Horizon Scanning in Oncology

Ipilimumab for pre-treated patients with advanced/metastatic melanoma

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1 Drug description

Generic/Brand name/ATC code:

Ipilimumab, MDX-010, MDX-101/ Yervoy (proposed trade name)/not yet available

Developer/Company:

Bristol-Myers-Squibb and Medarex

Description:

Ipilimumab is a fully human monoclonal antibody directed against the cytotoxic T-lymphocyte antigen 4 (CTLA-4), an antigen which is expressed on T-cells only after activation [1]. CTLA-4 down-regulates T-cell mediated immune responses. By blocking this antigen, T-cell suppression is reduced and thus an anti-tumour immune response enhanced [2, 3].

ipilimumab, a monoclonal antibody, induces anti-tumour immune response by reducing T-cell suppression

Due to its mode of action, a novel set of side-effects, the so called "immune-related adverse events" (irAEs) appear to be related to anti-CTLA4 antibodies [4]. These AEs are associated with breaking the tolerance to self-antigens and are dose-related, cumulative and schedule dependent [3]. A relationship between occurrence of these side-effects and anti-tumour activity is being discussed [3, 4].

associated with immune-related adverse events

Ipilimumab is administered intravenously. Evidence suggests that multiple doses should be preferred over single doses: frequently used regimens in phase I/II and phase II studies were induction therapy with either 3mg/kg or 10mg/kg every three weeks over 12 weeks, followed by maintenance therapy, mostly 10mg/kg every 12 weeks [3].

dose ranging from 3mg/kg – 10mg/kg

2 Indication

Ipilimumab is indicated for the treatment of pre-treated patients with advanced/ metastatic cutaneous melanoma.

for pre-treated patients with advanced melanoma

3 Current regulatory status

Ipilimumab is currently not approved, neither by the EMA nor by the FDA, but has received orphan drug status of both institutions [5].

In August 2008, Bristol-Myers Squibb Company announced that the FDA has granted priority review for ipilimumab for the treatment of adult patients with advanced melanoma who have been previously treated [6]. Regulatory filings were submitted to both the FDA and the EMA in 2010. At first, the FDA announced that the review of the application will be completed in

not approved yet

December 2010, but the review deadline has been extended until March 2011 [7, 8].

4 Burden of disease

risk factors for melanoma: positive family history, genetic factors, sun exposure…

Melanomas are malignant tumours of melanocytes. Suspicious lesions are nevi (i.e. moles or birthmarks) with, for example, variable discoloration, growth or development of satellites [9]. Risk factors for developing melanomas include prior melanomas, a positive family history and multiple clinically atypical moles/dysplastic nevi. In addition, genetic factors and sun exposure can contribute towards the development of melanomas [10]. To confirm the diagnosis of melanoma a biopsy, at best by local excision, should be performed [9]. Median age at diagnosis is 59 years [9].

based on TNM system for staging, 4 prognostic groups are differentiated

gender, age, LDH levels and localisation are important factors for prognosis

Staging of melanomas based on the tumour, node, metastasis (TNM) system includes describing the spread, aggressiveness and the size of the tumour. By taking into account characteristics like thickness, ulcerations and the mitotic rate of the primary tumour, by assessing the spread to regional lymph-nodes including satellite lesions (tumour cells separated from the primary tumour) and in-transit metastases and by evaluating distant metastases, patients are grouped into four prognostic categories (stage I –IV) [11]. Other factors which influence prognosis are gender, age and localisation of the tumour where younger patients, women and patients with tumours on the extremities have a better prognosis [9]. For patients suffering from stage IV disease, sites of metastases and elevated lactate-dehydrogenase (LDH) levels are also associated with poor outcomes [10]. If the tumour has spread beyond near-by lymph-nodes, it is called advanced or metastatic melanoma which corresponds to stage IV disease. Metastases most often occur in the skin or in lymph-nodes, or in organs such as the lungs, the liver, the brain and in the bones. Staging is also an important factor for the determination of the most appropriate treatment [11].

