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First-in-human clinical trial of the GDF-15 neutralizing antibody visugromab (CTL-002)

The „GDFATHER“ phase 1 - trial (CTL-002-001)

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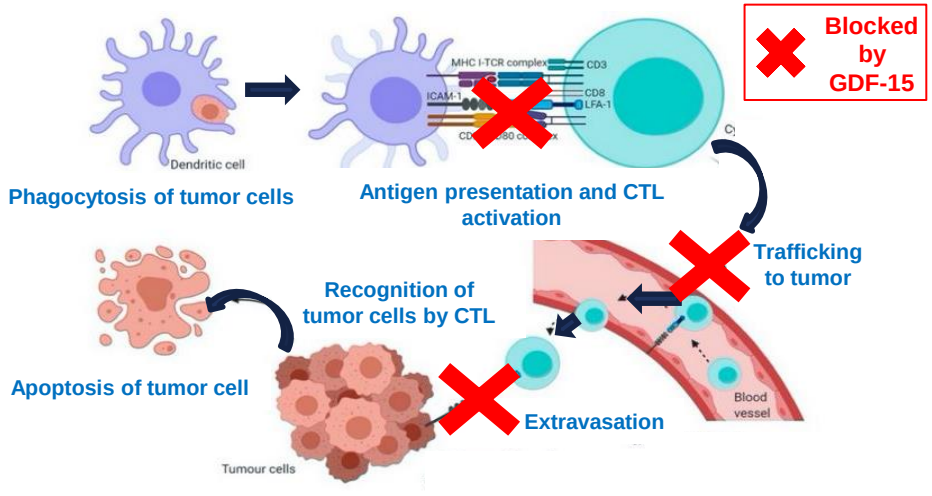
GDFATHER-1

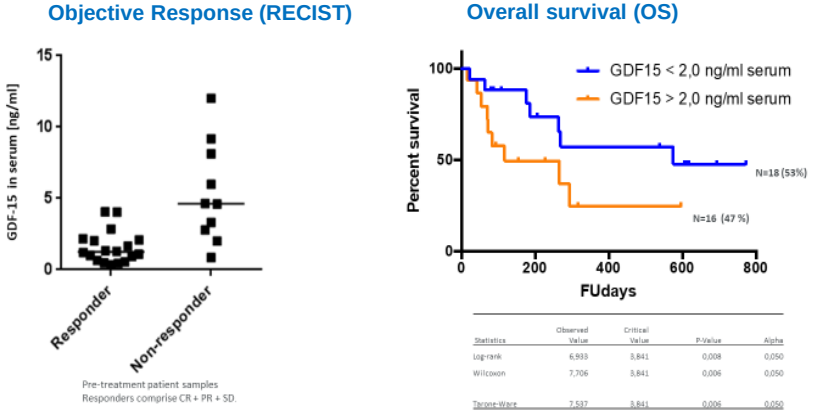
GDF-15: Background

A potent tumor-derived immunosuppressant

- **GDF-15** is a mainly **stress-induced** remote member of the **TGF-ß superfamily** and has been shown to mediate
  - **Anorexia** ***(metabolic function)*** and
  - **Potent local inhibition of immune cell infiltration and activation** (e.g. in injured tissue or fetomaternal tolerance) ***(immunomodulatory function)***
- **GDF-15** is **overexpressed** and released by a wide variety of **solid tumors** and linked to shorter survival
- **GDF-15** is a **major tumor-derived immunosuppressant** [*Front Imm 2020;11:951*], blocking **T cell entry** into the TME, and **T cell priming** and **activation** (see upper right figure)
- **GDF-15** has been linked to **resistance to anti-PD1/PD-L1 treatment** (lower right figure)



Adapted from Looi et al, *Biomedicines* **2020**, 8, 334.

