The TEAM trial (Tasigna efficacy in advanced melanoma): A randomized, phase III, open label, multi-center, two-arm study to compare the efficacy of Tasigna® versus dacarbazine (DTIC) in the treatment of patients with metastatic and/or inoperable melanoma harboring a c-Kit mutation

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Primary objective:* To compare the clinical efficacy of nilotinib to DTIC, based on progression free survival (PFS), in the treatment of c-Kit mutated melanoma in patients who have not received prior therapy with TKIs.Key secondary objectives:* To…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON34305

Source
ToetsingOnline

Brief title
The TEAM trial

Condition

- Skin neoplasms malignant and unspecified

Synonym
disseminated skin cancer, metastatic melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: c-Kit mutated melanoma, dacarbazine (DTIC), nilotinib, Phase III

Outcome measures

Primary outcome

PFS, defined as the time from randomization to the first documented progression

or death due to any cause.

Secondary outcome

Key secondary endpoints:

* ORR, calculated as the proportion of patients with a best overall response of

confirmed complete response or partial response (CR+PR).

* DORR, calculated as the rate of patients with a CR or PR lasting * 12 weeks.

* OS

Other secondary endpoints:

* PFS6

* OS12

* TOR, calculated as the time from date of randomization until first documented

response of CR or PR

* DOR, calculated as the time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer

* DCR, calculated as the proportion of patients with an overall response of CR, PR or stable disease (SD) for a minimum of 12 weeks from randomization.

Exploratory endpoints

* Pathway inhibition by changes in pAkt, pS6, pMEK/ERK, pSTAT5 levels.

* Resistance mechanisms: PTEN loss, PI3K activation, acquisition of novel c-Kit mutations.

* Soluble markers: normalization of MIA, decreases in soluble c-Kit.

* Patient reported outcomes: health status and utility measured by EQ-5D; functioning and QoL measured by FACT-G.

Safety endpoints:

Safety and tolerability.

Study description

Background summary

Melanoma is the most common tumor of the skin that develops from a neoplastic transformation of melanocytes. The incidence of cutaneous melanoma is increasing at a faster rate than for any other solid tumor (Rigel 1996, Marks 2000, SEER 2009) and is estimated as 68,000 new cases annually in the USA. Globally, the incidence of melanoma varies by region, and according to World Health Organization over 130,000 new cases of melanoma are recognized annually around the world (WHO 2009). Melanoma is a tumor with significant impact on society and when found to be metastatic, there is no effective treatments for most patients. Although most patients have localized disease at the time of diagnosis and are cured by surgical excision of the primary tumor metastases

can develop and most of these patients die of melanoma-associated causes. In the USA, over 8,000 yearly deaths in 2008 have been associated with melanoma (American Cancer Society).
Most melanomas develop in the skin (cutaneous melanoma).
Acral melanoma, which originates in the palms, soles and subungual regions, represents about 5% of all melanomas, while mucosal melanomas, arising most often on mucosal surfaces in the anorectal, vaginal and nasal sinus regions, accounts for 1-2% (McLaughlin, et al 2005).
As acral and mucosal melanomas are often thicker at the time of diagnosis than superficial melanoma, they have a higher propensity to recur and metastasize.
The overall median survival from diagnosis of stage IV melanoma has been estimated to be 8 months (Lee, Tomsu, and Von Eschen 2000). One year survival for these patients has been reported as approximately 25%, with approximately 15% of patients surviving 5 years (SEER 2009). In metastatic melanoma, chemotherapy is used mostly with palliative intent. Currently registered agents for the treatment of melanoma include the alkylating agent dacarbazine (DTIC) and high dose IL-2. The administration of DTIC is a standard treatment with response rates in the range of 5-15% and progression free survival of approximately 8 weeks (Chapman, et al 1999). Cytotoxic therapies have not been reported to prolong overall survival.
Recent investigations have provided some insight into the molecular events which may lead to melanoma development and progression offering clues into possible therapy options. Preliminary findings suggest that distinct subtypes of melanoma are associated predominantly with the activation of BRAF, NRAS or GNAQ, while others could be driven by the c-Kit pathway. The efforts to refine the classification of melanoma have also proposed two subcategories of superficial skin melanoma, chronic sun damaged (CSD) and non-CSD melanoma, as well as better characterized melanomas of the acral and mucosal categories (Curtin, et al 2006). Others have noted that melanomas associated with BRAF and NRAS mutations have anatomic and age distribution differences compared with patients harboring a mutation of c-Kit. Patients with cutaneous melanomas associated with c-Kit mutations tend to be older and have lesions on the skin in areas of chronic sun exposure. Mutations of c-Kit are also more prominent in patients with acral and mucosal melanomas (Viros, et al 2008). Recently, three Phase II trials employing imatinib in patients with metastatic/inoperable melanoma harboring c-Kit mutations have reported early results. Response rates have ranged from 28-50% with durable responses reported lasting 4-6+ months.

