012; 95:157-176.

Prospective study of adjuvant fixed-dose gemcitabine plus docetaxel for stage I-II uterine leiomyosarcoma

Niveen A Abo-Touk, Rasha Hamdy Hamed

Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt

Correspondence:
Rasha Hamdy Hamed,
Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt,
e-mail: rashahamdy532@yahoo.com

ABSTRACT

Background: The aim of this prospective study was to assess the efficacy and toxicity of adjuvant chemotherapy among patients with completely resected stage I-II uterine leiomyosarcoma.

Patients & Methods: Thirty-four stage I and II uterine leiomyosarcoma patients with no gross or microscopic evidence of residual disease after total abdominal hysterectomy and bilateral salpingo-oophorectomy received adjuvant intravenous infusion of gemcitabine 900mg/m^2 on days 1 and 8 over 90min, followed by docetaxel 75mg/m^2 on day 8 over 1h, every 3 weeks for a total of 4 cycles.

Results: Disease recurrence occurred in 14 patients. Lung metastases occurred in 2 patients (5.9%); local recurrence in 7 patients (20.6%); and 5 patients (14.7%) developed both distant and local recurrence. The median disease-free survival was 47 months. Disease-free survival at 2 years was 66% of patients and 50% of patients at 3 years. Overall survival was 71% and 65% at 2 and 3 years, respectively. The most predominant grade III or IV toxicity was leukopenia, which was considered of grade III in 14.7% patients and grade IV in 5.9% patients, while grade III neutropenia was observed in 11.8% patients and grade IV in 2.9% patients. No patients suffered from grade IV non-hematological toxicity.

Conclusions: Fixed-dose gemcitabine plus docetaxel as adjuvant therapy for stages I-II uterine leiomyosarcoma yields 2-year disease-free and overall survival rates that appear superior to historical rates. Gemcitabine-docetaxel was associated with low rates of serious toxicities in the adjuvant setting and these toxicities were tolerable and manageable.

Key words: uterine sarcomas; leiomyosarcoma; gemcitabine plus docetaxel.

INTRODUCTION

Uterine sarcomas are a rare, heterogeneous group of neoplasms (about 3% of all uterine neoplasms). They are stromal/mesenchymal tumors that are generally categorized into leiomyosarcoma (LMS); endometrial stromal sarcoma (ESS); and undifferentiated stromal sarcoma [1]. Uterine leiomyosarcoma accounts for approximately 1% of all uterine malignancies and thus is diagnosed in only a few thousand women each year in the United States [2]. Although approximately 60% of women with uterine leiomyosarcoma present with the disease limited to the uterus, cure rates range from 20% to 60% [3]. The risk of recurrence is greater for patients with higher-stage disease, and is likely greater for tumors with higher mitotic rates [4].

Although the risk for recurrence is high, no adjuvant treatment strategy is considered as standard, since there are no trials demonstrating that adjuvant treatment improves progression-free or overall survivals, compared with surgical resection alone. The role of adjuvant radiotherapy is controversial; however, a randomized phase III trial of adjuvant pelvic radiation versus observation for stage I and II uterine sarcomas (carcinosarcoma, leiomyosarcoma or endometrial stromal sarcoma) showed that pelvic radiation did not improve outcomes for leiomyosarcoma patients in terms of local control, progression-free, or overall survivals [5]. The role of chemotherapy is even more poorly defined for patients with uterine-confined disease but has been considered because of the high risk of relapse. An early randomized study in the

1980s found that adjuvant doxorubicin compared with observation in early stage disease had no impact on recurrences, PFS or OS. In the subgroup of patients with leiomyosarcoma the recurrence rate was higher among patients assigned to observation versus patients assigned to doxorubicin [6].

Fixed-dose rate gemcitabine plus docetaxel achieves high objective response rates in patients with advanced, recurrent uterine leiomyosarcoma as first- or second-line therapy [7-9]. As no standard adjuvant therapy has been identified and given the activity of fixed-dose rate gemcitabine plus docetaxel regimen in advanced disease, we sought to conduct this phase II study to determine disease-free and overall survivals among women with completely resected stage I-II uterine leiomyosarcoma who were treated with adjuvant fixed-dose rate gemcitabine plus docetaxel.

PATIENTS AND METHODS

Inclusion criteria

Women were eligible for the study if they had pathologically confirmed operable stage I and II uterine leiomyosarcoma according to FIGO staging for uterine sarcomas [10] and with an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 1. The patients were included if there was no gross or microscopic evidence of residual disease after total abdominal hysterectomy and bilateral salpingo-oophorectomy. No patients had prior malignancies or received pelvic radiation. Written informed consent was obtained from all patients before registration.

Pretreatment evaluation

A complete medical history and physical examination with performance status evaluation were assessed. Laboratory investigations included complete blood counts, and assays of creatinine, AST, ALT, bilirubin and albumin. All patients had normal hematological function (absolute neutrophil count $\geq 1.5 \times 10^3/\mu L$, platelet count $\geq 100 \times 10^3/\mu L$); serum creatinine <1.5x upper normal limit (UNL); aspartate or alanine aminotransferase (AST or ALT) level <2.5xUNL; serum bilirubin <1.5xUNL.

Radiological examinations, including chest CT scan, abdominal and pelvic MRI, and echocardiogram had to be performed preceding study entry.

Treatment administration

Chemotherapy regimen was delivered as an intravenous infusion of gemcitabine 900mg/m^2 on days 1 and 8 over 90min, followed by docetaxel 75mg/m^2 on day 8 over 1h, every 3 weeks for a total of 4 cycles.

All patients received premedication with dexamethasone 8mg orally every 12 hours the day prior to docetaxel, and continuing for two days after. Patients also received 5-hydroxytryptamine-3-receptor antagonist as a 30min drip infusion before chemotherapy. Early intervention with diuretics was encouraged for signs of docetaxel-related fluid retention. Recombinant granulocyte colony-stimulating factor was subcutaneously injected if patients had grade III, IV leukopenia or febrile neutropenia.

Dose-limiting toxicity (DLT) was defined as any of the following findings during treatment: a neutrophil count of <500/μl; grade III febrile neutropenia; platelet count of <50,000/μl; grade III or IV non-hematological toxicity; excluding nausea and anorexia, according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) (version 3) [11]. If the WBC count was <3,000/μl, the neutrophil count <1,500/μl, or the platelet count <100,000/μl, further cycle was delayed until recovery. If blood counts failed to recover after treatment hold of up to 2 weeks, the study treatment was discontinued.

Follow-up

Physical examination and blood chemistries were performed in every cycle. Specific adverse events were listed

Table 1.
Baseline characteristics of patients.

Characteristics	Patients (n=34), No. (%)
Age (years)	
Range	(29-66)
Median	50.5
Presenting symptoms	
Vaginal bleeding	20 (58.8)
Abdominal pain	10 (29.4)
Abdominal mass	4 (11.8)
ECOG performance status	
0	26 (76.5)
1	8 (23.5)
Tumor size (cm)	
Range	(3-15)
Median	8
Stage	
IA	9 (26.5)
IB	18 (52.9)
IIA	5 (14.7)
IIB	2 (5.9)
Grade	
I	6 (17.6)
II	12 (35.3)
III	14 (41.1)
Tumor mitotic index (mitoses/10 high-power fields)	
≤10	13 (38.2)
>10	21 (61.8)

ECOG: Eastern Cooperative Oncology Group

and graded according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) (version 3) throughout the treatment period.

Chest radiography and abdominopelvic magnetic resonance imaging or computed tomography were also performed at the end of treatment and every 3 months for 2 years, then every 6 months to identify the presence of disease recurrence.

Statistical analysis

Statistical analysis was done using the SPSS (Statistical Package for Social Science) program version 15. The qualitative data was presented in the form of number and percentage. Quantitative data was presented as range and median. Disease-free survival (DFS) was defined as the time from date of surgery to the earliest time of recurrence in local or distant sites, death from any cause or last follow-up if no relapse or death occurred. Overall survival was defined as time to death (including deaths with or without recurrence) or last follow-up for those who were still alive. The survival endpoints were analyzed using the Kaplan-Meier method.

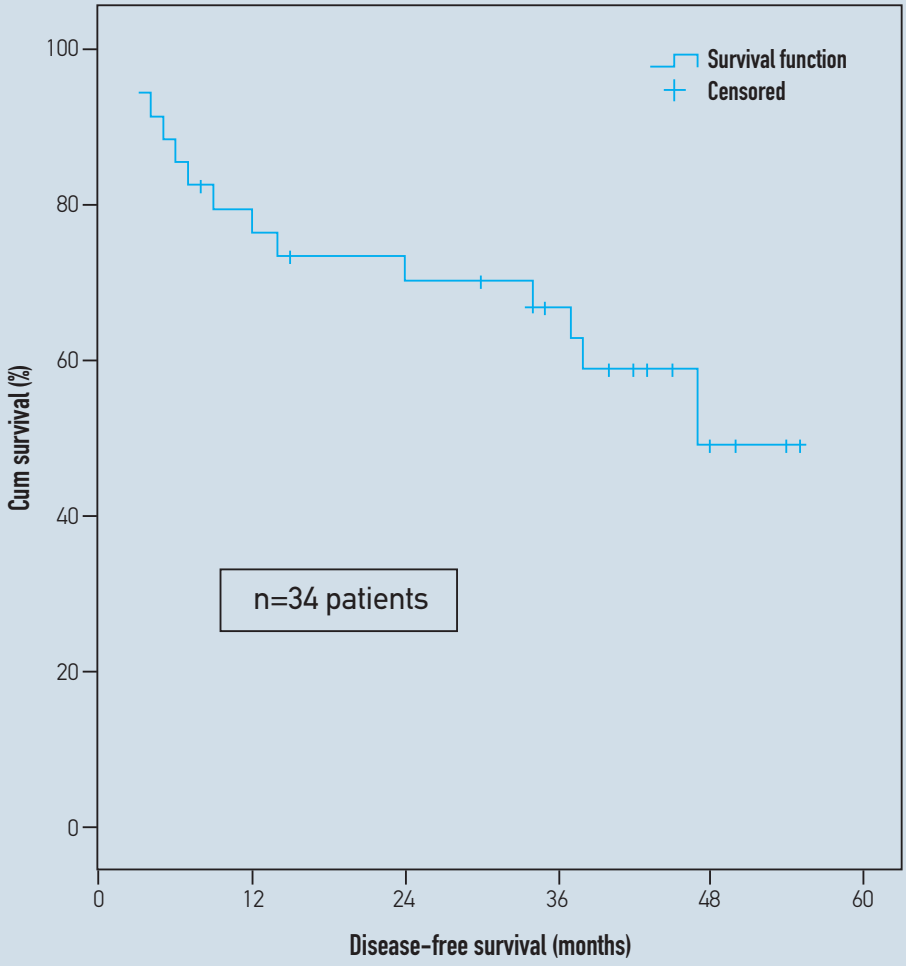
RESULTS

Patient population

During the period from January 2008 to May 2011, thirty-four patients with uterine leiomyosarcoma who presented to the department of Clinical Oncology & Nuclear Medicine, Mansoura University Hospital, were enrolled in this study.

The baseline characteristics of patients enrolled in the study are shown in Table 1. The median age of patients at the start of treatment was 50.5 years (range: 29 to 66 years). The

Figure 1.
Disease-free survival in 34 patients with stage I and II uterine leiomyosarcoma.



majority of patients presented with vaginal bleeding (58.8%); 10 patients (29.4%) suffered from abdominal pain; and 4 patients (11.8%) had abdominal mass. Prior to study entry, most patients (76.5%) had an ECOG performance status score of 0, while 23.5% had a score of 1.

The patients comprised 18 (52.9%) with stage IB disease and 9 (26.5%) with stage IA; stage IIA was diagnosed in 5 patients (14.7%) and stage IIB in 2 patients (5.9%). The median tumor size among patients was 8cm (range: 3-15cm). Fourteen patients (41.1%) had grade III tumors. The tumor mitotic index was >10 mitoses per 10 high-powered fields in 21 patients (61.8%).

Efficacy

During the follow-up period, with a median duration of 40 months (range: 2 to 55), disease recurrence was observed in 14 patients. Lung metastases occurred in 2 patients (5.9%); local recurrence in 7 patients (20.6%); and 5 patients (14.7%) developed both distant and local recurrence. The median disease-free survival was 47 months. Disease-free survival at 2 years was 66% of patients and 50% at 3 years (Figure 1). Overall survival was 71% and 65% at 2 and 3 years, respectively (Figure 2).

Tolerability

All patients were evaluated during the period of treatment regarding chemotherapy side-effects; toxicities observed are summarized in Table 2. The most predominant grade III or IV toxicity was leucopenia; grade III was present in 14.7% patients and grade IV in 5.9% patients, while neutropenia grade III was observed in 11.8% patients and grade IV in 2.9% patients; however, only one patient had neutropenic fever

Figure 2.
Overall survival in 34 patients with stage I and II uterine leiomyosarcoma.

