

Initial results from a Phase 1 study of an A2a receptor antagonist, administered as monotherapy and in combination with anti-PD1 therapy in patients with advanced non-small cell lung cancer

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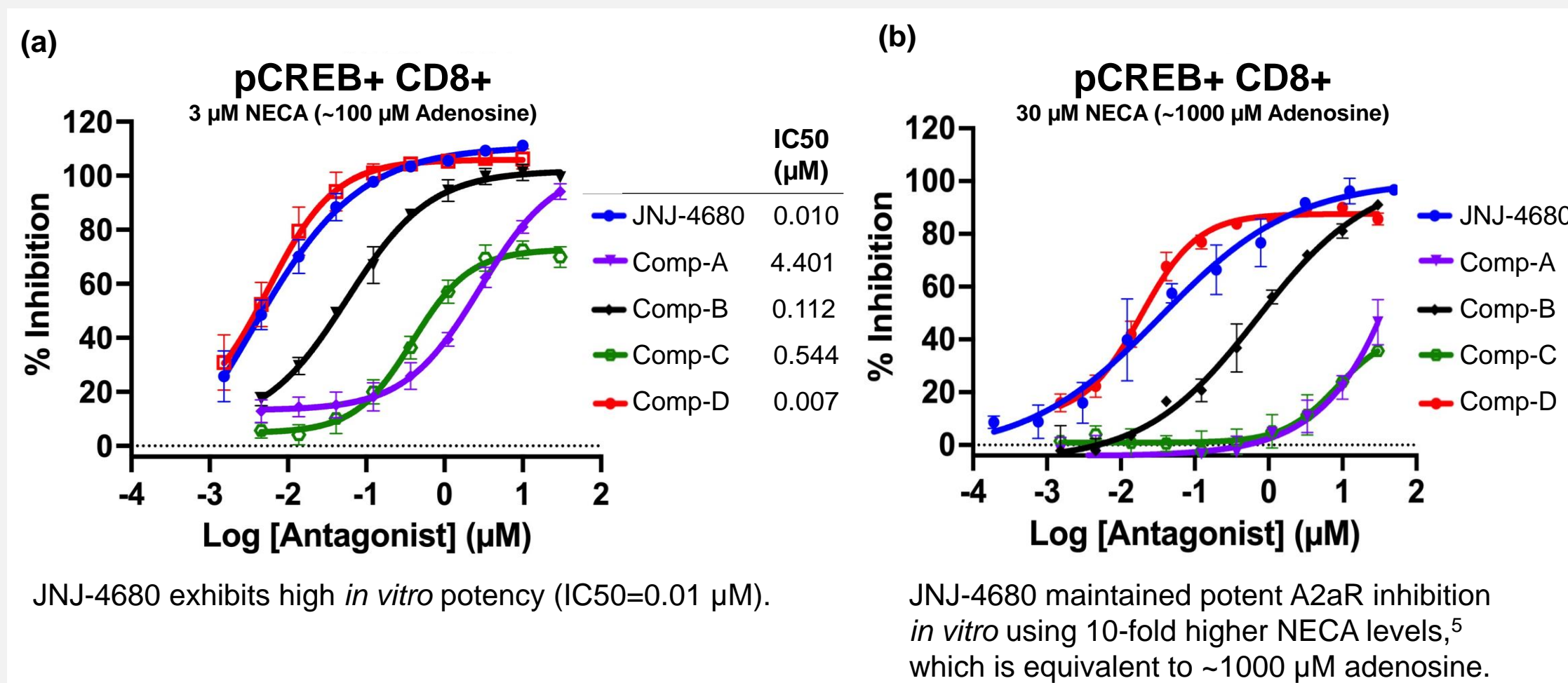
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BACKGROUND

- IO is a vital treatment option for patients with NSCLC; however, most do not achieve durable responses with anti-PD1.¹
- Adenosine is an immunosuppressive molecule that can limit the activity of anti-PD1 by inhibiting both adaptive and innate immune cells through A2aRs.²
- Effective inhibition of adenosine is hypothesized to be synergistic with anti-PD1 therapies.³
- JNJ-86974680 (JNJ-4680) is a small molecule selective A2aR antagonist that inhibits adenosine signaling (Fig. 1).

