Journal of Hematology & Oncology

RESEARCH

Open Access

Long-term follow-up of a phase 1/2 trial of anti-GDF-15 antibody visugromab plus anti-PD-1 antibody nivolumab in anti-PD-1/-L1 relapsed/refractory solid tumors

Ignacio Melero[1,2*], María de Miguel[3], Elena Garralda Cabanas[4], Guillermo de Velasco[5], Markus Joerger[6], Juan Martín-Liberal[7], Maria Reig[8,9,10], David König[11], Joerg Trojan[12], Maria-Elisabeth Goebeler[13], Martin Schuler[14,15], Guzman Alonso[16], Reinhard Dummer[17], Maria E. Rodríguez-Ruiz[1], Ramón Yarza[3], Giulia Pretelli[4], Jorge Esteban-Villarubia[5], Kira-Lee Koster[6], Paula Sabat Viltro[7], Marco Sanduzzi-Zamparelli[8,9,10], Heinz Läubli[11], Christine Koch[12], Cyrus Sayehli[13], Tanja Gromke[14,15], Fabricio Racca[16], Egle Ramelyte[17], Peter R. Galle[18], Andrea Necchi[19,20], Martin Reck[21], Zlatko Trajanoski[22], Hubert Hackl[22], Falk Gogolla[21], Jaclyn Billing[23], Teresa Sattmann[24], Jörg Wischhusen[25], Christine Schuberth-Wagner[26], Julia Akdemir[26], Felix S. Lichtenegger[26], Alexandra Auckenthaler[26], Marlene Fox[26], Kathrin Klar[26], Petra Fettes[26], Mara Liebig[26], Aasim Amin[26], Sheena Sachdeva[26], Frank Hermann[26†] and Eugen Leo[26†]

Abstract

Background Resistance to anti–PD-1/PD-L1 therapy is a major unmet need. Growth Differentiation Factor 15 (GDF-15) has been identified as a key resistance factor for anti–PD-1/PD-L1 immunotherapy. Visugromab, a neutralizing anti–GDF-15 antibody, plus the anti–PD-1 antibody nivolumab (V+N) was evaluated in the first-in-human phase 1/2a GDFATHER-01 trial in heavily pretreated participants with locally advanced/metastatic non-squamous non-small-cell lung cancer (nsq NSCLC), urothelial carcinoma (UC), or hepatocellular carcinoma (HCC), stringently defined as anti–PD-1/PD-L1-relapsed/refractory, and showed encouraging objective responses. This analysis reports long-term follow-up of these three phase 2 expansion cohorts of the GDFATHER-01 trial.

Methods Seventy-seven participants with nsq NSCLC (N=22), UC (N=27), and HCC (N=28) received visugromab (10 mg/kg) plus nivolumab (240 mg) every two weeks until disease progression or unacceptable toxicity.

Results Objective response rates (RECIST v1.1) were 18.2% for nsq NSCLC (4/22; 95%CI 5.2–40.3), 18.5% for UC (5/27; 95%CI 6.3–38.1), and 14.3% for HCC (4/28; 95%CI 4.0–32.7). Median duration of response (DoR) was 32.2 months (95%CI 5.5–38.0), 28.8 months (95%CI 7.4–39.4), and 19.4 months (95%CI 5.8–39.7; with protracted recruitment), respectively, with 7/13 responses (53.8%) ongoing. Confirmed complete response or complete metabolic response

[†]Frank Hermann and Eugen Leo shared senior authorship.

*Correspondence:
Ignacio Melero
imelero@unav.es

Full list of author information is available at the end of the article

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

(CR or CMR) among responders was 61.5% (8/13), with 7/8 ongoing. In addition, 46.2% (6/13) of responders achieved a deeper response on V+N per RECIST v1.1 than with the prior anti–PD-(L)1 therapy; median DoR on V+N was 28.8 months (95%CI 7.4–38.0) versus 12.0 months (95%CI 8.0–24.0) on initial anti–PD-1/PD-L1 treatment. V+N was generally well tolerated.

Conclusions In heavily pretreated, advanced/metastatic participants with nsq NSCLC, UC, or HCC who were anti–PD-1/PD-L1-relapsed/refractory, V+N achieved deep and durable objective responses. The observed DoR, depth of response, and CR+CMR rate among responders exceeded those reported for their initial anti–PD-1/PD-L1 therapy. These findings suggest that GDF-15 blockade with visugromab can overcome resistance and enhance the magnitude and durability of anti–PD-1/PD-L1 responses, and warrant further exploration in randomized trials.

Registry ClinicalTrials.gov, TRN: NCT04725474, Registration date: 25 January 2021; EudraCT, TRN: 2020-002103-19, Registration date 16 Dec 2020

Keywords GDF-15, Visugromab, Anti–PD-(L)1-relapsed/refractory solid tumors, Non-squamous non-small-cell lung cancer, Urothelial carcinoma, Hepatocellular carcinoma

Background

Immune checkpoint inhibitors targeting PD-1/PD-L1 have transformed the therapeutic landscape of solid tumor treatment [1–3]. Yet, the vast majority of patients with advanced/metastatic solid tumors ultimately experience relapse or progression on anti–PD-1/PD-L1 therapy. Once anti–PD-1/PD-L1 relapsed/refractory, outcomes are dismal, representing a major unmet medical need [4–6].

Anti–PD-1/PD-L1 resistance appears to be mainly driven by tumor-induced immunosuppression and immune escape [4, 7]. Various approaches have been explored to overcome anti–PD-1/PD-L1 resistance, including combinations with checkpoint inhibitors targeting TIGIT, LAG-3, TIM-3, and other mechanisms [8, 9]. However, apart from possibly targeting CTLA-4 [10], no single resistance factor has been identified whose modulation results in consistent reinvigoration and potentiation of anti–PD-1/PD-L1 activity across multiple solid tumors.

Growth Differentiation Factor 15 (GDF-15) is linked to feto-maternal tolerance and tissue stress responses [11, 12]. It has been identified as the most overexpressed cytokine in solid tumors [13, 14], and its overexpression is associated with reduced overall survival in many solid tumor types. Recent investigations have revealed that GDF-15 acts as a potent local immunosuppressant by disconnecting LFA-1 from the actin cytoskeleton [15]. As a result, T-cell infiltration into tissues, particularly within the tumor microenvironment, is inhibited. LFA-1 destabilization also suppresses antigen presentation and the adaptive immune response, further contributing to an immunosuppressive tumor microenvironment [14, 15].

Visugromab (CTL-002), a humanized, hinge-stabilized, GDF-15–neutralizing IgG4 monoclonal antibody, was evaluated in combination with nivolumab in a first-in-human, phase 1/2a trial (GDFATHER-01; NCT04725474). Transcriptomic analyses of The Cancer Genome Atlas (TCGA) and various translational research datasets suggested prominent GDF-15–mediated immunosuppression in non-squamous non-small cell lung cancer (nsq NSCLC), urothelial carcinoma, and hepatocellular carcinoma (HCC) [16], directing initial clinical exploration of visugromab to these tumor types. Immune monitoring of interferon-γ-inducible chemokines supported the combination treatment concept [16]. All enrolled participants had exhausted available treatment options, including prior treatment—either as monotherapy or in combination—with an approved anti–PD-1/PD-L1 agent. Observed overall response rates (ORR) per RECIST v1.1 were encouraging, with overall good tolerability, as reported previously [16].

Here, with a 15 months later cut-off date and >90% of trial participants having completed treatment, we report mature long-term safety and efficacy results of the GDFATHER-01 trial for the three fully recruited, phase 2 expansion cohorts in nsq NSCLC, urothelial carcinoma, and HCC.

Methods

Trial design and participants

The GDFATHER-01 trial (NCT04725474) is a first-in-human, phase 1/2a study of the GDF-15–neutralizing antibody visugromab in combination with the anti–PD-1 antibody nivolumab. Participants were required to have either primary progression on ongoing, continuous, initial anti–PD-1/PD-L1 treatment for at least 12 weeks without a RECIST v1.1 like response ("primary refractory") or, if an initial response had been achieved on therapy, to have relapsed while still receiving the same anti–PD-1/PD-L1 regimen ("secondary refractory"); i.e. they had to meet strict criteria for PD-1/PD-L1 refractoriness/relapse. Eligible in terms of refractoriness were hence only patients who achieved progression whilst being still on initial PD-1/PD-L1 therapy. Participants who had discontinued anti–PD-1/PD-L1 treatment for

other reasons, such as intolerable adverse events (AEs) or completion of the protocol-defined maximum treatment duration, were excluded.

Apart from the required PD-1/PD-L1 refractoriness/relapse criterion, eligible participants (≥18 years , no upper age limit) were required to have ECOG performance status of 0 or 1, radiologically measurable disease at baseline and adequate organ function.

Participants with a history of ongoing immune-related adverse events (irAEs) and/or AEs of grade ≥2 that had not resolved from prior therapies, or a history or clinical evidence of CNS primary tumors or metastases, including leptomeningeal metastases, were not eligible.

In the phase 1 part, escalating doses of visugromab (0.1, 1, 3, 10, and 20 mg/kg Q2W) were administered in combination with the anti–PD-1 antibody nivolumab (240 mg Q2W), identifying 10 mg/kg Q2W as the recommended phase 2 dose for visugromab [16]. The design and results of the dose-escalation phase 1 part were described previously [16]. In the phase 2a part, expansion cohorts in various advanced/metastatic anti–PD-1/PD-L1-relapsed/refractory solid tumor types were treated at this dose level, including NSCLC (non-squamous and squamous), urothelial carcinoma, HCC, melanoma, and microsatellite-stable colorectal cancer, following Simon two-stage designs. After data review by an independent review committee, protocol-defined further expansion of the NSCLC, HCC, and urothelial carcinoma cohorts was implemented. Indication selection was supported by a large translational research program, including transcriptomic analyses of 11,000 tumor samples from TCGA, which identified nsq NSCLC and urothelial carcinoma as key GDF-15–immunosuppressed target indications [16]. Notably, for HCC, substantial GDF-15 overexpression has been reported across all major underlying liver disease conditions predisposing to HCC [17–20], suggesting a GDF-15–saturated tumor microenvironment.