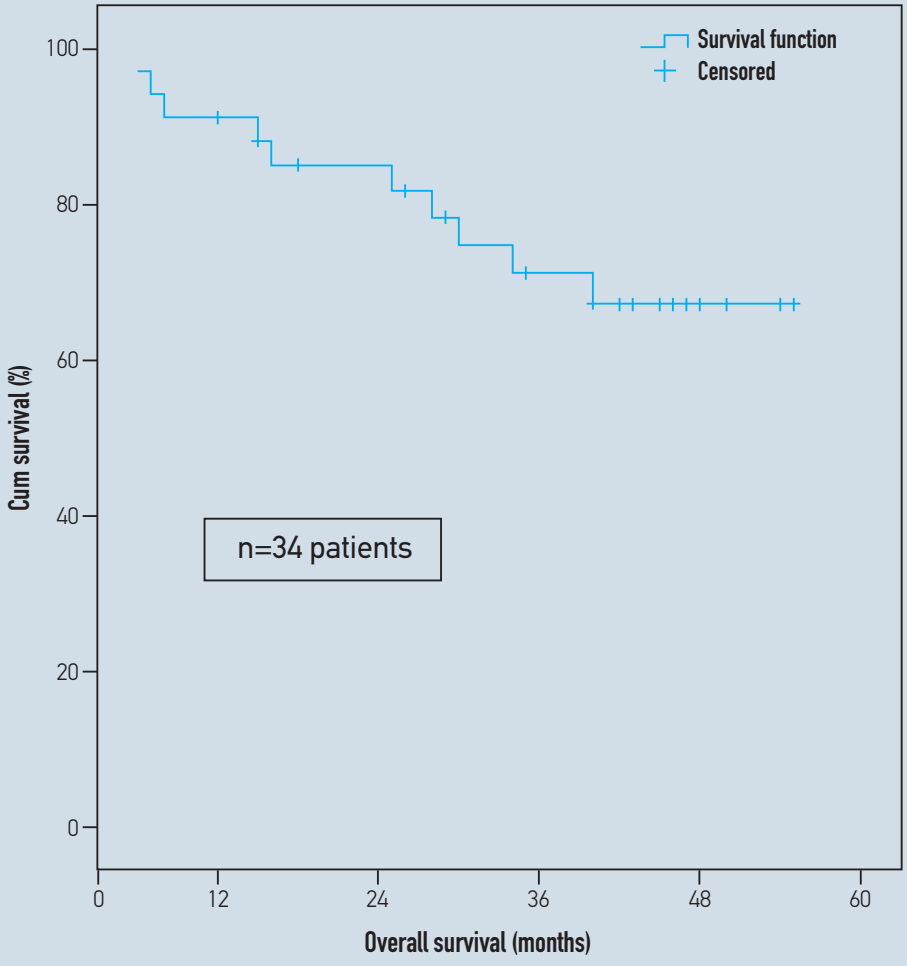


Table 2.
Adverse events during treatment (n=34).

Toxicity	Grade I, II		Grade III		Grade IV	
	No. of patients	%	No. of patients	%	No. of patients	%
Hematological						
Anemia	18	52.9	5	14.7	0	0
Leukopenia	14	41.2	5	14.7	2	5.9
Neutropenia	9	26.5	4	11.8	1	2.9
Thrombocytopenia	15	44.1	3	8.8	0	0
Neutropenic fever	3	8.8	1	2.9	0	0
Non-hematological						
Nausea / vomiting	15	44.1	3	8.8	0	0
Diarrhea	7	20.6	2	5.9	0	0
Neuropathy	5	14.7	2	5.9	0	0
Allergic reaction	4	11.8	1	2.9	0	0
Pulmonary	1	2.9	1	2.9	0	0
Edema	9	26.5	4	11.8	0	0
Dermatologic	10	29.4	3	8.8	0	0
Fatigue	8	23.5	2	5.9	0	0

grade III. Recombinant granulocyte colony-stimulating factor was received if patients had grade III, IV leukopenia or febrile neutropenia (7 patients). Anemia grade III was found in 14.7% of patients. Grade III thrombocytopenia was observed in 3 patients (8.8%), however, no patients suffered from hemorrhage.

No patients suffered from grade IV non-hematological toxicity. The most frequent grade III non-hematological complications were nausea and vomiting, reported in 3 patients (8.8%). Two patients (5.9%) developed grade III diarrhea. There were 2 patients (5.9%) complaining of grade III neuropathy. One patient experienced a grade III allergic reaction to docetaxel. Pulmonary toxicity has been reported in one patient. Four patients experienced grade III edema (11.8%), but dermatological complications of grade III were observed in 3 patients (8.8%).

DISCUSSION

The pattern of relapse among women with completely resected FIGO stage I-II uterine leiomyosarcoma is mostly distant metastases, often with locoregional disease [12, 13]. Hence, the use of adjuvant chemotherapy to reduce local and distant relapses and improve cure rates has been attractive. However, there is only limited data available to support the use of adjuvant chemotherapy specifically for uterine sarcoma. The largest randomized trial by the Gynecologic Oncology Group study evaluated adjuvant chemotherapy in stage I or II uterine sarcoma. A total of 225 patients were enrolled within 9 years, with 46 ineligible and 23 non-evaluable patients. 156 evaluable patients (48 with LMS, 93 with mixed mesodermal sarcoma and 15 with other sarcoma) were randomized to receive eight courses of Adriamycin 60mg/m^2 every 3 weeks or no further treatment. 24 of 75 cases receiving Adriamycin had protocol deviations. Adjuvant radiotherapy prior to chemotherapy was allowed, 11 of 25 patients (44%) with LMS receiving Adriamycin suffered from recurrences compared with 14 of 23 patients (61%) with LMS receiving no adjuvant chemotherapy. There seemed to be a trend toward reduced recurrence rates and improved survival in the chemotherapy group. However, the subgroup analysis did not reach any statistical significance. Neither overall survival (60% versus 52%) nor recurrence-free survival (59% versus 47%) was significantly improved with adjuvant chemotherapy [6]. The validity of this study was compromised by the high dropout rate, heterogeneous histology group and protocol deviations. In addition, the use of chemotherapy that would now be considered suboptimal, and the statistical under-powering of the study, means that the study question was not adequately addressed.

A matched case-controlled study compared adjuvant chemotherapy with cisplatin, ifosfamide, and doxorubicin followed by radiotherapy versus radiotherapy alone or no adjuvant therapy in localized uterine sarcomas. A total of 18 patients receiving combination chemotherapy and radiotherapy were compared to 18 patients of historic matched group with radiotherapy alone or no adjuvant therapy. The 3-year OS (100% versus 76%) and recurrence free survival (76%

versus 43%) rates were better for the chemoradiation arm. Five patients relapsed, but all were still alive because of short follow-up interval [14]. In another study [15], 13 patients with completely resected uterine sarcoma (6 - carcinosarcoma, 6 - leiomyosarcoma, 1 - rhabdomyosarcoma) were treated with 3 cycles of adjuvant ifosfamide between 1992 and 1999. Two-year progression-free survival among the leiomyosarcoma patients was 33%. In another prospective study [16], 24 patients with stage I uterine sarcomas (11 with leiomyosarcoma; 8 with carcinosarcoma; 4 with stromal sarcomas; 1 with adenosarcoma) were treated with vincristine, doxorubicin, cyclophosphamide, and dacarbazine for 9 cycles. Eight of 24 patients recurred (33% overall, 4 of 11 patients with leiomyosarcoma) at a median time of 19 months. Among 70 patients with stages I or II leiomyosarcoma presenting to the Memorial Sloan-Kettering Cancer Center (1982-2005), 49 recurred (70%) at a median of 8.5 months, with approximately 45% progression-free at 2 years and 35% progression-free at 3 years [17]. While interpretation of this data for patient recommendations may be limited by the small numbers of patients with leiomyosarcoma histology and other design limitations, these and other studies serve to demonstrate a high risk for disease recurrence for women with stages I and II disease.

A combination of gemcitabine and docetaxel has been shown to be active in metastatic LMS [7], and in particular uterine LMS [8, 18]. In view of this, a single arm phase II study was performed investigating the efficacy of this doublet in the adjuvant setting in uterine LMS, to determine two-year progression-free survival (PFS) in completely resected FIGO stage I-IV disease [9]. As historical data indicated that approximately 30% of patients with resected stage I-IV disease would be expected to be progression-free at 2 years, observation of a two year PFS rate of at least 40% would indicate a clinically meaningful outcome worthy of further investigation. Of 23 patients, 45% remained progression-free at 2 years, with a median PFS of 13 months. Furthermore, of 18 patients with stage I or II disease, 59% remained progression free at 2 years, with a median PFS of 39 months. These outcomes certainly were superior to historical data.

In our study, the goal was to determine whether treatment with fixed dose-rate gemcitabine plus docetaxel was associated with improving disease-free survival and overall survival for patients with completely resected stage I and II disease. Among all 34 patients, 66% and 50% of patients remain disease-free at 2 years and at 3 years, respectively, with a median disease free survival of 47 months, which compares favorably with the 2-year progression-free survival rate of 45%, and the 3-year progression-free survival rate of 35%, observed among the 70 patients with stage I and II uterine leiomyosarcoma in the MSKCC retrospective study [17], and were similar to the reports of Hensley *et al.* [18] .

In our study, we reported low rates of serious toxicities associated with gemcitabine plus docetaxel in the adjuvant setting in comparison to high rates of these events which were observed in the advanced disease trials. The toxicity is primarily myelosuppression. One patient had grade IV neutropenia, however, there were no episodes of neutropenic fever grade IV. Five patients had grade III anemia, and 3 patients had grade III thrombocytopenia. The frequencies of myelosuppression of fixed-dose gemcitabine plus docetaxel as adjuvant therapy was much lower than that of studies of this regimen as second-line or first-line treatment [8, 9] most likely reflecting the effects of prior chemotherapy on bone marrow reserves among patients in this study. No patient suffered from grade IV non-hematological toxicity. Pulmonary toxicity has been reported in one patient. This treatment was generally well tolerated in the adjuvant setting and no deaths were reported.

The rarity of uterine LMS limited previous efforts investigating the role of adjuvant chemotherapy. Although a significant trend in favor of postoperative adjuvant chemotherapy is demonstrated in our prospective study using a chemotherapy regimen with high objective response rates in metastatic disease to treat patients with histologically confirmed uterine leiomyosarcoma with no evidence of disease on post-resection imaging, the limited sample size and single institution study make it premature to strongly advocate the use of this adjuvant chemotherapy. Prospective multicenter trials are necessary to clarify its role.

CONCLUSION

Fixed-dose gemcitabine plus docetaxel as adjuvant therapy for stage I-II uterine leiomyosarcoma yields 2-year disease-free and overall survival rates that appear superior to historical rates. Gemcitabine-docetaxel was associated with low rates of serious toxicities in the adjuvant setting and these toxicities were both tolerable and manageable.

REFERENCES

1. D'Angelo E, Part J. Uterine sarcomas: a review. Gynecol Oncol 2010; 116: 131-139.
2. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. Cancer 1993; 71:1702-1709 [PubMed: 8381710].
3. Nordal R, Kristensen GB, Kaern J, et al. The prognostic significance of stage, tumor size, cellular atypia and DNA ploidy in uterine sarcoma. Acta Oncol 1995; 34:797-802.
4. Pautier P, Genestie C, Rey A, et al. Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of a grading score validated for soft tissue sarcoma. Cancer 2000; 88:1425-1431.
5. Reed NS, Mangioni C, Malmstrom H, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stage I and II: an European Organisation for Research and Treatment of Cancer Gynaecologic Cancer Group Study (protocol 55874). Eur J Cancer 2008; 44:808-818.
6. Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant

adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. J Clin Oncol 1985; 3:1240-1245.
7. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: Results of a phase II trial. J Clin Oncol 2002; 20:2824-2831.
8. Hensley ML, Blessing J, Degeest K, et al. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol Oncol 2008; 109(3):323-328.
9. Hensley ML, Blessing J, Mannel R, et al. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008; 109(3):329-334.
10. FIGO committe on gynecologic oncology. FIGO staging for uterine sarcomas. Int J Gynecol Cancer 2009; 104:179.
11. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. March 31, 2003. Publish Date: August 9, 2006.
12. Gadducci A, Landoni F, Sartori E, et al. Uterine leiomyosarcoma: analysis of treatment failures and survival. Gynecol Oncol 1996; 62(1):25-32.
13. Gadducci A, Sartori E, Landoni F, et al. Endometrial stromal sarcoma: analysis of treatment failures and survival. Gynecol Oncol 1996; 63(2):247-253.
14. Pautier P, Rey A, Haie-Meder C, et al. Adjuvant chemotherapy with cisplatin, ifosfamide, and doxorubicin followed by radiotherapy in localized uterine sarcomas: results of a case-control study with radiotherapy alone. Int J Gynecol Cancer 2004; 14:1112-1117.
15. Kushner DM, Webster KD, Belinson JL, et al. Safety and efficacy of adjuvant single-agent ifosfamide in uterine sarcoma. Gyncol Oncol 2000; 78:221-227.
16. Odunsi K, Monede V, Tammela J, et al. Efficacy of adjuvant CYVADIC chemotherapy in early-stage uterine sarcomas: Results of long-term follow-up. Int J Gynecol Cancer 2004; 14:659-664.
17. Zivanovic O, Iasonos A, Hensley ML, et al. Stage-specific survival of patients with uterine leiomyosarcoma: A comparison of FIGO and AJCC staging system. Submitted to Gynecologic Oncology, August 2008.
18. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: Results of a prospective study. Gynecol Oncol 2009; 112(3):563-567.

