First-in-Human Study of REGN3767, a Human LAG-3 Monoclonal Antibody, ± Cemiplimab in Patients with Advanced Malignancies

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Abstract # 2508

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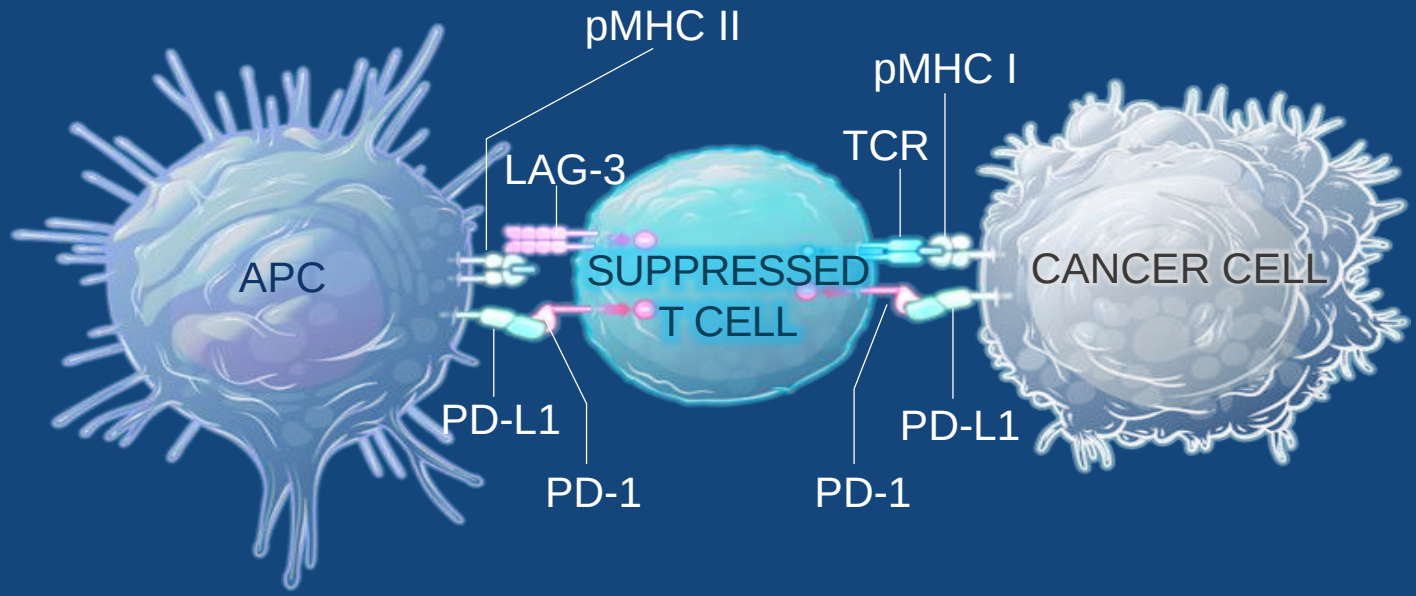
ClinicalTrials.gov: NCT03005782

LAG-3 and PD-1 Biology Overview

- LAG-3 is an immune checkpoint receptor that delivers an inhibitory signal to activated T cells upon MHC class II binding.[1] Alternative LAG-3 suppressive ligands have been reported[2–4]
- LAG-3 is upregulated on infiltrating T cells in many cancer types[5]
- LAG-3 expression in melanoma biopsies is significantly associated with therapeutic resistance to anti-PD-1,[6] suggesting that LAG-3 immunosuppressive activity may be complimentary to PD-1

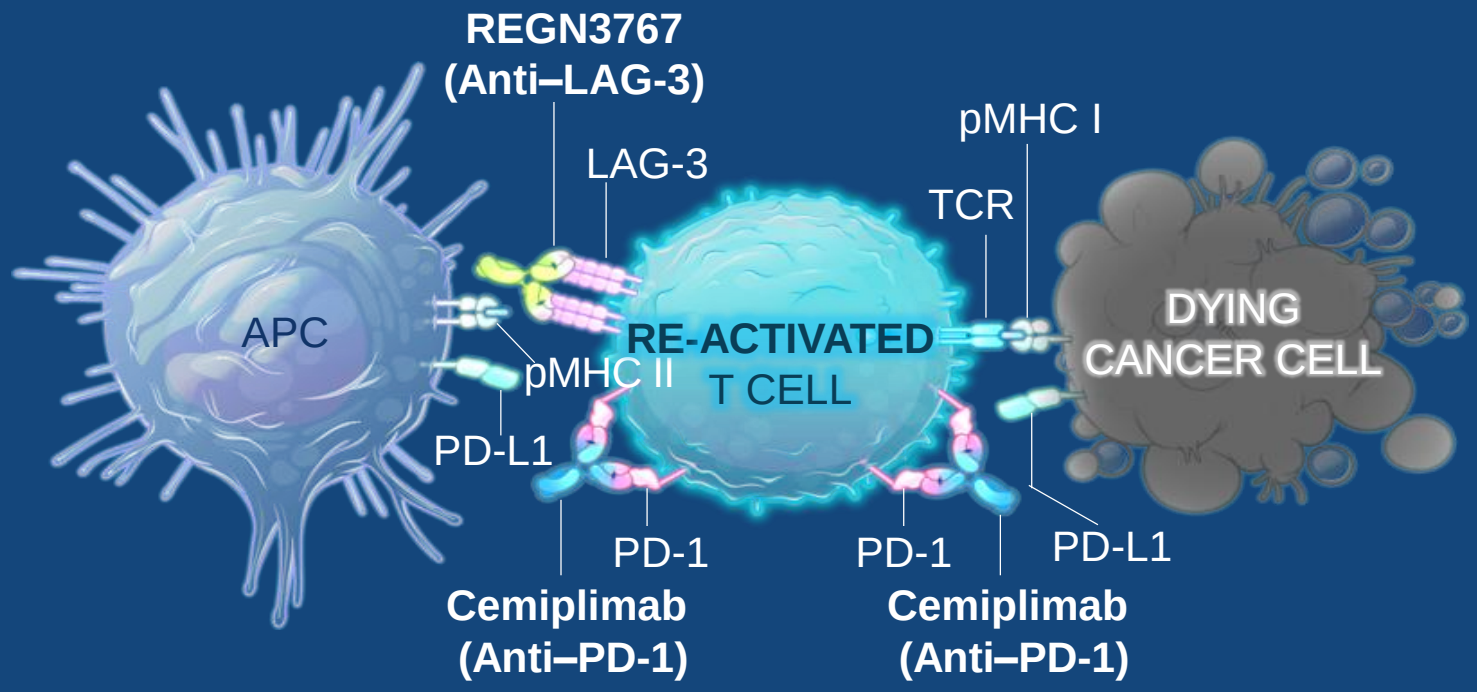


APC, antigen-presenting cell; IgG, immunoglobulin G; LAG, lymphocyte activation gene; mAb, monoclonal antibody; MHC, major histocompatibility complex; pMHC, peptide-MHC; PD; programmed cell death; PD-L, programmed cell death-ligand; TCR, T cell receptor.

1. Huard B et al. *PNAS*. 1997;94:5744–5749. 2. Andrews LP et al. *Immunol Rev*. 2017;276:80–96. 3 Wang J et al. *Cell*. 2019;176:334–347. 4. Maruhashi T et al. *Nature Immunology*. 2018;19:1415–1426. 5. Thommen DS et al. *Cancer Immunol Res*. 2015;3:1344–1355. 6. Chen PL et al. *Cancer Discov.* 2016;6:827–837.

LAG-3 and PD-1 Biology Overview

- REGN3767 and cemiplimab are both high affinity, human, hinge-stabilized IgG4 mAbs to LAG-3 and PD-1 receptor, respectively
  - REGN3767 blocks LAG-3/MHC class II-driven T cell inhibition
  - Cemiplimab blocks the interactions of PD-1 with PD-L1 and PD-L2[1]



