The TEAM trial (Tasigna efficacy in advanced melanoma): A phase II, open label, multi-center, single-arm study to assess the efficacy of Tasigna® in the treatment of patients with metastatic and/or inoperable melanoma harboring a c-Kit mutation

Published: 22-11-2011
Last updated: 01-05-2024

Primary objective:* To assess the clinical efficacy of nilotinib, based on overall response rate (ORR), in thetreatment of c-Kit mutated melanoma in patients who have not received prior therapy withTKIs.Key secondary objectives:To assess the durable...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON37871

Source
ToetsingOnline

Brief title
TEAM (am2)

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, nilotinib, Phase II

Outcome measures

Primary outcome

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

of confirmed

complete response or partial response (CR+PR).

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

* 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 assess the clinical efficacy of nilotinib, based on overall response rate (ORR), in the
treatment of c-Kit mutated melanoma in patients who have not received prior therapy with
TKIs.

Key secondary objectives:
To assess the durable overall response rate (DORR) of patients treated with

nilotinib.
* To assess progression free survival (PFS) of patients treated with nilotinib.
* To assess overall survival (OS) of patients treated with nilotinib.

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

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

exploratory objectives
To assess changes in patient reported outcomes (PROs) including health status, functioning, and quality of life (QoL).

Study design

This is a open-label, multi-center, single-arm, phase II study to assess the efficacy of nilotinib (400 mg bid) every 3 weeks) in patients with c-Kit mutated metastatic and/or inoperable melanoma. The primary efficacy endpoint is ORR
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 41 patients will be enrolled
The doses of nilotinib will be 400 mg bid every 3 weeks,

The study will use the Simon*s two stage min-max design. The first stage will consist of 23 patients. The stage 1 decision point will be when all 23 patients have either reached the 24 Week visit, have discontinued the study, or a confirmed response to treatment has been
observed. If 2 or fewer responses are observed in stage 1, the trial will be stopped. The continuous recruitment of patients into stage 2 will be reassessed if the number of responders in stage 1 is less than the minimum required. Depending on the pace of patient
screening, a few more patients than the defined stage 1 number may be enrolled (overrecruitment).

Due to the rarity of the disease and slow patient accrual rate, enrollment will not be stopped during the analysis of stage 1. The patients recruited beyond stage 1 will not be included in the decision making analysis at the end of stage 1. The second stage will include an additional 18 patients. The final analysis will occur when all 41 patients have reached the 24 Week visit or have discontinued the study.Patients will follow
the study design shown in Figure 4-1 and have study assessments as described in Section 7.

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.

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.

Risks:
* Toxicity due to the use of nilotinib
* 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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6824 DP Arnhem
NL
Scientific
Novartis

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6824 DP Arnhem
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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 or acral
2. Presence of a c-Kit mutation of exon 9, 11 or 13, or mutations D820G, N822H, N822K, D820Y, Y822D or 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) or double the slice thickness to be considered a target lesion. Target lesions should not be selected in previously irradiated fields unless there is clear evidence of progression.
5. WHO performance status 0 - 2.
6. At least 28 days since major surgery prior to straing study drug
7. Age 18 or greater.
8. Patients must have adequate bone marrow and organ function as defined by the following laboratory values:
* Serum potassium within the normal limits or corrected to within normal limits with supplements
* Total calcium (corrected for serum albumin) within the normal limits or corrected to within normal limits with supplements

* Serum magnesium within the normal limits or corrected to within normal limits with supplements
* Serum phosphate within the normal limits or corrected to within normal limits with supplements
* 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 D820G, N822H, N822K, D820Y, Y822D or Y823D) or any other exon not allowed by the inclusion criteria.
2. Patients with c-Kit amplifications without mutations.
3. Patients with any history of brain metastases ,
4. Patients who have had any prior treatment with TKIs,
5. Patients receiving medications or herbal extracts which interfere with nilotinib metabolism which are not discontinued by the time of the baseline visit.
6. 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 enrollment
* 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).
7. 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).
8. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis.
9. Acute or chronic liver or renal disease considered unrelated to melanoma.

10. 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.
11. 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/drug-lists/printable-drug-list.cfm.
12. Patients currently receiving therapy with strong CYP3A4 inhibitors. See link for list of these medications: http://medicine.iupui.edu/flockhart/table.htm.
13. Patients receiving therapy with strong CYP3A4 inducers. See link for list of these medications: http://medicine.iupui.edu/flockhart/table.htm.
14. Patients who have received 2 or more prior regimens of systemic anticancer therapy for melanoma.
15. Patients with no evidence of clear progression of disease, either with or without prior systemic anticancer therapy.
16. Patients with less than 12 weeks between their last dose of an anti-CTLA4 agent (i.e. ipilimumab or tremelimumab) and the Screening/Baseline visit.
17. 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.
18. Patients who have received immunotherapy * 1 week prior to starting study drug or who have not recovered from the side effects of such therapy.
19. 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.
20. 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.
21. Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.
22. 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:	2
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	22-11-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-03-2012
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	NL38641.091.11