Application of three-dimensional NLS-diagnostics in oncology. New trends and prospects of development

V.I. Nesterova, L.A. Yankina, O.R. Kojemyakin

Institute of Practical Psychophysics, Russia

Correspondence:
V.I. Nesterova,
Institute of Practical Psychophysics,
2, 1st Proizvodstvennaya str., 644001,
Omsk, Russia, Tel./Fax: +7 3812 364526,
e-mail: v.i.nesterov@inbox.ru

ABSTRACT

The article presents modern principles of three-dimensional image rendering in accordance with NLS-graphy data. It also gives a generalized evaluation of three-dimensional NLS-graphy effectiveness in revealing oncological diseases in comparison with conventional two-dimensional NLS-graphy studies.

Key words: therapy; oncology; diagnostics; NLS.

Diagnostics and treatment of malignant neoplasms are the most urgent issues in modern medicine. Oncologists face not only problems of primary and updating diagnostics of tumoral diseases, but also evaluation of various methods of tumor treatment efficiency and well-timed diagnosis of recurrent tumors after treatment procedures. The introduction of new three-dimensional technologies of NLS-pictures acquiring into clinical practice allows the solving of the abovementioned diagnostic problems at a qualitatively new and higher level.

Application of three-dimensional visualization of organs and tissues significantly extended the potential of NLS-diagnostics [1]. Today we may speak of truly early diagnostics of tumoral diseases at the first, pre-clinical stage of patient examination. Three-dimensional NLS-examination allows not only to reveal minimal structural changes in organs and tissues, but precise evaluation of tumoral process spreading extent. Further, when combined with the use of spectral-entropy analysis, it makes possible to identify disease stage and choose the adequate method of patient treatment [6]. The Institute of Practical Psychophysics has great experience of three-dimensional NLS-graphy applications which is impossible to be properly described in an article of this limited extent [2]. Due to this fact, we decided to dwell on those issues of three-dimensional NLS-diagnostics which have great practical importance, but are still not widely spread in clinical practice.

In group of malignant tumors of liver, metastatic invasion holds leading positions. It is well-known that the most frequent reasons for liver metastatic disease are malignant tumors of the large intestine, rectum, stomach, pancreas, mammary glands and lungs [8]. At metastatic disease, the shape, structure, size of parenchyma and vascular pattern of the liver are more or less changed, depending on tumor existence duration, as well as number and size of tumoral nodes. In addition to three-dimensional NLS-graphy, diverse variants of dopplerography (initially energy color mapping) may be used to solve the problem of differential diagnostics of benign and malignant changes in the liver parenchyma. **Three-dimensional NLS-graphy method** allows the visualization of a three-dimensional picture of vessel location and form, marking them by a certain color in the background of the organ's normal picture. In this aspect, the method is rather close to x-ray angiography and allows to accurately visualize large and minute vessels.

Vascular pattern in single metastases is broken due to the constriction and dislocation of certain vessels' hepatic branches. In massive affection, there is significant breach of vascular pattern. In some cases a physician may detect local, chaotic changes of vascular pattern, when hypervascularization of tumoral nodes is present. However, tumoral nodes in liver metastatic disease may have both increased and decreased vascularization. Due to this fact, data acquired with NLS-graphy is not always sufficient and should be complemented with results of x-ray angiography.

Differential diagnostics of tumoral affection of the liver is complicated by not only the marked multiformity of changes, but also by its frequent combination with diffuse and dystrophic changes of the organ's parenchyma. All of the above stipulate the necessity for wide **application of spectral-entropy analysis of affection nidus**. Our experience proves that availability of NLS-diagnostics equipment allows for a detailed examination of three-dimensional hepatic neoplasms sized less than 3mm. Therefore, at the early stages of pathology development, a clinician is able to update the morphological substrate of detected changes and obtain sufficient information for diagnosis updating.

It is well-known that one of the leading methods of solitary hepatic metastases treatment is surgical operation. Proof of operation efficacy is the absence of metastases in other parts of the liver. This problem may be successfully **solved using three-dimensional NLS-ultramicroscopy with the application of spectral-entropy analysis** [5]. For a long time, widespread application of ultramicroscopic NLS-examination was limited by the absence of special equipment with high resolution. Nowadays, devices with super-high frequency non-linear generators (40GHz) are available, making it possible to carry out three-dimensional ultramicroscopic revision and evaluation of chromosomal aberrations of almost any cell in the human organism. Three-dimensional NLS-research may help specify character, localization and number of pathological nidi when the clinician plans liver resection due to metastatic disease. Our experience shows that the application of three-dimensional NLS-graphy in cancer metastases of the large intestine allows the detection of additional nidi, not registered by any type of introscopy, in 20% of the cases. Data acquired using three-dimensional NLS-graphy of the liver makes it possible to evaluate the extent of the operation; avoid unjustified surgical interventions; and decrease the risk of developing post-operative complications.

Joint application of video-laparoscopy and NLS-research allows the physician to combine proper examination of abdominal organs and tissues with a study of their structure by applying spectral-entropy analysis in selected areas, and carry out updating diagnostics of tumoral diseases of organs in the abdominal cavity and the retroperitoneal space. In stomach cancer, the number of mistakes in pre-operative diagnostics of liver metastatic disease reaches 25% - 30%. The first application of such research technology proves that the number of mistakes decreases to 3% - 5%.

Nowadays, onco-urology is the sphere in which methods of three-dimensional NLS-graphy may also be widely applied. However, until today, the application of three-dimensional NLS-research on patients operated for urinary bladder tumor consisted in the dynamic monitoring of the organ's condition, in order to detect recurrent tumors and metastases at an early stage. The introduction of three-dimensional NLS-methods in clinical practice will allow a complete change in our point of view to this problem. We believe that this issue is in fact topical, since the majority of surgically operated patients were subjected to traumatic transurethral resections.

Three-dimensional NLS-research with the application of spectral-entropy analysis, carried out during surgical oncotomy, allowed us to detect additional tumoral neoplasms, not registered by two-dimensional NLS research in 37% of the patients. Application of three-dimensional methods makes it possible to specify the extent of tumor local spreading process; control the depth of urinary bladder wall resection; and decrease the risks of developing complications during the oncotomy.

Usually, the diagnostics and morphological verification of rectal cancer does not present difficulties. However, evaluating the organ wall's degree of invasion is not always possible using standard diagnostic methods [7]. Traditional two-dimensional NLS-research is already widely used as a diagnostics method of recurrent rectal cancer after organ extirpation [3]. Nevertheless, primary diagnostics of the disease using two-dimensional NLS-graphy is hindered due to several reasons; first and foremost, given that in two-dimensional NLS-scanning the rectum is visualized only partially (80% of the whole organ surface area).

Application of **three-dimensional NLS-graphy** makes it possible to accurately differentiate between all layers of rectum walls, and thus to diagnose the depth of tumor infiltration and identify the stage of the disease, using spectral-entropy analysis [4]. This method helps detect changed lymph nodes over 1.5mm in size in pararectal lymph node metastatic disease. During the monitoring of pre-operational radiotherapy, three-dimensional NLS-graphy helps detect accurately the decrease in tumor size; identify changes in their structure, related to medical pathomorphism; and identify the decrease in pararectal tissue tumoral infiltration. Therefore, three-dimensional NLS-graphy may be considered as a method of rectal cancer primary diagnostics. It allows physicians to resolve the most important diagnostic issues, related to identifying tumoral process length, the extent of the tumor's local spreading and monitoring pre-operative treatment efficiency. In organ-preserving operations, three-dimensional NLS-graphy may be used as an efficient method of recurrent tumors early diagnostics in the anastomosis area.

In conclusion, as to the characteristics of modern, three-dimensional NLS-graphy method, we should like to emphasize that this method allows efficient meeting of such objectives as detection of tumoral changes, identifying disease stage and qualitative evaluation of treatment.

REFERENCES

1. Nesterov VI. Main tendencies of NLS-method development. 3D computer NLS-graphy. Moscow Prospect 2012, p. 4-6.
2. Artukh V, Shovkoplyas U, Gavrilov A. Computer non-linear analysis and its role in diagnostics. Collection of scientific papers of the Institute of Practical Psychophysics "Current problems of NLS-diagnostics". Tome 1. Moscow Katalog 2006, p. 9-12.
3. Svetlova PA, et al. Possibilities of NLS-method in diagnostics of stomach and large intestine cancer. Collection of scientific papers of the Institute of Practical Psychophysics "Current problems of NLS-diagnostics". Tome 1. Moscow Katalog 2006, p. 13-17.
4. Nesterova VI, et al. NLS-method – new possibilities in diagnostics of large intestine neoplasms. Collection of scientific papers of the Institute of Practical Psychophysics "Current problems of NLS-diagnostics". Tome 1. Moscow Katalog 2006, p. 18-23.
5. Shvack AY, et al. Certain aspects of NLS-diagnostics of liver pathology. Collection of scientific papers of the Institute of Practical Psychophysics "Current problems of NLS-diagnostics". Tome 3. Moscow Katalog 2010, p. 13-19.
6. Fazylov SS, et al. Magnetic resonance imaging and computer NLS-graphy and in evaluation of surgical intervention extent for brain tumors treatment. Collection of scientific papers of the Institute of Practical Psychophysics "Current problems of NLS-diagnostics". Tome 3. Moscow Katalog 2010, p. 49-53.
7. Galvin JM, Ezzell G, Eisbrauch F, et al. Implementing IMRT in clinical practice: A joint document of the American society for therapeutic radiology and oncology and the American association of physicists in medicine. Int J Radiat Oncol Biol Phys 2004; 58:1616-1634.
8. Shih HA, Jiang SB, Auarrah KM. Internal target volume determined with expansion margins beyond composite gross tumor volume in three-dimensional conformal radiotherapy for lung cancer. Int J Radiat Oncol Biol Pays 2004; 60:613-622.
9. Xia P, Amols HI, Ling CC. Three-dimensional conformal radiotherapy and intensity-modulated radiotherapy breast. Textbook of Radiation Oncology, 2nd ed. / Ed. by Leibl SA and Phillips TL. Philadelphia: W. B. Saunders Company, 2004; 163-186.

Vulvar apocrine adenocarcinoma: case report and literature review

Marios Bakogeorgos[1], Giannis Mountzios[1], Konstantinos Dritsakos[2], Nikolaos Kentepozidis[1]

[1]Department of Medical Oncology, 251 Air Force General Hospital, Athens, Greece
[2]Department of Pathology, 251 Air Force General Hospital, Athens, Greece

Correspondence: Giannis Mountzios, Department of Medical Oncology, 251 Air Force General Hospital, Athens, Greece, e-mail: gmountzios@med.uoa.gr

ABSTRACT

Primary vulvar adenocarcinomas are rare tumors comprising distinct disease entities, such as sweat gland carcinoma, primary "breast-like" adenocarcinoma of the vulva and extra-mammary Paget's disease. Despite the recent advances in vulvar tumor molecular characterization, the histogenesis of the different subtypes remains obscure. Clear guidelines for diagnosis and therapy are still unavailable. Herein we present an unusual case of an apocrine "mammary-like" primary adenocarcinoma of the vulva in a 64-year old woman. Features that classify vulvar adenocarcinoma as "mammary-like" include the presence of normal mammary-like glands in the vicinity of the tumor; the existence of a transition zone with variable malignant changes between the tumor and the normal mammary-like glands; demonstration of typical breast-like morphology and the expression of hormone receptors; but the features separating the lesions originating from native sweat glands and those arising from mammary-like glands need to be further delineated. In our case, all these features were present. Overall, the overlapping of the histological and immunohistochemical features makes the distinction difficult. Meticulous clinical examination and imaging studies are mandatory in order to exclude adenocarcinoma from other primary sites (breast, alimentary and female reproductive tract) before diagnosing primary vulvar adenocarcinoma.

Key words: vulvar cancer; apocrine; mammary-like; adenocarcinoma.

INTRODUCTION

Vulvar cancer accounts for approximately 5% of all female genital malignancies. With an incidence of 1.5 per 100,000 women-years in developed countries and 2-3 times more frequently in underdeveloped countries, it is one of the least diagnosed human malignancies [1]. Almost half of the patients are aged 70 years or older, with 15% being 80 years or older at the time of initial diagnosis [2]. The rarity of the disease along with the advanced patient age often result in delayed diagnosis or misdiagnosis and application of local treatment modalities for microbial or fungal infections, without biopsy for definitive diagnosis.

More than 90% of cases are classified as squamous cell carcinoma (SCC); Melanoma is the second most frequent histological type and represents less than 5% of vulvar cancers [1]. Primary vulvar adenocarcinomas are very rare tumors; they have traditionally been classified into the following histological subtypes: sweat gland carcinomas, primary "breast-like" adenocarcinomas of the vulva and extra-mammary Paget's disease [3]. Despite the recent advances in vulvar tumor molecular characterization, their histogenesis is still not fully understood, and the question of whether they arise from the native apocrine sweat glands or from anogenital mammary-like glands, is still debatable [4]. Herein, we present a case of primary vulvar apocrine adenocarcinoma and discuss the histogenesis and the special clinicopathological and molecular features of this rare entity.

