Strategy, efficacy and safety of combination regimens using immunotherapy

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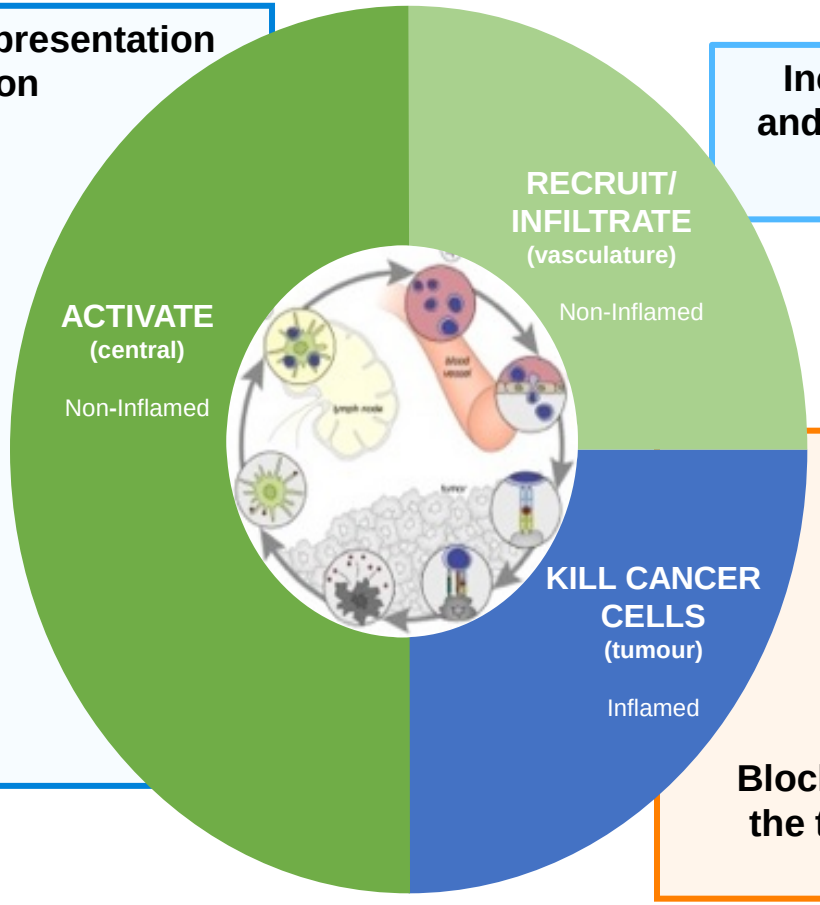
Disclosures

- Advisory Board: Clovis, AstraZeneca, VBL, Janseen, Tesaro

Combination opportunities in cancer immunotherapy



Enhance antigen presentation and T-cell activation

EGFR inhibitors
ALK inhibitors
BRAF inhibitors
MEK inhibitors
Chemotherapy
HDAC
Radiotherapy
Anti-CD40
IFN-g
Oncolytic viruses
Neo-epitope vaccine
Anti-CEA-IL2v
Anti-FAP-IL2v
Anti-OX40
Anti-CTLA4
Anti-CD27
Anti-41BB
PARPi

Increase T-cell trafficking and infiltration into tumors

Anti-VEGF

TCBs
ImmTACs
CAR-T
BiTes
Anti-PDL1
Anti-PD1
Anti-CSF-1R
IDO inhibitors
Anti-TIGIT
Anti-TIM3
Anti-LAG3

Block immunosuppression within the tumor microenvironment and enhance tumor cell death

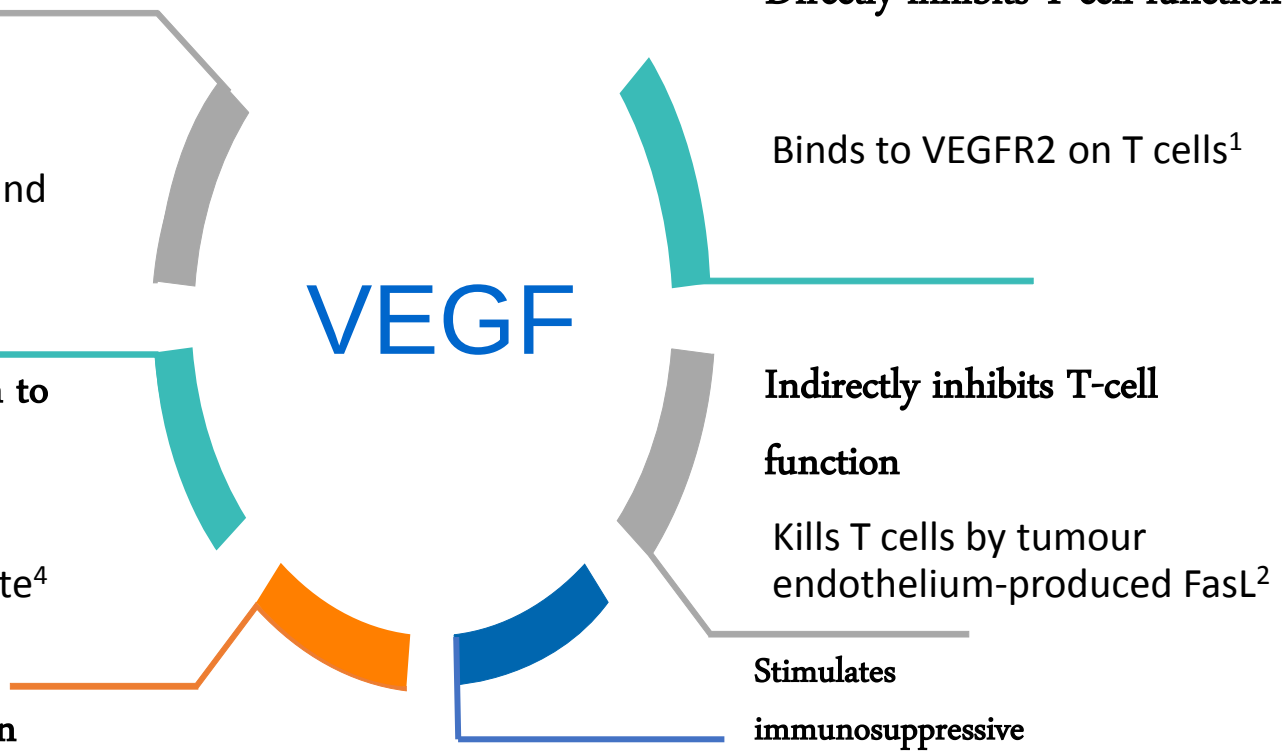
Chen & Mellman. Immunity 2013
Galluzzi, et al. Nat Rev Drug Discov 2012
Hannani, et al. Cancer J 2011; Vanneman and Dranoff. Nat Rev Cancer 2012

Novel combination strategies in development

- VEGFi + T cell modulators
- PARPi + I/O agents
  - PARP inhibition may increase immunogenicity
- I/O + chemotherapy
- I/O + I/O
- Triple Combos

I/O + VEGFi

Rationale for combining cancer immunotherapy with anti-VEGF



Induces abnormal tumor vasculature

Reducing T-cell trafficking and infiltration into the tumour bed[5,6]

Reduces lymphocyte adhesion to vessel walls

Decreases immune-cell recruitment to the tumor site[4]

Inhibits dendritic cell function

Drives them into an immature state[3]

Directly inhibits T-cell function

Binds to VEGFR2 on T cells[1]

