Horizon Scanning in Oncology

Dabrafenib (Tafinlar®) in previously untreated subjects with BRAF mutation-positive advanced (stage III) or metastatic (stage IV) melanoma

Ludwig Boltzmann Institut
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1 Drug description

Generic/Brand name/ATC code:

Dabrafenib/Tafinlar®/GSK2118436

Developer/Company:

GlaxoSmithKline Trading Services Limited

Description:

dabrafenib inhibits BRAF

Dabrafenib is a selective adenosine triphosphatase (ATP)-competitive rapidly accelerated fibrosarcoma (RAF) kinase inhibitor and it inhibits, based on in-vitro data, all types of BRAF protein kinase activity [1]. Since BRAF is involved in stimulating proliferation, this gene, when mutated, may lead to uncontrolled tumor cell division and the development of cancer. Dabrafenib is exclusively used for the treatment of patients with a melanoma caused by a BRAF V600 mutation [2].

a BRAF V600 mutation is mandatory

The therapy with dabrafenib requires the supervision by a doctor experienced in cancer treatment. Before the prescription of the drug, patients have to undergo a test to confirm tumor BRAF V600 mutation [2].

capsules for oral administration

The recommended dose of dabrafenib is 150 mg twice a day. 50 and 75 mg capsules are available for oral administration. Therapy should be continued until the disease deteriorates or unacceptable adverse effects occur [2].

2 Indication

patients with BRAF mutation-positive melanoma

Previously untreated subjects with BRAF mutation-positive advanced (stage III) or metastatic (stage IV) melanoma.

3 Current regulatory status

EMA: monotherapy for adults with BRAF mutation-positive melanoma

In August 2013, the European Medicines Agency (EMA) authorized dabrafenib as “monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600 mutation”. BRAF V600 mutation must be detected by a test and the drug should not be used in patients with wild-type BRAF melanoma [2]. The market authorisation followed the recommendation of the Committee for Medicinal Products for Human Use (CHMP), which stated a positive benefit-to-risk balance for the drug [3].

FDA: treatment of patients with melanoma with BRAF V600E mutation detected by an FDA-approved test

In May 2013 the U.S. Food and Drug Administration (FDA) authorized dabrafenib “for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test”. The drug is not indicated for the treatment of wild-type BRAF melanoma [4].

4 Burden of disease

severe type of skin cancer with rising incidence

Melanoma is the most severe type of skin cancer with its incidence increasing worldwide. While in 1990 the estimated age-standardized incidence rates of melanoma in men and women were 2.3 and 2.2/100,000 people, respectively, in 2008 they were 3.1 and 2.8/100,000 people. According to the National Cancer Institute's SEER Cancer Statistics Review, the age-adjusted incidence rate of melanoma in the US was 21.1/100,000 people per year (based on cases diagnosed in 2006-2010). Melanoma was diagnosed at a medium age of 61 years. At the same time the age-standardized mortality rate was 2.7/100,000 people with a medium age of death of 69 years [5]. The incidence of melanoma is rising in Central Europe as well, having reached a rate of 10-15/100,000 people in the year 2000 [6]. About 10-15% of all patients with cutaneous melanoma will develop metastases [7].
About 50% of all melanomas have BRAF mutations and more than 75 somatic mutations in the BRAF gene have been identified in melanoma. All of these mutations are at V600 with 80-90% of these showing a V600E (i.e. V600Glu) and 10-20% a V600K (i.e. V600Lys) mutation [8, 9]. In small subsets of melanoma also other activating mutations like c-KIT mutations or platelet-derived growth factor receptor alpha (PDGFRA) mutations have been described [10, 11].

genetic and environmental risk factors
four stages of melanoma according to the TNM system

For the development of melanoma, genetic and environmental risk factors can be identified. Ten percent of melanomas are induced by familial factors and it is assumed that multiple genes are involved. Further 10-20% of melanomas develop from atypical nevi, ascribing a 3-20 times higher risk to people with this feature. Furthermore it is suspected that people with a high number of nevi (more than 25) are at greater risk of developing melanoma. Other risk factors include the exposure to sunlight and ultraviolet radiation (e.g. tanning beds) and phenotypic traits such as light skin [6, 12].

