AGMT_MM-3

Denosumab for high risk SMM and SLiM CRAB positive, early myeloma patients – a randomized , placebo controlled, phase II trial "DEFENCE" (DEnosumab For the rEductioN of the smoldering myeloma transformatioN inCidence ratE)

EudraCT Number: 2018-000924-32

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Protocol Synopsis

Indication: High risk Smoldering Multiple Myeloma or early "SLiM CRAB" Multiple Myeloma

Study design: Randomized, placebo controlled, phase II study

Number of Patients: 164

Duration: First patient in (FPI): Q2 2019 (expected)
Last patient in (LPI): Q3 2021 (expected)
Last patient last visit (LPLV): Q3 2025 (expected)

Study medication: Denosumab / Placebo

Status: Approval IEC in Austria: 07.12.2018

Planned countries: Austria, Germany, Israel

Planned sites in Austria:
- Wilhelminenspital
- UK Innsbruck
- PMU Salzburg
- UK Graz
- LKH Hochsteiermark
- LKH Steyr
- Ordensklinikum Linz
- UK Wien
- LK Wr. Neustadt
- UK St. Pölten
- Kepler UK Linz

Primary endpoint:
Time from randomization to transformation to symptomatic, active MM (defined as progression to active multiple myeloma according to IMWG diagnosis criteria 2014) or progression of disease according to IMWG response criteria 2016

Secondary endpoints:
- Percentage of patients with high-risk SMM and early "SLiM CRAB" positive MM transforming to CRAB positive multiple myeloma and/or developing serological progression (as defined by IMWG criteria 2016 for MM) within 3 years
- Percentage of high risk SMM patients progressed to active, symptomatic MM within 3 years
- Percentage of ultra-high risk SMM (asymptomatic, early MM, defined by "SLiM CRAB") patients progressed to active, symptomatic MM within 3 years
- Incidence of bone lesions as MM defining events
- Time to first skeletal-related event
- Time to symptomatic skeletal-related event
- Time to first anti-myeloma treatment
- Overall survival

Inclusion Criteria (selected)

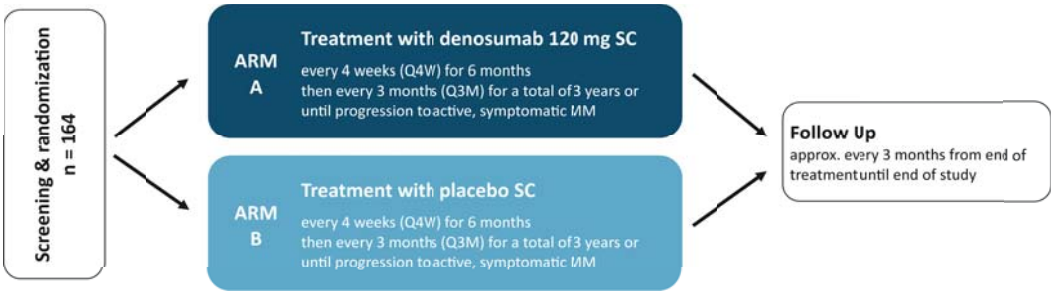
High risk smoldering MM or early "SLiM CRAB" MM based on the criteria described below:

- High-risk SMM as defined by the Mayo Clinical algorithm:
  - → Bone marrow clonal plasma cells ≥ 10% +
  - → Serum M protein ≥ 3.0g/dL +
  - → Serum free light chain ratio < 0.125 or ≥ 8 (but less than 100)
- Early "SLiM CRAB" multiple myeloma:
  Patients must present with one or more of the following features:
  - → Bone marrow clonal plasma cells ≥ 60%, or
  - → Serum FLC ratio ≥ 100, or
  - → >1 Focal bone lesion of ≥ 5mm (PET-CT)
- Age > 18 years, all sexes

Exclusion Criteria (selected)

- ECOG > 3
- Active, symptomatic MM (fulfilling CRAB-criteria)
- Non-secretory MM
- MGUS
- Hypocalcemia (can be corrected by drug intervention before start of treatment)
- Second malignancy within the past 5 years with exceptions
- Prior administration of denosumab
- Use of oral bisphosphonates with a cumulative exposure of more than 1 year
- More than 1 previous dose of IV bisphosphonate administration
- Prior history or current evidence of osteonecrosis/ osteomyelitis of the jaw

Study Design



This is a randomized, placebo controlled, double-blinded, multicenter study of denosumab in patients with high risk SMM (Smoldering Multiple Myeloma) and "ultra-high risk" SMM (=now defined as "SLiM CRAB" positive early MM without symptoms).

Eligible patients will be randomized 1:1 (stratification according to high risk SMM and "SLiM CRAB" positive early Multiple Myeloma).

The study duration for each patient will be a maximum of 36 months treatment plus a minimum of 12 months of Follow up. End of study will be 12 months after end of treatment of last patient.

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An academic clinical trial
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