Indirectly inhibits T-cell function

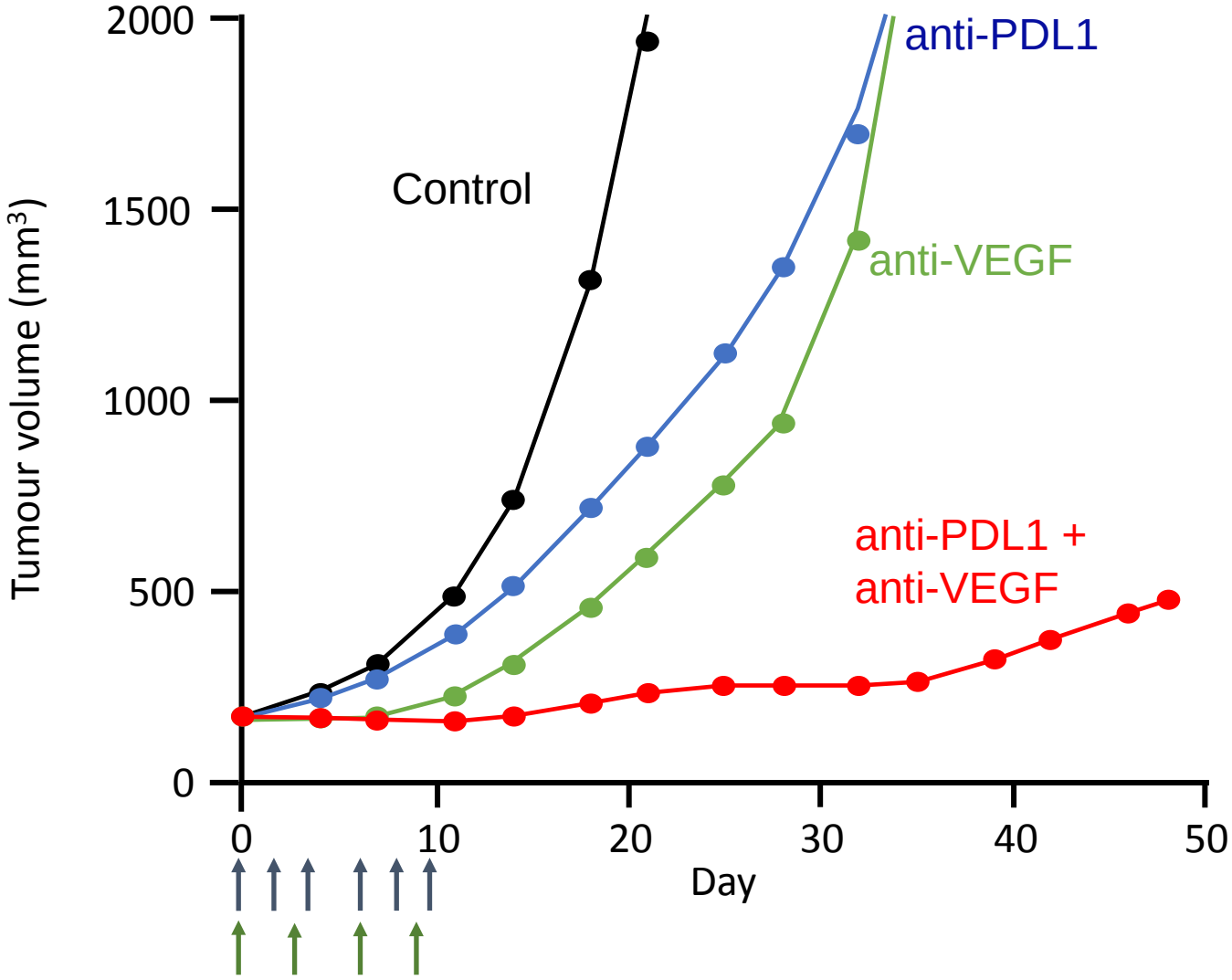
Kills T cells by tumour endothelium-produced FasL[2]

Stimulates immunosuppressive regulatory T cells[2]

1. Gavalas et al. Br J Cancer 2012; 2. Terme et al. Cancer Res 2013
3. Coukos. Br J Cancer 2005; 4. Bouzin et al. J Immunol 2007
5. Shrimali et al. Cancer Res 2010; 6. Chen & Mellman. Immunity 2013

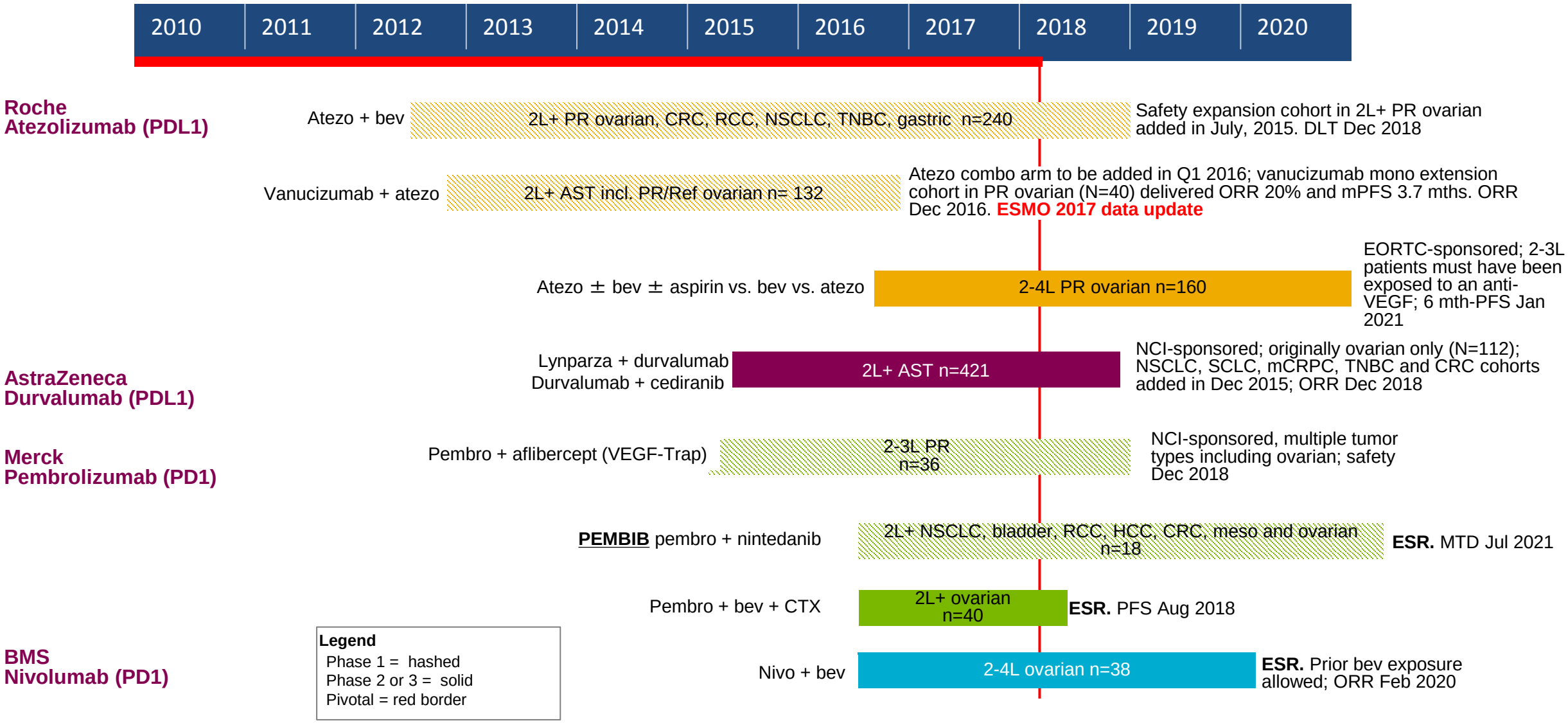
Pre-clinical data for combining anti-PD-L1 and VEGF blockade

Combined treatment with these two agents synergistically inhibited tumour growth in the Cloudman mouse tumour model



