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Vemurafenib for patients with BRAF V600E mutation positive advanced/metastatic melanoma

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1 Drug description

Generic/Brand name/ATC code:

Vemurafenib (PLX4032)/ Zelboraf™ (USA)/ L01XE15

Zelboraf™ (USA)

Developer/Company:

Originator: Plexxikon. Licensee: Hoffmann-La Roche

Roche

Description:

Mutated genes are frequently present in melanomas. One of the most common one is a mutation in BRAF, a serine-threonine kinase, which can be found in about 47% of patients with melanoma [1]. The majority of BRAF mutations (i.e. 80%-90%) are V600E mutations, followed by V600K mutations and others [1, 2]. Mutations in this protein have been found not only in approximately 50% of melanoma, but in 30-70% of thyroid tumours, in 30% of serous low-grade ovarian tumours and in 10% of colorectal cancers [3].

kinase inhibitor of the BRAF mutation

PLX4032/Vemurafenib, a kinase which also inhibits the BRAF V600E mutation, is one in a series of BRAF-kinase inhibitors: Non-selective inhibitors are sorafenib and RAF265, selective inhibitors are vemurafenib and GSK2118436 [1]. Vemurafenib showed marked selectivity in biochemical and cellular assays. Additionally it showed good oral bioavailability and was therefore further developed in human trials [4]. Preclinical studies showed that PLX4032 and its analogue PLX4720 inhibit the kinase activity of BRAF with the V600E mutation at low nanomolar concentrations, abrogate signalling through the MAP/ Mitogen-Activated protein kinase Pathway and block proliferation of cells carrying BRAF with the V600E mutation. PLX4032 therefore inhibits the growth and induces the progression in human melanoma tumours transplanted into immune-compromised mice.

None of these effects are observed in normal tissue or in tumour cells that lack a BRAF mutation [5, 6].

2 Indication

Vemurafenib is indicated for patients with BRAF V600E mutation positive advanced/metastatic unresectable melanoma as detected by an FDA-approved test (cobas® 4800 BRAF V600 mutation test by Roche Molecular Systems) [7]. Vemurafenib is not recommended for use in patients with wild-type (i.e. unmutated) BRAF melanoma.

for patients with advanced melanoma pretested for BRAF

3 Current regulatory status

approved by FDA Aug 2011, not yet by EMA, but recommended

Vemurafenib is currently not approved by the EMA, but was recommended by the Committee for Medicinal Products for Human Use (CHMP) of EMA for approval of first-in-class treatment for metastatic or unresectable melanoma in December 2011 [8]. The approval is expected for February 2012 [9].

Vemurafenib was approved by the FDA in August 2011 based on the (ongoing) BRIM-3 study [10, 11] for the treatment of patients with unresectable or metastatic melanoma with the BRAFV600E mutation as detected by an FDA-approved test.

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 [12]. 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 [13]. To confirm the diagnosis of melanoma a biopsy, at best by local excision, should be performed [12]. Median age at diagnosis is 59 years [12].

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) [14]. 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 [12]. For patients suffering from stage IV disease, sites of metastases and elevated lactate-dehydrogenase (LDH) levels are also associated with poor outcomes [13]. 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 [14].

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% [13]. Median survival is 6 to 9 months [15].

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 [16]. 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 [15].

In 2008, the EU incidence rate (per 100,000) of skin melanoma was 14.0, being 13.5 among males and 14.5 among females (overall cumulative risk of 0.93%). Mortality rate (per 100,000) was of 2.9, being 3.2 among males and 2.5 among females [17].

Metastases develop in 10-15% of patients with cutaneous melanoma [18].

The frequency of BRAF mutations ranges from 36% to 45% in primary melanomas and 42-55% in metastatic melanoma. More than 75 somatic mutations in the BRAF gene have been identified in melanoma and all mutations at V600 (74-90% V600E; 16-29% V600K) in exon 15 constitutively activate BRAF [18]. For Austria this means 25-33 patients present with BRAF mutations in metastatic melanoma each year.

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 [13]. Thus, cure is rarely possible [14].

treatment options:

Generally, metastatic melanoma is difficult to treat, because advanced melanomas are refractory to most standard systemic therapies [12]. 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), which is licensed in Austria for melanoma, is currently the most active chemotherapy and has often been used as standard comparator (as monotherapy) for new therapeutic regimens [13]. However, only 10%-20% of patients respond to this treatment, showing mainly partial remissions with a median response duration of 3-4 months [13]. DTIC is used also in polychemotherapy regimes, particularly those including Platinum.
  - fotemustine for the treatment of disseminated malignant melanoma, foremost if the tumour has spread to the brain [19].
  - 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 [14].

