

**Clinical trial results:****A Phase II Trial of Nilotinib in the Treatment of Patients with c-KIT Mutated Advanced Acral and Mucosal Melanoma (NICAM)****Summary**

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2009-012945-49   |
| Trial protocol           | GB               |
| Global end of trial date | 12 December 2016 |

**Results information**

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 25 March 2018 |
| First version publication date | 25 March 2018 |

**Trial information****Trial identification**

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | CCR3261 |
|-----------------------|---------|

**Additional study identifiers**

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | ISRCTN39058880   |
| ClinicalTrials.gov id (NCT number) | NCT01395121  |
| WHO universal trial number (UTN)   | -  |
| Other trial identifiers            | Cancer Research UK: CRUK/09/028 , MHRA CTA: 15983/0226/001 , Main REC Reference: OXFORDSHIRE C 09/H0606/103, ICR-CTSU Protocol Number: ICR-CTSU/2009/10020 |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | The Institute of Cancer Research  |
| Sponsor organisation address | 15 Cotswold Road, Sutton, United Kingdom, SM2 5NG   |
| Public contact               | NICAM Trial Manager, The Institute of Cancer Research, nicam-icrctsu@icr.ac.uk            |
| Scientific contact           | NICAM Trial Manager, The Institute of Cancer Research, nicam-icrctsu@icr.ac.uk            |
| Sponsor organisation name    | The Royal Marsden Hospital Foundation Trust   |
| Sponsor organisation address | Downs Road, Sutton, United Kingdom, SM2 5PT   |
| Public contact               | NICAM Trial Manager, The Royal Marsden Hospital Foundation Trust, nicam-icrctsu@icr.ac.uk |
| Scientific contact           | NICAM Trial Manager, The Royal Marsden Hospital Foundation Trust, nicam-icrctsu@icr.ac.uk |

Notes:

**Paediatric regulatory details**

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No                                | No |

Notes:

**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 09 January 2017  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 12 December 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 12 December 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

**General information about the trial**

Main objective of the trial:

To evaluate the safety and effectiveness of the drug nilotinib in the treatment of acral and mucosal melanomas which have mutations in a cell surface protein known as c-KIT.

Protection of trial subjects:

For cKIT mutation status testing, trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information. Those providing the verbal explanation and discussion had training and experience in dealing with patients with advanced acral or mucosal melanoma. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.

The patients were given as much time as they needed to come to a decision about screening for the trial prior to giving consent for registration and cKIT screening. It took at least 3 weeks for the results of the cKIT test to be returned to the specialist centre during which time the patient had further opportunity to consider the trial. Once eligibility had been confirmed, patients were given as much time as they needed to come to a decision about trial entry, as long as they remained eligible.

The patient information sheet, which was provided to the patient prior to obtaining consent for screening and discussed again with the patient prior to consent for trial entry, described fully which parties would have access to their identifiable personal information and patients were asked to give their consent to this.

The trial treatment was less onerous than standard treatment with intravenous DTIC chemotherapy given every 3 weeks (i.e. less frequent visits and blood tests and orally administered treatment). Some medications interact with nilotinib and advice was given in both the patient information sheet and protocol on which medications should be avoided.

As the trial continued any relevant information was conveyed to the patient via the patient's oncologist. The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 15 December 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 29 |
| Worldwide total number of subjects   | 29                 |
| EEA total number of subjects         | 29                 |

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Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 13 |
| From 65 to 84 years                       | 16 |
| 85 years and over                         | 0  |

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## Subject disposition

### Recruitment

Recruitment details:

Initial consent was obtained from patients for registration into the screening stage of the trial. Screening evaluations, including c-KIT sequencing, were performed to confirm eligibility for trial entry. Once confirmed, consent was obtained from patients for entry into the treatment stage of the trial.

