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1 Drug description

Generic/Brand name/ATC code:

Ipilimumab, MDX-010, MDX-101/Yervoy®/ L01XC11

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) are 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. Frequently used regimens 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]. However, in Europe the licensed dose is 3mg/kg every 3 weeks for a total of four doses [5].

dose ranging from 3mg/kg – 10mg/kg

2 Indication

Ipilimumab is indicated for the first-line therapy of patients with advanced/ metastatic cutaneous melanoma.

for untreated patients with advanced/metastatic cutaneous melanoma

3 Current regulatory status

In Europe, ipilimumab is licensed for

- adults with melanoma who have been previously treated, but for whom treatment has not worked or has stopped working since July 2011. The approved dose is 3 mg/kg ipilimumab intravenously every 3 weeks for a total of four doses [5].

licensed in Europe for ≥2nd line therapy

in the U.S. for 1st and 2nd line therapy

In the US, ipilimumab has orphan drug status and is licensed for:

- the treatment of unresectable or metastatic melanoma. The recommended dosage is 3mg/kg every 3 weeks for a total of four doses. [6].

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 [7]. The "ABCD" method of identification, originally described by *Friedman et al.* [8], has been a useful tool in facilitating the diagnosis of malignant melanoma. This method analyses four clinical characteristics to identify melanoma: asymmetry, border irregularity, colour variegation, and a diameter of 6 mm or more.
Risk factors for developing melanomas include prior melanomas, a positive family history, skin phototype and multiple clinically atypical moles/dysplastic nevi. In addition, genetic factors and sun exposure can contribute towards the development of melanomas [9]. To confirm the diagnosis of melanoma a biopsy, at best by local excision, should be performed [7]. Several parameters of prognostic value should be considered in the histopathological report on “microstaging” of the disease. The microstaging is based on the histologic examination of the vertical thickness of the lesion, which is expressed in millimetres (Breslow classification) and/or on the anatomic level of local invasion (Clark classification). Due to its reproducibility and its capability in accurately predicting the evolution of malignant melanoma with lesions thicker than 1.5 mm, the Breslow thickness should always be reported. Accurate microstaging of the primary tumour requires careful histologic evaluation of the entire specimen by an experienced pathologist [10].

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 [7]. For patients suffering from stage IV disease, sites of metastases and elevated lactate-dehydrogenase (LDH) levels are also associated with poor outcomes [9]. 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, but also gastrointestinal secondary involvement is not rare in disseminated disease. Staging is also an important factor for the determination of the most appropriate treatment [11].

metastatic melanoma: median survival of 6 - 9 months

Median age at diagnosis of malignant melanoma is 59 years [7]. 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% [9]. Median survival is 6 to 9 months [12].

Malignant melanoma accounts for 2-3% of all malignant tumours in North-Europe and USA; incidence is rising, with an increase of 4% per year in the USA. In 2008, the EU incidence rate (per 100,000) of skin melanoma was 10.0, being 9.5 among males and 10.4 among females (overall cumulative risk of 0.93%). Mortality rate (per 100,000) was 2.4, being 2.6 among males and 2.1 among females [13]. In Austria, the incidence of melanomas is about 15 newly diagnosed cases/100,000 persons per year and is constantly rising [14]. In 2007, overall 1,300 people were newly diagnosed with malignant melanoma in Austria. Of these, about 5% of the tumours were already disseminated, resulting in about 65 persons with advanced melanoma per year [12].

about 65 patients/year diagnosed with advanced melanoma in Austria

5 Current treatment

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 [9]. Thus, cure is rarely possible [11].

cure rarely possible

Little consensus on the standard of care exists and enrolment onto clinical trials is highly recommended. Therapy may involve:

treatment options:

- 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.

surgery,

- Single-agent chemotherapy:
  - dacarbazine (DTIC), which is licensed for melanoma in Austria, is currently the most active chemotherapy and has often been used as standard comparator for new therapeutic regimens [9]. However, only 10%-20% of patients respond to this treatment, showing mainly partial remissions with a median response duration of 3-4 months [9].
  - 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].

chemotherapy,

- 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].

immunotherapy,

- ipilimumab is approved for the second-line therapy of advanced melanoma. Some guidelines recommend it for patients without V600 mutation in BRAF who will not be treated with interleukin-2 [9].

