Horizon Scanning in Oncology

Trametinib for advanced or metastatic BRAF V600 mutation-positive melanoma

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1 Drug description

Generic/Brand name/ATC code:

Trametinib, GSK1120212/not available yet/L01X

Developer/Company:

GlaxoSmithKline (GSK)

Description:

Mutated genes are frequently present in melanomas. In particular, activating mutations in BRAF gene which resides on chromosome 7 q occur frequently in human melanoma, thus constituting a possible target for molecular therapy [1]. The BRAF protein, a critical serine/threonine kinase in the RAS/mitogen-activated protein kinase pathway, is activated by somatic mutation in about 50 % of melanoma tumours [2, 3]. The most common BRAF mutations involve the kinase domain, leading to constitutive activation of the protein, which results in an increase of its basal kinase activity. The majority of BRAF mutations (i.e. 80 %-90 %) are V600E mutations, followed by V600K mutations and others [2, 4]. These mutations have been found not only in melanoma, but also in 30-70 % of papillary thyroid tumours, in 30 % of serous low-grade ovarian tumours, in 15 % of cholangiocarcinomas and in 10 % of colorectal cancers [5].

trametinib indicated for metastatic melanoma with BRAF V600 mutations

The first in class selective inhibitor of the BRAF serine-threonine kinase is vemurafenib which is approved in the USA and in Europe for melanoma treatment. Since mutations of BRAF result from the extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase pathway (MEK-ERK) in unregulated cell proliferation [3, 6, 7], direct inhibition of MEK has also proven to be effective in reducing melanoma cell proliferation. Trametinib, a MEK 1/2 kinase inhibitor, reduces growth factor-mediated cell signalling and cellular proliferation in various cancers with mutant BRAF [3, 8]. Since trametinib is only indicated for malignant melanomas with BRAF V600 mutations, testing of presence of these mutations prior to treatment initiation has to be performed [7].

administered orally 2 mg/d

Trametinib is administered orally at a recommended dose of 2 mg/day until disease progression or unacceptable toxicity [9].

2 Indication

Trametinib is indicated for the treatment of patients with advanced (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive malignant melanoma.

3 Current regulatory status

neither licensed in Europe nor in the U.S.

Trametinib is currently neither licensed in Europe nor in the U.S., but according to a press release GSK announced the filing of marketing applications in August 2012 [10].

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 [11]. 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 [12]. To confirm the diagnosis of melanoma a biopsy, at best by local excision, should be performed [11]. Median age at diagnosis is 59 years [11].

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 (i.e. according to the Breslow criteria for microstaging), 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) [13]. 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 [11]. For patients suffering from stage IV disease, sites of metastases and elevated lactate-dehydrogenase (LDH) levels are also associated with poor outcomes [12]. 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 [13].

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 % [12]. Median survival is 6 to 9 months [14].

about 30 patients/year with BRAF mutations in metastatic melanoma in Austria

In 2008, 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 [15]. 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 [14]. The fre-

quency 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 [17]. For Austria this means 25-33 patients present with BRAF mutations in metastatic melanoma each year.

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 [12].

cure not possible treatment options:

Treatment options for metastatic melanoma are:

- Chemotherapy:

chemotherapy:

  - dacarbazine (DTIC), has been the standard comparator (as monotherapy) for new therapeutic regimens [12]. However, only 10 %-20 % of patients respond to this treatment, showing mainly partial remissions with a median response duration of 3-4 months [12].

dacarabazine,

  - fotemustine, also licensed for disseminated malignant melanoma, foremost if the tumour has spread to the brain, is an option especially for the 2nd line treatment [18].

fotemustine,

  - 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 [13].

others …

- ipilimumab a monoclonal antibody targeting the CTLA-4 was approved only as second-line therapy of advanced melanoma in Europe in 2011 [19].

ipilimumab,

- vemurafenib, approved for BRAF V600 mutation-positive disease [20].

vemurafenib for patients with BRAF mutations,

- 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.

IL-2,

- participation in clinical trials.

participation in clinical trials

If clinical trials or approved new targeted compounds are not available, cytotoxic drugs such as dacarbazine (historically it had been the drug of reference), temozolomide, taxanes, fotemustine, platin derivatives or others, c-kit-inhibitors (e.g. imatinib), cytokines (IFN, IL-2) or combinations may be applied.

