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): Preliminary assessment of safety and efficacy

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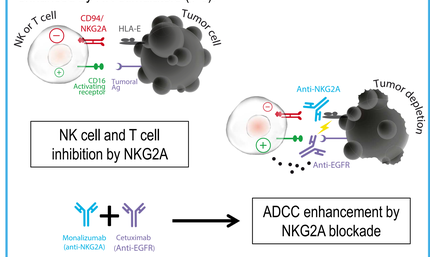
Background

Monalizumab (IPH2201) is a first-in-class humanized IgG4 targeting NKG2A (Natural Killer Group 2A), 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 provide 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 SCCHN (squamous cell carcinoma of the head and neck), 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).



NK cell and T cell inhibition by NKG2A

ADCC enhancement by NKG2A blockade

The activity of single agent cetuximab in recurrent and/or metastatic SCCHN (R/M SCCHN) is limited with a 13% ORR (objective response rate), a median DoR (duration of response) of 4 months and a median OS (overall survival) of 6 months (7).

Hypothesis: Combination of monalizumab and cetuximab will provide greater antitumor activity than cetuximab alone.

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).
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). 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 (pts) was used; the overall phase II study will include 40 patients.

Key eligibility criteria

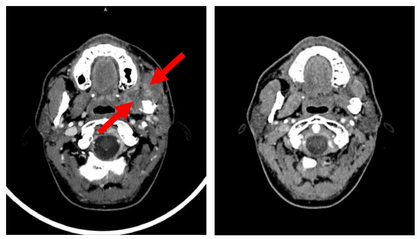
- R/M SCCHN histologically confirmed, HPV (+) or HPV (-).
- Progression after platinum-based chemotherapy.
- Maximum of 2 prior systemic treatment regimens for R/M disease; prior IO allowed; prior cetuximab allowed if used for the treatment of locally advanced disease, with no progressive disease for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

Results

Interim results of the now fully enrolled phase II trial are presented.
As of March 9, 2018, 31 patients with R/M SCCHN were treated and evaluable for safety, 26 patients were evaluable for efficacy (including 1 patient who died from progressive disease at week 8 without post-baseline imaging), and 5 patients are too early on study to have post baseline assessment.

Example of response after treatment with monalizumab combined with cetuximab

in a patient with recurrent oral cavity cancer (left masticator space) previously treated with surgery, cisplatin and radiation



Baseline (July 2017) ***Target lesion = 41mm***

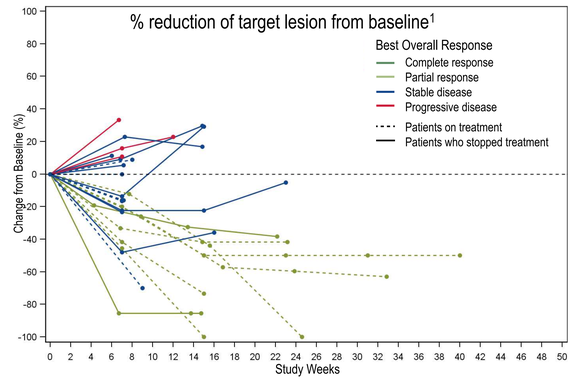
Under treatment (February 2018) ***Target lesion = 0 mm***

100% reduction in target lesion, no non-target lesions, no new lesions.

Patient Characteristics

Patient Characteristics		N=31 n (%)
Age, median [range]		64 [34-76]
Sex	Female	10 (32%)
	Male	21 (68%)
ECOG	0	12 (39%)
	1	19 (61%)
HPV status	Positive	4 (13%)
	Negative	15 (48%)
	To be determined	12 (39%)
Tobacco	Never	6 (19%)
	Former	20 (65%)
	Current	5 (16%)
Alcohol	Never	6 (19%)
	Former	15 (48%)
	Current	8 (26%)
	Unknown	2 (6%)
Disease Characteristics		**N=31 n (%)**
Tumor site	Oral cavity	14 (45%)
	Oropharynx	10 (32%)
	Larynx	4 (13%)
	Hypopharynx	2 (6%)
	Nasopharynx	1 (3%)
Histology	Squamous	31 (100%)
Grade	G1	8 (26%)
	G2	7 (23%)
	G3	5 (16%)
	GX	11 (35%)
Type of recurrence	Local	18 (58%)
	Distant	13 (42%)
Previous treatment		**N=31 n (%)**
Primary treatment		
Surgery		18 (58%)
Radiation		21 (68%)
Systemic therapy		24 (77%)
Prior lines of systemic therapy (overall)		
Number of previous lines		
1		16 (52%)
2		10 (32%)
3		5 (16%)
Prior platinum		31 (100%)
Prior IO		14 (45%)
Prior cetuximab		3 (10%)
Best response to most recent systemic therapy		
Complete Response (CR)		1 (3%)
Partial response (PR)		5 (16%)
Stable disease (SD)		5 (16%)
Progressive disease (PD)		16 (52%)
Unknown		4 (13%)