- Signal transduction inhibitors:
  - mono-therapy with vemurafenib a BRAF inhibitor is licensed for adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in Europe since February 2012 [11, 16] .

and radiation therapy

- Radiation therapy either to metastases outside the brain for symptom palliation or as whole brain radiation therapy which can prolong survival in selected cases, especially if the tumour outside the brain is controlled [11].
- Multi-agent chemotherapy and bio-chemotherapy
  - The medical literature reports numerous phase II and III trials employing various drug combinations. Clear evidence of the superiority of multi-agent chemotherapy is still lacking, while combination therapies have shown greater toxicity [17].
  - Several studies on bio-chemotherapy have been conducted. The results of a meta-analysis show that bio-chemotherapy improves response rates compared with chemotherapy. However, these regimens were associated with an increase in haematologic toxicity without significant improvement in survival [18].

or clinical trials

Recommendations differ to some extent which of these treatment options should be used first [7, 9, 19]. To conclude, no standard therapy exists for the treatment of metastatic melanoma, but dacarbazine is at least considered as reference drug, even though its impact on overall survival is limited. Thus, inclusion into a clinical trial is highly recommended [7, 20, 21].

6 Evidence

1 phase III, 1 phase II trial

Based on a literature search (15th of May 2012) in Medline, EMBASE, DARE (Database of the Centre for Review Dissemination of the National Institute of Health) and Cochrane Central, 390 references were identified overall. Of these, 1 phase III [22] and 1 phase II trial [23] were included. 1 study which had included both previously treated as well as untreated patients was excluded because no separate results were provided for previously untreated patients [24]. However, a retrospective analysis of this primary study provides results for the first-line therapy only and was therefore included [25].

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma [22, 26]			
Study identifier	Clinical trial identifier: NCT00324155, EUDRACT Number 2005-006082-14, Protocol Number: CA184-024		
Design	Multinational, randomized, double-blind, placebo controlled phase 3 study		
	Duration	Enrolment: August 2006 - January 2008 Median follow-up: 54 months Cut-off date for final analysis: February 2013	
Hypothesis	Superiority Among patients with previously untreated Stage IIIc, N3 (unresectable) or Stage IV melanoma (American Joint Committee on Cancer 2001 and measurable per modified World Health Organization [WHO] criteria), overall survival (OS) in patients receiving dacarbazine plus 10 mg/kg ipilimumab will be superior to that in patients receiving dacarbazine with placebo.		
Funding	Bristol-Myers Squibb		
Treatment groups	Intervention (n= 250)	Induction phase: Ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m²) at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22 Maintenance phase: from week 24, patients with stable disease or an objective response during the induction phase who did not have a dose-limiting adverse event received ipilimumab every 12 weeks until progression of the disease, development of toxic effects, or the end of the study.	
	Control (n= 252)	Induction phase: Dacarbazine (850 mg/m²) plus placebo at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22 Maintenance phase: after week 24, patients with stable disease or an objective response during the induction phase who did not have a dose-limiting adverse event received placebo every 12 weeks until progression of the disease, development of toxic effects, or the end of the study.	
Endpoints and definitions	Overall survival (primary outcome)	OS	time between randomization date and death.
	Progression-free survival	PFS	time between randomization date and the date of progression or death, whichever occurs first.
	Best overall response rate	BORR	total number of randomized patients in the arm whose BOR is CR or PR, divided by the total number of randomized patients in the arm.
	Disease control rate	DCR	total number of randomized patients in the arm with BOR of CR, PR or SD, divided by the total number of randomized patients in the arm.

	Time to response	-	time from randomization date until measurement criteria are first met for overall response of PR or CR (whichever status is recorded first, and if subsequently confirmed).
	Duration of the response	-	time between the date measurement criteria are first met for overall response of PR or CR (whichever status is recorded first, and if subsequently confirmed) and the date of disease progression or death, whichever occurs first.

