GDFATHER-01 Trial Long Term Follow-Up: GDF-15 Neutralization Combined With Nivolumab Can Enable Deep, Long-Term Remission In Heavily Pretreated, Anti-PD1/-L1 Relapsed/ Refractory Major Solid Tumor Types

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Abstract
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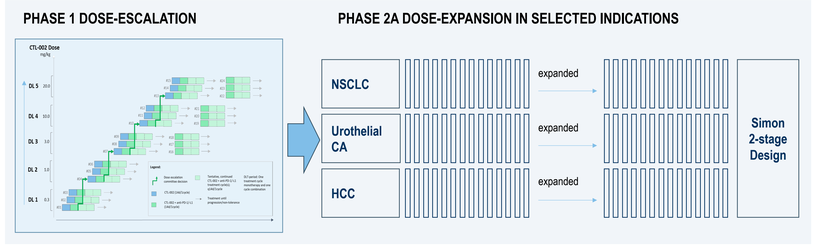
CATALYM
catalyzing immunotherapy

Background

- Growth and Differentiation Factor 15 (GDF-15) is the most overexpressed cytokine in cancer and has emerged as an attractive novel target in oncology and cancer cachexia[1]
- GDF-15 is a potent local immunosuppressant playing a critical role in resistance to immune checkpoint inhibition[2] and a key driver of weight loss and appetite suppression in cancer cachexia[3]
- Visugromab is a monoclonal antibody designed to neutralize GDF-15 to enable immune cell activation, proliferation and induction of interferon-γ while mitigating cancer cachexia, a severe condition affecting a significant number of advanced cancer patients
- The GDFATHER-01 trial (NCT04725474) investigates visugromab (V; anti-GDF-15) in combination with nivolumab (N; anti-PD-1) in heavily pretreated, by strict criteria anti-PD1 / PD-L1-relapsed / refractory patients with locally advanced/metastatic non-squamous non-small cell lung cancer (nsq NSCLC), urothelial cancer (UC) and hepatocellular cancer (HCC)[4]
- The results presented here highlight the long-term outcomes of the Phase 1/2a first-in-human trial as well as a comprehensive safety analysis

Study Design

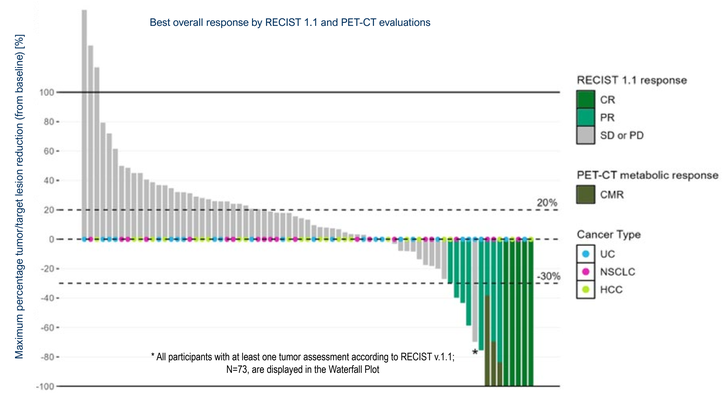
Phase 1 dose escalation and Phase 2a expansion cohorts included a total of N=77 patients with nsq NSCLC (N=22), UC (N=27), and HCC (N=28) patients treated with visugromab (10mg/kg q2wk) and nivolumab (240mg) combination



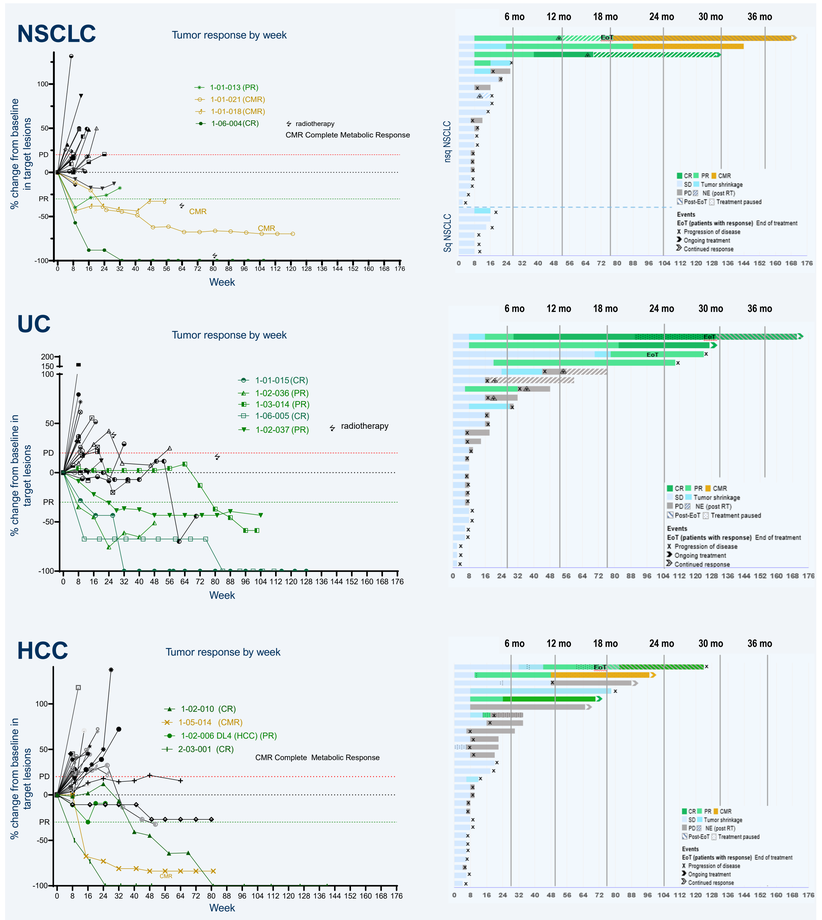
Patient Demographics

	ALL (N=77)	NSQ NSCLC (N=22)	UC (N=27)	HCC (N=28)
Median age, years (range)	67.0 (42.0-82.0)	67.5 (42.0-81.0)	67.0 (52.0-82.0)	65.5(48.0-77.0)
Gender (%)				
Female	17 (22.1)	6 (27.3)	5 (18.5)	6 (21.4)
Male	60 (77.9)	16 (72.7)	22 (81.5)	22 (78.6)
ECOG, n (%)				
0	41 (53.2)	6 (27.3)	12 (44.4)	23 (82.1)
1	36 (46.8)	16 (72.7)	15 (55.6)	5 (17.9)
Stage of cancer at enrollment, n (%)				
Locally advanced	9 (11.7)	0	2 (7.4)	7 (25.0)
Metastatic	68 (88.3)	22 (100.0)	25 (92.6)	21 (75.0)
Prior cancer surgery, n (%)				
Yes	48 (62.3)	9 (40.9)	25 (92.6)	14 (50.0)
No	29 (37.7)	13 (59.1)	2 (7.4)	14 (50.0)
Prior cancer radiotherapy, n (%)				
Yes	40 (51.9)	18 (81.8)	15 (55.6)	7 (25.0)
No	37 (48.1)	4 (18.2)	12 (44.4)	21 (75.0)
Prior systemic therapies, median (range)	**2.0 (1-7)**	**3.5 (1-7)**	**3.0 (1-6)**	**2.0 (1-4)**
Prior systemic therapies, n (%)				
0	**0**	**0**	**0**	**0**
1-3	**54 (70.1)**	**11 (50.0)**	**18 (66.7)**	**25 (89.3)**
> 3	**23 (29.9)**	**11 (50.0)**	**9 (33.3)**	**3 (10.7)**
Prior anti-PD-1/PD-L1 therapy, n (%)	77 (100.0)	22 (100.0)	27 (100.0)	28 (100.0)

Efficacy: Best Change From Baseline



Efficacy: Long-Term Follow-up Analysis



Efficacy: Response Comparison To Prior Anti-PD(L)1

- 61.5% (8/13) of responders experienced better response quality than reported for initial, approved anti-PD(L)1-treatment
- Median Duration of Response (DoR: 28.8 months) exceeded DoR on initial anti-PD(L)1-treatment (12.2 months)
- 76.9% (10/13) of responders achieved a longer DoR compared to initial anti-PD(L)1-treatment

All Nivolumab + Visugromab Responder (N = 13)