6 Evidence

1 phase III trial and 1 phase I/II trial included

A literature search was conducted on the 19th of November in four databases (OVID, Embase, Cochrane, CRD Database) using the terms "melanoma". "skin neoplasm", "trametinib" and "GSK1120212". After de-duplication, 113 references were identified. Only phase III and phase II studies were eligible, thus one phase III trial [21] and one phase I/II trial [22] were included.

Furthermore, Pharmastar (an Italian online newsletter website), the R&D Database, GSK's website, press releases – pipeline and the ASCO Congress website were searched for "trametinib" in October 2012.

The manufacturer was also contacted, but no relevant publications which had not yet been included were submitted.

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

Study title Publication title: Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma [21, 23, 24] Official title: A Phase III Randomized, Open-label Study Comparing GSK1120212 to Chemotherapy in Subjects With Advanced or Metastatic BRAF V600E/K Mutation-positive Melanoma [25]		
Study identifier	Clinical trials identifier: NCT01245062; METRIC Study	
Design	Phase III, randomised, open-label, active-controlled trial, 2:1 randomisation, stratification according to baseline lactate dehydrogenase levels and status of prior chemotherapy	
	Duration	Enrolment: November 2010 Median follow-up: NA Cut-off date for primary outcome measure analysis: February 2012 Estimated study completion date: March 2013 [25]
Hypothesis	Superiority The study was designed with a power of at least 99 % at a one-sided alpha level of 0.025 to detect a relative improvement of 133 % in progression-free survival (hazard ratio for disease progression or death, 0.43)	
Funding	GlaxoSmithKline	
Treatment groups	Subject selection	1,022 patients were screened for V600E/K BRAF mutations from December 2010 – July 2011
	Overall study population (N = 322)	322 eligible patients (281 with the V600E mutation, 40 with the V600K mutation, and 1 with both mutations) were randomised in in a 2:1 ratio to either intervention of control group
	Intervention (N = 214)	2 mg/day oral trametinib
	Control (N = 108)	dacarbazine 1000 mg/m² of body-surface area or paclitaxel 175 mg/m², at the discretion of the investigator, every 3 weeks.

Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	time from randomization until the earliest date of disease progression (RECIST criteria 1.1 [26]) or death due to any cause on the basis of the site investigator's assessment
	Overall survival	OS	time from randomization until death due to any cause
	Best overall response rate	BORR	the percentage of subjects with evidence of CR or PR (RECIST 1.1 [26]); best overall response will be based on unconfirmed responses as OS/PFS are the primary endpoints.
	Duration of response	DOR	time from first documented evidence of CR or PR until disease progression or death due to any cause. Duration of response for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumour assessment.
	Health related quality-of-life	HRQL	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) version 3 and the EuroQoL-5D (EQ-5D)

Results and analysis

Analysis description	intention-to-treat (ITT) There were 322 patients in the ITT population, of whom 273 (85 %) were in the primary efficacy population. The primary efficacy population included patients with the V600E BRAF mutation who did not have brain metastases at baseline.			
Analysis population	Inclusion	age: ≥18 years; • histologically confirmed unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation-positive melanoma; • presence of brain metastases was allowed only if they were stable; • ≤1 prior chemotherapy treatment (excluding ipilimumab, BRAF or MEK inhibitors); • ECOG PS: 0-1		
	Exclusion	• history of clinically significant cardiovascular or interstitial lung disease; • evidence or a risk of retinal-vein occlusion or central serous retinopathy		
	Characteristics		I	C
		Median age – yr (range)	55 (23-85)	54 (21-77)
		Male sex – %	56	49
		White race – %	100	100
		ECOG – PS – 0/1	64/36	64/36
		Stage: M1a/M1b/M1c/ unresectable (IIIc) – %	11/16/67/5	14/20/58/7
		Previous Chemotherapy: No/Yes – %	67/33	65/35
		Previous immunotherapy – %	32	28
		LDH: ≤ULN/>ULN – &	63/36	61/39