Results and analysis

Analysis description	Target number of events for the primary analysis was 416 deaths, which was estimated to give the study approximately 90% power to detect a 37% increase in median overall survival to 11 months with ipilimumab plus dacarbazine, with a corresponding hazard ratio for death of 0.727, assuming a total sample of 500 patients (250 randomly assigned to each group) and a median survival of 8 months for the patients receiving dacarbazine plus placebo. For the analysis of overall survival, a log-rank test was performed, at a two-sided alpha level of 0.05, stratified according to metastasis stage (M0, M1a, M1b, or M1c) and ECOG performance status (0 or 1), as classified at the time of randomization. intention- to-treat population		
Analysis population	Inclusion	≥18 years, previously untreated stage III (unresectable) or stage IV melanoma (prior adjuvant therapy permitted) with measurable lesions, ECOG PS ≤1, life expectancy ≥ 16 weeks	
	Exclusion	prior treatment for metastatic disease; concomitant treatment with immunosuppressive agents or long-term use of systemic glucocorticoids (except for the management of adverse events during the course of the study) was not allowed, brain metastasis (as confirmed on imaging), primary ocular or mucosal melanoma, or autoimmune disease	
	Characteristics	Mean age (years): I 57.5 vs. C 56.4 Sex (%): males I 60.8 vs. C 59.1, females: I 39.2 vs. C 40.9 ECOG-PS (%): 0: I 70.8 vs. C 71.0, 1: I 29.2 vs. C 29.0 Metastasis stage (%): M0: I 2.4 vs. C 3.2, M1a: I 14.8 vs. C 17.1, M1b: I 25.6 vs. C 24.6, M1c: I 57.2 vs. C 55.2 LDH (%): ≤upper limit of normal range: I 62.8% vs. 55.6%, > upper limit of normal range: I 37.2% vs. C 43.7% Prior adjuvant therapy (%): I 26 vs. C 27	
Descriptive statistics and estimated variability	Treatment group	*Ipilimumab + dacarbazine*	*Placebo + dacarbazine*
	Number of subjects	N= 250	n= 252
	OS (months) Median 95%CI	 11.2 9.4 – 13.6	 9.1 7.8 – 10.5
	Survival rate (%) At 1 year (95%CI) At 2 years (95%CI) At 3 years (95%CI)	 47.3 (41.0–53.6) 28.5 (22.9–34.2) 20.8 (15.7–26.1)	 36.3 (30.4–42.4) 17.9 (13.3–22.8) 12.2 (8.2–16.5)
	PFS (months) Median 95%CI	 NA NA	 NA NA

	BORR (number (%)) CR PR SD PD Not evaluated	38 (15.2) 4 (1.6) 34 (13.6) 45 (18.0) 111 (44.4) 56 (22.4)	26 (10.3) 2 (0.8) 24 (9.5) 50 (19.8) 131 (52.0) 45 (17.9)
	DCR (%)	33.2	30.2
	Time to response	NA	NA
	Duration of response (months) Median 95% CI	 19.3* 12.1 to 26.1	 8.1 5.19 to 19.8
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	OS	HR	0.72
		95%CI	0.59–0.87
		P value	<0.001
	Progression	HR	0.76
		95%CI	0.63–0.93
		P value	0.006
	DCR	P value	0.41
	BORR	P value	0.09
Notes	In an amendment approved by the Food and Drug Administration on October 9, 2008, the primary end point was changed from PFS to OS before the treatment assignments were revealed.		

**p=0.03*

Table 2: most frequent adverse events

Grade (according to CTC 3.0)	Outcome (%)	Ipilimumab + dacarbazine (n= 247)	Placebo + dacarbazine (n=251)
Adverse events regardless of cause			
All grades (in more than 30% in either group)	Any event	244 (98.8)	236 (94.0)
	Diarrhoea	90 (36.4)	62 (24.7)
	Increase in alanine aminotransferase	82 (33.2)	14 (5.6)
	Pyrexia	91 (36.8)	23 (9.2)
Grade 3 (in more than 10% in either group	Any event	99 (40.1)	45 (17.9)
	Increase in alanine aminotransferase	40 (16.2)	2 (0.8)
	Increase in aspartate aminotransferase	36 (14.6)	3 (1.2)
Grade 4 (in more than 5% in either group)	Any event	40 (16.2)	24 (9.6)
	Increase in alanine aminotransferase	14 (5.7)	0
Grade 5	Drug-related death	0	1 (<1)
Immune-related adverse events			
All grades (in more than 30% in either group)	Any event	192 (77.7)	96 (38.2)
	Diarrhoea	81 (32.8)	40 (15.9)
Grade 3 (in more than 10% in either group	Any event	78 (31.6)	8 (3.2)
	Increase in alanine aminotransferase	37 (15.0)	2 (0.8)
	Increase in aspartate aminotransferase	34 (13.8)	1 (0.4)
Grade 4 (in more than 5% in either group)	Any event	25 (10.1)	7 (2.8)
	Increase in alanine aminotransferase	14 (5.7)	0

