Phase II study of monalizumab, a first-in-class NKG2A monoclonal antibody, in combination with cetuximab in previously treated recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)

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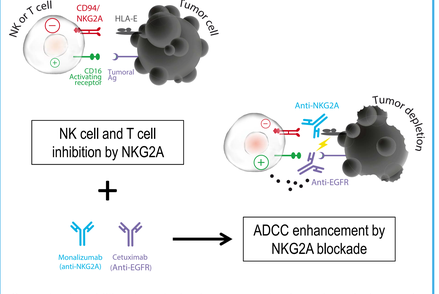
Background

Monalizumab (IPH2201) is a first-in-class humanized IgG4 targeting NKG2A (Natural Killer Group 2A), an immune checkpoint receptor which is expressed as a heterodimer with CD94 on subsets of NK cells, γδ T cells and tumor infiltrating CD8+ T cells. This inhibitory receptor binds to HLA-E (Human Leukocyte Antigen-E) molecules that are frequently upregulated on cancer cells and provides a negative regulatory signal to TILs (tumor-infiltrating lymphocytes).

Monalizumab blocks binding of CD94/NKG2A to HLA-E, reducing inhibitory signaling and thereby unleashing NK and T cell responses.

High expression of EGFR (epidermal growth factor receptor) occurs in most epithelial malignancies, including squamous cell carcinoma of the head and neck (SCCHN), and is associated with poor prognosis. The anti-EGFR monoclonal antibody cetuximab is thought to act by blocking oncogenic signaling and by inducing Fcγ receptor-mediated antibody dependent cell cytotoxicity (ADCC) which involves human NK cells. Preclinical experiments suggest that ADCC can be enhanced by NK-stimulators (1-6).



Currently, in addition to cetuximab, only pembrolizumab and nivolumab, two PD1 blockers are approved for SCCHN patients (pts) progressing after platinum-based therapy, with response rates ranging from 10-17%.

Hypothesis:

Dual targeting with the combination of monalizumab and cetuximab will provide greater antitumor activity than cetuximab alone.

References

1.Braud VM. et al. Nature 1998; 2. *Taylor RJ. et al.* Cancer Immunol Immunother. 2009; 3. *López-Albaitero A. et al.* Cancer Immunol Immunother. 2009; 4. *Luedke E. et al.* Surgery. 2012.; 5. *Dietsch G. et al.* PLoS One. 2016; 6. *Soulas C. et al,* AACR 2018 Abstract # 1690; 7. *Vermorken et al,* JCO 2007; 8. *Cohen RB. et al,* AACR 2017 abstract #5666; 9.*Cohen RB . et al,* AACR 2018 abstract #CT158; 10.*Lala et al,* Oral Oncology 2018.

Objectives

Primary objective

- To evaluate the objective response rate (ORR) of monalizumab in combination with cetuximab in patients who have received prior systemic therapy for R/M SCCHN.

Secondary objectives

- To assess the safety of monalizumab combined with cetuximab.
- To estimate duration of response (DoR), progression free survival (PFS), and overall survival (OS).
- To monitor the immunogenicity (HAHA) of monalizumab combined with cetuximab.

Study Design and Dosing regimen

- Multicenter, international (US and France), open label, single arm study to evaluate the antitumor activity of monalizumab in combination with cetuximab (NCT02643550) sponsored by Innate Pharma.
- Five dose levels of monalizumab (0.4, 1, 2, 4, 10 mg/kg every 2 weeks) in combination with the approved dosage of cetuximab (400 mg/m² load then 250 mg/m² weekly) were explored (8,9). The highest dose tested (10 mg/kg) was used for the phase II cohort expansion. A one-stage Fleming design with a futility analysis after the first 11 patients was used; the overall phase II study enrolled 40 patients.
- As of 31 of August, 2018, 40 patients with R/M SCCHN were treated and evaluable for safety and for efficacy.

Key eligibility criteria

- R/M SCCHN histologically confirmed, HPV (+) or HPV (-).
- Progression after platinum-based chemotherapy.
- Maximum of 2 prior systemic treatment regimens for R/M disease; prior IO allowed; prior cetuximab allowed if used for the treatment of locally advanced disease, with no progressive disease for at least 4 months.

Safety results

- The majority of adverse events (AE) were of Grade 1-2 severity, rapidly reversible and easily manageable.
- The most common AEs considered by investigator as related to monalizumab +/- cetuximab were fatigue (18%), rash (15%), hypophosphatemia (15%), hypomagnesemia (12%), headache (12%), and stomatitis (12%).
- No infusion-related reaction was observed (of note, patients received premedication for cetuximab according to the label).
- No treatment-related death was reported, 15 patients died from progressive disease (PD).
- The most frequent AEs described in the literature with cetuximab (7) are skin disorder (rash 49%, fatigue 24%, pyrexia 14%, nausea 13%); these toxicities were not exacerbated by monalizumab.