Fig. 1. Potency of A2aR antagonists assessed by inhibition of pCREB in human CD8+ T cells in response to NECA treatment⁴ would indicate adenosine analogue NECA



JNJ-4680 exhibits high *in vitro* potency (IC50=0.01 μM).

JNJ-4680 maintained potent A2aR inhibition *in vitro* using 10-fold higher NECA levels,⁵ which is equivalent to ~1000 μM adenosine.

Note: Comp-A to -D are other A2aR inhibitors that have been used in human trials.

- Study NCT06116786 is a 2-part, *first-in-human* Phase 1 study, evaluating the safety, PK, and preliminary efficacy of JNJ-4680 as a monotherapy, and in combination with cetrelimab, an investigational anti-PD1 monoclonal antibody, in pts with NSCLC who progressed after SoC.

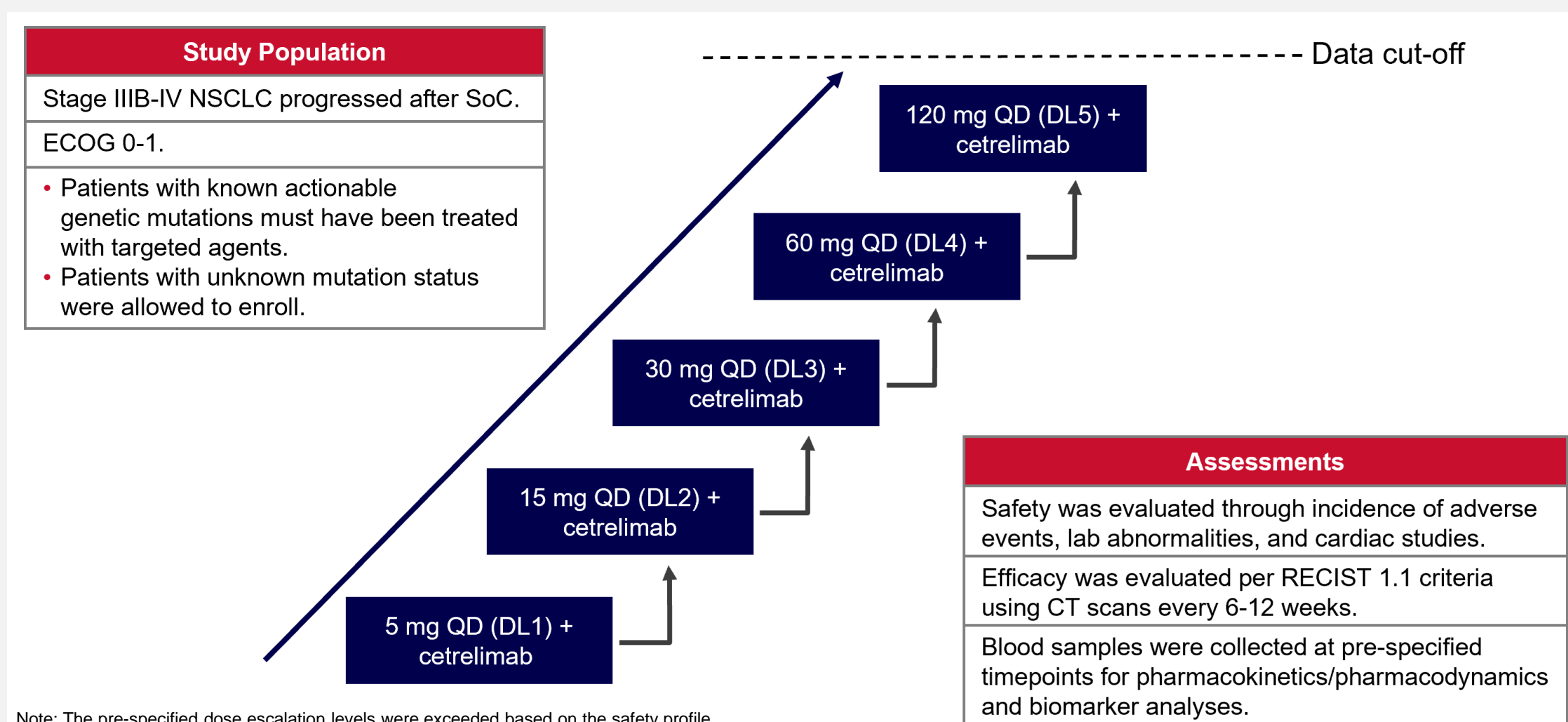
- Here, we present the initial results from Part 1 (dose escalation) of the study.

