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Combination of subcutaneous selicrelumab (CD40 agonist) and vanucizumab (anti-Ang2/VEGF) in patients with solid tumors demonstrates early clinical activity and a favorable safety profile

[1]Calvo E, [2]Schellens J, [3]Matos I, [3]Garralda E, [4]Mau Sorensen M, [5]Hansen A, [6]Martinez Garcia M, [7]Lolkema M, [8]Charo J, [9]Lambertini C, [9]Mancao C, [9]Bogman K, [9]Ferlini C, [8]Stern M, [2]Ros W

[1]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [2]The Netherlands Cancer Institute, Amsterdam, Netherlands; [3]Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain; [4]Rigshospitalet, Copenhagen, Denmark; [5]Princess Margaret Cancer Centre, Toronto, Canada; [6]Hospital del Mar, Barcelona, Spain; [7]Erasmus MC, University Medical Center, Rotterdam, Netherlands; [8]Roche Innovation Center Zurich, Switzerland;[9] F Hoffmann-La Roche Ltd, Basel, Switzerland

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Presenter Disclosure Information

Emiliano Calvo, MD, PhD

The following relationships exist related to this presentation:

Employment:	START Madrid, HM Hospitales Group
Stocks/ownership interests:	START Madrid, Oncoart Associated, International Cancer Consultants
Honoraria:	HM Hospitales Group
Consulting/advisory role:	Novartris, Nanobiotix, Janssen-Cilag, PsiOxus Therapeutics, Seattle Genetics, EUSA Pharma, Abbvie, Celgene, AstraZeneca, Roche/Genentech, GLG, Pfizer, Servier, Amcure
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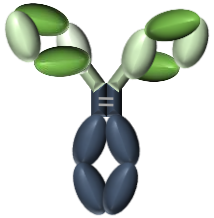
Other:	President and Founder of Foundation INTHEOS (Investigational Therapeutics in Oncological Sciences)

There will be discussion about the use of products for non-FDA approved indications in this presentation.

Selicrelumab and vanucizumab

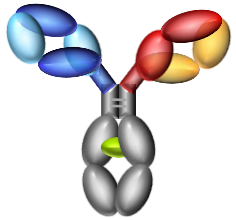
anti-CD40



selicrelumab
IgG2

Selicrelumab is a human **agonistic IgG2 monoclonal antibody to CD40**, a member of the TNF-receptor superfamily expressed on APCs, endothelial cells and some tumors

anti-VEGFA anti-Ang2



vanucizumab
IgG1

Vanucizumab, based on bevacizumab, is a human bispecific IgG1 molecule against **VEGF-A and Ang2**

Rationale for the **combination of a CD40 agonist and an anti-angiogenic drug**:

- Inhibition of Ang2-/VEGF-mediated immune suppression, along with stimulation of a T-cell response via APC activation by selicrelumab may enhance anti-tumor T-cell responses
- Tumor vasculature normalization by inhibition of angiogenesis may increase infiltration of tumor-reactive T-cells primed by CD40 ligation

Selicrelumab is given subcutaneously (s.c.) minimizing the risk of infusion-related reactions (IRR) observed previously with IV administration

Study design

Selicrelumab in combination with vanucizumab

Dose escalation part:

Dose-finding with multiple ascending dose (1mg–72mg) of selicrelumab in combination with fixed vanucizumab dose

Key eligibility criteria:

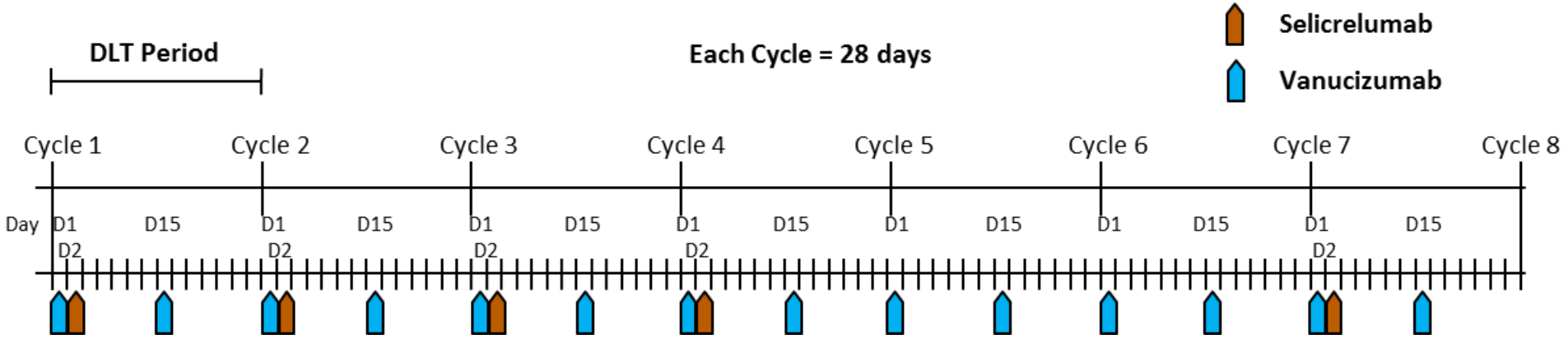
- Locally advanced/metastatic solid tumor not amenable to standard therapy
- Radiologically measurable disease (RECIST v1.1)

