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Non-Small Cell Lung Cancer Drug Development Summit

Can Neoantigen Immunotherapies Reverse Resistance to PD-1 Inhibitors & Progression in NSCLC?

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Background

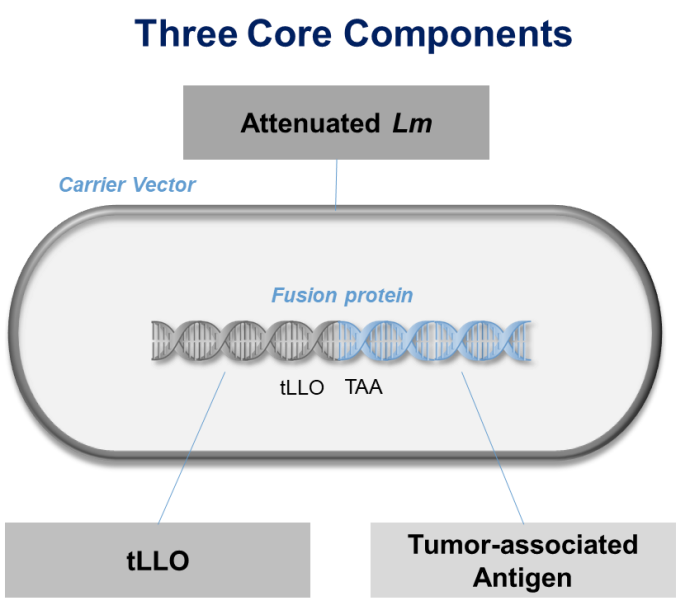
Efficacy of Immune Checkpoint Inhibitors Rechallenge in Non-Small-Cell Lung Cancer (NSCLC)

- Patients who progress on PD-1/PD-L1 blockade represent an unmet need with limited treatment options
- Outcomes with checkpoint inhibitor (CPI) re-challenge after disease progression include [1-6]:
  - Low objective response rate (ORR): 2.9%-13%; no CRs
  - Disease control rate (DCR) of up to 45% in one study
- Heterogenous populations across studies:
  - Baseline characteristics: PD-L1 TPS, TMB & MSI status, etc.
  - Initial CPI treatment line: 1st, 2nd, 3rd, further
  - PD-1 or PD-L1 blockade used initially and at rechallenge
  - Outcome with initial CPI: CR, PR, SD, PD
  - Duration of response
  - Reason for discontinuation: progression, toxicity, clinical decision, ongoing treatment
  - Definition of disease progression: during treatment, < >12 weeks of termination of immunotherapy, etc
  - Endpoints for rechallenge: ORR, DOR, PFS, OS
- What are predictive markers of response to CPI rechallenge?

1. Katayama Y, et al. 2019; 2. Gobbini E, et al. 2020
3. Gobbini E , et al. 2019; 4. Katayama Y, et al. 2019
5. Levra MG, et al. 2020; 6. Metro G et al. 2020

ADXS-503: An Off-The-Shelf Neoantigen Immunotherapy

- ADXS-503 is a live attenuated *Listeria monocytogenes (Lm)* immunotherapy designed to:
  - Reverse the resistance to CPI in patients progressing on PD-1/PD-L1 blockade
  - Increase the sensitivity to PD-1/PD-L1 blockade in first-line therapy
- ADXS-503 is bioengineered to secrete an antigen-adjuvant fusion proteins (tLLO-503) consisting of a truncated fragment of listeriolysin O (tLLO) fused to 22 tumor antigens commonly found in NSCLC

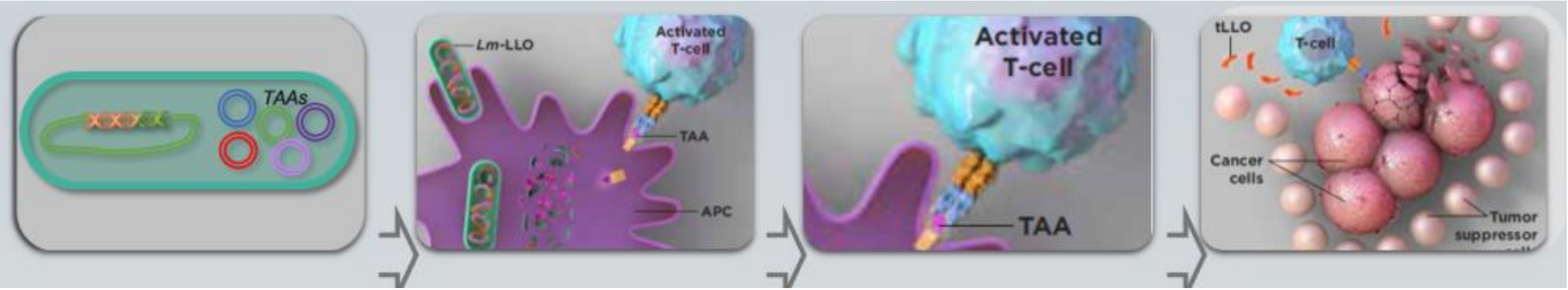


Hot-spot peptides		Proprietary TAA peptides	
Gene	Hot-spot	TAA	HLA allele
KRAS	G12C	*CEACAM5*	A*02:01
KRAS	G12V	*CEACAM5*	A*24:02
KRAS	G12A	*CEACAM5*	A*03:01
EGFR	L858R	*CEACAM5*	B*07:02
KRAS	G12D	*STEAP1*	A*02:01
U2AF1	S34F	*STEAP1*	A*24:02
BRAF	V600E	*RNF43*	B*07:02
PIK3CA	E545K	*MAGE-A6*	A*03:01
TP53	R158L	*NY-ESO1*	A*02:01
EGFR	L861Q	*MAGE-A4*	B*07:02
TP53	R273L	*GAGE1*	B*07:02