The trial was approved by the national competent authorities of the participating countries and by the institutional review boards at each participating site, and has been conducted in accordance with ICH-GCP and the Declaration of Helsinki. All participants provided written informed consent. A safety review committee met regularly throughout all parts of the trial to monitor participant safety and to evaluate dose-limiting toxicities (as defined in the protocol and reported previously [16]) during phase 1.

Trial endpoints and assessments

Primary endpoint for the phase 2a part was investigator-assessed ORR per RECIST v1.1 [21]. Additional efficacy endpoints included time-to-response (TTR), duration-of-response (DoR; measured from start of treatment until disease progression or trial discontinuation), progression-free survival (PFS), overall survival (OS), and the proportion of participants with tumor shrinkage. Tumor assessments (CT/MRI/PET) were done at 8-weekly intervals, a blinded copy of the images was sent to a central reader for monitoring purposes and post-hoc analysis. Investigators were required to use in each participant the assessment modality selected at baseline for subsequent assessments. For participants with durable partial responses (PR >12 months), FDG-PET/CT according to institutional standards was offered to assess metabolic response, including complete metabolic response (CMR).

For safety, clinical laboratory parameters, vital signs, ECGs, and physical examinations (including neurological examination) were assessed. Treatment-emergent adverse events (TEAEs) were coded using the current Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [22].

GDF-15 serum levels were assessed at baseline and at predefined time points throughout the trial (Quantitative solid-phase sandwich ELISA kit, manufactured by R&D Systems: GDF-15 DuoSet ELISA kit, catalogue no. DY957) [16].

Statistical analysis

For the three main expansion cohorts (NSCLC, urothelial carcinoma, HCC) reported here, a Simon two-stage design required initial recruitment of 14 response-evaluable participants per cohort in order to allow the detection of at least one response with 80% probability if the true response rate is 20% (minimal acceptable probability of response), the maximum unacceptable response rate is 5% and the alpha level is 5% [23]. If at least one response was observed, an additional 13 participants were to be recruited, to generate cohort-wise a total of ≥4/27 responders as proof of activity for early phase 2 testing; no cohort-specific null (H_0) and alternative (H_A) hypotheses were defined. For ORR (and disease control rate [DCR]) analyses, summary tables were generated presenting the number and proportion of responders with two-sided 95% Clopper–Pearson confidence intervals (95%CI).

Further summary statistics were calculated for DoR, TTR, PFS, OS, and duration of treatment based on all participants with available data for the respective parameters. No formal statistical analysis of survival times was performed to model censoring in participants without an observed event.

Results

Participant disposition and baseline characteristics

Between July 2021 and April 2024, three expansion cohorts in advanced/metastatic NSCLC, urothelial carcinoma, and HCC each enrolled 27 participants who were relapsed/refractory to prior anti–PD-1/PD-L1 therapy as defined by stringent criteria. Participants with HCC (N=1) and NSCLC (N=2) from phase 1 dose levels 4 and 5 were added to the analysis, as these dose levels were considered therapeutically active. In total, 84 participants with NSCLC (7 squamous and 22 non-squamous), urothelial carcinoma (N=27), and HCC (N=28) were available for analysis. Thirty-five participants had received prior anti–PD-1/PD-L1 treatment as monotherapy, 20 in combination with chemotherapy, and 29 in combination with other biologics or targeted therapies. In a single patient with HCC (from phase 1), an experimental anti–PD-L1 checkpoint inhibitor (LY3300054) had been administered, which had been shown to achieve an ORR similar to that of pembrolizumab in MSI-H/dMMR solid tumors [24].

Participants had received a mean of 2.8 (95%CI 2.5–3.2) prior lines of systemic therapy (median 2.0; range 1–7). Prior anti–PD-1/PD-L1 treatment had a median duration of 7.3 months (95%CI 5.8–9.0). Median follow-up was 10.2 months (95%CI 7.6–13.5), and median treatment duration (total population) was 2.4 months (95%CI 1.4–3.3). Baseline characteristics are summarized in Table 1.

The most common reason for treatment discontinuation was disease progression (76.1%), followed by death (7.1%), adverse events (3.6%), withdrawal of consent (2.4%), and other reasons (1.2%) (Suppl. Table S1). At the current data cutoff (August 21, 2025), eight of 84 participants (9.5%) remained on treatment. Although disease control was observed, no confirmed objective responses occurred among the seven participants with squamous NSCLC (sq NSCLC). This finding, together with TCGA-based *in silico* profiling suggesting that sq NSCLC may not be predominantly GDF-15–driven, led to its exclusion from the dedicated efficacy analyses (Suppl. Fig. S1). However, given the evidence of disease stabilization and the small number of participants, clinical activity in sq NSCLC should not be excluded.

Safety

The safety analysis set comprised 84 participants across all cohorts (squamous and non-squamous NSCLC, urothelial carcinoma, and HCC). TEAEs of any grade occurred in 83 of 84 participants (98.8%), and grade ≥3 TEAEs were reported in 39 participants (46.4%).

Treatment-related adverse events (TRAEs) were reported in 47 participants (56.0%), with grade ≥3 TRAEs occurring in 10 participants (11.9%). Three of 84 participants (3.6%) discontinued study treatment due to a TRAE (Table 2). Two grade 5 TRAEs occurred and both events were assessed as at least possibly related to visugromab and/or nivolumab (note: the latter case was reclassified as possibly related after data cutoff). One participant, a 70-year-old male with nsq NSCLC experienced multiple organ dysfunction syndrome with kidney and liver failure while on nivolumab plus visugromab. The participant had pre-existing renal vulnerability following a prior experimental antibody–drug conjugate (resolved to residual Grade 1 creatinine elevation at enrollment). One week after the first dose of visugromab plus nivolumab, he developed acute worsening renal function followed by rapid hepatic failure, both assessed as possibly related to one or both study drugs. On the day of death, after undergoing transjugular kidney and liver biopsies for diagnostic evaluation, he experienced sudden cardiac arrest; no resuscitation was attempted in accordance with a documented do-not-resuscitate order. Histology (pre-mortem biopsies and confirmatory autopsy) demonstrated a pattern overall suggestive of drug-induced renal and hepatic injury, with no evidence of malignancy. The other, a 56-year-old male also with nsq NSCLC, developed CT-confirmed pulmonary infiltrates and elevated CRP ~4 weeks after treatment initiation and was treated as respiratory infection with initial improvement. Respiratory decline recurred 2 weeks later; steroids were initiated for suspected pneumonitis in addition to adjusted antibiotics, but he progressed to Grade 5 respiratory decompensation of unclear cause. Death was attributed to respiratory insufficiency (death certificate) and no autopsy was conducted. Detailed case narratives are provided in the Supplementary Materials (pp. 5–6).

The most frequent TRAEs (≥5% of participants) of any grade included pyrexia (n=10 [11.9%]); rash in its different manifestations (n=7 [8.3%]); increased alanine aminotransferase (n=6 [7.1%]); diarrhea (n=6 [7.1%]); and asthenia and fatigue (each n=5 [6.0%]) (Suppl. Table S1). Increased aspartate aminotransferase (n=2 [2.4%]) and increased alanine aminotransferase, diarrhea, and hypertension (each n=1 [1.2%]) were the only grade ≥3 TRAEs occurring more than once (two events each) (Table 2).

In total, 176 TRAEs were reported, of which 76.1% had resolved or recovered at the time of this analysis. Among the 19 grade ≥3 TRAEs, 68.4% had resolved or recovered. TRAEs led to temporary treatment interruption in 7/84 (8.3%) participants (23 events in total) and to permanent treatment discontinuation in 3/84 (3.6%) participants (Suppl. Table S2).

Efficacy

Overall, the ORR was 13/77 (16.9%; 95%CI 9.3–27.1) across the three main target indications (nsq NSCLC, urothelial carcinoma, and HCC). Overall, 8/77 (10.4%)