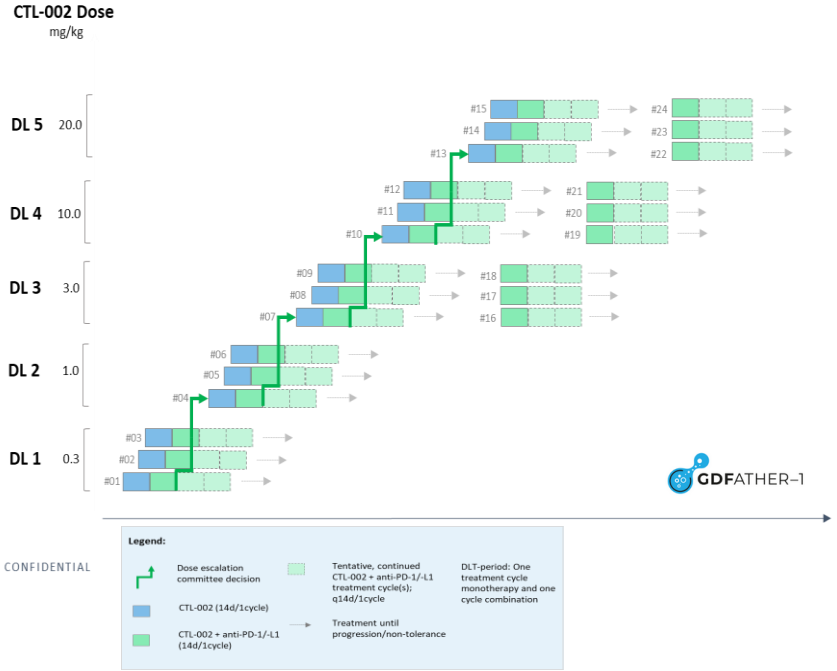


Collaboration with Dr. Reinhard Dummer/ETH Zurich and J. Wischusen/Würzburg

The visugromab phase 1 trial: Design

„**GDF**ATHER-1“ Trial [**GDF**-15 **A**ntibody-media**T**ed **H**uman **E**ffector T cell **R**elocation]

- **Visugromab (CTL-002)** is a **GDF-15 neutralizing antibody** currently developed in combination with anti-PD-1 for treatment of anti-PD1/L-1 relapsed/refractory tumors
- The Phase 1 trial is a **“3+3” dose escalation** with integrated **mono-/combo-exploration**
- Enrolled were **advanced-stage mixed solid tumor patients** in **last-line** treatment situation (4.3 prior lines of treatment on average) that were **also relapsed/refractory to prior anti-PD1/-L1 treatment** (with > 12 wks continuous exposure and progression on continued treatment)
- 5 dose levels (**0.3 – 20mg/kg**) Q2wks were explored for CTL-002 in mono-/combo with nivolumab



Results: Safety and pharmacokinetics

Excellent combination therapy tolerability and linear PK

Safety

- No Grade 4 or 5 TEAE
- No DLT
- Excellent tolerability in last-line patients

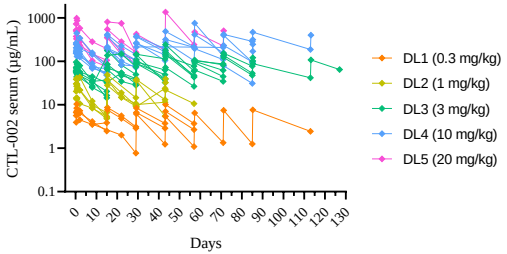
Pharmacokinetics

- No signs for ADA- or trough-formation

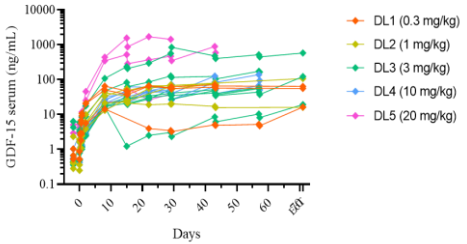
Pharmacodynamics

- Clear plateau formation of total GDF-15 levels confirming complete neutralization of GDF-15 (neutralizing serum baseline GDF-15 levels ranging from 0.4 – 9.5 ng/ml)