TAA: tumor associated antigens (oncofetal and cancer testis)

ADXS-503 elicits T-cell responses in practically all patients with NSCLC as 42% express ≥1 hotspot antigen and >90% express ≥1 TAAs targeted by ADXS-503

ADXS-503 vector leverages the *Lm* platform to trigger strong immune responses against tumor-associated antigens (TAAs)



Live irreversibly attenuated strains of *Lm* are bioengineered for ADXS-503 to secrete antigen-adjuvant fusion proteins containing 22 TAAs

Upon infusion, bioengineered *Lm* are phagocytosed by APCs where fusion protein is released to be processed – presented to MHC class I and II

***Lm* also activates NK cells**

Target peptides presented on APC surface stimulate TAA-specific CD8+ and CD4+ T cells[5]

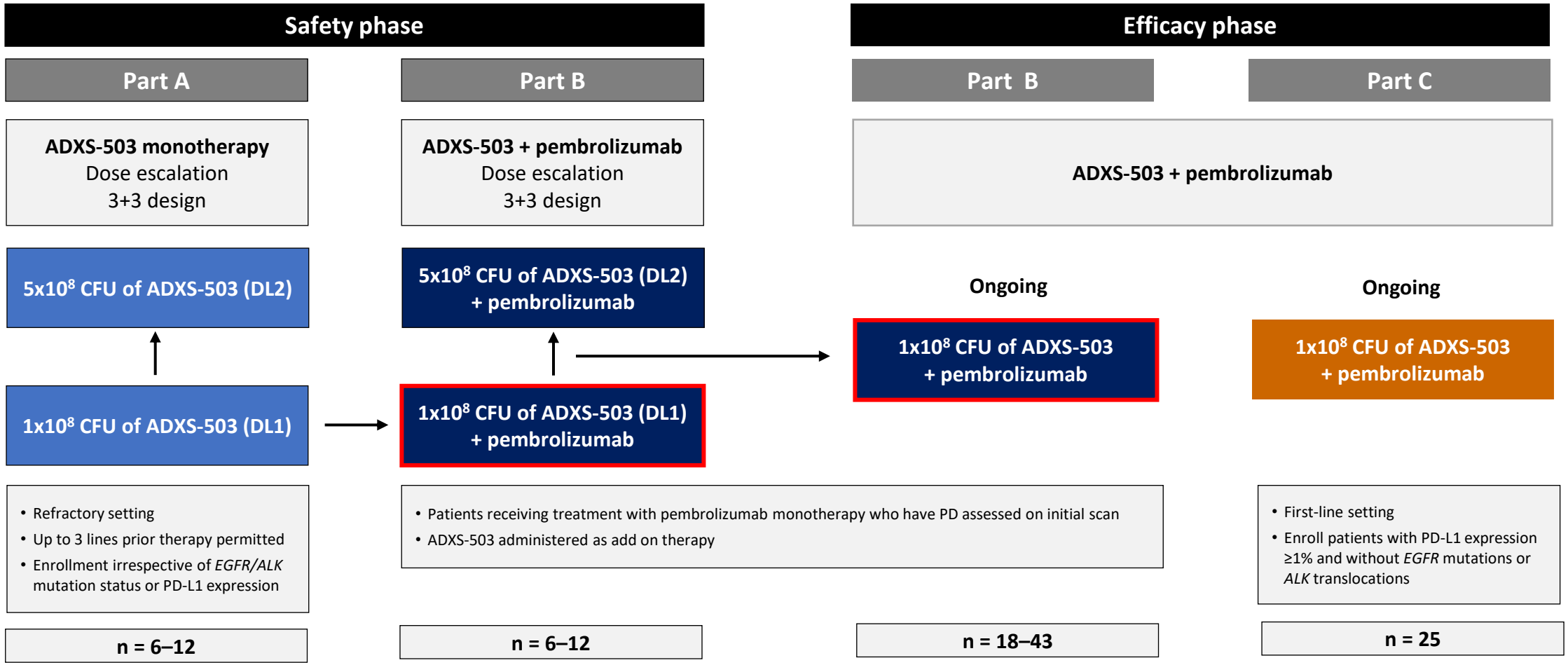
Activated CD8+ T cells seek out and kill TAA-expressing cancer cells and induce antigen spreading

***Lm* also neutralizes MDSCs and T-regs[8]**

- Published preclinical and clinical data have shown synergistic activity of the combination of ADXS *Lm*-based immunotherapies with a PD-1 blocking antibody[6,7]

6. Bongiorno EK, et al. 2017
7. Stein MN, et al. ASCO GU 2020;
8. Wallecha A, et al. 2013

ADXS-503-001: Study design



Part B dose level 1 (DL1) reported in this presentation

ClinicalTrials.gov Identifier: NCT03847519

Demographics and baseline characteristics (Part B DL1)

	n=10
Median age, years (range)	70 (55–87)
<65 years, n (%)	3 (30)
Male, n (%)	5 (50)
ECOG PS, n (%)	
0	3 (30)
1	7 (70)
Race	
Caucasian	5 (50)
Non-Caucasian	3 (30)
Not reported	2 (20)
Smoking status, n (%)	
Current	1 (10)
Former	8 (80)
Never	1 (10)
Histology, n (%)	
Squamous	2 (20)
Non squamous	8 (80)
Brain metastases, n (%)	4 (40)
Median lines of prior systemic therapy (range)	2 (1–6)
Previous thoracic radiotherapy, n (%)	3 (30)
PD-L1 score, n (%)	
<1%	2 (20)
1–49%	2 (20)
≥50%	6 (60)
Not reported	0

