Safety of the first-in-class anti-NKG2A monoclonal antibody 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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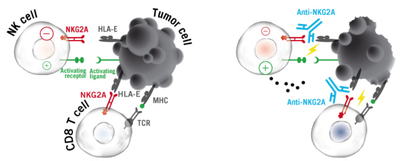
Background

Monalizumab (IPH2201) 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 (*1*). Expressing of HLA-E can protect from killing by CD94-NKG2A+ NK and T cells.

Monalizumab blocks the binding of CD94-NKG2A to HLA-E, and thereby enhances NK and T cell-mediated anti-tumor responses.

Mechanism of action of monalizumab



Cetuximab is an anti-EGFR monoclonal antibody blocking oncogenic signaling and inducing Fcγ receptor-mediated antibody dependent cellular cytotoxicity (ADCC). Genetic and preclinical experiments suggested that NK cells mediate cetuximab-induced ADCC towards SCCHN, and that this can be enhanced by NK-stimulators (*2-5, internal data).*

Hypothesis: Combination of monalizumab and cetuximab may provide greater antitumor activity than either drug alone.

Objectives

Primary objective

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

Secondary objectives

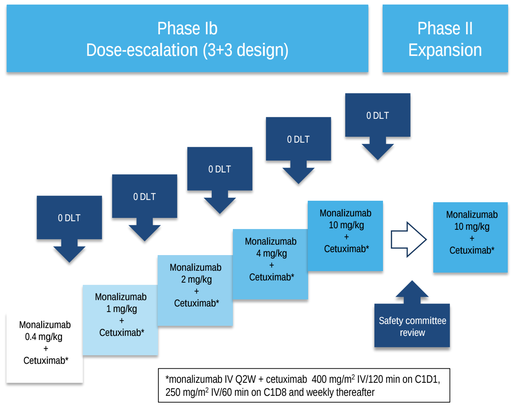
- To estimate the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of monalizumab given IV in combination with cetuximab,
- To determine the Pharmacokinetics (PK), Pharmacodynamics (PD) and monitor the immunogenicity (HAHA) of monalizumab + cetuximab,
- To assess the effects of monalizumab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

Study design and dosing regimen

Phase Ib: dose-escalation, multicenter, 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 at the RP2D to evaluate the antitumor activity of the combination (NCT02643550).



Treatment up to progression, unacceptable toxicity or other withdrawal criteria are met

Key eligibility criteria

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

References

1. *Braud VM. et al.* Nature 1998 Feb;391(6669): 795-799.
2. *Taylor RJ. et al.* Cancer Immunol Immunother. 2009 Jul;58(7):997-1006.
3. *López-Albaitero A. et al.* Cancer Immunol Immunother. 2009 Nov;58 (11):1853–1864.
4. *Luedke E. et al.* Surgery. 2012 Sep; 152(3): 431–440.
5. *Dietsch G et al.* PLoS One. 2016; 11(2): e0148764.

Results

Results of the phase Ib 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 Ib.

In the phase Ib dose-escalation, 17 patients received cetuximab at the approved dose and monalizumab at 0.4 m/kg (n=4), 1 mg/kg (n=3), 2 mg/kg (n=3), 4 mg/kg (n=3) and 10 mk/kg (n=4).

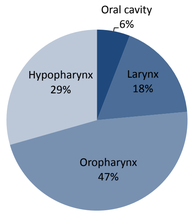
Fifteen patients were evaluable for DLT, 2 patients were replaced as withdrawn within 3 weeks after first treatment for reasons other than a DLT.