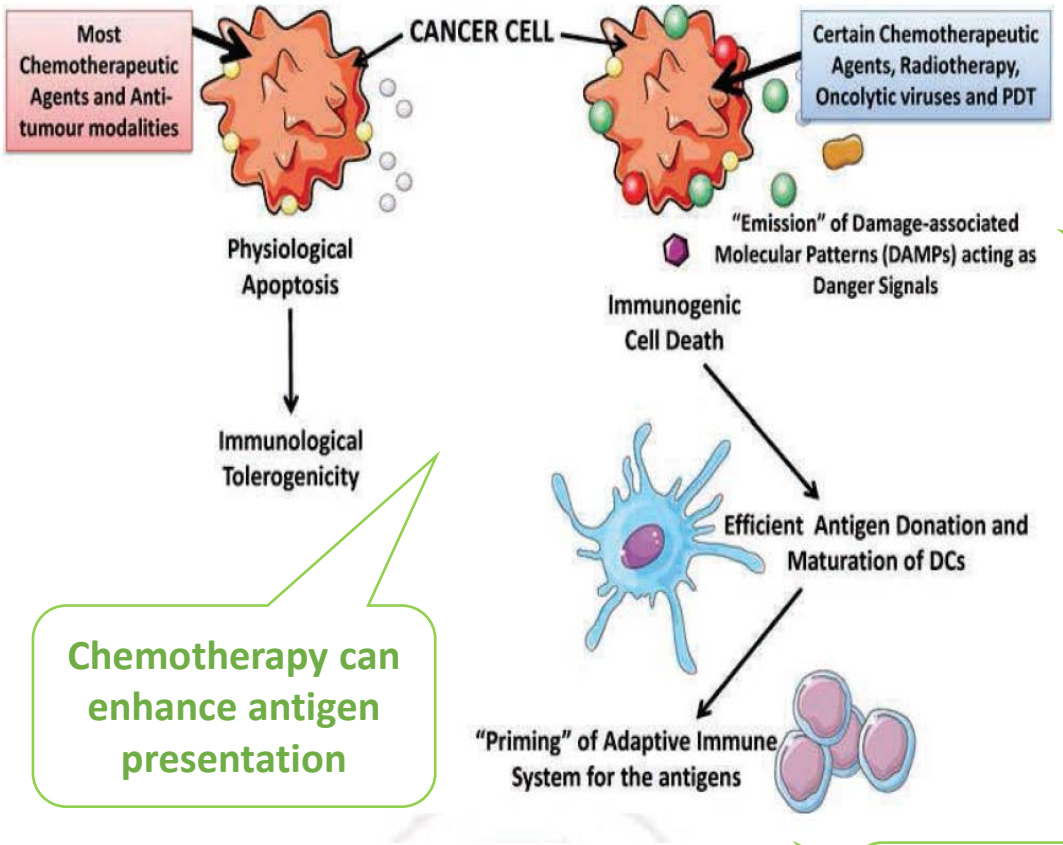
Irving. 1st Annual Expert Forum on Immuno-oncology, 2013

Immunotherapy with bevacizumab



I/O + chemo

Immunogenicity of chemotherapy



Chemotherapy can enhance immunogenicity (release of adjuvants by cells)

Chemotherapy can enhance antigen presentation

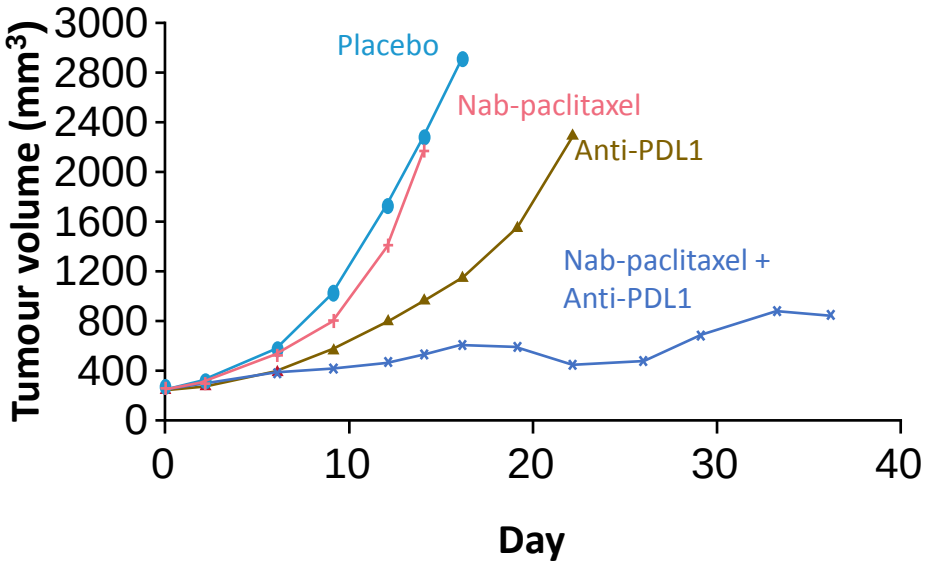
Chemotherapy can increase susceptibility to immune attack

DAMPs, danger-associated molecular patterns; DC, dendritic cell; PDT, photodynamic therapy

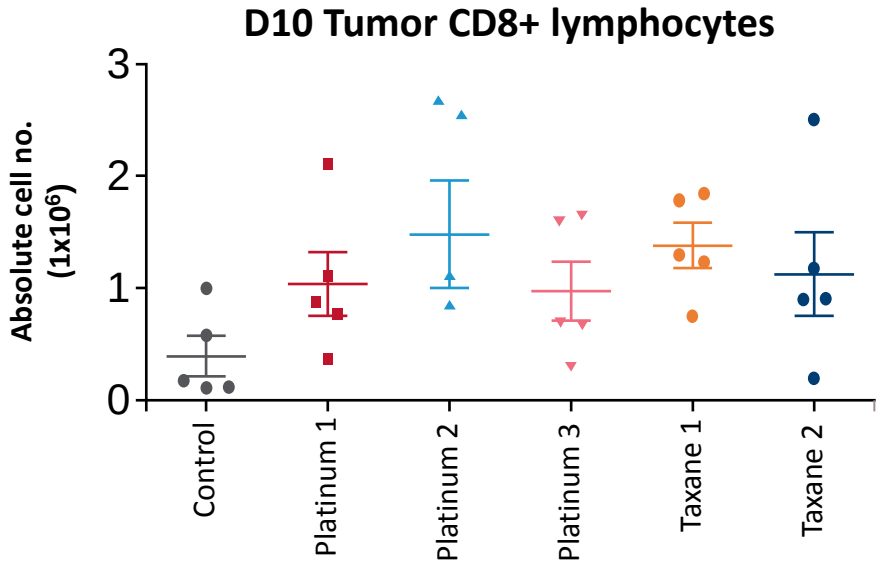
Garg et al. Biofactors 2013

Pre-clinical evidence for chemotherapy and anti-PDL1

Synergism of nab-paclitaxel plus anti-PDL1 in MC38 mouse tumour model



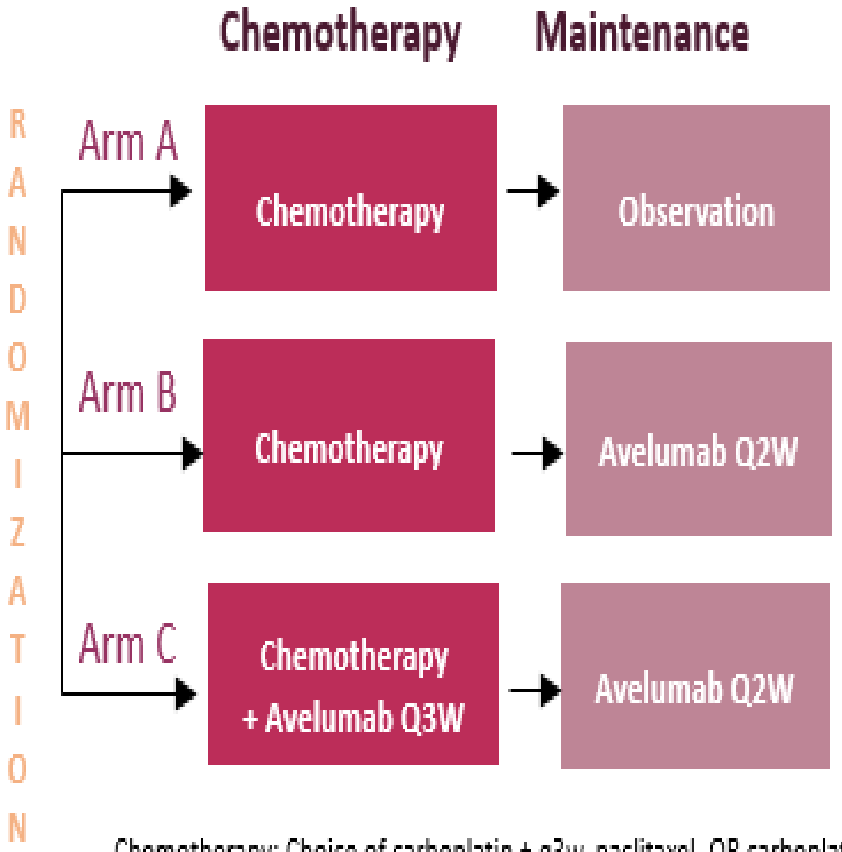
The synergism of nab-paclitaxel plus anti-PDL1 has been demonstrated in a MC38 mouse tumour model[1]