metastatic melanoma: median survival of 6 - 9 months

The majority of patients, about 85%, present with localised disease, corresponding to 5-year survival rates of up to 90%. In about 13% the regional lymph nodes are affected at diagnosis, leading to diminished survival rates of 20%-70%. About 2%-5% of patients present with distant metastases that is stage IV. Long-term survival of all patients with distant metastases is less than 10% [10]. Median survival is 6 to 9 months [12].

about 60 patients/year diagnosed with advanced melanoma in Austria

In Austria, the incidence of melanomas is about 15 newly diagnosed cases/100 000 persons per year and is constantly rising [13]. In 2007, overall 1,100 people were newly diagnosed with malignant melanoma in Austria. Of those, about 5% of the tumours were already disseminated, resulting in about 60 persons with advanced melanoma per year [14].

5 Current treatment

cure rarely possible

Treatment of un-resectable stage III melanoma and of stage IV melanomas focuses on symptom palliation, on preventing the tumour to spread, to reduce or getting rid of metastases and to maintain or achieve an acceptable quality-of-life [10]. Thus, cure is rarely possible [11].

treatment options:

Generally, metastatic melanoma is difficult to treat, because advanced melanomas are refractory to most standard systemic therapies [9]. Accordingly, little consensus on the standard of care exists due to the low levels of activity of all available options. Therapy may involve:

surgery,

- Surgical excision is the primary treatment for early stage melanomas, but is also indicated for metastatic melanoma. Resection should be performed for limited metastatic melanoma (i.e. if the disease has spread only to one site or only to a limited number of sites). If the tumour has spread to multiple sites such as the brain, the lungs, gastrointestinal tract or lymph-nodes, surgery may be used for symptom palliation.

chemotherapy,

- Single-agent chemotherapy:
  - dacarbazine (DTIC) is currently the most active chemotherapy and has often been used as standard comparator for new therapeutic regimens [10]. However, only 10%-20% of patients respond to this treatment, showing mainly partial remissions with a median response duration of 3-4 months [10].
  - fotemustine for the treatment of disseminated malignant melanoma, foremost if the tumour has spread to the brain [15].
  - temozolomide (off-label) shows similar benefits like DTIC. Due to its ability to penetrate into the brain and other parts of the nervous system, it is often used for the treatment of patients with brain metastases [11].

immunotherapy,

- Immunotherapy:
  - high-dose interleukin-2 (licensed in the US) has shown long-lasting effects including complete remissions, but only in the minority of patients. Because of its serious side-effects, it remains a treatment option for patients in good condition.
  - interferon-α is licensed for the adjuvant therapy of patients who are disease-free after surgery but who are at high risk of systemic recurrence [11].

and radiation therapy

- Radiation therapy either to metastases outside the brain for symptom palliation or as whole brain radiation therapy which can prolong survival, especially if the tumour outside the brain is controlled [11].

or clinical trials

- Due to the low effectiveness of the available treatment options, all newly diagnosed patients with advanced melanoma should be considered for participating in clinical trials [9].

6 Evidence

One phase III trial [16], 3 phase II trials [17-19] and one study reporting on a compassionate use programme were found [20].

1 phase III trial, 3 phase II trials and 1 report on compassionate use

The phase III trial evaluated ipilimumab either alone or in combination with a vaccine in comparison to that vaccine alone in 676 pre-treated patients with advanced melanoma [16]. With 10 months median overall survival (OS) was improved significantly for both groups treated with ipilimumab in comparison to 6.4 months for patients treated with the vaccine alone. Adverse events were very frequent and 12 (i.e. 2.3%) ipilimumab-related deaths were observed.

Three phase II studies were found which were either single-armed, dose-ranging studies or had the primary objective of assessing the addition of budesonide for the treatment of diarrhoea, an irAE associated with ipilimumab [18, 19, 21]. In addition, results of one study reporting on a compassionate use programme are reported [20]. Best overall response rates (BORR) ranged from 6% -16% for 10mg/kg ipilimumab and OS was 7 months to 19 months. Drug-related adverse events were also observed very frequently (in up to 95% of patients). irAEs of any grade were the most common adverse events and occurred in 65% - 84% of patients. One study mentioned that 5 deaths (i.e. approximately 3%) might have been treatment related.