phase III trial investigated ipilimumab at a dose of 10mg/kg + dacarbazine vs placebo + dacarbazine in the 1st-line setting

In this double-blind phase III trial, 502 patients with previously untreated metastatic melanoma were allocated to either ipilimumab + dacarbazine or to placebo + dacarbazine, followed by dacarbazine every 3 weeks (induction phase). Patients were about 57 years old and had in the majority ECOG-PS 0. Approximately 55% of patients had stage M1c disease. If patients had stable disease or an objective response at 24 weeks without dose-limiting AEs, they could enter a maintenance phase consisting either of placebo or ipilimumab every 12 weeks until disease progression, development of toxic effects, or the end of the study.

37% of patients allocated to the ipilimumab + dacarbazine group received all planned four doses of the induction therapy in comparison to 66% in the placebo +dacarbazine group. The corresponding numbers of patients receiving at least one maintenance dose were 17% in the ipilimumab + dacarbazine group and 21% in the placebo + dacarbazine group. Even though the most common reason for treatment discontinuation was progressive disease (I 46% vs C 77%), considerably more patients stopped treatment due to drug-related AEs in the ipilimumab + dacarbazine group (36.0%) than in the placebo + dacarbazine group (4.0%). Of these patients, 34% in the ipilimumab + dacarbazine group and 4.0% in the placebo + dacarbazine group discontinued due to a drug-related AE during the induction phase.

overall 502 patients

more patients discontinued ipilimumab therapy than in the control arm

only 37% of pts received all planned 4 doses

After disease progression, 55% of the patients in the ipilimumab + dacarbazine group and 59% in the placebo + dacarbazine group received subsequent therapy, consisting of chemotherapy (I 38% vs C 35%) or immunotherapy (2% in each group).

Median overall survival (OS), the primary outcome, was 11.2 months (95%CI 9.4 to 13.6) in the ipilimumab + dacarbazine group and 9.1 months (95% CI 7.8 to 10.5) in the control group, yielding a hazard ratio of 0.72 ($p<0.001$). Survival rates at 1, 2 and 3 years were 47.3%, 28.5% and 20.8% in the ipilimumab + dacarbazine group and 36.3%, 17.9% and 12.2% in the control group respectively. Median progression-free survival (PFS) was similar in the two groups, but since differences occurred later on (that is after week 12) a 24% reduction in the risk of progression was statistically significant. In contrast, disease control rates as well as best overall response were comparable. Of these, complete responses were observed rarely in both groups (ipilimumab + dacarbazine 1.6% vs placebo + dacarbazine 0.8%) and partial responses occurred in 13.6% in the ipilimumab + dacarbazine group and in 9.5% in the placebo +dacarbazine group. Amongst these patients, median duration of response was 19.3 months in the ipilimumab + dacarbazine group in comparison to only 8.1 months in the placebo + dacarbazine group ($p = 0.03$), but the limited number of observed events suggests, that these data should be carefully interpreted. Outcomes associated with quality-of-life were not evaluated.

