A phase III trial of docetaxel vs docetaxel and radium-223 (Ra-223) in patients with metastatic castration-resistant prostate cancer (mCRPC): DORA

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Objective

- To compare overall survival for patients (pts) with mCRPC treated with docetaxel versus pts treated with docetaxel plus Ra-223.

Background

- Ra-223 is an alpha particle-emitting radionuclide that accumulates in areas of increased bone turnover surrounding metastatic lesions and prolongs survival of pts with mCRPC. 1
- Docetaxel interferes with microtubule trafficking and cell division and improves survival of pts with mCRPC and metastatic hormone-sensitive prostate cancer. 2
- Earlier studies suggested clinical benefit of simultaneously targeting the tumor and the bony compartment of the disease using chemotherapy and a bone-seeking radiopharmaceutical, especially as these agents may be cross sensitizing and can prolong overall survival. 3

- A Phase II trial showed intravenous (IV) administration of docetaxel at 60 mg/m² every 3 weeks (q3w) with prednisone for up to 16 cycles with concurrent Ra-223 dosed at 55 kBq/kg every 6 weeks (q6w) for 5 cycles to be safe and well tolerated. 4
- The combination of Ra-223 with docetaxel resulted in greater declines in prostate specific antigen (PSA) and bone markers, delayed PSA progression, and was well tolerated (with adjusted dose/schedule) relative to standard docetaxel alone. 5
- These results prompted us to explore whether the combination of docetaxel and Ra-223 will prolong survival relative to docetaxel alone in a phase III clinical trial.

Methods

- DORA is an open-label, randomized, phase III study of docetaxel versus docetaxel in combination with Ra-223 in pts with mCRPC (NCT03574571; Figure 1).
- Eligible pts will be randomized 1:1 to receive docetaxel or docetaxel and Ra-223 after stratification by the following factors:
  - Prior docetaxel for castrate sensitive disease
  - Visceral disease (presence or absence)

Outcome measures

- Changes in PSA
- Time to first SSE
- Changes in bone biomarkers
- Total ALP response
- Changes in circulating tumor cell enumeration and biologic characterization
- Detection of androgen-receptor splice variant 7
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Key inclusion criteria

- Pts with ≥2 bone lesions.
- mCRPC progression based on at least one of the criteria:
  - PSA progression defined as ≥25% increase over baseline value with an increase in value that is confirmed by another PSA measurement with a minimum of 1 week interval
  - Soft-tissue progression defined as an increase by ≥20% in the sum of the longest diameter (LD) of all target lesions based on the smallest LD ≥2 cm in ≤8 weeks.
  - Time to total alkaline phosphatase (ALP) progression
  - Quality of life
  - Febrile neutropenia in pts treated with docetaxel plus Ra-223

Statistical considerations

- Use of antecedent therapy or external beam therapy ≤4 weeks before randomization.
- Use of systemic bone-seeking radiopharmaceuticals or chemotherapy in the castration-resistant setting.
- Four or more systemic antiancancer regimens for mCRPC.
- Bulky visceral metastases (≥3 lung and/or liver or a lesion ≥2 cm in ≥8 weeks).
- Symptomatic nodal disease or known bone marrow dysplasia.

Key exclusion criteria

- Recruitment start date: June 2018.
- The study is conducted in the US and the Netherlands.

References


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