CASE PRESENTATION

A 64-year old woman was admitted in our hospital with a palpable left inguinal mass of recent onset. Clinical examination was otherwise unremarkable. Her medical history included arterial hypertension, hyperlipidemia and depression. Laboratory tests were normal including tumor biomarkers, except from a marginal value of marker Ca 15-3 (37U/ml). Diagnostic imaging, including Computed Tomography (CT) of the abdomen and thorax, Magnetic Resonance Imaging (MRI) of the pelvis, mammography and intravaginal ultrasound were negative. A Tru-Cut biopsy of

the lesion was performed, followed by a wide local excision. Microscopic examination revealed an invasive, probably metastatic adenocarcinoma of moderate differentiation, most likely originating from the stomach or the female reproductive system. Immunohistochemically, the malignant cells were positive for cytokeratin (CK) 7, CK 19, and CEA, while immunostaining for hormonal (estrogen, androgen, progesterone) receptors, vimentin and CK 20 were negative (data not shown). Subsequent endoscopic studies (colonoscopy and gastroscopy with random stomach biopsies) and whole body positron-emission tomography (PET/CT) were negative.

On the basis of the aforementioned findings, the patient received first-line chemotherapy for metastatic carcinoma of unknown primary (CUP) with four cycles of Paclitaxel (175mg/m^2 on day 1) and Carboplatin (5 AUC on day 1) every three weeks. Primary prevention for neutropenia with pegfilgrastim was administered from the first cycle. Sensory neuropathy grade I was observed and led to 10% decrease in Paclitaxel dosing. Post-therapeutic imaging studies were negative for local or systemic relapse. On the basis of the tumor's possible histological origin, the patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) and omentectomy. The pathological examination did not reveal any signs of disease and the patient received four additional cycles of the former regimen.

One month after completion of first-line chemotherapy, clinical examination revealed a lesion on the left labia majora and local excision was performed. The surgical specimen encapsulated a firm, tan mass that measured 0.6cm in maximum dimension. Microscopic examination disclosed an invasive, moderately-differentiated adenocarcinoma, the morphology of which was compatible with apocrine differentiation (Figure 1). Normal eccrine and apocrine sweat glands were not identified in the vicinity of the tumor but a few mammary-like glands were recognized in the surgical specimen (Figure 1, horizontal green arrows). Isolated malignant cells were observed under the corneous layer of the epidermis (pagetoid spread), (Figure 1, black vertical arrows). Immunohistochemically, almost all malignant cells were positive for EMA, CEA, Pankeratin, CK 8/18 (Figure 2, black vertical arrows), CK 34Be12, CK 7. Few cells were positive for CK 5/6, CK 17, CK 20 and Vimentin. Very few cells were positively immunostained for estrogen (ER) and progesterone (PR) receptors, as well as for gross cystic disease fluid protein 15 (GCDFP-15) and cerbB-2 (data not shown). The tumor cells had large, clear and mainly eosinophilic

Figure 1.

Hematoxylin-Eosin stain of the surgical specimen (X 40) illustrating the presence of an invasive moderately-differentiated adenocarcinoma with morphology compatible with apocrine differentiation (black vertical arrows). A few mammary-like glands were recognized in the surgical specimen (green horizontal arrows).

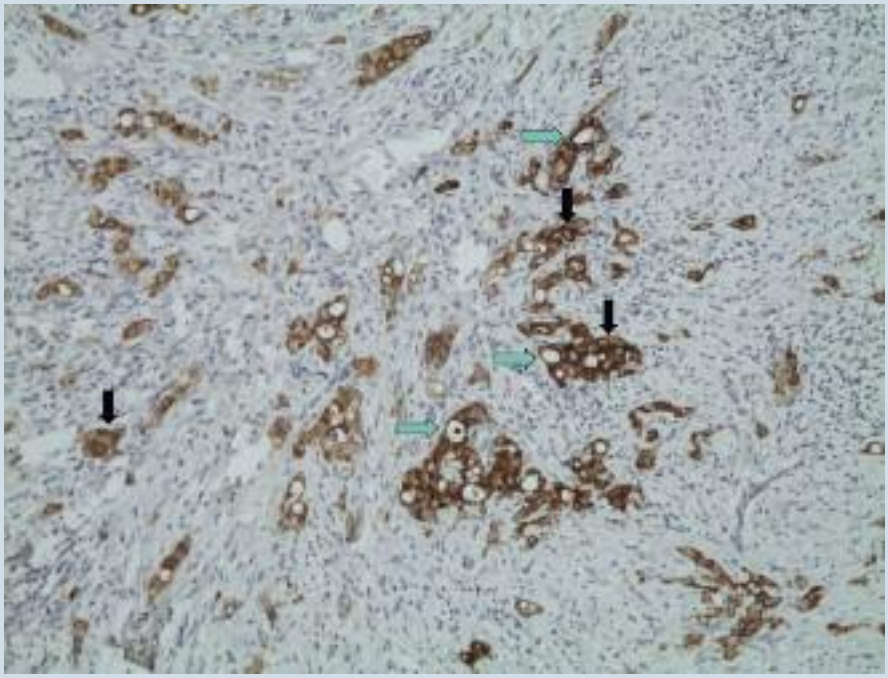
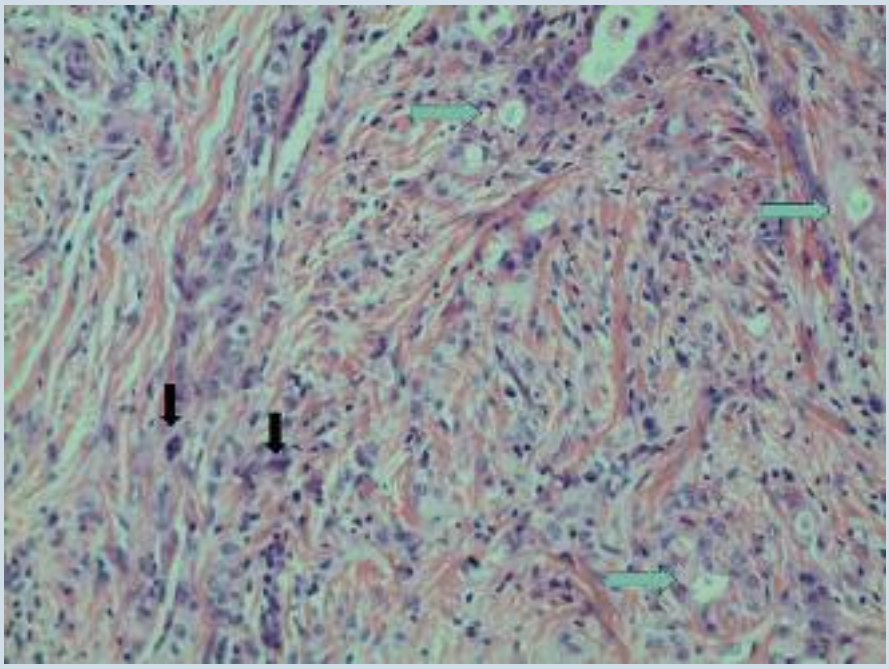


Figure 2.
Immunohistochemical stain of the surgical specimen (X 40) for cytokeratin 8/18 illustrating strong positivity for apocrine cancer cells (black vertical arrows). A few mammary-like glands are again evident (green horizontal arrows).



cytoplasm with a large, round, bullous nucleus (Figure 2, black vertical arrows). High nucleic pleomorphism and brisk mitotic activity with many atypical mitoses were also observed. A few mammary-like glands were again evident (Figure 2, green horizontal arrows). Taking into consideration clinical, imaging and pathology findings, it was believed that the tumor may have originated either from epithelial inclusions of the secondary Müllerian system or from modified, mammary-like glands of the anogenital area. Following local excision, the patient underwent locoregional external-beam radiotherapy.

Five months after completion of radiotherapy, the patient presented with a new firm lesion on the left labia majora. Gynecologic examination with colposcopy disclosed an additional mass at the posterior vaginal wall. Since diagnostic imaging studies again did not reveal any site of metastasis, both radical vulvectomy and a simultaneous local excision of the vaginal lesion were performed. The posterior vaginal wall tumor proved to be a benign fibroepithelial polyp, while microscopic examination of the vulvectomy specimen revealed invasion by a moderate-to-high grade adenocarcinoma with apocrine differentiation and an immunohistochemical profile identical to the former pathology report (data not shown). After a short recovering period, the patient received chemotherapy with six cycles of Cisplatin (20mg/m^2 on day 1 and day 2) and Topotecan (0.75mg/m^2 on days 1, 2 and 3) every three weeks. The patient completed the chemotherapy course four months ago and was referred to the outpatient Oncology clinic for periodical follow-up. Clinical examination and imaging studies performed after two and five months revealed neither local nor systematic relapse and the patient is free of symptoms to date.

DISCUSSION

The rarity of primary vulvar adenocarcinomas mitigates the efforts for a proper histological classification of the disease. They are usually classified into sweat gland carcinomas; primary "mammary-like" adenocarcinomas of the vulva; and extra-mammary Paget's disease. Adenocarcinomas originating from Bartholin glands can also present clinically as vulvar adenocarcinoma. Differential diagnosis also includes adenocarcinoma from epithelial inclusions of the secondary Müllerian system [3].

A multitude of ovarian, adnexal and pelvic masses are believed to originate from the secondary Müllerian system [5]. During embryogenesis, the distal segments of the two Müllerian ducts, which are also referred to as the "primary Müllerian system", fuse to form the uterus, cervix and

proximal one third of the vagina. The proximal Müllerian ducts remain separated to become the two fallopian tubes. Remnants of the most proximal Müllerian ducts that do not participate in organogenesis constitute the secondary Müllerian system [6], a term that was coined by Lauchlan in 1972 [7, 8] to refer to structures that reside outside the derivatives of the primary Müllerian system. The secondary Müllerian system is hypothesized to be the source of a wide spectrum of ovarian and paraovarian, neoplastic and non-neoplastic disorders, including a) paraovarian and paratubal cysts, b) endocervicosis [9], c) endosalpingiosis, d) müllerianosis (lesions containing admixtures of endosalpingiosis, endometriosis and endocervicosis), e) endometriosis, f) primary ovarian epithelial carcinomas and g) primary peritoneal serous carcinomas [5, 10, 11]. The exact role of the secondary Müllerian system in the pathogenesis of adnexal, ovarian and pelvic tumors remains to be elucidated, as histological evidence and knowledge continue to evolve.

Ectopic mammary gland tissue in the vulva, such as embryonic milk lines, is an uncommon clinical and pathological finding. Such ectopic tissue can be the site of the same physiological and pathological processes found in the normal breast [12]. Epithelial cells of fetal breast glandular structures, at the third trimester of pregnancy (28 weeks), produce GCDFP-15, in the absence of specific apocrine morphology. Apocrine epithelium of the breast may be a normal process of differentiation rather than a result of metaplasia, and it has been demonstrated that it is estrogen-receptor (ER), progesterone-receptor (PR0 and bcl-2) negative, but androgen-receptor (AR) positive. The apocrine epithelium is a normal constituent of apocrine glands found in axillary, anogenital skin, eyelids, ears and mammary glands and consists of cells with eosinophilic cytoplasm that may contain lipid, iron, lipofuscin, PAS-positive diastase-resistant granules and a large nucleus located near the base of the cell [13]. The apocrine epithelium is distinct, both morphologically and functionally, from that of cutaneous, sebaceous and sweat glands [14]. Glycoprotein GCDFP-15 (15 kDa), the major component of cyst fluid, represents an immunohistochemical marker of apocrine differentiation that is more reliable than morphology and the detection of prolactin-inducible protein (PIP/GCDFP-15) mRNA using *in situ* hybridization [15-17]. The gene is expressed in apocrine glands and in exocrine organs that have common phylogenetic features with apocrine glands, such as the bronchial epithelium, the sweat, salivary and lacrimal glands and the seminal vesicles. According to the human genome sequencing data, the *GCDFP/PIP* gene is located at 7q34 [18] and the corresponding peptide GCDFP-15 has 95% specificity and 74% sensitivity as a marker for breast cancer [19, 20] and is useful in supporting breast origin in metastatic carcinoma of unknown primary origin [13]. A discriminating feature between apocrine cells and normal luminal epithelial cells of the breast is that while the former expresses AR and lacks ER, PR and bcl-2; the latter is ER/PR positive and AR negative [21, 22].

Approximately 25% of patients with breast cancer develop clinically evident or indolent cutaneous metastases [23, 24]. Sweat gland carcinomas account for about 0.05% of all cutaneous neoplasms [25]. Cutaneous metastases from breast carcinoma (especially the ductal type) can be difficult to distinguish from sweat gland carcinomas. Treatment and prognosis for these two entities differ radically, rendering thus an accurate histological diagnosis crucial. Rollins-Raval *et al.* suggest an immunohistochemical panel, composed of mammaglobin, p63 and three basal cytokeratins (CK5, CK14 and CK 17) with sufficient value to aid in the differentiation between cutaneous metastases of breast carcinoma and sweat gland carcinomas [26].