- 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 [14].
  - ipilimumab, a monoclonal antibody targeting the CTLA-4, was recently (2011) approved in Europe and has been added as an option for the second-line therapy of advanced melanoma [20].

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 [14].

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 [12].

To conclude: there is no standard treatment for advanced or metastatic melanoma. The best choice is the inclusion into a clinical trial. Systemic treatments actually used include dacarbazine, ipilimumab, temozolomide, vinblastine, fotemustine interleukin-2, interferons, taxanes, cisplatin or carboplatin. Different combinations are possible [21, 22]. According to the European guidelines, dacarbazine represents the reference drug for the systemic metastatic disease [22]. Non-resectable in-transit metastases or inoperable primary tumours of the limbs without additional metastases may be treated with isolated limb perfusion using e.g. melphalan and/or tumour necrosis factor alfa [22]. In any case, radiation therapy can be an option, but evidence of its efficacy are lacking [21, 22].

6 Evidence

1 RCT-interim analysis

1 phase II

Based on a literature search in Medline, EMBASE, DARE (Database of the Centre for Review Dissemination of the National Institute of Health) and Cochrane Central, one phase II and one phase III trial was identified. Both the phase III trial (i.e. the BRIM-3 study as interim analysis [23, 24]) and the phase II trial (the BRIM-2 study only as abstracts [25, 26]) are still ongoing and are evaluating the efficacy and safety of vemurafenib in patients with advanced melanoma,

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title: Improved survival with Vemurafenib in melanoma with BRAF V600E mutation [23, 24, 27]			
Study identifier	ClinicalTrials.gov Nr:NCT01006980, Roche BRIM-3 NO25026, EudraCT Nr: 2009-012293-12		
Design	Phase III, randomised (1:1 ratio), multicentre (104 centres in 12 countries world-wide), open-label, two-arm, active control		
	Duration	Enrolment: Between Jan 2010 and Dec 2010 2107 pts screened for BRAF V600 mutation, 675 pts actually enrolled Median follow-up at time of interim analysis (December 2010): I: 3.8 vs. C: 2.3 [23], updated analysis: (March 2011) I 6.2 vs. 4.5 [27] Cut-off date for final analysis: completion planned in May 2014	
Hypothesis	Superiority		
Funding	Hoffmann-La Roche		
Treatment groups	Intervention	Vemurafenib 960 mg twice daily, orally	
	Control	Dacarbazine 1000 mg/ m^2 of body surface area i.v. every 3 weeks	
Endpoints and definitions	**Overall survival** (co-primary outcome)	OS	Time from randomization to death from any cause
	Progression-**free survival** (co-primary outcome)	PFS	Time from randomization to documented disease progression or death according to RECIST version 1.1 [28]
	Best overall response rate	BORR	Total number of patients whose best overall response is complete response (CR) or partial response (PR), divided by the total number of patients in the group for which the BORR is estimated [28]
	Complete response	CR	Disappearance of all known disease [28]
	Partial response	PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters [28]
	Response duration	RD	The interval (days) between the date of the earliest qualifying response and the date of PD or death for any cause
	Time to response	TTR	Time from date of the first dose of study medication to first documentation of objective tumour response (CR or PR)
	Quality of Life	QoL	Using FACT-M
Results and analysis			
Analysis description	Primary analysis: Intention-to-treat analysis of 672 pts, interim analysis Two-sided unstratified log-rank test to compare survival rates in the two study groups. Hazard ratios for treatment with vemurafenib, as compared with dacarbazine, were estimated with the use of unstratified Cox regression, event–time distributions were estimated using the Kaplan–Meier method		