median OS: +2.1 months for the ipilimumab group

similar results for disease control rates and for overall low response rates

but: duration of response longer in the ipilimumab group

Overall, AEs were very frequent in both groups, but those of higher grades were more often observed in the ipilimumab + dacarbazine group. Grade 3 or 4 AEs were seen in 56% of patients receiving ipilimumab + dacarbazine and in 28% of patients receiving placebo + dacarbazine ($p<0.001$). Of these, 40% were of grade 3 and 16% of grade 4 in the ipilimumab + dacarbazine group in comparison to 18% and 10% in the placebo + dacarbazine group. An additional safety analyses, concerning immune-related AEs was also performed, which were the most frequent study-drug related AEs (Overall: ipilimumab + dacarbazine 78% vs placebo + dacarbazine 38%). More severe immune-related AEs (i.e. grade ≥3) occurred in 38% in the ipilimumab + dacarbazine group and in 4% in the placebo group. The most common ones in the ipilimumab group were liver-associated AEs such as increase in liver enzymes and hepatitis (see table 2). AEs were also more frequent in the ipilimumab + dacarbazine group during the maintenance phase, but the most common ones of all grades were rash (I 26% vs C 6%), pruritus (I 16% vs C 4%) or diarrhoea (ipilimumab + dacarbazine 14% vs placebo + dacarbazine 6%).

AEs, also of higher grade, more frequent in the combination arm

grade 3+4 in 56% of pts in ipilimumab arm vs 28% in dacarbazine only arm

foremost immune-related AEs

6.2 Efficacy and safety - further studies

open-label phase II compared ipilimumab at 3mg/kg + dacarbazine to ipilimumab only

response rates also low but higher in the combination arm

increases in OS when ipilimumab was administered in addition to dacarbazine

AEs more frequent in combination arm

An open-label, randomised phase II trial [23] investigated ipilimumab with or without dacarbazine in chemotherapy-naïve patients. Overall 72 patients were assigned to either of the groups. Treatment with ipilimumab consisted of 3mg/kg every 4 weeks for four doses and dacarbazine was administered at 250mg/m^2 for five consecutive days every 3 weeks. 13 patients (of 37) initially assigned to ipilimumab only crossed over to ipilimumab + dacarbazine after disease progression. Like in the phase III trial, only the minority of patients (i.e. 30% in the mono-therapy arm and 46% in the combination arm) finished a full treatment course. Best objective response rate, the primary efficacy outcome, was 5.4% in the ipilimumab only group and 14.3% in the combination arm; in the ipilimumab only group all responses were partial responses, whereas the combination of ipilimumab + dacarbazine yielded in 5.7% complete responses and in 8.6% partial responses. At median follow-up (ipilimumab only: 16.4 months, ipilimumab + dacarbazine: 20.9 months), median OS was 11.4 months in the ipilimumab arm and 14.3 months in the combination arm. The corresponding 12-, 24 and 26-month survival rates were 45%, 21% and 9% in the ipilimumab alone group and 62%, 24% and 20% in the ipilimumab + dacarbazine group. Treatment-related AEs (safety population comprised 74 patients) of grade ≥3 were more frequent in the combination arm (23%) than in the single-drug group (13%). Immune-related AEs of any grade were observed in 54% (8% severe AEs, 10% serious AEs) in the ipilimumab only group and in 66% in the ipilimumab + dacarbazine group (17% severe AEs, 14% serious AEs). In each group, 1 patient had died; the death in the ipilimumab group was considered as related to therapy and that in the combination arm was considered possibly related to treatment.

retrospective analysis investigated budesonide + ipilimumab for reduction of diarrhoea in comparison to placebo

addition of budesonide did not improve rates of diarrhoea in previously untreated patients

A retrospective analysis of a phase II study which had enrolled treated as well as untreated patients, provides separate results for each of these groups [25]. The primary objective of the initial study [24] was to investigate whether addition of budesonide to ipilimumab reduced the rates of grade ≥2 diarrhoea in comparison to placebo. The retrospective analysis comprised 115 patients in total of which 53 were treatment-naïve. For these patients, median OS was 30.5 years and the 1-year survival rate was 69.4%. At a median follow-up of 18.5 months, the disease control rate (35.8%) and the best overall response rate (13.2%) were similar to the phase III study. Rates of grade ≥2 diarrhoea were 31.3% with placebo and 38.1% with budesonide and grade ≥2 diarrhoea or colitis were 31.3% with placebo and 47.6% with budesonide.

These safety data confirm those seen in the study on 676 *pre*-treated patients, submitted to obtain the authorisation of ipilimumab as second-line therapy in the EU [27].