Table 1 Demographics and baseline disease characteristics

Characteristic	NSCLC (sq.)	NSCLC (nsq.)	UC	HCC	Efficacy *	Total (safety)
	(n = 7)	(n = 22)	(n = 27)	(n = 28)	(n = 77)	(n = 84)
Age						
Median (range) – years	65.0 (51.0-74.0)	67.5 (42.0-81.0)	67.0 (52.0-82.0)	65.5 (48.0-77.0)	67.0 (42.0-82.0)	66.0 (42.0-82.0)
Age > 65 years – no. (%)	4 (57.1)	15 (68.2)	17 (63.0)	15 (53.6)	47 (61.0)	51 (60.7)
Sex – no. (%)						
Female	1 (14.3)	6 (27.3)	5 (18.5)	6 (21.4)	17 (22.1)	18 (21.4)
Male	6 (85.7)	16 (72.7)	22 (81.5)	22 (78.6)	60 (77.9)	66 (78.6)
Race, n (%)						
White	6 (85.7)	21 (95.5)	27 (100.0)	26 (92.9)	74 (96.1)	80 (95.2)
Not reported	1 (14.3)	1 (4.5)	0	2 (7.1)	3 (3.9)	4 (4.8)
ECOG performance status – no. (%)						
0	5 (71.4)	6 (27.3)	12 (44.4)	23 (82.1)	41 (53.2)	46 (54.8)
1	2 (28.6)	16 (72.7)	15 (55.6)	5 (17.9)	36 (46.8)	38 (45.2)
Stage of cancer at enrolment – no. (%)						
Locally advanced	0	0	2 (7.4)	7 (25.0)	9 (11.7)	9 (10.7)
Metastatic	7 (100.0)	22 (100.0)	25 (92.6)	21 (75.0)	68 (88.3)	75 (89.3)
Prior cancer surgery – no. (%)						
Yes	2 (28.6)	9 (40.9)	25 (92.6)	14 (50.0)	48 (62.3)	50 (59.5)
No	5 (71.4)	13 (59.1)	2 (7.4)	14 (50.0)	29 (37.7)	34 (40.5)
Prior cancer radiotherapy – no. (%)						
Yes	6 (85.7)	18 (81.8)	15 (55.6)	7 (25.0)	40 (51.9)	46 (54.8)
No	1 (14.3)	4 (18.2)	12 (44.4)	21 (75.0)	37 (48.1)	38 (45.2)
Prior systemic therapy						
Median (range) – no.	2.0 (1-7)	3.5 (1-7)	3.0 (1-6)	2.0 (1-4)	2.0 (1-7)	2.0 (1-7)
0 (i.e., no prior therapy)	0	0	0	0	0	0
1	1 (14.3)	3 (13.6)	3 (11.1)	11 (39.3)	17 (22.1)	18 (21.4)
2	4 (57.1)	4 (18.2)	6 (22.2)	12 (42.9)	22 (28.6)	26 (31.0)
3	0	4 (18.2)	9 (33.3)	2 (7.1)	15 (19.5)	15 (17.9)
≥4	2 (28.6)	11 (50.0)	9 (33.3)	3 (10.7)	23 (29.9)	25 (29.8)
Prior platinum-based therapy – no (%)						
Yes	6 (85.7)	22 (100.0)	25 (92.6)	0 (0.0)	nr	nr
Prior Anti-PD-1/-L1 therapy – no. (%)						
Yes	7 (100.0)	22 (100.0)	27 (100.0)	28 (100.0)	77 (100.0)	84 (100.0)
Duration of initial anti-PD-1/-L1						
Median (95% CI) – months	7.0 (5.1–63.5)	6.1 (4.9– 12.0)	6.9 (3.9–10.6)	9.2 (6.9–11.2)	7.4 (5.8–9.0)	7.3 (5.8–9.0)
Anti-PD-1/-L1 therapy as most recent therapy line						
Yes	5 (71.4)	9 (40.9)	11 (40.7)	17 (60.7)	37 (48.1)	42 (50.0)
No	2 (28.6)	13 (59.1)	16 (59.3)	11 (39.3)	40 (51.9)	42 (50.0)
Number of prior anti-PD-1/-L1 therapy lines						
0 (i.e., no prior anti-PD-1/-L1	0	0	0	0	0	0
1	6 (85.7)	18 (81.8)	22 (81.5)	22 (78.6)	62 (80.5)	68 (81.0)
2	1 (14.3)	3 (13.6)	4 (14.8)	6 (21.4)	13 (16.9)	14 (16.7)
≥3	0	1 (4.5)	1 (3.7)	0	2 (2.6)	2 (2.4)

na, not applicable, nr = not reported * comprising HCC, UC and nsq NSCLC cohorts only

participants achieved a PR and 5/77 (6.5%) a CR as best response, with all CRs and all but one PR confirmed per RECIST v1.1. Among participants with PR, 3/8 (37.5%) achieved a CMR. The disease control rate (DCR; CR+PR+SD) was 42.9% (95%CI 31.6–54.6) (Table 3). Tumor size reduction (median −41.5%; range −3.2% to −100%) was observed in 24/77 (31.2%) participants (Fig. 1).

The combined complete plus complete metabolic response rate was 10.4% (8/77). All complete responses

Table 2 Treatment-related adverse events (TRAE), visugromab plus nivolumab

TRAE, summary (all TRAE)	NSCLC (sq.)	NSCLC (nsq.)	UC	HCC	Total (safety)
	(n = 7)	(n = 22)	(n = 27)	(n = 28)	(n = 84)
Treatment-related Adverse events					
Any grade (Grade 1-5) – no. (%)	2 (28.6)	10 (45.5)	17 (63.0)	18 (64.3)	47 (56.0)
Grade 3-5 – no. (%)	0	4 (18.2)	3 (11.1)	3 (10.7)	10 (11.9)
Grade 5 (deaths) – no. (%)	0	2 (9.1)	0	0	2 (2.4)
Leading to discontinuation – no. (%)	0	1 (4.5)	1 (3.7)	1 (3.6)	3 (3.6)
TRAE (any grade), per MedDRA system organ class (in order of frequency)* – no. (%)					
General disorders	1 (14.3)	5 (22.7)	10 (37.0)	5 (17.9)	21 (25.0)
Skin & subcutaneous tissue	0	2 (9.1)	5 (18.5)	5 (17.9)	12 (14.3)
Investigations	0	3 (13.6)	3 (11.1)	5 (17.9)	11 (13.1)
Gastrointestinal	0	2 (9.1)	0	6 (21.4)	8 (9.5)
Musculoskeletal & connective tissue	0	0	3 (11.1)	5 (17.9)	8 (9.5)
Blood & lymphatic system	1 (14.3)	1 (4.5)	4 (14.8)	1 (3.6)	7 (8.3)
Metabolism & nutrition disorders	1 (14.3)	1 (4.5)	2 (7.4)	2 (7.1)	6 (7.1)
Nervous system	0	2 (9.1)	1 (3.7)	1 (3.6)	4 (4.8)
Infections & Infestations	0	2 (9.1)	0	1 (3.6)	3 (3.6)
Hepatobiliary	0	2 (9.1)	0	1 (3.6)	3 (3.6)
Respiratory, thoracic & mediastinal	0	1 (4.5)	1 (3.7)	0	2 (2.4)
Vascular	0	0	1 (3.7)	1 (3.6)	2 (2.4)
Renal & urinary	0	1 (4.5)	0	0	1 (1.2)
Cardiac	0	0	1 (3.7)	0	1 (1.2)
Endocrine	0	0	0	1 (3.6)	1 (1.2)
Immune system	0	0	1 (3.7)	0	1 (1.2)
TRAE (grade ≥3), per MedDRA Preferred Term (in order of frequency) – no. (%)					
Aspartate aminotransferase ↑	0 (0.0)	1 (4.5)	0 (0.0)	1 (3.6)	2 (2.4)
Alanine aminotransferase ↑	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)†	1 (1.2)
Transaminases ↑	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.2)
Cholestasis	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.2)
Hepatic failure	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.2)
Pneumonitis	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.2)
Immune-mediated pneumonitis	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (1.2)
Diarrhea	0 (0.0)	1 (4.5)†	0 (0.0)	0 (0.0)	1 (1.2)
Upper gastrointestinal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.2)
Hypokalemia	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.2)
Decreased appetite	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (1.2)
Pneumonia	0 (0.0)	*1 (4.5)*	0 (0.0)	0 (0.0)	1 (1.2)
Multiple organ dysfunction syndrome	0 (0.0)	*1 (4.5)*	0 (0.0)	0 (0.0)	1 (1.2)
Acute kidney injury	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.2)
Hypertension	0 (0.0)	0 (0.0)	1 (3.7)†	0 (0.0)	1 (1.2)

* System Organ Classes (SOC) with no reported TRAE (of any grade and/or for any cohort) are not listed

† Two events (at different time points) in one patient

Values (MedDRA Preferred Terms) in italics: grade 5 events; ↑, increased

(CRs) and CMRs were confirmed. Among the 13 responders, 5 (38.5%) achieved a CR and 3 achieved a CMR, resulting in a CR or CMR rate of 8/13 (61.5%).

Median DoR among responders was 28.8 months (95%CI 7.4–38.0), and median TTR was 2.8 months (95%CI 1.9–5.6). Responders remained on therapy for a median of 22.1 months (95%CI 10.8–30.0), with 7/13 (53.8%) responses (4 CR, 3 CMR) ongoing at the time of analysis (Fig. 2).

Non–small cell lung cancer

Of 29 participants with NSCLC, 7 (24.1%) had squamous (sq) and 22 (75.9%) non-squamous (nsq) histology. Overall, 28/29 (96.6%) participants had received prior platinum-based chemotherapy (first-line: N=25; second-line: N=3) (Table 1), 18/28 (64.3%) of these in combination with pembrolizumab (first-line: N=11; second-line: N=5; third-line: N=1; fourth-line: N=1) as initial approved anti–PD-1/PD-L1 treatment. Other prior anti–PD-1/PD-L1 regimens included nivolumab monotherapy