Analysis population	Characteristics	Median age (range) I: 56 yrs (21-86 yrs) vs. C: 52 yrs (17-86 yrs) males I: 59% vs. C: 54% white race I: 99% vs. C: 100%, ECOG: 0 I: 68% vs. C: 68%, ECOG 1 I: 32% vs. C:32% Disease stage: M1c I: 66% vs. C:65%, M1b I: 18% vs. C:19%, M1a I: 10% vs. C: 12%, unresectable IIIC I: 6% vs. C: 4% LDH ≤ upper limit of the normal range I: 42% vs. C: 42%	
	Inclusion	Age: ≥18 years; unresectable, previously untreated stage IIIC or stage IV melanoma, positive BRAF V600 mutation detected by the Roche investigational PCR-based Cobas 4800 BRAF V600 Mutation Test, life expectancy ≥3 months, ECOG PS 0 or 1; -adequate haematologic, hepatic, and renal function, as defined by laboratory values within 28 days prior to initiation of dosing	
	Exclusion	Cancer history within the previous 5 years (except for basal- or squamous-cell carcinoma of the skin or carcinoma of the cervix); CNS metastases, unless such metastases had been definitively treated >3 months previously with no progression and no requirement for continued glucocorticoid therapy; mean QTc interval ≥ 450 msec at screening; embolism	
Descriptive statistics and estimated variability	Treatment group	*Control (Dacarbazine)*	*Intervention (Vemurafenib)*
	Number of subjects	n = 338	n = 337
	OS (months) median/ interim [23] 95% CI median/updated analysis [27], 95% CI 6 months OS rate (%) 95% CI	 7.8 6.3 to 10.3 7.9 7.3 to 9.6 64 56 to 73	 9.2 8.0 to not reached not reached 9.6 to not reached 84 78 to 89
	Number of subjects	n = 274	n = 275
	PFS (months) median 95% CI 6 months event-free rate (%) 95% CI	1.6 1.6 to 1.7 12 7 to 18	5.3 4.9 to 6.6 47 38 to 55
	Number of subjects	n = 220	n =219
	BORR (%) 95% CI CR (n (%)) PR (n (%))	5.5 2.8 to 9.3 0 (0%) 12 (5.5%)	48.4 41.6 to 55.2 2 (0.9%) 104 (47.5%)
	Number of subjects	n = 12	n = 106
	RD (months) median 95% CI	 NR 4.60 to NR	 5.5 4.0 to 5.7

	TTR (months) median range	2.7 1.6 to 5.8	1.5 1.0 to 5.5
	QoL	-	-
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	OS	HR for death Interim updated analysis	0.37 0.44
		95%CI Interim updated analysis	0.26 to 0.55 0.33 to 0.59
		P value (interim and updated analysis)	<0.001
	PFS	HR	0.26
		95%CI	0.20;0.33
		P value	<0.001
	BORR	Point estimate	NR
		Variability	NR
		P value	<0.0001
	RD	Point estimate	NR
		Variability	NR
		P value	NR
	TTR	Point estimate	NR
		Variability	NR
		P value	NR
Comment:	**Statistical plan revision**: the original primary endpoint was OS only. After the interim analysis (at >50% of total events), the statistical plan was revised, including PFS as a co-primary end-point. **Protocol revision**: since the PFS endpoint met the statistical significance at the interim analysis, the protocol was amended on 14/01/2011 to allow patients in dacarbazine arm to cross over to vemurafenib.		

Abbreviations M1c = Metastases to other visceral sites with a normal serum LDH OR any metastasis associated with an elevated serum LDH, M1b = Lung metastases in patients with a normal serum LDH, M1a = Metastases to distant skin, subcutaneous, or lymph node sites, with a normal serum LDH, NR = not reported, ECOG PS – Eastern Cooperative Oncology Group performance status, HR = hazard ratio, CI= confidence interval.

Table 2: most frequent adverse events [23]

Grade (according to CTC version 4.0)	Outcome, n (%) Only <10%	*Control (Dacarbarzine)* (n= 282)	*Intervention (Vemurafenib)* (n=336)
Grade 2 (only <10%)	Arthralgia	1 (<1)	60 (18)
	Rash	0	33 (10)
	Fatigue	33 (12)	38 (11)
	Nausea	32 (11)	25 (7)
Grade 3 (only <5%)	Cutaneous squamous – cell carcinoma	1 (<1)	40 (12)
	Rash	0	28 (8)
	Neutropenia	15 (5)	0
Grade 4	Neutropenia	8 (3)	1 (<1)
Grade 5	Neutropenia	1 (<1)	0
All Grades	Arthralgia	9 (3)	165 (49)
	Rash	3 (1)	121 (36)
	Alopecia	6 (2)	117 (35)
	Photosensitivity reactions	10 (4)	101 (30)
	Nausea	115 (41)	101 (30)
	Diarrhoea	34 (12)	84 (25)
	Headache	26 (9)	72 (21)
Other outcomes	Patients with dose modification or interruption	44 (16)	129 (38)
	Patients interrupting only	12 (4,2)	34 (7,1)