[1]ECOG PS, ECOG performance status 1
CPI, checkpoint inhibitor

Treatment-related adverse events (all treated patients in Part B DL1)

n (%)	n=10
Grade ≥3 events	0
Grade 1–2 events	
Pyrexia	5 (50)
Chills	4 (40)
Fatigue	2 (20)
Infusion-related reaction	1 (10)
Nausea	2 (20)
General body aches	1 (10)
Rash	1 (10)
Blood creatinine increased	1 (10)
Mucositis	1 (10)

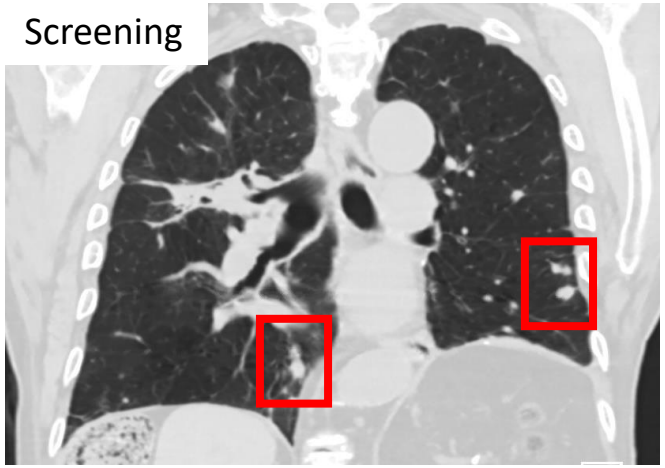
Data as of April 2021; includes most frequently occurring AEs that are likely or possibly treatment related

Clinical activity (Part B DL1)

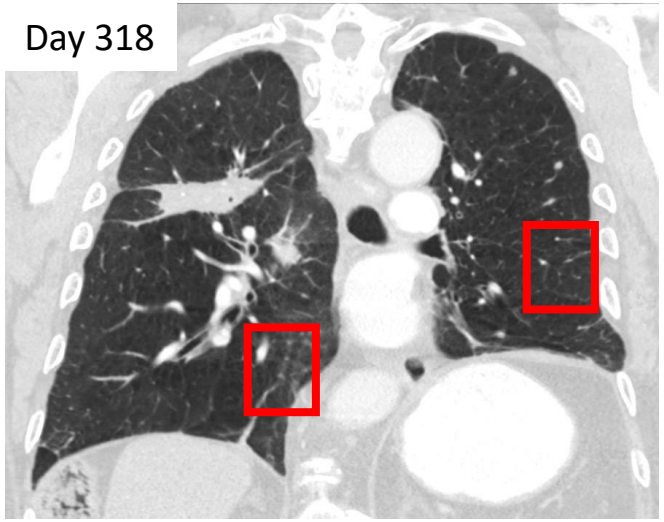
n (%)	n=9
Best overall response	1 (11)
Complete response (CR)	0
Partial response (PR)	1 (11)
Stable disease (SD)	3 (33)
Progressive disease (PD)	5 (56)
Objective response rate (ORR, RECIST)	1 (11)
Disease control rate (DCR)	4 (44)

PR sustained for 54 weeks with ADXS-503 + pembrolizumab in patient with recurrent NSCLC

Screening



Day 318



- 88-year-old man (Patient 1), former smoker, stage IIIA adenocarcinoma resected in 2012
- No driving mutations, PD-L1 55%
- Prior therapy with carboplatin/pemetrexed, erlotinib, vinorelbine, Met ADC, radiotherapy
- Recurrence in 2013
- Pembrolizumab monotherapy started in May 2017 achieving a PR. PD developed in December 2019
- ADXS-503 added on to pembrolizumab on in January 2020
- PR documented on day 39 and sustained for 54 weeks (PR image shown from Day 318)