6.1 Efficacy and safety - Phase III studies

Table 1.: Summary of efficacy

Study title: Improved survival with Ipilimumab in patients with metastatic melanoma [16]			
Study identifier	NCT00094653		
Sponsor	Bristol-Myers Squibb, Medarex		
Design	Phase III, randomized (3:1:1 ratio), double-blind, multicenter, three-arm, placebo controlled		
	Duration	Endpoint specific, patients were randomly assigned to study groups between September 2004 and August 2008	
Hypothesis	Superiority		
Treatment groups	Intervention 1	Ipilimumab 3mg/kg body weight i.v. + gp 100 vaccine s.c once every 3 weeks for 4 treatments, 403 patients	
	Intervention 2	ipilimumab 3mg/kg body weight i.v. + placebo once every 3 weeks for 4 treatments, 137 patients	
	Control	gp100 vaccine s.c. + placebo once every 3 weeks for 4 treatments, 136 patients	
Endpoints and definitions	Overall survival	OS	Time from randomization to death from any cause
	Progression-free survival	PFS	Time from randomization to documented disease progression or death
	Best overall response rate	BORR	Proportion of patients with a partial or complete response
	Complete response	CR	Disappearance of all known disease

	Partial response	PR	A 50% or more decrease in the sum of the products of the longest diameter and the greatest perpendicular diameter of all target lesions compared to baseline, by 2 observations (not necessarily consecutive) not less than 4 weeks apart. There must be no evidence of intercurrent progressive disease between the first measurement showing the 50%decrease and the confirmatory observation.
	Stable disease	SD	Neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease
	Progressive disease	PD	An increase of 25% or more in the sum of the products of the longest diameter and the greatest perpendicular diameter of target lesions compared to the smallest recorded sum (nadir) during the study, or appearance of one or more new lesions. A single progressing lesion that does not raise the overall sum of the product of the diameters by 25% will not be considered progressive disease
	Disease control rate	DCR	Percentage of patients with a partial or complete response or stable disease
Database lock	August 2009 (Final data collection date for primary outcome measure)		
Results and analysis			
Analysis description	Primary analysis: Intention-to-treat analysis		
Analysis population	Characteristics: mean age 56 years, LDH ≤ upper limit of the normal range 62%, M0: 2%, M1a (= Metastases to distant skin, subcutaneous, or lymph node sites, with a normal serum LDH): 9%, M1b (= Lung metastases in patients with a normal serum LDH): 18%, M1c (= Metastases to other visceral sites with a normal serum LDH OR any metastasis associated with an elevated serum LDH): 71% Inclusion: un-resectable stage III or stage IV melanoma, previously treated (DTIC, temozolomide, fotemustine, carboplatin, IL-2), Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, positive status for HLA-A*0201, life expectancy of at least 4 months Exclusion: active, untreated metastases in the central nervous system		

Descriptive statistics and estimate variability	Treatment group	Intervention 1	Intervention 2	Control
	Number of subjects	403	137	136
	OS (months) Median 95%CI	10.0 8.5 to 11.5	10.1 8.0 to 13.8	6.4 5.5 to 8.7
	PFS (months) Median 95%CI	2.76 2.73 to 2.79	2.86 2.76 to 3.02	2.76 2.73 to 2.83
	PFS rate at 12 weeks (%) 95% CI	49.1 44.1 to 53.9	57.7 48.9 to 65.5	48.5 39.6 to 56.7
	BORR (%) 95% CI	5.7 3.7 to 8.4	10.9 6.3 to 17.4	1.5 0.2 to 5.2
	CR (%)	0.2	1.5	0
	PR (%)	5.5	9.5	1.5
	SD (%)	14.4	17.5	9.6
	PD (%)	59.3	51.1	65.4
	DCR (%) 95% CI	20.1 16.3 to 24.3	28.5 21.1 to 36.8	11.0 6.3 to 17.5
	OS rates (%) at: 12 months 18 months 24 months	 43.6 30.0 21.6	 45.6 33.2 23.5	 25.3 16.3 13.7