Descriptive statistics and estimated variability	Treatment group	*Intervention (trametinib)*	*Control (chemotherapy)*
	Number of subjects	N = 214	N = 108
	PFS, months		
	Median	4.8	1.5
	95 %CI	NA	NA
	OS	NR	NR
	6-months OS, %	81	67
	BORR, %	22	8
	95 %CI	17-28[1]	4-15
	Confirmed Response CR, n (%)	4 (2)	0
	PR, n (%)	43 (20)	9 (8)
	SD, n (%)	119 (56)	34 (31)
	PD, n (%)	38 (18)	50 (46)
	Response NR, n (%)	10 (5)	15 (14)
	DOR, months		
	Median	5.5	NR
	95 %CI	4.1-5.9	
	HRQL	NA	NA
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	PFS (by site investigator)	HR	0.45
		95 %CI	0.33-0.63
		P value	p<0.001
	PFS (by independent review blinded to treatment)	HR	0.42
		95 %CI	0.29-0.59
		P value	≤ 0.001
	OS	HR	0.54
		95 %CI	0.32-0.92
		P value	0.01
Notes	According to a protocol amendment adopted on February 16, 2012, the independent data and safety monitoring committee and study steering committee concluded that both progression-free survival and overall survival were significantly longer in the trametinib group than in the chemotherapy group and that immediate crossover to trametinib should be permitted.		

NR = not reached, NA = not available, HR = Hazard ratio, ECOG PS = Eastern Cooperative Oncology Group Performance Status, OS = overall survival, PFS = progression free survival, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, BORR = best overall response rate, CI = confidence interval, n = number, QoL = quality-of-life

[1] *For I vs C: P=0.01*

Table 2: most frequent adverse events

Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma [21, 23, 24]			
Grade (according to CTC version 4.0)	**AEs, n (%)**	**Intervention (N=211)**	**Control (N=99)**
All grades	Rash	121 (57)	10 (10)
	Diarrhoea	91 (43)	16 (16)
	Fatigue	54 (26)	27 (27)
	Peripheral oedema	54 (26)	3 (3)
	Acneiform dermatitis	40 (19)	1 (1)
	Nausea	38 (18)	37 (37)
	Alopecia	36 (17)	19 (19)
	Hypertension	32 (15)	7 (7)
	Constipation	30 (14)	23 (23)
	Vomiting	27 (13)	19 (19)
Grade 3	Fatigue	8 (4)	3 (3)
	Peripheral oedema	2 (1)	0
	Acneiform dermatitis	2 (1)	0
	Nausea	2 (1)	1 (1)
	Alopecia	1 (<1)	0
	Hypertension	26 (12)	3 (3)
	Constipation	0	1 (1)
	Vomiting	2 (1)	2 (2)
Grade 3 or 4[1]	Rash	16 (8)	0
	Diarrhoea	0	2 (2)
Other outcomes	Ocular events	9°	–
	Decreased ejection fraction	14 (7)*	–
	Cardiac-related events	2 (1)	–
	Discontinuations due to AEs	NA (35)	NA (22)
	Dose-reductions	NA (27)	NA (10)

[1] *Only one patient experienced grade 4 side-effect in each group; * = 11 decreased ejection fraction, and 3 left ventricular dysfunction, ° = 4 % blurred vision, <1 % reversible chorio-retinopathy*

pivotal phase III with 322 patients with BRAF mutations previously treated and previously untreated

comparison of trametinib with chemotherapy at the investigator's discretion

In this pivotal phase III, open-label trial 322 patients with histologically confirmed unresectable (stage IIIc) or metastatic (stage IV) melanoma harbouring the mutation BRAF V600E or BRAF V600K, were randomised to receive oral trametinib (2 mg/day) or chemotherapy (either intravenous dacarbazine or paclitaxel). To identify patients with these mutations, 1,022 patients were initially screened. Of the 737 patients excluded from the study, the majority (458 patients) were BRAF V600 negative, 268 did not meet inclusion criteria and 11 patients declined [24]. Thus 281 patients were enrolled with BRAF V600E, 40 patients with BRAF V600K and 1 patient with both mutations. Choice of chemotherapy was at the investigator's discretion. Of the 108 patients randomised to chemotherapy, only 99 received therapy of which 62 were treated with dacarbazine and 37 with paclitaxel [24].