Key objectives:

- Define safety and tolerability
- Define maximum tolerated dose (MTD) and/or optimal biological dose (OBD)
- Obtain preliminary anti-tumor activity

Baseline characteristics	All cohorts
Age (median, range)	58.0 (23–80)
Gender, male, n (%)	26 (44%)
ECOG PS 0 / 1, n (%)	20 (34%) / 39 (66%)
Most frequent site of primary tumor	
Colon and rectum	16 (27%)
Breast	6 (10%)
Head & neck	5 (9%)
Ovarian	5 (9%)
Prior regimens (median, min-max)	3 (0-11)

Study drug administration



** DLT criteria: study drug related Gr 3+ toxicity, with usual exceptions*

Selicrelumab in combination with vanucizumab

Drug administration:

- **Vanucizumab**: 2g intravenous on D1 and D15 of each cycle (Q2W)
- **Selicrelumab**: s.c. at escalating doses on D2 of C1 through 4, and thereafter on D2 of every third cycle *

Safety profile (selicrelumab/vanucizumab)

	All dose escalation cohorts (N=59)
Patients with ≥1 AE	59 (100%)
Total number of patients with ≥1 AE	
Grade 3/4 AE	45 (76%)
Grade 3/4 AEs related to selicrelumab irrespective of relationship to vanucizumab	21 (36%)
Grade 3/4 AEs related to selicrelumab only	7 (12%)
Grade 3/4 AEs related to vanucizumab	26 (44%)
Serious AEs	29 (49%)
AEs leading to withdrawal of selicrelumab	6 (10%)
AEs leading to withdrawal of vanucizumab	5 (8%)
Dose limiting toxicity*	1 (2%)
AEs leading to death**	2 (3%)

	1–4mg selicrelumab (N=11)	8–18mg selicrelumab (N=19)	24–40mg selicrelumab (N=17)	48–72mg selicrelumab (N=12)	All cohorts (N=59)
Grade 3/4 AEs related to selicrelumab irrespective of relationship to vanucizumab (reported in ≥2 patients)					
Alanine aminotransferase increased	2	1		1	4 (7%)
Aspartate aminotransferase increased	1		2	1	4 (7%)
Injection related reaction		2		2	4 (7%)
Hypertension	1	2			3 (5%)
Asthenia	1	1			2 (3%)
Grade 3/4 AEs related to selicrelumab only (reported in ≥2 patients)					
Injection site reaction		2		2	4 (7%)

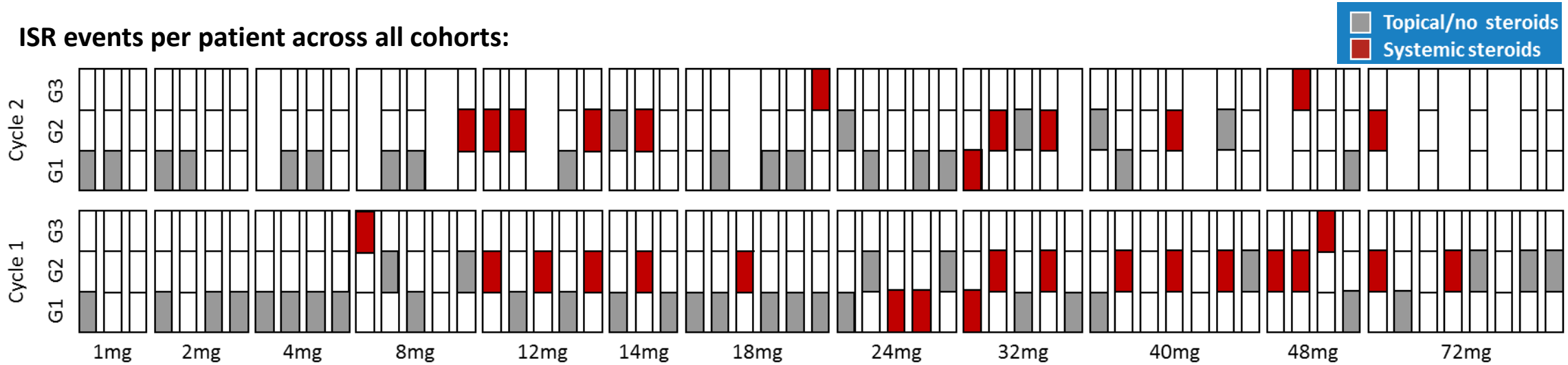
Gr3/4 toxicity driven by vanucizumab, and typical for anti-VEGF (mainly hypertension), without evidence for synergistic toxicity (Gr3+ AE for vanucizumab single agent: 41%)***

No MTD identified up to 72mg of selicrelumab. No immune-related AEs (irAE) at any dose level

**Dose limiting toxicity: one dose limiting toxicity of Grade 3 injection site reaction was reported in 1 of 59 patients (8mg selicrelumab) and considered related to selicrelumab*
***AEs with fatal outcome: one event of myocardial infarction (Cohort 12) was related to vanucizumab, but not related to selicrelumab; one event of ascites was observed (Cohort 9, unrelated to either drug).*
**** Hidalgo et al. Clin Cancer Res. 2018*