METHODS

Study Design

- Part 1 (dose escalation) utilized sequential DLT periods, to evaluate JNJ-4680 QD safety first as monotherapy, and then in combination with cetrelimab (Fig. 2).

Fig. 2. Part 1 (Dose Escalation) - JNJ-4680 monotherapy and in combination with anti-PD1 (cetrelimab)



- Following the DLT periods, treatment continued as combination therapy.

- A validated pCREB inhibition assay, in which pCREB was induced by NECA *ex vivo*, was used to detect A2aR target engagement by JNJ-4680. All on-treatment samples were collected at pre-dose except for Cycle 1, Day 1 (2 h).

- Protocol allowed for intraparticipant dose escalation.

Objectives/Endpoints

- Primary:** AEs and DLTs; **Secondary:** PK

ABBREVIATIONS
A2aR, A2a receptor; AE, adverse event; anti-PD-1, anti-programmed cell death-1; AUC, area under the curve; BOR, best overall response; CET, cetrelimab; C_{max}, maximum concentration; CRF, case report form; CT, computed tomography; D/C, discontinued; DCO, data cut-off; DE, disease evaluation; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; mg, milligram; IO, immunotherapy; MTD, maximum tolerated dose; NECA, 5'-N-ethylcarboxamidoadenosine; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed death ligand 1; pCREB, CREB phosphorylation; PK, pharmacokinetics; p(±), participant(s); QD, once a day; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SoC, standard of care; TEAE, treatment-emergent adverse event; T_{max}, time to maximum concentration; TME, tumor microenvironment; W/D, withdrawal.

Baseline Demographics and Clinical Characteristics

- As of the DCO (3 February 2025), 32 pts were enrolled, with a median age of 65.5 years (range: 40–88 years) and most were male (78.1%).
- 19 (61.3%) pts were PD-L1 positive and 10 (32.3%) were negative.
- Pts without actionable mutations were required to have prior anti-PD-1/L1 therapy.
- Other pt demographics and characteristics are shown in Table 1.

Table 1. Baseline demographics and clinical characteristics

Variables	Overall
All, n (%)	32 (100.0)
Age, median (range)	65.5 (40–88)
Gender, n (%)	
Male	25 (78.1)
Female	7 (21.9)
NSCLC subtype, n (%)	
Adenocarcinoma	22 (68.8)
Squamous cell carcinoma	9 (28.1)
Others	1 (3.1)
PD-L1 expression status, n (%)	N=31
Positive	19 (61.3)
Negative	10 (32.3)
Not evaluable	2 (6.5)
Prior lines of therapies, n (%)	
<3	19 (59.4)
≥3	13 (40.6)

Safety

- Overall summary of TEAEs in the study is shown in Table 2.
- At the time of DCO, there were no DLTs.
- Of the 32 pts, 31 (96.9%) had ≥1 TEAE and 18 (56.3%) had ≥1 drug-related TEAE reported.
- 7 (21.9%) and 3 (9.4%) had ≥1 Grade 3 or 4 event, respectively. None were reported as drug-related.

Table 2. Overall summary of TEAEs

	JNJ-4680 5 mg QD + CET	JNJ-4680 15 mg QD + CET	JNJ-4680 30 mg QD + CET	JNJ-4680 60 mg QD + CET	JNJ-4680 120 mg QD + CET	Total
Analysis set: All Treated, n	4	7	6	6	9	32
Pts with ≥1 TEAE, n (%)	4 (100.0)	7 (100.0)	5 (83.3)	6 (100.0)	9 (100.0)	31 (96.9)
Drug-related ^a	2 (50.0)	4 (57.1)	4 (66.7)	2 (33.3)	6 (66.7)	18 (56.3)
Maximum toxicity grade						
Grade 1	0	0	1 (16.7)	2 (33.3)	3 (33.3)	6 (18.8)
Grade 2	2 (50.0)	5 (71.4)	3 (50.0)	2 (33.3)	3 (33.3)	15 (46.9)
Grade 3	2 (50.0)	2 (28.6)	1 (16.7)	0	2 (22.2)	7 (21.9)
Grade 4	0	0	0	2 (33.3)	1 (11.1)	3 (9.4)
Grade 5	0	0	0	0	0	0
Serious TEAE	2 (50.0)	1 (14.3)	1 (16.7)	2 (33.3)	3 (33.3)	9 (28.1)
Drug-related ^a	0	0	0	0	0	0
TEAEs leading to treatment discontinuation ^b	0	0	0	0	0	0
Drug-related ^a	0	0	0	0	0	0
TEAEs leading to death ^c	0	0	0	0	0	0

^aTEAE related to any study treatment. ^bTreatment discontinuation due to AE on the end of treatment CRF page. ^cDeath due to AE on the AE CRF page. AEs are reported using MedDRA latest Version 27.1. Percentages are calculated with the number of pts in each group as denominator.

RESULTS

- The most frequently reported TEAEs were nausea (n=8, 25%), abdominal pain, cough, and vomiting (n=7, 21.9%, each) (Table 3).
- None of the reported Preferred Terms occurred in >25% of pts; all but 2 TEAEs were Grade 1/2.
- 2 Grade 3 TEAEs (Anemia and Fall) occurred in individual pts, both were reported as unrelated to the study drugs.

Table 3. TEAEs with incidence of ≥10% in 120 mg combination cohort and all treatment groups

	JNJ-4680 120 mg QD + CET		Total	
	Total	Grade 3/4	Total	Grade 3/4
Analysis set: All Treated, n	9	0	32	0
Pts with ≥1 TEAE, n (%)	9 (100.0)	0	31 (96.9)	0
Preferred Term				
Nausea	3 (33.3)	0	8 (25.0)	0
Abdominal pain	1 (11.1)	0	7 (21.9)	0
Cough	2 (22.2)	0	7 (21.9)	0
Vomiting	3 (33.3)	0	7 (21.9)	0
Fatigue	1 (11.1)	0	6 (18.8)	0
Diarrhea	3 (33.3)	0	5 (15.6)	0
Dizziness	1 (11.1)	0	5 (15.6)	0
Headache	1 (11.1)	0	5 (15.6)	0
Insomnia	2 (22.2)	0	5 (15.6)	0
Anemia	1 (11.1)	0	4 (12.5)	1 (3.1)*
Aspartate aminotransferase increased	1 (11.1)	0	4 (12.5)	0
Constipation	1 (11.1)	0	4 (12.5)	0
Fall	1 (11.1)	1 (11.1)*	4 (12.5)	1 (3.1)*
Pruritus	1 (11.1)	0	4 (12.5)	0

*Anemia and Fall were Grade 3 events.

Preferred Terms are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the pt with the worst toxicity is used. AEs are reported using MedDRA latest Version 27.1.

Pharmacokinetics/Pharmacodynamics

- Plasma concentrations increased post-dose reaching peak concentrations (median T_{max} 1–2 h) within each dose level on Days 1 and 8 of Cycle 1 (Fig. 3).