Effect estimate per comparison	OS (primary outcome : intervention 1 vs. control)	Comparison groups	Intervention 1 vs Control
		Hazard ratio	0.68
		95% CI	0.55 to 0.85
		P value	<0.001
		Comparison groups	Intervention 2 vs Control
		Hazard ratio	0.66
		95% CI	0.51 to 0.87
		P value	0.003
		Comparison groups	Intervention 1 vs Intervention 2
		Hazard ratio	1.04
		95% CI	0.83 to 1.30
		P value	0.76
	PFS	Comparison groups	Intervention 1 vs Control
		Hazard ratio	0.81
		95% CI	NA
		P value	<0.05
		Comparison groups	Intervention 2 vs Control
		Hazard ratio	0.64
		95% CI	NA
		P value	<0.001
		Comparison groups	Intervention 1 vs Intervention 2
		Hazard ratio	1.25
		95% CI	NA
		P value	0.04
Notes	• The original primary endpoint was best overall response rate but the primary endpoint was amended to overall survival with the amendment approved in January 2009 • Re-induction therapy was offered to patients with stable disease of ≥ 3 months from week 12 or to patients who achieved a partial or complete response at week 12 • Patients with progressive disease who were not eligible for continued therapy or for re-induction were permitted to receive non-study cancer therapy		

Table 2: Most frequent adverse events

Grade (CTC version 3.0)	Outcome	Intervention 1 (n=380)	Intervention 2 (n=131)	Control (n=132)
All Grades	Any event (%)	98.4	96.9	97.0
	Any drug related event (%)	88.9	80.2	78.8
	Any immune-related event (%)	58.2	61.1	31.8
Grade 3	Any event (%)	38.7	37.4	40.9
	Any drug related event (%)	16.3	19.1	11.4
	Diarrhea (%)	4.2	5.3	0.8
	Anaemia (%)	2.9	3.1	8.3
	Any immune-related event (%)	9.7	12.2	3.0
	Colitis (irAE)[1] (%)	2.9	5.3	0
Grade 4	Any event (%)	6.8	8.4	6.1
	Any drug related event (%)	1.1	3.8	0
	Any immune-related event	0.5	2.3	0
	Dyspnea (%)	0.5	0.8	0
	Gastrointestinal (irAE) (%)	0.5	0	0
Other outcomes	Deaths related to study drug (no/%)	8 (2.1)	4 (3.1)	2 (1.5)

[1] irAE = immune-related adverse event

ipilimumab in comparison to an experimental vaccine

This phase III study investigated ipilimumab either in combination with gp 100 or alone in comparison to gp100 alone. Gp100 is an experimental vaccine derived from a melanosomal protein comprising HLA-A*0201-restricted peptides that had previously shown some benefit in melanoma. Therefore positive status for HLA-A*0201 was one inclusion criteria. Further eligibility criteria were previously treated patients with un-resectable stage III or stage IV melanoma and with a good performance status. About 70% of patients had M1c metastatic disease, defined as metastases to other visceral sites with a normal serum LDH or any metastasis associated with an elevated serum LDH, a stage associated with a poor prognosis [11].

676 pre-treated patients

primary outcome was changed to overall survival

median OS about 10 months for ipilimumab groups in comparison to 6.4 months for vaccine group

Overall 676 patients were allocated in a 3:1:1 ratio to three groups: ipilimumab + gp100, ipilimumab alone and gp100 alone. The initial primary outcome, best overall response rate, was changed to OS after the study's start. Both groups which had received ipilimumab showed improved outcomes in OS. In the ipilimumab + gp100 group median OS was 10 months in comparison to 6.4 months for the gp100 only group, resulting in a HR of 0.68 ($p<0.001$). When ipilimumab alone (median OS was 10.1 months) was assessed in comparison to gp100 alone, HR was 0.66 ($p=0.003$). No differences were found between the two ipilimumab groups. In a subgroup analysis, these effects appeared to be independent of gender, age, metastasis stage of disease, and prior interleukin-2 treatment. Median progression-free survival (PFS) was similar for all groups at 12 weeks; afterwards, however, differences occurred in the risk of progression between patients treated with ipilimumab and those treated with gp100.

With approximately 11%, the highest best overall response rate (BORR), defined as patients with either partial or complete response, was found in the ipilimumab alone group. An objective response for at least 2 years was maintained in 9 of 15 patients (60%) in the ipilimumab alone group and in 4 of 23 patients (17%) in the ipilimumab+gp100 group. 2 patients in the vaccine only group had a partial response, but none of them maintained the response for 2 years.

Of the 31 patients who received re-induction therapy with ipilimumab, 1 patient showed a complete response, 5 a partial response and the remaining 15 patients had stable disease.

adverse events very frequent

most frequent: immune-related adverse events

Adverse events were very frequent in each group. Drug related events of any grade were observed in 89% of patients in the ipilimumab+gp100 group, in 80% of the ipilimumab alone group and in 79% of the gp100 alone group. IrAEs, defined as AEs associated with exposure to the study drug and consistent with an immune phenomenon, occurred in about 60% of patients treated with ipilimumab, whereas 32% of the gp100 only group experienced these side-effects. For irAEs of grade ≥ 2 to resolve, it took about 6 weeks in the ipilimumab + gp100 group, 5 weeks for the ipilimumab only group and 3 weeks for the gp100 alone group. In total, 14 deaths related to the study drugs were observed out of which 12 occurred in patients treated with ipilimumab (2.3%).

6.2 Efficacy and safety - further studies

single-arm phase II study showed best overall response rate of 6%

OS: 10 months

drug-related adverse events in 84% of patients

A single-arm phase II study [17] evaluated induction therapy (every 3 weeks) followed by maintenance therapy (every 3 months) with 10mg/kg ipilimumab in 155 previously treated patients with un-resectable stage III/IV melanoma. The BORR, the primary outcome of this study, was 5.8% At a median follow-up time of 10 months, median OS was 10.2 months (95% CI 7.6-16.3); the 12 months, 18 months and 24 months survival rates were 47.2%, 39.4% and 32.8% respectively - follow-up is still on-going. Drug-related adverse events were observed in 84% of patients. 54% of patients experienced serious adverse events where 32% were considered drug related. irAEs of any grade were the most frequent adverse events and occurred in 70% of patients. 5 deaths might have been treatment related.

dose-ranging study:

BORR: 11%

OS: 11 months

immune-related adverse events in 70%

A phase II dose-ranging study conducted by *Wolchok et al.* [18] comprised 213 previously treated with stage III/IV melanoma. Three different dosing regimens (0.3 mg/kg; 3mg/kg; 10mg/kg) were administered for induction therapy, followed by maintenance therapy every three months. The highest BORR (11.1%) was found for the group with 10mg/kg ipilimumab therapy, followed by 4.2% for the 3mg/kg group and 0% for the 0.3mg/kg study arm. Median OS was 11.4 (95% CI 6.9 - 16.1) months in the 10mg/kg group, whereas for the two other groups it was about 8.6 months (95% CI 6.9-12.1 and 7.7-12.7 for the 3mg/kg and the 0.3mg/kg groups, respectively). irAEs of any grade, again the most frequent AEs, increased with the dose applied and were seen in 70% of patients in the 10mg/kg group, in 65% in the 3mg/kg group and in 26% of the 0.3mg/kg group. No serious irAEs were reported in the 0.3mg/kg dose, but in the 10mg/kg group the most frequent irAEs of grade 3 or 4 were gastrointestinal (15%) and dermatologic (4%) ones.

