nature portfolio

https://doi.org/10.1038/s41586-024-08305-z

Supplementary information

Neutralizing GDF-15 can overcome anti-PD-1 and anti-PD-L1 resistance in solid tumours

In the format provided by the authors and unedited

Supplementary Information

Supplementary Table 1: Phase 1 part – Patient baseline characteristics (N = 25)

Age — (years)	
Mean / Median	62.0 / 61.0
Range	34 - 79
Sex — n (%)	
Male	13 (52.0)
Female	12 (48.0)
Race — n (%)	
White	24 (96.0)
Asian	0 (0.0)
Black	0 (0.0)
Other	0 (0.0)
Race not reported	1 (4.0)
ECOG performance-status score — n (%)	
0	11 (44.0)
1	14 (56.0)
Not reported	0 (0.0)
Cancer indication	
Cohort 1 (n=3)	Pleural Mesothelioma, Colon carcinoma, Mucosal melanoma
Cohort 2 (n=4)	Cervix carcinoma, Breast cancer, Cutaneous melanoma, Head & neck cancer
Cohort 3 (n=6)	Carcinoma of unknown primary, Mucosal melanoma [2], Ocular melanoma, Non-small cell lung cancer, Ovarian carcinoma
Cohort 4 (n=6)	Cutaneous melanoma, Mucosal melanoma, Cholangiocellular carcinoma, Non-small cell lung cancer, Hepatocellular carcinoma, Renal carcinoma
Cohort 5 (n=6)	Cutaneous melanoma [2], Mesothelioma, Non-small cell lung cancer, Uveal melanoma, Endometrial carcinoma
Disease stage at initial diagnosis — n (%)	
I	3 (12.0)
II	5 (20.0)
III	5 (20.0)
IV	11 (44.0)
Unknown	1 (4.0)
Status of disease at study entry — n (%)	
Metastatic	25 (100.0)
Locally advanced	0 (0.0)
Prior therapy — n (%)	
Prior surgery	
Yes	21 (84.0)
No	4 (16.0)
Prior radiotherapy	
Yes	18 (72.0)
No	7 (28.0)
Prior lines of systemic therapy	
Mean / median (range)	4.5 / 4 (2 - 11)
1 to 3 — n (%)	11 (44.0)
≥ 4 — n (%)	14 (56.0)
Prior Anti-PD(1)-containing therapy *	
N (%)	25 (100)
Duration of treatment (months; mean / median)	10.0 / 8.3
Most recent treatment before study entry — n (%)	
Yes	12 (48.0)
No	13 (52.0)
Lines of prior ICI-containing treatment n (%)	
Any	25 (100)
1	16 (64.0)
2	9 / (33.3)
≥ 3	0 (0.0)

* Duration of prior anti-PD(L)1-containing therapy was not always given in days and was calculated then with full months

Supplementary Table 2: Phase 1 part – Response outcome for phase 1 part (N = 25)

Best Overall Response	
ORR — n (%)	3 (12.0)
DCR — n (%)	18 (72.0)
CR — n (%)*	0 (0.0)
PR — n (%)*	3 (12.0)
SD — n (%)*	15 (60.0)
PD — n (%)*	7 (28.0)
Duration of response (months; mean / median)	12.9 / 7.1
Duration on study treatment (months; mean / median)	4.5 / 1.9

* Percentages may not total 100 due to rounding

Supplementary Table 3: Phase 2a part – Patient baseline characteristics, NSCLC Cohort (N = 27)

Age — (years)	
Mean / Median	65.0 / 67.0
Range	42 - 81
Sex — n (%)	
Male	20 (74.1)
Female	7 (25.9)
Race — n (%)	
White	25 (92.6)
Asian	0 (0.0)
Black	0 (0.0)
Other	0 (0.0)
Race not reported	2 (7.4)
ECOG performance-status score — n (%)	
0	10 (37.0)
1	17 (63.0)
Not reported	0 (0.0)
Histology — n (%)	
Non-squamous	21 (77.8)
Squamous	6 (22.2)
Disease Stage at initial diagnosis — n (%)	
I	1 (3.7)
II	2 (7.4)
III	6 (22.2)
IV	15 (55.6)
Unknown	3 (11.1)
Status of Disease at study entry — n (%)	
Metastatic	26 (96.3)
Locally Advanced	1 (3.7)
Prior Therapy — n (%)	
Prior tumour surgery	
Yes	9 (33.3)
No	18 (66.7)
Prior radiotherapy	
Yes	21 (77.8)
No	6 (22.2)
Prior lines of systemic therapy	
Mean/median	3.4/3 (1 - 8)
1 to 3	16 (59.3)
≥ 4	11 (40.7)
Anti-PD1/PD-L1-containing	27 (100.0)
Platinum-containing regimen	27 (100.0)
Docetaxel	9 (33.3)
Prior anti-PD(L)1-containing therapy *	
Duration of Treatment (months; mean / median)	9.6 / 6.9
Most recent before study entry	
Yes	12 (44.4)
No	15 (55.6)
Lines of prior anti-PD(L)1-containing therapy	
Any	27 (100.0)
1	25 (92.6)
2	2 (7.4)

