Monalizumab in combination with cetuximab post platinum and anti-PD-(L)1 in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): updated results from a phase 2 trial

Abstract 235
Poster 81P

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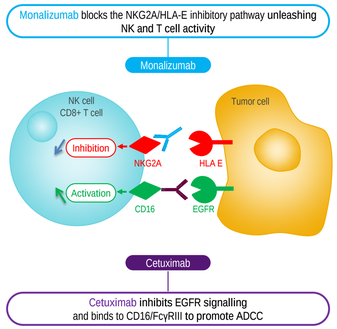
Background

- Monalizumab is a first-in-class, humanized IgG4 checkpoint inhibitor targeting the NKG2A receptor, which is expressed on CD8+ T cells and NK cells.
- Cetuximab inhibits oncogenic EGFR signaling and binds to CD16/FcγRIII to promote ADCC.
- NK cell stimulation with monalizumab may enhance ADCC induced by cetuximab and thereby provide greater antitumor activity than cetuximab alone.[1-5]
- Blocking NKG2A and triggering CD16 constitutes a novel form of dual immunotherapy that includes blockade of a novel immune checkpoint.



- We previously reported the clinical activity and safety of monalizumab in combination with cetuximab in R/M SCCHN after platinum-based chemotherapy. [8-9]
- Cetuximab single agent was approved in the US in R/M SCCHN[6-7] progressing after platinum-based therapy with ORR 12.6%, median PFS of 2.3 months, median OS of 5.6 months, 6 months OS < 50%, and 12 months OS < 20%.
- More recently, two anti-PD-1, Nivolumab and Pembrolizumab, were approved as single agent in R/M SCCHN with disease progression on or after platinum-containing chemotherapy with ORR 13-15%, median PFS~2 months, and median OS of 7.5-8.4 months[10-11].
- To date, no treatment options are currently approved in patients progressing after platinum and anti-PD-(L)1 treatment. We present here data on the combination of monalizumab and cetuximab in this setting.

Study Design

This is a multicenter, single arm, phase Ib-II trial with different cohorts to evaluate the combination of monalizumab and cetuximab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) (NCT02643550). Dose escalation and cohort 1 in patients post platinum (anti-PD-(L)1 naïve or pretreated) were previously presented [8-9]. Cohort 2 enrolled patients post-platinum and post-anti-PD-(L)1. We report here analysis for Cohort 2 (ORR was earlier presented[12]) and an exploratory analysis of all patients treated with platinum and anti-PD-(L)1 in both cohorts.

Key eligibility criteria in cohort 2

- R/M SCCHN histologically confirmed, HPV (+) or HPV (-)
- Progression (PD) after platinum-based chemotherapy and prior anti-PD-(L)1
- Maximum of 2 prior systemic treatment regimens for R/M disease
- Prior cetuximab allowed if for locally advanced disease with RT and no PD for at least 4 months

Primary endpoint

- Objective Response Rate (ORR) RECIST 1.1

Secondary endpoints

- Safety
- Duration of Response (DoR)
- Progression Free Survival (PFS)
- Overall Survival (OS)

Exploratory endpoints

- Translational analyses

Treatment

Monalizumab (750 mg Q2W)	+	Cetuximab (as per label)	until progression or unacceptable toxicity

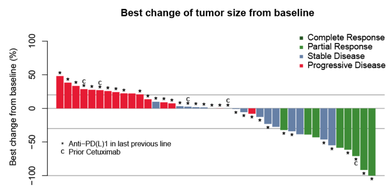
Main results

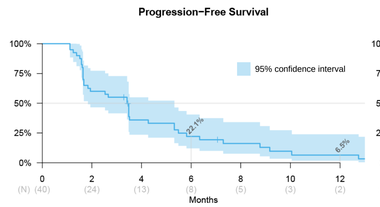
✓As of August 31, 2020, 40 patients with R/M SCCHN post platinum and anti-PD-(L)1 were included in cohort 2 in US and France (Table 1). Median duration of follow-up (FU) was 13.1 months (range 7.9-15.9).

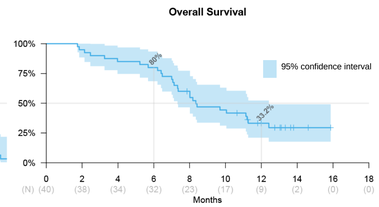
✓Figure 1 shows responses, PFS and OS of patients enrolled in Cohort 2.

✓In cohort 1 of the study, 19 patients received platinum and post anti-PD-(L)1, and were enrolled with the same selection criteria and similar characteristics than cohort 2. Thus an exploratory analysis combining these patients to those enrolled in Cohort 2 is provided in Figure 2.