The seventh edition of the tumor node metastasis (TNM) system classifies melanoma into four stages (I-IV). The division is based on the thickness, mitotic rate and ulceration of the primary tumor (T), the affection of lymph nodes (N) including satellite lesions and in-transit metastases and the presence of distant metastases (M). Further prognostic factors include age, gender and location whereas younger patients, women and patients with tumors affecting the upper extremities have a better prognosis [13]. While stages I and II describe local early melanomas, stages III and IV indicate more advanced cancer [14]. Stage III includes the affection of regional lymph nodes or the presence of satellite metastases or in-transit metastases and stage IV is characterized by the presence of distant metastases. There are subclassifications for all stages [13].

about 65 metastatic melanomas with BRAF mutations in Austria per year

In 2010, 1,436 people in Austria were diagnosed with melanoma, which correlates with an age-standardized incidence rate of 11.8/100,000 people [15]. Of those, about 9% had already disseminated tumors or died from melanoma [16], resulting in about 130 persons with advanced melanoma per year. Considering the proportion of BRAF mutations in melanoma, the number of patients present with BRAF-positive metastatic melanoma each year is about 65 patients in Austria. The age-standardized mortality rate was 2.4/100,000 people, which means that 376 Austrians died of melanoma in 2010 [17]. Both melanoma incidence and mortality tend to be higher in men [15, 17].

5 Current treatment

treatment focuses on symptom reduction, prevention of tumour spread and palliative care

Since melanoma that has spread to distant sites (e.g. unresectable stage III and stage IV) is rarely curable, the treatment of these melanomas focuses on the reduction of symptoms caused by metastases, the prevention of further tumor spread and on palliative care [10]. Some approaches may provide clinically relevant benefits for appropriately chosen patient groups with metastatic melanoma. These include surgical metastasectomy, immunotherapy, targeted therapy and radiation therapy to symptomatic sites of metastases [18]. Until recently, cytotoxic chemotherapy was widely used as standard treatment of metastatic melanoma.

surgery

- Surgery: Surgical excision is the primary treatment for localized melanoma. But also for metastatic melanoma, it is an option to delay the need for systemic treatment, especially in patients with a very limited number of metastases. Metastasectomy may also be used to eradicate residual disease with patients having shown good response to systemic therapy [18].

chemotherapy

- Chemotherapy: Common agents being used include dacarbazine, temozolomide, or fotemustine. Their response rates are typically less than 20 percent and they have not been shown to improve overall survival in patients with advanced melanoma [10]. Consequently the role of chemotherapy is limited to patients who are not candidates for treatment with immunotherapy and those who have progressed after optimal treatment with other options [18].

immunotherapy

- Immunotherapy: Immunotherapy is an established method for the treatment of metastatic melanoma. It includes treatment with high-dose interleukin-2 (IL-2) that has shown long-term disease-free survival in a small minority of treated patients and may result in cure. Because of its severe toxicities (cardiovascular, respiratory, infectious), it remains a treatment option only for patients in good condition [18].
  Treatment with ipilimumab, a monoclonal antibody that targets CTLA-4, significantly increases median overall survival in both previously untreated and previously treated patients with metastatic or unresectable melanoma, but it is also associated with a variety of clinically significant autoimmune side effects [18].

targeted therapy

- Targeted therapy: Approximately one half of melanomas have a V600 BRAF mutation that activates the mitogen-activated protein kinase (MAPK) pathway. BRAF inhibition produces rapid tumor regression in the majority of patients with V600-mutant melanoma, including those with an extensive tumor burden and disease-related symptoms. For the inhibition of BRAF, vemurafenib or dabrafenib are currently used. The downstream inhibition of the mitogen-activated ERK-[extracellular signal-regulated kinase]activating kinase (MEK) with trametinib may also be a treatment option [18]. Furthermore, for patients with melanoma harbouring c-KIT or PDGFRA mutations, early data suggest that therapy with imatinib or nilotenib may be a treatment option [10, 19, 20].

radiation therapy

- Radiation therapy: Radiation therapy may play a palliative role for symptomatic localized areas of disease or as a whole-brain radiation therapy which can prolong survival, especially if the tumor outside the brain is controlled [10, 18].

6 Evidence

A systematic literature search was conducted on the 9th of October 2013 in medical databases Ovid Medline/Pubmed, EMBASE, the Cochrane Library and the CRD, and resulted in 288 records. Of those, 9 records reporting results of one phase III trial [21-25] and 2 phase I/II trials [26-29] were included.