* Duration of prior anti-PD(L)1-containing therapy was not always given in days and was calculated then with full months

Supplementary Table 4: Phase 2a part – Response outcome for NSCLC Cohort (N = 27)

Best Overall Response – All histologies (N=27)	
ORR — n (%)	4 (14.8)
DCR — n (%)	18 (66.7)
CR — n (%)*	2 (7.4) †
PR — n (%)*	2 (7.4)
SD — n (%)*	14 (51.9)
PD — n (%)*	9 (33.3)
Duration of response (months; mean / median)	15.3 / 16.6
Duration of study treatment (months; mean / median)	3.9 /2.3
Non-squamous (N=21)	
ORR — n (%)	4 (19.0)
DCR — n (%)	13 (61.9)
CR — n (%)*	2 (9.5) †
PR — n (%)*	2 (9.5)
SD — n (%)*	9 (42.9)
PD — n (%)*	8 (38.1)
Squamous (N=6)	
ORR — n (%)	0 (0.0)
DCR — n (%)	5 (83.3)
CR — n (%)*	0 (0.0)
PR — n (%)*	0 (0.0)
SD — n (%)*	5 (83.3)
PD — n (%)*	1 (16.7)

* Percentages may not total 100 due to rounding

† Lasting PR achieved on study treatment, in week 48 seemingly one lymph node region showed enlarging lymph nodes and underwent focal irradiation immediately. Thereafter, all lesions decreased further, and study treatment was terminated at week 72 due to an AE making the patient desire to end treatment (pneumonitis). Scans at week 78 and thereafter then demonstrated and confirmed a CR. In hindsight the Investigator felt that the lymph node enlargement most likely represented pseudoprogression

Supplementary Table 5: Best overall response and duration of response (DoR) on prior/initial anti-PD-(L)1 treatment compared to response on trial treatment for visugromab+nivolumab responders in the NSCLC, Urothelial cancer, Melanoma and Hepatocellular carcinoma (HCC) cohorts

		Prior anti-PD(L)1-containing therapy			Study treatment	
Cohort	**Trial participant**	**Drug/agent name**	**Best response to prior regimen**	**DoR (months)**	**Best response to study treatment**	**DoR (months)[†]**
Non-squamous NSCLC	1-01-013[*]	Nivolumab	PR	25.0	PR	5.5
	1-01-018	Pembrolizumab, Carboplatin Pemetrexed	PR	9.0	PR/CR[‡]	22.4
	1-01-021[*]	Atezolizumab	PR	17.0	PR	18.2
	1-06-004[*]	Pembrolizumab Cisplatin Pemetrexed	PR	22.0	CR	14.9
	DoR (mean / median)			**18.3 / 19.5**		**15.3 / 16.6**
Urothelial cancer	1-01-015[*]	Atezolizumab	PR	25.0	CR	23.7
	1-02-036[*]	Avelumab (maintenance)	PR	2.9	PR	7.1
	1-02-037[*]	Atezolizumab	PD	NA	PR	12.5
	1-03-014	Pembrolizumab GSK33 (ICOS agonist)	PR	45.6	PR	24.2
	1-06-005[*]	Atezolizumab	PD	NA	PR	14.4
	DoR (mean / median)			**25.5 / 25.0**		**16.4 / 14.4**
Mel.	3-01-013	Nivolumab	CR	NA[§]	CR	20.6
	DoR (mean / median)			NA[§]		**20.6 / 20.6**
HCC	1-02-010[*]	Atezolizumab Bevacizumab	CR	29.1	CR[‖]	**25.9**
	1-05-014[*]	Atezolizumab Bevacizumab	SD	NA	PR	**6.5**
	2-03-001[*]	Pembrolizumab Atezolizumab Bevacizumab	PD	NA	PR	**1.0**
	DoR (mean / median)			**29.1 / 29.1**		**11.1 / 6.5**