The discrimination between "mammary-like", apocrine adenocarcinoma and primary vulvar adenocarcinoma can be particularly challenging: According to recent literature, features that classify vulvar adenocarcinoma as "mammary-like", include the presence of normal mammary-like glands in the vicinity of the tumor, as in our case (Figures 1 and 2, green horizontal arrows); the existence of transition zone with variable malignant changes between the tumor and the normal mammary-like glands; the demonstration of typical breast-like morphology; and the expression of ER and PR [3, 27-29] (unlike our case). However, the features separating the lesions originating from native sweat glands and those arising from mammary-like glands need to be further delineated. It is also important to note that the presence of pagetoid spread around the invasive tumor indicates the possibility that the invasive apocrine adenocarcinoma originates from a recurrent Paget's disease (EMPD) [30].

The rarity of the tumor is also responsible for the absence of uniform guidelines for treating the disease [12]; Nevertheless, the initial aggressive locoregional control of the tumor, usually by extensive radical excision, should be emphasized; however, since definitive diagnosis is often delayed or obscured, extensive surgery is frequently applied later in the course of the disease, usually following initial local excision. In most cases, as in ours, the origin of the tumor is considered unknown and the patient is treated within the context of "adenocarcinoma of unknown primary subtype of peritoneal adenocarcinoma in a female patient"; chemotherapeutic regimens are mostly empirical and include the Paclitaxel-Carboplatin combination and schemes currently used for gynecological malignancies, with clinically doubtful outcomes. When indicated, wide local excision and re-excision must always be considered as an option and the role of local radiotherapy remains debatable.

CONCLUSION

This report describes a rare case of vulvar apocrine adenocarcinoma, a clinical and pathological entity whose histogenesis remains controversial. The features separating the lesions originating from native sweat glands and those arising from mammary-like glands need to be further

delineated. Overlapping of the histological and immunohistochemical features makes the distinction difficult. Meticulous clinical examination to exclude adenocarcinoma from other primary site, especially from the breast, is mandatory before diagnosing primary vulvar adenocarcinoma. Treatment is based on chemotherapy regimens for "adenocarcinoma of unknown primary" and due to the rarity of the tumor, remains largely empirical.

REFERENCES

1. Creasman WT, Lifford KL, Talavera F, Barnes D, Gaupp FB, Huh WK. Malignant vulvar lesions. http://emedicine.medscape.com/article/264898-overview.
2. Henson D, Tarone R. An epidemiologic study of cancer of the cervix, vagina, and vulva based on the Third National Cancer Survey in the United States. Am J Obstet Gynecol 1977; 129:525-532.
3. Alsaad KO, Obaidat N, Dube V, Chapman W, Ghazarian D. Vulvar apocrine adenocarcinoma: A case with nodal metastasis and intranodal mucinous differentiation. Pathology - Research and Practice 2009; 205:131-135.
4. Klemba A, Kukwa W, Semczuk A, Czarnecka AM. Vulvar cancer as a target for molecular medicine. Front Biosci (Schol Ed) 2011 Jan 1; 3:136-44.
5. Katre R, Morani AK, Prasad SR, Surabhi VR, Choudhary S, Sunnapwar A. Tumors and pseudotumors of the secondary Müllerian system: Review with emphasis on cross-sectional imaging findings. AJR Am J Roentgenol 2010 Dec; 195(6):1452-9.
6. Dubeau L. The cell of origin of ovarian epithelial tumours. Lancet Oncol 2008; 9:1191-119.
7. Lauchlan SC. The secondary Müllerian system. Obstet Gynecol Surv 1972; 27:133-146.
8. Lauchlan SC. The secondary Müllerian system revisited. Int J Gynecol Pathol 1994; 13:73-79.
9. Batt RE, Smith RA, Buck Louis GM, et al. Müllerianosis. Histol Histopathol 2007; 22:1161-1166.
10. Clement PB, Young RH. Florid cystic endosalpingiosis with tumor-like manifestations: A report of four cases including the first reported cases of transmural endosalpingiosis of the uterus. Am J Surg Pathol 1999; 23:166-175.
11. Young RH, Clement PB. Endocervicosis involving the uterine cervix: A report of four cases of a benign process that may be confused with deeply invasive endocervical adenocarcinoma. Int J Gynecol Pathol 2000; 19:322-328.
12. Fracchioli S, Puopolo M, De La Longrais IA, Scozzafava M, Bogliatto F, Arisio R, Micheletti L, Katsaros D. Primary "breast-like" cancer of the vulva: A case report and critical review of the literature. Int J Gynecol Cancer 2006 Jan-Feb; 16 (Suppl 1):423-8.
13. Zagorianakou P, Zagorianakou N, Stefanou D, Makrydimas G, Agnantis NJ. The enigmatic nature of apocrine breast lesions. Virchows Arch 2006; 448:525-531.
14. Rosen PP. Rosen's Breast Pathology, 2nd edition. Lippincott Williams & Wilkins, Philadelphia, 2001.
15. Eusebi V, Damiani S, Losi L, Millis RR. Apocrine differentiation in breast epithelium. Adv Anat Pathol 1997; 4:139-155.
16. Pagani A, Sapino A, Eusebi V, Bergnolo P, Bussolati G. PIP/GCDFP-15 gene expression and apocrine differentiation in carcinomas of the breast. Virchows Arch 1994; 425:459-465.
17. Losi L, Lorenzini R, Eusebi V, Bussolati G. Apocrine differentiation in invasive carcinoma of the breast. Comparison of monoclonal and polyclonal gross cystic disease fluid protein-15 antibodies with prolactin-inducible protein mRNA gene expression. Appl Immunohistochem 1995; 3:91-98.
18. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, Funke R, Gage D, et al. Initial sequencing and analysis of the human genome. Nature 2001; 409:860-921.
19. Wells CA, McGregor IL, Makunura CN, Yeomans P, Davies JD. Apocrine adenosis: A precursor of aggressive breast cancer? J Clin Pathol 1995; 48:737-742.
20. Wick MR, Lillemoe TJ, Copland GT, Swanson PE, Manivel JC, Kiang DT. Gross cystic disease fluid protein-15 as a marker for breast cancer: Immunohistochemical analysis of 690 human neoplasms and comparison with a-lactalbumin. HumPathol 1989; 20:281-287.
21. Selim AG, Wells CA. Immunohistochemical localization of androgen receptor in apocrine metaplasia and apocrine adenosis of the breast: Relation to oestrogen and progesterone receptors. J Clin Pathol 1999; 52:838-841.
22. Gatalica Z. Immunohistochemical analyses of apocrine breast lesions. Consistent over-expression of androgen receptor accompanied by the loss of estrogen and progesterone receptors in apocrine metaplasia and apocrine carcinoma in situ. Pathol Res Pract 1997; 193:753-758.
23. Krathen RA, Orengo IF, Rosen T. Cutaneous metastasis: A meta-analysis of data. South Med J 2003; 96(2):164-167.
24. Spencer PS, Helm TN. Skin metastases in cancer patients. Cutis 1987; 39(2):119-121.
25. Cooper PH. Carcinomas of sweat glands. Pathol Annu 1987; 22 (pt 1):83-124.
26. Rollins-Raval M, Chivukula M, Tseng GC, Jukic D, Dabbs DJ. An immunohistochemical panel to differentiate metastatic breast carcinoma to skin from primary sweat gland carcinomas with a review of the literature. Arch Pathol Lab Med 2011 Aug; 135(8):975-83.
27. van der Putte SC. Ultrastructure of the human anogenital "sweat" gland. Anat Rec 1993; 235:583-590.
28. Piura B, Gemer O, Rabinovich A, Yanai-Inbar I. Primary breast carcinoma of the vulva: Case report and review of literature. Eur J Gynaecol Oncol 2002; 23:21-24.
29. van der Putte SC. Anogenital "sweat" glands. Histology and pathology of a gland that may mimic mammary glands. Am J Dermatopathol 1991; 13:556-567.
30. James LP, Worsham GF, Hoskins WJ, Belcik R. Apocrine adenocarcinoma of the vulva with associated Paget's disease. Diagnosis of lymph node metastases by fine needle aspiration biopsy. Acta Cytol 1984; 28:178-184.

Fluoropyrimidine-based chemotherapy as induction, maintenance and rechallenge treatment for gastric carcinomatosis presenting with bone marrow infiltration, microangiopathic haemolytic anaemia and disseminated intravascular coagulation: a case report and literature review

Georgios Ioannidis[1], Froso Iacovou[2], Aristi Kourri[3], Rena Ioannou[1]

[1]Oncology Department, Nicosia General Hospital, Cyprus
[2]Histopathology Department, Nicosia General Hospital, Cyprus
[3]Radiology Department, Nicosia General Hospital, Cyprus

Correspondence:
Georgios Ioannidis,
213, Nicosia-Limassol Old Road,
Strovolos 2029, Nicosia, Cyprus,
Tel.: +357 22603000,
Fax: +357 22604333,
e-mail: geo_ioann@hotmail.com
(permission for publication)

ABSTRACT

We report a rare case of an elderly Caucasian man with advanced gastric signet-ring cell carcinoma (SRCC) presenting with the combination of bone marrow infiltration, microangiopathic haemolytic anaemia (MAHA) and acute disseminated intravascular coagulation (DIC). Despite his impaired performance status, the patient was started on weekly, 24-hour infusional, high-dose 5-fluorouracil and leucovorin (HDFL), combined with monthly zoledronic acid, and achieved a complete remission of the paraneoplastic haematological syndromes within the first four weeks. Partial marrow response was confirmed after three months of treatment. The induction regimen was well-tolerated and followed by maintenance capecitabine on a continuous, fixed, low-dose schedule. After a total five-month period of disease control, MAHA and DIC relapsed. Although the patient was successfully rechallenged with HDFL, he became refractory to subsequent intensification chemotherapy and died of progressive disease. Overall, protracted fluoropyrimidine-based chemotherapy appears an effective and low-toxic option for induction, maintenance and rechallenge treatment of this grave condition.

Key words: gastric cancer; microangiopathic haemolytic anaemia; disseminated intravascular coagulation; bone marrow infiltration; fluoropyrimidine-based chemotherapy.

Abbreviations

MAHA:	Microangiopathic haemolytic anaemia
DIC:	Disseminated intravascular dissemination
SRCC:	Signet-ring cell carcinoma
GC:	Gastric cancer/carcinoma
TMA:	Thrombotic microangiopathy

INTRODUCTION

The combination of microangiopathic haemolytic anaemia (MAHA), acute disseminated intravascular coagulation (DIC) and malignant bone marrow infiltration (BMI) is a rare, ominous presentation of advanced gastric cancer (GC), without established standard treatment.

CASE REPORT

A 71-year-old Caucasian man presented with a two-month history of anorexia, weight loss and bone pains, along with two weeks' duration of epigastric discomfort and dark-red urine discolouration. His past medical history included smoking-related chronic obstructive pulmonary disease and chronic gastritis, which, despite successful Helicobacter (H.) pylori eradication therapy, had been persistent on follow-up endoscopy three years earlier. Physical examination revealed paleness, jaundice, diffuse petechiae and severe dorsalgia with tenderness on spinal percussion.

Laboratory workup, including peripheral blood count and smear, biochemical profile and urinalysis, along with clotting studies, serum haptoglobin levels and direct Coomb's test, was compatible with severe MAHA and acute

Figures 1A & B.
Representative haematoxylin and eosin-stained bone marrow sections showing multiple clusters of signet-ring-like cells within the marrow space (A) and vessels (B).

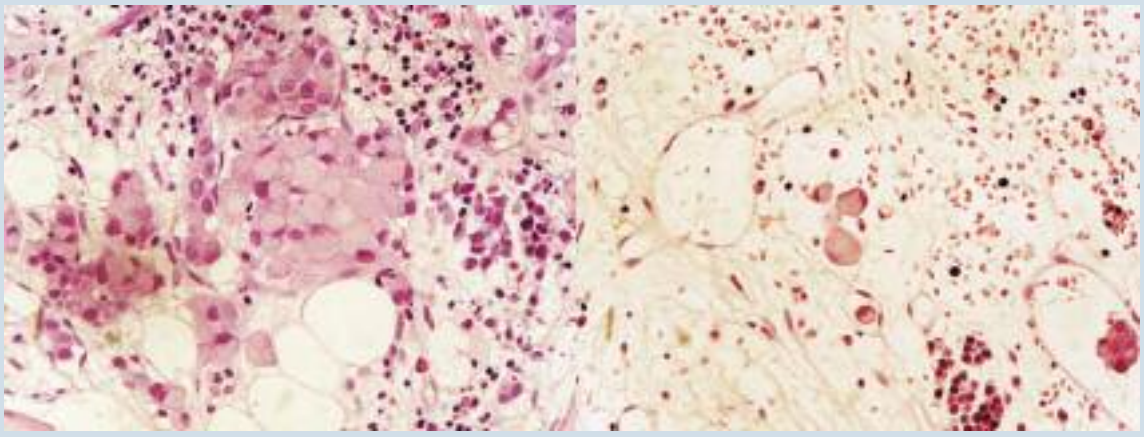


Table 1.
Immunohistochemical analysis of the malignant bone marrow infiltrates.

Markers	CK7	CK20	CK5/6	BerEP4	mCEA	pCEA	TTF-1	PSA	CDX-2	HepPar-1
Expression	+	+	-	+	+	+	-	-	-	-

CK: cytokeratin, BerEP4: human epithelial antigen, m/pCEA: mono/polyclonal carcinoembryonic antigen, TTF-1: thyroid transcription factor-1, PSA: prostate specific antigen, CDX-2: caudal-related homeobox protein-2, HepPar-1: hepatocyte paraffin-1.