Study objective

Primary objective:
* To compare the clinical efficacy of nilotinib to DTIC, based on progression free survival (PFS), in the treatment of c-Kit mutated melanoma in patients who have not received prior therapy with TKIs.

Key secondary objectives:
* To compare objective overall response rate (ORR) between nilotinib and DTIC.

* To compare durable objective response rate (DORR) between nilotinib and DTIC.
* To compare overall survival (OS) between nilotinib and DTIC.

Other secondary objectives:
* To assess the PFS rate at 6 months (PFS6) and OS at 12 months (OS12) for nilotinib and DTIC treatment.
* To assess the time to objective response (TOR) and duration of objective response (DOR) to nilotinib and DTIC treatment.
* To assess the disease control rate (DCR) to nilotinib and DTIC treatment.

Exploratory objectives:
* To assess effects on cellular signaling (pAkt, pMEK, pSTAT5) in response to nilotinib.
* To assess mechanisms of resistance to nilotinib (acquisition of new mutations in c-Kit, presence of other factors i.e. PTEN loss etc.).
* To assess changes in potential circulating marker of target inhibition (soluble c-Kit) and tumor burden (MIA) after treatment.
* To assess changes in patient reported outcomes (PROs) including health status, functioning, and quality of life (QoL).

Safety objectives:
* To assess the safety and tolerability profiles of nilotinib and DTIC in this patient population.

Study design

This is a randomized, open-label, multi-center, two-arm, cross-over, phase III study to compare the efficacy and safety of nilotinib (400 mg bid) versus DTIC (850 mg/m2 iv every 3 weeks) in patients with c-Kit mutated metastatic and/or inoperable melanoma. The primary efficacy endpoint is PFS.
Patients potentially eligible for the study will be consented for a pre-screening visit. All patients must have their c-Kit status confirmed at a central laboratory on paraffin embedded tissue.
Once c-Kit mutation has been centrally confirmed, the patient can be consented to the trial, the screening/baseline performed and the patient can proceed to randomization if all inclusion criteria and none of the exclusion criteria have been met.
A total of 120 patients will be randomized 1:1 to the two treatment arms (nilotinib and DTIC).
The doses of nilotinib and DTIC will be 400 mg bid and 850 mg/m2 iv every 3 weeks, respectively.
The study will have one futility interim analysis (IA) and one final analysis.Enrolment of patients will continue during the IA. The futility IA will occur once the first 30% (29) of the total planned PFS events have occurred on the randomized treatment. The final analysis will occur when the planned total of 94 PFS events have occurred.
The study will be open-ended, consisting of visits every 3 weeks from week 3

onwards, during which patients will be followed for PFS and OS. Once the planned total of 94 PFS events have occurred, or if the study is closed early due to the outcomes of the interim analysis, any patients remaining on the study will be transferred to an extension study. Patients will continue to receive study drug for as long as they continue to receive benefit in the opinion of the Investigator.
Patients randomized to the DTIC arm will have the option to crossover to the nilotinib arm of the study upon progression. Patients randomized to the nilotinib arm, or who crossover to the nilotinib arm, who progress will exit the study and will receive further treatment at the discretion of the Investigator.
Patients who discontinue study drug for any reason other than disease progression will continue to have tumor assessments on study. Tumor assessment for these patients will continue until the patient has a documented disease progression, starts another cancer therapy, or dies.
All patients who discontinue study medication will be followed for 28 days to evaluate adverse events and serious adverse events.
All patients who withdraw from the study and cease tumor assessment will befollowed for survival status every 3 months. Follow-up will cease only in cases of death, withdrawal of consent to follow-up or loss to follow-up.

Intervention

The dose of nilotinib will be 400 mg orally b.i.d. administered continuously. Dose reduction is required in cases of clinically relevant toxic effects (to 400 mg q.d.) provided criteria for withdrawal from study drug are not met, which is described in the protocol.

DTIC will be administered as 850 mg/m2 body surface area every 3 weeks by intravenous injection. A dose modification schema will be provided based on AEs and cycle day 1 laboratory values to maintain a 3-week dosing schedule whenever possible.

Study burden and risks

Study assessments will be performed at screening, baseline, week 1, week 2, week 3 and every 3 weeks until the planned total of 94 PFS events have occurred, whereupon all patients will complete the End of Treatment visit. Patients withdrawing for any reason will be asked to attend the End of Treatment visit. Please refer to Table 7-1 and Table 7-2.
Patients crossing-over to nilotinib will re-start the study schedule (i.e. with visits at weeks 1, 2, 3, 6, etc) in order to assess safety parameters.