	Trial Cohort participant	Tumor type	Prior anti-PD(L)1-containing therapy: Drug/agent name	Best response to prior regimen	DoR on prior regimen (months)	Nivolumab + Visugromab treatment: Best response to trial regimen	DoR on study treatment (months)	Response ongoing? (Y/N)
nsq NSCLC	1-01-013	non-sq NSCLC	Nivolumab	PR	24.8	PR	5.5	N
	1-01-018‡*	non-sq NSCLC	Pembrolizumab Carboplatin Pemetrexed	PR	9.0	PR/CMR	38.0	Y
	1-01-021	non-sq NSCLC	Atezolizumab	PR	16.0	PR/CMR	33.9	Y
	1-06-004	non-sq NSCLC	Pembrolizumab Cisplatin Pemetrexed	PR	22.4	CR	30.5	Y
UC	1-01-015	UC	Atezolizumab	PR	24.0	CR	39.4	Y
	1-02-036	UC	Avelumab (maintenance)	PR	3.0	PR	7.4	N
	1-02-037	UC	Atezolizumab	PD	3.0	PR	28.1	N
	1-03-014	UC	Pembrolizumab GSK33 (ICOS agonist)	PR	43.0	PR	28.8	N
	1-06-005	UC	Atezolizumab	SD	5.0	CR	28.2	Y
HCC	1-02-006** (Ph 1)	HCC (Ph1)	LY3300054; LY3321367 (JLDA Clinical trial)	SD	12.0	PR	5.7	N
	1-02-010^	HCC	Atezolizumab Bevacizumab	CR	29.4	CR	39.7	N
	1-05-014	HCC	Atezolizumab Bevacizumab	SD	8.0	PR/CMR	22.1	Y
	2-03-001	HCC	Atezolizumab Bevacizumab Pembrolizumab	CR	12.0	CR	14.8	Y
				Median	**12.2**		**28.8**	

* CMR after EoT; ** Patient in Phase 1 part (Part A) Dose Level 4; ^ Lasting PR on study treatment; treatment discontinuation due to irAE (Grade 2 arthralgia). CR detected post EoT with no other treatment provided since study treatment; ‡ Lasting PR achieved on study treatment. At week 48, lymph node enlargement led to focal irradiation. Lesions decreased further, but study treatment discontinued at week 72 due to unrelated AE and patient's wish to stop. Scans at weeks ≥ 78 confirmed CR.

Better
Equal
Worse than on prior anti-PD1/PD-L1 therapy

Safety Profile Of Visugromab/Nivolumab Combination

- Most frequent TRAEs* (≥5% of participants) included pyrexia (n=10 [12%]), rash (n=8 [10%]), increased alanine aminotransferase (n=7 [8%]), diarrhea (n=6 [7%]), increased gamma-glutamyltransferase, increased aspartate aminotransferase, asthenia, and fatigue (all n=5 [6%])
- AE profile did not seem to differ substantially from nivolumab monotherapy in retreatment

	NSQ NSCLC, UC, HCC (N=77)	NSQ NSCLC (N=22)	UC (N=27)	HCC (N=28)
Any TEAE, n** (%)	76 (98.7)	22 (100.0)	27 (100.0)	27 (96.4)
TEAE ≥ Grade 3, n** (%)	**38 (49.4)**	13 (59.1)	16 (59.3)	9 (32.1)
Any TRAE, n** (%)	45 (58.4)	10 (45.5)	17 (63.0)	18 (64.3)
TRAE ≥ Grade 3, n**† (%)	**10 (13.0)**	4 (18.2)	3 (11.1)	3 (10.7)
TRAE leading to discontinuation, n** (%)	**3 (3.9)**	1 (4.5)	1 (3.7)	1 (3.6)

*In total, 175 participants were treated in the Phase 2 expansion cohorts with visugromab 10 mg/kg + nivolumab; in this presentation, a subset is reported.
**Number of participants with at least one adverse event; † Grade 5 Multiple organ dysfunction syndrome and Grade 5 Respiratory failure in 2 pts. with NSCLC (Phase 1 and Phase 2a expansion).
TRAE: treatment-related adverse events, TEAE: treatment-emergent adverse events

Summary And Conclusions

- GDF-15 blockade re-sensitized tumors to immunotherapy and demonstrated favorable safety and tolerability in heavily pretreated patients
- Visugromab/Nivolumab combination shows remarkable durability of response in heavily pre-treated, late-stage patient population exceeding 32 months in nsq NSCLC, 28 months in UC and 19 months in HCC with majority of responses still ongoing
- 61.5% of responders experienced either CR or CMR, and had a deeper response than on initial anti-PD(L)1 treatment
- Data underscore the potential of GDF-15 blockade to establish immune sensitivity in resistant tumors and provide novel strategy to overcome immune resistance
- Phase 2b program with randomized trials in 1L NSCLC (NCT07098988; recruiting), 2L NSCLC, 2L HCC (NCT07219459) and cachexia (NCT07112196) under way

Data partly non-SDV'd; Cut-off date: 21-Aug-2025

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