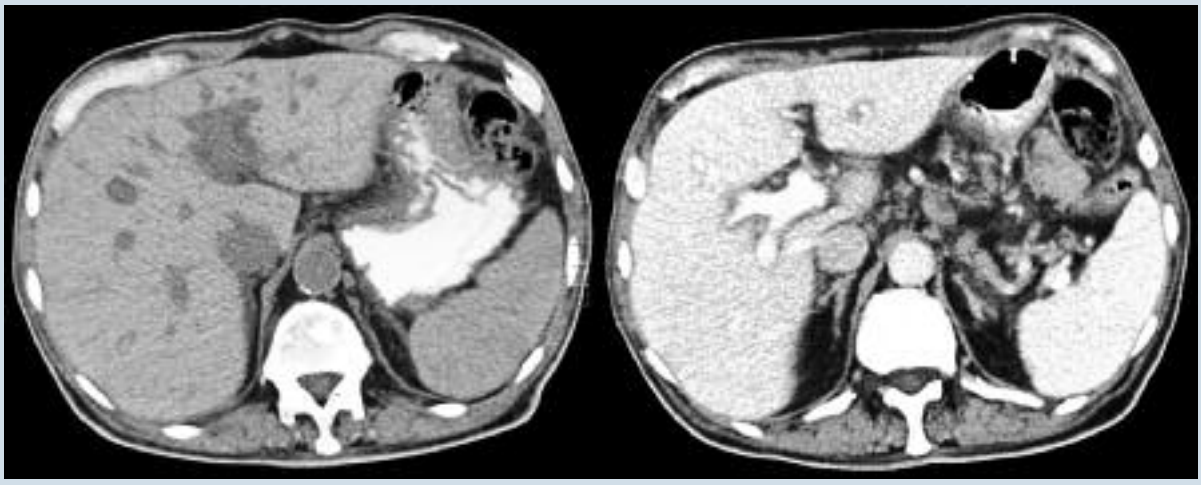
DIC. Peripheral leukoerythroblastosis was further investigated with a transiliac bone marrow biopsy that revealed BMI by signet-ring cell carcinoma (SRCC) (Figures 1A & B). Table 1 summarises the immunohistochemical results for cytokeratins 7 and 20, thyroid transcription factor-1 (TTF-1), prostate-specific antigen (PSA), caudal-related homeobox protein-2 (CDX-2) and hepatocyte parrafin-1 (HepPar-1). The expression patterns were most consistent with a gastric primary tumour.

After failure of high-dose corticosteroids and plasmapheresis, the patient was referred to our Department for further management. His baseline performance status (PS) was ECOG 3, partially due to a lower-limb haematoma that had complicated the trephine biopsy procedure. Although upper gastrointestinal endoscopy and biopsy showed only atrophic gastritis of the corpus and antrum, contrast-enhanced computed tomography (CT) disclosed marked, abnormal wall thickening of the gastric body; lymphadenopathy of the lesser curvature, mesenteric and aortocaval regions; as well as periportal hepatic oedema (Figures 2A & B). Along with the CT images, bone scintigraphy was compatible with mixed-type metastases, mainly affecting the axial skeleton (Figure 3). Combined with the aforementioned clinicopathological features, radiological findings were interpreted as supporting the diagnosis of disseminated GC. We did not pursue an endoscopic confirmation of the primary tumour site, given the diagnostic limitations of the examination, the patient's impaired PS, and the fact that this would not affect our treatment plan.

Initial management focused on pain control, as well as treating anaemia and bleeding diathesis with packed red-cell and platelet transfusions. The patient was started on palliative chemotherapy with weekly, 24-hour infusional, high-dose 5-fluorouracil (2,600mg/m^2) and leucovorin (300mg/m^2) (HDFL, modified Ardalan protocol) [1], combined with monthly zoledronic acid (ZA). Within the first four weeks, his condition improved dramatically, with complete resolution of MAHA and DIC manifestations. He soon returned to daily activities and was tapered off opioids. After three months of continuous treatment, CT-scans remained

Figures 2A & B.

Contrast-enhanced CT scan images of the abdomen and pelvis revealing abnormal wall thickening of the gastric corpus (A); lymphadenopathy at the level of the gastric lesser curve, the mesenteric and aortocaval regions; and periportal liver oedema (B).



essentially unchanged, while a repeat trephine biopsy showed partial marrow response.

Despite good tolerance of induction HDFL, the patient was reluctant on switching to a more aggressive regimen. Therefore, he was offered maintenance capecitabine at a continuous, fixed dose of 1000mg bd po, without remarkable side-effects, while retaining ZA. Following three additional months of disease control, MAHA and DIC relapsed, signalling progressive disease. The patient was rechallenged with HDFL for a total of two months, achieving a second complete remission of the paraneoplastic syndromes, but became refractory to subsequent intensification therapy with the combination of epirubicin, oxaliplatin and capecitabine. He died approximately 11 months after initial diagnosis.

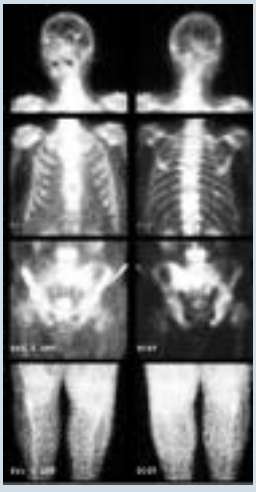
DISCUSSION

SRCC is a poorly differentiated adenocarcinoma, with more than half the tumour represented by signet-ring-like morphology, i.e. cells with the nuclei eccentrically displaced by abundant intracytoplasmic mucin. It arises from the stomach, breast and colon in more than 90% of cases, but can also present as metastases of unknown primary. Although in an immunophenotypic study of SRCCs of various sites, HepPar-1 positivity and weak, heterogeneous CDX-2 staining favoured a gastric origin [2], the frequency of CDX-2 immunoreactivity was only 21% in an analysis of various-stage gastric SRCCs [3]. Furthermore, in another GC case-series, the combined CDX-2 and HepPar-1 expression was significantly lower in diffuse-type carcinomas [4]. In the case reported herein, bone marrow infiltrates by SRCC were negative for the two markers.

SRCC comprises up to 39% of all GCs, and reportedly affects more frequently female and younger patients. It meets most of Lauren's criteria for diffuse-type carcinoma, and commonly involves the proximal stomach [5, 6]. Due to its

Figure 3.

Whole-body ^{99m}Tc-MDP-bone scan showing multifocal increased uptake, mainly in the axial skeleton, compatible with osseous metastases.



tendency for transmural spread; the associated scirrhous reaction; and its non-specific macroscopic appearance overlapping with that of benign infiltrative disorders, standard endoscopic detection can be challenging, with a false-negative biopsy rate as high as 30% [7, 8]. Compared with the intestinal-type, diffuse-type GC can similarly be induced by H. pylori infection despite eradication therapy, but characteristically lacks precursor lesions [9]. In the case presented, endoscopic biopsy failed to detect malignancy within chronic gastritis, and final diagnosis was based on the immunohistopathological features of BMI, together with the radiological evidence of gastric-wall and regional lymph-node involvement, including the periportal halo sign [10]. Whereas history of H. pylori exposure did favour the diagnosis, the patient's gender and age were atypical for a gastric SRCC. A more unusual aspect of this case was the disease's initial manifestation with MAHA, DIC and BMI.

Paraneoplastic MAHA is detected in up to 6% of metastatic cancer patients, rarely preceding tumour diagnosis. Mucinous adenocarcinoma of the stomach is the commonest underlying malignancy, accounting for around 50% of cases. Cancer cells are proposed to produce platelet-activating and pro-coagulant factors that initiate systemic intravascular microthrombi formation, which in turn results in mechanical haemolysis. In at least half the cases, DIC probably coexists with the primary pathogenetic mechanism. An adenocarcinoma-secreted, mucin-derived protease is one of the paraneoplastic factors that directly activate the coagulation cascade [11, 12].

Despite a subclinical hypercoagulopathy among most cancer patients, the frequency of clinically overt paraneoplastic DIC does not exceed 20%, and only up to 12% of such cases are associated with GC. Unlike the chronic form, acute DIC mostly complicates haematological malignancies and mucin-producing adenocarcinomas, with a predominant bleeding tendency, as in the case reported [13]. The courses of malignant MAHA and DIC are not necessarily parallel, as haemolysis can persist despite improvement in the latter's profile. Another proposed mechanism for paraneoplastic MAHA is tumour-emboli interaction with the pulmonary microvessel endothelium, which induces platelet deposition and intimal hyperplasia. In contrast to non-malignant thrombotic microangiopathy (TMA), severe deficiency of ADAMTS-13 (von Willebrand factor-cleaving protease) is usually absent, while, in distinction to chemotherapy-associated TMA, renal failure is not a typical feature [14, 15]. The lack of response to plasmapheresis and corticosteroids in the case presented underlines the distinct, complex pathogenesis of cancer-triggered MAHA.

Bone marrow is seldom the first site of distant spread of solid tumours. Breast, prostate and lung carcinomas are the most likely to manifest with BMI in adults, although a wider tumour spectrum may prove to have occult marrow metastases [16]. In a GC autopsy series, the prevalence of BMI was overall 20% and highest in patients with SRCC. Marrow stromal reaction was most often of the osteoblastic type, also correlating with signet-ring histology [17]. Peripheral leukoerythroblastosis and symptomatic osseous secondaries are useful diagnostic correlates [18]. Although regarded as two separate systems, bone and marrow function as a single unit. Illustrating the "seed and soil" hypothesis, marrow microenvironment serves as a sanctuary for cancer cells that metastasise to the bones, and any skeletal spread actually reflects marrow involvement [19].

GC osseous metastases with diffuse BMI have long been recognised to run an aggressive course, with paraneoplastic haematological phenomena cited as a probable cause of poor outcome [20-25]. The association between carcinomatous BMI and MAHA was supported by a retrospective analysis of TMA cases, speculating that tumour growth and angiogenesis within bone marrow, along with secondary myelofibrosis, may injure the marrow vasculature to induce platelet aggregation [26]. Therefore, bone marrow biopsy can prove a valuable diagnostic tool for patients with refractory MAHA, thrombocytopenia and leukoerythroblastic reaction, where disseminated malignancy is a key consideration, as in this case report [27].

Signet-ring histology is relatively common in potentially curable early GCs, and is probably not an independent adverse prognostic factor per se. Instead, intestinal phenotypic expression may indicate an aggressive biological behaviour [28, 29]. On the other hand, gastric carcinomatosis with MAHA and/or DIC seems to represent a rare, biologically distinct entity within the disease spectrum. Prominent clinicopathological features include relatively young patient age; poorly differentiated adenocarcinoma, such as SRCC; preferential bone and marrow metastases; and grave prognosis, with most patients on supportive care alone succumbing within four weeks from diagnosis. As optimal management of this subset of patients remains uncertain, effective control of the underlying malignancy appears a reasonable strategy [20-22, 30-33]. Despite the moderate chemosensitivity of GC, myelotoxicity of standard regimens prohibits their use in the particular setting. Instead, the safety and efficacy of fluoropyrimidine-based chemotherapy is supported by the limited retrospective data available, mostly derived from Eastern Asian report studies (Table 2) [22, 33-39].

The choice of treating our patient with HDFL was based on one of the largest relevant case-series to date, demonstrating a 74% remission rate of acute DIC among 19 advanced-GC patients from Taiwan [33]. Around half the initial responders continued with intensified chemotherapy and achieved an eight-month median survival, similar to those without paraneoplastic DIC and comparable with historical data for the general population with advanced GC. HDFL-related myelosuppression was minimal, consistent with the bone marrow pharmacokinetics of prolonged 5-fluorouracil infusion, as previously described [40]. The most

striking, albeit reversible, non-haematological toxicity was acute hyperammonaemic encephalopathy. The improved clinical activity of HDFL compared with conventional bolus 5-fluorouracil regimens was reinforced by in vitro pharmacodynamics studies showing enhanced cytotoxicity with 24-hour exposure of GC cells to low 5-fluorouracil concentrations, compared with short-duration exposure to high drug-concentrations [41]. To our knowledge, this is the first case-report to demonstrate effectiveness and tolerability of HDFL as first line treatment in a Caucasian patient with this grave condition, similar to the results of the original study.

Given the only short-lasting response of the particular patient group to induction chemotherapy, consolidation of disease control with more aggressive regimens might be considered once paraneoplastic cytopenias resolve [33, 37]. Within this context, HDFL was successfully combined with cytotoxics such as cisplatin and paclitaxel, but it remains to investigate the role of other, more gastrointestinal-specific agents. Alternatively, in view of the overall poor outcome and palliative treatment intent in this setting, a more conservative approach might be adopted, especially for frail patients opting for low-toxic regimens. As oral capecitabine is considered to simulate protracted-infusion schedules of 5-fluorouracil, the concept of continuous, fixed, low-dose capecitabine as maintenance chemotherapy for advanced gastrointestinal cancers was preliminarily explored with promising results [42]. This case report is the first, to our knowledge, to show benefit from maintenance metronomic capecitabine in the particular clinical setting, translating into a three-month-long disease control, without remarkable toxicity. Also of note is the complete remission of the paraneoplastic haematological syndromes to rechallenge with HDFL upon disease progression, despite the relatively short interval from the last infusion and the fluoropyrimidine-based maintenance therapy.