PK CTL-002



Total GDF-15 in serum

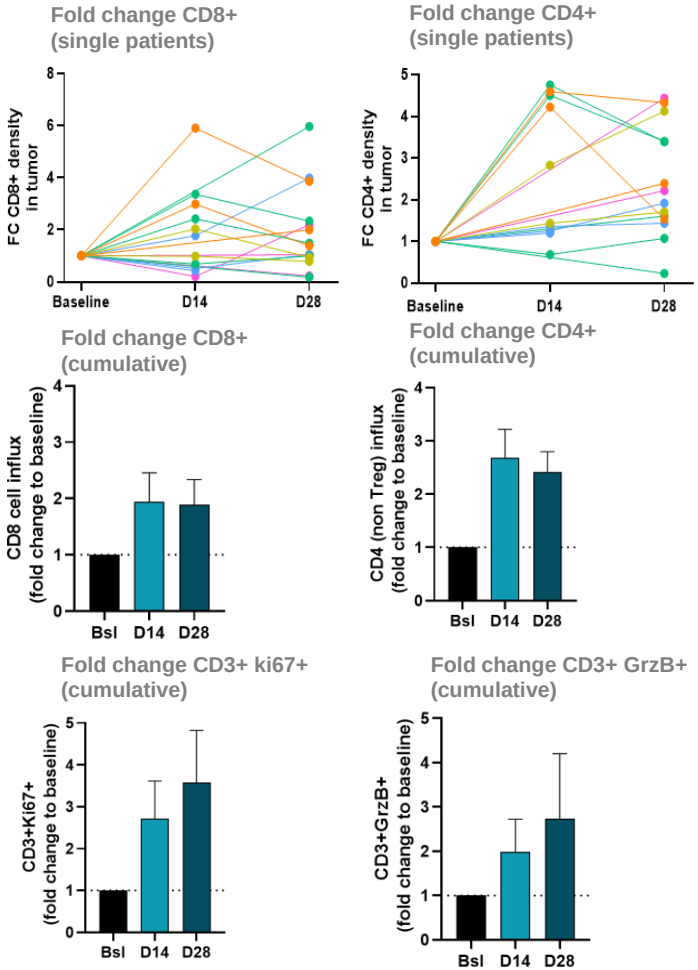


Results: Immune cell shift

Analysis of 3 sequential tumor biopsies

- Biopsies taken at Day 0, 14 (mono) and 28 (combo)
- A significant and **tumor-selective increase** in T cell infiltration into the tumor upon treatment with **monotherapy** and maintained **in combination** with nivolumab was observed in the majority of patients treated
- **Increase** in **Ki67+ T cells** > 2-fold in 55% of evaluable patients
- **Increase** in **GrzB+ T cells** > 2-fold in 50% of evaluable patients

➡ **Proof-of-mechanism #1** for visugromab (T cell infiltration to TME achieved with monotherapy and maintained with combo)



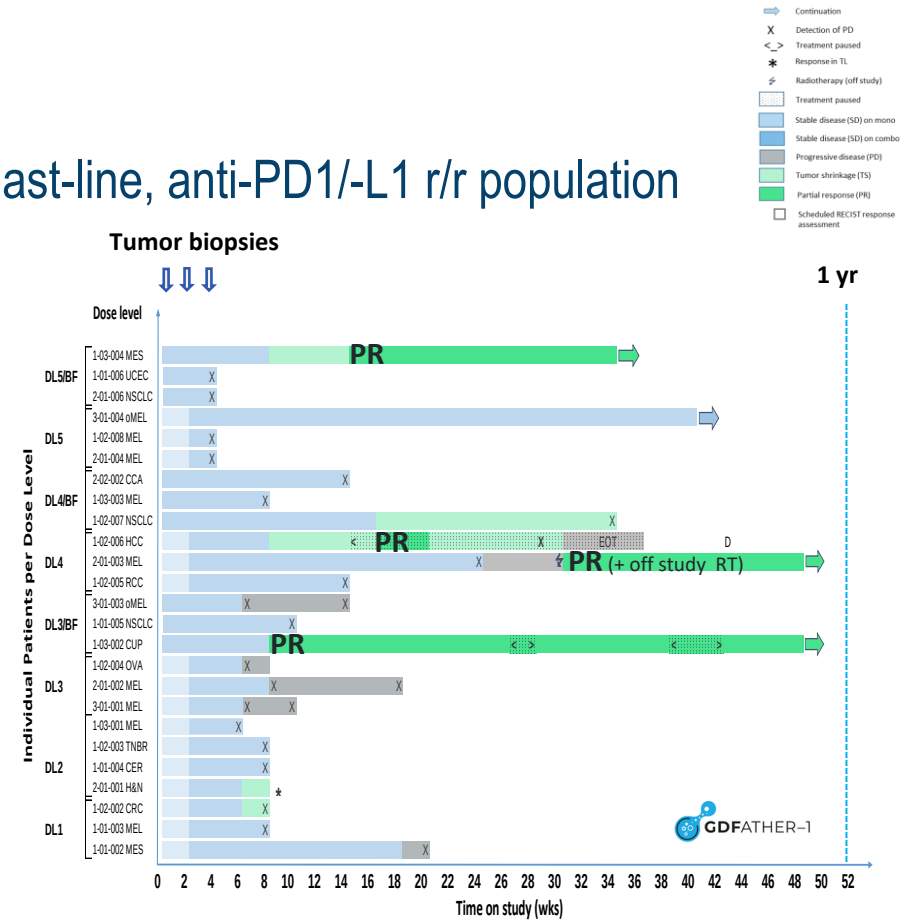
Results: Clinical efficacy

Significant tumor regression/response rate in last-line, anti-PD1/-L1 r/r population