Treatment with platinum agents or taxanes increased the percentage of CD8+ tumour-infiltrating lymphocytes in immunocompetent mouse models[2]

1. Adams et al. SABCS 2015
2. Jeong Kim, Genentech; unpublished data

Javelin 100



Primary endpoint:

PFS from randomization (A vs B, A vs C)

Secondary endpoints:

Maintenance PFS, OS, ORR, duration of response, pCR, PFS2, PROs, safety, PK

Chemotherapy: Choice of carboplatin + q3w, paclitaxel, OR carboplatin + weekly paclitaxel

Maintenance avelumab up to 24 months

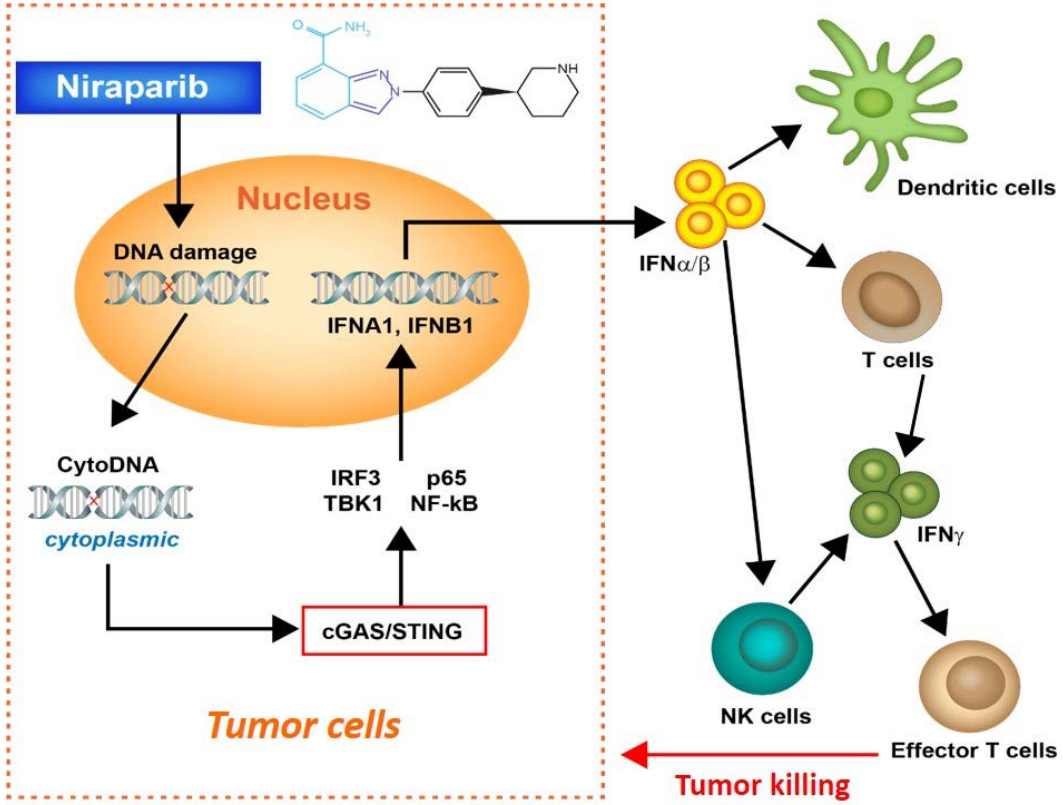
I/O + PARPi

Scientific rationale for PARPi in combination with PD-1 inhibitor

Preclinical models exhibit synergy with combination PARPi + anti-PD-1 agents regardless of BRCA mutation status or PD-L1 expression

- Unrepaired DNA damage resulting from niraparib treatment leads to the abnormal presence of DNA in the cytoplasm, which activates the stimulator of interferon gene (STING) pathway

- Activation of the STING pathway leads to increased expression and release of type 1 interferons, subsequent induction of γ-interferon, and intratumoral infiltration of effector T cells