BRIM-3: 675 pts untreated, OS and PFS as primary endpoints

In the pivotal phase III, randomised, open-label on-going BRIM-3 study (NCT01006980) [10, 23, 24], 675 previously untreated patients (17-86 years) with stage IIIc-IV metastatic melanoma presenting the BRAF V600E mutation were randomised to receive oral vemurafenib 960 mg twice daily or intravenous dacarbazine. The primary endpoints were overall survival (OS) and progression-free survival (PFS) in the intention to treat population.

interim analysis: PFS 5.3 vs. 1.6 3 months in favour of vemurafenib

BORR: I: 48% vs .C: 5%

CR only in 1% (I)

At the interim analysis median OS was 9.2 months in the vemurafenib group and 7.8 months in the control group, but these result were considered "unreliable" by the investigators due to the limited number of patients with longer periods of follow-up [24]. The OS rate also favoured patients treated with vemurafenib (I 84% vs C 64%) and risk of death was reduced by 63%. At the same time, the final analysis of PFS was performed which also showed improved results for vemurafenib (HR = 0.26; 95% CI: 0.20; 0.33; p<0.0001) [23]. Due to these results the data and safety monitoring board recommended that the protocol should be amended to allow patients to cross-over to the vemurafenib group. These changes were implemented in February 2011.

only immature/unreliable data for OS due to lack of follow-up,

since cross-over: no "mature" OS data

Nonetheless updated results for OS at a cut-off date of March 2011 are available [11] where median OS was not reached for vemurafenib (95% CI: 9.69; NR) but was 7.9 months (95% CI: 7.3; 9.6) for dacarbazine; the HR for death was with 0.44 (95% CI: 0.33; 0.59; p<0.0001) similar to that of the interim analysis.

48% vs 5% in the vemurafenib vs. dacarbazine showed confirmed objective responses. BORR in the vemurafenib groups was mainly due to partial responses, since complete responses were achieved in only 2 patients (i.e. 1%), whereas the majority that is 104 (48%) experienced partial responses. The median time to response was 1.5 months (vemurafenib) vs. 2.7 months (dacarbazine).

The most frequent adverse events (AEs) at the interim analysis were cutaneous events (rash, photosensitivity skin reactions), arthralgia, alopecia, nausea, vomiting, diarrhoea and headache. The most frequent grade 3 AE was squamous skin cell carcinoma (I 12% vs. C <1%) [23].

AE-induced modification or interruption: 7% vs. 4% in favour of dacarbazine

Overall, drug related AEs were observed in 94% in the vemurafenib group and in 69% in the dacarbazine group respectively [24]. Similarly, serious AEs were more frequent in the intervention group than in the control group (I 33% vs C 16%). Serious AEs which were classified as drug-related occurred in I 26% vs C 5%, consequently leading to dose modification or interruption in 129 of 336 patients (38%) in the vemurafenib group and in 44 of 282 patients (16%) in the dacarbazine group of which the majority were drug modifications [23]. Permanent discontinuation was observed in 6% vemurafenib group vs. 4% in the dacarbazine group [27]. 66 patients died overall in the dacarbazine group and 42 in the vemurafenib group, but the main cause of death was disease progression. Deaths due to other causes occurred in 17% in the vemurafenib group and in 5% in the dacarbazine group.

The BRIM-3 trial is ongoing. More publications are to be expected.

6.2 Efficacy and safety - further studies

BRIM 2: only as abstract, 132 pre-treated pts

RR primary endpoint: 52%

In the on-going phase II, single-arm BRIM-2 trial, is published as preliminary results, [25, 26]) only: 132 previously treated patients received oral V 960 mg, twice daily. After a median follow-up of 7 months, the best overall response rate (primary endpoint) was of 52.3% (95% CI 43; 61%): complete response rate was 2.3%. Median duration of response and median PFS were of 6.8 and 6.2 months, respectively.

The most common grade 3 AE was cutaneous squamous cell carcinoma (24.2%), the majority centrally reviewed as keratoacanthoma-type. AEs were generally reversible with dose modification or interruption. 42% of pts required dose reductions, most commonly for rash, arthralgia and LFT abnormalities.

7 Estimated costs

The costs of ipilimumab have not been determined yet in Austria. As vemurafenib is indicated as treatment of BRAF-mutated advanced/metastatic melanoma only, the companion genetic mutation test costs of about 120 € have to be taken into consideration for *all* advanced/metastatic melanoma patients.

estimated monthly costs: 7.200 - 12.620 €

The monthly costs for Zelboraf™ 240 mg 56 film tablets, with a recommended daily dose of twice 960 mg, is estimated to range between 7.200 € [29] and 12.620 € [30].

On the duration of the therapy nothing is said in the published data. Nevertheless, 6 months (time from representation till death) and more might be calculated (range 43.200 € to 75.900 €).

8 On-going research

NCT01307397: An open-label, multicentre expanded access study of RO5185426 in patients with metastatic melanoma. Phase III, open-label, non-randomised, single-arm. 900 patients *(planned)*.

Other active comparators in development

Dabrafenib (originator: GSK)

- **Dabrafenib (originator: GSK), oral.** A phase III, randomised, open-label, dacarbazine-controlled trial (NCT01227889) in 200 patients with previously untreated advanced (unresectable stage III) or metastatic (stage IV) melanoma that is BRAF mutation positive (V600E) was initiated in January 2011. Primary endpoint is PFS. Final results are expected at the end of 2012.

Trametinib (originator: Japan Tabacco; licensee: GSK)

- **Trametinib (originator: Japan Tabacco; licensee: GSK), oral.** A phase III, randomised, open-label, crossover, chemotherapy-controlled trial (NCT01245062) is ongoing in 322 patients with previously untreated advanced (unresectable stage III) or metastatic (stage IV) melanoma that is BRAF mutation positive (V600E). Primary endpoint is PFS. Final results are expected at the end of 2012.

Masitinib (originator: AB Science)

- **Masitinib (originator: AB Science), oral.** A phase III, open-label, dacarbazine-controlled trial (NCT01280565) was initiated in January 2011 in 200 (planned) patients with non-resectable or metastatic stage III or stage IV melanoma carrying a mutation in the juxta membrane domain of c-kit. Primary endpoint is PFS. Primary results are expected in December 2013.

Talminogene laherparepvec (originator: Amgen)

- **Talminogene laherparepvec (originator: Amgen), intratumoral**. It is an oncolytic Herpes Simplex Virus encoding human granulocyte macrophage-colony stimulating factor (GM-CSF) A phase III, randomised, open-label, GM-CSF-controlled trial (NCT00769704) is currently ongoing in 430 patients with stage IIIb, IIIc or stage IV unresectable melanoma. Primary endpoint is durable response rate and the estimated study completion date is June 2012.

Velimogene (originator: Vical)

- **Velimogene (originator: Vical), intratumoral**. A phase III, randomised, open-label, controlled (vs. dacarbazine or temozolamide) trial (NCT00395070) is currently ongoing in 390 patients with previously untreated stage III or IV recurrent metastatic melanoma. Estimated study completion date is June 2012.

9 Commentary

metastatic melanoma has a poor prognosis

Metastatic melanoma has a poor prognosis with a median survival for patients with stage IV melanoma ranging from 6 to 9 months and a 3-year survival rate of only 10-15% [1, 31]. Generally, metastatic melanoma is difficult to treat, because advanced melanomas are refractory to most standard systemic therapies and therapeutic options are limited [12]. Even though dacarbazine was considered as standard therapy for the treatment of systemic metastatic disease, response rates are low (7-12% of patients) [23]. Accordingly, little consensus on the standard of care exists and participation in clinical trials is highly recommended [4]. However, in 2011, ipilimumab, a new drug, was licensed in both Europe and the U.S. for the treatment of advanced/metastatic melanoma.

dacarbazine, as one option of a chemotherapeutic agent

vemurafenib approved by FDA based on interim analysis for treatment of unresectable or metastatic melanoma, although dacarbazine available

no reliable OS data available,

will not be available since cross-over was allowed after interim-analysis

In addition, the FDA approved vemurafenib in August 2011 based on the interim results of an open-label phase III trial, the BRIM-3 study [23, 24, 27] which investigated the drug for unresectable advanced/ metastatic melanoma in previously untreated patients in comparison to dacarbazine. Improved results for PFS (i.e. 3.7 months gain in PFS for patients treated with vemurafenib), as well as for OS were found. Due to the fact that median OS was not yet reached at the time of the last analysis, the FDA expects the market applicant to submit further updated results from the on-going trial with a minimum follow-up of 24 months after the last patient was enrolled into the trial [32]. Due to more favourable results for the vemurafenib group in an interim analysis, the study protocol was amended in February 2011 allowing patients to cross-over to vemurafenib, thus any further OS results will be compromised. Since PFS "has not been demonstrated as a reliable surrogate for clinical benefit in this disease setting as both clinical trials involving ipilimumab demonstrated an overall survival benefit in the absence of PFS benefit" [27], only mature OS data of "a clinically significant magnitude" would "represent direct evidence of clinical benefit" [27].