In addition, a hand search including reference lists of topic-related reviews or articles and the websites of the EMA and the FDA was performed, resulting in no additional publications. Among the material that the manufacturer had sent on request, one poster publication of an already identified conference abstract was retrieved [30].

1 phase III trial and 2 phase II trials

In summary, 3 full-text publications and 7 conference abstracts or poster publications reporting on 1 phase III trial [22-24, 30] and 2 phase I/II trials [11-14] were included.

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial (BREAK-3)		
Study identifier	NCT 01227889, EudraCT 2009-015298-11	
Design	Randomised controlled, open-label, international, multi-centre trial; crossover assignment; N = 250 (187 vs. 63); allocation randomly (3:1 ratio) to dabrafenib or dacarbazine (DTIC);	
	Duration	*Enrolment:* December 2010 to September 2011 *Median follow-up:* Dabrafenib: 10.5 months (NR) DTIC: 9.9 months (NR) *Cut-off dates for analyses:* June 2012 (and December 2012 for OS)
Hypothesis	Superiority	
Funding	GlaxoSmithKline	
Treatment groups	Intervention (n=187)	Dabrafenib 150 mg twice daily PO
	Control (n=63)	Dacarbazine (DTIC) 1000 mg/m², every 3 weeks until initial progression; Subjects who initially receive DTIC will be allowed to receive dabrafenib 150 mg twice daily after initial progression.

Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from randomisation to the earliest date of radiographic or photographic disease progression or death due to any cause. PFS was assessed by the individual investigator.
	Overall survival (secondary outcome)	OS	Time from randomisation to death due to any cause.
	Progression-free survival 2 (secondary outcome)	PFS 2	For subjects randomised to the DTIC treatment group the time to progression or death after cross-over to dabrafenib after initial progression on DTIC.
	Objective response rate (secondary outcome)	ORR	Percentage of subjects achieving either a complete or partial tumour response (CR/PR) according to RECIST version 1.1 (assessed by the investigator and a masked independent review committee (IRC)).
	Progression-free survival (secondary outcome)	PFS - I	Progression-free survival as assessed by the IRC.
	Duration of response (secondary outcome)	DOR	Time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause.
	Quality of life (secondary outcome)	QoL	Patient self-reported; EORTC-QLQ-C30 and EQ-5D were used for evaluation.
	Safety and tolerability (secondary outcome)	S+T	NR
Results and analysis			
Analysis description	ITT-analysis; Primary endpoint: PFS assessed by the individual investigator; sample size: 200 patients were needed to observe 102 PFS events with statistical power of 99.7% to detect a HR of 0.33 (median PFS of 2 months in patients who received DTIC and 6 months in patients who received dabrafenib) using a one-sided log-rank test with α=0.02.		
Analysis population	Inclusion	✵ adults at least 18 years of age ✵ advanced (unresectable stage III) or metastatic (stage IV) melanoma that is BRAF-mutation positive (V600E) ✵ treatment-naive for advanced (unresectable) or metastatic melanoma, with the exception of Interleukin 2 (IL-2) ✵ measurable disease according to RECIST 1.1 criteria ✵ Eastern Cooperative Oncology Group (ECOG) performance status of 0-1	
	Exclusion	✵ cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy or surgery) within 4 weeks ✵ previous treatment for metastatic melanoma, including treatment with BRAF or MEK inhibitor ✵ previous malignancy within the past 5 years ✵ history of Human Immunodeficiency Virus infection ✵ active central nervous system disease ✵ acute coronary syndrome, coronary angioplasty, placement of stents or cardiac arrhythmia (other than sinus arrhythmias) within the previous 24 weeks	
	Characteristics	Median age (years): 50 (21-82) vs. 53 (22-93)	