Figure 1: waterfall plot, PFS and OS in cohort 2, median FU 13.1 months (7.9-15.9)





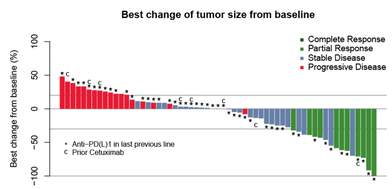


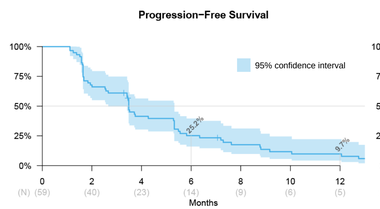
ORR	20% [11-35]
Median Time to Response	1.6 mo [1.6-5.3]
Median Duration of Response	5.2 mo [3.9-not reached]

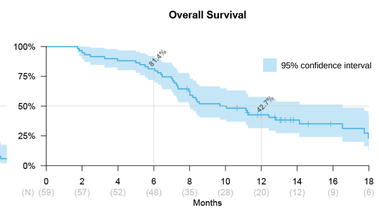
Median PFS	3.4 mo [1.8-5.3]

Median OS	8.3 mo [7.3-12.4]
6 months OS	80% [69-93]
12 months OS	33% [21-52]

Figure 2: waterfall plot, PFS and OS in all platin and post-anti PD(L)1 patients, median FU 14.6 months (7.9-28.4)







ORR	18.6% [11-30]
Median Time to Response	1.6 mo [1.6-5.3]
Median Duration of Response	5.6 mo [3.9-not reached]

Median PFS	3.5 mo [2.7-5.3]

Median OS	10.1 mo [8-16.5]
6 months OS	81% [72-92]
12 months OS	43% [32-58]

Table 1: Patients demographic and disease characteristics

Patient Characteristics		Cohort 2 n=40 n (%)
Age, median [range]		63 [38-83]
Sex	Female	5 (12%)
	Male	35 (88%)
ECOG	0	16 (40%)
	1	24 (60%)
Tobacco	Never	11 (28%)
	Former	25 (62%)
	Current	3 (8%)
	Not known	1 (2%)
Alcohol	Never	10 (25%)
	Former	19 (48%)
	Current	10 (25%)
	Not known	1 (2%)

Disease and prior treatment Characteristics		Cohort 2 n=40 n (%)
Tumor site	Oral cavity	12 (30%)
	Oropharynx	20 (50%)
	Larynx	4 (10%)
	Hypopharynx	4 (10%)
	Nasopharynx	0 (0%)
Type of recurrence	Local	14 (35%)
	Distant	26 (65%)
Sum of all target lesions in mm, median [range]		80 [15-201]
# of previous R/M systemic lines	1	20 (50%)
	2	20 (50%)
Prior platinum resistant*		19 (47%)
Prior platinum sensitive		21 (53%)
Prior anti-PD-(L)1 sensitive (CR, PR or SD)		17 (43%)
Prior anti-PD-(L)1 resistant (best response PD)		23 (57%)
Prior cetuximab in LA setting		5 (12%)
Last line anti-PD-(L)1		34 (85%)
Last line other than anti-PD-(L)1		6 (15%)
Time from last treatment to C1D1, median [range]		5.1 mo [1.3-56.3]

* platinum resistant if PD under or within 6 months after the end of treatment
Of note, one additional patient in cohort 2 who received only one dose of cetuximab and no monalizumab was replaced and is not included in the analyses.

Safety results

- All 40 patients had at least one adverse event.
- 18 patients (45%) had Grade 3-4 AEs regardless of causality, and only 4 patients (10%) had Grade 3-4 AEs related to any study drug.
- The most common (> 10% of patients) AEs related to monalizumab or cetuximab were dermatitis acneiform (72%), dry skin (35%), pruritus (22%), fatigue (20%), hypomagnesemia (20%) , skin fissures (20%), infusion related reaction (18%), mucosal inflammation (18%), nausea (18%), paronychia (18%), rash (15%), and diarrhea (12%).
- Only 1 patient (2%) had AE grade 3-4 considered related to monalizumab: peripheral sensory neuropathy and subclavian vein thrombosis.
- There was no fatal AE nor AE leading to treatment discontinuation (of note, one patient left the study after the first administration of cetuximab and did not receive monalizumab; he was replaced and is not included in the analyses).

Conclusion

- The monalizumab and cetuximab combination therapy demonstrates good safety profile and promising activity in R/M SCCHN post platinum and post anti-PD-(L)1 where no treatment options are currently approved.
- In this population with a high medical need, we observed a high response rate of 20% and promising 6- and 12-month OS of 80% and 33% with monalizumab combined to cetuximab.
- Based on these results, a randomized phase 3 trial is underway to evaluate the combination monalizumab+cetuximab versus cetuximab+placebo in R/M SCCHN post platinum and post anti-PD-(L)1 patients.

References

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