### Pre-assignment

Screening details:

Initial consent for c-kit mutation determination and screening was obtained for 219 patients. c-kit mutation status could be determined for 191 patients, with 39 being identified as c-kit positive. Ten patients did not enter study due to: death (2), metastases (3), pt choice/responding on current treatment (2), too ill (3).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|  |               |
|--|---------------|
| Arm title                              | Nilotinib     |
| Arm description: -                     |               |
| Arm type                               | Experimental  |
| Investigational medicinal product name | Nilotinib     |
| Investigational medicinal product code | L01XE08       |
| Other name                             | Tasigna       |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

800 mg daily (2 x 200 mg capsules twice a day) administered to the patient for as long as patient is gaining clinical benefit.

| Number of subjects in period 1    | Nilotinib |
|-----------------------------------|-----------|
| Started                           | 29        |
| Completed                         | 28        |
| Not completed                     | 1         |
| Relapsed prior to start treatment | 1         |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description:

All patients enrolled in this single stage phase II trial

| Reporting group values                             | Overall Trial | Total |  |
|--|---------------|-------|--|
| Number of subjects                                 | 29            | 29    |  |
| Age categorical                                    |               |       |  |
| Units: Subjects                                    |               |       |  |
| In utero   |               | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) |               | 0     |  |
| Newborns (0-27 days)                               |               | 0     |  |
| Infants and toddlers (28 days-23 months)           |               | 0     |  |
| Children (2-11 years)                              |               | 0     |  |
| Adolescents (12-17 years)                          |               | 0     |  |
| Adults (18-64 years)                               |               | 0     |  |
| From 65-84 years                                   |               | 0     |  |
| 85 years and over                                  |               | 0     |  |
| Age continuous                                     |               |       |  |
| Units: years                                       |               |       |  |
| arithmetic mean                                    | 67.1          |       |  |
| standard deviation                                 | ± 9.1         | -     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female   | 20            | 20    |  |
| Male   | 9             | 9     |  |

## End points

### End points reporting groups

|   |                                   |
|---|-----------------------------------|
| Reporting group title   | Nilotinib                         |
| Reporting group description: -  |                                   |
| Subject analysis set title  | Evaluable population              |
| Subject analysis set type   | Per protocol                      |
| Subject analysis set description:   |                                   |
| Patients enrolled into the study evaluable for the primary endpoint (eligible and possible to establish RECIST assessment by 6 months or prior progression or death). |                                   |
| Subject analysis set title  | Evaluable population (as planned) |
| Subject analysis set type   | Per protocol                      |
| Subject analysis set description:   |                                   |
| This phase II trial was planned on 24 patients, but due to replacement of unevaluable patients, the trial over-recruited to 26 evaluable patients.                    |                                   |
| Subject analysis set title  | Safety population                 |
| Subject analysis set type   | Safety analysis                   |
| Subject analysis set description:   |                                   |
| All patients who received at least 1 dose of study treatment.   |                                   |

### Primary: Proportion alive and progression free at 6 months

|  |  |
|--|--|
| End point title  | Proportion alive and progression free at 6 months <sup>[1]</sup> |
| End point description:   |  |
| The primary endpoint of NICAM is the proportion of patients alive and progression free according to RECIST criteria (as assessed locally at the participating site) at 6 months.   |  |
| Under a 2-stage design, the trial was planned with 24 overall patients: if 7 or more out of 24 were alive and progression free at 6 months, nilotinib would have shown worthwhile activity to pursue further investigation. Because more than 24 patients were recruited to replace non-evaluable patients, the primary endpoint was assessed in the first 24 evaluable patients and in the overall 26 evaluable patients. The SAP specified that a one-sided binomial test would be used to disprove the null hypothesis that 6 month proportion alive and free of progression is $\leq 15\%$ . |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| 6 months from trial entry  |  |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single arm study and no comparative analysis is performed, but the system expects at least 2 groups to be identified. All methods and options specified in analysis section apply to statistical methods and summary measures to report and compare at least 2 independent groups, which is not the case in this single arm trial. There is no way of reporting one-group inference and summary values without triggering an error or reporting inaccurate information.

| End point values                | Evaluable population | Evaluable population (as planned) |  |  |
|---------------------------------|----------------------|-----------------------------------|--|--|
| Subject group type              | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed     | 26                   | 24                                |  |  |
| Units: Patients                 |                      |                                   |  |  |
| Alive and progression free      | 6                    | 6                                 |  |  |
| Progressed <6 months            | 11                   | 10                                |  |  |
| Died <6 months & no progression | 1                    | 1                                 |  |  |
| Progressed and died <6 months   | 8                    | 7                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion alive and progression free at 6 months (central review)

|                 |  |
|-----------------|--|
| End point title | Proportion alive and progression free at 6 months (central review) |
|-----------------|--|

End point description:

Proportion of patients alive and progression free according to RECIST criteria as assessed by central review at 6 months. Central review of the CT on trial scans was performed for all evaluable patients. A single independent reviewer assessed centrally all available scans. In case of discrepancy between local and central review, a 3rd independent reviewer assessed the scans to resolve the discrepancy. The SAP specified that a one-sided binomial test would be used to disprove the null hypothesis that 6 month proportion alive and free of progression is  $\leq 15\%$ .