7 Estimated costs

Cost estimates for ipilimumab range from € 16,660.- to € 20,893.- for one 40 ml vial a 5mg/ml Yervoy® containing 200mg and from € 4,250.- to € 5,266.- for one 10 ml vial containing 50mg ipilimumab [28, 29].

cost estimates depend on dosing regimen and range from € 20,825 for 3mg/kg to € 58,310 for 10mg/kg for one treatment cycle

Even though the licensed dosage is 3mg/kg (in the U.S. this dosage is also used for the first-line setting) 10mg/kg ipilimumab were administered in the phase III trial. Assuming an average body weight of 70 kg and a therapy with 3 mg/kg, the costs for one infusion with ipilimumab would range from € 20,825.- to € 26,116.- (= 1x200mg vial + 1x50mg vial). Total treatment costs for induction therapy consisting of four cycles of ipilimumab add therefore up to € 83,300.- and € 104,465.-.

resulting in € 83,300.- - € 104,465 for four cycles

If 10 mg/kg were used instead, costs would increase considerably. One course would then be € 58,310.- or € 73.126.- (= 3x200mg vials + 2x50mg vials), resulting in total cost of € 233,240.- or € 292,502.- for four cycles.

8 On-going research

No on-going phase III studies were found for the indication investigated on www.clinicaltrials.gov or on www.clinicaltrialsregister.eu/ctr-search, but two trials assessing the efficacy of ipilimumab after complete resection of advanced melanoma are on-going. Furthermore, other indications currently tested in phase III are small cell lung cancer and prostate cancer.

no on-going phase III trials for 1st –line therapy of melanoma

but for other tumours, e.g. NSCLC or ovarian cancer

Ipilimumab is under investigation in phase II trials for other cancer types including ovarian cancer, pancreatic cancer and non-small cell lung cancer.

9 Commentary

Ipilimumab is licensed only for *pre*-treated patients in Europe [5]. In the U.S., the drug was approved for both previously treated as well as untreated patients. FDA's decision to also include first-line therapy rested upon the fact that they had already top line OS results of the phase III study conducted in the first line setting [30].

phase III compared ipilimumab + dacarbazine to placebo + dacarbazine only, which is reference drug but with limited activity itself

This phase III trial compared ipilimumab + dacarbazine to placebo + dacarbazine in previously untreated patients. Even though dacarbazine is the reference drug currently, its own activity for the treatment of melanoma is limited. However, OS was significantly longer in the ipilimumab group, but the gain was with 2.1 months rather modest. Moreover, although duration of response was considerably longer in the combination arm than in the control arm, responses occurred in both groups only in a minority of patients and were not statistically significant in between the two groups (ipilimumab + dacarbazine: 15% vs placebo + dacarbazine: 10%).

longer lasting responses observed but only in few patients

gain in OS of 2.1 months

AEs also more frequent

only 1/3 of pts receive full 4 cycles due to AEs

The incidence of grade 3 or grade 4 AEs, foremost driven by immune-related AEs, was also higher in the combination arm than in the dacarbazine + placebo group. Subsequently, considerably more patients stopped treatment due to drug-related AEs in the ipilimumab + dacarbazine group (36%) than in the placebo + dacarbazine group (4%), resulting in only 37% who received all four doses of the induction therapy in the ipilimumab + dacarbazine group in comparison to 66% in the placebo + dacarbazine group. Furthermore, the kind of AEs did not match those observed in previous studies since hepatic toxicity was more frequent and other immune related toxicities (e.g. colitis, rash, hypophysitis) were less frequent [11, 31]. Unfortunately, outcomes associated with quality-of-life were not reported. One explanation might be that the immune toxicity profile of ipilimumab was altered by the addition of dacarbazine, a fact potentially associated with a change in the anti-tumour effect too [11].

combination with dacarbazine might have changed safety profile and efficacy?

but unclear why ipilimumab was tested in combination with dacarbazine

this combination not recommended

Besides the fact that it remains unclear why ipilimumab was tested in combination with dacarbazine and not alone, it is doubtful that combining these two agents offers advantages beyond single-agent therapy [11, 19, 31]. In the light of low response rates other combinations are being explored to increase activity of ipilimumab, for example, in combination with bevacizumab, IL-2 or vemurafenib [19, 32]. Other ways which are discussed currently and which may increase the efficacy of ipilimumab are determination of factors which allow selection of patients and identification of predictive variables for treatment response [32]. Some authors mention molecular status [32] or baseline inducible co-stimulatory molecule T-cells as a potential options, but until now no reliable predictors of response to this immuno-therapy exist [19].