		Female (%): 41 vs. 40 Ethnicity_Caucasian/Asian/Others (%): 100/0/0 vs. 98/0/2 ECOG performance status 0/≥1/unknown (%): 70/25/5 vs. 66/33/1 BRAF V600 mutation subtype_V600E/V600K (%): 98/2 vs. 99/1 Disease staging_unresectable III+IVM1a+IVb/IVM1c (%): 33/67 vs. 34/66 Baseline LDH_elevated/normal/unknown (%): 27/63/10 vs. 35/62/3 No previous treatment/previous treatment (%): 2/98 vs. 3/97	
Results (interim analysis 10 mo f/up)	Treatment group	DTIC	Dabrafenib
	Number of subjects	N = 63	N = 187
	PFS (months) median 95% CI	 2.7 1.5 - 3.2	 6.9 5.2 - 9.0
	ORR (%) median 95% CI	 24 14.0 - 36.2	 59 51.4 - 66.0
	DOR (months) median 95% CI	 7.6 5.0 - 9.7	 8.0 6.6 - 11.5
Results (interim analysis 15 mo f/up)	OS (months) median 95% CI	 15.6 12.7 - NR	 18.2 16.6 -NR
Effect estimate per comparison(interim analysis 10 mo f/up)	*Comparison groups*		*Dabrafenib vs. DTIC*
	PFS	HR	0.37
		95% CI	0.24 - 0.58
		P value	<0.0001
	ORR	Difference in response rates	35%
		95% CI	20.9% - 48.7%
		P value	NR
	DR	Point estimate	NR
		95% CI	NR
		P value	NR
Effect estimate per comparison(interim analysis 15 mo f/up)	OS	HR	0.76
		95% CI	0.48 - 1.21
		P value	NR

Abbreviations: BRAF … B type of rapidly accelerated fibrosarcoma; CI … Confidence interval; DOR … Duration of response; DTIC … Dacarbazine; ECOG … Eastern Cooperative Oncology Group; f/up …Follow-up; HR … Hazard ratio; ITT … Intent-to-treat; mo…Months; MEK … Mitogen-activated ERK-[extracellular signal-regulated kinase] activating kinase; NR … Not reported; ORR … Overall response rate; OS … Overall survival; PFS … Progression-free survival; QoL … Quality of life; RECIST … Response Evaluation Criteria in Solid Tumors; S + T… Safety and tolerability

Table 2: Most frequent treatment-related adverse events (interim analysis 10 mo f/up)

BREAK-3 (NCT 01227889)			
Grade (according to CTC version 4.0)	**Outcome** [n (%)]	**Dabrafenib** (n=187)	**DTIC** (n=59)
Serious adverse events (SAE)	Any event	53 (28)	14 (24)
	Squamous cell carcinoma, keratoacanthoma	18 (10)	0
	Pyrexia	9 (5)	0
	Basal cell carcinoma	4 (2)	0
	Chills	3 (2)	0
	Atrial fibrillation	3 (2)	0
	Ejection fraction decreased	3 (2)	0
	Malignant melanoma	3 (2)	0
	Myocardial infarction	2 (1)	0
	Vomiting	2 (1)	1 (2)
	Hypotension	2 (1)	0
All Grades	Hyperkeratosis	67 (36)	1 (2)
	Rash	56 (30)	0
	Alopecia	50 (27)	2 (3)
	Skin papilloma	42 (22)	0
	Palmar-plantar hyperkeratosis	36 (19)	1 (2)
	Arthralgia	36 (19)	0
	Fatigue	33 (18)	13 (22)
	Headache	34 (18)	2 (3)
	Pyrexia	30 (16)	0
	Nausea	26 (14)	23 (39)
	Asthenia	27 (14)	7 (12)
	Squamous cell carcinoma, keratoacanthoma	18 (10)	0
Grade 3	Squamous cell carcinoma, keratoacanthoma	14 (7)	0
	Pyrexia	5 (3)	0
	Palmar-plantar hyperkeratosis	4 (2)	0
	Arthralgia	2 (1)	0
	Fatigue	2 (1)	0
	Hyperkeratosis	2 (1)	0
	Alopecia	1 (<1)	0
Grade 4	Hyperkeratosis	1 (<1)	0

Abbreviations: CTC … Common Terminology Criteria; DTIC … dacarbazine; SAE … Serious adverse event

ongoing international open-label RCT

The BREAK-3 trial is an ongoing international, multi-centre, open-label phase III randomised controlled trial (RCT) with study centres in the European Union, North America and Australia [6-10]. The aim of the study is to compare the efficacy, safety, and tolerability of dabrafenib to dacarbazine (DTIC), in subjects with BRAF-mutant advanced (stage III) or metastatic (stage IV) melanoma and an ECOG performance status of 0 or 1. 250 patients aged 18 years or older with previously untreated stage IV or unresectable stage III BRAF V600E mutation-positive melanoma were included. 187 patients were randomly assigned to dabrafenib 150 mg orally twice daily, and 63 were allocated to DTIC, 1000 mg/m^2 every 3 weeks until initial progression. Subjects who progressed on DTIC were allowed to cross over to an optional extension arm of the study to receive dabrafenib.