Enrolment criteria allowed up to 1 prior therapy (excluding ipilimumab, BRAF or MEK inhibitors), thus about 66 % of included patients had received chemotherapy and approximately 30 % immunotherapy. The majority of patients (i.e. 78 %) were younger than 65 years, had ECOG performance status 0 (i.e. 64 %) and normal LDH levels.

The primary efficacy analysis, conducted in the intention-to-treat population, was based on analyses from February 2012 (the pre-specified numbers of PFS events had been reached in October 2011).

PFS, primary outcome, + 3.3 months for trametinib group, HR =0.45

According to the investigators, progression-free survival (primary endpoint) was 4.8 months in the trametinib group vs 1.5 months in the chemotherapy group (HR 0.45; 95 %CI 0.33-0.63; p<0.001). Results for subgroups according to mutation-status and prior treatment, age, LDH levels, disease stage and sex mainly favoured the trametinib group. Only older patients (≥65 years) and patients with V600K mutations did not show statistically significant results, but both groups comprised rather few patients. 71 patients were ≥65 years and only 40 had V600K mutations.

6months OS: I 81 % vs C 67 %

but cross-over of 47 % in chemotherapy group

ORR: I 22 % vs C 8 %, mainly partial responses

duration of response was 5.5 months

Six-month overall survival rate was 81 % vs 67 % (HR for death 0.54; p=0.01); median OS had not been reached at time of analysis, but follow-up continues. The authors mention that these results might underestimate the difference between the two groups, because 47 % of patients in the chemotherapy group crossed-over to trametinib after disease progression. Overall response rate was 22 % vs 8 %, including complete responses of 2 % in the trametinib group vs 0 % in the chemotherapy groups and partial response of 20 % vs 8 % respectively. Stable disease was observed in the trametinib group in 56 % vs 31 % in the chemotherapy groups; the corresponding numbers for progressive disease were 18 % vs 46 %. Duration of response was 5.5 months in the trametinib group, but was not reached in the chemotherapy group.

most common AEs: rash, diarrhoea, fatigue

dose-interruptions: I 35 % vs C 22 % and dose-reductions: I 27 vs C 10 %

Most common adverse events (AE) of all grades were rash (I 57 % vs C 10 %), diarrhoea (I 43 % vs C 16 %), fatigue (I 26 % vs C 27 %) and nausea (I 18 % vs C 37 %). AEs of grade 3 were hypertension (I 12 % vs C 3 %), rash (I 8 % vs C 0 %), diarrhoea (I 0 % vs C 2 %), fatigue (I 4 % vs C 3 %) and nausea (I 1 % vs C 1 %). Of note, more dose-interruptions (I 35 % vs C 22 %) and dose reductions (I 27 % vs C 10 %) due to AEs were observed in the trametinib group. No cutaneous squamous-cell carcinomas or hyperproliferative skin lesions were diagnosed while patients were receiving trametinib.

Based on results for PFS and OS, the data and safety monitoring committee recommended allowing immediate cross-over to the trametinib group. In addition, a total of 8 % of patients in the trametinib group and 6 % in the chemotherapy group received vemurafenib, and 5 % in the trametinib group and no patients in the chemotherapy group received ipilimumab after the study therapy. Hence, even though follow-up for median OS continues, this result has to be interpreted with caution.

6.2 Efficacy and safety – further studies

one further phase I/II trial compared different dosages of trametinib + dabrafenib and dabrafenib monotherapy

One open-label phase I/II trial comprising 247 patients with metastatic melanoma and BRAF V600 mutations was identified [27]. 85 patients initially received oral dabrafenib (75 or 150 mg twice daily), an experimental BRAF inhibitor, and trametinib (1, 1.5, or 2 mg daily) and then 162 patients were randomly assigned to receive combination therapy with dabrafenib (150 mg) plus trametinib (1 or 2 mg) or dabrafenib monotherapy. The primary end points were the incidence of cutaneous squamous-cell carcinoma, survival free of melanoma progression, and response.