clinical trial assessing rates of diarrhoea of ipilimumab ± budesonide

Another phase II study had the primary objective of assessing the rates of grade ≥2 diarrhoea, an irAE associated with ipilimumab, if ipilimumab was administered at 10mg/kg either alone or in combination with prophylactic budesonide [19]. No advantages for the prophylactic administration of budesonide were shown in a total of 115 patients. BORR ranged from 12.1% to 15.8%; 1 year survival rates were 55.9% (95% CI 42.7-68.6) to 62.4% (95% CI 49.4-75.1) and the median OS was 17.7 months and 19.3 months. Any drug-related events were very frequently observed (90% in the combination arm, 95% in the ipilimumab only arm) as well were irAEs of any grade (81% in the combination arm, 84% in the ipilimumab only arm). The incidence of higher grade irAEs was about 40%, with 28% attributable to grade 3 and 12% attributable to grade 4% events.

compassionate use: OS 7 months

irAEs of grade 3/4 in 29%

Ku et al. [20] report results of 51 patients with advanced refractory melanoma which were treated with 10mg/kg ipilimumab in an compassionate use setting. Median PFS was 2.6 months (95% CI 2.3-5.2 months) and median OS was 7.2 months (95% CI 4.0-13.3 months). Objective response rate was 12% (95% CI 5%-25%). In terms of side-effects, no treatment-related deaths were observed, but irAEs of grade 3 or 4 were seen in 29% of patients. The most common grade 3 AEs included diarrhoea (16%), lymphopenia (18%), dyspnoea, anaemia and fatigue (each 8%). Elevations of the liver enzymes and infections (each 4%) were the most common grade 4 AEs.

7 Estimated costs

costs unknown

The costs of ipilimumab have not been determined yet. In the investigated indication, it is clear that the expenses will occur in addition to prior therapies and costs for the treatment of side-effects. Nonetheless, as long as ipilimumab will be used for the treatment of advanced/metastatic melanoma only, the overall costs will be kept within a limit due to the limited number of eligible patients.

8 On-going research

3 on-going phase III trials on melanoma

NCT00162123: evaluates the continued use of ipilimumab in patients who had clinical benefit in a prior/parent study and are now eligible to receive either re-Induction at the time of disease progression or to continue maintenance treatment. The planned end is March 2011.

NCT00324155: compares ipilimumab + DTIC to DTIC alone in *untreated* patients with un-resectable stage III or IV melanoma. The trial is on-going but not recruiting anymore. Final data collection date is November 2010 and the expected end of the study is November 2011.

NCT00636168 is currently recruiting patients and assesses ipilimumab versus placebo to prevent recurrence after complete resection of high risk stage III melanoma. The study will be completed in September 2014.

further trials evaluate ipilimumab for other types of cancer

In addition, two phase III studies are recruiting patients to evaluate ipilimumab for the treatment of prostate cancer.

Plenty phase I or phase II studies for melanoma were found, including various combinations (e.g. temozolomide, bevacizumab, sargramostim). Besides melanoma, other indications under investigation are prostate cancer, non-small cell lung cancer, breast cancer and pancreatic cancer.

9 Commentary

not yet approved - FDA decision in March 2011

Ipilimumab for pre-treated patients with un-resectable stage III or stage IV melanomas has not been approved yet, neither by the FDA nor by the EMA. The FDA has announced that first decisions on market approval will be released in March 2011.

phase III trial showed improvements in OS

Marketing authorization is sought mainly based on a phase III trial which evaluated ipilimumab either alone or in combination with gp100, an experimental vaccine, in comparison to that vaccine alone [16]. 676 previously treated patients suffering from un-resectable stage III or stage IV melanoma were included. The primary outcome had initially been best overall response rate, but was changed to OS during the study. Median OS in comparison to gp100 alone was prolonged by 3.6 and 3.7 months in the groups treated with ipilimumab. Improvements were also found for other outcomes such as PFS,

where the risk of progression was diminished by 19% with ipilimumab + gp100 in comparison to gp100 alone, and by 36% with ipilimumab alone as compared to gp100 alone. The addition of gp100 to ipilimumab did not result in better outcomes than ipilimumab alone.