dabrafenib vs. dacarbazine (DTIC)

The included patients were about 50 years of age and by the majority men (60%). Nearly all of them were Caucasians [24].

interim analysis after 10 months follow-up

In an interim analysis in June 2012 after a median follow-up of about 10 months, 38% of patients treated with dabrafenib and 8% of patients treated with DTIC were still on therapy and continue to be followed for progression [22]. For the primary endpoint, progression-free survival (PFS), the interim analysis showed a statistically significant improvement in favour of the intervention group assessed by the individual investigator (dabrafenib 6.9 months vs. DTIC 2.9 months; HR 0.37 (95% CI 0.24 - 0.58; p<0.0001). The secondary end point, objective response rate (ORR) was higher with 59% in the dabrafenib compared with 24% in the DTIC group, but it was not reported whether these were complete responses (CR) or partial responses (PR). The estimated median duration of response (DOR) was 8.0 and 7.6 months, respectively [22].

significantly longer PFS

no significant difference in OS at 15 months follow-up, but data are immature

At the time of an updated interim analysis in December 2012 (median follow-up of about 15 months), 78 patients (42%) in the dabrafenib group and 28 patients (44%) in the DTIC group had died. There was no statistically significant difference in overall survival (OS) (dabrafenib 18.2 months vs. DTIC 15.6 months; HR 0.76 (95% CI 0.48 - 1.21)), but data are still not mature and may be confounded by the crossover of patients in the DTIC group after disease progression to dabrafenib (at the date of analysis 36 of the 63 patients in the DTIC group had crossed over) [22].

no meaningful data on quality of life

Quality of life (QOL) was measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and the EuroQol 5D (EQ-5D) questionnaires. There was no statistically significant or clinically meaningful difference between dabrafenib and DTIC in overall global health status scores, the functionality scores and cognitive functioning scores at week 6 and week 12, but improvements in the emotional functioning scores and in symptom dimensions in favour of dabrafenib were reported without information on the statistical significance [21].

Nevertheless, there are no meaningful data on QoL after week 15 of the study period, since the number of assessments decreased throughout the trial [31].

At the time of the interim analysis in June 2012 there was no difference in serious adverse events (SAE) between the two treatment groups (dabrafenib 28% vs. DTIC 24%), with one fatal SAE in the intervention group (myocardial infarction/acute coronary syndrome, possibly related to study treatment) and none in the DTIC group. The most frequent SAEs in the dabrafenib group were squamous cell carcinoma/keratoacanthoma (10%) and pyrexia (5%), while none of these SAEs occurred in the DTIC group (see Table 2) [22].

number of SAEs comparable

most frequent SAE: squamous cell carcinoma/keratoacanthoma and pyrexia

In general, the majority of the adverse events (AEs) were lower-grade, and toxic effects of grade 3 - 4 were rather uncommon. In patients receiving dabrafenib, the most common AEs were hyperkeratosis, rash, alopecia, and skin papillomas, while nausea, vomiting, fatigue, and neutropenia were more frequent in the DTIC group. A publication presenting data of an earlier interim analysis in December 2011 (5 months follow-up) reported a dose reduction of dabrafenib due to an AE in 52 (28%) patients, and 5 (3%) patients discontinued the drug because of AEs. In the DTIC group, dose reduction was needed in 10 (17%) patients and 2 (3%) patients discontinued the drug [24].

majority of the AEs were lower-grade

6.2 Efficacy and safety – further studies

A multicentre, single-arm phase II trial (BREAK-2) [26, 29] assessed the safety and clinical activity of dabrafenib. 76 patients (83%) with histologically confirmed stage IV BRAF V600E and 16 patients (17%) with histologically confirmed stage IV BRAF V600K-mutant melanoma with or without (16%) previous systemic therapy received orally 150 mg dabrafenib twice daily until disease progression, death, or unacceptable AEs. Confirmed response was reported in 59% (95% CI 48.2 - 70.3) of the BRAF V600E group and in 13% (95% CI 0 - 28.7) of the BRAF V600K group. Median PFS in the BRAF V600E and BRAF V600K groups was 6.3 months and 4.5 months, and median OS was 13.1 months and 12.9 months, respectively.
The most common AEs were arthralgia (33%), hyperkeratosis (27%), and pyrexia (24%). SAEs occurred in 27% of the patients and 10% of all patients developed squamous cell carcinoma.

