



## Clinical trial results:

**A randomized phase II study to explore the efficacy and feasibility of upfront bi-monthly rotations between Everolimus and Pazopanib with sequential treatment of first line Pazopanib and second line Everolimus until progression in patients with advanced or metastatic clear cell renal cancer.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-000127-32 |
| Trial protocol           | NL             |
| Global end of trial date | 05 April 2016  |

### Results information

|                                   |                                                               |
|-----------------------------------|---------------------------------------------------------------|
| Result version number             | v1 (current)                                                  |
| This version publication date     | 15 June 2022                                                  |
| First version publication date    | 15 June 2022                                                  |
| Summary attachment (see zip file) | Statistical report (M2. Statistical Report dd 22-06-2018.pdf) |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | ROPETAR |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01408004 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                      |
|------------------------------|--------------------------------------------------------------------------------------|
| Sponsor organisation name    | WIN-O                                                                                |
| Sponsor organisation address | Postbus 821, Zeist, Netherlands, 3700 AV                                             |
| Public contact               | Medical oncology/G.A. Cirkel, UMC Utrecht, +31 887556265, g.a.cirkel-2@umcutrecht.nl |
| Scientific contact           | Medical oncology/G.A. Cirkel, UMC Utrecht, +31 887556265, g.a.cirkel-2@umcutrecht.nl |
| Sponsor organisation name    | WIN-O                                                                                |
| Sponsor organisation address | Postbus 821, Zeist , Netherlands, 3700 AV                                            |
| Public contact               | Jeanine Eikmans, WIN-O, +31 639488702 , nfo@win-o.nl                                 |
| Scientific contact           | Jeanine Eikmans, I WIN-O, +31 639488702 , info@win-o.nl                              |

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 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 11 March 2016 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 11 March 2016 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 05 April 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to assess the progression-free survival of patients who receive bi-monthly rotations of Pazopanib and Everolimus versus patients who receive Pazopanib as a first line treatment.

Protection of trial subjects:

NA

Background therapy:

NA

Evidence for comparator:

COMPARZ trial

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 15 July 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 101 |
| Worldwide total number of subjects   | 101              |
| EEA total number of subjects         | 101              |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| 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)                      | 60 |
| From 65 to 84 years                       | 41 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Within time limits, between September 2012 and April 2014

### Pre-assignment

Screening details:

NA

### Period 1

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

Blinding implementation details:

NA

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Experimental |

Arm description:

Experimental: rotating treatment

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | pazopanib     |
| Investigational medicinal product code |               |
| Other name                             | Votrient      |
| Pharmaceutical forms                   | Coated tablet |
| Routes of administration               | Oral use      |

Dosage and administration details:

800mg 1dd 8 weeks (rotating)

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | everolimus |
| Investigational medicinal product code |            |
| Other name                             | afinitor   |
| Pharmaceutical forms                   | Capsule    |
| Routes of administration               | Oral use   |

Dosage and administration details:

10 mg QD, 8 weeks, rotating

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Comparator |
|------------------|------------|

Arm description:

pazopanib until PD, then everolimus

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | pazopanib         |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Coated tablet     |
| Routes of administration               | Oral use          |

Dosage and administration details:

800mg QD until PD

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Capsule    |
| Routes of administration               | Oral use   |

Dosage and administration details:

10 mg QD, until PD

| <b>Number of subjects in period 1</b> | Experimental | Comparator |
|---------------------------------------|--------------|------------|
| Started                               | 52           | 49         |
| Completed                             | 52           | 49         |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values                                                                                                                                                                                                         | Overall trial | Total |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-------|--|
| Number of subjects                                                                                                                                                                                                             | 101           | 101   |  |
| Age categorical                                                                                                                                                                                                                |               |       |  |
| Age<br>Median<br>Experimental: 65<br>Comparator: 67<br>Overall: 66<br>0% 25% 75% 100% quantile<br>Experimental: 44 59 71 87<br>Comparator: 38 58 72 82<br>Overall: 38 58 72 87<br>Mean 65 65 65<br>Standard Deviation 10 10 10 |               |       |  |
| Units: Subjects                                                                                                                                                                                                                |               |       |  |
| In utero                                                                                                                                                                                                                       | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                                                                                                                                                                          | 0             | 0     |  |
| Newborns (0-27 days)                                                                                                                                                                                                           | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)                                                                                                                                                                                       | 0             | 0     |  |
| Children (2-11 years)                                                                                                                                                                                                          | 0             | 0     |  |
| Adolescents (12-17 years)                                                                                                                                                                                                      | 0             | 0     |  |
| Adults (18-64 years)                                                                                                                                                                                                           | 0             | 0     |  |
| From 65-84 years                                                                                                                                                                                                               | 0             | 0     |  |
| 85 years and over                                                                                                                                                                                                              | 0             | 0     |  |
| Age > 18 years                                                                                                                                                                                                                 | 101           | 101   |  |
| Gender categorical                                                                                                                                                                                                             |               |       |  |
| Units: Subjects                                                                                                                                                                                                                |               |       |  |
| Female                                                                                                                                                                                                                         | 32            | 32    |  |
| Male                                                                                                                                                                                                                           | 69            | 69    |  |
| Reference                                                                                                                                                                                                                      |               |       |  |
| Please refer to JAMA Oncol. 2017;3(4):501-508 for a complete overview of baseline characteristics                                                                                                                              |               |       |  |
| Units: Subjects                                                                                                                                                                                                                |               |       |  |
| Link to paper                                                                                                                                                                                                                  | 101           | 101   |  |

