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 (FRG101) is a first-in-class humanized IgG targeting NKG2A (Natural Killer Group 2A) which is expressed on a variety of cell types such as cancer cells, NK cells, T cells and tumor infiltrating CD8+ T cells. This inhibitory receptor limits to HLA-E (Human Leukocyte Antigen-E) molecules that are highly expressed on cancer cells. Blockade of NKG2A reduces the ability of NK cells to activate other antitumoral NK and T cell responses.

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 (NCCTD040355). Five dose levels of monalizumab (0.4, 1, 2, 4, 10 mg/kg every 2 weeks) for 12 cycles, up to six cycles with the dose level of 10 mg/kg. The highest dose level (10 mg/kg) was used for patients with prior disease progression. Dose escalation design was used for the phase I cohort expansion. The majority of anti-NKG2A monoclonal antibodies tested in preclinical studies and in patients result in significant reduction of HLA-E expression on cancer cells and provide a negative regulatory signal on NK cells.

Key eligibility criteria

- R/M SCCHN histologically confirmed, HPV (+) or HPV (-).
- Prior platinum therapy (at least one prior line of chemotherapy).
- Number of previous lines: ≤4.
- Among the 8 patients with a partial response, 2 patients received previous immunotherapy.
- The activity of single agent cetuximab in recurrent and/or metastatic SCCHN (R/M SCCHN) is limited to 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).

Endpoints

The primary objective was 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.

Objective

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

Antitumor activity of monalizumab and cetuximab

Best % reduction of target lesion from baseline

<table>
<thead>
<tr>
<th>Disease Characteristics</th>
<th>n (%)</th>
<th>Best Overall Response</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progression</th>
<th>Best % Reduction</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Local recurrence</td>
<td>12 (38%)</td>
<td>Complete response</td>
<td>5 (16%)</td>
<td>6 (19%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>6 (19%)</td>
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<tr>
<td>Previous treatment</td>
<td>12 (38%)</td>
<td>Partial response</td>
<td>11 (35%)</td>
<td>11 (35%)</td>
<td>5 (16%)</td>
<td>5 (16%)</td>
<td>8 (26%)</td>
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<tr>
<td>Primary treatment</td>
<td>12 (38%)</td>
<td>Stable disease</td>
<td>28 (93%)</td>
<td>10 (33%)</td>
<td>17 (57%)</td>
<td>2 (6%)</td>
<td>14 (45%)</td>
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<td>Number of previous line</td>
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<td>Progressive disease</td>
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</table>

Results

5 (16%) patients were evaluable for safety, 25 patients were evaluable for efficacy. For the 8 patients with partial response, 2 patients received previous immunotherapy. The median duration of follow-up was not reached, 4 patients were still on treatment.

Conclusions

- The majority of adverse events (AE) were Grade 1-2 severity, rapidly reversible and easily manageable.
- The most common AEs related to the combination was fatigue (17%), anemia (15%) and headache (10%).
- The most frequent AEs described in the literature with cetuximab (7) were skin disorder 16%, dry skin 14%); these toxicities were not exacerbated by monalizumab.
- No skin-related reactions were observed (of note, patients received pemigatinib for cetuximab according to the label).
- No treatment-related death was reported. 4 patients died from disease progression.

References


Safety and tolerability of monalizumab and cetuximab

Control group: 4 (13%) 10 (33%) 17 (57%) 2 (6%)}

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

- NKG2A immune checkpoint blockade potentiates cetuximab induced ADCC in head and neck cancer (abstract #5666). 5. The patient with early death from progression before the first 11 patients have been enrolled, was declared the trial result positive has been reached.

The trial has now enroled all planned patients (n=40) and will follow these patients for response, DoR, PFS and OS.

Acknowledgments

- The patients and families who made this trial possible.
- The clinical study teams that participated in this trial.

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