single-arm phase II trial

about 13 months median OS

AEs: arthralgia, hyperkeratosis and pyrexia

Another multicentre, open-label, phase II trial (BREAK-MB) [27, 28] evaluated the effect of 150 mg dabrafenib twice a day in 172 patients with histologically confirmed V600Glu or V600Lys BRAF-mutant melanoma with (cohort A) or without previous local treatment for brain metastases (cohort B).
39.2% (95% CI 28.0 - 51.2) of the patients with V600Glu BRAF-mutant melanoma in cohort A and 30.8%, (95% CI 19.9 - 43.4) in cohort B achieved an overall intracranial response. Of the patients with V600Lys BRAF-mutant melanoma, 6.7% (95% CI 0.2 - 31.9) in cohort A and 22.2% (95% CI 6.4 - 47.6) in cohort B achieved an overall intracranial response.
Treatment-related AEs of grade 3 or worse occurred in 22% of all patients and (6%) patients developed squamous-cell carcinoma. The three most frequent AEs were pyrexia (6%), intracranial haemorrhage (6%) and squamous-cell carcinoma (6%).

second open-label phase II trial

overall intracranial response: 6.7 to 39.2% depending on subtype of mutation and on previous treatment

AEs: pyrexia, intracranial haemorrhage, squamous -cell carcinoma

7 Estimated costs

monthly costs: € 8,550

For Austria, the price of dabrafenib is not known yet. In Germany one package of dabrafenib containing 120 75 mg tablets will cost € 8,551 [32]. For patients with BRAF mutation-positive advanced or metastatic melanoma, the recommended dose is 150 mg twice daily as a continuous treatment. This results in costs of about € 285 per day, which equals € 8,550 per month.

8 Ongoing research

3 further phase III trials for BRAF V600-positive melanoma

Besides the BREAK-3 trial (NCT 01227889), of which interim results have been presented in this report, 3 further on-going phase III trials investigating dabrafenib were identified by a search in the databases ClinicalTrials.gov and cinicaltrialsregister.eu. All trials are conducted in patients with BRAF mutation-positive melanoma.

NCT01584648 (EudraCT 2011-006087-49): A randomised, double-blind study for dabrafenib in combination with the MEK inhibitor trametinib to dabrafenib alone as first-line therapy in subjects with unresectable (stage IIIC) or metastatic (stage IV) $BRAF^{V600E/K}$ mutation-positive cutaneous melanoma. The completion of the study is planned for January 2015.

NCT01682083 (EudraCT 2012-001266-15): A randomised double-blind study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high-risk $BRAF^{V600}$ mutation-positive melanoma after surgical resection. The estimated study completion date is July 2015.

NCT01597908 (EudraCT 2011-006088-23): A randomised, open-label study comparing the combination of dabrafenib and trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIC) or metastatic (stage IV) $BRAF^{V600E/K}$ mutation-positive cutaneous melanoma. The estimated study completion date is June 2015.

18 phase I/II trials for other types of BRAF mutation-positive cancer

In addition, there are 6 ongoing phase I/II trials for dabrafenib alone or in combination for patients with BRAF mutation-positive melanoma and 12 ongoing phase I/II trials investigating dabrafenib in various other types of BRAF mutation-positive cancer (e.g. non-small cell lung cancer, thyroid cancer, colorectal cancer).

9 Commentary

metastatic melanoma has poor prognosis

dacarbazine was considered as standard therapy

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% [33, 34]. Generally, metastatic melanoma is difficult to treat because advanced melanomas are refractory to most standard systemic therapies and therapeutic options are limited [10]. Even though dacarbazine was considered as standard therapy for the treatment of systemic metastatic disease, response rates are low (7-12% of patients) [34]. Accordingly, little consensus on the standard of care exists and participation in

clinical trials is highly recommended [35]. For patients with BRAF-positive melanoma, targeted therapies focusing on the inhibition of BRAF or MEK have recently been approved [10].