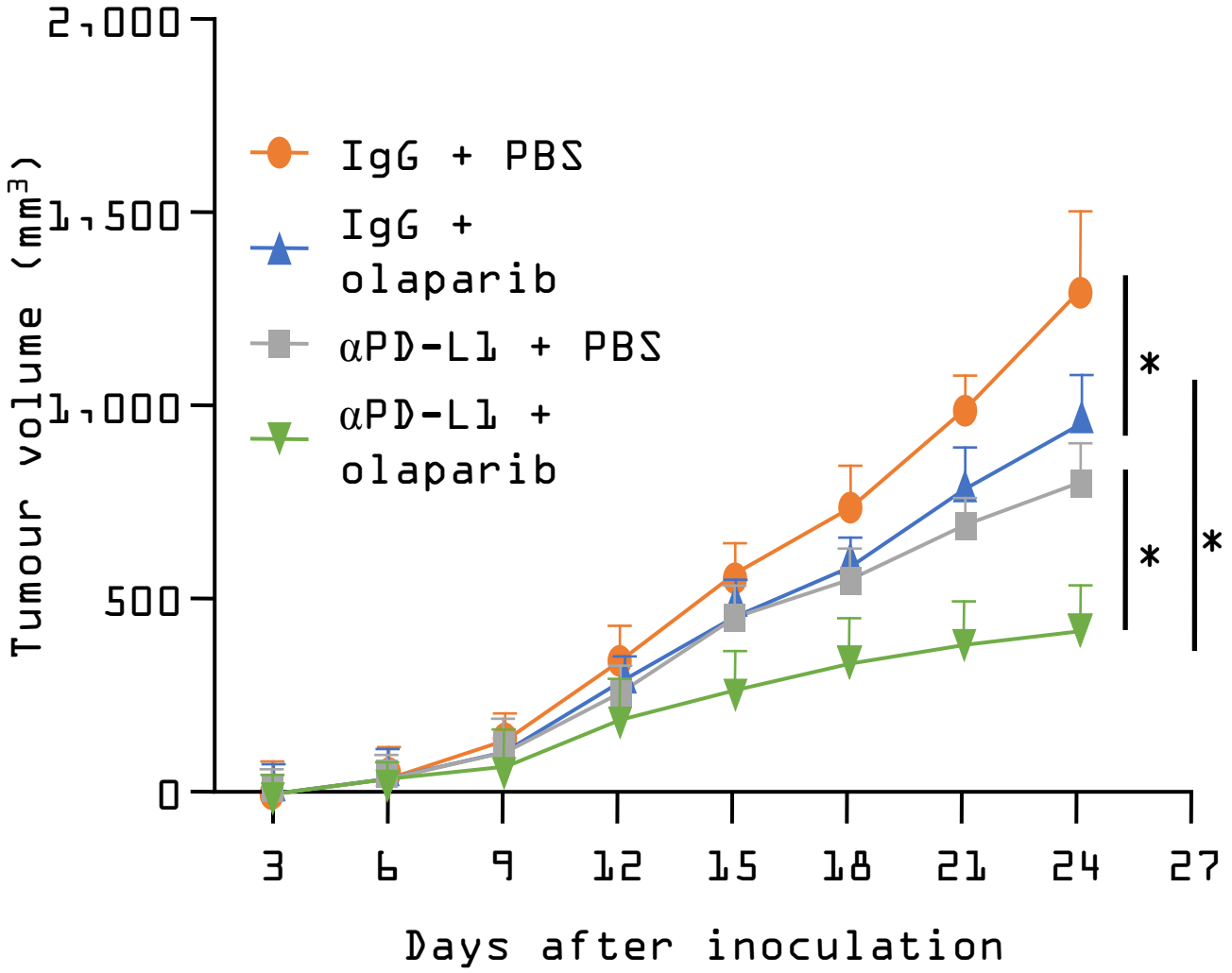


NCT02657889

Konstantinopoulos et al. SGO 2018

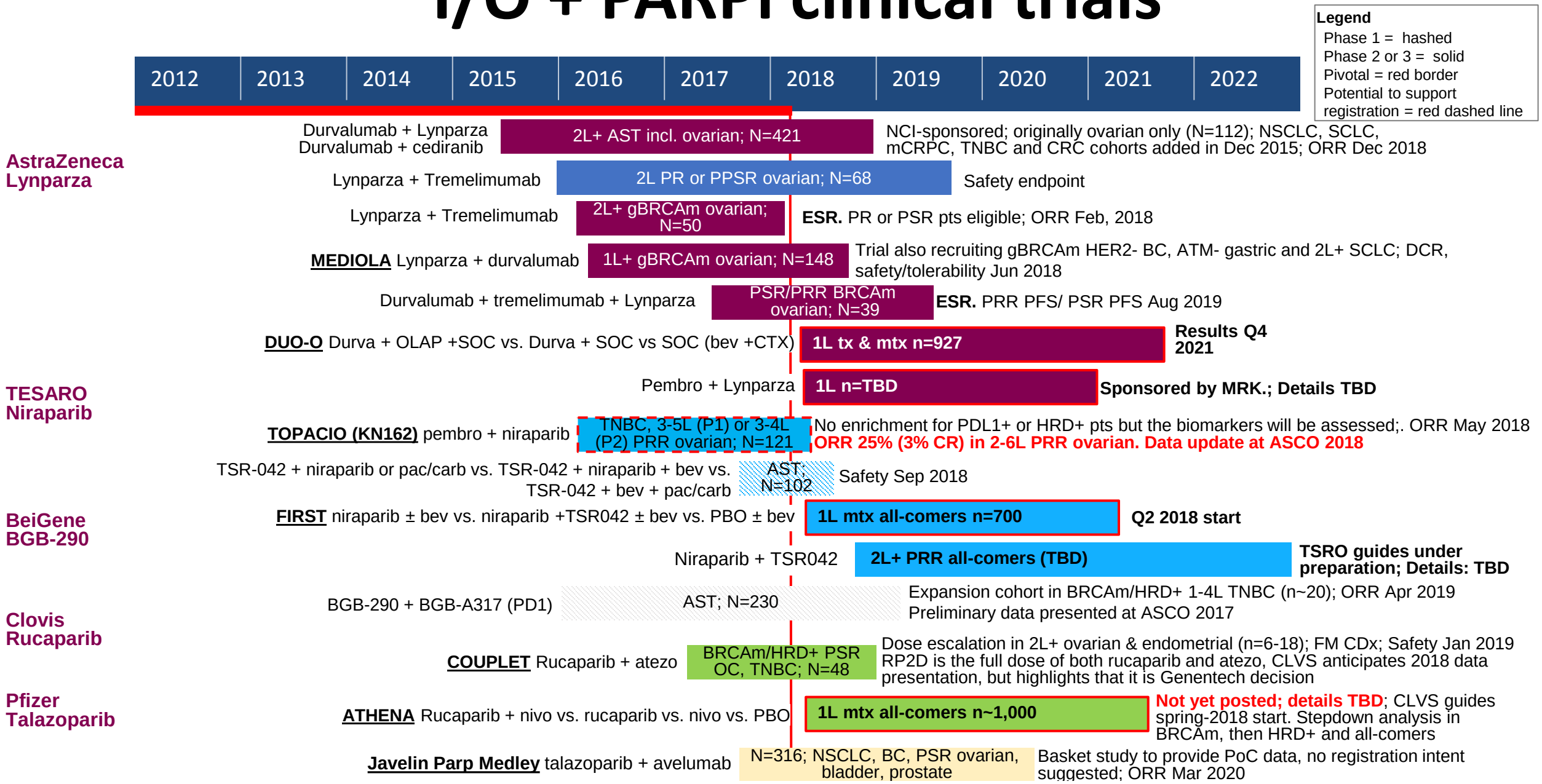
Pre-clinical evidence for anti-PDL1 and PARPi

Treatment with either olaparib or anti-PDL1 alone restricted tumour growth, but the combined treatment demonstrated enhanced therapeutic benefit



Jiao et al. Clin Cancer Res 2017

I/O + PARPi clinical trials



Anti-PD1 and PARPi: TOPACIO/Keynote-162

Phase I/II study dose-finding combination study of niraparib plus pembrolizumab in patients with metastatic TNBC or recurrent platinum-resistant epithelial OC

Evaluable patients*	Integrated Efficacy Analysis (combined phase 1+2) PROC Cohort N=60	
	n (%)	Still on Treatment, n
Complete response (CR)	3 (5%)	1
Partial response (PR)	12 (20%)	6
Stable disease (SD)	25 (42%)	2
Progressive disease (PD)	20 (33%)	
ORR (CR+PR)	25%	
Disease control rate (CR+PR+SD)	67%	

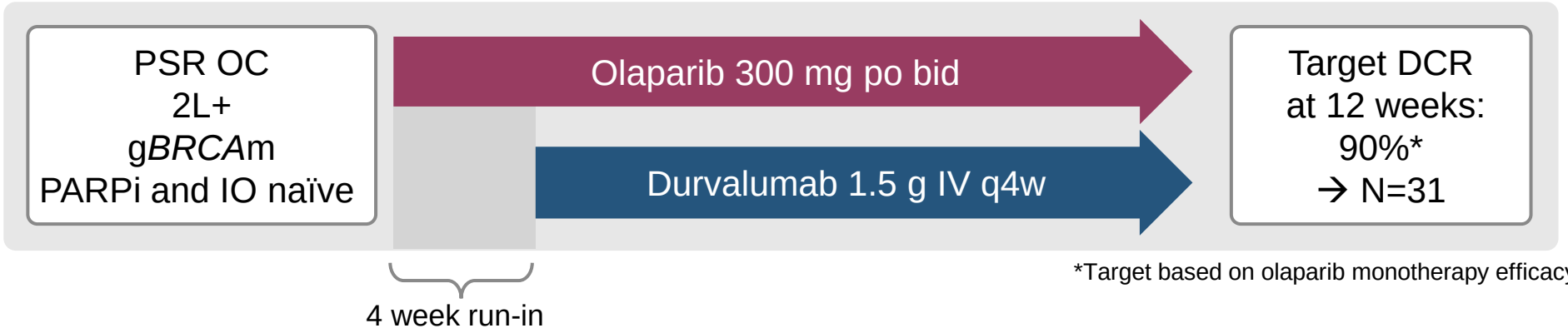
~60% (9/15) of responders (CR or PR) remain on treatment as data continue to mature; duration of response and PFS will be presented at an upcoming conference

NCT02657889
Konstantinopoulos et al. ASCO 2018

**Two patients were not evaluable for efficacy; data are immature, responses include both confirmed and unconfirmed; evaluable pts had at least one on-treatment scan; data as of April 2, 2018*

Anti-PD1 and PARPi: MEDIOLA

Initiation of therapy at the time of relapse



- Primary endpoints: DCR at 12 weeks, safety
- Secondary endpoints: DCR at 28 weeks, ORR, DoR, PFS, OS, PD-L1 expression
- Exploratory endpoints: TILs

