



Clinical trial results:

Randomized Phase IV Trial to Compare Cetuximab with Concomitant Radiation Therapy with Concomitant

Mitomycin-C and 5-FU with Radiation Therapy for Locally Advanced Squamous Cell Carcinomas of The Head and Neck

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-001296-20 |
| Trial protocol | AT |
| Global end of trial date | 19 April 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 19 February 2017 |
| First version publication date | 19 February 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MITOCET |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02015650 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Medical University of Innsbruck |
| Sponsor organisation address | Anichstraße 35, Innsbruck, Austria, 6020 |
| Public contact | OE Clinical Trial Center, Medical University of Innsbruck, 0043 512900370086, ctc@i-med.ac.at |
| Scientific contact | OE Clinical Trial Center, Medical University of Innsbruck, 0043 512900370086, ctc@i-med.ac.at |

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 | 18 August 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 April 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 April 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate that Cetuximab combined with radiation therapy has a higher life quality compared to 5-FU/MMC plus radiation therapy, because of decreased side effects.

Protection of trial subjects:

Participants

- must be between ≥ 18 and ≤ 70 years of Age
- must have specific laboratory values within a certain Limit e.g. neutrophil Count ≥ 1.5 G/l
- must be medically suitable to withstand a course of definitive radiation therapy and concomitant chemotherapy or antibody-therapy
- must have a Karnofsky performance status (KPS) of ≥ 70 at the time of screening
- must not be pregnant or breastfeeding
- must not be participating actively in another clinical trial

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 30 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Austria: 4 |
| Worldwide total number of subjects | 4 |
| EEA total number of subjects | 4 |

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) | 0 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The recruitment of cancer patients treated at the investigational centre was referred from other institutions or from the cancer patients presented in the local head and neck tumor board review. A record of the most recent pre-treatment evaluations has been reviewed to determine the suitability of the patient for the trial.

Pre-assignment

Screening details:

Day -21/-14: Check of inclusion and exclusion criteria, performing of physical examination, vital signs and laboratory test. Verification of histology, tumor imaging and tumor assessment.

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cetuximab |

Arm description:

Cetuximab in combination with radiotherapy

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | Erbitux |
| Pharmaceutical forms | Powder and solvent for solution for injection/infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

minimum of 10 weekly infusions
400 mg/m² loading dose on week 0;
250 mg/m² maintenance doses beginning on week 1 - 9

| | |
|------------------|--------------------------------|
| Arm title | Mitomycin C and 5-Flourouracil |
|------------------|--------------------------------|

Arm description:

Mitomycin-C and 5-Flourouracil in combination with radiotherapy

| | |
|--|-----------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Mitomycin C |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

10mg/m² (max. 15 mg/d) day 8 and day 43

| | |
|--|---|
| Investigational medicinal product name | 5- Flourouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for prolonged-release suspension for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

in total 1000 mg/m² (max. 1500mg/24h) days 8-12 and days 43-47

| Number of subjects in period 1 | Cetuximab | Mitomycin C and 5-Flourouracil |
|---------------------------------------|-----------|--------------------------------|
| Started | 2 | 2 |
| Completed | 0 | 0 |
| Not completed | 2 | 2 |
| tumor progression | - | 1 |
| Lost to follow-up | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------|
| Reporting group title | Cetuximab |
| Reporting group description: Cetuximab in combination with radiotherapy | |
| Reporting group title | Mitomycin C and 5-Flourouracil |
| Reporting group description: Mitomycin-C and 5-Flourouracil in combination with radiotherapy | |

| Reporting group values | Cetuximab | Mitomycin C and 5-Flourouracil | Total |
|---|-----------|--------------------------------|-------|
| Number of subjects | 2 | 2 | 4 |
| Age categorical | | | |
| In total 70 patients have been planned to be included in the trial, 35 patients for each arm. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 2 | 2 | 4 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 0 | 1 |
| Male | 1 | 2 | 3 |

Subject analysis sets

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Risk and benefit analysis |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Risk of the study have been the known side effects of the products: Mitomycin-C, 5-Fluorouracil, Cetuximab and radiation therapy. These are listed in the particular product description and the description of radiation therapy. Another risk would be that the primary objective cannot be fulfilled. So the patients would have a lower quality of life than expected. Some of the benefits for the Patient would have been a decrease of pain medication and side effects caused by pain medication, a decrease of surgical Intervention, Improving of patients social functioning, social eating, social contact, No interruptions of therapy and Increase of life Quality.

| Reporting group values | Risk and benefit analysis | | |
|---|---------------------------|--|--|
| Number of subjects | 4 | | |
| Age categorical | | | |
| In total 70 patients have been planned to be included in the trial, 35 patients for each arm. | | | |
| Units: Subjects | | | |

| | | | |
|---|---|--|--|
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | 4 | | |
| Gender categorical Units: Subjects | | | |
| Female | 1 | | |
| Male | 3 | | |

End points

End points reporting groups

| | |
|-----------------------------------|---|
| Reporting group title | Cetuximab |
| Reporting group description: | Cetuximab in combination with radiotherapy |
| Reporting group title | Mitomycin C and 5-Flourouracil |
| Reporting group description: | Mitomycin-C and 5-Flourouracil in combination with radiotherapy |
| Subject analysis set title | Risk and benefit analysis |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | Risk of the study have been the known side effects of the products: Mitomycin-C, 5-Fluorouracil, Cetuximab and radiation therapy. These are listed in the particular product description and the description of radiation therapy. Another risk would be that the primary objective cannot be fulfilled. So the patients would have a lower quality of life than expected. Some of the benefits for the Patient would have been a decrease of pain medication and side effects caused by pain medication, a decrease of surgical Intervention, Improving of patients social functioning, social eating, social contact, No interruptions of therapy and Increase of life Quality. |