best outcomes for dabrafenib + trametinib 2 mg/d

19 % of patients receiving dabrafenib experienced cutaneous squamous carcinoma in comparison to 2 % in the dabrafenib/1mg trametinib group and in 7 % in the dabrafenib/2mg trametinib group. The most frequent AEs observed in the combination 150/2 group were pyrexia (all grades: 71 %; grade 3 or 4: 5 %) and chills (all grades: 58 %; grade 3 or 4: 2 %). Besides pyrexia and chills, other AEs more common in the dabrafenib/2mg trametinib group than in the mono-therapy arm were fatigue (53 %), nausea (44 %), vomiting (40 %), and diarrhoea (36 %). Of these, only the minority were grade 3 or 4. The most frequent toxic AE of grade 3 or 4 in the combination 150/2 group was neutropenia (11 %). Median PFS was 9.4 months in the dabrafenib/2mg trametinib group and 5.8 months in the dabrafenib monotherapy group (HR = 0.39; 95 %CI 0.25 to 0.62; $p<0.001$). The rate of complete or partial response was 76 % dabrafenib/2mg trametinib group and 54 % in the monotherapy group ($p = 0.03$).

7 Estimated costs

no cost estimates available

No cost estimates are available for trametinib.

8 Ongoing research

3 on-going phase III trials for melanoma

Searching www.clinicaltrials.gov/ and www.clinicaltrialsregister.eu/ for "trametinib", "GSK1120212" and "melanoma" 3 phase III trials were identified:

- **NCT01682083:** two-arm, randomized, double-blind Phase III study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of melanoma after surgical resection. Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk cutaneous melanoma will be screened for eligibility. Estimated study completion date: July 2015.
- **NCT01584648/EudraCT Number: 2011-006087-49:** two-arm, double-blinded, randomized, Phase III study comparing dabrafenib and trametinib combination therapy to dabrafenib administered with a trametinib placebo (dabrafenib monotherapy) in previously untreated patients. Subjects with histologically confirmed cutaneous melanoma

that is either Stage IIIC or Stage IV, and BRAF V600E/K mutation positive will be screened f be allowed. Subjects will be followed for overall survival; crossover will not be permitted. Estimated study completion date: May 2015.

- **NCT01597908/EudraCT Number 2011-006088-23:** two-arm, open-label, randomised, Phase III study comparing dabrafenib and trametinib combination therapy to vemurafenib in previously untreated. Subjects with histologically confirmed cutaneous melanoma that is either stage IIIc or stage IV, and BRAF V600E/K mutation positive will be screened for eligibility. Estimated study completion date: June 2015.

several on-going phase II for other types of cancer

Several phase II trials were also found for other cancer such as non-small cell lung cancer, thyroid cancer, mouth neoplasms, leukaemia, and metastatic pancreatic cancer.

9 Commentary

trametinib not licensed yet

improved outcomes for PFS (+3.3 months)

median OS not yet reached but results will be compromised due to cross-over and ensuing lines of therapy

Trametinib, a MEK inhibitor, is currently neither licensed in Europe nor in the U.S. A phase III trial evaluated trametinib mono-therapy in comparison to chemotherapy in 322 patients with BRAF V600 mutation-positive melanoma. Included patients were either untreated (~66 %) or had received one prior chemotherapy (~34 %). Median PFS, the primary outcome, was prolonged by 3.3 months (HR 0.45; 95 %CI 0.33-0.63; p<0.001) for patients treated with trametinib in comparison to those treated with chemotherapy (68 % dacarbazine, 32 % paclitaxel). Improved results were consistent across subgroups with the exceptions of patients aged ≥65 years and patients with BRAF V600K mutations which yielded no statistically significant outcomes. Best overall response rates (=complete response + partial response) also favoured the trametinib group (I 22 % vs C 8 %), mainly driven by partial responses (20 %). Median OS was not reached at time of this analysis, but 6 months OS rates were 81 % in the trametinib group and 67 % in the chemotherapy group yielding a HR of 0.54 (95 %CI 0.32-0.92; p=0.01). Due to these results, crossing over from the chemotherapy group to the MEK inhibitor group was allowed. Further analysis of median OS will, also due to the fact that patients received ensuing therapies after disease progression, be compromised. The most frequent AEs in the trametinib group were rash, diarrhoea, acneiforme dermatitis and fatigue, but no case of cutaneous squamous cell carcinoma occurred.