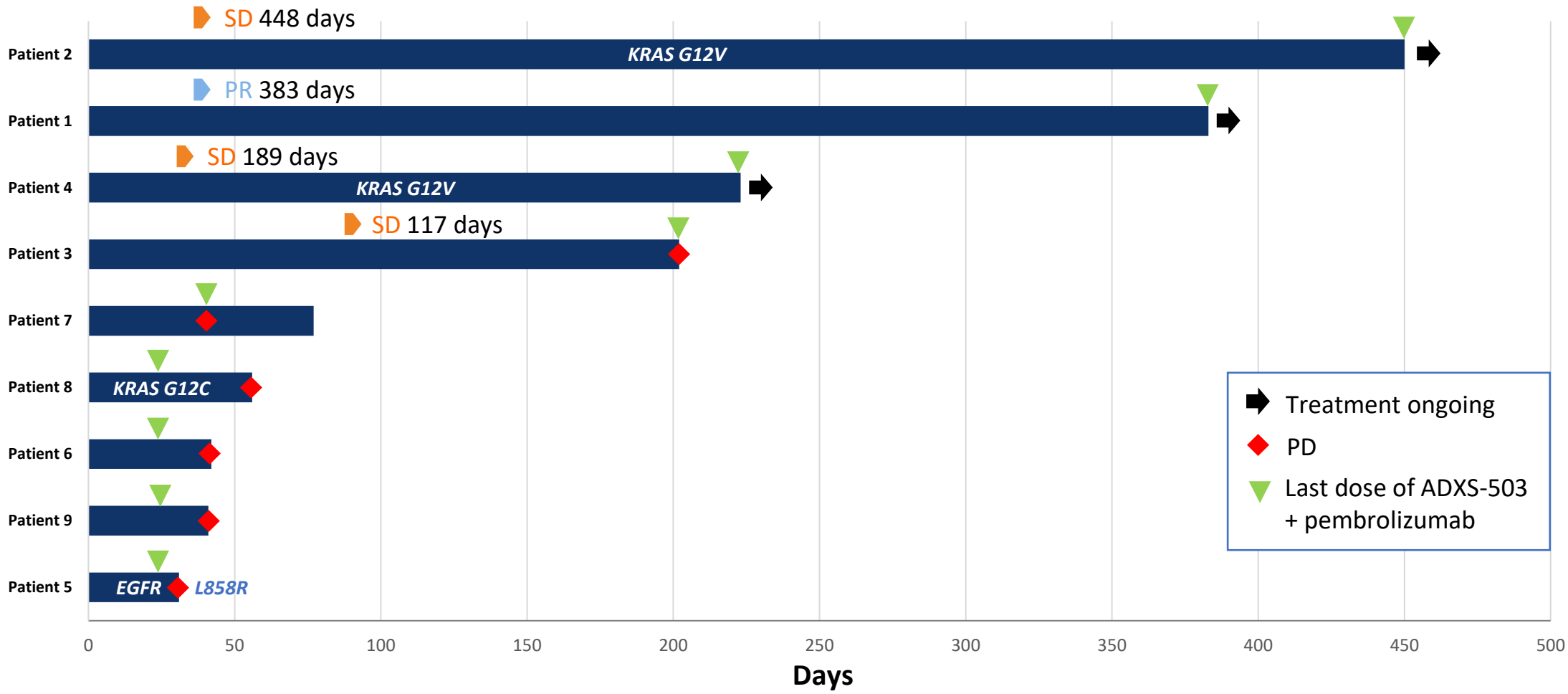
Results

Clinical activity: Part B DL1

- A total of 10 patients who progressed on pembrolizumab have received ADXS-503 ($1x10^8$ CFU) in addition to pembrolizumab
- **DCR is 44% and ORR is 11%** in 9 evaluable patients:
  - **1 PR** with 60% tumor reduction seen on 8-week scan and **sustained at 54-week scan** (Patient 1)
  - **1 SD** with a 25% reduction in target lesion and **sustained at 64-week scan**; elderly patient (Patient 2) with non-squamous NSCLC and PD-L1 expression of 80%, who had received pembrolizumab for 33 months with a best overall response (BOR) of SD. This patient had a *KRAS G12V* mutation reported in the medical records
  - **1 SD** confirmed on 12-week scan; elderly patient (Patient 3) with squamous NSCLC and PD-L1 expression of 50%, who had received pembrolizumab for 14 months including combination with chemotherapy at start of therapy with a BOR of SD
  - **1 SD** on 6 week-scan and **sustained at 27-week scan**; 67-year-old female (Patient 4) with non-squamous NSCLC and PD-L1 expression of 90%, who had received pembrolizumab for 17 months, including combination with chemotherapy at start of therapy. This patient also had a *KRAS G12V* mutation reported in the medical records
  - **5 PD** within the first 8 weeks of therapy, including 1 patient with *EGFR L858R* mutation and 1 patient with *KRAS G12C* mutation. All of these patients had PD-L1 expression ≤50%
- **Duration of clinical benefit** has ranged from **18 to 64 weeks for SD** and **54 weeks for PR**

SD, stable disease | PR, partial response | PD, progressive disease

Treatment exposure and response duration to ADXS-503 + pembrolizumab in Part B patients (as of 22 April 2021)



SD, stable disease | PR, partial response | PD, progressive disease

ADXS-503-001: PD-L1 expression, prior therapies and outcomes (as of 22 Apr 21)

PID#	PD-L1 %	Prior Therapies (Time onTherapy /BOR)							Outcome / DOR (days)
2	80	Pembro (~35m /SD)	Pembro + 503						SD 448
1	55	Crizo	Carbo-Alimta	Erlo	Vinorelbine	Abbvie Ab	Pembro (~30 m / SD)	Pembro +503	PR 383
5	0	Osimertinib	Carbo+Alimta+ Pembro (~4.5m/PD)	Pembro + 503					PD
3	50	Carbo-Taxol (3m / SD)	Pembro (~15 m /PD)	Pembro + 503					SD 117
4	90	Carbo+Alimta+ Pembro (~2.5 m /PR)	Pembro (~17 m/UNK)	Pembro + 503					SD 189
6	1	Carbo+Alimta+ Pembro (~ 2m /UNK)	Pembro (~8 m / UNK)	Pembro + 503					PD
7	50	Carbo + n taxol+Pembro (~2.5 m / SD)	Pembro (~4m/ SD)	Pembro + 503					PD
9	1	Carbo+Alimta Pembro (~4 m/ PD)	Pembro (~1 m/ SD)	Pembro + 503					PD
8	10	Carbo+Taxol + Pembro (~2m/ UNK)	Pembro (~7m/ UNK)	Pembro + 503					PD