Table 3 Treatment outcomes per Indication

Outcome	NSCLC (sq.)	NSCLC (nsq.)	UC	HCC	Total (efficacy)
	(n = 7)	(n = 22)	(n = 27)	(n = 28)	(n = 77)
Overall response rate (ORR) – no.	0	4	5	4	13
Percentage – (95% CI)	--	18.2 (5.2–40.3)*	18.5 (6.3–38.1)	14.3 (4.0–32.7)	16.9 (9.3–27.1)
Partial response (PR) – no. (%)	0	3 (13.6)	3 (11.1)	2 (7.1)	8 (10.4)
Complete response (CR) – no. (%)	0	1 (4.5)	2 (7.4)	2 (7.1)	5 (6.5)
Complete metabolic response (CMR)					
CMR rate – no. (%)	0	2 (9.1)	0	1 (3.6)	3 (3.9)
CR or CMR (Rate, combined) – no. (%)	0	3 (13.6)	2 (7.4)	3 (10.7)	8 (10.4)
Responses ongoing (PR, CMR & CR)					
Number (%)	--	3 (75.0)	2 (40.0)	2 (50.0)	7 (9.1)
Duration of Response†: (DoR)					
Median (95% CI) – months	--	32.2 (5.5–38.0)	28.8 (7.4–39.4)	19.4 (5.8–39.7)	28.8 (7.4–38.0)
Time to response (TTR)					
Median (95% CI) – months	--	1.9 (1.8–5.6)	3.7 (1.9– 18.2)	3.3 (1.8–8.6)	2.8 (1.9–5.6)
Disease control rate (DCR) – no.	4	9	13	11	33
Percentage – (95% CI)	57.1 (18.4–90.1)	40.9 (20.7–63.6)	48.1 (28.7–68.1)	39.3 (21.5–59.4)	42.9 (31.6–54.6)
Progression-free survival (PFS)					
Median (95% CI) – months	3.2 (1.4–25.0)	1.8 (1.4–5.2)	2.5 (1.7–4.2)	2.0 (1.8–3.5)	1.9 (1.8–3.2)
Overall survival (OS)					
Median (95% CI) – months	14.0 (3.5–25.0)	8.8 (3.1–14.9)	11.6 (4.4–20.6)	9.8 (6.0–15.5)	10.0 (5.7–12.7)
Duration of treatment (DOT)					
Median (95% CI) – months	2.7 (1.0–7.6)	2.2 (1.4–4.6)	2.5 (1.4–6.5)	2.6 (1.4–3.7)	2.3 (1.4–3.5)
Treatment ongoing – no. (%)	0	2 (9.1)	2 (7.4)	4 (14.3)	8 (10.4)

*All but one response confirmed per RECIST v1.1; † Measured from start of treatment until progression / end of study [Am J Cancer Res 2021;11:1121-1131]

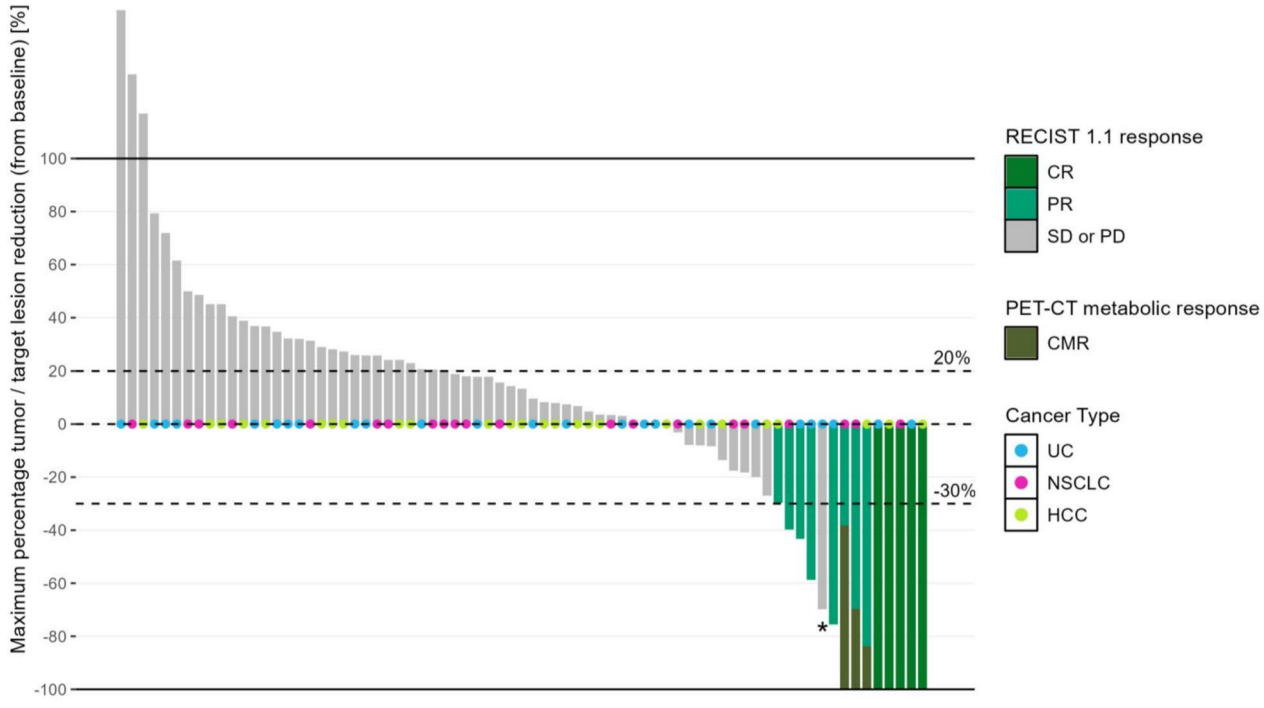


Fig. 1 Overall response assessment: best overall response as per RECIST v1.1 and metabolic response. all participants with at least one tumor assessment according to RECIST v.1.1, i.e., currently N=73, are displayed in the waterfall Plot, indicating reductions in main target lesion (measurable disease). NSCLC, non-small cell lung cancer (non-squamous); UC, urothelial carcinoma; HCC, hepatocellular carcinoma. *PR on target lesions with simultaneous occurrence of new lesion (PD by RECIST)

(second-line: N=1; third-line: N=2), pembrolizumab monotherapy (first-line: N=2; second-line: N=1), atezolizumab monotherapy (second-line: N=1; third-line: N=1; fourth-line: N=1), and nivolumab plus ipilimumab plus relatlimab (second-line: N=1). In addition, 10/29 (34.5%) participants received prior docetaxel (second or later line).

In nsq NSCLC, the ORR was 18.2% (4/22; 95%CI 5.2–40.3), with PR as best response in 13.6% (3/22) and CR in 4.5% (1/22). Two CMRs (9.1%) were observed among participants with PR, resulting in a combined CR or CMR rate of 3/22 (13.6%) in nsq NSCLC. The median DoR for nsq NSCLC at data cut-off is 32.2 months (95%CI 5.5–38.0). Median PFS was 1.8 months (95%CI 1.4–5.2) and median OS 8.8 months (95%CI 3.1–14.9) (Table 3). The DCR in nsq NSCLC was 40.9% (9/22; 95%CI 20.7–63.6), 57.1% (4/7; 95%CI 18.4–90.1) in sqNSCLC, and 44.8% (13/29; 95%CI 26.4–64.3) overall in NSCLC. No responses were observed in sqNSCLC.

At data cutoff, three responses are ongoing (two CMR and one CR), and two participants remain on study treatment (Fig. 3). One participant with PR discontinued due to PD, while another discontinued study treatment due to grade 3 pneumonitis with PR ongoing at 16.0 months; CMR was achieved two months after treatment discontinuation and remains ongoing at 20.3 months. This participant had also received, per treating physician's decision and off protocol, focal irradiation to a single lung lesion (among several bilateral lesions) after 12 months of visugromab plus nivolumab, owing to isolated enlargement not yet meeting formal PD criteria. Under continued visugromab plus nivolumab, CMR was subsequently documented after 18.0 months of treatment.

In another nsq NSCLC participant, CR was achieved after 7.0 months. At later follow-up, an FDG PET-CT (performed at the treating physician's discretion) revealed a hypermetabolic retroperitoneal lymph node; although this did not meet RECIST v1.1 criteria for PD/relapse, stereotactic radiotherapy was administered off

A

	Participant	Cohort (Tumor)	Pre-treatment (prior regimen)	BOR ** (prior regimen)	DoR [months] (prior regimen)	BOR Visu + Nivo (Study treatment)	DoR [months] (Study treatment)	Response ongoing (Yes/No)	Treatment ongoing (Yes/No)
NSCLC	1-01-013	NSCLC, nsq	Nivolumab mono	PR	24.8	PR	5.5	N	N
	1-01-018	NSCLC, nsq	Pembrolizumab + CTx *	PR	9.0	PR/CMR	24.3	Y	N
	1-01-021	NSCLC, nsq	Atezolizumab	PR	16.0	PR/CMR	30.1	Y	Y
	1-06-004	NSCLC, nsq	Pembrolizumab + CTx *	PR	22.4	CR	25.7	Y	Y
UC	1-01-015	Urothelial	Atezolizumab mono	PR	24.0	CR	35.8	Y	N
	1-02-036	Urothelial	Avelumab mono (maintenance)	PR	3.0	PR	7.1	N	N
	1-02-037	Urothelial	Atezolizumab mono	PD	*na*	PR	24.3	N	N
	1-03-014	Urothelial	Pembrolizumab + ICOS ant. †	PR	43.0	PR	28.8	N	N
	1-06-005	Urothelial	Atezolizumab mono	SD	5.0	CR	26.3	Y	Y
HCC	1-02-006 (Ph1)	HCC	Anti-PD-L1 + anti-TIM-3 ‡	SD	12.0	PR	5.7	N	N
	1-02-010	HCC	Atezolizumab + anti-VEGFR	CR	29.4	CR	37.8	N	N
	1-05-014	HCC	Atezolizumab + anti-VEGFR	SD	8.0	PR/CMR	18.4	Y	Y
	2-03-001	HCC	Pembrolizumab mono	CR	12.0	CR	12.9	Y	Y

BOR, Best Overall Response
DoR, median Duration of Response
na, not applicable

*: Chemotherapy (Carboplatin + Pemetrexed) ** all (SD, PR, or CR) showing progressive disease, whilst still on anti-PD-1/-L1 therapy
†: Experimental drug (GSK33 (ICOS-antagonist)
‡: Experimental PD-L1 inhibitor (LY3300054) plus experimental anti-TIM-3 inhibitor (LY3321367)
§: i.e., Bevacizumab

