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

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Presenter Disclosure Information

Roger B. Cohen, MD

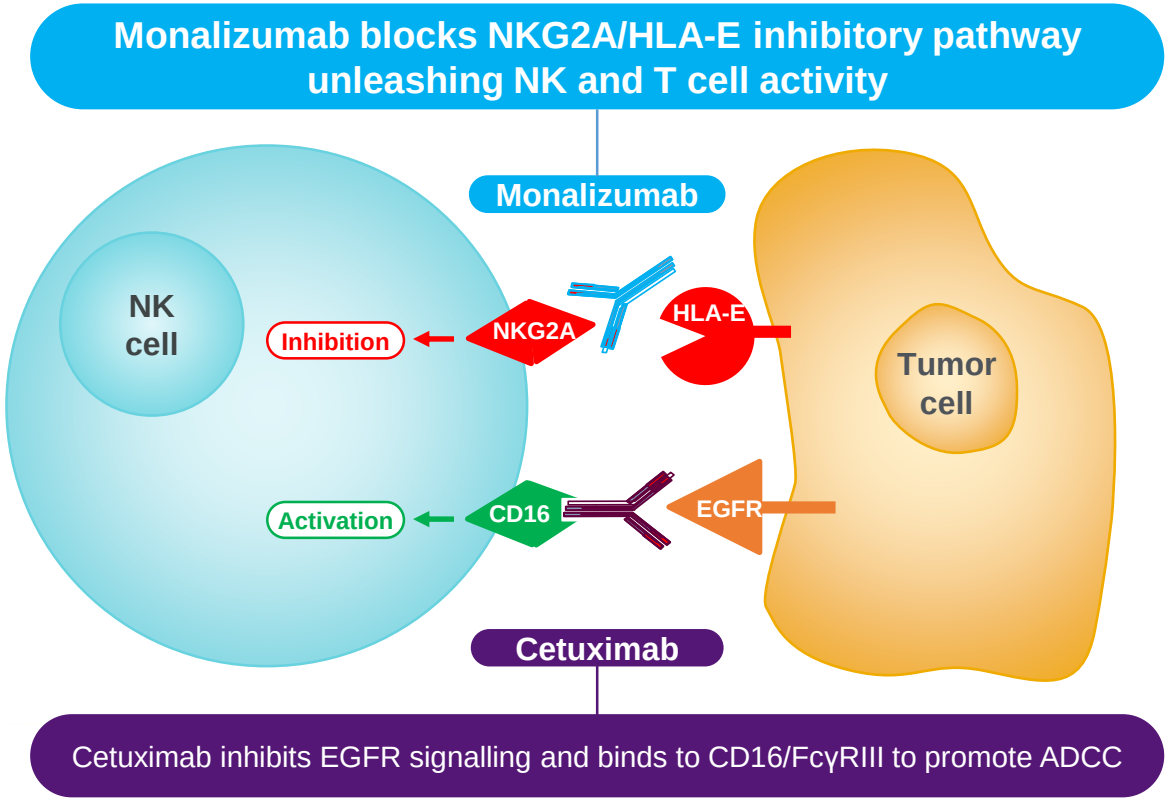
The following relationships exist related to this presentation:

- 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 IgG_4 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).
- N= 40 patients enrolled. Data cut-off August 31, 2018.

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

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

* For oropharynx (n=13): 4 HPV $^{+}$, 9 HPV $^{-}$

Previous treatment (N=40)		N (%)
Prior lines of overall systemic therapy	1 2 ≥3	20 (50%) 13 (33%) 7 (18%)
	Prior platinum *platinum resistant*** *platinum sensitive*	40 (100%) *21 (53%)* *19 (48%)*
	Prior IO *IO resistant*** *IO sensitive*	17 (43%) *13 (33%)* *4 (10%)*
	Prior cetuximab *cetux resistant*** *cetux sensitive*	5 (13%) *0* *5 (13%)*

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

Objective responses with monalizumab and cetuximab

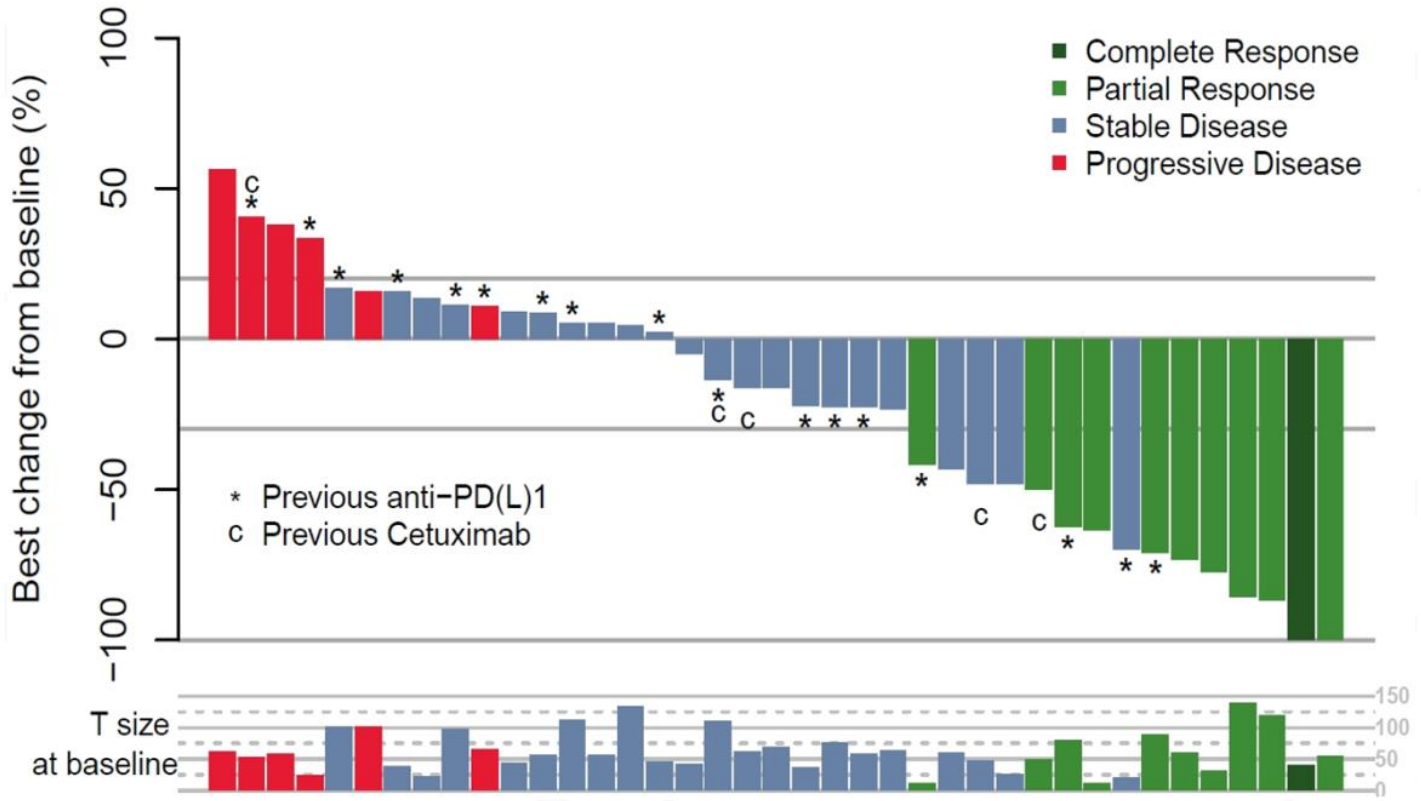
Overall Response Rate is 27.5%

[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

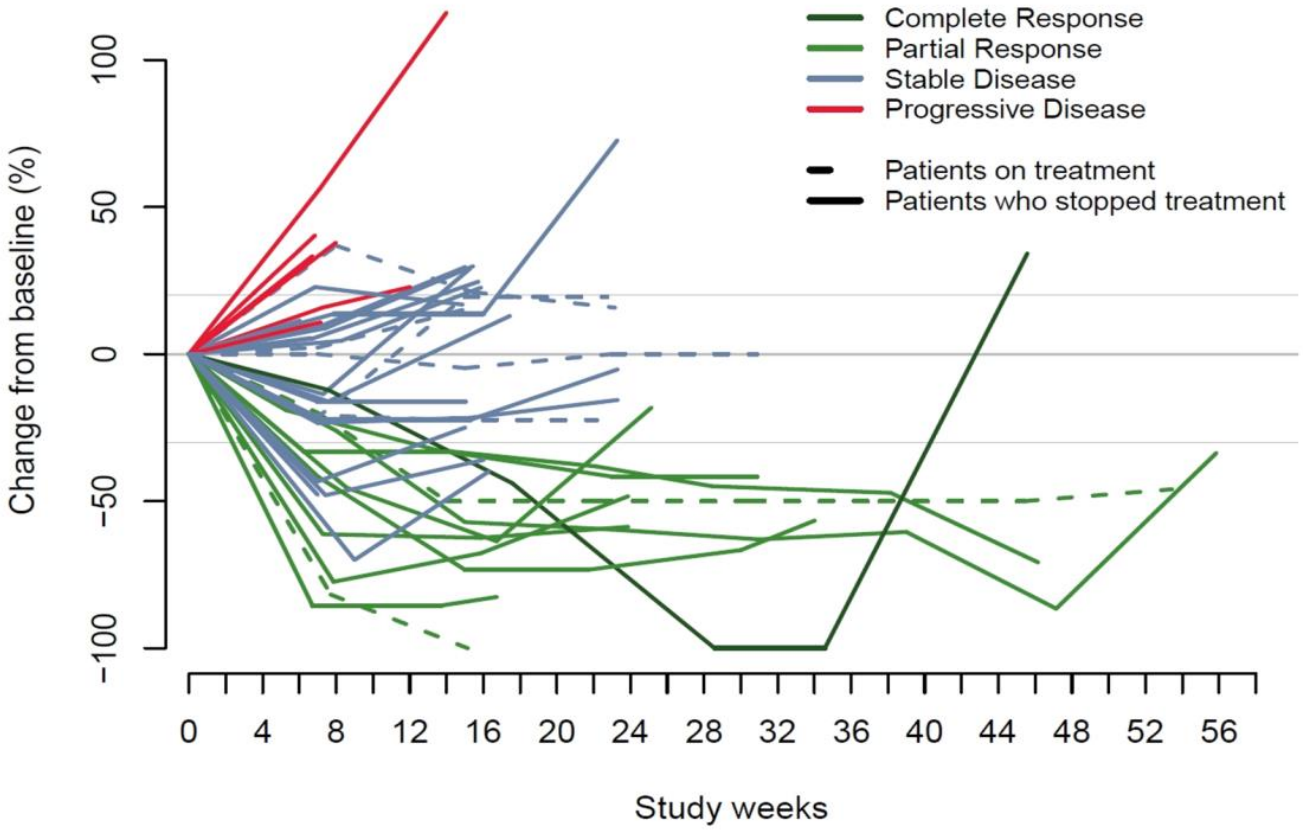
Best change of tumor size from baseline

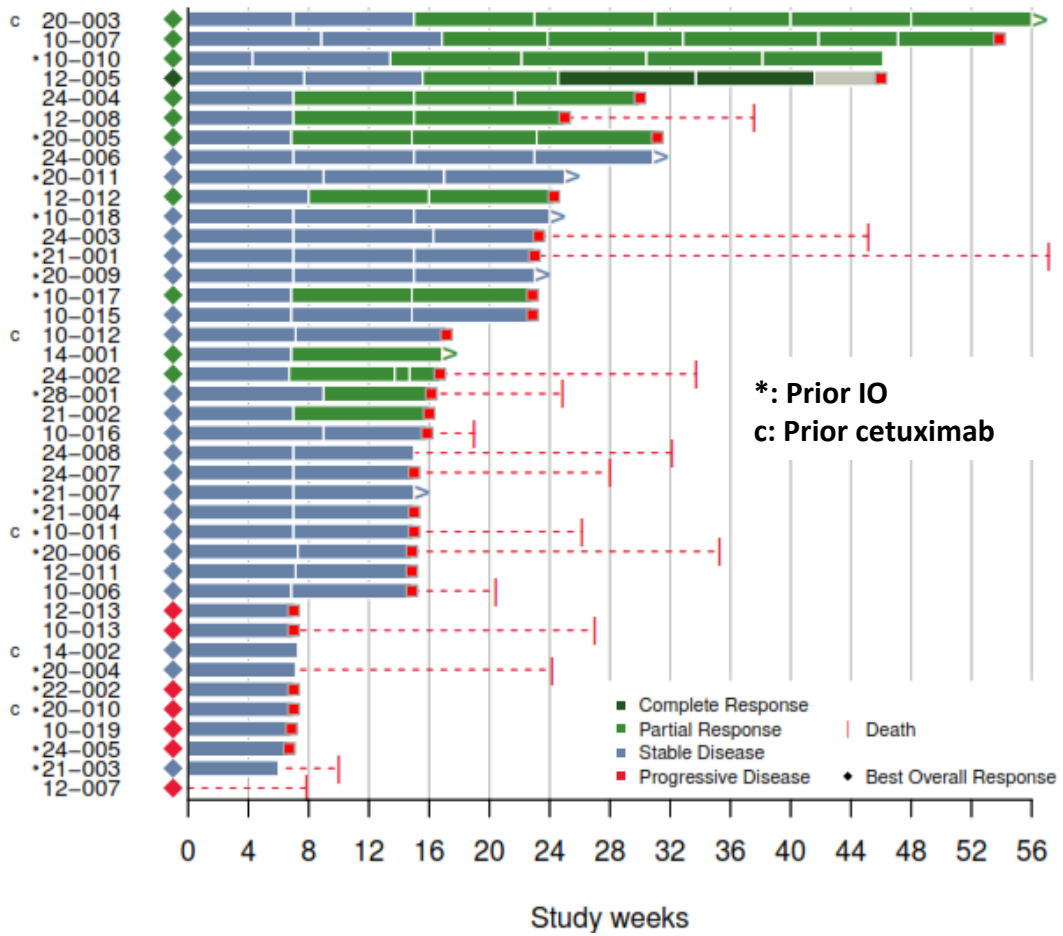


One patient with death from clinical progression before the 1st post baseline radiological assessment is not represented in the graphs

Early and Durable responses with monalizumab and cetuximab

Change of tumor size from baseline





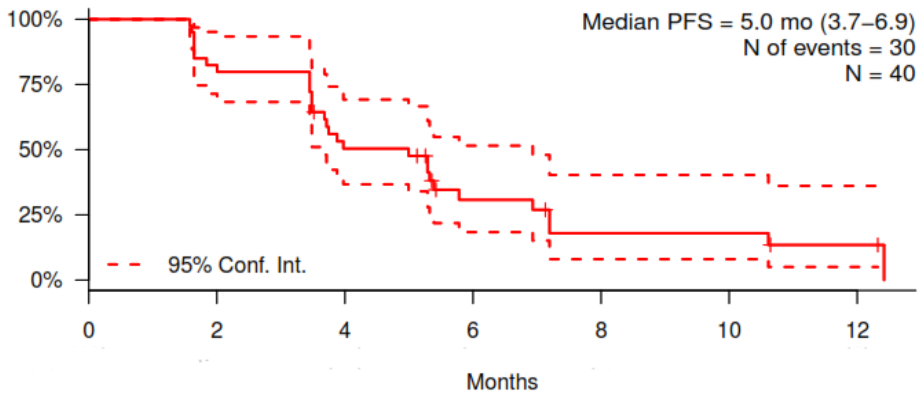
Median time to response is 1.6 months [1.5-3.9]

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

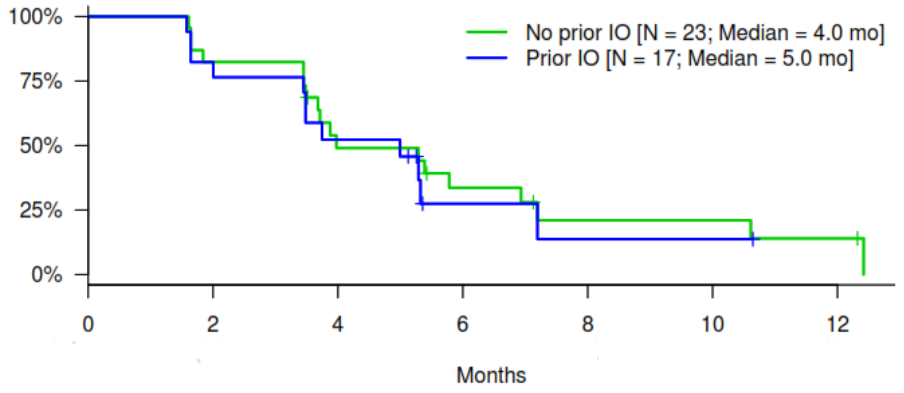
*NR = Not Reached

PFS and OS in all patients and according to prior IO

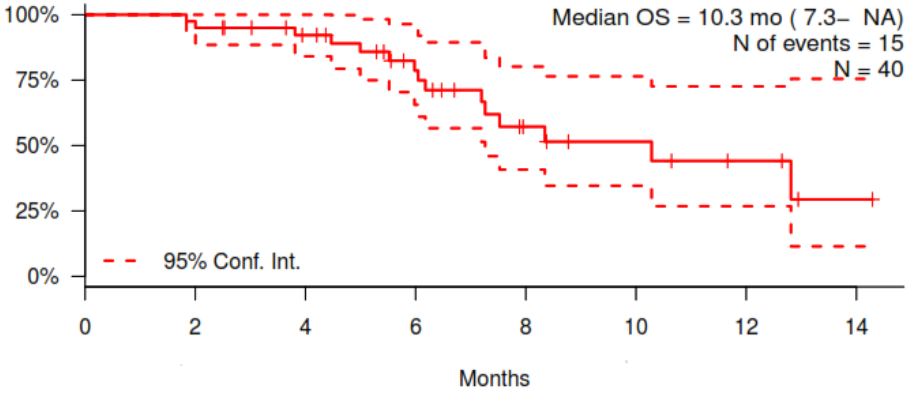
PFS in all patients



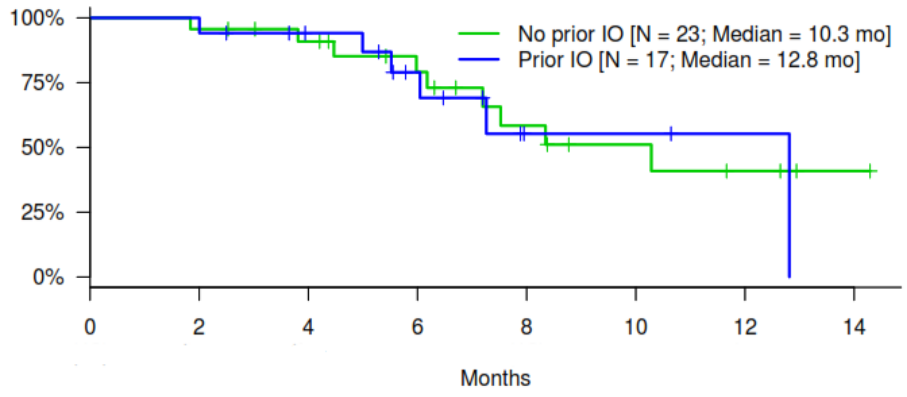
PFS according to prior IO



OS in all patients

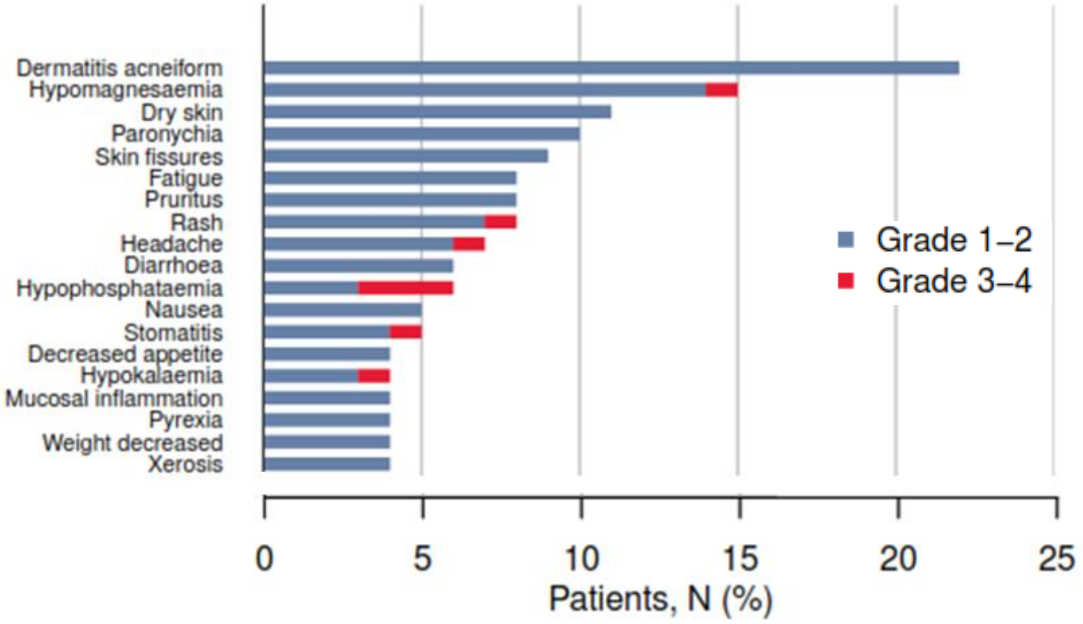


OS according to prior IO



Safety profile of the combination

AEs related to the monalizumab cetuximab combination



	All TEAEs N (%)		Monalizumab related TEAEs N (%)	
	All	**Grade 3-4**	All	**Grade 3-4**
AEs	40 (100%)	**20 (50%)**	30 (75%)	**7 (18%)**
SAEs	16 (40%)	**12 (30%)**	3 (8%)	**3 (8%)**

- 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

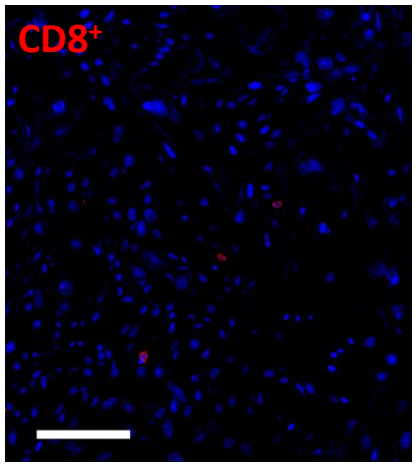
- At 10 mg/kg every 2 weeks monalizumab concentration remained well above 20 µg/mL preclinical target concentration in all patients.
- Cetuximab administration had no impact on monalizumab PK.
- No clinically significant immunogenicity was observed in this study.
- Complete and continuous NKG2A saturation was achieved in all patients.
- Monalizumab treatment did not induce significant changes in peripheral $NKG2A^+$ NK and $CD8^+$ T cells (% and absolute counts).

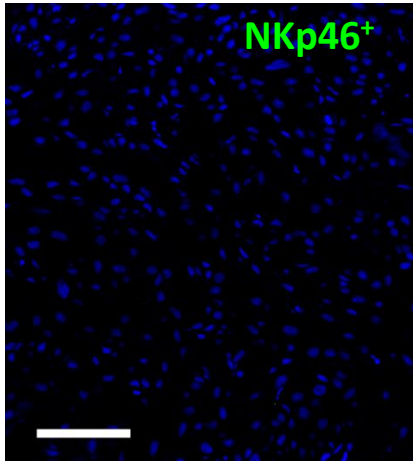
Preliminary biomarker results summary

- 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.

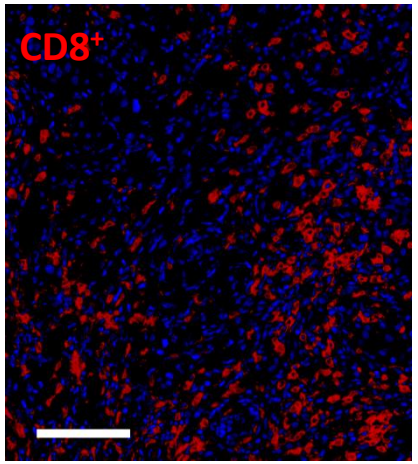
Infiltration of CD8+ T cells and NK cells 15 days after first administration of monalizumab and cetuximab in responding patients

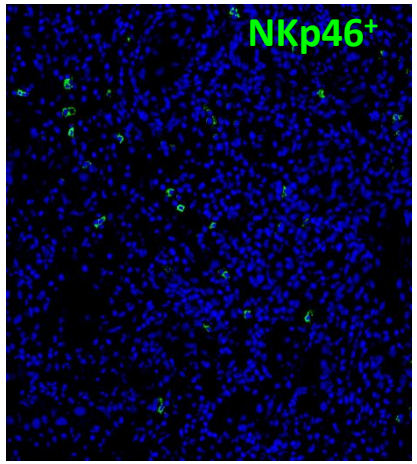
Baseline



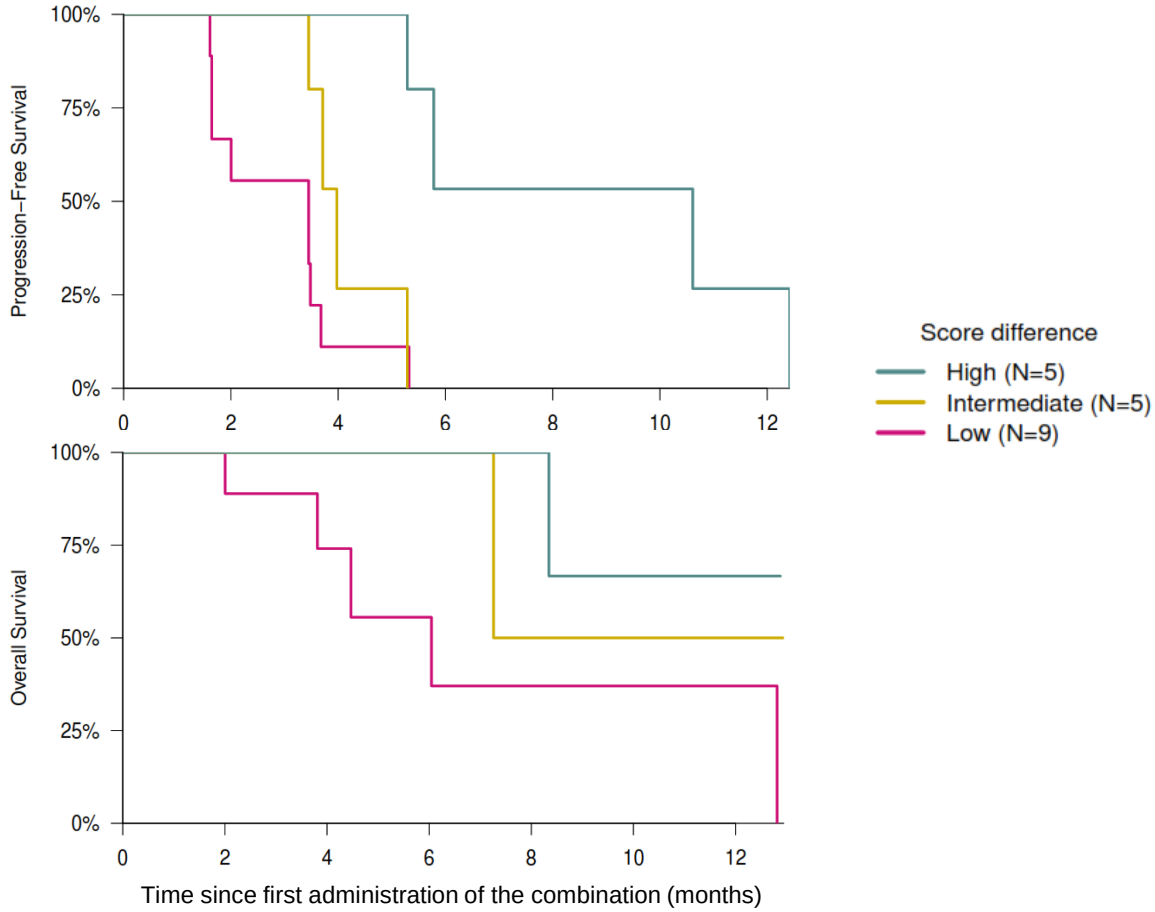


15 days after first administration of monalizumab and cetuximab





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

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