Patient characteristics

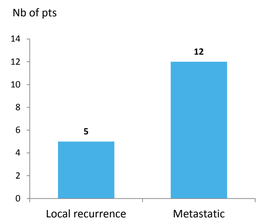
Patient Characteristics		N=17 n (%)
Age median [range]		59 [39-73]
Sex	Female Male	2 (12%) 15 (88%)
ECOG	0 1	8 (47%) 9 (53%)
HPV expression	Positive Negative Unknown	3 (18%) 7 (41%) 7 (41%)
Alcohol	Never Former Current Unknown	5 (29%) 6 (35%) 4 (24%) 2 (12%)
Tobacco	Never Former Current	2 (12%) 14 (82%) 1 (6%)

Previous treatment	N=17 n (%)
Primary treatment	
Surgery	6 (35%)
Systemic therapy	13 (76%)
Radiotherapy	15 (88%)
Treatment for R/M SCCHN	
Platinum-based chemotherapy	17 (100%)
Prior cetuximab	14 (82%)
Best response to last treatment	
Complete response (CR)	1 (5.9%)
Partial response (PR)	2 (11.8%)
Stable disease (SD)	3 (17.6%)
Progression disease (PD)	10 (58.8%)
Unknown	1 (5.9%)

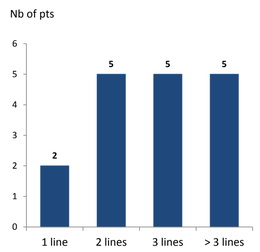
Tumor location



Type of recurrence



Number of prior systemic treatment



Safety and tolerability of monalizumab and cetuximab

- Most of the AEs (85%) were grade 1-2. There were 18 grade 3-4 AEs and only one grade 3-4 treatment-related AE (TRAE) reported: grade 3 fatigue.
- There were no DLTs reported with monalizumab and cetuximab.
- The MTD was not reached, therefore the cohort expansion was initiated at 10 mg/kg Q2W.

Summary of safety profile

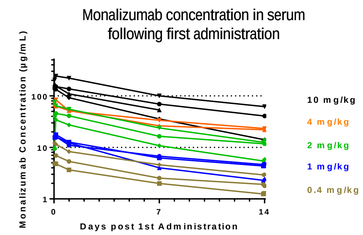
	0.4 mg/kg N=4	1 mg/kg N=3	2 mg/kg N=3	4 mg/kg N=3	10 mg/kg N=4	All doses N=17
DLT	0	0	0	0	0	0
AE all grades	31	25	14	28	20	118
AE G3-4	9	2	3	3	1	18
TRAE all grades	4	2	2	7	5	20
TRAE G3-4	1	0	0	0	0	1
SAE	3	2	0	1	1	7

Monalizumab-related adverse events

Monalizumab -related AE	0.4 mg/kg N=4	1 mg/kg N=3	2 mg/kg N=3	4 mg/kg N=3	10 mg/kg N=4	All doses N=17
Total Number of AEs	4	2	2	7	5	20
Headache		1		1	1	3 18%
Asthenia	1				1	2 12%
Fatigue	1				1	2 12%
Hypothyroidism				1		1 6%
Periorbital edema			1			1 6%
Erythema			1			1 6%
Constipation				1		1 6%
Diarrhea				1		1 6%
Dysphagia					1	1 6%
Nausea				1		1 6%
Dysgeusia				1		1 6%
Stomatitis	1					1 6%
Nasopharyngitis	1					1 6%
Hepatic enzyme increased				1		1 6%
Hypokalemia		1				1 6%

- All monalizumab-related AEs were grade 1 or 2 except one grade 3 fatigue at 0.4 mg/kg.
- The most common TRAEs were asthenia/fatigue (24%) and headache (18%).
- No infusion-related reactions, no discontinuations attributable to treatment-related adverse events, or treatment-related deaths were reported.

Pharmacokinetics



Nominal times were used for plotting. Below Limit of Quantitation (BLQ) samples (<0.1 µg/ml) were not represented.

Dose 0.4 mg/kg: all samples for patient 11-002 were BLQ.

Dose 4 mg/kg: samples for patient 11-004 were not available at the time of poster preparation.

Monalizumab PK pattern appears dose dependent, with intermediate 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 IV 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

- The patients and families who made this trial possible.
- The clinical study teams that participated in this trial.