Lastly, although little is known about the optimal utility of bisphosphonates in treating GC skeletal metastases, the inclusion of ZA in the management of the case presented was based on the drug's potential antineoplastic activity and synergism with chemotherapy, as suggested by preclinical evidence and, at least for early breast cancer, as supported by clinical trials [43-46]. Pathogenesis of bone destruction in the context of BMI by GC was investigated in a case-series, where most patients had SRCC/poorly differentiated-adenocarcinoma presenting with DIC. The study showed a significant tumour expression of the osteoclast-differentiation regulator RANKL, and implied a role for bone-targeted therapy in this difficult clinical setting [22].

Table 2.

Case-series reports of gastric carcinomatosis with paraneoplastic haematological syndromes (DIC/MAHA) treated with fluoropyrimidine-based regimens.

Study and year	Chemotherapy regimen	Number of patients with DIC	Efficacy results
Kobayashi T *et al.*, 1992	Weekly MTX 30-100mg/m^2 IV bolus Day 1, followed in 3h by 5-FU 600mg/m^2 IV bolus	10	Response rate of DIC: 80% Median duration of DIC response: 17 weeks
Chao Y *et al.*, 2000	Weekly EEPFL: Etoposide 40mg/m^2, epirubicin 10mg/m^2, CDDP25 mg/m^2, infusional 5-FU 2200mg/m^2 & LV 120mg/m^2	6	Rate of DIC control: 100% Median duration of DIC control: 24 weeks
Hironaka SI *et al.*, 2000	Weekly MTX 100mg/m^2 IV bolus, followed in 3h by 5-FU 600mg/m^2 IV bolus & LV rescue 10mg/m^2 po/IV qid Day 2 & 3 (6 doses)	9	Recovery rate from DIC: ~89% Median duration of DIC control: 32 weeks
Tokar M *et al.*, 2006	Infusional 5-FU 200mg/m^2/day→(if response) ECF	6	Rate of DIC control: ~83% Median duration of response: 23 weeks
Huang TC *et al.*, 2008	Weekly infusional HDFL (5-FU 2600mg/m^2 & LV 300mg/m^2, the two drugs mixed n 500ml of NS)→(if response) weekly infusional HDFL + CDDP or paclitaxel or etoposide	19	Recovery rate from DIC: ~74% Median PFS for the responders: 24 weeks
Takashima A *et al.*, 2010	Weekly MTX 100mg/m^2 IV bolus, followed in 3h by 5-FU 600mg/m^2 IV bolus & LV rescue 10mg/m^2 po/IV qid Day 2 & 3 (6 doses)	22	Response rate of DIC: 77% Median time to treatment failure: ~25 weeks

MTX: methotrexate, 5-FU: 5-fluorouracil, LV: leucovorin, CDDP: cisplatin, ECF: epirubicin, CDDP and infusional 5FU, HDFL: infusional high-dose 5-FU/LV, S-1: tegafur + 5-chloro-2,4-dihydroxypyridine + potassium oxonate, IV: intravenous, PFS: progression-free survival, h: hours.

REFERENCES

1. Yeh KH and Cheng AL. Gastric cancer associated with acute disseminated intravascular coagulation: successful initial treatment with weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin. Br J Haematol 1998; 100(4):769-772.
2. Chu PG, Weiss LM. Immunohistochemical characterization of signet-ring cell carcinomas of the stomach, breast, and colon. Am J Clin Path 2004; 121(6):884-892.
3. Tian MM, Zhao AL, Li ZW, Li JY. Phenotypic classification of gastric signet ring cell carcinoma and its relationship with clinicopathologic parameters and prognosis. World J Gastroenterol 2007; 13(23):3189-98.
4. Fan Z, Li J, Dong B, Huang X. Expression of Cdx2 and hepatocyte antigen in gastric carcinoma: correlation with histologic type and implications for prognosis. Clin Cancer Res 2005; 11(17):6162-70.
5. Theuer CP, Nastanski F, Brewster WR, Butler JA, Anton-Culver H. Signet ring cell histology is associated with unique clinical features but does not affect gastric cancer survival. Am Surg 1999; 65(10):915-21.
6. Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. Arch Pathol Lab Med 2004; 128(7):765-70.
7. Levine MS, Kong V, Rubesin SE, Laufer I, Herlinger H. Scirrhous carcinoma of the stomach: radiologic and endoscopic diagnosis. Radiology 1990; 175(1):151-4.
8. Sung IK, Kim YC, Yun JW, Seo HI, Park DI, Cho YK, et al. Characteristics of advanced gastric cancer undetected on gastroscopy. Korean J Gastroenterol 2011; 57(5):288-93.
9. Parsonnet J, Vandersteen D, Goates J, Sibley RK, Pritikin J, Chang Y. Helicobacter pylori infection in intestinal- and diffuse-type gastric adenocarcinomas. J Natl Cancer Inst 1991; 83(9):640-3.
10. Lawson TL, Thorsen MK, Erickson SJ, Perret RS, Quiroz FA, Foley WD. Periportal halo: a CT sign of liver disease. Abdom Imaging 1993; 18(1):42-6.
11. Lohrmann H, Adam W, Hyemer B, et al. Microangiopathic hemolytic anemia and cancer. Report of eight cases. Ann Intern Med 1973; 79(3):368-75.
12. Antman KH, Skarin AT, Mayer RJ, Hargreaves HK, Canellos GP. Microangiopathic hemolytic anemia and cancer: A review. Medicine 1979; 58(5):377-384.
13. Saba HI, Morelli GA, Saba RI. Disseminated intravascular coagulation in cancer. Cancer Treat Res 2009; 148:137-156.
14. Doll DC, Weiss RB. Neoplasia and the erythron. J Clin Oncol 1985; 3(3):429-46.
15. Murgo AJ. Cancer- and chemotherapy-associated thrombotic microangiopathy. In: Kaplan BS, Trompeter RS, Moake JL, editors. Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. New York: Marcel Dekker; 1992. p. 271-85.
16. Ozkalemkas F, Ali R, Ozkocaman V, Ozcelik T, Ozan U, Ozturk H, et al. The bone marrow aspirate and biopsy in the diagnosis of unsuspected nonhematologic malignancy: a clinical study of 19 cases. BMC Cancer 2005; 5:144.
17. Shosuke M, Koichi M, Keitaro Y, Akira K, Kenji J. Bone marrow metastases found at autopsy in cases of gastric cancer. Gan No Rinsho 2000; 46(4):339-348. (Article in Japanese with abstract in English).
18. Papac RJ. Bone marrow metastases. A review. Cancer 1994; 74(9):2403-13.
19. Bianco P, Riminucci M, Robey PG. Metastasis in the bone marrow microenvironment. In: Singh G, Orr W, editors. Bone metastasis and molecular mechanisms: pathophysiology. Dordrecht: Kluwer Academic Publishers, 2004. p. 71-86.
20. Etoh T, Baba H, Taketomi A, Nakashima H, Kohnoe S, Seo Y, et al. Diffuse bone metastasis with hematologic disorders from gastric cancer: clinicopathological features and prognosis. Oncol Rep 1999; 6(3): 601-5.
21. Nakanishi H, Araki N, Kuratsu S, Narahara H, Ishikawa O, Yoshikawa H. Skeletal metastasis in patients with gastric cancer. Clin Orthop Relat Res 2004; (423):208-12.
22. Kusumoto H, Haraguchi M, Nozuka Y, Oda Y, Tsuneyoshi M, Iguchi H. Characteristic features of disseminated carcinomatosis of the bone marrow due to gastric cancer: the pathogenesis of bone destruction. Oncol Rep 2006; 16(4):735-40.
23. Lee J, Lim T, Uhm JE, Park KW, Park SH, Lee SC, et al. Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. Ann Oncol 2007; 18(5):886-91.
24. Kim HS, Yi SY, Jun HJ, Lee J, Park JO, Park YS, et al. Clinical outcome of gastric cancer patients with bone marrow metastases. Oncology 2007; 73(3-4):192-7.
25. Kwon JY, Yun J, Kim HJ, Kim KH, Kim SH, Lee SC, et al. Clinical outcome of gastric cancer patients with bone marrow metastases. Cancer Res Treat 2011; 43(4): 244-249.
26. Chang JC, Naqvi T. Thrombotic thrombocytopenic purpura associated with bone marrow metastasis and secondary myelofibrosis in cancer. Oncologist 2003; 8(4):375-80.
27. Francis KK, Kalyanam N, Terrell DR, Vesely SK, George JN. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: A report of 10 patients and a systematic review of published cases. Oncologist 2007; 12(1):11-9.
28. Ohkura Y. Histological diversity of early gastric carcinoma. In: Kaminishi M, Takubo K, Mafune K, editors. The diversity of gastric carcinoma: pathogenesis, diagnosis, and therapy. Tokyo: Springer-Verlag; 2005. p. 117-126.
29. Tian MM, Zhao AL, Li ZW, Li JY. Phenotypic classification of gastric signet ring cell carcinoma and its relationship with clinicopathologic parameters and prognosis. World J Gastroenterol 2007; 13(23):3189-98.
30. Morimatsu M, Shirouzu K, Irie K, Tokunaga O, Sasaguri Y. Gross and microscopic characteristics of stomach cancer with microangiopathic hemolytic anemia and/or disseminated intravascular coagulopathy. Acta Pathol Jpn 1985; 35(4):809-22.
31. Ali N, Kamran N, Adil S, Pervez S. Metastatic signet ring gastric adenocarcinoma presenting with microangiopathic hemolytic anemia. Indian J Gastroenterol 2007; 26(4):185-6.
32. Rhee J, Han SW, Oh DY, Im SA, Kim TY, Bang YJ. Clinicopathologic features and clinical outcomes of gastric cancer that initially presents with disseminated intravascular coagulation: A retrospective study. J Gastroenterol Hepatol 2010; 25(9):1537-42.
33. Huang TC, Yeh KH, Cheng AL, Hsu CH. Weekly 24-hour infusional 5-fluorouracil as initial treatment for advanced gastric cancer with acute disseminated intravascular coagulation. Anticancer Res 2008; 28(2B):1293-7.
34. Kobayashi T, Sasaki T, Ibuka T, Imai K, Monma K, Sakai N, et al. Sequential MTX and 5-FU therapy for gastric cancer patients with systemic bone metastasis and DIC. Jpn J Cancer Chemother 1992; 19(1):69-74. (Article in Japanese with abstract in English).
35. Chao Y, Teng HC, Hung HC, King KL, Li CP, Chi KH, et al. Successful initial treatment with weekly etoposide, epirubicin, cisplatin, 5-fluorouracil and leucovorin chemotherapy in advanced gastric cancer patients with disseminated intravascular coagulation. Jpn J Clin Oncol 2000; 30(3):122-5.
36. Hironaka SI, Boku N, Ohtsu A, Nagashima F, Sano Y, Muto M, et al. Sequential methotrexate and 5-fluorouracil therapy for gastric cancer patients with bone metastasis. Gastric Cancer 2000; 3(1):19-23.
37. Tokar M, Bobilev D, Ariad S, Geffen DB. Disseminated intravascular coagulation at presentation of advanced gastric cancer. Isr Med Assoc J 2006; 8(12):853-5.
38. Nishioka K, Kobayashi K, Aoki T, Hatano H, Komori T, Matsumoto T, et al. Two patients of progressive gastric cancer accompanied by disseminated carcinomatosis of bone marrow due to bone metastasis with DIC successfully controlled by combination of S-1 and CDDP. Gan To Kagaku Ryoho 2007; 34(12):2135-7. (Article in Japanese with abstract in English).
39. Takashima A, Shirao K, Hirashima Y, Takahari D, Okita NT, Nakajima TE, et al. Sequential chemotherapy with methotrexate and 5-fluorouracil for chemotherapy-naive advanced gastric cancer with disseminated intravascular coagulation at initial diagnosis. J Cancer Res Clin Oncol 2010; 136(2):243-8.
40. Fraile RJ, Baker LH, Buroker TR, Horwitz J, Vaitkevicius VK. Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and by slow infusion. Cancer Res 1980; 40(7):2223-8.
41. Yeh KH, Yeh SH, Hsu CH, Wang TM, Ma IF, Cheng AL. Prolonged and enhan-

ced suppression of thymidylate synthase by weekly 24-h infusion of high-dose 5-fluorouracil. Br J Cancer 2000; 83(11):1510-5.

42. Raftery L, O'Neil BH. Maintenance capecitabine for high-risk gastrointestinal tumors: everything that's old is new again. Gastrointest Cancer Res 2009; 3(4):163-4.

43. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008; 19(3):420-32.

44. Yamada J, Tsuno HN, Kitayama J, Yoneyama S, Tsuchiya T, Asakage M, et al. Zoledronic acid inhibits gastric cancer cells by induction of apoptosis (abstract). In: Proceedings of the 97th Annual Meeting of the American Association for Cancer Research; 2006 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; 2006. p. 895. Abstract nr 3806.

45. Trojan J, Kim SZ, Engels K, Kriener S, Mitrou PS, Chow KU. In vitro chemosensitivity to gemcitabine, oxaliplatin and zoledronic acid predicts treatment response in metastatic gastric cancer. Anticancer Drugs 2005; 16(1):87-91.

