Combination of monalizumab and cetuximab in patients with recurrent or metastatic head and neck squamous cell cancer previously treated with platinum-based chemotherapy and PD-(L)1 inhibitors: a phase II expansion study

Abstract 6516
Poster 177

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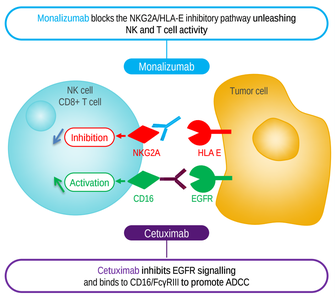
Background

- 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.



- In a Phase 1 study, the combination of monalizumab and cetuximab was well tolerated. In an initial expansion cohort (cohort 1) of 40 patients (pts) who had progressed after platinum-based therapy, we reported an overall response rate (ORR) of 27.5%, a 4.5 month median PFS and an 8.5 month median OS. In the subset of patients (n=18) previously treated with PD-(L)1 inhibitors (IO), corresponding efficacy results were 17%, 5.1, and 14.1 months, respectively (ESMO 2019[9]). Here, we present data from a second expansion cohort (cohort 2, n=40) conducted specifically in the post-IO (and post-platinum) setting to independently confirm the cohort 1 results.

Study Design

Multicenter, single arm, phase Ib-II trial 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 were previously presented.[8-9] We report here expansion Cohort 2.

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

References

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- Prospective cohort of 40 patients with R/M SCCHN treated with monalizumab and cetuximab
- Response rate of 20% in patients previously treated with both prior platinum-based chemotherapy and PD-(L)1 inhibitors, including IO resistant patients
  - ✓ This confirms the activity previously reported in the *post hoc* subset analysis in the IO-pretreated subgroup in cohort 1
  - ✓ and benchmarks favorably with historical data
- Randomized phase 3 trial planned in this setting

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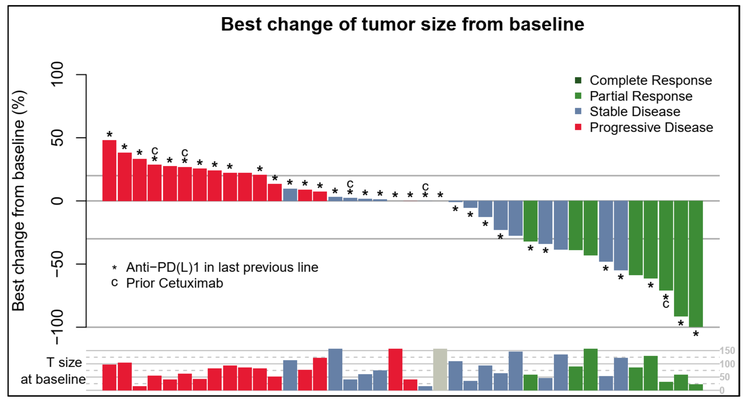
Activity

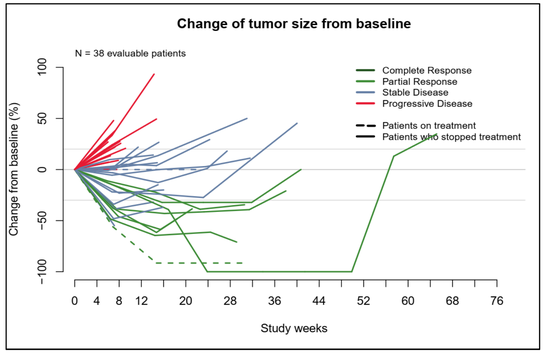
	Cohort 2, n=40
PR n (%)	8 (20%)
SD n (%)	15 (37.5%)
PD n (%)	15 (37.5%)
NE n (%)	2* (5%)
ORR %, [95% CI]	20% [10.5-34.8]
Time to Response median, [95% CI]	1.6 mo [1.6-5.3]
Duration of Response median, [95% CI]	5.2 mo [3.9-NR]

*1 patient died before first evaluation; another patient stopped treatment for clinical PD without RECIST documentation.



Main results

- ✓ As of March 31, 2020, 40 patients were enrolled with a median follow-up of 9.6 months (1.9-15.9).
- ✓ Cohort 2 demonstrates an ORR of 20%, which confirms the activity previously reported in the *post hoc* subset analysis in the IO-pretreated subgroup in cohort 1 (ORR = 18%).[8]
- ✓ While the study was not randomized, these data compare favorably with historical data reported for cetuximab alone[6-7] (ORR 12.6%) or for IO single agent (ORR 11-18%)[10-11] in R/M SCCHN after 1 line of previous systemic therapy. In our trial, 50% of the patients had received 1 prior line and 50% 2 prior lines.
- ✓ In *post hoc* analyses, response rate does not seem to vary in a clinically relevant manner in various subgroups:
  - o platinum-sensitive (3 PR/21) vs. resistant patients (5 PR/19);
  - o IO-sensitive (3 PR/17) vs. resistant patients (5 PR/23);
  - o patients exposed to IO as last previous therapy (5 PR/34) vs. IO as earlier treatment (3 PR/6);
  - o Overweight BMI≥25 (3 PR/13) vs. normal weight patients (5 PR/27);
  - o 3 PRs were reported in the 15 patients with resistance to both platinum-based chemotherapy and IO;
  - o given the small number of patients in each subgroup, all of these data must be interpreted cautiously.
- ✓ PFS, OS and biomarker data are not available yet and will be presented at a later date.



Patient 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%)
Type of recurrence	Local	14 (35%)
	Distant	26 (65%)
# of previous R/M systemic lines	1	20 (50%)
	2	20 (50%)
Prior platinum resistant		19 (47%)
Prior platinum sensitive		21 (53%)
Prior IO sensitive (PR or SD)		17 (43%)
Prior IO resistant (best response PD)		23 (57%)
Prior cetuximab		5 (12%)
Last line IO		34 (85%)
Last line other than IO		6 (15%)
Time from last treatment to C1D1, median [range]		5.1 mo [1.3-56.3]

Of note, one additional patient who received only one dose of cetuximab and no dose of monalizumab was replaced and is not included in the analyses.

Safety results

- All 40 patients had at least one adverse event.
- 17 patients (42%) had Grade 3-4 AEs.
- 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%), asthenia (12%), diarrhea (12%).
- Only 1 patient (2%) had AE grade 3-4 considered related to monalizumab: peripheral sensory neuropathy and asthenia.
- There was no 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).
- There was no fatal AE.
- There was no potentiation of cetuximab side-effects.
- The overall safety profile is similar to that reported in the dose escalation and expansion cohort 1.

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