## End points

### End points reporting groups

|                                       |              |
|---------------------------------------|--------------|
| Reporting group title                 | Experimental |
| Reporting group description:          |              |
| Experimental: rotating treatment      |              |
| Reporting group title                 | Comparator   |
| Reporting group description:          |              |
| pazopaninbg until PD, then everolimus |              |

### Primary: Progression free survival

|                                                             |                           |
|-------------------------------------------------------------|---------------------------|
| End point title                                             | Progression free survival |
| End point description:                                      |                           |
| survival until first progression or death.                  |                           |
| End point type                                              | Primary                   |
| End point timeframe:                                        |                           |
| Randomisation to survival until first progression or death. |                           |

| End point values                 | Experimental      | Comparator        |  |  |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type               | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed      | 52                | 49                |  |  |
| Units: month                     |                   |                   |  |  |
| median (confidence interval 95%) | 7.4 (5.6 to 18.4) | 9.4 (6.6 to 11.9) |  |  |

|                                   |                                                            |
|-----------------------------------|------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Charts in paper/jamaoncology_cirkel_2016_oi_160080 (1) (1) |
|-----------------------------------|------------------------------------------------------------|

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Statistical Methods              |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                  |
| A total sample size of 100 patients was planned. From literature it was estimated that the 1-year PFS1 in the control arm would be 50%. An increase from 50% to 80% 1-year PFS of the rotating schedule over standard of care with first-line VEGFR-TKI was considered to be clinically relevant. Primary analysis was planned when over 60 events (first progression or death) were recorded, enabling detection of an increase in 1-year PFS to 80% (power 90%, $\alpha=.05$ , 2-tailed test). |                                  |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Experimental v Comparator        |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 101                              |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Pre-specified                    |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | superiority                      |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | = 0.05                           |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Regression, Cox                  |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Median difference (final values) |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 50                               |

|                      |                    |
|----------------------|--------------------|
| Confidence interval  |                    |
| level                | 95 %               |
| sides                | 2-sided            |
| lower limit          | 50                 |
| upper limit          | 80                 |
| Variability estimate | Standard deviation |
| Dispersion value     | 0                  |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Time between first drug dose and 30 days after EOT

Adverse event reporting additional description:

NA

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

### Dictionary used

|                 |     |
|-----------------|-----|
| Dictionary name | CTC |
|-----------------|-----|

|                    |      |
|--------------------|------|
| Dictionary version | 4.03 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Experimental |
|-----------------------|--------------|

Reporting group description:

Experimental: rotating treatment

|                       |            |
|-----------------------|------------|
| Reporting group title | Comparator |
|-----------------------|------------|

Reporting group description:

pazopanib until PD, then everolimus

| Serious adverse events                            | Experimental                                                                                                                                                                     | Comparator       |  |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|--|
| Total subjects affected by serious adverse events |                                                                                                                                                                                  |                  |  |
| subjects affected / exposed                       | 22 / 52 (42.31%)                                                                                                                                                                 | 24 / 49 (48.98%) |  |
| number of deaths (all causes)                     | 5                                                                                                                                                                                | 7                |  |
| number of deaths resulting from adverse events    | 2                                                                                                                                                                                | 2                |  |
| Investigations                                    |                                                                                                                                                                                  |                  |  |
| Adverse event                                     | Additional description: It;s impossible to enter all SAEs manually. Please refer to fullpaper: JAMA Oncol. 2017;3(4):501-508 and separate uploaded PDF with all AEs/SAEs details |                  |  |
| subjects affected / exposed                       | 22 / 52 (42.31%)                                                                                                                                                                 | 24 / 49 (48.98%) |  |
| occurrences causally related to treatment / all   | 22 / 22                                                                                                                                                                          | 24 / 24          |  |
| deaths causally related to treatment / all        | 0 / 2                                                                                                                                                                            | 1 / 2            |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Experimental      | Comparator        |  |
|-------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 52 / 52 (100.00%) | 49 / 49 (100.00%) |  |
| Investigations                                        |                   |                   |  |
| Adverse event                                         |                   |                   |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 52 / 52 (100.00%) | 49 / 49 (100.00%) |  |
| occurrences (all)           | 52                | 49                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Not all required data are available and/or impossible to enter in this overview. PLEASE REFER TO FULL PAPER IN JAMA ONCOLOGY OR ATTACHED STATISTICAL REPORT FOR VALIDATED DATA |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27918762>