B

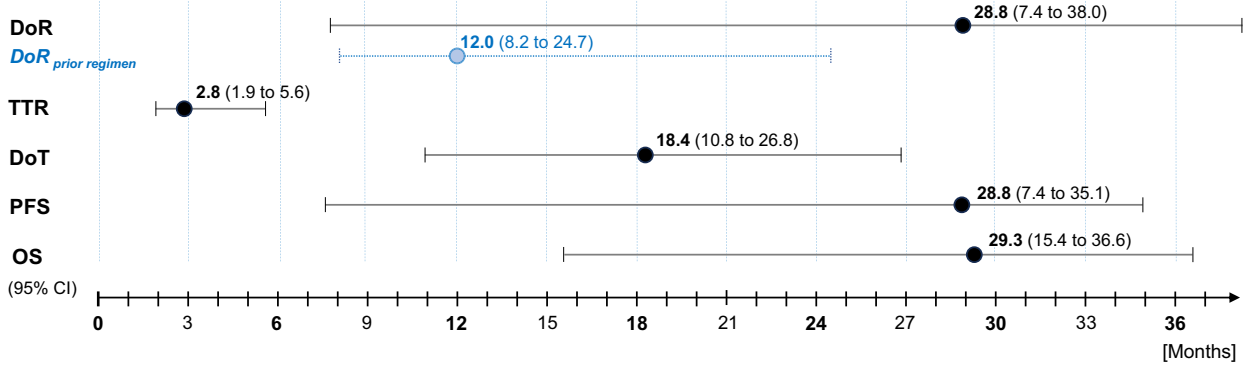


Fig. 2 Characterization of visugromab-plus-nivolumab responders (N=13). (**A**) Comparison of response to initial anti-PD-1/-L1 treatment versus response to study treatment; (**B**) Graphical presentation of duration of response and time-to-event endpoints

protocol to this region. A prior biopsy of this lymph-node region had not demonstrated malignancy. The CR in this participant is ongoing at 30.5 months (Fig. 3).

Urothelial carcinoma

Of the urothelial carcinoma participants, 25/27 (92.6%) had received platinum-based chemotherapy, and 10 (37.0%) had received avelumab maintenance therapy as the initial prior anti–PD-1/PD-L1-containing regimen (Table 1). Other initial anti–PD-1/PD-L1-containing therapies included atezolizumab monotherapy (first-line: N=1; second-line: N=4; third-line: N=1; fourth-line: N=1), pembrolizumab monotherapy (first-line: N=1; second-line: N=1; third-line: N=3), atezolizumab plus chemotherapy (first-line: N=2), pembrolizumab plus enfortumab vedotin (first-line: N=1), pembrolizumab plus an anti-ICOS-directed antibody (third-line: N=1), and nivolumab plus trastuzumab deruxtecan (third-line: N=1).

Confirmed ORR was 18.5% (5/27; 95%CI 6.3–38.1), with PR in 3/27 (11.1%) and CR in 2/27 (7.4%); the DCR was 48.1% (13/27; 95%CI 28.7–68.1). Median DoR at data-cut-off is 28.8 months (95%CI 7.4–39.4). Median PFS was 2.5 months (95%CI 1.7–4.2) and median OS 11.6 months (95%CI 4.4–20.6) (Table 3).

At data cutoff, two responses are ongoing (two CR), and one participant remains on study treatment (Fig. 3). One participant with PR discontinued due to PD. No irradiation or other off-protocol treatments were administered in any participant with urothelial carcinoma.

Hepatocellular carcinoma

Of the 28 participants with HCC, 22 (78.6%) had received atezolizumab plus bevacizumab as the initial anti–PD-1/PD-L1-containing regimen, 20/22 (90.9%) in the first-line setting. Other initial anti–PD-1/PD-L1-containing therapies were nivolumab monotherapy (first-line: N=2), pembrolizumab monotherapy (first-line: N=1), pembrolizumab plus lenvatinib (first-line: N=1), an investigational anti–PD-1/PD-L1 plus anti–TIM-3 antibody (third-line: N=1), and tislelizumab (first-line: N=1). In addition, 3/28 (10.7%) had received transarterial chemoembolization (TACE), and 2/28 (7.1%) radiofrequency ablation (RFA) as locoregional therapies either prior to or in conjunction with adjuvant systemic treatment.

The confirmed ORR was 14.3% (4/28; 95%CI 4.0–32.7), with PR in 7.1% (2/28), including one short-lived confirmed response at dose level 4 in phase 1, and CR in 7.1% (2/28). One durable PR was identified as a CMR, resulting in a combined CR or CMR rate of 3/28 (10.7%) (Table 3). The DCR was 39.3% (11/28; 95%CI 21.5–59.4). Median DoR is 19.4 months (95%CI 5.8–39.7) at the time of this analysis, reflecting the more protracted recruitment of the HCC cohort compared with the NSCLC and urothelial carcinoma cohorts. Median PFS was 2.0 months (95%CI 1.8–3.5) and median OS 9.8 months (95%CI 6.0–15.5).

At data cutoff, two responses are ongoing (one PR/CMR and one CR), and two participants remained on study treatment. One participant with an ongoing CR discontinued treatment in CR after 27.9 months because of a persistent grade 2 pruritus considered immune-mediated. Another participant discontinued treatment in PR after 15.0 months due to a persistent grade 2 arthritis, also considered immune-mediated. Notably, CR was detected two months after treatment discontinuation and persisted for 23.8 months off treatment until disease progression was observed (Fig. 3). No irradiation or other off-protocol treatments were administered in any participant with HCC.

Comparing visugromab plus nivolumab response versus response to prior anti-PD1/-L1 treatment

Of the 13 participants with a response, 6 (46.2%) achieved a deeper RECIST v1.1 response level compared with their best overall response to initial approved anti–PD-1/PD-L1 treatment (Fig. 2). When CMR is included as an additional marker of response quality, 8/13 (61.5%) responders achieved an improved, deeper response level (with limitation of no information on metabolic activity during PR on prior anti–PD-1/PD-L1 treatment). All remaining responders achieved at least the same response level as with prior anti–PD-1/PD-L1 therapy. Median DoR was 28.8 months with visugromab plus nivolumab versus 12.0 months on initial anti–PD-1/PD-L1 treatment (Fig. 2).

Exemplary case narratives for responders are provided in the Supplementary Materials (page 7 ff).

Discussion

Here we report the long-term follow-up of the first-in-human phase 1/2a trial of visugromab (GDFATHER-01), with a main emphasis on the three expansion cohorts in NSCLC, urothelial carcinoma, and HCC. Extensive translational research investigations, including high-throughput immune-transcriptomic analyses, had identified these tumor types (among others) as likely to be GDF-15–immunosuppressed.

Strict criteria for defining anti–PD-1/PD-L1 relapsed/refractory status were applied to ensure that retreatment with an anti–PD-1/PD-L1 antibody alone (here nivolumab) would not be expected to yield substantial antitumor activity. Multiple retrospective studies in similarly stringently defined anti–PD-1/PD-L1 relapsed/refractory populations have shown that response rates remain in the range of 0–5% with anti–PD-1/PD-L1 retreatment as monotherapy where relapse/progression

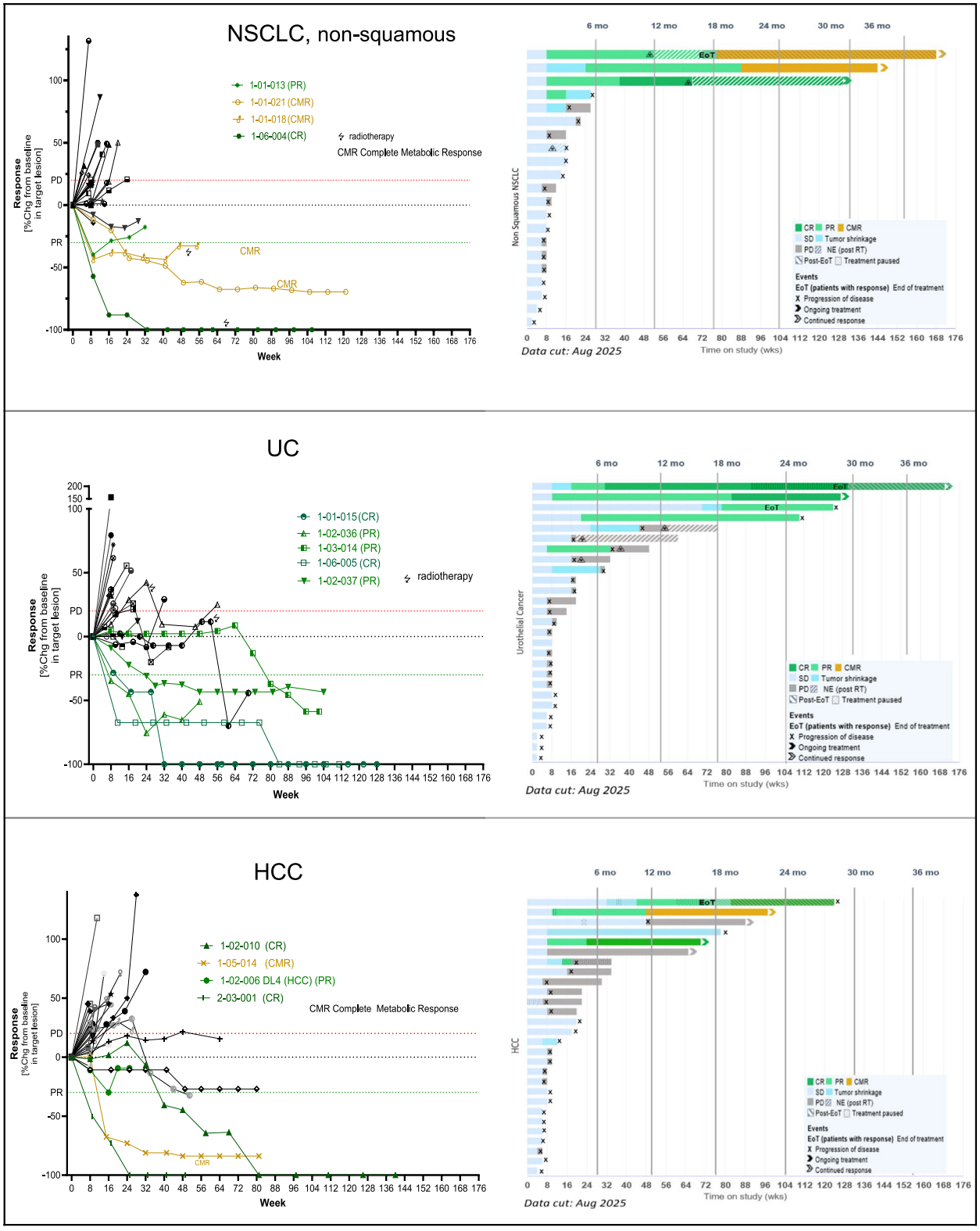


Fig. 3 Change in tumor size ("Spider plots") and time to and duration of response ("Swimmer Plots"). Patients with squamous cell NSCLC (N=7, no responder) were omitted from the upper graphs for the sake of clarity. Left side: Spider plots (per cancer type); right side: Swimmer plots (per cancer type). NSCLC, non-small cell lung cancer; UC, urothelial carcinoma; HCC, hepatocellular carcinoma