46. Mahtani R, Jahanzeb M. Bisphosphonates as anticancer therapy for early breast cancer. Clin Breast Cancer 2010; 10(5):359-66.

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 εξάνθημα 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 τη 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) παρουσιάστηκε 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 με τη 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 διαχείριση αισθητικής νευθροπάθειας και πρέπει να ξεκινήσουν αμέσως ενδοφλέβια θεραπεία με κορτικοστεροειδή (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Προοδευτικά σημάδια κινητικής νευροπάθειας θα πρέπει να θεωρείται ότι σχετίζονται με το ανοσοποιητικό και να αντιμετωπίζονται ανάλογα. Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) κινητική νευροπάθεια ανεξαρτήτως αιτιολογίας (βλέπε παράγραφο 4.2). Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό: Το YERVOY μπορεί να προκαλέσει φλεγμονή των οργάνων του ενδοκρινικού συστήματος, συγκεκριμένα υποφυσίτιδα, υποϋποφυσισμό, επινεφριδιακή ανεπάρκεια και υποθυρεοειδισμό και οι ασθενείς μπορεί να παρουσιάσουν μη ειδικά συμπτώματα, τα οποία μπορεί να μοιάζουν με άλλα αίτια, όπως μετάσταση στον εγκέφαλο ή υποκείμενη νόσο. Στη συχνότερη κλινική εικόνα συμπεριλαμβάνεται η κεφαλαλγία και η κόπωση. Στα συμπτώματα μπορεί να συμπεριλαμβάνονται ελλείμματα του οπτικού πεδίου, αλλαγές της συμπεριφοράς, διαταραχές των ηλεκτρολυτών και υπόταση. Επινεφριδιακή κρίση ως αίτιο των συμπτωμάτων του ασθενούς πρέπει να αποκλείεται. Η κλινική εμπειρία με ενδοκρινοπάθεια σχετιζόμενη με το YERVOY είναι περιορισμένη. Για ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 24) ενδοκρινοπάθειας σχετιζόμενης με το ανοσοποιητικό κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την έναρξη της θεραπείας. Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με ανοσοκατασταλτική θεραπεία και θεραπεία υποκατάστασης ορμονών. Εάν υπάρχουν οποιαδήποτε σημεία επινεφριδιακής κρίσης, όπως σοβαρή αφυδάτωση, υπόταση ή καταπληξία, συνιστάται άμεση χορήγηση ενδοφλέβιων κορτικοστεροειδών με αλατοκορτικοειδική δράση και ο ασθενής θα πρέπει να αξιολογηθεί για την παρουσία σηψαιμίας ή λοιμώξεων. Εάν υπάρχουν σημεία επινεφριδιακής ανεπάρκειας, αλλά ο ασθενής δεν βρίσκεται σε επινεφριδιακή κρίση, πρέπει να εξεταστούν περαιτέρω παρακλινικές εξετάσεις στις οποίες συμπεριλαμβάνεται η αξιολόγηση εργαστηριακών και απεικονιστικών ελέγχων. Η αξιολόγηση των αποτελεσμάτων των εργαστηριακών ελέγχων για την έλεγχο της ενδοκρινούς λειτουργίας πρέπει να πραγματοποιείται πριν από την έναρξη θεραπείας με κορτικοστεροειδή. Εάν οι απεικονιστικοί έλεγχοι της υπόφυσης ή εργαστηριακοί έλεγχοι της ενδοκρινούς λειτουργίας είναι μη φυσιολογικοί, συνιστάται βραχύ σχήμα θεραπείας με υψηλές δόσεις κορτικοστεροειδών (π.χ. δεξαμεθαζόνη 4 mg ανά 6 ώρες ή ισοδύναμο) ώστε να αντιμετωπιστεί η φλεγμονή του προσβεβλημένου αδένα και η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί (βλέπε παράγραφο 4.2). Αυτή τη στιγμή είναι άγνωστο εάν η θεραπεία με κορτικοστεροειδή αναστρέφει την αδενική δυσλειτουργία. Θα πρέπει επίσης να ξεκινήσει κατάλληλη υποκατάσταση ορμονών. Είναι πιθανό να είναι απαραίτητη μακροχρόνια θεραπεία με υποκατάσταση ορμονών. Όταν τεθούν υπό έλεγχο τα συμπτώματα ή οι μη φυσιολογικές εργαστηριακές τιμές και είναι εμφανής η βελτίωση του ασθενούς συνολικά, μπορεί να συνεχιστεί η θεραπεία με YERVOY και η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν πεπτιδικό εμβόλιο με YERVOY 3 mg/kg + gp100 στην MDX01020 (βλέπε παράγραφο 4.8). Αν οι αντιδράσεις είναι σοβαρές (Βαθμού 3 ή 4) είναι πιθανό να απαιτηθεί άμεσα θεραπεία με υψηλές δόσεις κορτικοστεροειδών και διακοπή του YERVOY (βλέπε παράγραφο 4.2). Για ραγοειδίτιδα, ιρίτιδα ή επισκληρίτιδα που συνδέεται με το YERVOY, θα πρέπει να εξετάζεται η χρήση τοπικών κορτικοστεροειδών στη μορφή των οφθαλμικών σταγόνων όπως ενδείκνυται ιατρικά. Ειδικοί πληθυσμοί: Ασθενείς με οφθαλμικό μελάνωμα, πρωτοπαθές μελάνωμα του ΚΝΣ και ενεργές μεταστάσεις του εγκεφάλου δεν συμπεριελήφθησαν στην πιλοτική κλινική δοκιμή (βλέπε παράγραφο 5.1). Αντίδραση στην έγχυση: Υπήρχαν μεμονωμένες αναφορές σοβαρών αντιδράσεων στην έγχυση σε κλινικές δοκιμές. Σε περίπτωση σοβαρής αντίδρασης στην έγχυση, η έγχυση YERVOY πρέπει να διακόπτεται και να χορηγείται κατάλληλη ιατρική θεραπεία. Ασθενείς με ήπια ή μέτρια αντίδραση στην έγχυση, μπορούν να λάβουν YERVOY με προσεκτική παρακολούθηση. Μπορεί να ληφθεί υπόψη η προφαρμακευτική αγωγή με αντιπυρετικό και αντισταμινικό. Ασθενείς με αυτοάνοση νόσο: Ασθενείς με ιστορικό αυτοάνοσης νόσου (εκτός από λεύκη και επαρκώς ελεγχόμενη ανεπάρκεια ενδοκρίνης, όπως υποθυρεοειδισμός), συμπεριλαμβανομένων αυτών για τους οποίους απαιτείται συστηματική ανοσοκατασταλτική θεραπεία για προϋπάρχουσα ενεργό αυτοάνοση νόσο ή για διατήρηση μοσχεύματος μετά από μεταμόσχευση οργάνου, δεν αξιολογήθηκαν σε κλινικές δοκιμές. Το ipilimumab είναι ενισχυτής των Τκυττάρων που καθιστά δυνατή την ανοσολογική ανταπόκριση (βλέπε παράγραφο 5.1) και είναι πιθανό να παρέμβει στην ανοσοκατασταλτική θεραπεία, γεγονός που οδηγεί σε παροξυσμό της υποκείμενης νόσου ή αυξημένο κίνδυνο απόρριψης του μοσχεύματος. Το YERVOY πρέπει να αποφεύγεται σε ασθενείς με σοβαρή ενεργό αυτοάνοση νόσο, σε περιπτώσεις στις οποίες περαιτέρω ενεργοποίηση του ανοσοποιητικού είναι ενδεχομένως άμεσα απειλητική για τη ζωή και χρησιμοποιείται με προσοχή σε άλλους ασθενείς με ιστορικό αυτοάνοσης νόσου, μετά από προσεκτική εξέταση του ενδεχόμενου κινδύνου-οφέλους σε ατομική βάση. Ασθενείς που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. Κάθε ml αυτού του φαρμακευτικού προϊόντος περιέχει 0,1 mmol (ή 2,30 mg) νατρίου. Θα πρέπει να λαμβάνεται υπόψη κατά την θεραπεία ασθενών που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. **4.8 Ανεπιθύμητες ενέργειες: Περίληψη του προφίλ ασφάλειας:** Το YERVOY έχει χορηγηθεί σε > 3.000 ασθενείς σε ένα κλινικό πρόγραμμα το οποίο αξιολόγησε τη χρήση του με διάφορες δόσεις και τύπους όγκων. Εκτός εάν ορίζεται διαφορετικά, τα δεδομένα παρακάτω αποτυπώνουν την έκθεση σε YERVOY στα 3 mg/kg σε κλινικές δοκιμές μελανώματος. Στη μελέτη Φάσης 3 MDX01020, (βλέπε παράγραφο 5.1), οι ασθενείς έλαβαν ένα διάμεσο 4 δόσεων (εύρος 14). Το YERVOY σχετίζεται πολύ συχνά με ανεπιθύμητες ενέργειες που προκύπτουν από αυξημένη ή εντεταμένη δράση του ανοσοποιητικού. Οι περισσότερες από αυτές, στις οποίες συμπεριλαμβάνονται σοβαρές αντιδράσεις, υποχώρησαν μετά από την έναρξη κατάλληλης ιατρικής θεραπείας ή τη διακοπή του YERVOY (βλέπε παράγραφο 4.4 για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, οι ανεπιθύμητες ενέργειες που αναφέρθηκαν συχνότερα (≥ 10% των ασθενών), ήταν διάρροια, εξάνθημα, κνησμός, κόπωση, ναυτία, έμετος, μειωμένη όρεξη και κοιλιακό άλγος. Στην πλειονότητά τους ήταν ήπιες έως μέτριες (Βαθμού 1 ή 2). Η θεραπεία με YERVOY διακόπηκε λόγω ανεπιθύμητων ενεργειών στο 10% των ασθενών. Κατάλογος ανεπιθύμητων ενεργειών σε πίνακα: Ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ασθενείς με προχωρημένο μελάνωμα, οι οποίοι έλαβαν YERVOY 3 mg/kg σε κλινικές δοκιμές (n = 767), παρουσιάζονται στον Πίνακα 2. Αυτές οι αντιδράσεις παρουσιάζονται ανά κατηγορία συστήματος οργάνων σύμφωνα με την συχνότητα. Η συχνότητα ορίζεται ως εξής: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000). Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες εμφανίζονται κατά φθίνουσα σειρά σοβαρότητας. Τα ποσοστά ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό σε HLAA2*0201 θετικούς ασθενείς οι οποίοι έλαβαν YERVOY στην MDX01020, ήταν παρόμοια με εκείνα που παρατηρήθηκαν στο κλινικό πρόγραμμα συνολικά.

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

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

β Συμπεριλαμβάνεται η θανατηφόρος έκβαση.

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

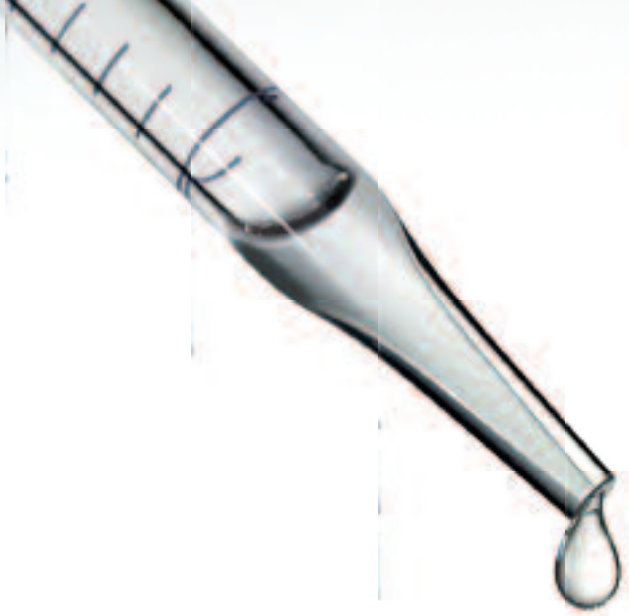
δ Αναφέρονται σε πρόσφατες μελέτες εκτός των ολοκληρωμένων κλινικών δοκιμών στο μελάνωμα.

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

Βοηθήστε να γίνουν όλα τα φάρμακα πιο ασφαλή: Συμπληρώστε την **"ΚΙΤΡΙΝΗ ΚΑΡΤΑ"**
Αναφέρατε: **ΟΛΕΣ** τις ανεπιθύμητες ενέργειες για τα **ΝΕΑ ΦΑΡΜΑΚΑ** Ⓝ
Τις **ΣΟΒΑΡΕΣ** ανεπιθύμητες ενέργειες για τα **ΓΝΩΣΤΑ ΦΑΡΜΑΚΑ**

Bristol-Myers Squibb

Bristol-Myers Squibb A.E. Αττικής 49-53 & Προποντίδος 2, Τ.Κ. 152 35 Βριλήσσια, Αττική. ΤΘ 63883 - Βριλήσσια Τ.Κ. 152 03, Αττική.
Τηλ. 210 6074300 & 210 6074400, Φαξ 210 6074333. ΑΡ.Μ.Α.Ε. 62772/01ΑΤ/Β/07/148



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™

Bristol-Myers Squibb

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.