further developments might increase efficacy of ipilimumab, e.g. combination with other drugs or criteria for patient selection

comparative data are missing

Another open question concerns comparative efficacy data of ipilimumab and other available treatment options for the first-line therapy such as IL-2 or vemurafenib. Yet, the optimal sequencing and timing of different therapies in the first-line setting remains undefined [6]. Even though some recommendations indicate that IL-2 should be preferred if patients are able to tolerate this rather toxic therapy, vemurafenib should be restricted to patients with certain mutations (V600 mutation in BRAF), whereas ipilimumab can be considered in patients without these mutations and who are not eligible for IL-2 [11, 33]. This reasoning is caused by the mode of action of ipilimumab. Due to its impact on the immune system, immune cells infiltrate the tumour, cause swelling and therefore increase tumour-related symptoms initially. Thus, ipilimumab therapy might not be indicated in patients with a high disease burden but preferably in asymptomatic, oligometastatic subjects [31]. The initial swelling has also led to calls for new criteria, besides the commonly used RECIST criteria, since response to ipilimumab may be mistaken as disease progression.

ipilimumab causes initial swelling of tumours and thus enhances symptoms initially

therefore not indicated in patients with high tumour load

Comparative data become even more important since several new drugs for the first-line therapy of melanoma are in advanced phases of clinical development. For example, trametinib, an oral selective MEK inhibitor demonstrated in a phase III trial improvements in PFS (primary endpoint) in comparison to dacarbazine + paclitaxel (4.8 vs 1.4 months). Other agents under development are, for example, albumin-bound paclitaxel (NCT00864253: primary results anticipated in July 2012), masitinib (NCT01280565: primary results anticipated in December 2013) or talimogene laherparepvec (NCT00769704: primary results anticipated in 2012).

further drugs in advanced phase of development for 1st-line therapy

A further important point concerns the optimal dosing of ipilimumab. The approved dose of ipilimumab is 3mg/kg but 10mg/kg were used in the phase III trial, a regimen being also used in on-going phase III trials. Although the two different regimens will be compared in a phase III trial (NCT01515189) its results cannot be expected prior to 2017. In addition to consequences for efficacy, the impact of the two dosing regimens on treatment costs cannot be neglected. Estimates indicate that cost differences of nearly € 170,000.- over a course of four cycles might incur, not taking any extra costs for maintenance therapy into account.

optimal dosing regimen not yet determined: 3mg/kg vs. 10mg/kg

changes in efficacy possible and high impact on costs

difference of € 170.000.- per full treatment

Despite advances in the development of novel treatment strategies for advanced melanoma, a gain of only 2.1 months in OS with a considerable increase in toxicities and at high costs might not justify ipilimumab therapy currently. Further selection criteria may improve the potential to benefit, but as long as more convincing data are missing, enrolment in clinical trials is still indicated.