many new agents available for melanoma

no consensus currently exits but vemurafenib commonly used for BRAF V600 mutation positive melanoma

but no direct head-to-head comparisons

Treatment of melanoma has undergone substantial changes in the last years. Until recently, only few drugs with rather limited activity have been available. With the development of targeted drugs, e.g. the BRAF inhibitor vemurafenib or the human monoclonal antibody ipilimumab, new treatment options have become available. Even though no consensus on therapy exists, vemurafenib is often the recommended therapy for patients with BRAF V600 mutation-positive melanoma [20]. Even though trametinib was compared at least in some patients with dacarbazine, which was considered reference standard at study initiation but has limited activity itself, direct head-to-head comparisons of newly available agents are missing. In addition, despite the fact that the phase III trial had included previously untreated as well as previously treated patients (with chemotherapy or immunotherapy), yield-

ing improved PFS in both subgroups, the latter group included only relatively few patients (~34 %). Furthermore, if trametinib will also be active in patients previously treated with vemurafenib remains unknown and preclinical studies indicate that acquired resistance to BRAF inhibitors (in that case dabrafenib) also led to a reduced sensitivity to trametinib [28]. Conversely, MEK mutations have also been reported to cause secondary resistance not only to MEK inhibitors but also cross-resistance to BRAF inhibitors [29]. Thus the optimal sequencing of new agents for the treatment of melanoma remains unknown and the population trametinib might be used for should be better characterised.

PFS gains in previously treated and previously untreated, but latter group rather small

best sequence of new agents unknown, also due to secondary resistance

Further, secondary resistance can also be held accountable for the rather short durations of response (between 2-18 months, median 8-9 months) to BRAF inhibitors [6, 28, 29]. For patients responding to trametinib (22 %), median duration of response was also only 5.5 months. Even though GSK obviously seeks approval for single-agent trametinib as well as for dabrafenib, which was used in combination with trametinib in the phase I/II trial [27, 29, 30], combining different agents is believed to delay resistance. Two ongoing phase III trials therefore investigate the combination of the BRAF inhibitor dabrafenib (also GSK) in combination with the MEK inhibitor trametinib as first-line therapy. Results can be expected in 2013 (NCT01584648) and 2014 (NCT01597908). When trametinib, which costs are not yet known, will receive market authorization in combination with a BRAF inhibitor, treatment costs are likely to be substantial.

short duration of response due to resistance, combination therapies to overcome this problem?

trametinib tested in combination with dabrafenib – combination therapy likely to be expensive

Besides acquired resistance, primary resistance to BRAF or MEK inhibitors is reported to exist in less than 15 % of patients [29]. Exploring the impact of further mutations on clinical outcomes and choice of therapy may be useful in better characterising patients for specific therapies and in determining optimal combination regimens [7]. Nonetheless, testing for mutations further increases costs, foremost when not only single mutations are being tested [31]. Concerning selection of patients with BRAF V600 mutations the BRAF mutation assay used in the phase III trial, was undergoing validation but these results are not available yet [23], but the same test will also be used in the two on-going phase III studies. Besides, determination of mutation status, other companion diagnostics which allow prediction of duration of response are currently subject of research [32].

further characterisation of patients for better selection needed

but extensive mutation testing – expensive

test used in phase III study, was undergoing validation – no results available yet

Besides the rather heterogeneous population (pre-treated/untreated, different comparators) in the phase III trial, the majority of patients were younger than 65 years and had a performance status of grade 0, corresponding to "fully active, able to carry on all pre-disease performance without restriction" [33]. More dose interruptions (I 35 % vs C 22 %) and dose-reductions (I 27 % vs 10 %) were necessary in the trametinib group than in the chemotherapy group, which are likely to be even higher in older, comorbid and frail patients. Also, quality-of-life data are missing but are of utmost importance for patients with metastatic melanoma.

besides heterogeneous study population, patients quite young, good performance status

higher rates of dose reductions/interruptions possible when older, frail and comorbid patients are treated

despite advances in melanoma therapy, still no curative therapy available and unresolved questions

best treatment option enrolment onto clinical trials?

Despite advances in the treatment of melanoma, no curative therapy exists and gains in either PFS or OS are incremental. Even though trametinib has shown activity in comparison to the former reference standard dacarbazine which has limited activity itself, and in previously treated as well as in previously untreated patients, the optimal sequencing of available agents as well as their combinations remains unknown in the absence of direct comparative trials. Until then enrolment onto clinical trials might be the best strategy to treat patients with advanced/metastatic malignant melanoma [34].

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