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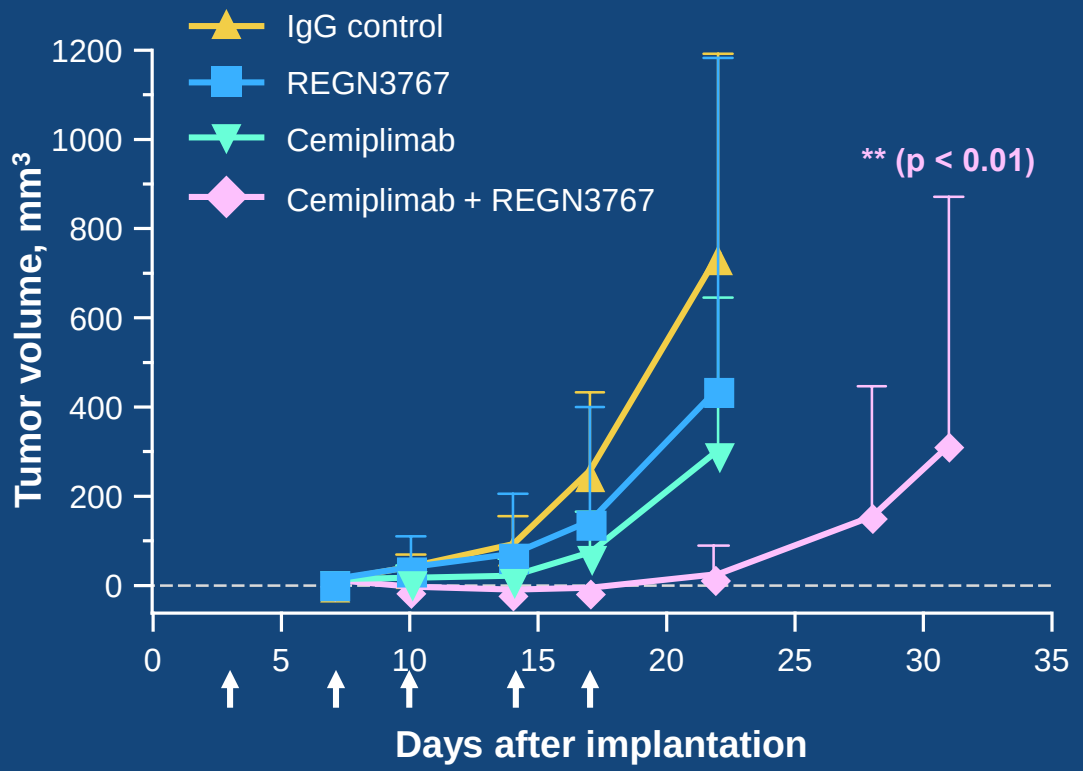
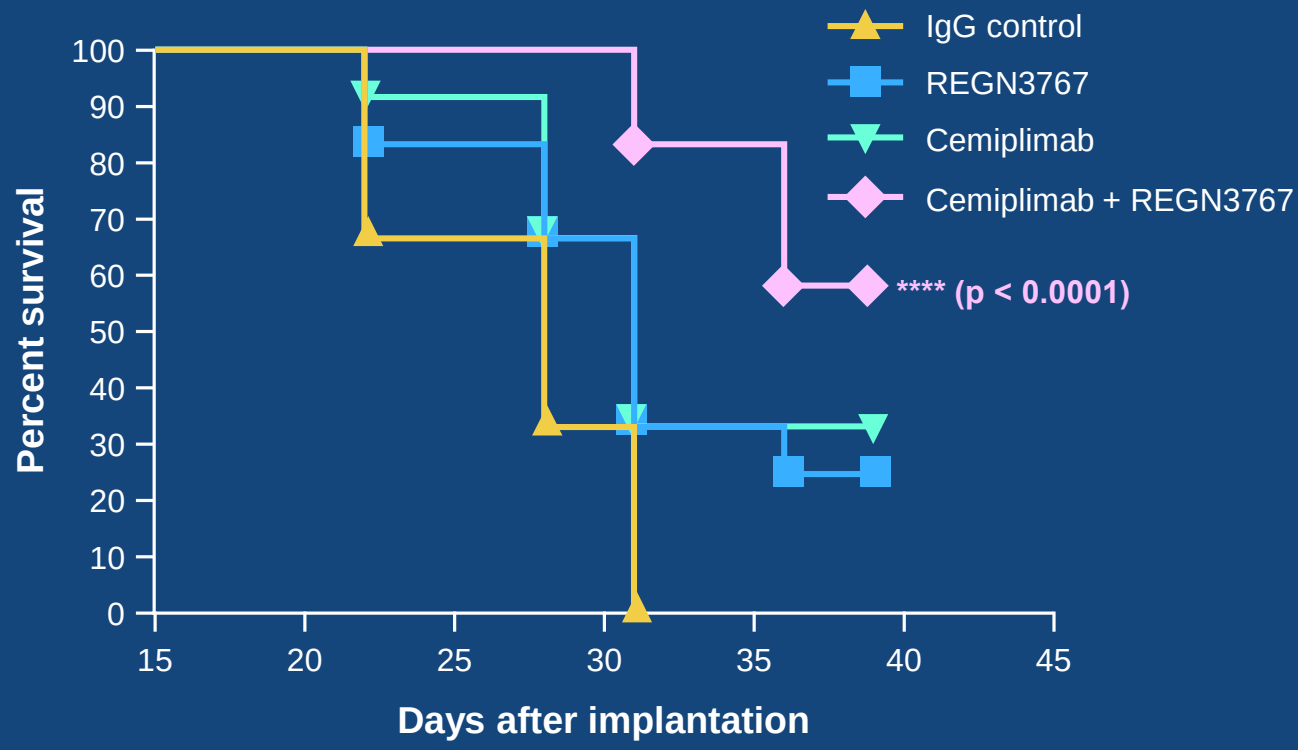
1. Burova E et al. *Mol Cancer Ther*. 2017;16:861–870.

Preclinical Rationale for Anti-LAG-3 in Combination with Anti–PD-1

- REGN3767 + cemiplimab demonstrated encouraging antitumor effects in mouse models





Dual humanized PD-1$^{hum/hum}$/LAG-3$^{hum/hum}$ mice were engrafted with MC38.Ova cells subcutaneously on Day 0. Treatment days are indicated by arrows.

IgG, immunoglobulin G; LAG, lymphocyte activation gene; PD; programmed cell death.

Ioffe E et al. Oral presentation at the Immuno-Oncology Summit, 2017, Boston MA, USA.

First-in-Human Study of REGN3767 ± Cemiplimab in Patients with Advanced Malignancies – Dose Escalation

Primary objective:

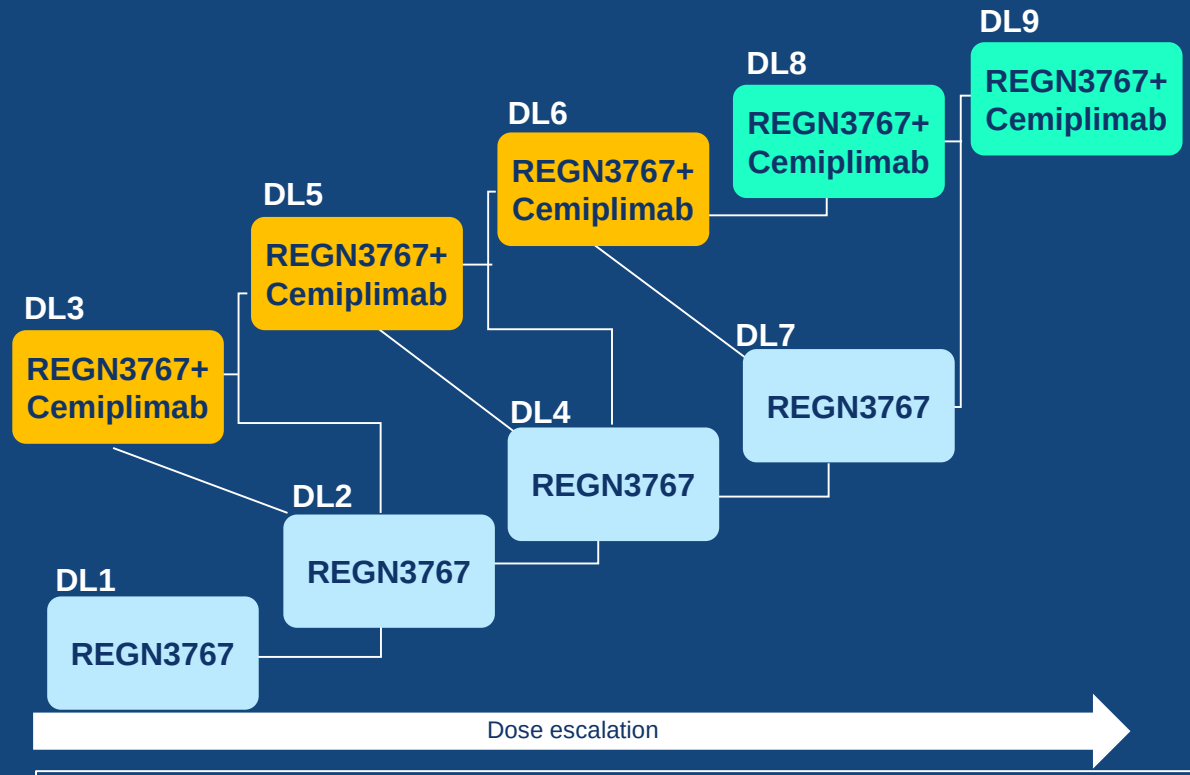
- **To evaluate the safety and PK of REGN3767 monotherapy or REGN3767 + cemiplimab in order to determine the dose level(s) for expansion.**

Preliminary antitumor activity and pharmacodynamics were also examined.

PK, pharmacokinetics; Q[n]W, every [n] weeks.

