Monalizumab in combination with cetuximab in R/M SCCHN: Clinical results and preliminary biomarker analyses.

Roger B. Cohen

Jérôme Fayette, Marshall Posner, Gautier Lefebvre, Jessica Bauman, Sébastien Salas, Caroline Even, Dimitrios Colevas, Antonio Jimeno, Esma Saada, Barbara Burtness, Franceline Calmels, Robert Zerbib, Agnès Boyer-Chammard, Pascale André, Tanguy Seiwert

1- Abramson Cancer Center, Philadelphia, PA; 2- Centre Léon Bérard, Lyon, France; 3- Mount Sinai Medical Center, New York, NY; 4- Oscar Lambret Institute, Lille, France; 5- Fox Case Cancer Center, Philadelphia, PA; 6- AP-HM, Marseille, France; 7- Gustave Roussy, Paris, Villejuif, France; 8- Stanford University Medical Center, Stanford, CA; 9- University of Colorado Cancer Center, Denver, CO; 10- Centre A. Lacassagne, Nice, France; 11- Yale University, New Haven, CT; 12- Innate Pharma, Marseille, France; 13- University of Chicago, Chicago, IL.
Roger B. Cohen, MD

The following relationships exist related to this presentation:

- Advisory board member with honoraria: Genocea, Innate
- Funding to institution for research support: Celldex, Genocea, Innate, Macrogenics, Merck
- Uncompensated advisory role: Celldex
Dual antibody targeting in cancer immunology

Monalizumab:
- First-in-class humanized IgG4 targeting NKG2A on NK and tumor infiltrating CD8+ T cells.
- Blocks binding of CD94/NKG2A to HLA-E reducing inhibitory signaling and thereby unleashing NK and T cell responses.

Hypothesis: Dual targeting with the combination of monalizumab and cetuximab will provide greater antitumor activity than cetuximab alone.

André et al., Cell in press
IPH2201-203 study design

- Multicenter single arm study to evaluate the combination of monalizumab and cetuximab in patients with recurrent and/or metastatic SCCHN (R/M SCCHN)
- Cohort expansion in recurrent and/or metastatic SCCHN patients (NCT02643550).

Key eligibility criteria
- R/M SCCHN, HPV(+) or HPV(-)
- PD after platinum-based CT
- Maximum of 2 prior systemic regimens for R/M disease
- Prior IO allowed*

Treatment
monalizumab (10mg/kg Q2W)
+ cetuximab (approved dosage)
until progression or unacceptable toxicity

Primary objective
- ORR (RECIST 1.1)

Secondary objectives
- DoR, PFS, OS
- Safety

Exploratory objectives
- Translational analyses

* prior cetuximab allowed if for locally advanced disease with no PD for at least 4 months
# Key Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics (N=40)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median [range] 64 [34-76]</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female 12 (30%) Male 28 (70%)</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td>0 14 (35%) 1 26 (65%)</td>
</tr>
<tr>
<td><strong>HPV status</strong>*</td>
<td>Positive 6 (15%) Negative 30 (75%) Unknown 4 (10%)</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td>Never 7 (18%) Former/current 33 (83%)</td>
</tr>
<tr>
<td><strong>Tumor site</strong></td>
<td>Oral cavity 17 (43%) Oropharynx 13 (33%) Other 10 (25%)</td>
</tr>
<tr>
<td><strong>Type of recurrence</strong></td>
<td>Local 21 (53%) Distant 19 (48%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous treatment (N=40)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior lines of overall systemic therapy</strong></td>
<td>1 20 (50%) 2 13 (33%) ≥3 7 (18%)</td>
</tr>
<tr>
<td>Prior platinum platinum resistant**</td>
<td>21 (53%)</td>
</tr>
<tr>
<td>platinum sensitive</td>
<td>19 (48%)</td>
</tr>
<tr>
<td>Prior IO IO resistant**</td>
<td>17 (43%)</td>
</tr>
<tr>
<td>IO sensitive</td>
<td>13 (33%) 4 (10%)</td>
</tr>
<tr>
<td>Prior cetuximab cetux resistant**</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>cetux sensitive</td>
<td>0 5 (13%)</td>
</tr>
</tbody>
</table>

