Safety of the first-in-class anti-NKG2A monoclonal monalizumab in combination with cetuximab: a phase Ib/II study in recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)


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Monalizumab (PH2031) is a first-in-class immune checkpoint inhibitor targeting CD94-NKG2A receptors. CD94-NKG2A is expressed on subsets of tumor-infiltrating cytotoxic CD8 T lymphocytes and Natural Killer (NK) cells. The ligand of CD94-NKG2A is HLA-E, a non-classical HLA (Human Leucocyte Antigen) class I molecule that is often upregulated in cancer, including head and neck cancers. Engagement of HLA-E can protect tumor cells from killing by CD94-NKG2A positive NK and T cells. Monalizumab blocks the binding of CD94-NKG2A to HLA-E, and thereby stabilizes NK and T cell-mediated anti-tumor responses.

Mechanism of action of monalizumab

Background

Objectives

Primary objectives

- To evaluate the safety of monalizumab given IV in combination with cetuximab in patients who have received prior systemic therapy for recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN).

Secondary objectives

- To estimate the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of monalizumab given IV in combination with cetuximab.
- To determine the Pharmacokinetics (PK), Pharmacodynamics (PD) and monitor the immunogenicity (PMI) of monalizumab + cetuximab.
- To assess the effects of monalizumab and cetuximab on biomarkers in the peripheral blood and in tumor.

Methods

Study design and dosing regimen

Phase I: dose-escalation, multinational, open-label, single-arm study to evaluate 5 dose levels of monalizumab given IV in combination with cetuximab. Toxicity assessment was continuous during the treatment period. Safety assessment and dose-escalation decisions were performed by a safety committee consisting of the lead investigators and a sponsor representative.

Phase II: cohort expansion to the RP2D to evaluate the antitumor activity of the combination (NCT02483936).

Results

Safety of the phase Ia are presented hereafter. The study was conducted in France and in the United States. Enrollment began in December 2015. As of January 11, 2017, 17 patients with R/M SCCHN were enrolled in phase Ia.

In the phase Ib dose-escalation, 12 patients received cetuximab at the approved dose and monalizumab at 0.4 mg/kg (n=1), 1 mg/kg (n=4), 2 mg/kg (n=3), 4 mg/kg (n=3) and 10 mg/kg (n=1). Three patients were evaluable for DLT. Of 2 patients were replaced and withdrawn within 3 weeks after first treatment for reasons other than a DLT.

There were no DLTs reported with monalizumab and cetuximab.

The MTD was not reached, therefore the cohort expansion was initiated at 10 mg/kg C2W.

In phase II, monalizumab concentration in serum following first administration

There were no infusion-related reactions, no discontinuations attributable to treatment-related adverse events (TRAE). The most common TRAEs were asthenia/fatigue (24%) and headache (18%).

- No signiﬁcant elevation of proinﬂammatory cytokines following administration of monalizumab at all dose levels.

Monalizumab PK pattern appears dose dependent, with interindividual interpatient variability.

Pharmacodynamics

- Following the first administration of monalizumab, full saturation of CD94/NKG2A on peripheral blood NK and CD8 T cells at all dose levels and in all the patients (from 3 hours post monalizumab ﬁrst administration and at all the following time points assessed).

- No signiﬁcant elevation of proinﬂammatory cytokines following administration of monalizumab at all dose levels.

Conclusions

- This is the ﬁrst report of safety with the anti-NKG2A, monoclonal antibody monalizumab in combination with cetuximab in patients with SCCHN.
- The combination was well tolerated with no additional safety concerns compared to monalizumab or cetuximab alone.
- The RP2D of monalizumab is 10 mg/kg every 2 weeks.
- Further evaluation of the safety and efﬁcacy of monalizumab plus cetuximab is ongoing in the phase II part of the study.

Acknowledgments

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- The clinical study teams that participated in this trial.

Key eligibility criteria

- Histologically or cytologically conﬁrmed, HPV (+) or HPV (-) squamous cell carcinoma of the nasopharynx (NPC Type 1), larynx, hypopharynx, larynx or oropharynx.
- Recurrent and/or metastatic disease.
- Pretreated patients not amenable to further therapy with curative intent, with no evidence of disease progression or adverse effects of prior treatment (for phase Ib only).
- Progression after platinum-based chemotherapy.

References