Chemo or targeted therapies | Chemo + pembro combo | Pembro | Pembro + 503

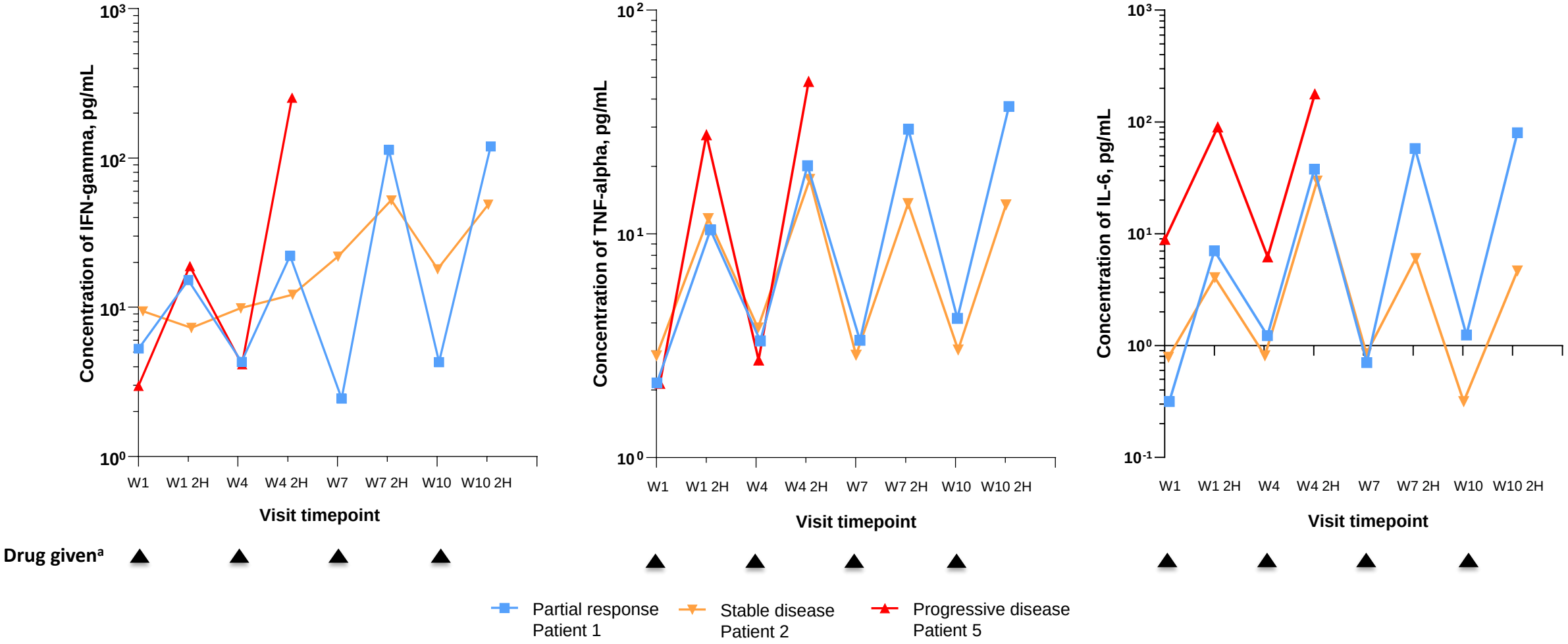
BOR, Best Overall Response
DOR, Duration od Response

Results

Immune correlative data (n=7)

- **Transient increased secretion of cytokines after each infusion of ADXS-503 is indicative of adaptive (Th1) immune stimulation in all patients**
  - This finding suggests the speed by which ADXS-503 stimulates innate immunity. These cytokines are secreted by antigen APC in response to the phagocytosis of bacteria and may support the induction of the antitumoral adaptive immune response. Of note, in most cases by 4 hours the levels of acute cytokines begin to diminish from peak levels at 2 hours (data not shown)
  - However, the increased secretion of cytokines does not seem to predict clinical benefit, as shown in 3 patients with different outcomes
- **100% priming by ADXS-503 in all 7 patients evaluated by FluoroSpot**
  - Efficient priming for neoantigens in ADXS-503 generated specific CD8+ T cells against hot-spot mutations, and/or sequence optimized heteroclitic OFAs/CTAs and/or wild-type OFAs/CTAs and/or against other antigens not included in the ADXS-503 construct (i.e., antigen spreading; Table 1)
  - Generation of CD8+ T cells against neoantigens in one or more pools observed within 2 months of starting therapy in most cases
- **Patients showing proliferation and/or activation of NK cells and CD8+ T cells after the addition of ADXS-503 seem to achieve SD**. These changes induced by ADXS-503 occurred early in the course of treatment of these patients, including:
  - Increased NK cell counts, suggesting the activation of an innate response
  - Increased naïve CD8+ and CD4+ T-cell counts, suggesting response to novel antigens
  - Induction of CD8+ T cell proliferation, cytotoxicity and emergence of memory cells
  - Up-regulation of PD-1 and CD38 in NK & CD8+ T cells, suggesting cell activation
  - Elevation of NK and CD8+ T cell populations were also observed at week 25 in patient 1 (data not shown; earlier samples not available)

ADXS-503 in combination with pembrolizumab induces transient elevation of cytokines after infusion (representative samples)



[a]Drug given every 3 weeks at W1, W4, W7, etc
W = week; 2H = 2 hours post-infusion

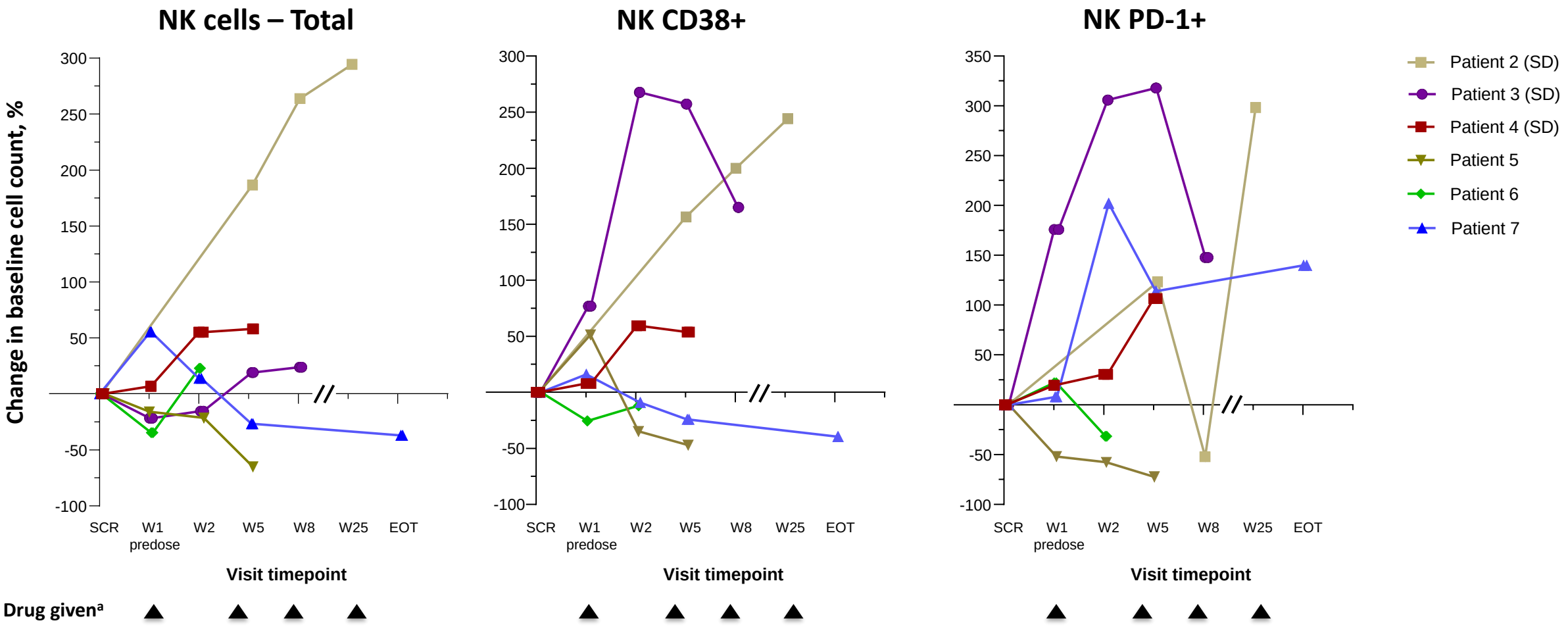
Timing of T-cell responses to antigens in ADXS-503 and antigen spreading in patients receiving ADXS-503 + pembrolizumab (Part B DL1)

	Pool 1 Hot-spot mutations	**Pool 2** Heteroclitic TAAs	**Pool 2** Wild-type TAAs	**Pool 3** Antigen spreading
Patient 1	W25*	W25*	W25*	W2
Patient 2	W8	W25	n.d.	W8
Patient 3	W2/W8	W2	W5/W8	n.d.
Patient 4	W2	W2	W2	n.d.
Patient 5	n.d.	W5	n.d.	n.d.
Patient 6	n.d.	n.d.	W2	n.d.
Patient 7	W2	W2	W2	W2

- Three pools containing neoantigens included in ADXS-503 (i.e., HSM, heteroclitic and wt TAAs), and one pool with other antigens not included in the construct (i.e., antigen spreading), were tested for CD8+ T cell activation by FluoroSpot in 7 patients
- IFN gamma & Granzyme B secretion detection data are shown. Representative plots have been presented previously[7]
- All tested patients generated CD8+ T cells against neoantigens in ADXS-503 at different time points after the start of therapy (represented in weeks)
- *Early samples from patient 1 who achieved PR are not available
- n.d. = not detected

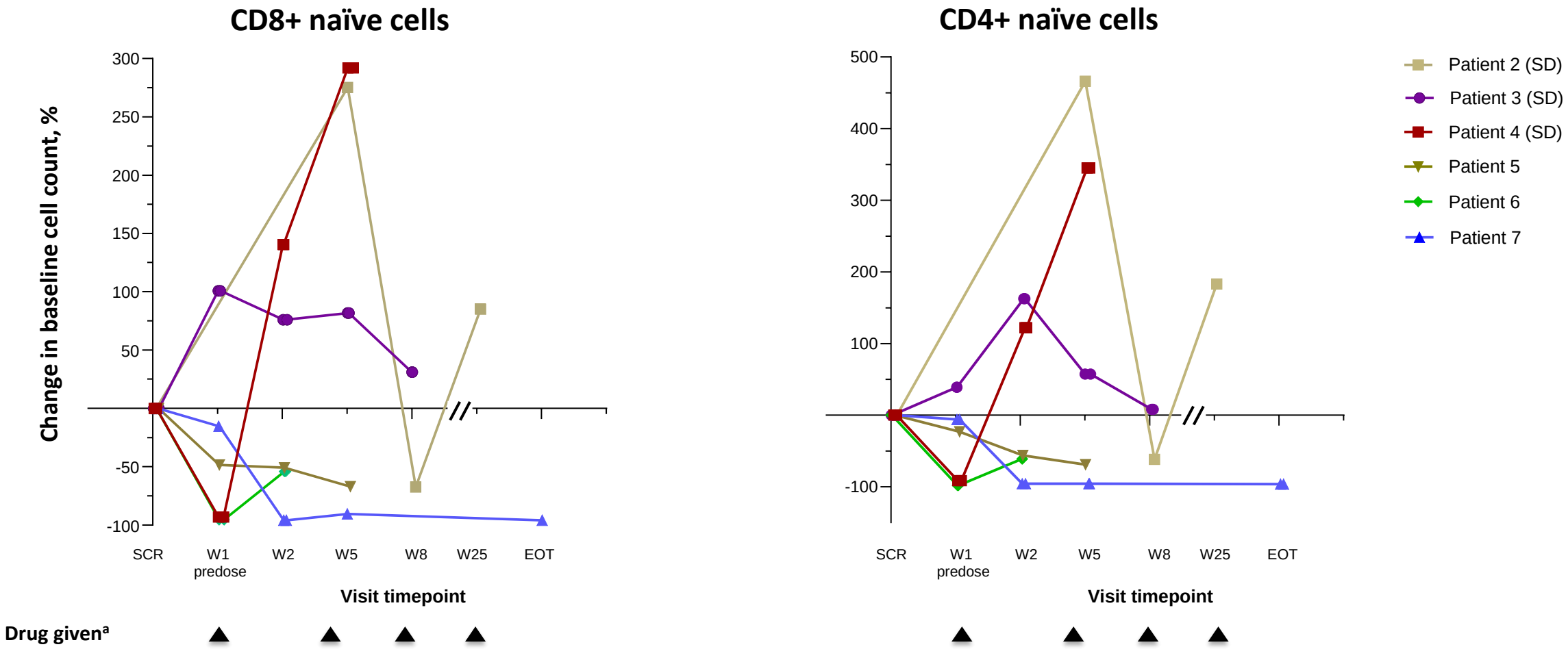
7. Goldman JW, et al. 2020

Addition of ADXS-503 to patients failing pembrolizumab increases NK cell counts and up-regulates PD-1 and CD38 in patients who achieve SD



[a]Drug given every 3 weeks at W1, W4, W7, etc
W = week; SCR = screening ; SD = stable disease

Addition of ADXS-503 to pembrolizumab at PD increases naïve CD8+ and CD4+ T-cell counts suggesting response to novel antigens in patients achieving SD



[a]Drug given every 3 weeks at W1, W4, W7, etc
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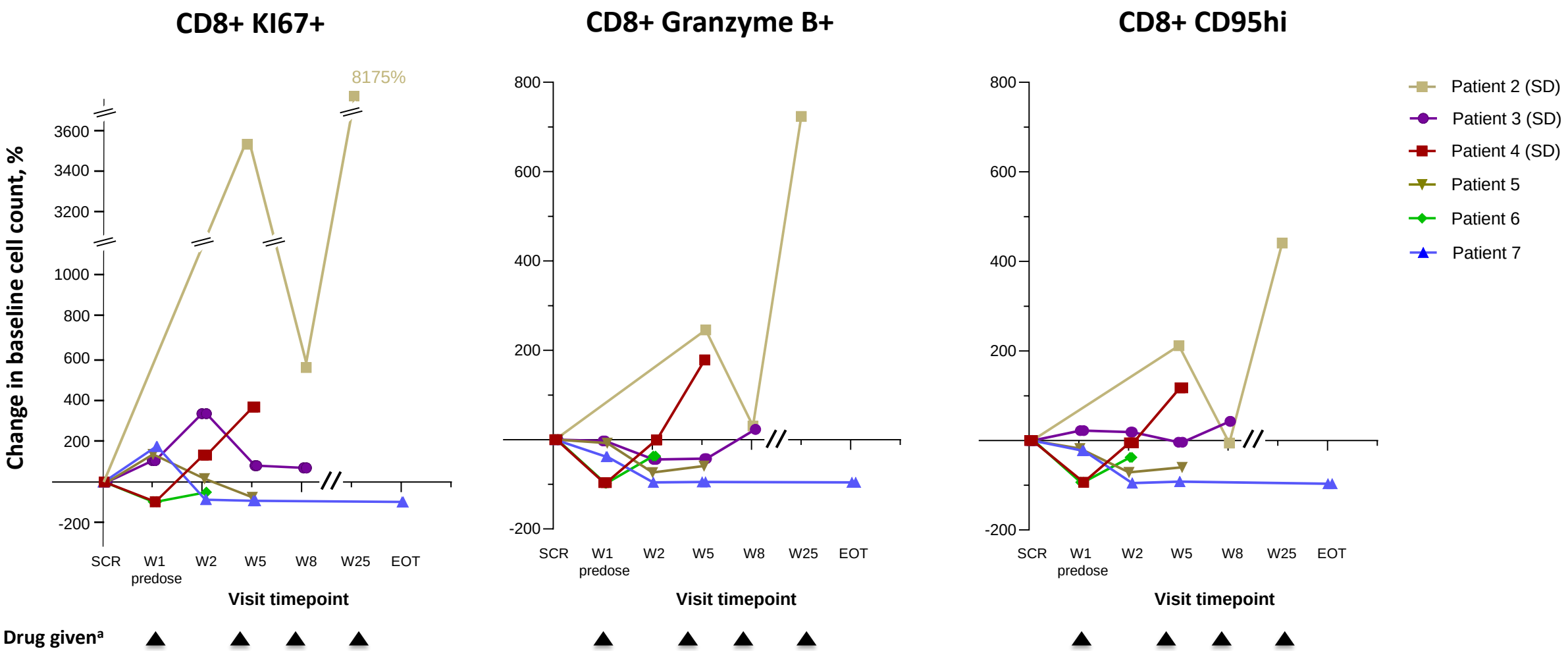
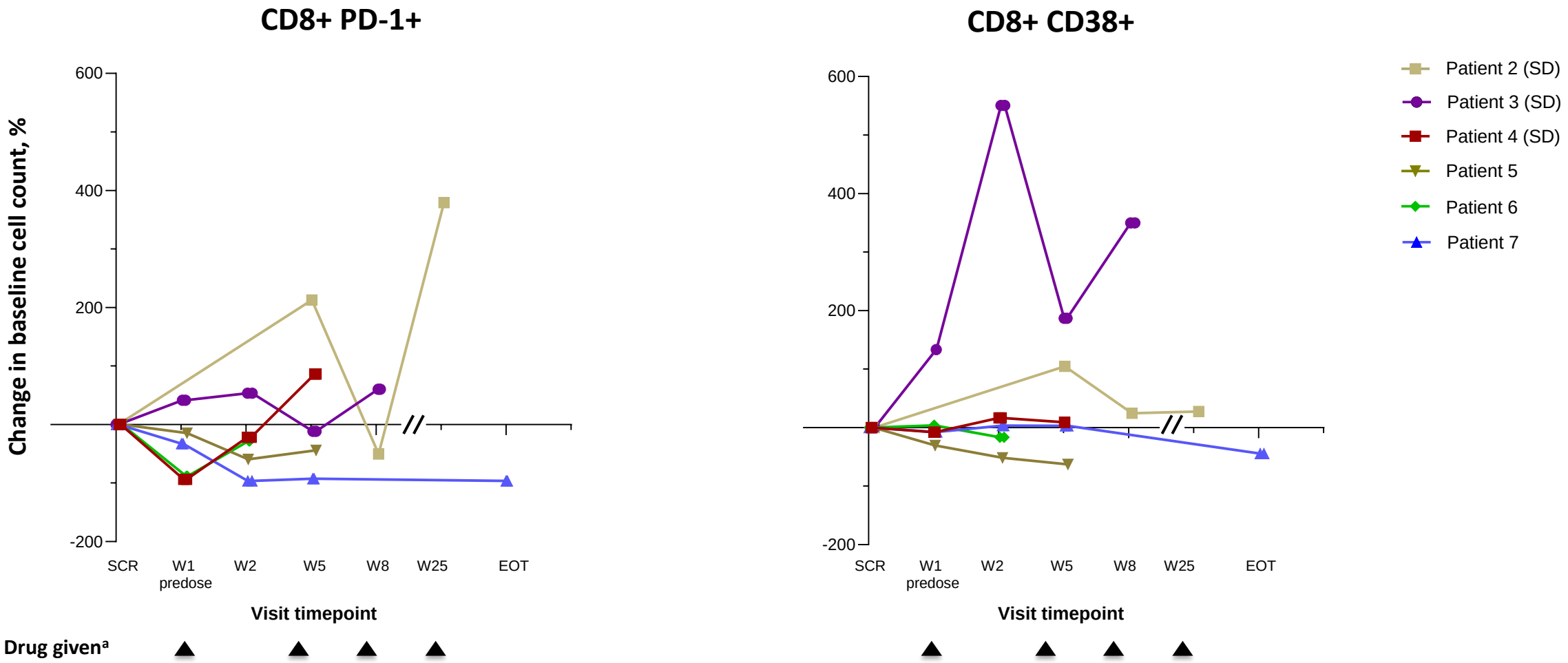
Addition of ADXS-503 to pembrolizumab at PD induces CD8+ T-cell proliferation, cytotoxicity and emergence of memory cells in patients who achieve SD



[a]Drug given every 3 weeks at W1, W4, W7, etc
W = week; SCR = screening ; SD = stable disease

Addition of ADXS-503 to pembrolizumab at PD induces up-regulation of PD-1 and CD38 in CD8+ T cells suggesting activation of these cells in patients who achieve SD



[a]Drug given every 3 weeks at W1, W4, W7, etc
W = week; SCR = screening ; SD = stable disease

Conclusions

- ADXS-503 ($1x10^8$ CFU) as an add on therapy to pembrolizumab at time of PD has been safe and well tolerated
- Adding on ADXS-503 to patients failing pembrolizumab as last therapy may prevent further clinical progression in select patients:
  - ORR is 11% and DCR is 44% in 9 evaluable patients
  - Durable PR and SD sustained for over a year and one SD for over 6 months
  - SD for ~4 months achieved in another patient
- Patients with observed clinical benefit seem to be those with PD-L1 expression ≥50%, secondary resistance disease to pembrolizumab[9] and show proliferation and/or activation of NK and CD8+ T cells within the first weeks of therapy
- Addition of ADXS-503 may lead to clinical benefit by restoring sensitivity to PD-1 blockade and/or by enhancing responsiveness to pembrolizumab:
  - Antitumoral T-cell responses were elicited against hot-spot mutation antigens and/or TAAs
  - Emergence of naive CD8+ T-cell clones after the addition of ADXS-503 suggest reactivity against novel antigens
  - ADXS-503 may have also induced the proliferation and/or activation of pre-existing CD8+ T-cell clones, including PD-1 upregulation
  - cfDNA and NGS data is ongoing, including TCR analysis to further evaluate the specificity of the activated T-cell clones
- Enrollment in Part B DL1 will continue to further evaluate clinical and immune correlative data following a Simon's 2-stage design

9. Kluger HM, et al. 2020

Secondary resistance = drug exposure ≥ 6 months and best response (CR, PR, SD) ≥ 6 months

Acknowledgements

Patients and their families

Investigators

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