NCT02734004
Drew et al. SGO 2018

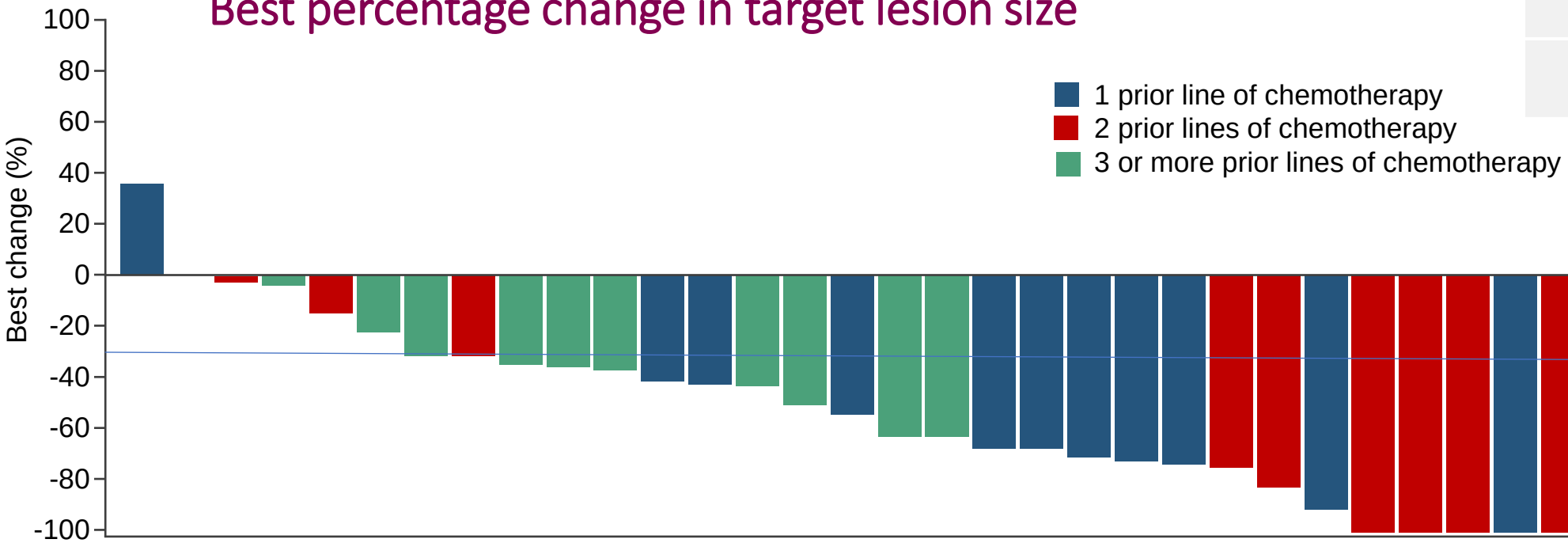
DCR, disease control rate; DoR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; po, oral; TILs, tumor-infiltrating lymphocytes

MEDIOLA: tumor responses

	1 prior (2L)	2 prior (3L)	3+ prior (4L)	All lines
ORR	10/13=**77%**	6/9=**67%**	7/10=**70%**	23/32=**72%**
95% CI	(46%, 95%)	(30%, 93%)	(35%, 93%)	(53%, 86%)

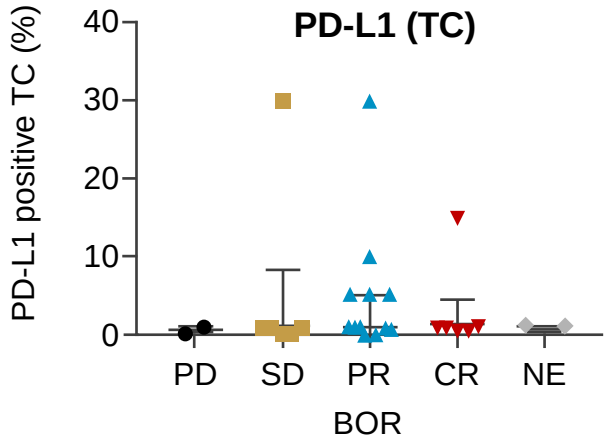
Best Response	N (%)
CR	**6 (19)**
PR	**17 (53)**
SD	3 (9)
PD	3 (9)
NE	3 (9)

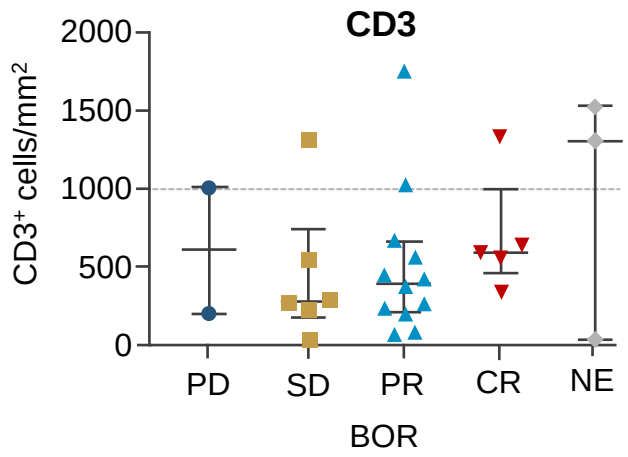
Best percentage change in target lesion size