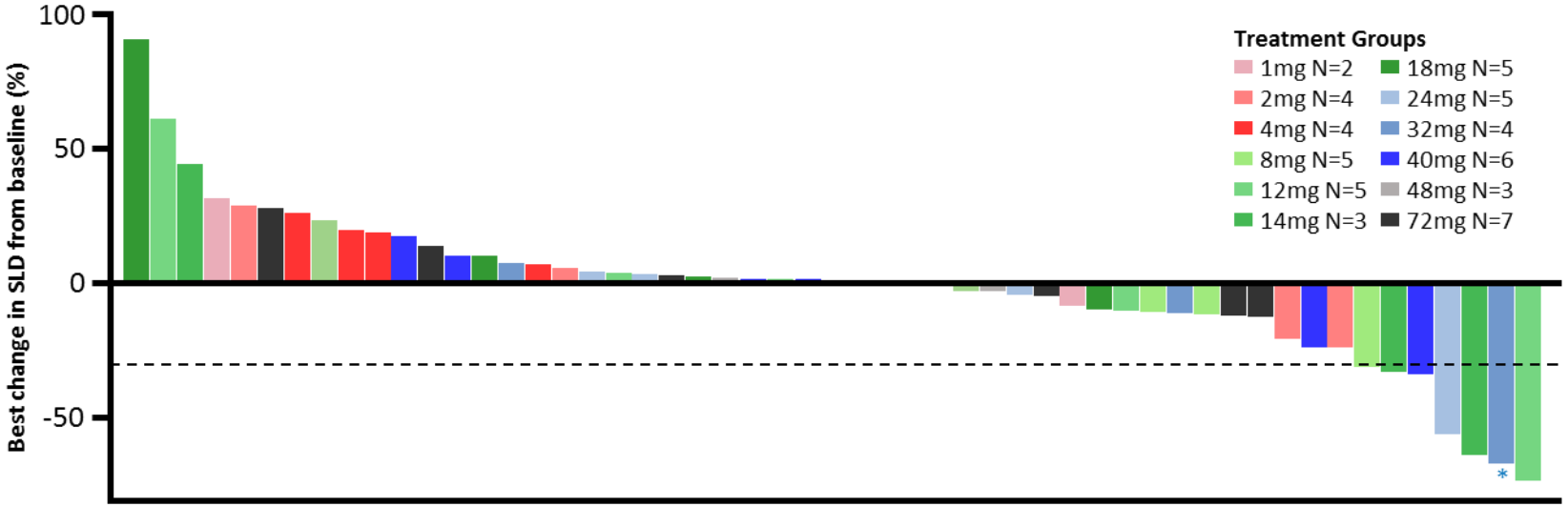
Safety profile (s.c. administration)

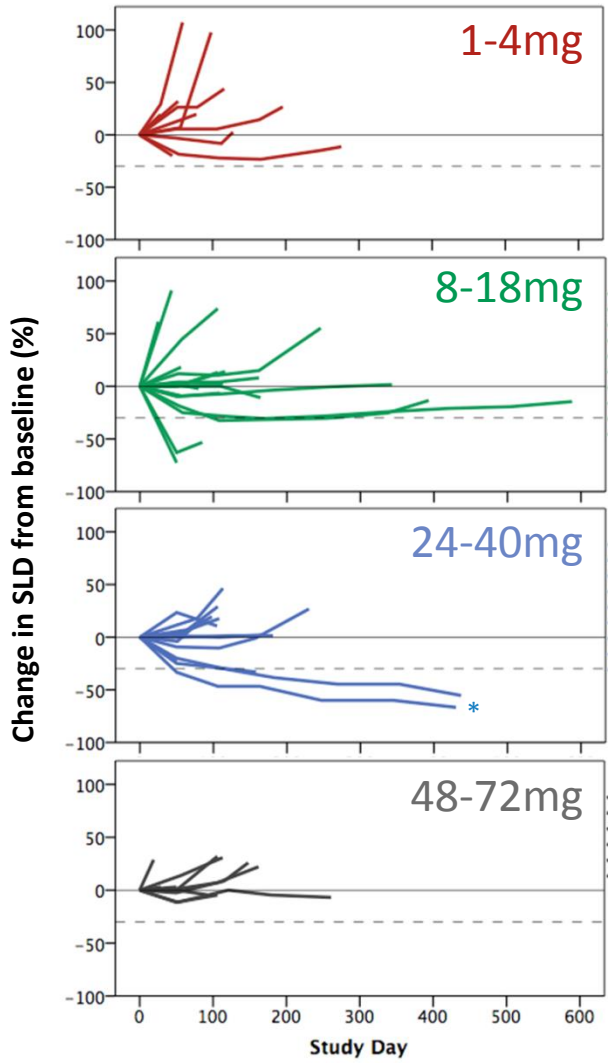
ISR events per patient across all cohorts:



- No cytokine release syndrome (CRS) has been reported in patients treated with s.c. administration
- Safety events are primarily injection site reactions (ISRs), starting 3.4 days (mean) after dosing, with no clear association to selicrelumab dose
- Low grade ISRs managed with no or topical steroids, higher grade ISRs resolve with low doses of systemic steroids (10–20mg prednisone)
- Histological evaluation of skin biopsies in patients with ISRs show granuloma formation in some patients
- To reduce the risk of ISRs, doses ≥8mg were split into multiple (up to 4) s.c. injections to different sites to reduce the local dose administered

Anti-tumor activity





- Clinical responses observed between **8 and 40mg selicrelumab** in combination with vanucizumab, generally in indications considered cancer immunotherapy sensitive:
  - **medullary thyroid** (8mg, unconfirmed PR*)
  - **head & neck** (12mg, unconfirmed PR*)
  - **esophageal** (14mg, unconfirmed PR*)
  - **adrenal** (14mg, irPR**)
  - **ovarian** (24mg and 40mg, confirmed and unconfirmed PR*)
  - **bladder** (32mg, confirmed CR*)
- Two patients (H&N and esophageal) stopped treatment due to wound healing complications after rapid and deep responses

* RECIST v1.1
** Unidimensional immune-related Response Criteria (irRC)

* = *ongoing*

Anti-tumor activity (RECIST v1.1)

- Best response by RECIST in 54 efficacy-evaluable patients was 1 confirmed CR + 1 confirmed PR, 30 SD (including 4 unconfirmed PRs) and 1 irPR

	1–4mg selicrelumab (N=11)	8–18mg selicrelumab (N=19)	24–40mg selicrelumab (N=17)	48–72mg selicrelumab (N=12)	All cohorts (N=59)
CR	0	0	**1 (6%)**	0	1 (2%)
PR	0	0	**1 (6%)**	0	1 (2%)
SD **Unconfirmed PR***	4 (36%)	13 (68%) **3**	10 (59%) **1**	3 (25%)	30 (51%) 4
PD **irPR***	6 (55%)	5 (26%) **1**	3 (18%)	8 (67%)	22 (37%) 1
Missing or unevaluable**	1 (9%)	1 (5%)	2 (12%)	1 (8%)	5 (9%)

* within RECIST v1.1 SD or PD (irPR as per unidimensional irRC)
** Patients who discontinued either due to AEs or symptomatic deterioration

Patient vignette

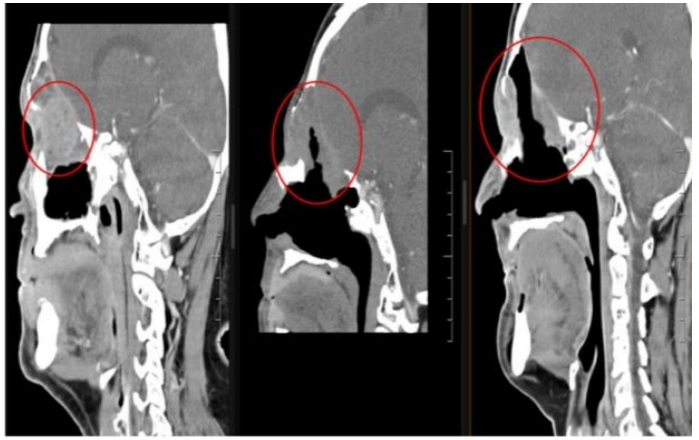
- Male, 59 years

Presentation

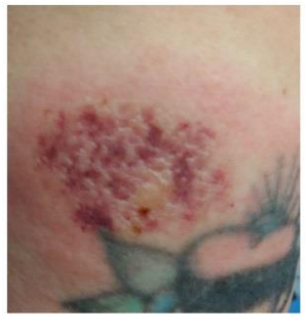
- Squamous cell cancer of sinonasal mucosa
- Diagnosed 22 months previously and treated with cisplatin/radiotherapy, and surgery

Treatment

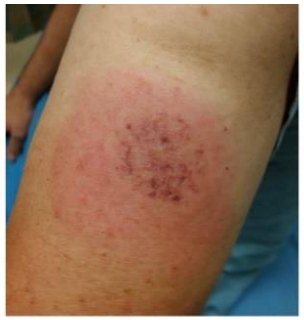
- Selicrelumab dose: 12mg (3 x 4mg)
- ISR Grade 2, treated with systemic corticosteroids
- Experienced rapid clinical and radiological tumor shrinkage
- Dural breach (impaired wound healing at tumor infiltration site) led to treatment discontinuation on Cycle 2 despite deep radiological response



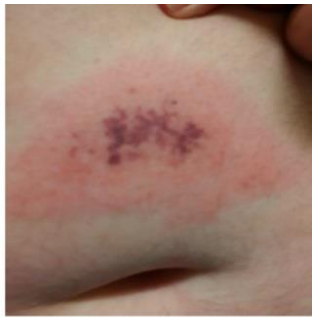
Baseline C1D11 C2D22



Right arm

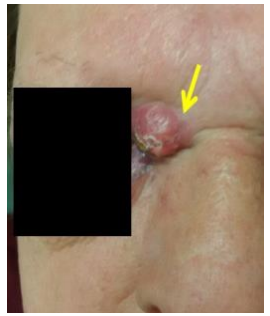


Left arm

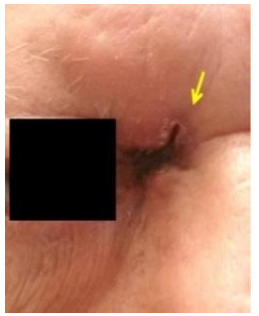


Abdomen

C1D6



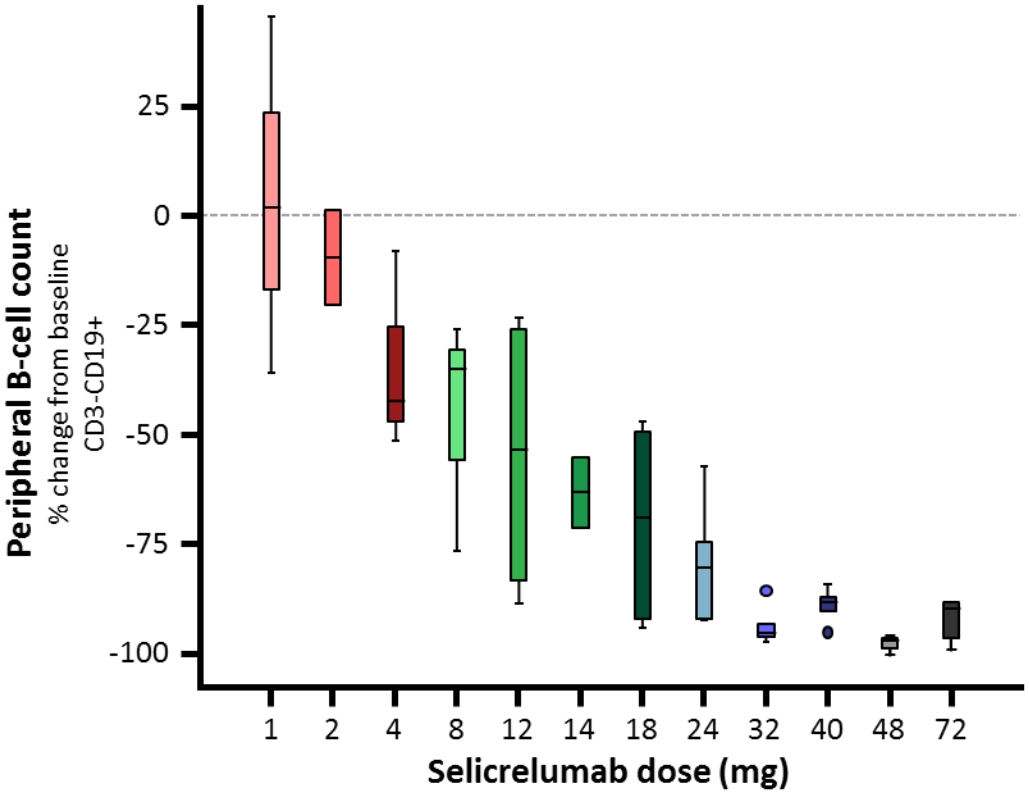
Baseline



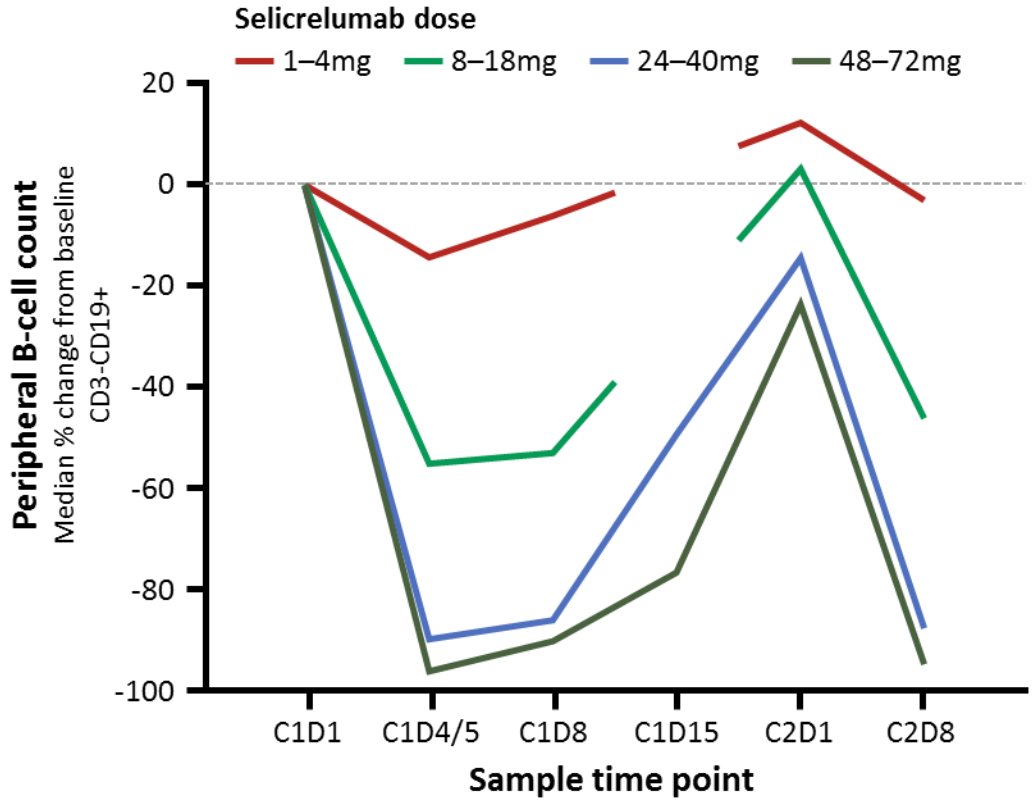
C1D7

Pharmacodynamic effects

Dose-dependent peripheral B-cell redistribution on Day 4 post dose



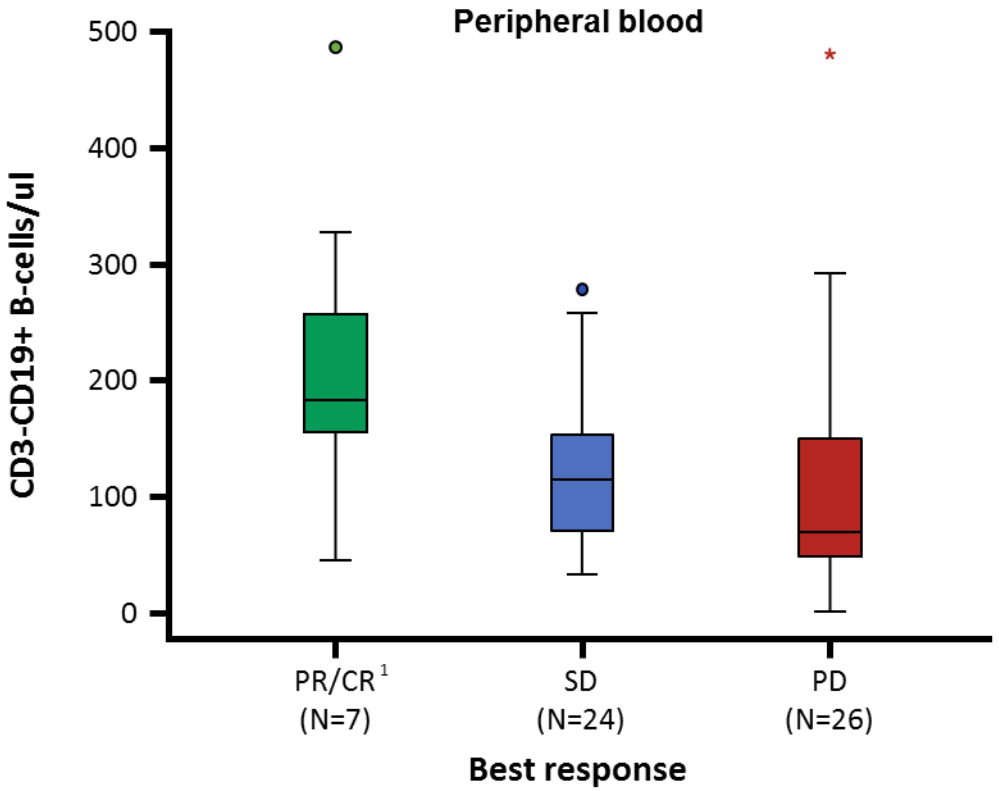
Transient drug-induced peripheral B-cell redistribution lasting for >1 week suggesting a B-cell activation

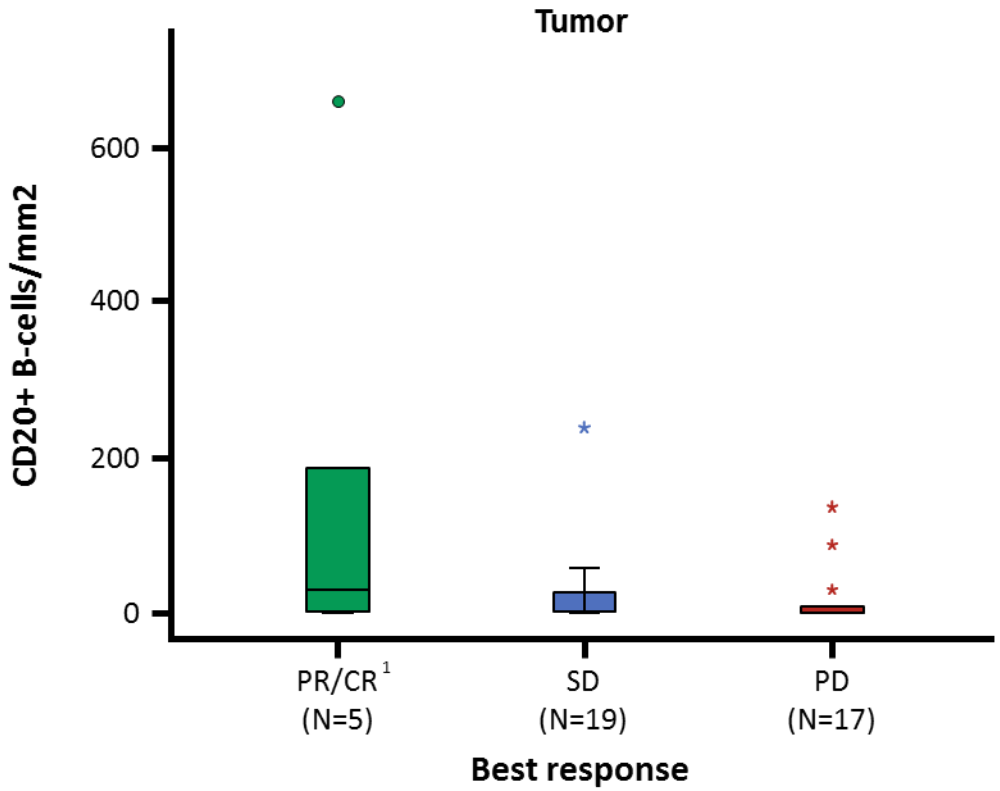


PK data: Only sporadic selicrelumab serum concentrations close to the lower limit of quantification (50 ng/mL) could be measured at doses ≥ 14 mg

B-cells as predictors of response

Baseline B-cell count in tumor and peripheral blood is highest in patients with radiological response