had to have occurred during ongoing anti–PD-1/PD-L1 treatment [25–30], as in our trial.

This first-in-human trial of visugromab had previously demonstrated that GDF-15 neutralization can reinduce sensitivity to anti–PD-1/PD-L1 treatment [16]. The long-term follow-up data presented here now provide evidence that GDF-15 neutralization may also enable substantially deeper and more durable remissions than those achieved with initial anti–PD-1/PD-L1 therapy.

Notably, visugromab plus nivolumab showed an acceptable safety and tolerability profile. Retrospective studies investigating retreatment of patients with anti-PD-1/L1 therapy reported rates of higher grade irAEs in the range of 13-30% in NSCLC, HCC or across multiple tumor types [31–33]. The 11.9% rate of grade ≥3 TRAE in our combination therapy study reflects these experiences that retreatment not only may reinduce responses but also known or new irAE, even of higher grade. However, the two possibly treatment-related deaths show that caution is needed in all patients exposed to such immunotherapy. The adverse event profile of visugromab plus nivolumab largely resembled that of anti–PD-1/PD-L1 monotherapy. To note that the GDFATHER-01 population may reflect individuals who previously tolerated anti–PD-1/PD-L1 therapy, as those with serious immune-mediated adverse events during prior exposure were excluded. Additionally, patients treated at earlier disease stages often remain on therapy for extended periods, which can increase the likelihood of late-onset irAEs.

As general limitations of our dataset, the relatively small number of participants analyzed for efficacy (N=77) and the absence of randomized controlled data must be acknowledged. The total number of responders, the depth and duration of responses compared with their responses to initial anti–PD-1/PD-L1 therapy (serving here as an internal benchmark), and the observation of this effect across three major solid tumor types nonetheless provide some confidence in the observed therapeutic signal. However, randomized controlled trials will be required to confirm and more precisely define the effect size achievable with GDF-15 blockade in combination with anti–PD-1/PD-L1 therapy in different clinical settings. Ongoing biomarker analyses of this and other ongoing trials will need to further decipher the potential responder population for GDF-15 blockade and the role of GDF-15 as a predictive marker or factor for enrichment strategies.

With regard to DoR and response depth in comparable PD-1/PD-L1–relapsed/refractory populations, the results with visugromab plus nivolumab appear encouraging when benchmarked against other current immunotherapeutic combination concepts or standard-of-care options. Overall, the DoR and CR+CMR rates achieved with visugromab plus nivolumab in nsq NSCLC, urothelial carcinoma, and HCC can be considered clinically meaningful (see comprehensive literature analysis and detailed comparative benchmarking data in Additional Materials). In advanced/metastatic nsq NSCLC, approved second-line therapies (docetaxel or docetaxel plus nintedanib) achieve ORRs of 3.6–14% [34], and docetaxel plus ramucirumab yields ORRs of 23–34% [35]. However, CRs with these regimens are rare, and DoR generally remains poor at <6 months. Experimental immunotherapy combinations have produced ORRs in the range of ≈5–20%, again with CRs being virtually absent, DoR of 2.0–12.9 months, PFS of 2.1–5.6 months, and OS of 6.2–17.4 months. Other treatment approaches, such as ADCs, can yield higher ORRs but are similarly characterized by limited durability, with DoR of 6.7–11.6 months, PFS of 2.7–6.4 months, and OS of 8.8–14.6 months. Comparable patterns are seen in benchmarking analyses for urothelial carcinoma and HCC in the anti–PD-1/PD-L1 relapsed/refractory setting (see Additional Materials).

Initial biomarker analyses from this trial have been reported previously. Various factors were evaluated, but no single marker has yet been identified that reliably predicts response [16]. Of note, responses were observed independent of tumoral PD-L1 status. Potentially predictive biomarker candidates identified through tumor and blood transcriptional analyses will be investigated in more detail in currently ongoing randomized clinical trials.

Beyond its tumor-immunosuppressive effect, GDF-15 has recently gained major attention as a mediator of anorexia, nausea, and cancer cachexia [36, 37]. These metabolic effects are mediated via the GFRAL receptor in the brainstem and may occur independently of the immune-mediated effects of GDF-15. The anti–GDF-15 antibody ponsegromab has successfully completed a phase 2 trial, demonstrating weight gain and increased activity in a manifestly cachectic cancer population with elevated GDF-15 [38, 39]. Phase 3 development is ongoing. In our trial, the majority of participants did not have manifest cachexia, and no weight gain was observed in non-cachectic individuals. However, the small subset of participants who were cachectic at baseline appeared to experience a comparable degree of weight gain [16]. This dual effect may be synergistic: effective control of cancer cachexia may allow affected or at-risk patients to remain on therapy for prolonged periods, during which the antitumor activity of GDF-15 blockade combined with anti–PD-1/PD-L1 treatment can fully unfold. It is also known that platinum compounds [40], ADCs [41], and kinase inhibitors induce GDF-15, often to substantial and sustained levels. Thus, GDF-15 blockade may act on multiple fronts, preventing nausea, emesis, and cachexia, as well as reversing immunosuppression that would

otherwise attenuate or suppress the antitumoral activity of anti–PD-1/PD-L1 therapy.

GDF-15 neutralization by visugromab resulted in resensitization to and enhancement of anti–PD-1/PD-L1 activity in a subset of patients with advanced/metastatic nsq NSCLC, urothelial carcinoma, and HCC who were, by strict criteria, anti–PD-1/PD-L1 relapsed/refractory and had exhausted available treatment options. Median DoR among responders across these tumor types exceeded 24 months, and a notable number of CRs and CMRs were achieved. These findings are unprecedented in comparable patient populations retreated with checkpoint inhibitors or other immunotherapies and suggest that GDF-15 blockade may both reinvigorate and substantially enhance the magnitude and durability of anti–PD-1/PD-L1 therapy.

Recently, initial results from the GDFATHER-Neo trial (NCT06059547), which compares visugromab plus nivolumab versus placebo plus nivolumab in neoadjuvant muscle-invasive bladder cancer, were reported [42]. In this small (N=30), blinded, placebo-controlled, biomarker-oriented phase 2 trial, addition of visugromab to nivolumab in a checkpoint inhibitor–naïve setting resulted in a threefold increase in pathologic and radiologic response rates compared with anti–PD-1 monotherapy. Based on these encouraging data, further investigations in anti–PD-1/PD-L1–naïve populations, including nsq NSCLC, are ongoing.

In summary, our findings may open a new avenue for the treatment of anti–PD-1/PD-L1 relapsed/refractory advanced/metastatic solid tumors, with an overall favorable tolerability profile and as a strategy with the potential to substantially potentiate checkpoint inhibitor activity. Ongoing and future randomized controlled trials in earlier lines of therapy, particularly in anti–PD-1/PD-L1–naïve populations, will be crucial to define the full therapeutic potential of GDF-15 neutralization in these tumor types.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-026-01818-2.

Additional file 1.

Acknowledgements

We thank all participants in the trial and their families, as well as all investigators, study staff, and employees of the sponsor who supported, initiated, conducted, and analyzed the GDFATHER-01 trial. Medical writing and technical editing support was provided by Markus Hartmann, PhD, European Consulting & Contracting in Oncology, Trier, Germany. The trial was funded by CatalYm GmbH, Munich, Germany, which also served as the legal sponsor of the GDFATHER-01 trial.

Author contributions

All authors had access to study data and reviewed, revised, and approved the final manuscript. M.d.M., E.G.C., G.d.V., M.J., J.M.L., M.R., D.K., J.T., M.E.G., M.S., G.A., M.R.R., R.Y., G.P., J.E.V., K.L.K., P.S.V., M.S.Z., H.L., C.K., C.S., T.G., F.R., E.R. and P.G. screened, enrolled and monitored participants at study sites and/or oversaw trial conduct at their study site. F.L., A.A., M.F., M.L., J.A., A.A., S.S. and J.B. were involved in study conduct and monitoring, and data curation and analysis processes. TS contributed to the comparative analyses of other therapies. Z.T., H.H. and F.G. were involved, among other authors, into the bioanalytical validation and acquisition of translational data. K.K. led the translational research work and biomarker analyses. R.D., A.N. and M.R. advised on visugromab's clinical development. J.W., in line with C.S.W. and K.K. led the discovery and early development of visugromab. F.H. and P.F. oversaw and guided the patient enrolment, study follow-up and data curation process, with full access to all data. E.L., as the trial's study director, had full access to all the data in the study and had designed and supervised the study. I.M., as the international coordinating investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

The GDFATHER-01 trial was initiated, sponsored and funded by CatalYm GmbH (Munich, Germany).