Europe: not yet approved by EMA

expected for Feb 2012

In Europe, vemurafenib is currently not yet approved by the EMA, but the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending approval as first-in-class treatment for metastatic or unresectable melanoma in December 2011 [8]. The approval is expected for February 2012. It will be of interest, if the EMA will adopt a more narrow indication than the FDA, in terms of restricting therapy with vemurafenib to the first-line setting. Even though the BRIM-3 trial had enrolled only *un*treated patients, this is not reflected in the label approved in the U.S. Differences between the two agencies also occurred for ipilimumab, which was licensed for previously *treated* patients in Europe [33] and for unresectable or metastatic melanoma without further restrictions in the U.S. [34]. It is therefore unknown what the optimal sequencing of these therapies is and how efficacious ipilimumab would be in patients pretreated with vemurafenib. Recent trial results report that a combination therapy of ipilimumab with dacarbazine showed an OS benefit of 2.1 months, but with 56.3% Grade 3 or 4 AE [35].

resistance eventually develops

resistance: underlying mechanisms are not well understood

even with response: no difference in survival

Even though the underlying mechanisms are not well understood yet [36], resistance to vemurafenib eventually develops and patients relapse despite initial response. "Most concerning is the non-clinical data suggesting that treatment with vemurafenib and other B-Raf inhibitors in the setting of a RAS mutation is pro-proliferative"…… A post-hoc exploratory analysis was conducted in which patients who had a reduction in target lesion size but had a progressive event with a new lesion were identified and overall survival was compared to those patients who had progressive disease with no evidence of tumour response. Conceivably, the tumours of those patients who developed new lesions in the setting of their target lesions decreasing in size developed an acquired resistance to therapy while the tumours of those patients who did not have a response had a primary resistance to therapy. It is interesting to see that there is no difference in survival for the two groups, suggesting that the patients who had an initial response in their target lesions did not have a survival benefit compared to the patients who were primarily resistant to the tumour" [27].

combination therapies, new therapies in development

It might thus be the case, that by exploring these mechanisms improved outcomes with vemurafenib therapy are possible. To mitigate the problem of resistance, a combination of therapies is also suggested [36], which would increase costs and potentially adverse events too. The choice of which combination of agents to use in any given situation remains to be determined and represents a challenge to the field [4], foremost since several other therapies (e.g. dabrafenib, trametinib, masitinib, talminogene laherparepvec, velimogene) all targeting mutation-specific melanoma are in development [4].

Cobas 4800 BRAF V600 test has small spectrum

Another issue concerns the selection of patients eligible for vermurafenib therapy. In the BRIM-3 trial, inclusion was tied to BRAF mutation detected with the Roche investigational Cobas 4800 BRAF V600 Mutation Test. Since the test used to detect the V600 mutations demonstrated to be specific for the V600E mutation, the FDA has consequently approved vemurafenib for patients with that mutation only. Control sequencing (Sanger method, reference standard) of BRAF V600 data were available for 542 patients (214 from phase III; 328 from phase II): V600K mutation was found in 40 patients only, 26 of whom were positive to the Cobas test (BRAF V600E) and 14 were not. Other mutations were not detected by the test [7]. Even though patients were selected using the Cobas Test, further characteristics or markers might be discovered which allow identification of patients with a higher potential to benefit.

combination of therapies: ev. less resistance, but more costs and AE

cutaneous squamous cell carcinoma as secondary cancer/ AE needs special attention

Finally about one third of the patients treated with vemurafenib develop – as a side effect – squamous cell carcinoma of the skin. Other frequent AE are: Arthralgia, rash and alopecia. The rapid appearance of these cutaneous squamous cell carcinoma may result from a shared risk factor with melanoma, the ultraviolet light exposure. This second cancer indicates a need for additional monitoring to survey patients with specific risk factors for this secondary cancer (e.g. smoking, alcohol, family history etc.) [37, 38]. Although the response rates are higher with vemurafenib, the toxicity is considerably higher compared to dacarbazin. Special attention is needed to address the described cutaneous squamous cell carcinoma.

no information on QoL

No data and information is available on quality of life.

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