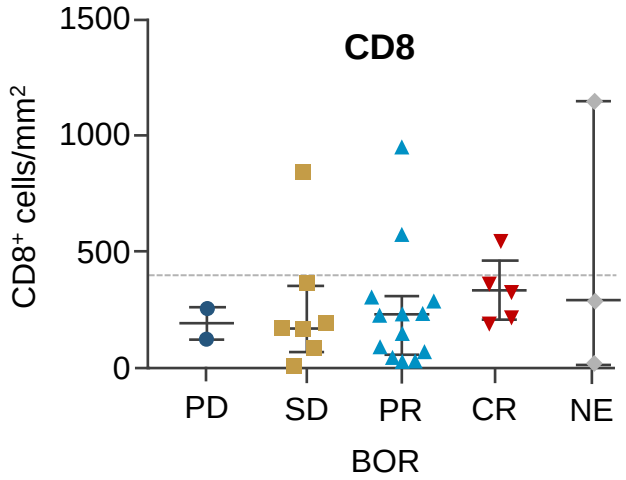


PD-L1 and TILs in archival tissue: association with clinical response

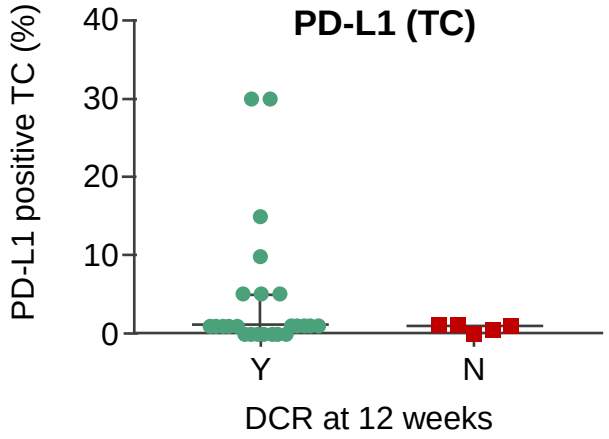
BOR







DCR

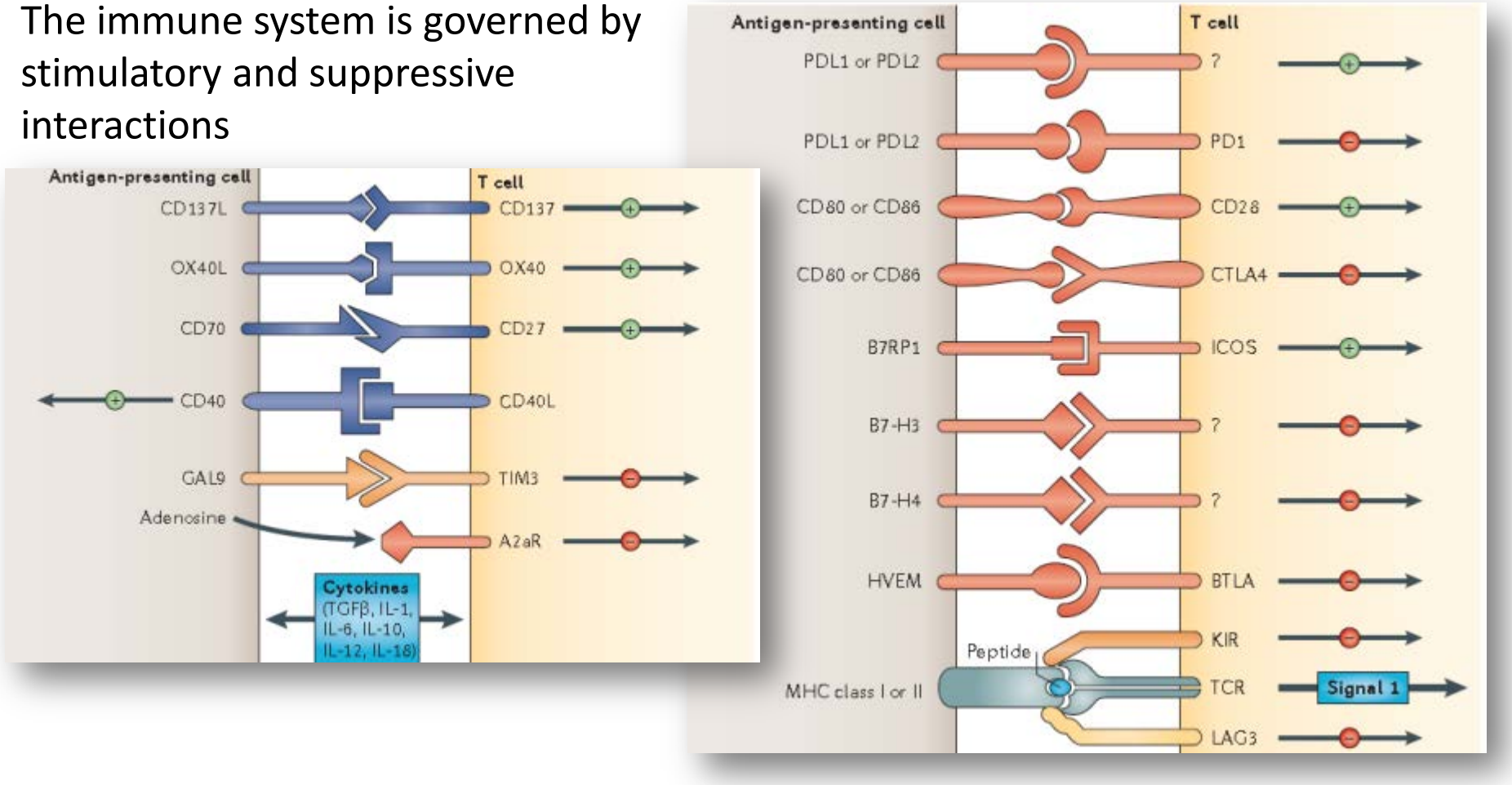


- No statistically significant associations were observed between PD-L1 TC positivity or CD3 and CD8 TILs and positive BOR
- However, a trend was observed where higher PD-L1 and increased TIL densities were observed in archival samples in patients who had SD/PR/CR – this was not seen in patients with PD
- Higher PD-L1 (TC) was observed in patients with DCR at 12 weeks

Dotted lines indicate CD3 (1000 cells/mm^2) and CD8 (400 cells/mm^2) 'hot/cold' thresholds established from unpublished data. Error bars present the median ± interquartile range.
BOR, best objective response; TC, tumor cell; TILs, tumor infiltrating lymphocytes; Y, Yes; N, No

Dual signals control immune function

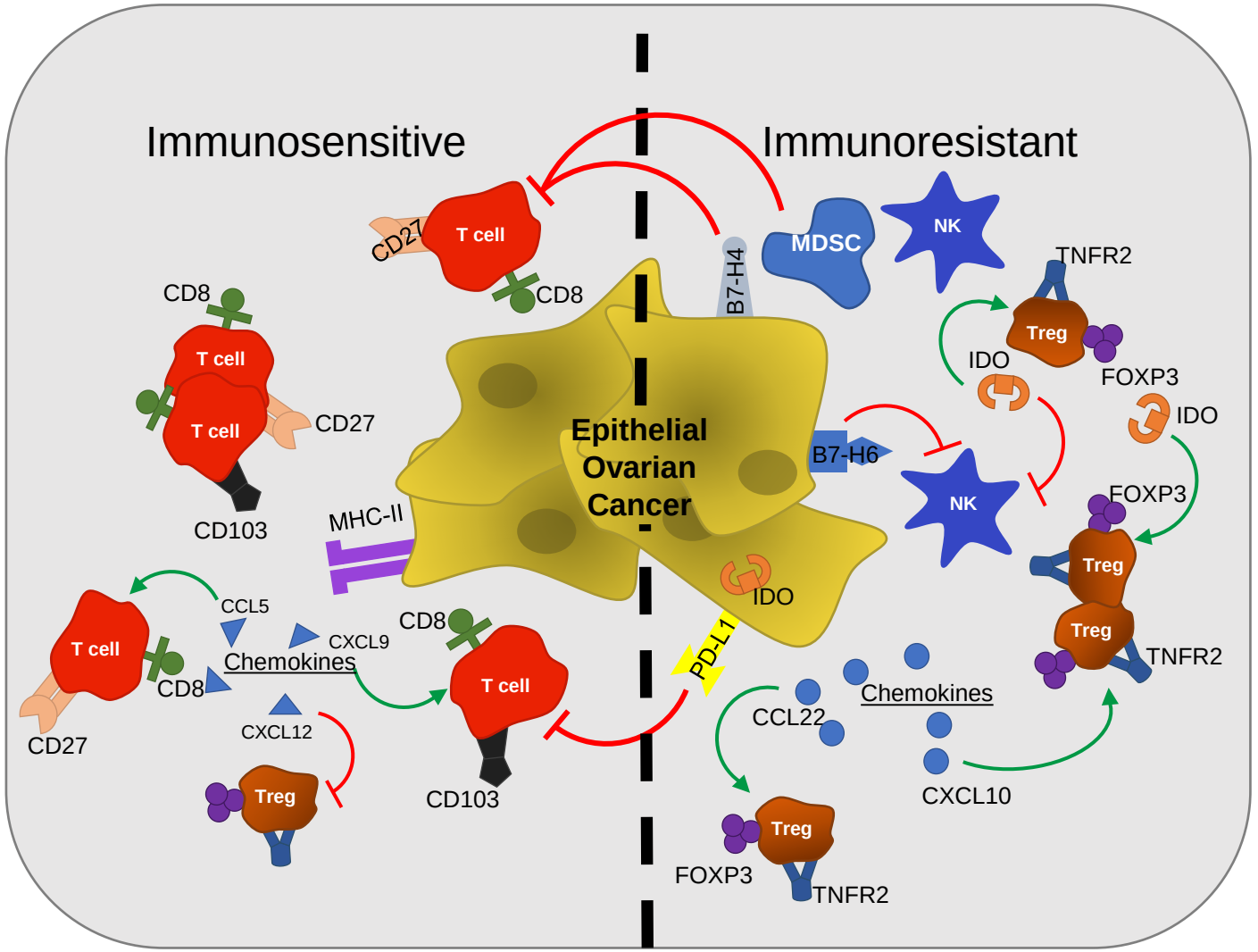
The immune system is governed by stimulatory and suppressive interactions

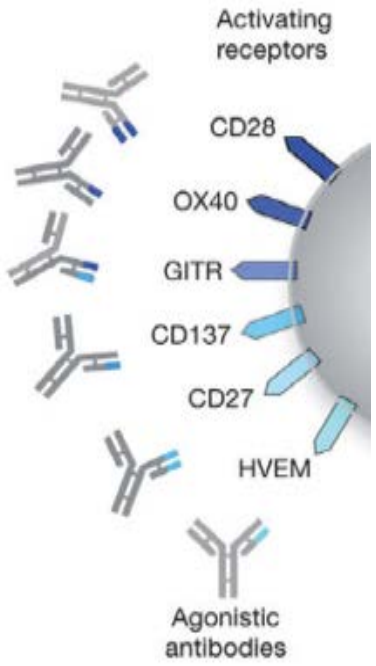


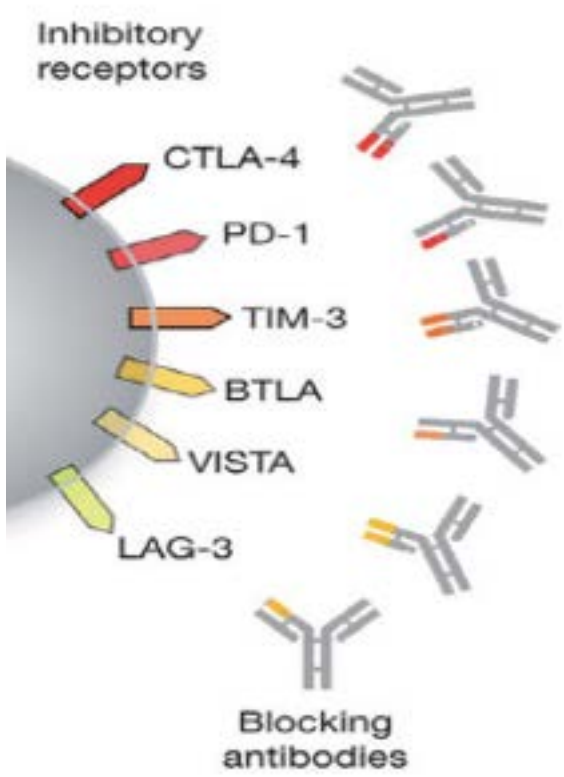
Pardoll DM. Nature Rev Cancer. 2012;12:252-264

I/O + I/O

TURN UP the GOOD and TURN DOWN the BAD







NRG GY003: nivo vs nivo/ipi

- Phase II trial in recurrent ovary CA
- Hypothesis: enhancing CD8 T cell accumulation and activity will reduce the population of T_{reg} cells and promote anti-tumor activity
- Dual blockade of PD-1 and CTLA-4:
  - Tumor reactive TILs contain both
  - Mice model showed that dual blockade reversed $CD8^+$ TIL dysfunction and increased multiple immunogenic markers (↑Ag specific CD8+, CD4+, cytokine release, ↓ suppressive Treg cell function, etc)

NCT#02498600

DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (central and peripheral attack)

- Phase II, single arm trial with 31 histologic cohorts
- 1^{o} objective: evaluate ORR in pts with advanced rare tumors treated with nivo + ipi
- Given the impressive RR with combination nivo/ipi in melanoma (versus either as monotherapy), the combination therapy is expected to be the most efficient approach to testing immune checkpoint blockade efficacy across a variety of rare tumor types.