Antitumor activity of monalizumab and cetuximab



[1] The patient with early death from progression before the 1st assessment is not represented in these graphs.

Best overall response[2]	N=26 n (%)
Partial response (PR)	8 (31%)
Stable disease (SD)	14 (54%)
Progressive disease (PD)	3 (11%)
Early death from PD	1 (4%)

[2]According to RECIST 1.1, confirmation of response was required

Among the 8 patients with a partial response, 2 patients received previous immune therapy.

Median duration of response was not reached; 6 responding patients are still on treatment.

The median time of follow-up is 129 days [101-213]:

- 17 patients (55%) are still on treatment.
- 14 patients (45%) have stopped treatment:
  - 12 (38%) for progressive disease,
  - 1 for adverse event,
  - 1 for investigator decision.

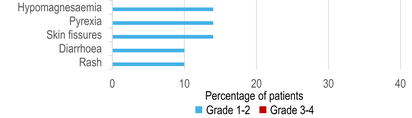
Safety and tolerability of monalizumab and cetuximab

N=31	All TEAE N (%)		Monalizumab Related TEAE N (%)	
	All grades	Grade 3-4	All grades	Grades 3-4
AE	28 (93%)	10 (33%)	17 (57%)	2 (6%)
AE leading to treatment discontinuation	2 (7%)		1* (3%)	
SAE	7 (23%)		1 (3%)	
Fatal AE	0		0	

Most frequent (≥10%) or most severe monalizumab-related AE	All grades	Grade 3-4
Fatigue	5 (17%)	-
Pyrexia	4 (13%)	-
Headache	3 (10%)	-
Interstitial lung disease*	1 (3%)	1 (3%)
Colitis*	1 (3%)	1 (3%)
Hypophosphatemia	2 (7%)	1 (3%)

N: number of patients ; AE: adverse event; SAE: serious AE; TEAE: treatment emergent AE
**The same patient had grade 4 AE Interstitial lung disease and colitis reported as related by the investigator, not related per sponsor assessment in a context of sepsis leading to cessation of monalizumab after one dose.*

Most frequent AE (≥10%) related to the combination of monalizumab and cetuximab



- The majority of adverse events (AE) were of Grade 1-2 severity, rapidly reversible and easily manageable. The most common AEs related to monalizumab were fatigue (17%), pyrexia (13%) and headache (10%).
- The most frequent AEs described in the literature with cetuximab (7) are skin disorder (rash 49%, acne 26%, nail disorder 16%, dry skin 14%); these toxicities were not exacerbated by monalizumab.
- No infusion-related reactions were observed (of note, patients received premedication for cetuximab according to the label).
- No treatment-related death was reported, 4 patients died from disease progression.

Conclusions

- This is the first report of activity of monalizumab, an anti-NKG2A monoclonal antibody, in combination with cetuximab in patients with SCCHN.
- The safety profile is similar to the single agent experience with either agent. There was no potentiation of cetuximab side-effects (7). No new or unusual safety signals were observed with the combination of monalizumab and cetuximab.
- According to the study hypothesis of achieving an ORR of 25%, using 10% as inactivity cut-off rate, α =0.05, with power 0.76, the predefined number of 8 responses to declare the trial result positive has been reached.
- The trial has now enrolled all planned patients (n=40) and will follow these patients for response, DoR, PFS and OS.

References

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Acknowledgments

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