dabrafenib approved by FDA and EMA

In May and August 2013, respectively, the BRAF inhibitor dabrafenib was approved by the FDA and the EMA for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600 mutation. Both approvals were mainly based on the interim results of one ongoing phase III trial [2, 4]. While the EMA has licensed dabrafenib for all types of V600 mutation, the FDA has limited its approval to patients with V600E mutations only. This is due to a different assessment of the phase II-trial results by the authorities. The reviewers of the FDA pointed out that the antitumor activity in V600K patients was limited and V600K patients may represent a distinct subset of melanoma patients with distinct clinicopathologic features [36]. In contrast, the committee for medicinal products at the EMA concluded that, based on the same results, there was enough evidence for a broader indication of "V600 mutation", although the inhibiting activity of dabrafenib seems to be lower in V600K patients [31]. Aside from this, there are no limitations in the European or US approval regarding the pretreatment of the patients, although the confirmatory trial had been restricted to previously untreated patients only.

EMA and FDA differ in assessment of benefit for V600K patients

one RCT comparing dabrafenib to DTIC

significantly longer PFS

no difference in OS

In this trial (BREAK-3) [22-24, 30], dabrafenib was investigated as first-line therapy in comparison to standard chemotherapy with DTIC. For patients in the chemotherapy group, crossing over to dabrafenib was allowed after initial disease progression. After a median follow-up of about 10 months, statistically significant better PFS (6.9 months vs. 2.7 months) and ORR (59% vs. 24%) for dabrafenib were reported. At the time of a further interim analysis after 15 months follow-up, OS was comparable between the two groups (HR 0.76, 95% CI 0.48 - 1.21), but this HR is uncertain because the OS data were not mature and the results may be confounded by a cross-over rate of 59% of all patients in the DTIC group.

most AEs were lower-grade

number of SAEs comparable

10% of the patients developed squamous cell carcinoma of the skin as secondary tumor

The majority of AEs was lower-grade and there were quite similar rates of serious AEs of about 25% in both groups. The most frequent AEs in the dabrafenib group were hyperkeratosis, rash, alopecia, and skin papillomas, while nausea, vomiting, fatigue, and neutropenia were more frequent in patients treated with DTIC. Beside this, it has to be mentioned that 10% of the patients treated with dabrafenib developed squamous cell carcinoma of the skin. This development of cutaneous squamous cell carcinoma may result from a shared risk factor with melanoma, the ultraviolet light exposure, and therefore the need for additional monitoring to survey patients with specific risk factors for this secondary cancer (e.g. smoking, alcohol, family history, etc.) may be indicated [37, 38]. To date, it is unknown whether a longer duration of treatment or a combination of dabrafenib with other drugs lead to an even higher rate of patients developing secondary cancers. These questions may in part be answered by the currently ongoing phase III trials investigating the safety and efficacy of dabrafenib in combination with the MEK inhibitor trametinib.

no meaningful results for QoL

Although health-related QoL was defined as a secondary endpoint in the BREAK-3 trial, to date no meaningful results are available, since the number of assessments decreased throughout the trial and data were only reported for the first 15 weeks [31].

development of resistance to BRAF inhibitor

Despite improvement in PFS and a good response rate under treatment with BRAF inhibitors compared to standard chemotherapy, the majority of patients will develop disease progression following tumour regression within 6-8 months [34, 39]. For this acquired resistance of melanoma to BRAF inhibitors, several mechanisms have been described in the literature, and due to further explorations of these mechanisms improved outcomes with BRAF inhibitor therapy might be possible. Therefore a number of studies are either underway or planned to determine the best strategies in overcoming and/or delaying this intrinsic and acquired resistance [40].

a number of studies are underway to overcome this resistance

dabrafenib has longer PFS but higher toxicity

actual costs for Austria are as yet unknown

In summary, on the one hand, results of the BREAK-3 trial indicate higher response rates and a longer PFS with dabrafenib compared to standard chemotherapy. But on the other hand, one has to consider a quite high toxicity and especially a rapid development of cutaneous squamous cell carcinoma as a secondary cancer under treatment with dabrafenib. Furthermore, meaningful data on patients' quality of life are not available yet and the actual costs for the treatment of melanoma patients with dabrafenib for Austria are not yet known. One also has to consider that expenses in future will be double or even higher if dabrafenib will be combined with other new agents like trametinib, a combination which for instance is currently under investigation.

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