Fig. 3. Mean JNJ-4680 plasma concentration over time on Cycle 1, Day 8

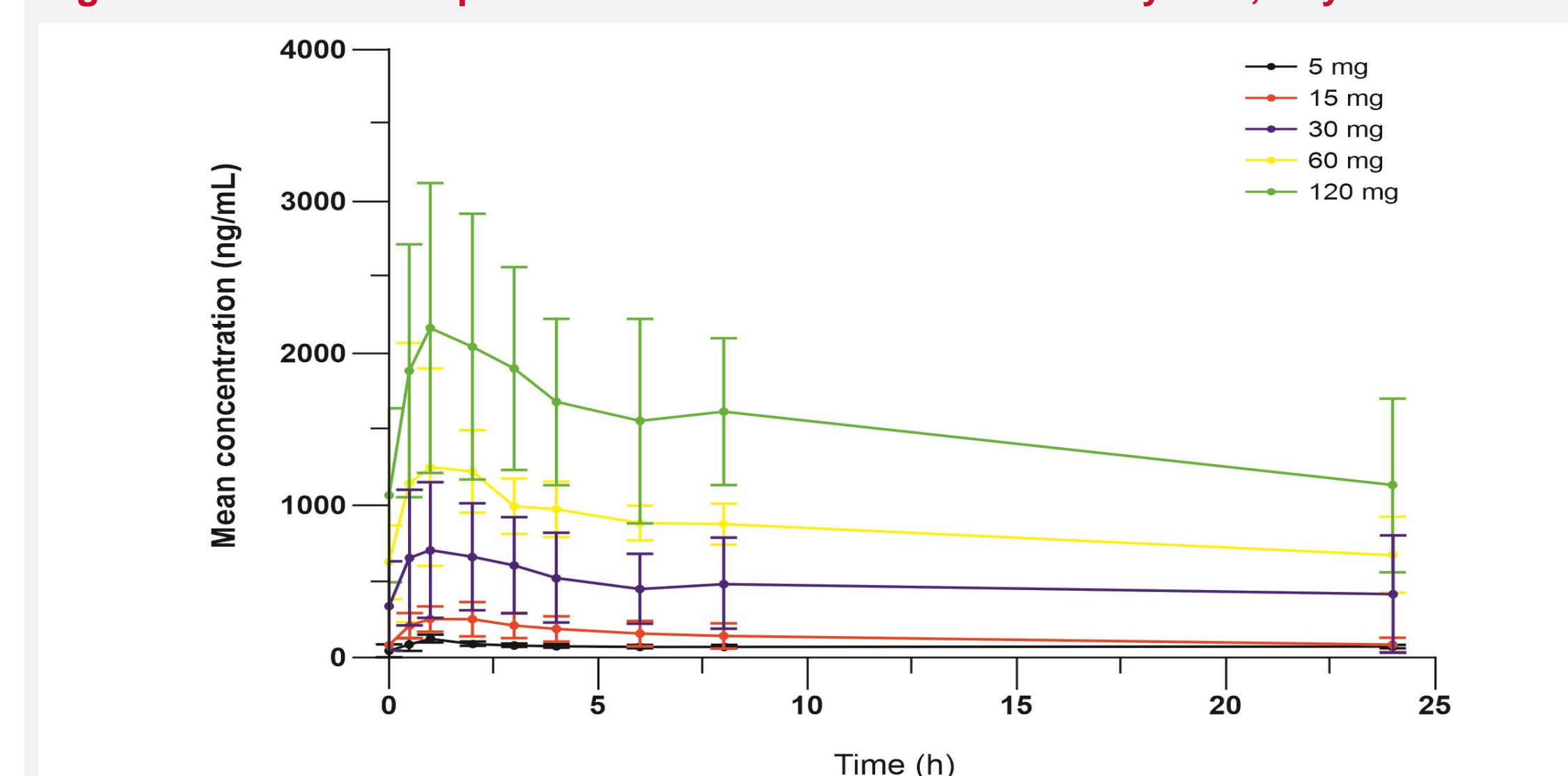
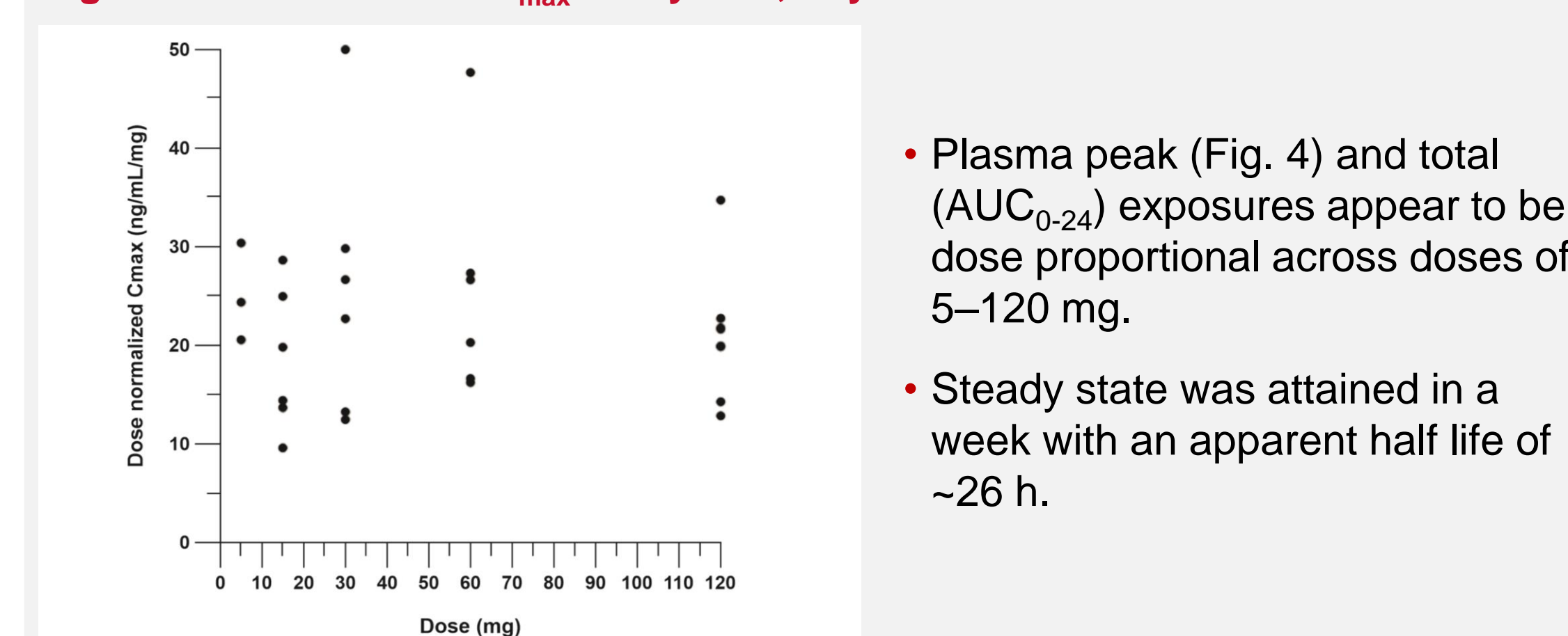


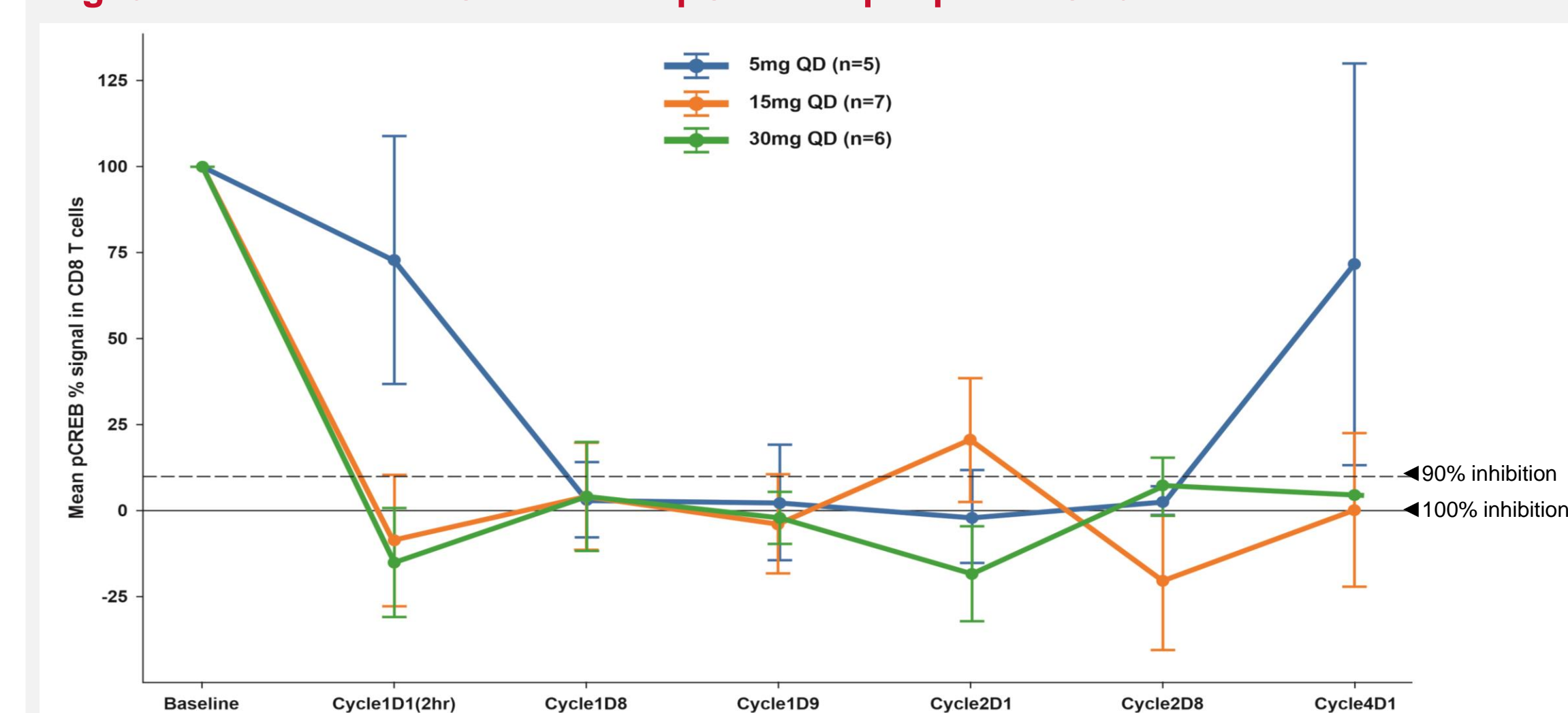
Fig. 4. Dose normalized C_{max} on Cycle 1, Day 8



- Plasma peak (Fig. 4) and total (AUC₀₋₂₄) exposures appear to be dose proportional across doses of 5–120 mg.
- Steady state was attained in a week with an apparent half life of ~26 h.

- >90% A2aR inhibition was observed at trough concentrations at the first 3 dose levels (5 mg, 15mg, 30 mg) in peripheral CD8+ T cells (Fig. 5).

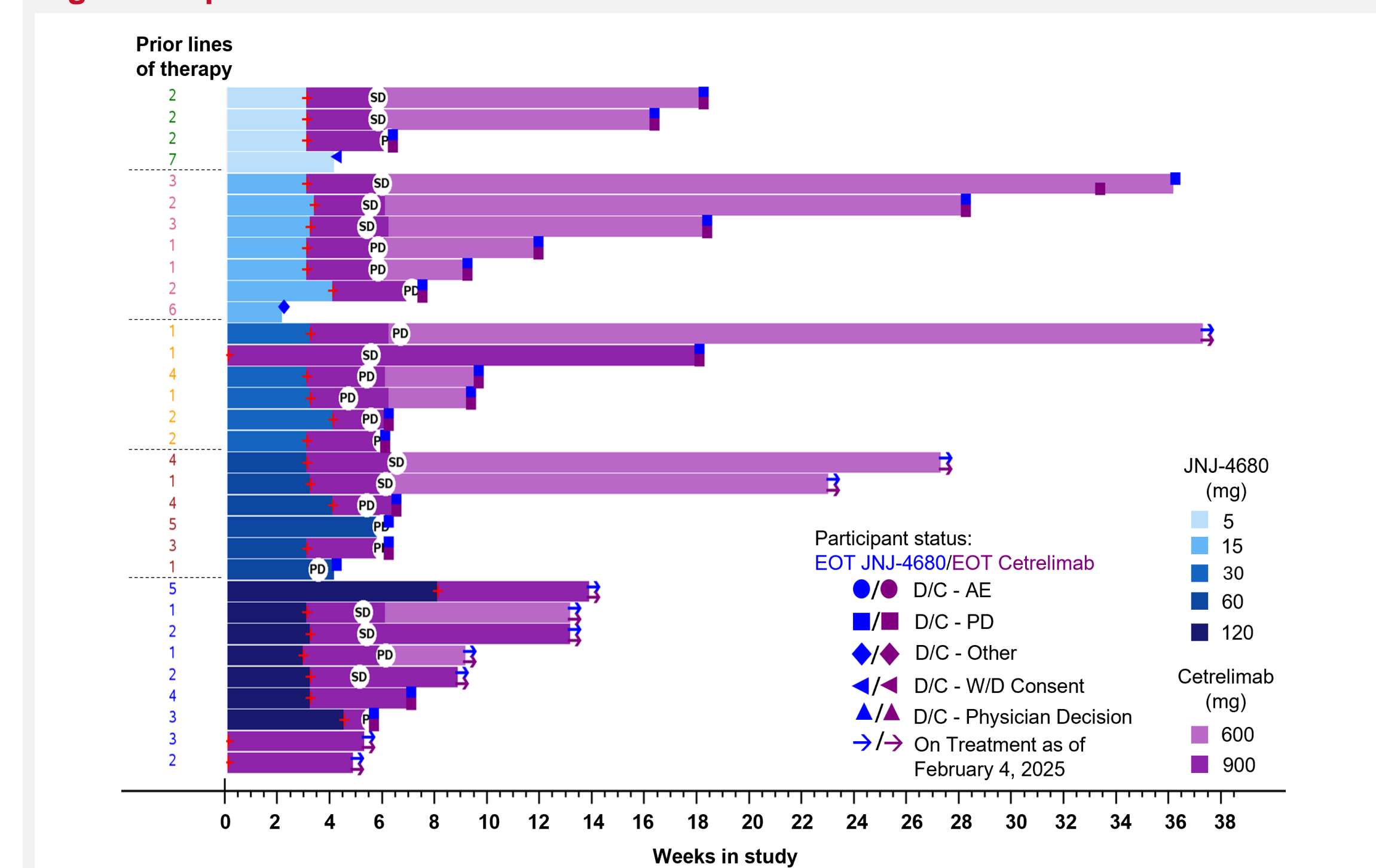
Fig. 5. Inhibition of NECA-induced pCREB in peripheral CD8+ T cells



Efficacy

- By the DCO, the BOR has been SD in 11 pts, with 8 having SD at subsequent DEs and 3 of 5 in the 120 mg cohort having SD at their first DE (Fig. 6).
- 3 SD pts were treated for >6 months, with 1 pt remaining on study for >8 months.
- 1 pt was treated beyond disease progression for >8 months, based on observed clinical benefit.

Fig. 6. Response over time



CONCLUSIONS

- JNJ-4680 demonstrates potent *in vitro* inhibition of A2aR at high concentrations of adenosine.
- JNJ-4680 was tolerable as monotherapy, and in combination with cetrelimab, with dose escalation through 120 mg without identification of a DLT or MTD.
- Most common TEAE was Grade 1/2 nausea, occurring in 25% of pts.
- pCREB data demonstrated sustained A2aR pathway inhibition in the peripheral CD8+ T cells at doses of 15 mg and 30 mg.
- PK supported daily dosing and a steady state being reached at ~1 week.
- 120 mg JNJ-4680 QD dose in combination with cetrelimab was selected as the initial dose for evaluation in Part 2.