[*] Treatment still ongoing at data cut-off date, therefore DoR on study treatment is expected to mature further

[†] Data cut-off 3 May 2024

[‡] Lasting PR achieved on study treatment, in week 48 seemingly one lymph node region showed enlarging lymph nodes and underwent focal irradiation immediately. Thereafter, all lesions decreased further, and study treatment was terminated at week 72 due to an unrelated AE making the patient desire to end treatment. Scans at week 78 and thereafter then demonstrated and confirmed a CR. In hindsight the Investigator feels that the lymph node enlargement most likely represented pseudoprogression

[§] This patient received (in violation of the protocol) anti-PD1 as adjuvant treatment, only; relapse in unresectable/metastatic stage occurred 18 months after end of formal completion of this treatment. Inclusion had been granted in error, retrospectively documented as major protocol violation)

[‖] Lasting PR achieved on study treatment; treatment discontinuation due to irAE (Grade 2 arthralgia). In planned follow-up scans (post EoT) CR detected and confirmed with no other treatment provided since study treatment

Note: DoR (in months) is calculated from start of treatment [*see* Delgado, A. *et al. Am. J. Cancer Res.* **11**: 1121–1131 (2023)];
NA, not available

Supplementary Table 6: Phase 2a part – Treatment emergent adverse events (TEAE) of grade 3 or greater, NSCLC Cohort (N = 27)

SOC	Grade 3	Grade 4	Grade 5	Total
Subjects reporting at least one TEAE	15 (55.6%)	1 (3.7%)	3 (11.1%)	16 (59.3%)
Infections and infestations	4 (14.8%)	0	1 (3.7%)	4 (14.8%)
Gastrointestinal disorders	2 (7.4%)	0	1 (3.7%)	2 (7.4%)
Respiratory, thoracic and mediastinal disorders	4 (14.8%)	0	0	4 (14.8%)
General disorders and administration site conditions	2 (7.4%)		1 (3.7%)	3 (11.1%)
Blood and lymphatic system disorders	2 (7.4%)	0	0	2 (7.4%)
Musculoskeletal and connective tissue disorders	4 (14.8%)	0	0	4 (14.8%)
Investigations	1 (3.7%)	0	0	2 (7.4%) *
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (11.1%)	0	0	3 (11.1%)
Metabolism and nutrition disorders	1 (3.7%)	0	0	1 (3.7%)
Renal and urinary disorders	0	1 (3.7%)	0	1 (3.7%)
Nervous system disorders	2 (7.4%)	0	0	2 (7.4%)
Injury, poisoning and procedural complications	1 (3.7%)	0	0	1 (3.7%)
Cardiac disorders	0	0	0	0
Hepatobiliary disorders	0	1 (3.7%)	0	1 (3.7%)
Reproductive system and breast disorders	2 (7.4%)	0	0	2 (7.4%)
Vascular disorders	1 (3.7%)	0	0	1 (3.7%)
Endocrine disorders	0	0	0	0
Psychiatric disorders	0	0	0	0

* TEAE grading was missing for one patient

Supplementary Table 7: Phase 2a part – Patient baseline characteristics, Urothelial carcinoma (UC) Cohort (N = 27)

Age — (years)	
Mean / Median	66.6 (67.0)
Range	52 - 82.0
Sex — n (%)	
Male	22 (81.5)
Female	5 (18.5)
Race — n (%)	
White	27 (100.0)
Asian	0 (0.0)
Black	0 (0.0)
Other	0 (0.0)
Race not reported	0 (0.0)
ECOG performance-status score — n (%)	
0	12 (44.4)
1	15 (55.6)
Not reported	0 (0.0)
Disease stage at initial diagnosis — n (%)	
I	3 (11.1)
II	5 (18.5)
III	7 (25.9)
IV	6 (22.2)
Unknown	6 (22.2)
Status of disease at study entry — n (%)	
Metastatic	25 (92.6)
Locally advanced	2 (7.4)
Prior therapy — n (%)	
Prior tumour surgery	
Yes	26 (96.3)
No	1 (3.7)
Prior radiotherapy	
Yes	14 (51.9)
No	13 (48.1)
*Prior lines of systemic therapy**	
Mean / median	3.3 / 3
1 to 3	16 (59.3)
≥ 4	11 (40.7)
Anti-PD1/PD-L1 containing	27 (100.0)
Avelumab maintenance	10 (37.0)
Platinum-containing regimen	25 (92.6)
Prior anti-PD(L)1-containing therapy†	
Duration of treatment (months; mean / median)	9.4 / 6.9
Most recent before study entry	
Yes	12 (44.4)
No	15 (55.6)
Lines of prior anti-PD(L)1-containing therapy	
Any	27 (100)
1	26 (96.3)
2	1 (3.7)

* Avelumab maintenance was calculated as separate line of therapy

† Duration of prior anti-PD(L)1-containing therapy was not always given in days and was calculated then with full months

Supplementary Table 8: Phase 2a part – Response outcome for Urothelial carcinoma (UC) Cohort (N = 27)

Best Overall Response	
ORR — n (%)	5 (18.5)
DCR — n (%)	15 (55.6)
CR — n (%)*	1 (3.7)
PR — n (%)*	4 (14.8)
SD — n (%)*	10 (37.0)
PD — n (%)*	12 (44.4)
Duration of response (months; mean / median)	16.4 / 14.4
Duration on study treatment (months; mean/median)	5.4 /2.5

* Percentages may not total 100 due to rounding

Supplementary Table 9: Phase 2a part – Treatment emergent adverse events (TEAE) of grade 3 or greater, Urothelial carcinoma (UC) Cohort (N = 27)

SOC	Grade 3	Grade 4	Grade 5	Total
Subjects reporting at least one TEAE	14 (51.8%)	0	1 (3.7%)	14 (51.8%)
Infections and infestations	3 (11.1%)	0	1 (3.7%)	4 (14.8%)
Gastrointestinal disorders	2 (7.4%)	0	0	2 (7.4%)
Respiratory, thoracic and mediastinal disorders	3 (11.1%)	0	0	3 (11.1%)
General disorders and administration site conditions	0	0	0	0
Blood and lymphatic system disorders	2 (7.4%)	0	0	2 (7.4%)
Musculoskeletal and connective tissue disorders	0	0	0	0
Investigations	2 (7.4%)	0	0	2 (7.4%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (3.7%)	0	0	1 (3.7%)
Metabolism and nutrition disorders	2 (7.4%)	0	0	2 (7.4%)
Renal and urinary disorders	3 (11.1%)	0	0	3 (11.1%)
Nervous system disorders	1 (3.7%)	0	0	1 (3.7%)
Injury, poisoning and procedural complications	1 (3.7%)	0	0	1 (3.7%)
Cardiac disorders	0	0	0	0
Hepatobiliary disorders	0	0	0	0
Reproductive system and breast disorders	0	0	0	0
Vascular disorders	1 (3.7%)	0	0	1 (3.7%)
Endocrine disorders	0	0	0	0
Psychiatric disorders	0	0	0	0

Supplementary Table 10: Phase 2a part – Patient baseline characteristics, Melanoma Cohort (N = 14)

Age — (yrs)	
Mean/Median	62.9 / 63.0
Range	35 – 87
Sex — n (%)	
Male	8 (57.1)
Female	6 (42.9)
Race — n (%)	
White	13 (92.9)
Asian	0 (0.0)
Black	0 (0.0)
Other	0 (0.0)
Race not reported	1 (7.1)
ECOG performance-status score — n (%)	
0	11 (78.6)
1	3 (21.4)
Not reported	0 (0.0)
Disease Stage at Diagnosis — n (%)*	
0	0 (0.0)
I	1 (7.1)
II	1 (7.1)
III	4 (28.6)
IV	7 (50.0)
Unknown	1 (7.1)
Status of Disease at Study Entry — n (%)	
Metastatic	14 (100.0)
Locally Advanced	0 (0.0)
Prior Therapy — n (%)	
Prior Tumor Surgery	
Yes	14 (100.0)
No	0 (0.0)
Prior Radiotherapy	
Yes	5 (35.7)
No	9 (64.3)
Prior Lines of Systemic Therapy	
Mean/median	2.3 / 2
1	4 (28.6)
2	6 (42.9)
≥ 3	4 (28.6)
Prior Anti-PD(L)1-containing Therapy†	
DoT (months; mean/median)	14.5 / 11.3 (2.8 – 76.9)
Most recent before study entry	
Yes	12 (85.7)
No	2 (14.3)
Lines of prior Anti-PD(L)1-containing Therapy	
1	3 (21.4)
2	11 (78.6)

* Percentages may not total 100 because of rounding

† Duration of prior anti-PD(L)1-containing therapy was not always given in days and was calculated then with full months

Supplementary Table 11: Phase 2a part – Patient baseline characteristics, Hepatocellular carcinoma (HCC) Cohort (N = 26) *

Age — (yrs)	
Mean/Median	64.2 / 64.5
Range	48 - 77
Sex — n (%)	
Male	20 (76.9)
Female	6 (23.1)
Race — n (%)	
White	24 (92.3)
Asian	0 (0.0)
Black	0 (0.0)
Other	0 (0.0)
Race not reported	2 (7.7)
ECOG performance-status score — n (%)	
0	22 (84.6)
1	4 (15.4)
Not reported	0 (0.0)
Disease Stage at Diagnosis — n (%)	
0	0 (0.0)
I	4 (15.4)
II	2 (7.7)
III	5 (19.2)
IV	6 (23.1)
Unknown	6 (23.1)
Status of Disease at Study Entry — n (%)	
Metastatic	18 (69.2)
Locally Advanced	8 (30.8)
Prior Therapy — n (%)	
Prior Tumor Surgery	
Yes	11 (42.3)
No	15 (57.7)
Prior Radiotherapy	
Yes	5 (19.2)
No	21 (80.8)
Prior RF ablation	
Yes	4 (15.4)
No	22 (84.6)
Prior TACE	
Yes	3 (11.5)
No	23 (88.5)
Prior Lines of Systemic Therapy	
Mean/median	1.8 / 2
1	10 (38.5)
2	13 (50.0)
≥ 3	3 (11.5)
Anti-PD1/PD-L1 containing	26 (100.0)
Prior Anti-PD(L)1-containing Therapy†	
DoT (months; mean/median)	11.7 / 10.0
Most recent before study entry	
Yes	15 (57.7)
No	11 (42.3)
Lines of prior Anti-PD(L)1-containing Therapy	
1	21 (80.8)
2	5 (19.2)

***** At the data cut-off date, 27 patients have been recruited but data for one patient were not yet available in the database for one patient, therefore, characteristics are only displayed for 26 patients

† Duration of prior anti-PD(L)1-containing therapy was not always given in days and was calculated then with full months

Supplementary Table 12: Phase 2a part – Patient baseline characteristics, Colorectal carcinoma (CRC) Cohort (N = 10)

Age — (yrs)	
Mean/Median	61.4 / 59.5
Range	36 – 89
Sex — n (%)	
Male	5 (50.0)
Female	5 (50.0)
Race — n (%)	
White	10 (100.0)
Asian	0 (0.0)
Black	0 (0.0)
Other	0 (0.0)
Race not reported	0 (0.0)
ECOG performance-status score — n (%)	
0	6 (60.0)
1	4 (40.0)
Not reported	0 (0.0)
Disease Stage at Diagnosis — n (%)	
0	0 (0.0)
I	0 (0.0)
II	1 (10.0)
III	4 (40.0)
IV	5 (50.0)
Unknown	0 (0.0)
Status of Disease at Study Entry — n (%)	
Metastatic	10 (100.0)
Locally Advanced	0 (0)
Prior Therapy — n (%)	
Prior Tumor Surgery	
Yes	7 (70.0)
No	3 (30.0)
Prior Radiotherapy	
Yes	4 (40.0)
No	6 (60.0)
Prior Lines of Systemic Therapy	
Mean/median	4 / 3.5
1 to 3	5 (50.0)
≥ 4	5 (50.0)
Anti-PD1/PD-L1 containing	0 (0)

¶ 16 patients still continue on study treatment at data cut-off

Supplementary Table 13: Phase 2a part – Response outcome for HCC Cohort (N = 19)†

Best Overall Response	
ORR — n (%)	3 (15.8)
DCR — n (%)	11 (57.9)
CR — n (%)* ‡	1 (5.3)
PR — n (%)* §	2 (10.5)
SD — n (%)*	8 (42.1)
PD — n (%)*	8 (42.1)
DoR (months; mean/median)‖	11.1 / 6.5
Duration on Study Treatment (months; mean/median) ¶	2.3 /1.4

* Percentages may not total 100 due to rounding

† Seven patients were enrolled close to current data cut-off date and have not yet reported post-treatment evaluations; therefore, they are excluded from the BOR calculation. Additionally, two patients died from PD before their initial assessment and were categorized as PD.

‡ Lasting PR achieved on treatment and CR post end of treatment (due to irAE (Grade 2 arthralgia))

§ PR reported post data cut-off, result included in table based on available, validated eCRF entry

‖ All responses are ongoing at data cut-off

Supplementary Table 14: Phase 2a part – Response outcome for Melanoma Cohort (N = 14)

Best Overall Response	
ORR — n (%)	1 (7.1)
DCR — n (%)	8 (57.1)
CR — n (%)*	1 (7.1)†
PR — n (%)*	0 (0.0)
SD — n (%)*	7 (50.0)
PD — n (%)*	6 (42.9)
DoR (months; mean/median)	20.6 / 20.6
Duration on Study Treatment (months; mean/median)	4.7 / 2.1

* Percentages may not total 100 due to rounding

† This patient received (in violation of the protocol) anti-PD1 as adjuvant treatment, only; relapse in unresectable/metastatic stage occurred 18 months after end of formal completion of this treatment. Inclusion had been granted in error, retrospectively documented as major protocol violation)

Supplementary Table 15: Phase 2a part – Response outcome for Colorectal carcinoma (CRC) Cohort (N = 10)

Best Overall Response	
ORR — n (%)	0 (0.0)
DCR — n (%)	5 (50.0)
CR* — n (%)*	0 (0.0)
PR* — n (%)*	0 (0.0)
SD* — n (%)*	5 (50.0)
PD* — n (%)*†	5 (50.0)
	NA
DoR (months; mean/median)	
Duration on Study Treatment (months; mean/median)	1.8 / 1.2

* Percentages may not total 100 due to rounding

† No documented radiologic progression for 1 patient. Reason for death recorded by Investigator as clinical progression, therefore reported as PD

Supplementary Table 16: Phase 2a part – Treatment emergent adverse events (TEAE) of grade 3 or greater, Melanoma (cutaneous and mucosal) Cohort (N = 14)

SOC	Grade 3	Grade 4	Grade 5	Total
Subjects reporting at least one TEAE	7 (50.0%)	0	0	7 (50.0%)
Infections and infestations	2 (14.3%)	0	0	2 (14.3%)
Gastrointestinal disorders	1 (7.1%)	0	0	1 (7.1%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0
General disorders and administration site conditions	1 (7.1%)	0	0	1 (7.1%)
Blood and lymphatic system disorders	1 (7.1%)	0	0	1 (7.1%)
Musculoskeletal and connective tissue disorders	0	0	0	0
Investigations	2 (14.3%)	0	0	2 (14.3%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (7.1%)	0	0	1 (7.1%)
Metabolism and nutrition disorders	0	0	0	0
Renal and urinary disorders	0	0	0	0
Nervous system disorders	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0
Cardiac disorders	0	0	0	0
Hepatobiliary disorders	1 (7.1%)	0	0	1 (7.1%)
Reproductive system and breast disorders	0	0	0	0
Vascular disorders	0	0	0	0
Endocrine disorders	0	0	0	0
Psychiatric disorders	0	0	0	0

Supplementary Table 17: Phase 2a part – Treatment emergent adverse events (TEAE) of grade 3 or greater, HCC Cohort (N = 12)

SOC	Grade 3	Grade 4	Grade 5	Total
Subjects reporting at least one TEAE	4 (33.3%)	0	0	4 (33.3%)
Infections and infestations	2 (16.7%)	0	0	2 (16.7%)
Gastrointestinal disorders	1 (8.3%)	0	0	1 (8.3%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0
General disorders and administration site conditions	1 (8.3%)	0	0	1 (8.3%)
Blood and lymphatic system disorders	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0
Investigations	0	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (8.3%)	0	0	1 (8.3%)
Metabolism and nutrition disorders	0	0	0	0
Renal and urinary disorders	0	0	0	0
Nervous system disorders	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0
Cardiac disorders	1 (8.3%)	0	0	1 (8.3%)
Hepatobiliary disorders	0	0	0	0
Reproductive system and breast disorders	0	0	0	0
Vascular disorders	0	0	0	0
Endocrine disorders	0	0	0	0
Psychiatric disorders	0	0	0	0

Supplementary Table 18: Phase 2a part – Treatment emergent adverse events (TEAE) of grade 3 or greater, Colorectal carcinoma (CRC) Cohort (N = 11)

SOC	Grade 3	Grade 4	Grade 5	Total
Subjects reporting at least one TEAE	3 (27.3%)	0	1 (9.1%)	4 (36.4%)
Infections and infestations	0	0	0	0
Gastrointestinal disorders	1 (9.1%)	0	1 (9.1%)	2 (18.2%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0
General disorders and administration site conditions	0	0	0	0
Blood and lymphatic system disorders	1 (9.1%)	0	0	1 (9.1%)
Musculoskeletal and connective tissue disorders	0	0	0	0
Investigations	0	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (9.1%)	0	0	1 (9.1%)
Metabolism and nutrition disorders	1 (9.1%)	0	0	1 (9.1%)
Renal and urinary disorders	0	0	0	0
Nervous system disorders	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0
Cardiac disorders	0	0	0	0
Hepatobiliary disorders	0	0	0	0
Reproductive system and breast disorders	0	0	0	0
Vascular disorders	0	0	0	0
Endocrine disorders	0	0	0	0
Psychiatric disorders	0	0	0	0

Supplementary Note 1: Summary of histologic findings in patient 3-02-003

This 70-year-old male with non-small cell lung cancer (NSCLC) experienced on study treatment acute damage to the hepatic and renal tissue resulting in multi-organ failure with fatal outcome. The patient had a concurrent medical condition at baseline (provided as “metabolic syndrome”) and prior treatments had included apart from standard of care for metastatic non-squamous NSCLC most recently also an experimental antibody drug conjugate (ADC) with last administration just 34 days prior to study treatment, resulting in renal toxicity during ADC treatment. This toxicity resolved to Grade 1 creatinine elevation immediately prior to CTL-002-001 study entry, allowing enrolment and study treatment start.

The autopsy showed an inhomogeneous coloration of the kidney as an expression of acute renal damage. A diagnostic kidney transjugular biopsy performed pre-mortem on the day of death had revealed renal cortical and medullary tissue with up to 10 glomeruli in part with slightly increased cellularity, consistent capillary loops and one glomerulus with capsular fibrosis. Focal mixed cell inflammatory infiltrate including numerous eosinophil granulocyte and edema in the interstitium with widespread acute tubular necrosis was noted. The intrarenal arteries had slight intimal fibrosis and tubules were dilated. Further examinations revealed acute damage to the renal tubules (tubular necrosis) with adjacent microabscesses and reactive cell changes. All the histological findings were consistent with an acute interstitial nephritis, compatible with a drug-toxic renal injury however no granulomas, fibrosis, significant tubulitis, and vasculitis were noted. The unusual widespread acute tubular necrosis without significant tubulitis confirmed the acute tubular injury could be due to an additional cause. Immunofluorescence microscopy revealed renal tissue with up to 7 glomeruli, one of which completely sclerosed, factor VIII and fibrinogen in normal patterns, and IgG, IgM, IgA, complement factors C1q and C3 all negative. The pre-mortem liver transjugular biopsy (also performed on the day of death) revealed regular architecture and more than 15 portal tracts in which mixed cell inflammatory infiltrate including numerous eosinophil granulocytes, interface hepatitis, signs of bile duct damage and ductular reaction (CK19 staining) were observed. There was no portal fibrosis and no fibrous septa. The lobular parenchyma was noted with several necroinflammatory lesions with numerous granulocytes, individual cell necrosis, Kupffer cell siderosis and hepatocellular cholestasis. No steatosis and no PAS positive, diastase resistant glomerular inclusions were noted and consistent central veins were present. There was no evidence of malignancy. Acute hepatic cell damage was detected and overall hepatic histologic findings were suggestive of drug induced liver injury (DILI) with no indication of chronic hepatopathy. The investigations from the main autopsy confirmed the findings of the pre-mortem biopsies with no additional or diverging findings.