Patient Characteristics

Patient Characteristics		N=40 n (%)
Age, median [range]		64 [34-76]
Sex	Female	12 (30%)
	Male	28 (70%)
ECOG	0	14 (35%)
	1	26 (65%)
HPV status	Positive	6 (15%)
	Negative	30 (75%)
	Unknown	4 (10%)
Tobacco	Never	7 (18%)
	Former	28 (70%)
	Current	5 (12%)
Alcohol	Never	7 (18%)
	Former	20 (50%)
	Current	13 (32%)

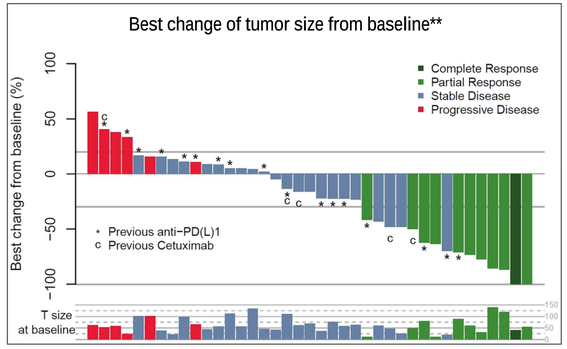
Disease Characteristics		N=40 n (%)
Tumor site	Oral cavity	17 (42 %)
	Oropharynx	13 (33 %)
	Larynx	6 (15%)
	Hypopharynx	3 (8%)
	Nasopharynx	1 (2 %)
Histology	Squamous	40 (100%)
Grade	G1	11 (28%)
	G2	10 (25%)
	G3	7 (18%)
	GX	12 (30%)
Type of recurrence	Local	21 (52%)
	Distant	19 (48%)

Previous treatment	N=40 n (%)
Primary treatment	
Surgery	23 (57%)
Radiation	29 (72%)
Systemic therapy	33 (82%)
Prior lines of systemic therapy (overall)	
Number of previous lines	
1	20 (50%)
2	13 (32.5%)
≥3	7 (17.5%)
Prior platinum	40 (100%)
Prior IO	17 (42%)
Prior cetuximab	5 (12%)
Best response to most recent systemic therapy	
Complete Response (CR)	7 (18%)
Partial response (PR)	6 (15%)
Stable disease (SD)	6 (15%)
Progressive disease (PD)	17 (42%)
Unknown	4 (10%)

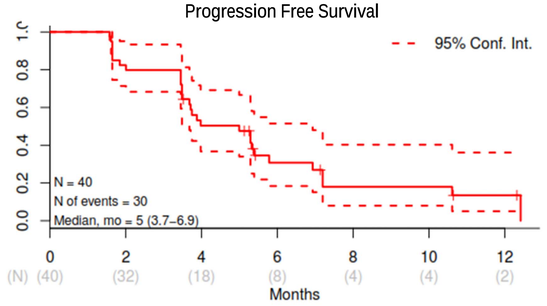
Activity results

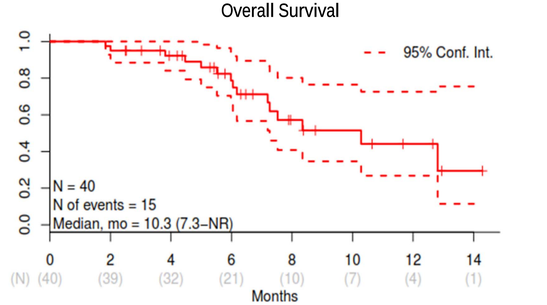
Best overall response	N=40 n (%)
Complete Response (CR)	1 (2.5%)
Partial response (PR)*	10 (25%)
Stable disease	22 (55%)
Progressive disease**	7 (17.5%)
Overall Response Rate (ORR)	27.5% [95%CI: 16.1-42.8]
Disease Control Rate at 24 weeks	35% [95%CI: 22.1-50.5]
Median Time to Response [min-max]	1.6 months [1.5- 3.9]
Median Duration of Response	5.6 months [3.8-NR]
Median progression free survival	5.0 months [3.7-6.9]
Median overall survival	10.3 months [7.3.-NR]

* 3 PR among the 17 patients treated with previous PD-(L)1 inhibitor



** One patient with early death for clinical PD before radiological assessment is not represented in the waterfall plot





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- The clinical study teams who made this trial possible.

Conclusions

- These data confirm the anti-tumor activity of monalizumab in combination with cetuximab in patients with R/M SCCHN showing deep and durable responses.
- The activity of monalizumab combined with cetuximab (ORR of 27.5 %, median PFS of 5 months and median OS of 10 months) appears superior to cetuximab alone based on historical data (ORR 12.6%, PFS 2.3 m, OS 5.6 m) (7,10).
- The combination monalizumab and cetuximab is well tolerated without potentiation of cetuximab side effects (7).
- This study continues to enroll additional patients with R/M SCCHN who received both prior platinum based chemotherapy and PD-(L)1 inhibitors.

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