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months from trial entry

| End point values                | Evaluable population | Evaluable population (as planned) |  |  |
|---------------------------------|----------------------|-----------------------------------|--|--|
| Subject group type              | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed     | 26                   | 24                                |  |  |
| Units: Patients                 |                      |                                   |  |  |
| Alive and progression free      | 7                    | 7                                 |  |  |
| Progressed <6 months            | 10                   | 9                                 |  |  |
| Died <6 months (no progression) | 1                    | 1                                 |  |  |
| Progressed and died <6 months   | 8                    | 7                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Response rate at 12 weeks as assessed locally

|                 |   |
|-----------------|---|
| End point title | Response rate at 12 weeks as assessed locally |
|-----------------|---|

End point description:

Response at 12 weeks is defined as partial or complete response, as assessed using RECIST criteria, at the 12 week assessment. As for the primary endpoint, the analysis is performed in the first 24 patients entered and evaluable, and repeated in all 26 evaluable patients. The proportion of patients with CR or PR at 12 weeks is reported with 95% confidence intervals.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
12 weeks from trial entry

| End point values            | Evaluable population | Evaluable population (as planned) |  |  |
|-----------------------------|----------------------|-----------------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed | 26                   | 24                                |  |  |
| Units: Patients             |                      |                                   |  |  |
| Complete response           | 1                    | 1                                 |  |  |
| Partial response            | 4                    | 4                                 |  |  |
| Stable disease              | 9                    | 8                                 |  |  |
| Progressive disease         | 12                   | 11                                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival at 12 months

|   |                               |
|---|-------------------------------|
| End point title   | Overall survival at 12 months |
| End point description:<br>Time from trial entry to death is summarised by overall survival, estimated by Kaplan-Meier. The timepoint of interest (12 months) is reported with 95% confidence intervals. |                               |
| End point type  | Secondary                     |
| End point timeframe:<br>12 months   |                               |

| End point values                 | Safety population    |  |  |  |
|----------------------------------|----------------------|--|--|--|
| Subject group type               | Subject analysis set |  |  |  |
| Number of subjects analysed      | 28                   |  |  |  |
| Units: percentage survival       |                      |  |  |  |
| number (confidence interval 95%) | 46.5 (26.9 to 63.9)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From trial entry to 30 days after last dose of trial treatment.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 14 |
|--------------------|----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description:

Patients who received at least 1 dose of experimental treatment.

In the non-serious adverse events section we report all serious and non-serious adverse events reported with grade 3 or 4 according to the CTCAE grading, that were present in more than 5% of patients.

| Serious adverse events  | Safety population |  |  |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed   | 10 / 28 (35.71%)  |  |  |
| number of deaths (all causes)                                       | 28                |  |  |
| number of deaths resulting from adverse events                      | 0                 |  |  |
| Investigations  |                   |  |  |
| Blood bilirubin increased   |                   |  |  |
| subjects affected / exposed   | 1 / 28 (3.57%)    |  |  |
| occurrences causally related to treatment / all                     | 1 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Liver function test abnormal  |                   |  |  |
| subjects affected / exposed   | 1 / 28 (3.57%)    |  |  |
| occurrences causally related to treatment / all                     | 4 / 4             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Breast cancer   |                   |  |  |
| subjects affected / exposed   | 1 / 28 (3.57%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Tumour pain   |                   |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Injury, poisoning and procedural complications       |                |  |  |
| Fall   |                |  |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vascular disorders                                   |                |  |  |
| Oedema peripheral                                    |                |  |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Embolism   |                |  |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Nervous system disorders                             |                |  |  |
| Seizure  |                |  |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Muscular weakness                                    |                |  |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Pain   |                |  |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Abdominal pain                                       |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea  |                |  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Oesophageal pain                                |                |  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 2 / 28 (7.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Chest pain                                      |                |  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Cellulitis                                      |                |  |  |
| subjects affected / exposed                     | 2 / 28 (7.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lower respiratory tract infection               |                |  |  |
| subjects affected / exposed                     | 2 / 28 (7.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Safety population |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 12 / 28 (42.86%)  |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed                           | 3 / 28 (10.71%)   |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Gastrointestinal disorders                            |                   |  |  |
| Abdominal pain  |                   |  |  |
| subjects affected / exposed                           | 3 / 28 (10.71%)   |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Nausea  |                   |  |  |
| subjects affected / exposed                           | 2 / 28 (7.14%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Vomiting  |                   |  |  |
| subjects affected / exposed                           | 2 / 28 (7.14%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Infections and infestations                           |                   |  |  |
| Cellulitis  |                   |  |  |

