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


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Background

• Monalizumab, 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 tends to C2G2/PRF1 to promote ADCC.
• Combination of monalizumab may enhance ADCC induced by cetuximab and thereby provide greater antitumor activity than cetuximab alone.1
• Blocking NKG2A and targeting 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 [n]), who had progressed after platinum-based therapy, we reported an overall response rate (ORR) of 37.5%, a 4.3 month median PFS, and a 13.5 month OS in the subset of patients (>10 previously treated with PD-L1 inhibitors, COI), corresponding efficacy results were 17%, 5.3, and 14.9 months respectively (EASCO 2020).
• 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 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) (NCT0323298). Dose escalation and cohort 1 were previously published.10 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-L1/D1
• Maximum of 2 prior systemic treatment regimens for R/M disease
• Prior cetuximab allowed for locally advanced disease with VT and NS for at least 4 months

Treatment

Monalizumab (750 mg Q2W) + Cetuximab (as per label)

Best change of tumor size from baseline

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
• Confirms the activity previously reported in the post hoc subset analyses in the IO-pretreated subgroup in cohort 1
• And benchmarks favorably with historical data
• Randomized phase 3 trial planned in this setting

Safety results
• All 40 patients had at least one adverse event
• 17 patients (42.5%) had Grade 3-4 AEs
• The most common (≥10% of patients) AEs related to monalizumab or cetuximab were dermatitis acneiform (74%, dry skin (58%), pruritus (30%), nausea (28%), vomiting (14%), diarrhea (13%), fatigue (12%), dyspnea (10%), rash (9%), hand (9%), arthralgia (9%), and headache (9%)
• Only 5 patients (12.5%) had AE grade 3-4 considered related to monalizumab peripheral sensory neuropathy and/or myalgia
• 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 enrolled in cohort 2 and was considered as a post hoc analysis, response rate does not seem to vary in a clinically relevant manner in various subgroups:

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 a ORR of 20%, which confirms the activity previously reported in the post hoc subset analyses 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 consumed alone (ORR 12%)6 or for IO single agent (ORR 11-18%)7 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 rates did not seem to vary in a clinically relevant manner in various subgroups:
  • platinum-sensitive (3 PR/21) vs. resistant patients (5 PR/19);
  • platinum-sensitive (3 PR/21) vs. platinum-resistant patients (5 PR/19);
  • patients exposed to IO at last previous therapy (7 PR/16) vs. ID as earlier treatment (3 PR/19);
  • Overall response rate (ORR) 20% (95% CI) 20% [10.5-34.8]
• Time from last treatment to C1D1, median 1.9 (1.3-56.3)
• Duration of response, median 13.5 (9.8-27.8)

References
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20. Fernandez et al. ASCO 2019: A phase I study of monalizumab, a first-in-class NKG2A humanized monoclonal antibody, in combination with cetuximab in patients with R/M SCCHN previously treated with or not treated with PLD/L1 inhibitors, COI; (as per label).

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