- 6/18 patients on DL 3-5 experienced apparent, significant clinical benefit
- 3/6 patients (CUP, mesothelioma and HCC) achieved **confirmed partial responses (PR)** with up to 12 months duration (1 ongoing), being pretreated with up to 6 lines of prior treatment including anti-PD1/-L1
- 3/6 patients experienced long-term disease stabilization (SD) with one moving to a PR after local irradiation of a single progressing lesion, including abscopal antitumor effects being observed

➡ **Tumor regression rate** for DL 3-5/4-5: **22% - 25%**

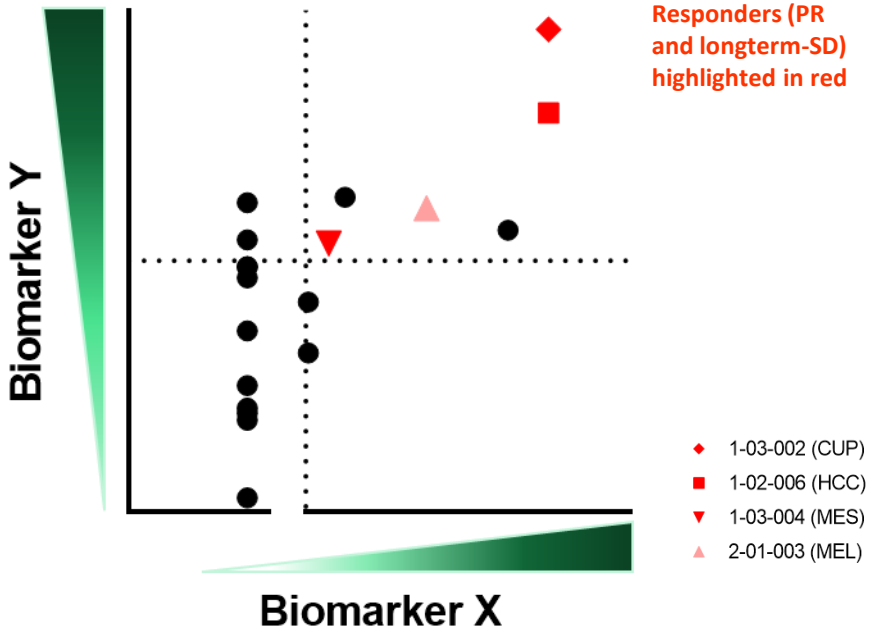
➡ **RECIST ORR** for DL 3-5: **17%**



Results: Potential response-predictive biomarker identified

Two key biomarkers may allow to select patients benefitting most from visugromab

- Biomarker x and y largely overlap and are **present in approx. 30-35%** of **last-line cancer patients**
- **All 3 PRs** and **1 longterm-SD** showed **biomarker-elevations for marker x and y** at baseline
- If patients would have been selected e.g. based upon biomarker x an **ORR = 50%** (3/6) and **CBR > 65%** (4/6) would have been achieved, similarly with biomarker y
- Currently, in phase 2 a biomarker-selected cohort is ongoing **to validate the preliminary findings** on biomarker x and y
- Results of this confirmatory cohort and the biomarker analyses will be reported in the course of **2023**



Summary

Visugromab phase 1 dose-escalation

- **Visugromab** has demonstrated **excellent safety and tolerability** in last-line treatment in monotherapy and combination with nivolumab
- A **tumor-selective**, significant **T cell-influx, T cell proliferation** and **Granzyme B release** could be observed in the majority of patients treated
- In **last-line solid tumor patients** with hard-to-treat tumors such as CUP, HCC, MES, NSCLC that were **relapsed/refractory to prior anti-PD1/-L1 treatment** several **partial remissions** with **long durability** and long-term disease stabilizations could be observed
- Two **potentially predictive biomarkers** were identified, present in approx. 1/3 of last-line patients treated, resulting if applied in an **ORR of 50%** and a **CBR of > 65%** in these patients

Future outlook:

- **IND** submitted
- **Phase 2 development commenced Feb 01, 2022** and is ongoing with

  (1) **signal-finding studies** in 5 dedicated indications

  (2) a dedicated, **predictive biomarker-selected cohort** &

  (3) exploration in **neoadjuvant setting**

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Thanks to all **participating patients** and their **relatives**, to all **Investigators** and **study staff** for their significant contributions to this trial!

Thank you for your attention!

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