Data availability

Aggregated, more detailed trial data will be provided later – in alignment with the European Union rules for conducting clinical trials (Regulation EU No. 536/2014 of 16 April 2024) and the rules for the registration and transparent reporting of clinical trials in WHO Primary Registers – in form of a full Clinical Study Report. Additional information is provided inside the Supplement Materials published with the original article. In addition, interested researchers may submit a substantiated request for access to data to the trial sponsor (info@catalym.com)

Declarations

Ethics approval and consent to participate

The GDFather-001 trial was approved by the national competent authorities (Paul-Ehrlich-Institut for Germany; Agencia Espanola de Medicamentos y Productos Sanitarios for Spain, and Swissmedic for Switzerland) of the participating countries and by the institutional review boards (i.e., by the ethics committees) at each participating site. All participants provided written informed consent.

Competing interests

J.H. is a co-founder of the biotech company CatalYm GmbH, owner of GDF-15 related patents and stock owner of Catalym GmbH. C.S.W., J.A., F.L., A.A., M.F., K.K., P.F., M.L., A.A., S.S., F.H. and E.L. are current or former employees of CatalYm GmbH and/or hold stock options of Catalym GmbH. J.W., I.M. and H.H. have received research funding or consulting and/or advisory fees from Catalym GmbH. Several coauthors declare potentially competing interests (grants or contracts and/or royalties or licenses, stock or stock options, consulting fees, honoraria, travel or meeting support, or advisory or data safety monitoring board participation) apart from their relationship with CatalYm GmbH: I.M. (research grants from Roche, Bristol-Myers Squibb, Genmab and AstraZeneca; honoraria from Genmab, Mestag, Flagship, Bright Peak, Curon, Pharmamar, AstraZeneca, Bioinvent, Warewolf, Qbiotics, AstraZeneca and Johnson & Johnson); E.G.C. (grants from Novartis, Roche, ThermoFisher, AstraZeneca, Taiho, BeiGene, Janssen, Anaveon; honoraria from Roche, Ellipses Pharma, Boehringer Ingelheim, Janssen Global Services, Seattle Genetics, SeaGen, Skypta, Sotio, Sanofi, Anaveon, Abbvie, Astex Therapeutics, Alentis Therapeutics, Marengo Therapeutics, Incyte, Lilly, Medpace, Pfizer, Amgen, GenMab, Genentech, GreyWolf, Gilead, Daiichi Sankyo, Takeda Pharmaceuticals, Pyramid Biosciences; stock options from 1TrialSP); G.d.V. (Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Ipsen, Janssen Merck Sharp & Dohme, Merck Serono, Pfizer and Roche); M.J. (grants from AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Immunophotonics, Innomedica, Lilly, Merck Sharp & Dohme, Novartis, Intensity Therapeutics, Roche, Sanofi, Takeda, Incyte, Debiopharm, Anaveon; honoraria from AstraZeneca, Bayer, Bristol-Myers Squibb, Johnson & Johnson, Merck Sharp & Dohme, Roche, Sanofi); J.M.L. (grants and research contracts from Astellas, BMS, Highlight Therapeutics, Ipsen, Merck Serono, Merck Sharp & Dohme, Novartis, Roche, Pfizer, PharmaMar, Pierre Fabre, Regeneron, Sanofi and Trialing Health); M.R. (institutional research grants from Bayer and Ipsen; consultancy/

advisory roles for AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, Geneos, Ipsen, Merck, Roche, Universal DX, Boston Scientific, Engitix Therapeutics, Parabilis Medicines Inc, Boehringer Ingelheim); D.K. (grant from Geistlich-Stucki-Stiftung; honoraria/fees from Amgen, AstraZeneca, Amgen, Bristol-Myers Squibb, Iaculis, Johnson & Johnson, Merck Serono, Merck Sharp & Dohme, Mirati, Novartis, PharmaMar, Roche and Sanofi); J.T. (AstraZeneca, Bristol Myers Squibb, Institut fur Qualitatssicherung und Transparenz im Gesundheitswesen, Merck Serono, Merck Sharp & Dome, Oncolytics Biotech, onkowissen.de, Roche); M.S. (grants from Bristol-Myers Squibb and Johnson & Johnson; honoraria/consultancy from/for Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Johnson & Johnson, Lilly, Merck Sharp & Dohme, Novartis, Regeneron, Roche, Sanofi); R.D. (consultancy/advisory roles for Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, T3 Pharma, MaxiVAX SA, Pfizer, Simcere and Iovance, Oncobit. Derma2go); M.R.R. (AstraZeneca, Bristol-Myers Squibb, Roche); R.Y. (honoraria/fees from Merck, Boehringer Ingelheim, Kura Oncology, BioNTech); G.P. (Roche and Pierre Fabre); J.E.V. (research funding and honoraria from Astellas Pharma); M.S.Z. (AstraZeneca, BTG, Captor, Bayer, Eisai-MSD, Roche); C.K. (honoraria/fees from Ipsen, Astra Zeneca, StreamedUp, NeoConnect, Merck, Sharp & Dohme, Servier, Bristol-Myers Squibb, Incyte, Takeda, Amgen, BeiGene, Roche, Jazz Pharma, GI-OnkoNET Rhein Main, DGVS, Leo Pharma); C.S. (Bristol-Myers Squibb, Boehringer Ingelheim, Ipsen); E.R. (BMS, Eli Lilly, Kyowa Kirin, Leo Pharma, Merck Sharp & Dohme, Pierre Fabre and Sanofi); P.G. (Bayer, AstraZeneca, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche); A.N. (AstraZeneca, Merck Sharp & Dohme, Incyte, Bristol-Myers Squibb, Gilead Science, Seattle Genetics, Astellas, Geneta Science, Janssen, PeerView, PeerVoice, Merck Serono, Samsung Bioepis, Bicycle Therapeutics); M.R. (honoraria/fees from Accord, Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Merck Serono, Merck Sharp & Dohme, Mirati, Novartis, Pfizer, Regeneron, Roche, Sanofi, Daiichi-Sankyo, Janssen); M.F. (Stock options from Thermo Fisher Scientific); P.F. (Stock options from Amgen and BionTech); C.S.W. (Stock options from Merck Sharp & Dohme and RNhale). M.d.M., M.E.G., G.A., K.L.K., P.S.V., H.L., T.G., Z.T., H.H., F.G., J.B. and T.S. disclosed no other relationships or conflicts of interest.

Author details

[1]Clinica Universidad de Navarra, CIMA, IDISNA and CIBERONC, PÍO XII Avenue 36, Pamplona 31008, Spain
[2]Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
[3]START Madrid-CIOCC, Centro Integral Oncologico Clara Campal, Madrid, Spain
[4]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Barcelona, Spain
[5]Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain
[6]Department of Medical Oncology & Hematology, Cantonal Hospital, St Gallen, Switzerland
[7]Medical Oncology Department, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain
[8]Liver Oncology Unit, Liver Unit, BCLC group, Hospital Clinic of Barcelona, Barcelona, Spain
[9]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[10]Centro de Investigacion Biomedica en Red en Enfermedades Hepaticas y Digestivas (CIBEREHD), Madrid, Spain
[11]Department of Medical Oncology, University Hospital Basel, Basel, Switzerland
[12]Medical Clinic 1, Goethe University Frankfurt, University Hospital, Frankfurt, Germany
[13]Interdisciplinary Trial Center and ECTU, University Hospital Wurzburg, Wurzburg, Germany
[14]West German Cancer Center, Department of Medical Oncology, University Hospital Essen, Essen, Germany
[15]National Center for Tumor Diseases (NCT), NCT West, Essen, Germany
[16]NEXT Oncology Phase I Unit/IOB - Hospital Quironsalud Barcelona, Barcelona, Spain
[17]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland
[18]1st Medical Clinic, University Medical Center of the Johannes Gutenberg University Mainz, Main, Germany
[19]Department of Medical Oncology, Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milan, Italy
[20]Vita Salute San Raffaele University, Milan, Italy
[21]Airway Research Center North (ARCN), German Center for Lung Research (DZL), LungenClinic, Grosshansdorf, Germany
[22]Institute of Bioinformatics, Biocenter, Medical University of Innsbruck, Innsbruck, Austria
[23]Metronomia Clinical Research GmbH, Munich, Germany
[24]Department of Medicine, Technical University Munich, Munich, Germany
[25]Department of Gynecology, University Hospital Wurzburg, Wurzburg, Germany
[26]CatalYm, Planegg-Martinsried, Germany