ipilimumab currently not yet justified

References

1. Maker, A.V., et al., *Tumor regression and autoimmunity in patients treated with cytotoxic T lymphocyte-associated antigen 4 blockade and interleukin 2: a phase I/II study.* Ann Surg Oncol, 2005. **12**(12): p. 1005-16.
2. Attia, P., et al., *Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4.* Journal of Clinical Oncology, 2005. **23**(25): p. 6043-6053.
3. Hoos, A., et al., *Development of ipilimumab: contribution to a new paradigm for cancer immunotherapy.* Semin Oncol. **37**(5): p. 533-46.
4. Weber, J., *Ipilimumab: controversies in its development, utility and autoimmune adverse events.* Cancer Immunol Immunother, 2009. **58**(5): p. 823-30.
5. European Medicines Agency. *Yervoy.* 2011 [cited 15.05.2012; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002213/human_med_001465.jsp&mid=WC0b01ac058001d124.
6. U.S. Food and Drug Administration. *Yervoy - Label and Approval History.* 2011 [cited 15.05.2012; Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo.
7. National Cancer Institute. *Melanoma Treatment.* 2012 [cited 11.06.2012; Available from: www.cancer.gov.
8. Friedman, R.J., et al., *Malignant melanoma in the 1990s: the continued importance of early detection and the role of physician examination and self-examination of the skin.* CA Cancer J Clin, 1991. **41**(4): p. 201-26.
9. National Comprehensive Cancer Network. *Melanoma, Version 3.2012.* 2012 [cited 30.05.2012; Available from: www.nccn.com.
10. Hurt, M.A. and D.J. Santa Cruz, *Malignant melanoma microstaging. History, premises, methods, problems, and recommendations--a call for standardization.* Pathol Annu, 1994. **29 (Pt 2)**: p. 51-74.
11. UpToDate Online. 2012 [cited 15.06.2012]; Available from: http://www.uptodate.com.
12. Statistik Austria. *Bösartiges Melanom der Haut.* 2012 [cited 28.05.2012]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/haut/index.html.
13. GLOBOCAN - International Agency for Research on Cancer. 2008 [cited 04. 06.2012]; Available from: http://globocan.iarc.fr/.
14. Rath, T., et al., *Malignes Melanom der Haut.* 2010, Österreichische Gesellschaft für Chirurgische Onkologie.
15. AMI - Inf - Arzneispezialitäten und Wirkstoffe, 2010.
16. European Medicines Agency. *Zelboraf - vemurafenib.* 2012 [cited 11.06.2012; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002409/human_med_001544.jsp&mid=WC0b01ac058001d124.
17. Huncharek, M., J.F. Caubet, and R. McGarry, *Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials.* Melanoma Res, 2001. **11**(1): p. 75-81.

18. Ives, N.J., et al., *Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients.* J Clin Oncol, 2007. **25**(34): p. 5426-34.
19. Finn, L., et al., *Therapy for metastatic melanoma: the past, present, and future.* BMC Medicine, 2012. **10**(23).
20. Marsden, J.R., et al., *Revised U.K. guidelines for the management of cutaneous melanoma 2010.* Br J Dermatol, 2010. **163**(2): p. 238-56.
21. Dummer, R. and e. al., *Melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up.* Annals of Oncology, 2010. **21(Suppl 5):**: p. 194-v197.
22. Robert, C., et al., *Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.* New England Journal of Medicine, 2011. **364**(26): p. 2517-26.
23. Hersh, E.M., et al., *A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma.* Investigational New Drugs, 2011. **29**(3): p. 489-98.
24. Weber, J., et al., *A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma.* Clinical Cancer Research, 2009. **15**(17): p. 5591-8.
25. Thompson, J.A., et al., *Ipilimumab in treatment-naive and previously treated patients with metastatic melanoma: retrospective analysis of efficacy and safety data from a phase II trial.* Journal of Immunotherapy, 2012. **35**(1): p. 73-7.
26. Robert C, Thomas L, and Bondarenko I, *Protocol for: Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.* N Engl J Med, 2011. **364**: p. 2517-26.
27. Hodi, F.S., et al., *Improved survival with ipilimumab in patients with metastatic melanoma.* N Engl J Med, 2010. **363**(8): p. 711-23.
28. Arzneimittelinformationen für Deutschland - Rote Liste Online. 2012 [cited 05.06.2012]; Available from: http://www.rote-liste.de.
29. Anstaltsapotheke LKI-Universitätskliniken Innsbruck, *Arzneimittelinformation und Pharmakovigilanz.* 2012.
30. Center for Drug Evaluation and Research, *Application Number: 125377Orig1s000 - Medical Review(s).* 2011.
31. Bhatia, S., et al., *Systemic therapy for metastatic melanoma in 2012: dawn of a new era.* Journal of the National Comprehensive Cancer Network, 2012. **10**(3): p. 403-12.
32. Spagnolo, F., et al., *Upcoming strategies for the treatment of metastatic melanoma.* Archives of Dermatological Research, 2012. **304**(3): p. 177-84.
33. Prieto, P.A., et al., *Cytotoxic T lymphocyte-associated antigen 4 blockade with ipilimumab: Long-term follow-up of 179 patients with metastatic melanoma.* Journal of Clinical Oncology, 2010. **28**(15).