REGN3767-ONC-1613, NCT03005782

First-in-Human Study of REGN3767 ± Cemiplimab in Patients with Advanced Malignancies – Dose Escalation Cohorts



Dose levels	REGN3767 Q3W	Cemiplimab Q3W
1	1 mg/kg monotherapy	NA
2	3 mg/kg monotherapy	NA
3	1 mg/kg	3 mg/kg
4	10 mg/kg monotherapy	NA
5	3 mg/kg	3 mg/kg
6	10 mg/kg	3 mg/kg
7	20 mg/kg monotherapy	NA
8	10 mg/kg	350 mg
9	20 mg/kg	350 mg

Modified 3+3 (4+3) design with 3-4 additional patients added to select dose levels to further evaluate tolerability

Monotherapy to combination therapy: Patients in REGN3767 monotherapy cohorts who tolerate monotherapy and subsequently progress have the option of adding cemiplimab to their treatment regimen

Tumor response assessments: Q6W for the first 24 weeks, subsequently Q9W

DL, dose level; NA, not applicable; Q[n]W, every [n] weeks.

REGN3767-ONC-1613, NCT03005782

Key Eligibility Criteria – Dose Escalation

Key inclusion	Key exclusion
• ≥18 years • Patients with advanced malignancies who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit, and patients with malignancies that are incurable and have failed to respond to or have shown tumor progression despite standard therapy - Patients do not require measurable disease per RECIST 1.1 or Lugano criteria • ECOG Performance Status of 0 or 1 • Adequate organ function (bone marrow, kidney, liver)	• Autoimmune disease within 5 years • Active brain metastases • Immunosuppressive doses of steroids (>10 mg prednisone daily or equivalent) • Recent treatment with an approved systemic therapy within 3 weeks, investigational treatment within 4 weeks, or other systemic antitumor treatment within five half-lives of initial dose of study drug (whichever is the longest period) • Prior therapy with an anti-LAG-3 agent • History of solid organ transplant • Ongoing or recent evidence of significant autoimmune disease

ECOG, Eastern Cooperative Oncology Group; LAG, lymphocyte activation gene; RECIST, Response Evaluation Criteria In Solid Tumors.

Patient Characteristics

	REGN3767 monotherapy (N=27)	REGN3767 + cemiplimab (N=42)	Mono to combo (N=13)
Median age, years (range)	68 (22–83)	60 (30–83)	64 (22–83)
Female, n (%)	14 (51.9)	24 (57.1)	7 (53.8)
ECOG PS 0; 1, n (%)	4 (14.8); 23 (85.2)	15 (35.7); 27 (64.3)	3 (23.1); 10 (76.9)
Most common primary site of cancer, n (%)			
Colon	2 (7.4)	10 (23.8)	2 (15.4)
Lung†	2 (7.4)	4 (9.5)	1 (7.7)
Biliary tract	1 (3.7)	3 (7.1)	0
Ovary	2 (7.4)	2 (4.8)	1 (7.7)
Pancreas	1 (3.7)	3 (7.1)	0
Prior lines of systemic therapy, n (%)			
Any	25 (92.6)	42 (100)	12 (92.3)
1–2	9 (33.3)	16 (38.1)	7 (53.8)
≥3	16 (59.3)	26 (61.9)	5 (38.5)
Prior anti–PD-1/PD-L1	0	3 (7.2)	0
Prior radiotherapy	15 (55.6)	27 (64.3)	9 (69.2)

†Includes 1 adenoid cystic carcinoma, 1 squamous non-small cell lung cancer and 4 small cell lung cancer patients.
Combo, REGN3767 + cemiplimab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mono, REGN3767 monotherapy; PD; programmed cell death; PD-L, programmed cell death-ligand.

Patient Disposition

n (%)	REGN3767 monotherapy (N=27)	REGN3767 + cemiplimab (N=42)	Mono to combo (N=13)
Completed treatment	1 (3.7)	0	0
Discontinued treatment	26 (96.3)	41 (97.6)	13 (100)
Primary reason for discontinuing treatment			
Disease progression	16 (59.3)	36 (85.7)	8 (61.5)†
Death‡	4 (14.8)	3 (7.1)	0
Other	3 (11.1)	0	0
Withdrawal of consent	2 (7.4)	1 (2.4)	0
Investigator decision	1 (3.7)	0	0
Patient decision	0	1 (2.4)	2 (15.4)
Adverse event	0	0	3 (23.1)

†Includes clinical progression/recurrence of disease (n=3; 23.1%) and radiologic progression/recurrence of disease (n=5; 38.5%). ‡in the monotherapy cohort, one patient died due to an adverse event of fulminant hepatic failure and another patient died after withdrawal by investigator due to clinical deterioration. In the combination therapy cohort, one patient died due to an adverse event of sepsis, which was unrelated to study treatment.
Combo, REGN3767 + cemiplimab; mono, REGN3767 monotherapy.

Exposure to REGN3767

	REGN3767 monotherapy (N=27)	REGN3767 + cemiplimab (N=42)	Mono to combo (N=13)
Duration of exposure, weeks, median (range)	12.0 (2–51)	9.1 (3–80)	16.7 (6–66)
Number of doses of study drug, median (range)	4 (1–17)	3 (1–23)	6 (2–20)

Combo, REGN3767 + cemiplimab; mono, REGN3767 monotherapy.

TEAEs in Patients Treated with REGN3767 Monotherapy

TEAEs regardless of attribution, n (%)	REGN3767 monotherapy (N=27)	
	Any grade	Grade ≥3
Any	23 (85.2)	11 (40.7)
Serious	6 (22.2)	5 (18.5)
Immune-related	2 (7.4)	1 (3.7)
Led to discontinuation	0	0
With an outcome of death	1 (3.7)	1 (3.7)
Most common (occurred in ≥15% of patients) by any grade		
Abdominal pain	5 (18.5)	0
Decreased appetite	5 (18.5)	0
Diarrhea	5 (18.5)	0
Fatigue	5 (18.5)	0
Nausea	5 (18.5)	1 (3.7)
Vomiting	5 (18.5)	1 (3.7)

Additional safety information

- No DLTs
- Grade ≥3 irAEs of increased ALT and AST (1 event each 3.7%) both reported in a single patient (REGN3767 3 mg/kg) with liver metastases
  - irAE treated with dexamethasone, LFTs recovered to grade 1, patient remained on study, dosing not resumed
  - Patient died on Study Day 85 due to fulminant hepatic failure
    - Death considered unrelated to study drug

The rate of irAEs appears low with REGN3767 monotherapy

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; irAEs, immune-related adverse events; LFTs, liver function tests; TEAEs, treatment-emergent adverse events.

TEAEs in Patients Treated with REGN3767 + Cemiplimab

TEAEs regardless of attribution, n (%)	REGN3767 + cemiplimab (N=42)	
	Any grade	Grade ≥3
Any	38 (90.5)	19 (45.2)
Serious	9 (21.4)	9 (21.4)
Immune-related	14 (33.3)	3 (7.1)
Led to discontinuation	0	0
With an outcome of death	1 (2.4)	1 (2.4)
Most common (occurred in ≥15% of patients) by any grade		
Fatigue	16 (38.1)	1 (2.4)
Nausea	10 (23.8)	0
Vomiting	9 (21.4)	1 (2.4)
Anemia	7 (16.7)	3 (7.1)
Chills	7 (16.7)	0
Decreased appetite	7 (16.7)	2 (4.8)
Diarrhea	7 (16.7)	0
Headache	7 (16.7)	0
Hypothyroidism	7 (16.7)	1 (2.4)

Additional safety information

- DLT in one patient
  - REGN3767 3 mg/kg + cemiplimab 3 mg/kg
  - irAEs: grade 4 elevated blood CPK, associated with grade 3 myasthenia syndrome and grade 1 elevated troponin (died due to PD)
- Additional grade 3 irAE:
  - Hypothyroidism (one patient); treated with levothyroxine; off study due to PD
  - DKA (one patient); continued on study until PD
- Death
  - REGN3767 20 mg/kg + cemiplimab 350 mg
  - Died on Study Day 36 due to sepsis; unrelated to study drug

The rate of irAEs appears to reflect the safety profile of cemiplimab

CPK, creatine phosphokinase; DKA, diabetic ketoacidosis; DLT, dose-limiting toxicity; irAEs, immune-related adverse events; PD, progressive disease; TEAEs, treatment-emergent adverse events.

TEAEs in Patients who Crossed from Monotherapy to Combination therapy

TEAEs regardless of attribution, n (%)	Mono to combo (N=13)	
	Any grade	Grade ≥3
Any	11 (84.6)	6 (46.2)
Serious	3 (23.1)	3 (23.1)
Immune-related	9 (69.2)	3 (23.1)
Led to discontinuation	3 (23.1)	2 (15.4)
With an outcome of death	0	0
Most common (occurred in ≥15% of patients) by any grade		
Fatigue	5 (38.5)	0
Maculo-papular rash	5 (38.5)	2 (15.4)
Nausea	5 (38.5)	1 (7.7)
Diarrhea	4 (30.8)	0
Decreased appetite	3 (23.1)	1 (7.7)
Peripheral edema	3 (23.1)	0
Hypokalemia	2 (15.4)	2 (15.4)
Other†	2 (15.4)	0

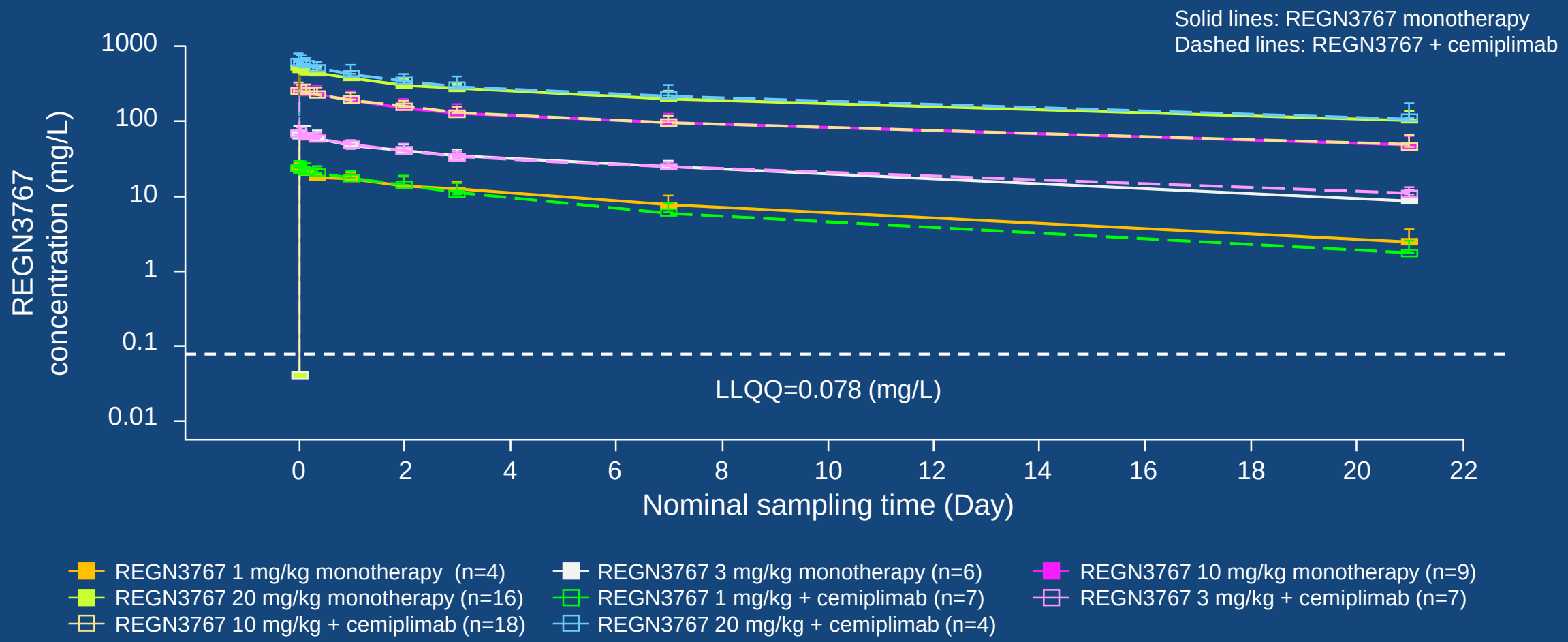
Additional safety information

- No DLTs
- Grade ≥3 irAEs:
  - Maculo-papular rash (two patients) and adrenal insufficiency and pneumonitis (one patient each)
  - Occurred after patients had been on study for >1 year
  - All resolved with treatment
  - One patient experienced both rash and pneumonitis; came off study due to pneumonitis

There were no new safety signals with REGN3767 monotherapy or in combination with cemiplimab

†Includes the following: arthralgia, cough, headache, skin infection, and vomiting; each n=2; 15.4% (any grade) and n=0 (grade ≥3).
Combo, REGN3767 + cemiplimab; DLT, dose-limiting toxicity; irAEs, immune-related adverse events; mono, REGN3767 monotherapy; TEAEs, treatment-emergent adverse events.

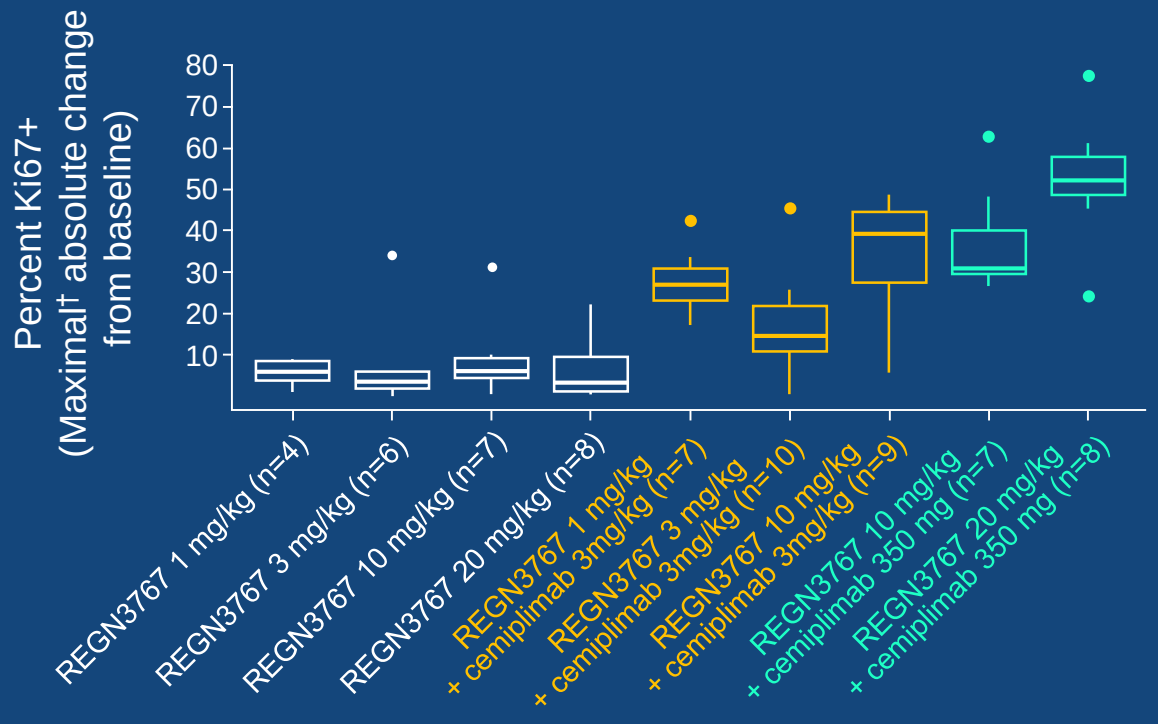
Mean (+SD) REGN3767 Concentrations Over Time After the First Monotherapy Dose of REGN3767 or REGN3767 + Cemiplimab



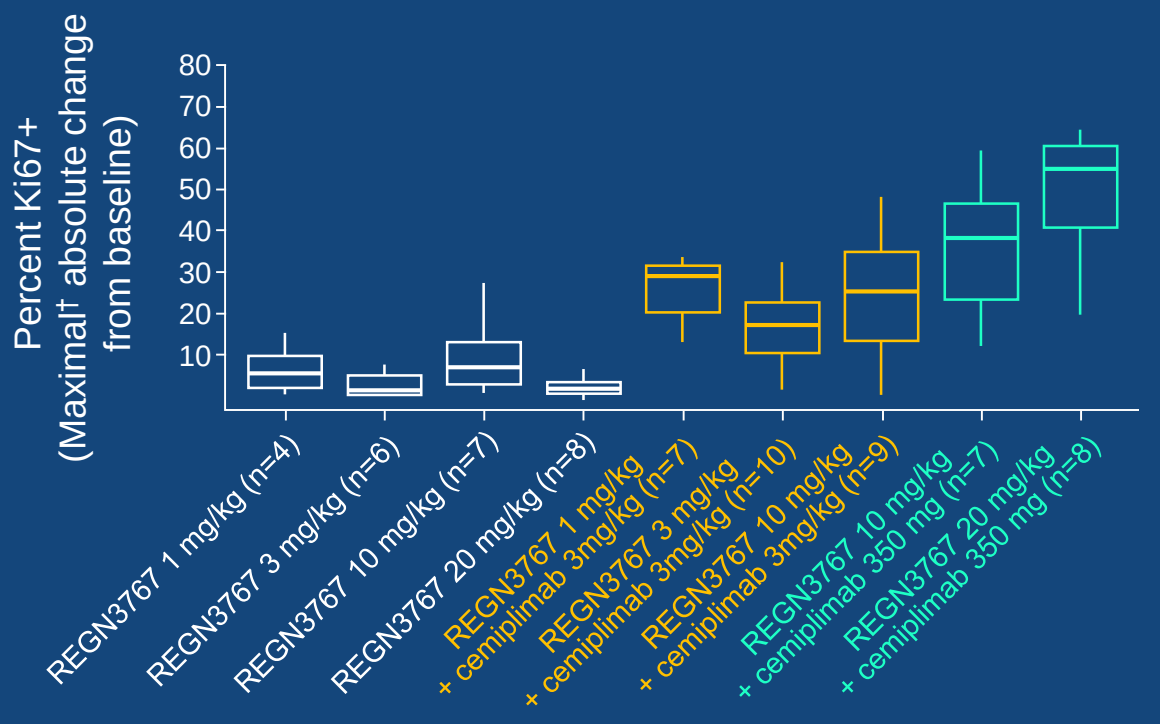
LLOQ, lower limit of quantification; SD, standard deviation.

Analysis of T Cell Subset Proliferation Following Initiation of REGN3767 Monotherapy or REGN3767 + Cemiplimab

CD4 effector memory T cells (PD-1+ subset)



CD8 effector memory T cells (PD-1+ subset)



†Maximal biomarker levels over two initial dosing cycles (4 weeks).

PD; programmed cell death.

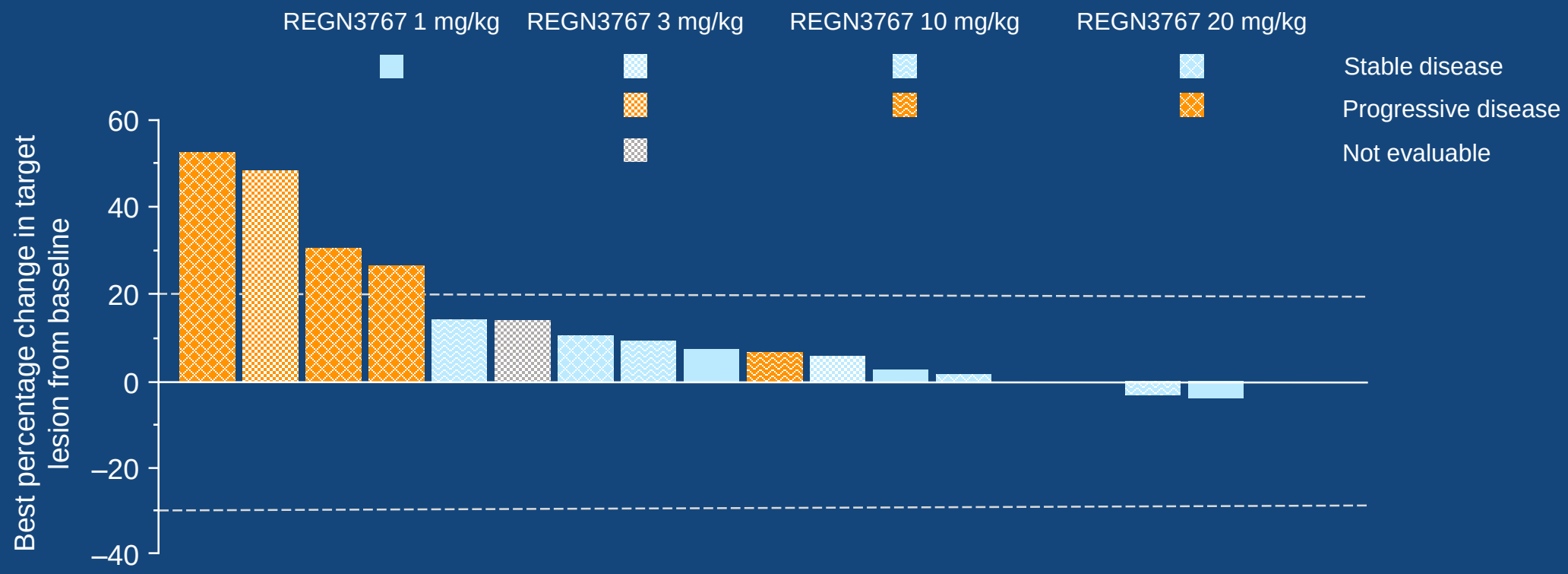
Investigator Assessed Preliminary Response Rate by RECIST 1.1

	REGN3767 monotherapy (N=25)†	REGN3767 + cemiplimab (N=42)	Mono to combo (N=12)†
Best overall response, n (%)			
Partial response	0	**2 (4.8)**	**2 (16.7)**
Stable disease	12 (48.0)	11 (26.2)	6 (50.0)
Progressive disease	7 (28.0)	24 (57.1)	3 (25.0)
Unknown‡	6 (24.0)	5 (11.9)	1 (8.3)
Range of DOR, months	NA	3.5 to 13.6+	12.5+ to 17.3+
Patients with ongoing response, n (%)§	NA	**1 (50.0)**	**2 (100)**

†Two patients in the REGN3767 monotherapy cohort and one from the mono to combo cohort were not evaluable by RECIST 1.1 as they had hematologic cancers. ‡Include patients who were unevaluable, or with tumor response not applicable, unknown, or missing. § Percentage based on the number of patients with confirmed response.
Overall response on or after radiotherapy is defined as progressive disease."+" in the DOR row denotes censored data.

Combo, REGN3767 + cemiplimab; DCR, disease control rate; DOR, duration of response; mono, REGN3767 monotherapy; NA, not applicable; RECIST, Response Evaluation Criteria In Solid Tumors.

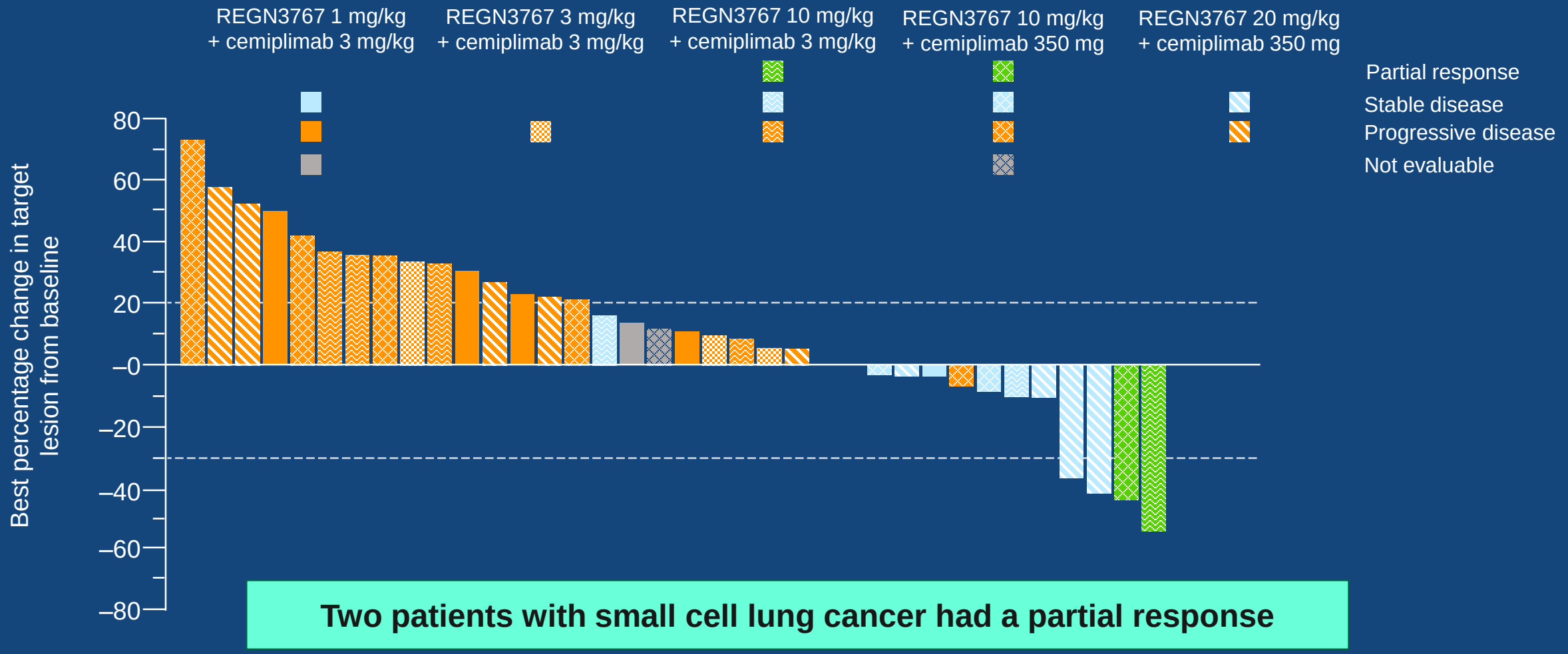
Clinical Activity in Patients Treated with REGN3767 Monotherapy



Best response with REGN3767 monotherapy: stable disease in 12 patients

Baseline sum of diameters are calculated from tumor assessment at screening. Sum of target lesion diameters following radiotherapy are set to missing. Eight patients do not appear in this figure (but are included in the investigator-assessed response analysis [slide 16]) as they did not have post-baseline tumor assessments or sum of diameters at first/second tumor assessments were missing.

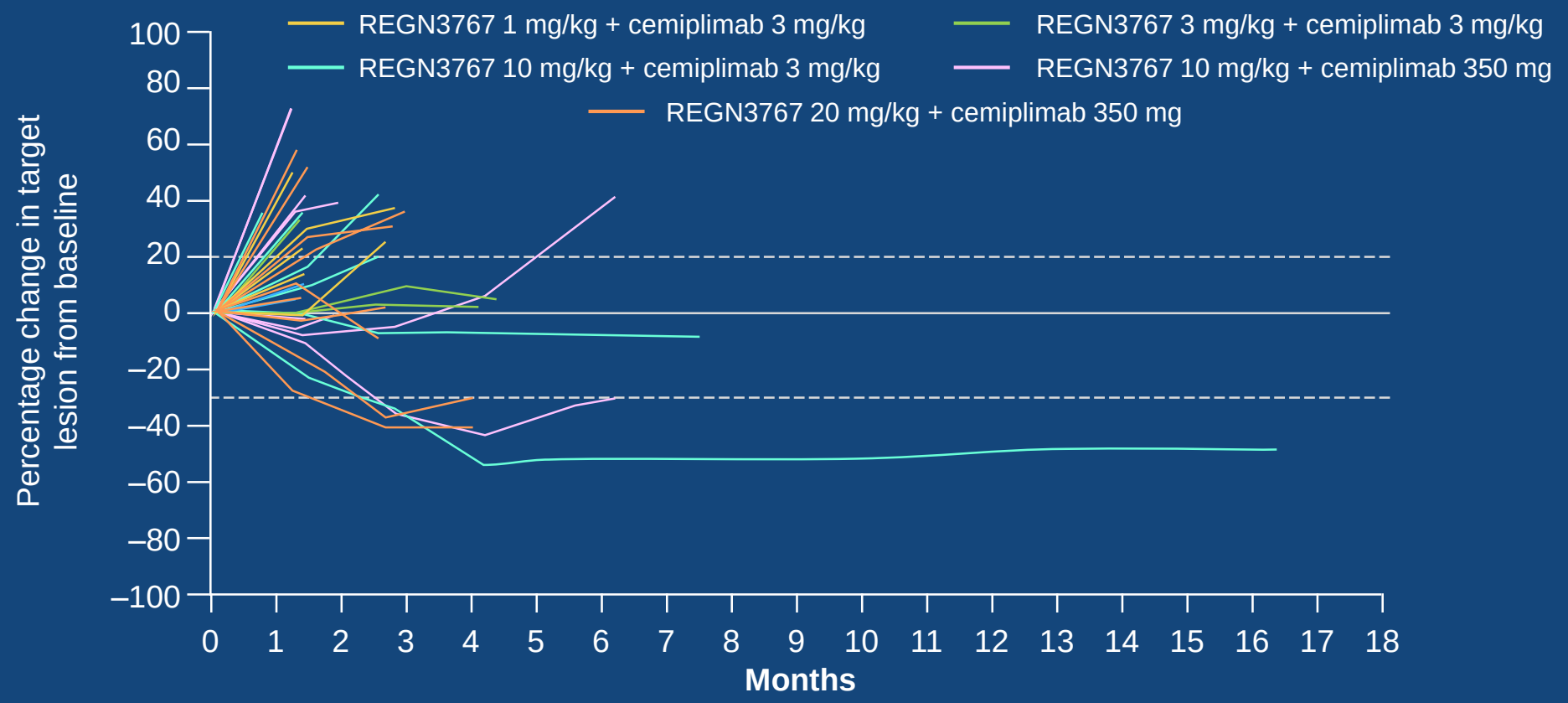
Clinical Activity in Patients Treated with REGN3767 + Cemiplimab



Two patients with small cell lung cancer had a partial response

Baseline sum of diameters are calculated from tumor assessment at screening. Sum of target lesion diameters following radiotherapy are set to missing. Six patients do not appear in this figure (but are included in the investigator-assessed response analysis [slide 16]) as they did not have post-baseline tumor assessments, were missing sum of diameters measurements at first tumor assessments, or had radiotherapy before tumor assessments (hence sum of tumor diameters were missing). Two patients with target lesion reductions ≥30% were classified as stable disease due to new lesions.

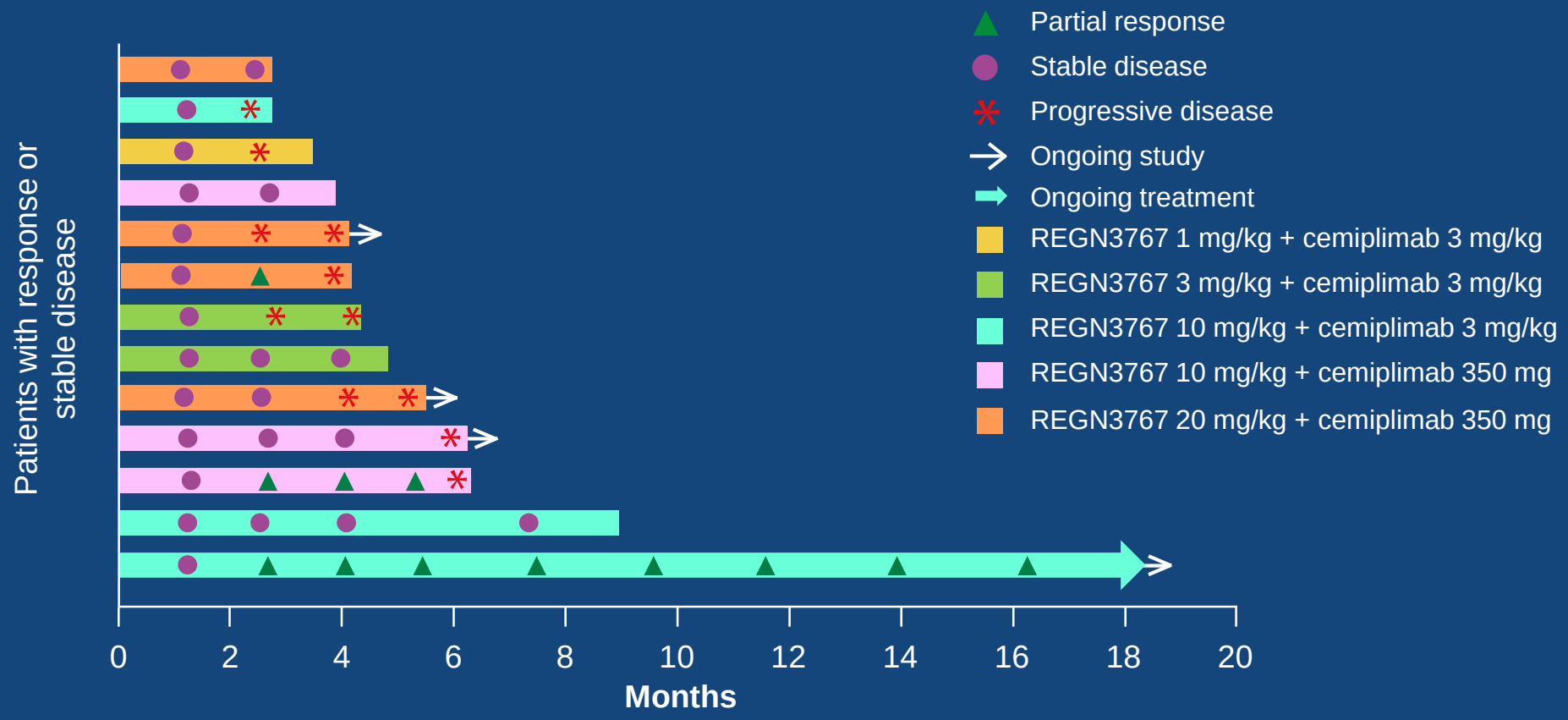
Changes in Target Lesion Over Time in Patients Treated with REGN3767 + Cemiplimab



One of the two patients with a partial response has an ongoing response (>12 months)

Baseline sum of diameters are calculated from tumor assessment at screening. Sum of diameters after radiotherapy are set to missing.

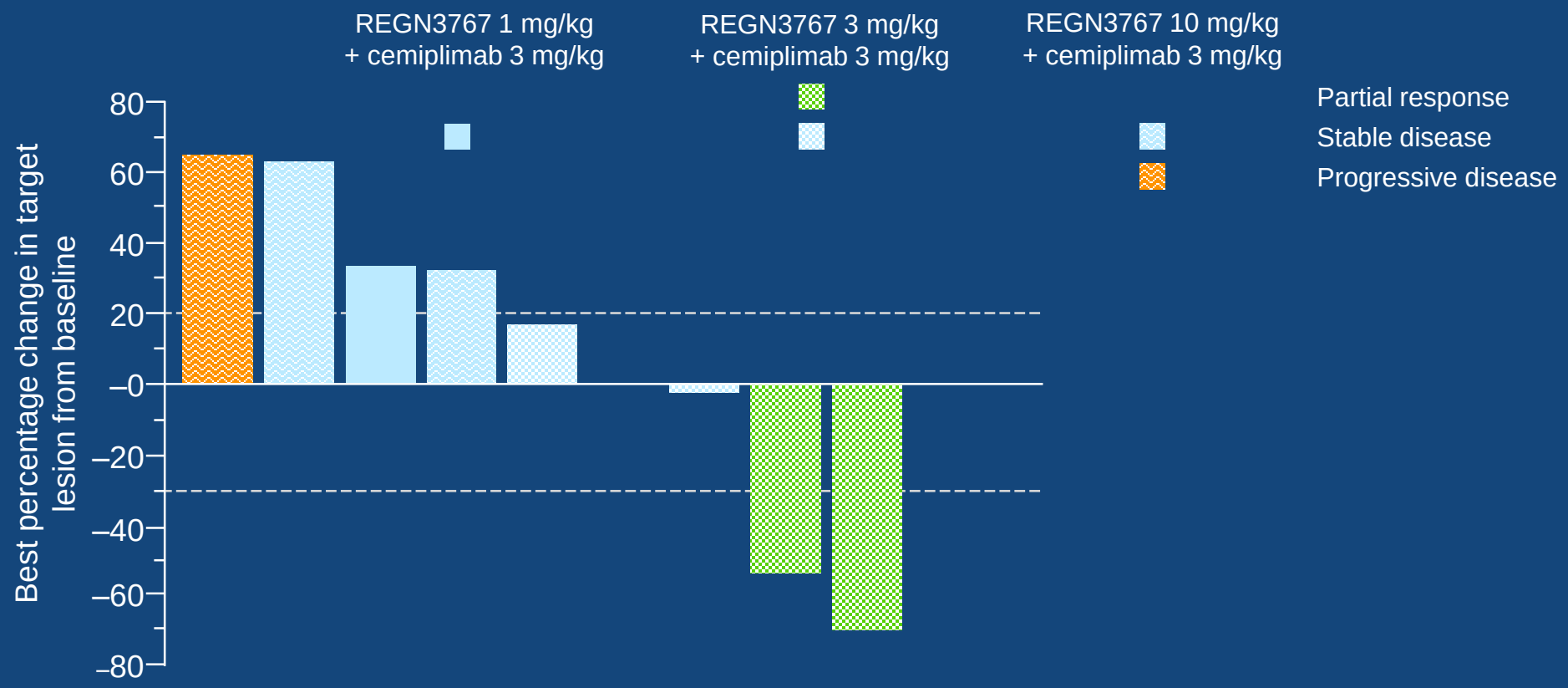
Duration of Response or Stable Disease in Patients Treated with REGN3767 + Cemiplimab



Response ongoing in one of the two patients with small cell lung cancer

Overall response on or after radiotherapy is defined as progressive disease.

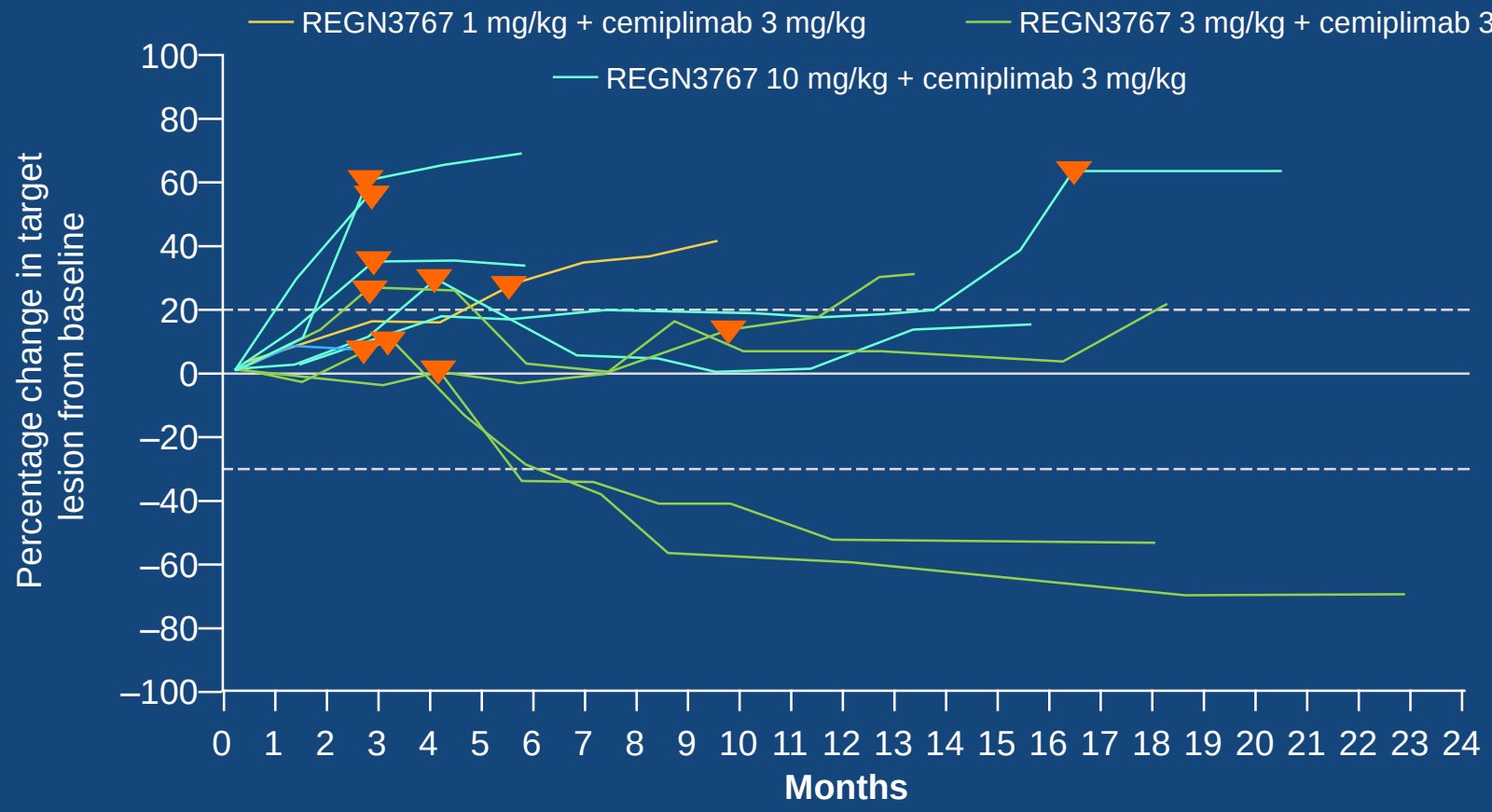
Clinical Activity in Patients Who Switched from Mono to Combo



One patient with endometrial cancer and another with cutaneous squamous cell carcinoma had a partial response

Baseline sum of diameters are calculated from tumor assessment at screening. Sum of target lesion diameters following radiotherapy are set to missing. Three patients do not appear in this figure (but are included in the investigator-assessed response analysis [slide 16]); one had no tumor measurements during the combination therapy, one had missing sum of diameters measurements at the third tumor assessment, and the third had radiotherapy before third tumor assessments (hence sum of tumor diameters was missing). Combo, REGN3767 + cemiplimab; mono, REGN3767 monotherapy.

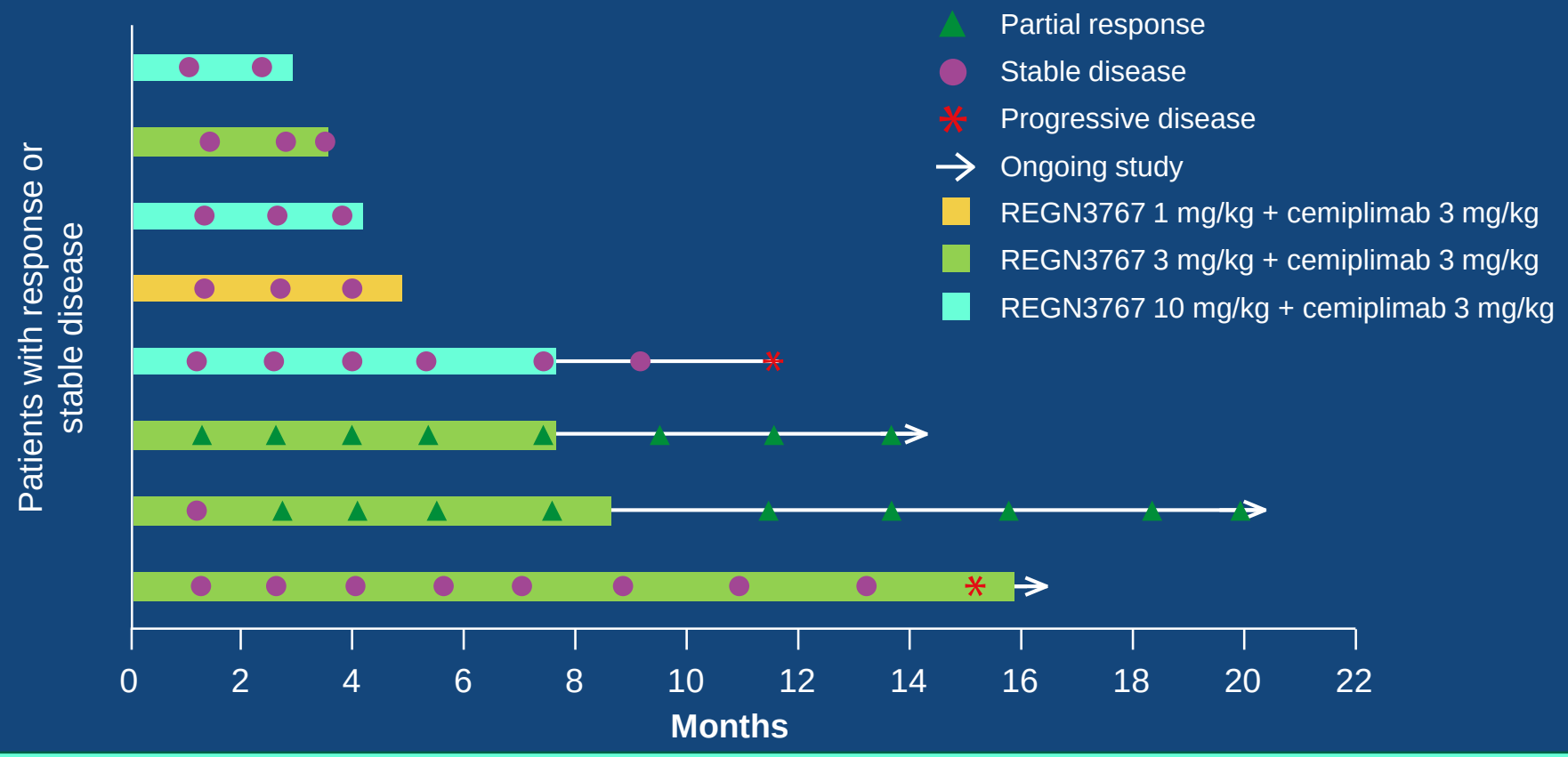
Changes in Target Lesion Over Time in Patients Who Switched from Mono to Combo



Durable responses: both patients with partial responses >1 year

Dose levels shown represent only combination dose levels; REGN3767 monotherapy doses are not depicted; orange triangles represent last tumor assessment on REGN3767 monotherapy.
Baseline sum of diameters are calculated from tumor assessment at screening. Sum of diameters after radiotherapy are set to missing. Combo, REGN3767 + cemiplimab; mono, REGN3767 monotherapy.

Duration of Response or Stable Disease in Patients Who Switched from Mono to Combo



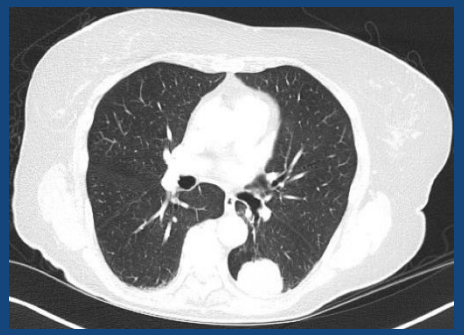
Response ongoing in both responders for 6 or 12 months after treatment was stopped

Overall response on or after radiotherapy is defined as progressive disease. Combo, REGN3767 + cemiplimab; mono, REGN3767 monotherapy.

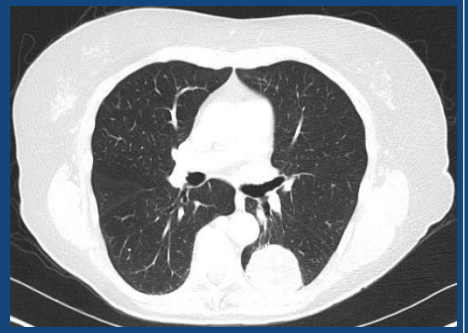
Progression on REGN3767 Monotherapy Followed by Partial Response with REGN3767 + Cemiplimab in a Patient with Endometrial Cancer

REGN3767 monotherapy

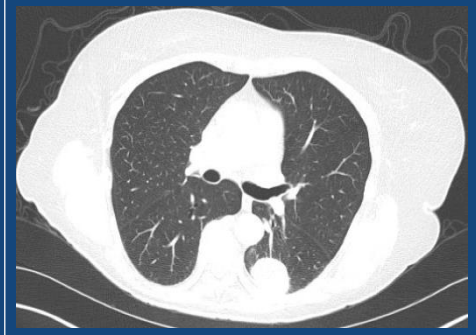
REGN3767 + cemiplimab



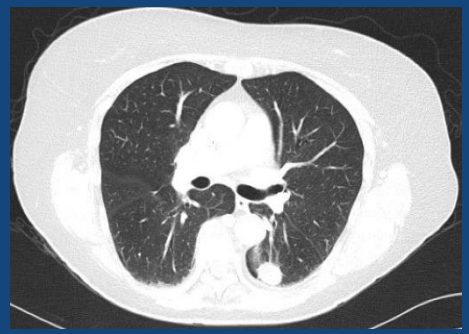
Baseline



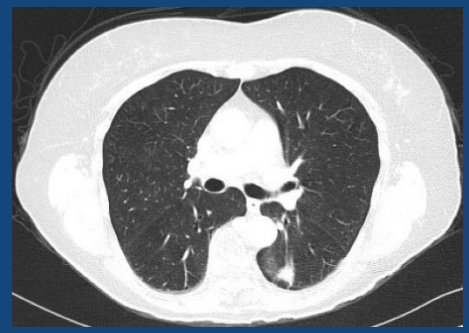
Progression after 2 cycles of treatment



PR after 2 cycles of treatment



PR at the end of treatment (12 months)

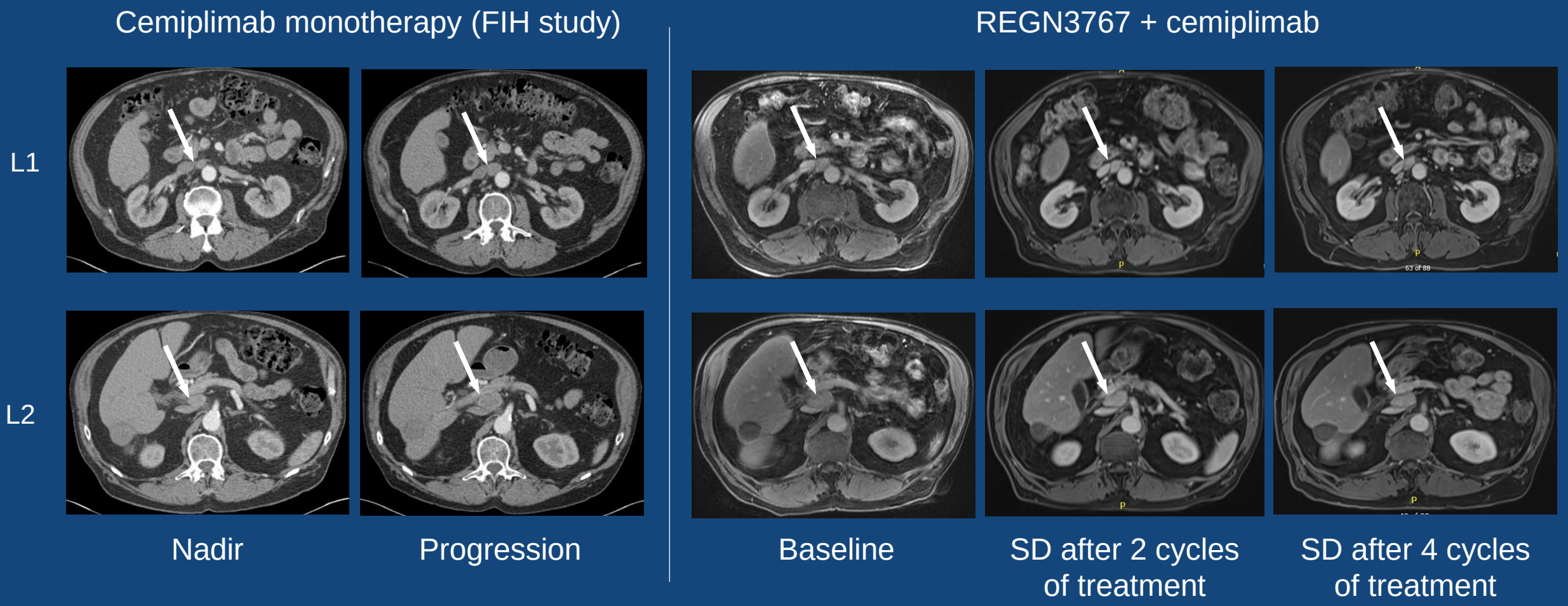


End of study (24 months)

Deepening response after treatment was stopped, ongoing for 12 months at the end of study

PR, partial response.

Progression on Cemiplimab Monotherapy (FIH Study) Followed by Tumor Shrinkage and Stable Disease with REGN3767 + Cemiplimab in a Patient with Intrahepatic Cholangiocarcinoma



FIH, first-in-human; SD, stable disease.

Summary and Conclusions

- REGN3767 + cemiplimab had an acceptable safety profile in patients with advanced malignancies
  - There were no new safety signals with REGN3767 monotherapy or REGN3767 + cemiplimab compared with those previously reported for cemiplimab and other checkpoint inhibitors
- REGN3767 concentrations increased in a dose-dependent manner and were unaffected by co-administration with cemiplimab
- There was no pharmacodynamic effect on peripheral T cells observed with REGN3767 monotherapy
- Preliminary data suggest a dose-dependent relationship between REGN3767 + cemiplimab dosing and generation of PD-1 expressing memory T cell subsets
- Some efficacy signals were detected; the dose escalation was not designed to determine efficacy of REGN3767 alone or in combination with cemiplimab
- REGN3767 20 mg/kg or 1600 mg fixed dose equivalent Q3W as monotherapy and in combination with cemiplimab were selected for further evaluation

PD, programmed cell death; Q3W, every 3 weeks.

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