AEs frequent, most common irAEs

treatment-related deaths in about 2%

Adverse events were very frequent. The most common ones were irAEs (immune-related adverse events due to the immune-based mode of action of ipilimumab), which occurred in about 60% of patients treated with ipilimumab and in 32% of the gp100 group. Treatment related deaths were observed in about 2% of patients treated with ipilimumab.

4 other studies

In addition, three phase II studies and one study on a compassionate use programme [18-21] reported best overall response rates ranging from 6% - 16% for 10mg/kg ipilimumab and OS of 7 months to 19 months. Drug-related adverse events were also observed very frequently (in up to 95% of patients). irAEs of any grade were the most common adverse events and occurred in 65% - 84% of patients. One study mentioned that 5 deaths (i.e. approximately 3%) might have been treatment related.

very few treatment options for advanced melanoma

ipilimumab first drug with OS improvements

Therapy of advanced melanomas proves very difficult as only few agents are licensed in Europe and treatment options in general show only limited activity, resulting in a median survival of 6 to 9 months. Against this background even a prolongation of OS by more than 3 months can be called a success, especially since ipilimumab is the first therapy which demonstrated improvements in OS in pre-treated advanced melanoma [3].

but many open questions remain: quality-of-life?

markers which predict response to treatment?

Despite these findings, many open questions concerning ipilimumab therapy remain. For one, it can be questioned whether choosing another experimental therapy (i.e.gp100) as comparator was reasonable or if delivering "best supportive care" to the control group would not have provided more meaningful results. Also, data on quality-of-life are missing but would be in the light of high rates of sometimes serious and life-threatening adverse events of utmost interest. Moreover, as the BORR (i.e. proportion of patients with partial or complete response) was 11%, only the minority of patients seem to respond to ipilimumab therapy [22]. Hence, markers are needed which allow to predict response to this treatment [3] and thus to spare patients, which are unlikely to respond, severe side-effects.

dosage, treatment duration?

new response criteria?

Other unresolved issues concern the optimal dosing and duration of ipilimumab therapy. For example, the dose (i.e. 3mg/kg), administered in the above mentioned phase III trial, was in comparison to other trials relatively low. Regarding the optimal treatment duration, some authors argue that new response criteria are necessary for immunotherapeutic agents such as ipilimumab, because response can occur even after an initial increase in tumour burden or after the development of new lesions. According to the standard response criteria, this response would be labelled as "progressive disease" and would therefore lead to the termination of ipilimumab therapy [3, 23, 24]. However, as these new criteria have not been evaluated, applying them wrongly might result in the very opposite effect, as patients would be exposed for a prolonged period of time to an ineffective, if not toxic therapy [25].

Other questions which need to be addressed in future clinical trials are if ipilimumab should be used as single agent or as combination therapy, as 1st or as 2nd-line therapy or how ipilimumab therapy compares to other available treatment options. Some of these questions might be answered by the results of an on-going trial which compares 1st -line ipilimumab with dacarabazine (end of study November 2011).

as single agent or combination therapy?

1st line or 2nd line therapy?

Even though the price of ipilimumab has not been determined, due to its orphan drug status and the rather limited treatment options for advanced melanoma, it might be sold at high prices – if licensed in the first place. Because of the limited number of patients with pre-treated advanced melanomas, even a high price will not have major implications for health care services. But since ipilimumab is under investigation for other types of cancers, including very frequent ones such as lung-cancer, pricing of ipilimumab might become important in the future.

costs?

Therapeutic options for advanced/metastatic melanoma are limited. If the EMA grants market authorization for ipilimumab, a treatment option for this difficult to treat disease will become available for which increases in OS have been demonstrated. However, this therapy is associated with sometimes severe and life-threatening adverse events and many unresolved questions still remain.

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