Primary: Quality of Life

| | |
|------------------------|---|
| End point title | Quality of Life |
| End point description: | |
| End point type | Primary |
| End point timeframe: | evaluation of assessment 5 times during active Phase and 9 times during Follow-Up |

| End point values | Cetuximab | Mitomycin C and 5-Flourouracil | | |
|--------------------------------------|-----------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: assessment of quality of life | 2 | 2 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistics primary endpoint active phase |
| Comparison groups | Cetuximab v Mitomycin C and 5-Flourouracil |
| Number of subjects included in analysis | 4 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| P-value | = 0.05 ^[2] |
| Method | Fisher exact |

Notes:

[1] - The primary objective of this study is to compare whether a combination therapy with Cetuximab improves patient's quality of life measured with EORTC QLQ-C30 plus H&N35.

The primary objective of this study is to compare whether a combination therapy with Cetuximab reduces toxicity regarding the occurrence of rash and mucositis.

[2] - The primary analysis population will comprise all randomized patients according to the intention-to-treat principle; a secondary per-protocol analysis will exclude patients with major protocol deviations.

Statistical

tests will generally be two-sid

Secondary: Response rate

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|-----------------|---------------|
| End point title | Response rate |
|-----------------|---------------|

End point description:

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

End point timeframe:

No assessment during active Phase, 4 times assessment during Follow-Up phase

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in locoregional disease control

| | |
|-----------------|---|
| End point title | Differences in locoregional disease control |
|-----------------|---|

End point description:

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

End point timeframe:

No assessment during active Phase, 4 times assessment during Follow-Up.

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From patient inclusion to drop-out respectively premature termination of the study

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

Dictionary used

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|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

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

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Cetuximab |
|-----------------------|-----------|

Reporting group description:

Cetuximab in combination with radiotherapy

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|-----------------------|--------------------------------|
| Reporting group title | Mitomycin C and 5-Flourouracil |
|-----------------------|--------------------------------|

Reporting group description:

Mitomycin-C and 5-Flourouracil in combination with radiotherapy

| Serious adverse events | Cetuximab | Mitomycin C and 5-Flourouracil | |
|--|---|--------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 1 / 2 (50.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Brachial plexopathy | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Reduced appetite | Additional description: Reduced general condition due to reduced appetite caused by combined radioimmunotherapy. | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia and thrombocytopenia | Additional description: Recently diagnosed pancreatic cancer with livermetastases. Patient received chemotherapy with cisplatin. Leucopenia, neutropenia and thrombopenia are caused by chemotherapy. | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|----------------|----------------|
| Gastrointestinal disorders Dysphagia | Additional description: Expected side effects like dysphagia and increase mucus production seem straining for the patient so that the patient couldn't continue therapy in an ambulant setting. | | |
| | subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders Tracheal stenosis and laryngeal dyspnoea | | | |
| | subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Cetuximab | Mitomycin C and 5-Flourouracil | |
|---|------------------------------------|--------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 2 / 2 (100.00%) | |
| General disorders and administration site conditions | | | |
| Fatigue | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Edema face | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Laryngeal mucositis | Additional description: Grade 1, 2 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 6 | 1 | |
| Sore throat | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Productive cough | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Hoarseness | Additional description: Grade 1, 2 | | |

| | | | |
|--|--|-----------------|--|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 2 | |
| Laryngeal stenosis | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Anorexia | Additional description: Grade 1, 2 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | Additional description: Grade 1 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Dermatitis radiation | Additional description: Grade 1, 2 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nervous system disorders | | | |
| Dysgeusia | Additional description: Grade1, 2 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 2 | 1 | |
| Lethargy | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| Vertigo | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Dysphagia | Additional description: Grade 1, 2, 3 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 2 / 2 (100.00%) | |
| occurrences (all) | 3 | 4 | |
| Dry mouth | Additional description: Grades 1, 2, 3 | | |

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|--|---|----------------|--|
| subjects affected / exposed | 2 / 2 (100.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 4 | 1 | |
| Vomiting | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | Additional description: Grade 3 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastritis | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mucositis oral | Additional description: Grade 1, 2 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 4 | |
| Stomach pain | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Gastroesophageal reflux disease | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash acneiform | Additional description: rash face and/or rash body; Grade 1, two and/or 3 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Erythema PEG placing | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Hyperthyroidism | Additional description: latent hyperthyroidism, Grade 1 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypothyroidism | Additional description: Grade 1 | | |

| | | | |
|---|---------------------------------|----------------|--|
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperthyroidism with isolated FT4 increase | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 2 | |
| Infections and infestations | | | |
| Paronychia | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract infection | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Hypophosphatemia | Additional description: Grade 1 | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypomagnesemia | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Hyperuricemia | Additional description: Grade 1 | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Hyperglycemia | Additional description: Grade 2 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoalbuminemia | Additional description: Grade 1 | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 2 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 February 2015 | Change of inclusion criteria in order to fullfill the recruitment rate |

Notes:

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.

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|----------------------|
| low recruitment rate |
|----------------------|

Notes: