Simlukafusp α and Cetuximab Combination in Patients with Recurrent, Unresectable or Metastatic Squamous Cell Carcinoma of the Head and Neck

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Conflict of Interest: ARH - Merck, GlaxoSmithKline, Bristol Myers Squibb, Eisai, Karyopharm Therapeutics, Boehringer Ingelheim, Roche/Genentech, Jenssen, Astra Zeneca/MedImmune, Astellas Pharma, Macrogenics

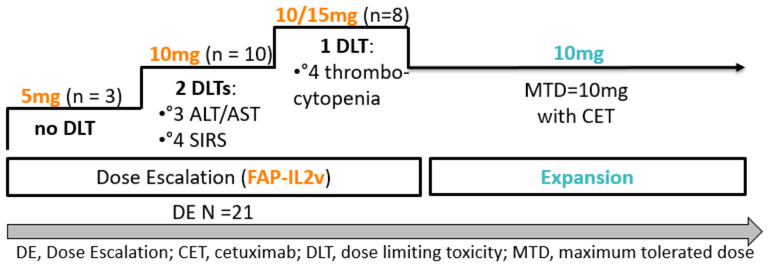
Background

- Simlukafusp α ([SIM], FAP-IL2v), a novel IL-2v immunocytokine, preferentially activates effector CD8 T and NK cells, but not regulatory T cells, due to abolished binding to IL-2 receptor α (IL-2Rα) and retained affinity to IL-2Rβγ
- High affinity binding of SIM to fibroblast activation protein (FAP), expressed on cancer-associated fibroblasts, mediates its accumulation in tumor lesions
- The study explored if SIM may enhance cetuximab (CET) induced ADCC to achieve deep and durable antitumor immune responses in squamous cell carcinoma of the head and neck (HNSCC) patients

Methods

- 58 Patients with recurrent, unresectable, or metastatic SCCHN
- In Dose-escalation (DE), 21 patients received SIM 5-20 mg weekly (QW) for 4 weeks and every 2 weeks (Q2W) thereafter
- In the Expansion (n = 37), SIM was given at the recommended dose of 10 mg QW for 4 weeks and Q2W thereafter. CET was dosed at 250 mg/m^2 QW or 500 mg/m^2 Q2W schedules after the initial 400mg/m^2

-- Study Design --



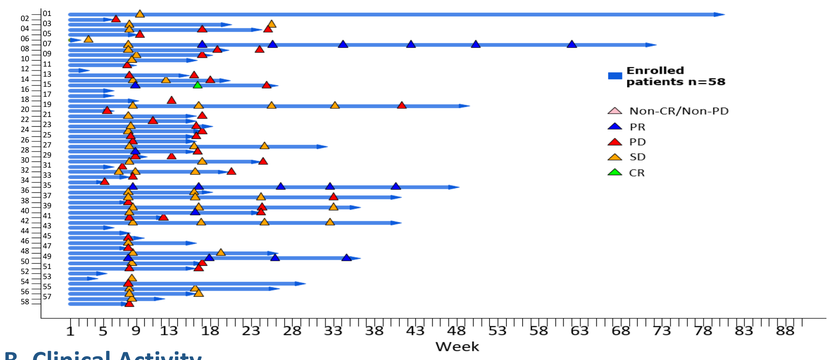
DE, Dose Escalation; CET, cetuximab; DLT, dose limiting toxicity; MTD, maximum tolerated dose

Patients

Demographics and tumor characteristics of the 49 response evaluable patients are: 41 males and 8 females; age range of 39-79 years. Primary tumor location: 19 oropharynx, 13 oral cavity, 6 larynx, 3 hypo-, 2 nasopharynx, 6 other. At study entry, 3 Stage III and 46 Stage IV. Patients with prior: radiation 43, surgery 25, (neo)adjuvant therapy 29. Patients with prior lines (L) of systemic therapy: 1L 13, 2L 15, ≥3 17. Median treatment duration 3.3 months (range 0-18)

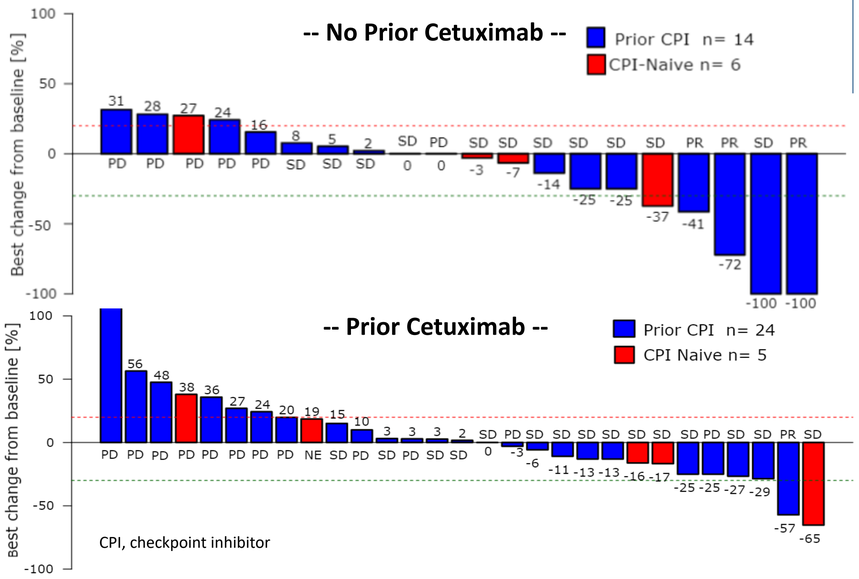
Results

A. Treatment Duration



B. Clinical Activity

In 49 response evaluable patients, ORR 7% (4 PR), DCR 54.4%, median PFS 3.7 mo (95% Confidence interval, 2.1, 4.0), mDoR 14.3 mo (95% CI 3.7, NE)



C. Safety

% Patients ≥ 1 (N=58):	
AE (SIM related)	100% (96.6%)
SAE (related)	53.4% (32.8%)
Gr 3 AE (related)	79.3% (55.2%)
Gr 4 AE (related)	29.3% (24.1%)
Gr 5 AE (related)*	3.4% (0%)
AE leading to SIM withdrawal	6.9%
AE resulting in SIM dose interruption/ modification	32.8%

SIM-Related Adverse Events (AEs)

AEs in >20% patients: pyrexia 63.8%, chills 44.8%, fatigue 43.1%, IRR 39.7%, nausea 36.2%, AST ↑ 27.6%, ALT ↑ 25.9%, hypophosphatemia 20.7%

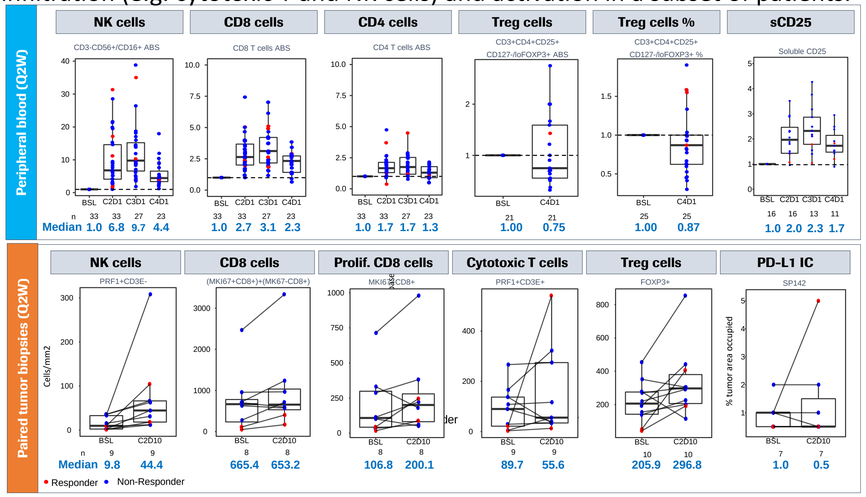
Serious AEs in >5% patients: IRR 19.0%, lymphopenia 8.6%

Grade 3-4 AEs in >10% patients: hypophosphatemia 19.0%, lymphopenia 15.5%, IRR 13.8%, ALT ↑10.3%

*Cardiac arrest, hemorrhage (neither SIM-related)

D. Pharmacodynamics

Supportive of MoA, SIM + CET lead to preferential expansion & activation of effector NK & T cells, but not Treg in peripheral blood and to augmented TIL infiltration (e.g. cytotoxic T and NK cells) and activation in a subset of patients.



Summary and Conclusions

- The safety profile of SIM in combination with CET was consistent with the safety of each component, and did not lead to increased overlapping toxicities
- Despite sporadic responders with prior CPI, overall low anti-tumor activity does not warrant further clinical exploration in HNSCC