Risks:
* Toxicity due to the use of nilotinib and/or dacarbazine.
* Reaction to the use of contrast fluid (used for CT scans)

* Side effects of bloodsampling and taking of the biopsies (optional)

Contacts

Public
Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologically confirmed mucosal, acral or cutaneous melanoma.
2. Presence of a c-Kit mutation of exon 11 or 13, or mutations Y822D and Y823D of exon 17, as confirmed by the central laboratory.
3. Stage III unresectable or stage IV disease.
4. The presence of one or more measurable lesions as detected by radiological or photographic methods and assessed according to RECIST.lesions must have a size of at least 10mm at longest diameter (using a slice thickness of 5 mm).
5. WHO performance status 0 - 2.
6. At least 28 days since major surgery and 7 days since skin/tumor biopsy until start of study

drug.
7. Age 18 or greater.
8. Patients must have adequate bone marrow and organ function as defined by the following laboratory values:
* Biochemistry parameters within normal ranges prior to and at the latest by the day of first dosing, achieved by correction with supplements if necessary.
* ALT and AST * 2.5 x ULN (upper limit of normal) or * 5.0 x ULN if considered due to tumor.
* Alkaline phosphatase * 2.5 x ULN or * 5.0 x ULN if considered due to tumor.
* Serum bilirubin * 1.5 x ULN.
* Serum creatinine * 1.5 x ULN
* Serum amylase * 1.5 x ULN and serum lipase * 1.5 x ULN.
* Hemoglobin * 9.0 g/dL, absolute neutrophil count *1.5 x 109/L, platelets *100 x 109/L.
9. The capacity to understand the patient information sheet and the ability to provide written informed consent.
10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

Exclusion criteria

1. C-Kit mutation of exons 17(except mutations Y822D or Y823D) or 18.
2. Patients with c-Kit amplifications only and no mutation.
3. Patients with any NRAS or BRAF mutation
4. Patients with known untreated or treated brain metastases as shown at the screening visit or earlier (metastatic disease M1a, M1b, M1c are allowed).
5. Patients who have had any prior treatment with TKIs or DTIC.
6. Patients receiving medications or herbal extracts which interfere with nilotinib metabolism which are not discontinued by the time of the baseline visit.
7. Impaired cardiac function, including any one of the following:
* LVEF < 45% or below institutional lower limit of the normal range (which ever is higher) as determined by MUGA scan or echocardiogram.
* Complete left bundle branch block.
* Use of a cardiac pacemaker.
* Congenital long QT syndrome.
* History of or presence of significant ventricular or atrial tachyarrhythmias.
* Clinically significant resting bradycardia (< 50 beats per minute).
* QTc > 450 msec on screening ECG (using the QTcF formula).
* Right bundle branch block plus left anterior hemiblock, bifascicular block.
* Myocardial infarction within 12 months prior to randomization.
* Unstable angina diagnosed or treated during the past 12 months.
* Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
8. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of nilotinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive gastric or small bowel resection).

9. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis.
10. Acute or chronic liver or renal disease considered unrelated to the tumor.
11. Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
12. Patients who are currently receiving treatment with any medications that have a significant potential to prolong the QT interval. See link for list of these medications: http://www.torsades.org/medical-pros/druglists/printable-drug-list.cfm.
13. Patients currently receiving therapy with strong CYP3A4 inhibitors. See link for list of these medications: http://medicine.iupui.edu/flockhart/table.htm.
14. Patients receiving therapy with strong CYP3A4 inducers. See link for list of these medications: http://medicine.iupui.edu/flockhart/table.htm.
15. Patients who have received cytotoxic chemotherapy * 4 weeks (6 weeks for nitrosurea or mitomycin-C) prior to starting study drug or who have not recovered from the side effects of such therapy.
16. Patients who have received immunotherapy * 1 week prior to starting study drug or who have not recovered from the side effects of such therapy.
17. Patients who have received any investigational drug * 4 weeks prior to starting study drug or who have not recovered from the side effects of such therapy.
18. Patients who have received wide field radiotherapy * 4 weeks or limited field radiation for palliation * 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
19. Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.
20. Women who are pregnant, breast feeding or adults of reproductive potential not employing an effective method of birth control. Post menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Female patients must agree to
employ an effective method of contraception during the study and for up to three months following discontinuation from the study. Effective methods of contraception are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-12-2010
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DTIC
Generic name:	dacarbazine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tasigna
Generic name:	nilotinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	24-06-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	09-09-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	19-10-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015514-21-NL
ClinicalTrials.gov	NCT01028222
CCMO	NL32250.091.10