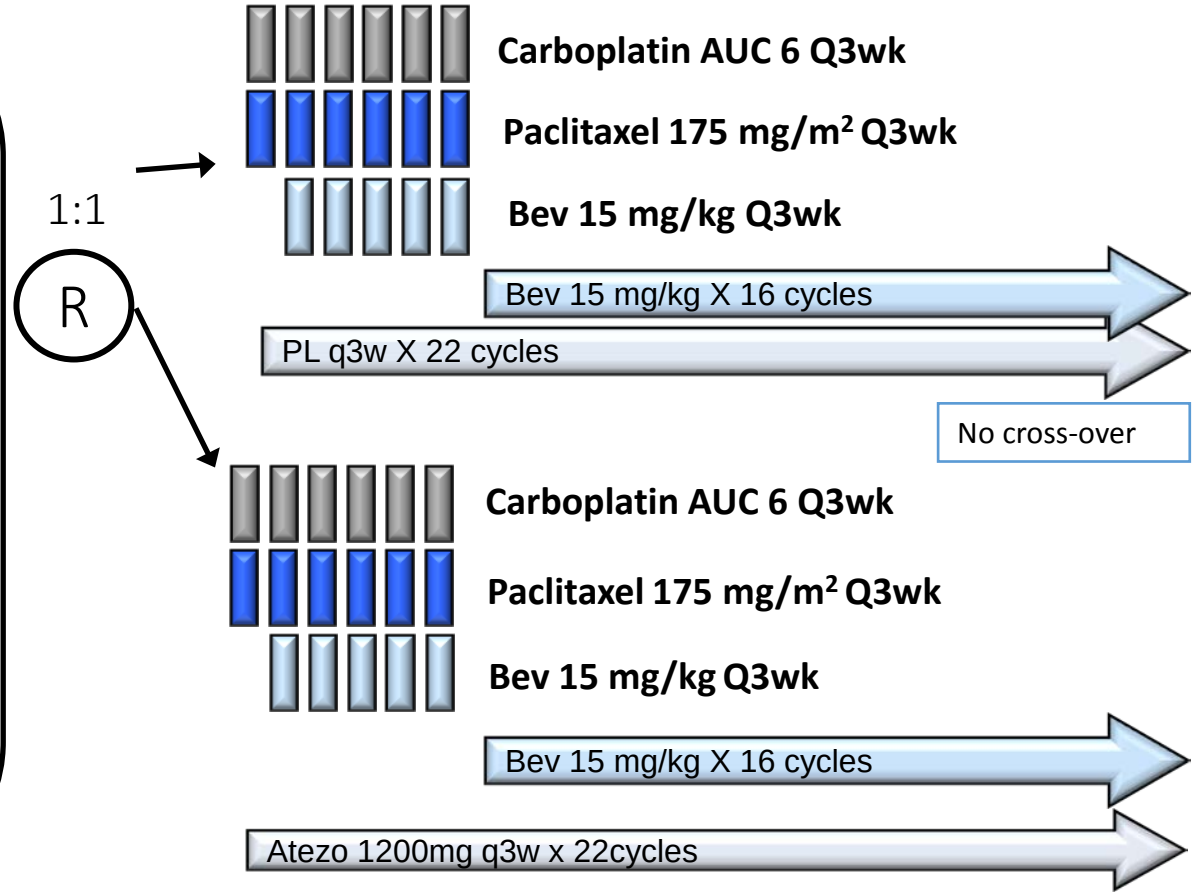
NCT#02834013

Triple Combos

Atezolizumab and bevacizumab: IMaGYN050

Double blinded, 1:1 randomized, placebo-controlled multi-center study

- Previously untreated epithelial ovarian, primary peritoneal, or fallopian tube cancer
- Stage III (sub-optimal/ optimal w/ macroscopic residual), Stage IV, or patients w/ advanced disease treated in the neo-adjuvant setting

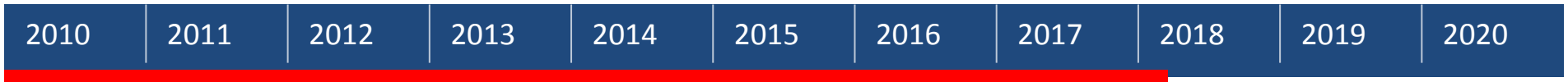


Co-Primary endpoint: PFS &OS in all comers and Dx+ (IC 1+)

NCT03038100

Other I/O combinations

Legend
Phase 1 = hashed
Phase 2 or 3 = solid
Pivotal = red border



BMS
Nivolumab (PD1)

Nivo + lirilumab **(KIR)** — Ovarian, RCC, CRC, NSCLC and mel n=650 — N=16 patients in each cohort

BMS-986016 **(LAG3)** ± nivo — AST n=1,000 — Safety Jun 2019; Ovarian cohort only in the dose escalation arm

CM032 Nivo vs nivo + ipi **(CTLA-4)** — Ovarian, TNBC, gastric, bladder pancreatic, SCLC n=1,150 — Signal finding for nivo + Ipi combo. Ovarian cohort added in Sept 2015; ORR Dec 2018

ECHO 204 Nivo + epacadostat **(IDO1)** — 2L+ ovarian, NSCLC, mel, CRC, SCCHN, NHL, HL, GBM n=485 — Incyte-sponsored; ORR/PFS Apr 2020

Nivo + varlilumab **(CD27)** — 2-6L ovarian, NSCLC, mel, CRC, SCCHN n=175 — Celldex-sponsored; ORR Apr 2019

NRG-GY003 nivo vs. Nivo + ipi **(CTLA-4)** — **2-4L PR or PPSR ovarian n=96** — NCI-sponsored; currently suspended for recruitment , 2-step design suggest pts needed for the first step have been enrolled in the first 4-weeks, ORR Dec 2020

FPA008 ± nivo **(CSF1R)** — 2L+ ovarian, NSCLC, SCLC, SCCHN, panc, RCC, Gliomas n=295 — Five Prime-sponsored; safety May 2019

Nivo + IFN-γ — 2L+ AST n=15 — **ESR.** safety Dec, 2019

Nivo + WT1 **(vaccine)** — 2L+ maintenance ovarian n=11 — **ESR.** WT1+; DLT Apr 2019

ABBV-428 ± nivo **(CD40)** — 2L+ AST incl. ovarian n=172 — Safety Apr 2019

Roche
Atezolizumab (PDL1)

Atezo + RO5509554 **(CSF1R)** — 1L+ ovarian, TNBC, gastric, bladder, sarcoma n=310 — Safety Nov 2018

Atezo + GDC-0919 **(IDO1)** — AST, n=158 — DLT Dec 2018; ovarian cohort added in Aug 2016

Atezo ±guadecitabine ± CDX-1401 vaccine **(HMA)** — 2L+ PRR ovarian, n=78 — NCI-sponsored; PFS Mar 2020

Merck Serono/Pfizer
Avelumab (PDL1)

Avelumab + defactinib **(FAK)** — 4-7L ovarian, n=98 — Verastem-sponsored; FPI announced Jan 2017; ORR Nov 2018

Avelumab + entinostat vs. avelumab **(HDAC)** — 4-7L ovarian, n=138 — Syndax-sponsored; ORR Apr 2018

Other I/O combinations

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