Received: 25 March 2026 / Accepted: 12 June 2026
Published online: 09 July 2026

References

1. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun. 2020;11:3801. https://doi.org/10.1038/s41467-020-17670-y.
2. Sharma P, Siddiqui BA, Anandhan S, et al. The Next Decade of immune checkpoint therapy. Cancer Discov. 2021;11:838–57. https://doi.org/10.1158/2159-8290.CD-20-1680.
3. Kreidieh FY, Tawbi HA, Alexaki A, Borghaei H, Kandalaft LE. Novel immunotherapeutics: perspectives on checkpoints, bispecifics, and vaccines in development. Am Soc Clin Oncol Educ Book. 2023;43:e391278. https://doi.org/10.1200/EDBK_391278.
4. Piper M, Kluger H, Ruppin E, Hu-Lieskovan S. Immune Resistance mechanisms and the road to personalized immunotherapy. Am Soc Clin Oncol Educ Book. 2023;43:e390290. https://doi.org/10.1200/EDBK_390290.
5. Santiago-Sánchez GS, Fabian KP, Hodge JW. A landscape of checkpoint blockade resistance in cancer: underlying mechanisms and current strategies to overcome resistance. Cancer Biol Ther. 2024;25:2308097. https://doi.org/10.1080/15384047.2024.2308097.
6. Reck M, Frost N, Peters S, et al. Treatment of NSCLC after chemoimmunotherapy - are we making headway? Nat Rev Clin Oncol. 2025;22:806–30. https://doi.org/10.1038/s41571-025-01061-7.
7. Zhang T, Forde PM, Sullivan RJ, et al. Addressing resistance to PD-1/PD-(L)1 pathway inhibition: considerations for combinatorial clinical trial designs. J Immunother Cancer. 2023;11:e006555. https://doi.org/10.1136/jitc-2022-006555.
8. Sanmamed MF, Berraondo P, Rodriguez-Ruiz ME, Melero I. Charting roadmaps towards novel and safe synergistic immunotherapy combinations. Nat Cancer. 2022;3:665–80. https://doi.org/10.1038/s43018-022-00401-1.
9. Perez-Gracia JL, Labiano S, Rodriguez-Ruiz ME, Sanmamed MF, Melero I. Orchestrating immune check-point blockade for cancer immunotherapy in combinations. Curr Opin Immunol. 2014;27:89–97. https://doi.org/10.1016/j.coi.2014.01.002.
10. Aya F, Gaba L, Victoria I, et al. Ipilimumab after progression on anti-PD-1 treatment in advanced melanoma. Future Oncol. 2016;12:2683–8. https://doi.org/10.2217/fon-2016-0037.
11. Lyu C, Ni T, Guo Y, et al. Insufficient GDF15 expression predisposes women to unexplained recurrent pregnancy loss by impairing extravillous trophoblast invasion. Cell Prolif. 2023;56:e13514. https://doi.org/10.1111/cpr.13514.
12. Lyu L, Xv C, Xu J, et al. Growth differentiation factor-15 predicts all-cause death and major adverse cardiovascular events in patients with coronary heart disease: a prospective cohort study. J Thromb Thrombolysis. 2024;57:1109–21. https://doi.org/10.1007/s11239-024-03019-5.
13. Welsh JB, Sapinoso LM, Kern SG, et al. Large-scale delineation of secreted protein biomarkers overexpressed in cancer tissue and serum. Proc Natl Acad Sci U S A. 2003;100:3410–5. https://doi.org/10.1073/pnas.0530278100.
14. Wischhusen J, Melero I, Fridman WH. Growth/differentiation factor-15 (GDF-15): from biomarker to novel targetable immune checkpoint. Front Immunol. 2020;11:951. https://doi.org/10.3389/fimmu.2020.00951.
15. Haake M, Haack B, Schäfer T, et al. Tumor-derived GDF-15 blocks LFA-1 dependent T cell recruitment and suppresses responses to anti-PD-1 treatment. Nat Commun. 2023;14:4253. https://doi.org/10.1038/s41467-023-39817-3.
16. Melero I, de Miguel Luken M, de Velasco G, et al. Neutralizing GDF-15 can overcome anti-PD-1 and anti-PD-L1 resistance in solid tumours. Nature. 2025;637:1218–27. https://doi.org/10.1038/s41586-024-08305-z.

17. Lee ES, Kim SH, Kim HJ, Kim KH, Lee BS, Ku BJ. Growth Differentiation factor 15 predicts chronic liver disease severity. Gut Liver. 2017;11:276–82. https://doi.org/10.5009/gnl16049.
18. Si Y, Liu X, Cheng M, et al. Growth differentiation factor 15 is induced by hepatitis C virus infection and regulates hepatocellular carcinoma-related genes. PLoS ONE. 2011;6:e19967. https://doi.org/10.1371/journal.pone.0019967.
19. Sometani E, Hikita H, Murai K, et al. High serum growth differentiation factor 15 is a risk factor for the occurrence of hepatocellular carcinoma in chronic hepatitis B patients treated with nucleos(t)ide analogs. Hepatol Res. 2024. https://doi.org/10.1111/hepr.14111.
20. Kim KH, Kim SH, Han DH, Jo YS, Lee YH, Lee MS. Growth differentiation factor 15 ameliorates nonalcoholic steatohepatitis and related metabolic disorders in mice. Sci Rep. 2018;8:6789. https://doi.org/10.1038/s41598-018-25098-0.
21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47. https://doi.org/10.1016/j.ejca.2008.10.026.
22. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. November 27, 2017. (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)
23. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1–10. https://doi.org/10.1016/0197-2456(89)90015-9.
24. Hollebecque A, Chung HC, de Miguel MJ, et al. Safety and antitumor activity of α-PD-L1 antibody as monotherapy or in combination with α-TIM-3 antibody in patients with microsatellite instability-high/mismatch repair-deficient tumors. Clin Cancer Res. 2021;27:6393–404. https://doi.org/10.1158/1078-0432.CCR-21-0261.
25. Fujita K, Uchida N, Kanai O, Okamura M, Nakatani K, Mio T. Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases. Cancer Chemother Pharmacol. 2018;81:1105–9. https://doi.org/10.1007/s00280-018-3585-9.
26. Watanabe H, Kubo T, Ninomiya K, Kudo K, et al. The effect and safety of immune checkpoint inhibitor rechallenge in non-small cell lung cancer. Jpn J Clin Oncol. 2019;49:762–5. https://doi.org/10.1093/jjco/hyz066.
27. Fujita K, Uchida N, Yamamoto Y, et al. Retreatment with anti-PD-L1 antibody in advanced non-small cell lung cancer previously treated with anti-PD-1 antibodies. Anticancer Res. 2019;39:3917–21. https://doi.org/10.21873/anticanres.13543.
28. Katayama Y, Shimamoto T, Yamada T, et al. Retrospective efficacy analysis of immune checkpoint inhibitor rechallenge in patients with non-small cell lung cancer. J Clin Med. 2019;9:102. https://doi.org/10.3390/jcm9010102.
29. Fujita K, Yamamoto Y, Kanai O, et al. Retreatment with anti-PD-1 antibody in non-small cell lung cancer patients previously treated with anti-PD-L1 antibody. Thorac Cancer. 2020;11:15–8. https://doi.org/10.1111/1759-7714.13241.
30. Makrakis D, Bakaloudi DR, Talukder R, et al. Treatment rechallenge with immune checkpoint inhibitors in advanced urothelial carcinoma. Clin Genitourin Cancer. 2023;21:286–94. https://doi.org/10.1016/j.clgc.2022.11.003.
31. Cai Z, Zhan P, Song Y, Liu H, Lv T. Safety and efficacy of retreatment with immune checkpoint inhibitors in non-small cell lung cancer: a systematic review and meta-analysis. Transl Lung Cancer Res. 2022;11:1555–66. https://doi.org/10.21037/tlcr-22-140.
32. Ito T, Shimose S, Saeki I, et al. Outcomes of sequential immune checkpoint inhibitor retreatment after atezolizumab plus bevacizumab in patients with unresectable hepatocellular carcinoma. J Gastroenterol Hepatol. 2026;41:302–11. https://doi.org/10.1111/jgh.70150.
33. Mizuno K, Ito T, Sawada T, et al. Safety and efficacy of retreatment with immune checkpoint inhibitors after severe immune-related adverse events. Oncologist. 2025;30:oyaf120. https://doi.org/10.1093/oncolo/oyaf120.
34. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014;15:143–55. https://doi.org/10.1016/S1470-2045(13)70586-2.
35. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384:665–73. https://doi.org/10.1016/S0140-6736(14)60845-X.
36. Borner T, Shaulson ED, Ghidewon MY, et al. GDF15 induces anorexia through nausea and emesis. Cell Metab. 2020;31:351-62.e5. https://doi.org/10.1016/j.cmet.2019.12.004.
37. Hüllwegen M, Kleinert M, von Haehling S, Fischer A. GDF15: from biomarker to target in cancer cachexia. Trends Cancer. 2025;11:1093–105. https://doi.org/10.1016/j.trecan.2025.06.007.
38. Groarke JD, Crawford J, Collins SM, et al. Ponsegromab for the treatment of cancer cachexia. N Engl J Med. 2024;391:2291–303. https://doi.org/10.1056/NEJMoa2409515.
39. Crawford J, Calle RA, Collins SM, et al. A phase Ib first-in-patient study assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of ponsegromab in participants with cancer and cachexia. Clin Cancer Res. 2024;30:489–97. https://doi.org/10.1158/1078-0432.CCR-23-1631.
40. Breen DM, Kim H, Bennett D, et al. GDF-15 neutralization alleviates platinum-based chemotherapy-induced emesis, anorexia, and weight loss in mice and nonhuman primates. Cell Metab. 2020;32:938-50.e6. https://doi.org/10.1016/j.cmet.2020.10.023.
41. Vashist N, Schätzlein D, Köhler A, et al. GDF-15 neutralization enhances the therapeutic activity of antibody-drug conjugates [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2025; Part 1 (Regular Abstracts); 2025 Apr 25-30; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2025;85(8_Suppl_1):Abstract nr 4777. https://doi.org/10.1158/1538-7445.AM2025-4777
42. Necchi A, Mercinelli C, Maiorano BA, et al. A blinded, exploratory phase 2 trial of nivolumab and the GDF-15 neutralizing antibody visugromab or placebo as neoadjuvant treatment of patients with muscle-invasive bladder cancer (MIBC): Primary results of the GDFATHER-NEO trial. Presented at: 2025 ESMO Congress; October 17-21, 2025; Berlin, Germany. Abstract LBA110. Ann Oncol (2025) 36 (suppl_2): S1-S60. https://doi.org/10.1016/annonc/annonc1965

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.