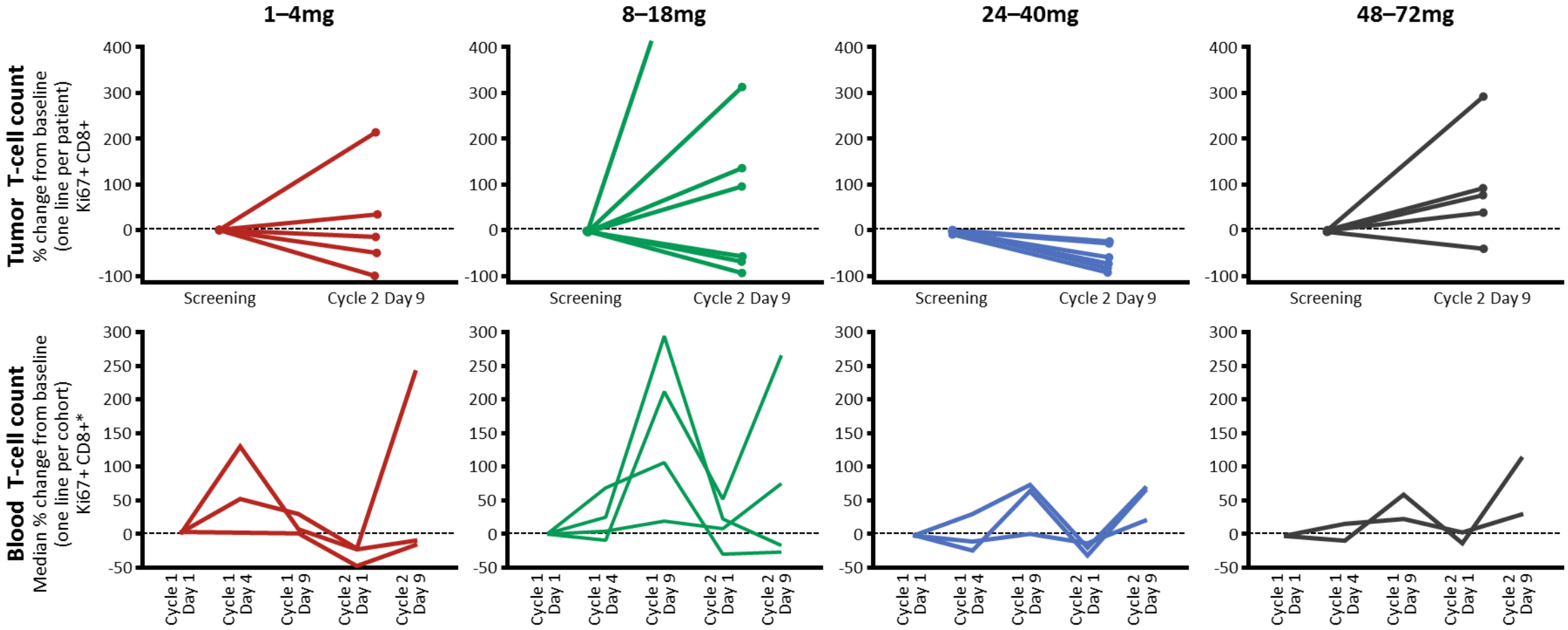




[1] Includes unconfirmed PRs

Dynamics of proliferating T-cells in tumor and blood

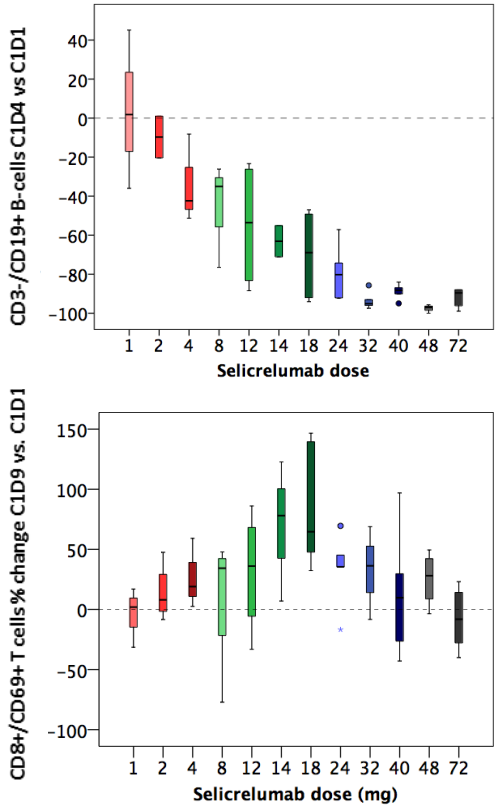
Selicrelumab/vanucizumab induces T-cell proliferation in peripheral blood and in the tumor, without clear dose dependency



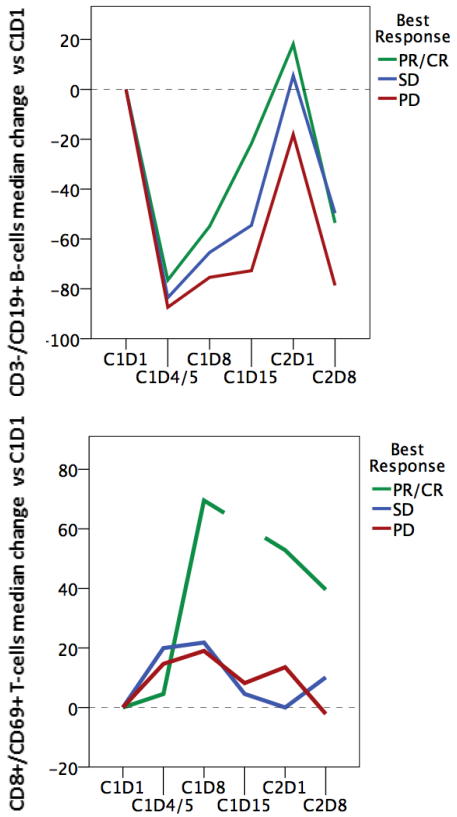
*Within CD8+ T cell pool

Dose selection

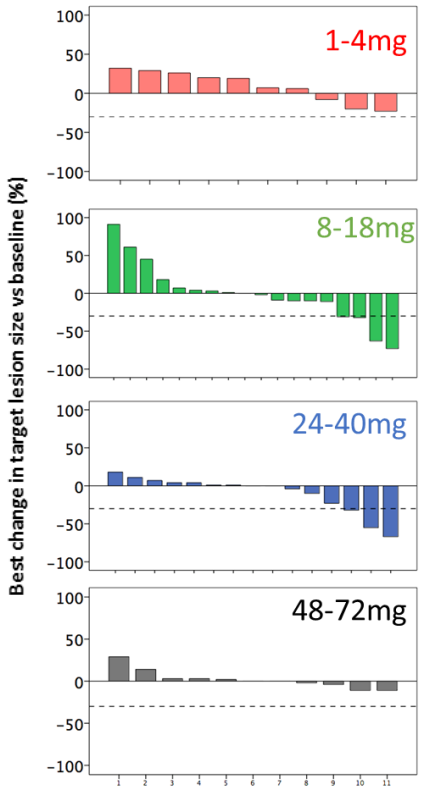
1. B-cell redistribution (APC activation) increases with dose, but not T-cell activation



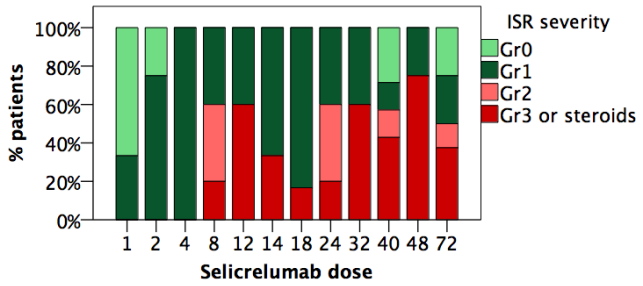
2. Potential association of response with T-cell activation, but not with B-cell redistribution



3. Objective responses at 8-40mg only



4. Safety (ISR) similar at doses ≥8mg



An intermediate-dose of 16mg (4 x 4mg) of selicrelumab was chosen for further development

Lessons and take home messages

- S.c. administration of selicrelumab represents a safe option to achieve immune activation without dose-limiting cytokine release
- The potential correlation of the clinical responses with immune activation suggests a positive combinatorial effect for the selicrelumab/vanucizumab combination, and warrants further evaluation in disease-specific expansions
- Study will continue as a combination of selicrelumab + bevacizumab (vanucizumab program discontinued)
- Selicrelumab/bevacizumab is currently tested in platinum-resistant ovarian cancer, head & neck squamous cell carcinoma, and post-checkpoint inhibitor non-squamous non-small cell lung cancer, at a selicrelumab dose of 16mg (4 x 4mg)

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