|                                   |                |  |  |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed       | 2 / 28 (7.14%) |  |  |
| occurrences (all)                 | 2              |  |  |
| Lower respiratory tract infection |                |  |  |
| subjects affected / exposed       | 2 / 28 (7.14%) |  |  |
| occurrences (all)                 | 2              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 16 February 2010 | <p>Eligibility criteria updated to change from at least 28 days from major surgery to 14 days and to remove the stipulation regarding time since biopsy (since patients have a biopsy whilst on study medication at days 1 and 15).</p> <p>Updated assessment schedule as follows: further clarification of the screening evaluation demographic details explicitly to include smoking history, family history of melanoma and Fitzpatrick skin classification and physical evaluation to include pulse; baseline assessments on day 1 updated to remove 'physical examination' (this would have been conducted at screening); assessment of height, weight, ECOG performance status, pulse and blood pressure added to all visits; adverse event reporting has been removed from day 1 since this was not applicable; and follow up schedule changed from every 4 weeks to every 4 weeks in year 1 and 8 weekly thereafter with tumour re-staging every 3 months.</p> <p>RECIST guidelines updated to include the addition of malignant lymph nodes must be <math>\geq 15</math> mm in the short axis when assessed by CT scan to be considered measurable under evaluation of measurable and non-measurable lesions.</p> <p>As requested by REC the date of birth was removed from the circulating tumour cells (CTCs) label details.</p> |
| 25 May 2010      | <p>Removal of the measurement of circulating tumours cells (CTCs) as recent data suggested that collection of CTCs in melanoma was not that useful therefore CTC analysis will not be performed.</p> <p>Inclusion criteria updated to include measurement of AST or ALT.</p> <p>Trial Steering Committee and the Independent Data Monitoring Committee combined into one committee.</p> <p>Removal of genomic analysis carried out on normal skin and addition of genomic DNA extraction from blood samples for analysis and comparison with tumour DNA.</p> <p>Removal of instruction relating to processing of bloods at local site, all processing to be conducted in the central research laboratory.</p>   |
| 03 December 2010 | <p>Addition of blood test for amylase and lipase added to the schedule of assessments for consistency with screening requirements plus administrative updates due to study personnel changes.</p>   |
| 27 May 2011      | <p>Schedule of assessments table updated to clarify the requirements for lipase and amylase blood tests and advise on requirement for blood tests to be repeated if there was clinical indication to do so.</p>   |
| 30 July 2012     | <p>Expected rate of c-KIT mutation in advanced acral and mucosal melanoma updated from 20% to 10-20% based on current literature and subsequent clarification that at least 120 patients would need to be screened in order to identify 24 patients eligible for the trial.</p> <p>Update made to allow accredited c-KIT laboratories to determine the c-KIT status of their own patients without the need to send for central confirmation at The Royal Marsden NHS Foundation Trust.</p> <p>Update to the study end date deemed to be the date of last data capture changed in line with the current regulatory requirements.</p> <p>Administrative updates due to study personnel changes.</p>   |
| 05 June 2013     | <p>Addition of further clarification regarding the testing process for patients from regional centres who may have their samples processed at a regional accredited laboratory without the need to send for central testing at the Royal Marsden NHS Foundation Trust.</p> <p>Summary of product information provided by the drug company no longer included proton pump inhibitors as recent research showed that these drugs were no longer thought to compromise the absorption of nilotinib therefore reference to proton pump inhibitors was removed from protocol.</p>  |

|                 |   |
|-----------------|---|
| 20 January 2015 | Change to schedule for restaging CT scans to be performed every 4 months after the patient has remained on study for 3 years to reduce the burden of clinic visits. |
|-----------------|---|

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported