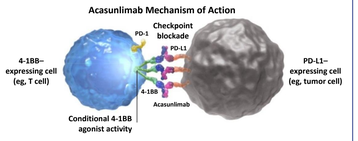
Dosing Regimen for Acasunlimab (DuoBody-PD-L1x4-1BB) in Combination With Pembrolizumab

Gaurav Bajaj,[1] Patricia Garrido Castro,[2] Enriqueta Felip,[3] Carole Helissey,[4] Dariusz Kowalski,[5] Benjamin Besse,[6] Luis Paz-Ares,[7] Michael J. Chisamore,[8] Beesan Tan,[9] Cem Gorgun,[9] Bruna de Andrade,[10] Ana Caroline Costa Sá,[1] Sri Sridhar,[1] Jordan Blum,[1] Gregg Masters,[1] Yunfei Zhou,[1] Summer Feng,[1] Craig Thalhauser,[1] Nora Pencheva,[2] Maria Jure-Kunkel,[1] Joachim Aerts[11]

[1]Genmab, Plainsboro, NJ, USA; [2]Genmab, Utrecht, Netherlands; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]Military Hospital Begin, Saint-Mandé, France; [5]The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [6]Gustave Roussy, Villejuif, France; [7]Hospital Universitario 12 de Octubre, Madrid, Spain; [8]Merck & Co., Inc., Rahway, NJ, USA; [9]BioNTech US Inc., Cambridge, MA, USA; [10]BioNTech SE, Mainz, Germany; [11]Erasmus MC, Rotterdam, Netherlands

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024
SAN DIEGO, CA USA

Background



- Acasunlimab (DuoBody®-PD-L1×4-1BB) is an investigational bispecific antibody immunotherapy designed to elicit an antitumor immune response via conditional 4-1BB activation that is strictly dependent on simultaneous PD-L1 binding[1]
- The PD-L1–specific arm of acasunlimab also functions as a classical CPI by blocking the PD-1/PD-L1 axis irrespective of 4-1BB binding
- A semi-mechanistic PK/PD model was used to determine acasunlimab 100 mg Q3W as the expansion dose, allowing optimum trimer (PD-L1:acasunlimab:4-1BB) formation and 4-1BB activation, with partial PD-L1 blockade[2]
- In the GCT1046-01 trial (NCT03917381), acasunlimab 100 mg Q3W monotherapy resulted in objective clinical responses in patients with R/R mNSCLC who had experienced progression on anti-PD-(L)1– containing therapy[3]
  - However, responses were not sufficiently durable, potentially due to the regimen favoring peak trimer formation at the expense of partial PD-L1 receptor occupancy
- Preclinical and PK/PD findings support combining acasunlimab with pembro for more complete blockade of PD-1 signaling[4]
- Here we describe translational, PK/PD, and E–R results that support the Q6W combo of acasunlimab with pembro for more favorable tolerability and a more durable clinical response[5]

Hypothesis

- A more complete blockade of the PD-1/PD-L1/PD-L2 axis, together with optimal trimer formation, may improve durability of response
- Intermittent 4-1BB stimulation resulting from Q6W dosing may reduce chronic T-cell stimulation that can lead to T-cell dysfunction

▶ A treatment regimen with less frequent acasunlimab dosing may allow for T-cell rest and resetting of T-cell function to enhance and prolong antitumor activity

References

1. Muik A, et al. SITC 2020. Poster 561.
2. Bajaj G, et al. *J Immunother Cancer*. 2021;9:A821.
3. Garralda E, et al. SITC 2020. Poster 412.
4. Capelo M, et al. *Cancer Res*. 2023;83(suppl 7):3283.
5. Aerts J, et al. *J Clin Oncol*. 2024;42(suppl 16):2533.
6. Glez-Vaz J, et al. *J Immunother Cancer*. 2022;10:e003532.
7. Sanmamed MF, et al. *Cancer Discov*. 2021;11:1700-15.

Abbreviations

AE, adverse event; $C_{avg\text{-}6wk}$, average exposure over first 6 weeks; CI, confidence interval; combo, combination regimen; CPI, checkpoint inhibitor; d, day(s); DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; E–R, exposure–response; FC, fold change; IHC, immunohistochemistry; IQR, interquartile range; IS, immunological synapse; IV, intravenous; mNSCLC, metastatic non-small cell lung cancer; NR, not reached; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamic; PD-1, programmed death protein 1; PD-L1, programmed death protein ligand 1; PD-L2, programmed death protein ligand 2; pembro, pembrolizumab; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; Q6W, every 6 weeks; QSP, quantitative systems pharmacology; RECIST, Response Evaluation Criteria in Solid Tumours; R/R, relapsed/refractory; s4-1BB, soluble 4-1BB; TIM3, T-cell immunoglobulin mucin family member 3; TRAE, treatment-related adverse event; wk, week(s).

Acknowledgments

This research was sponsored by Genmab A/S and BioNTech SE and in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Acasunlimab is a proprietary bispecific antibody created using Genmab's DuoBody® technology, jointly under development by Genmab and BioNTech. Graphical support was provided by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, and funded by Genmab.

GCT1046-04 Study Design

Phase 2, multicenter, randomized, open-label trial evaluating acasunlimab as monotherapy and in combination with pembro in patients with R/R mNSCLC after progression on standard-of-care therapy with an anti-PD-(L)1 treatment

Key Inclusion Criteria

- Age ≥18 years
- mNSCLC with disease progression after ≥1 prior anti-PD-(L)1 treatment
- Confirmed PD-L1 expression[a]
- ECOG PS 0–1
- Adequate hematologic and renal/hepatic function

RANDOMIZED

Arm A:	Arm B:	Arm C:
Acasunlimab 100 mg IV Q3W cycles 1–2, then 500 mg IV Q6W	Acasunlimab 100 mg IV + pembro 200 mg IV Q3W	Acasunlimab 100 mg IV + pembro 400 mg IV Q6W

Primary endpoint: ORR by RECIST v1.1 per investigator[b]
Key secondary endpoints: DOR, PFS, OS, AEs
Selected exploratory endpoints: PK, biomarkers

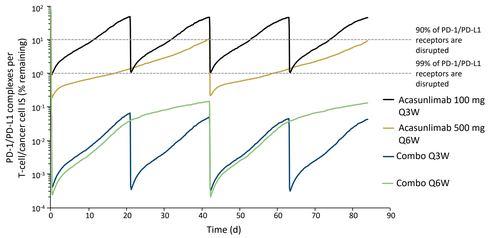
NCT05117242.
[a]Prior to cycle 1 day 1 with PD-L1 expression in ≥1% of tumor cells by a sponsor-designated central laboratory using the Dako PD-L1 IHC 22C3 pharmDx assay or by local assessment. [b]Efficacy was evaluated in all patients with centrally confirmed PD-L1[+] status.

Results

Model-Predicted Disruption of PD-1/PD-L1 Complexes With Acasunlimab Monotherapy or in Combination With Pembro

- QSP model predictions show that combining acasunlimab at a dose that favors optimum 4-1BB conditional agonism with an agent that fully blocks the PD-1 interaction with both PD-L1 and PD-L2 may allow for more effective concurrent targeting of the 4-1BB and PD-1 pathways

Figure 1A. QSP Model-Predicted Disruption of PD-1/PD-L1 Complexes

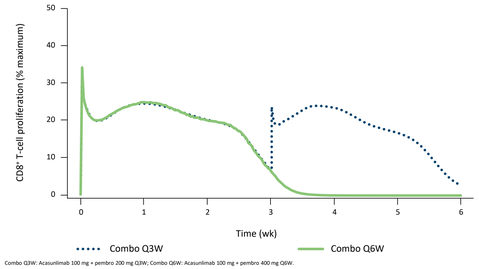


Combo Q3W: Acasunlimab 100 mg + pembro 200 mg Q3W; Combo Q6W: Acasunlimab 100 mg + pembro 400 mg Q6W.

Model-Predicted Proliferation of CD8⁺ T Cells With Acasunlimab Dosing Regimens

- QSP model-based predictions show that 4-1BB–induced CD8⁺ T-cell proliferation with acasunlimab 100 mg is sustained for approximately 3 weeks before returning to baseline as acasunlimab clears from the tumor microenvironment

Figure 1B. QSP Model-Predicted Time Course of 4-1BB–Mediated CD8⁺ T-Cell Proliferation With Acasunlimab



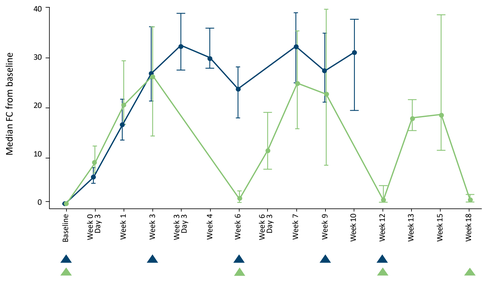
Combo Q3W: Acasunlimab 100 mg + pembro 200 mg Q3W; Combo Q6W: Acasunlimab 100 mg + pembro 400 mg Q6W.

Clinical PD Analyses

Less Frequent Dosing Leads to Intermittent 4-1BB Target Engagement

- Acasunlimab + pembro Q6W treatment showed intermittent induction of s4-1BB (a surrogate for target engagement[6]), allowing a T-cell resting period, compared with sustained induction with the Q3W combo

Figure 2A. On-Treatment Induction of Peripheral s4-1BB



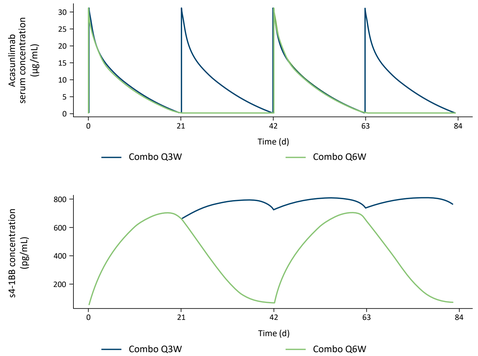
Q3W n =	33	31	29	25	26	25	20	-	16	17	14	-	-	-	-
Q6W n =	43	38	39	36	-	-	27	22	24	20	-	13	13	11	6

Combo Q3W: Acasunlimab 100 mg + pembro 200 mg Q3W; Combo Q6W: Acasunlimab 100 mg + pembro 400 mg Q6W.
Dots represent aggregated values at prespecified sampling time points; bars represent IQR.
Specific post-treatment sampling time points differ between arms due to dosing schedules, and s4-1BB levels were imputed (combo Q3W: week 6 day 3; combo Q6W: week 3 day 3, week 4, week 10).
s4-1BB data cutoff: June 27, 2024.

Model-Predicted PK and s4-1BB Levels With Acasunlimab Dosing Regimens

- A PK/PD model was developed to describe the kinetics of s4-1BB levels after acasunlimab administration in combination with pembro; the model predictions for PK and s4-1BB levels at 100 mg Q3W and Q6W were in line with observed clinical PK and PD data

Figure 2B. Model-Predicted Acasunlimab PK and s4-1BB Levels

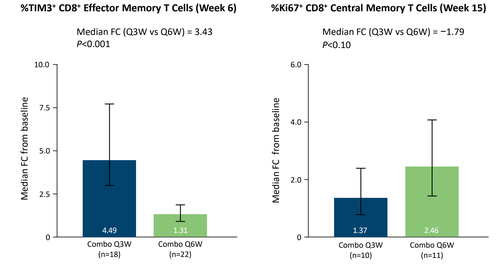


Combo Q3W: Acasunlimab 100 mg + pembro 200 mg Q3W; Combo Q6W: Acasunlimab 100 mg + pembro 400 mg Q6W.

Intermittent Target Engagement With Q6W Regimen Results in T-Cell Phenotype Associated With Improved Functionality

- Compared with the Q3W combo, patients treated with the Q6W combo had:
  - >3-fold lower induction of CD8⁺ T cells expressing co-inhibitory marker TIM3 (implicated in T-cell dysfunction[7])
  - Greater proliferation of CD8⁺ memory T cells in later cycles

Figure 3. On-Treatment Modulation of T-Cell Phenotype



Combo Q3W: Acasunlimab 100 mg + pembro 200 mg Q3W; Combo Q6W: Acasunlimab 100 mg + pembro 400 mg Q6W.
PBMC flow cytometry data cutoff: June 27, 2024. Bars represent IQR.

Exposure–Response (E–R) Analyses

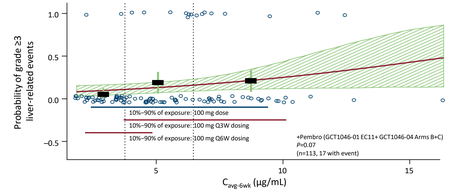
E–R Analysis of Efficacy (ORR)

- An E–R analysis of efficacy with respect to response rate was conducted in patients with centrally confirmed PD-L1⁺ status treated with the acasunlimab + pembro combo (Q3W and Q6W) in the GCT1046-04 trial
- A higher unconfirmed ORR was observed in patients treated with the acasunlimab + pembro Q6W combo (8/27 patients [29.6%]) in comparison with the Q3W combo (5/24 patients [20.8%])[5]
- Lower average exposures ($C_{avg\text{-}6wk}$) with Q6W dosing of acasunlimab + pembro in Arm C have comparable probability of response with respect to Q3W dosing in Arm B based on the E–R analysis

E–R Analysis of Safety

- E–R analysis of safety was conducted with respect to grade ≥3 liver-related events in patients with NSCLC who received an acasunlimab + pembro combo in expansion cohort 11 (EC11; Q3W or Q6W) of the GCT1046-01 trial (NCT03917381) or in Arm B (Q3W) or C (Q6W) of the GCT1046-04 trial (NCT05117242)
- A higher risk of grade ≥3 liver-related events was observed with increasing acasunlimab exposures ($C_{avg\text{-}6wk}$) evaluated at 100 mg Q3W and Q6W in combination with pembro, indicating a higher probability of grade ≥3 liver-related events with Q3W dosing compared with Q6W dosing

Figure 4. Model-Predicted Relationship Between Acasunlimab Exposure and Risk of Grade ≥3 Liver-Related Events



Time to Resolution of Liver-Related AEs in GCT1046-04

- Additional analyses showed faster resolution of grade ≥3 liver-related AEs in patients treated with acasunlimab + pembro Q6W in the GCT1046-04 trial

	Combo Q6W	Combo Q3W
Grade ≥3 liver-related TRAEs, % of patients	12.2	16.7
Time to resolution, days (95% CI)	10.0 (5.0–NR)	15 (8.0–NR)

Conclusions

- Clinical PD findings, QSP, PK/PD, and E–R modeling together favor Arm C (Q6W dosing) for acasunlimab + pembro
- Less frequent Q6W dosing may better maintain T-cell functionality over time by reducing chronic 4-1BB stimulation, allowing for periods of T-cell rest and resulting in improved tolerability and durability of clinical responses
  - Acasunlimab + pembro Q6W leads to intermittent 4-1BB target engagement, resulting in improved T-cell functionality compared with the Q3W combo, as evidenced by lower induction of TIM3-expressing CD8⁺ T cells and greater proliferation of memory CD8⁺ T cells in later cycles
  - Model predictions align with observed data showing intermittent target engagement and T-cell proliferation
  - Arm C with Q6W dosing of acasunlimab + pembro has comparable probability of response with respect to Arm B with Q3W dosing, and better survival outcome in PD-L1⁺ patients[5]
- Safety analyses:
  - Increasing acasunlimab exposures (evaluated at 100 mg Q3W and Q6W) in combination with pembro are associated with increased risk of grade ≥3 liver-related events in E–R analyses
  - Faster resolution of grade ≥3 liver-related AEs was observed with Q6W dosing in the GCT1046-04 trial

Presented at the 2024 World Conference on Lung Cancer (WCLC); September 7–10, 2024; San Diego, CA