**PD on treatment or within 6 months after the end of treatment

* For oropharynx (n=13): 4 HPV +, 9 HPV −
Objective responses with monalizumab and cetuximab

Overall Response Rate is 27.5%
[95% CI, 16.1-42.8]

1 confirmed CR & 10 confirmed PR

- Responses observed in IO naive (35% [19-55]) and IO pretreated patients (18% [6-41])

- Responses observed in platinum resistant patients and in HPV positive and negative disease

One patient with death from clinical progression before the 1st post baseline radiological assessment is not represented in the graphs
Early and Durable responses with monalizumab and cetuximab

Change of tumor size from baseline

Median time to response is 1.6 months [1.5-3.9]

Median duration of response is 5.6 months [3.8-NR*]

*NR = Not Reached
PFS and OS in all patients and according to prior IO

**PFS in all patients**
Median PFS = 5.0 mo (3.7–6.9)
N of events = 30
N = 40

**OS in all patients**
Median OS = 10.3 mo (7.3–NA)
N of events = 15
N = 40

**PFS according to prior IO**
- No prior IO [N = 23; Median = 4.0 mo]
- Prior IO [N = 17; Median = 5.0 mo]

**OS according to prior IO**
- No prior IO [N = 23; Median = 10.3 mo]
- Prior IO [N = 17; Median = 12.8 mo]
Safety profile of the combination

AEs related to the monalizumab cetuximab combination

- No new safety signals for monalizumab
- Only one patient stopped treatment for an AE
- No potentiation of cetuximab side effects
Preliminary PK, immunogenicity and PD

- At 10 mg/kg every 2 weeks monalizumab concentration remained well above 20 µg/mL preclinical target concentration in all patients.

- Cetuximab administration had no impact on monalizumab PK.

- No clinically significant immunogenicity was observed in this study.

- Complete and continuous NKG2A saturation was achieved in all patients.

- Monalizumab treatment did not induce significant changes in peripheral NKG2A⁺ NK and CD8⁺ T cells (% and absolute counts).
Preliminary biomarker results summary

- CD16 polymorphism was not found predictive of response in this cohort.

- High HLA-E expression was observed in all analyzed tumor samples - not predictive of response in this cohort of patients.

- Stromal NK cell (NKP46\(^+\) cells) and tumor CD8\(^+\) T cell infiltration was seen 15 days after first administration of combination treatment in responding patients.

- HPV status, TMB, PD-L1 expression were not predictive of response or progression in this small cohort of patients.

- RNA seq analyses are ongoing.
Infiltration of CD8+ T cells and NK cells 15 days after first administration of monalizumab and cetuximab in responding patients

Baseline

15 days after first administration of monalizumab and cetuximab

PFS and OS by CD8+ stromal Lymphocyte Proportion Score difference*

* Difference between 15 days after first administration of the combination and baseline
Conclusions

• The combination of monalizumab and cetuximab results in early, deep and durable responses in patients with R/M SCCHN
  • Encouraging PFS and OS in both IO naïve and IO pretreated patients
  • Combination has activity in platinum-resistant, HPV positive and negative patients
  • Activity appears higher than cetuximab alone based on historical data
• Safety of the combination is acceptable with no potentiation of cetuximab adverse events
• Preliminary translational analyses show stromal NK cell and tumor CD8⁺ T cell infiltration 15 days after first administration of monalizumab in responding patients.
• This study continues to enroll additional patients with R/M SCCHN who have progressed after both platinum-based chemotherapy and PD-(L)1 inhibitors, a population with a very high unmet medical need
• These results warrant further development of the combination of monalizumab and cetuximab in patients with SCCHN
Acknowledgement

• We thank the patients who participated in the IPH2201-203 study and their families

• The referring physicians, co-investigators and clinical study site staff at the participating institutions

• The study is sponsored by Innate Pharma and supported by AZ/MedImmune