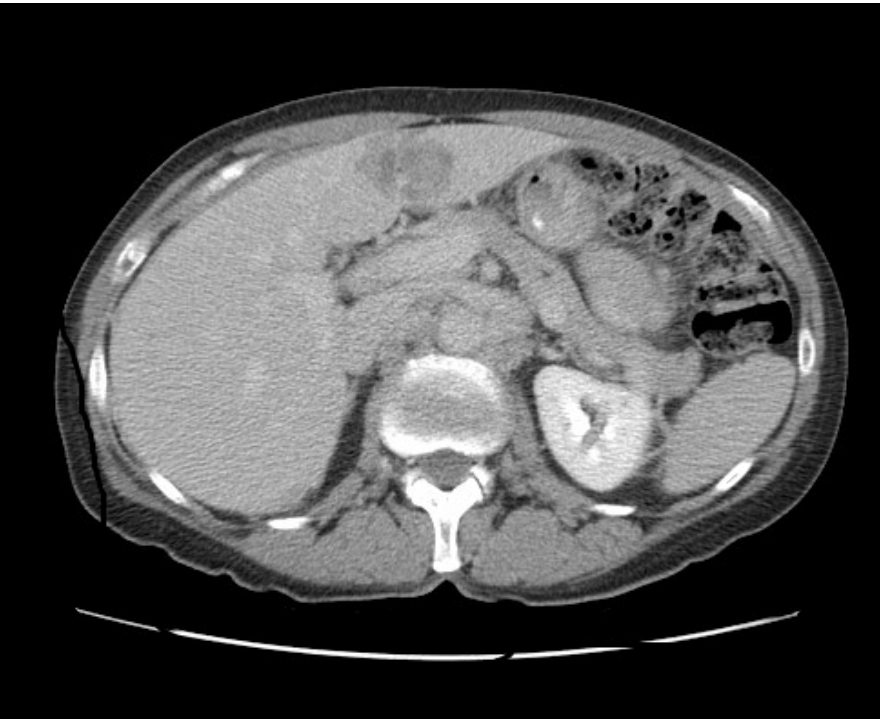
Novel Investigational Agents in Development and Emerging Role of Immunotherapy in Gynecologic Cancers

SGO, Washington DC March 2017

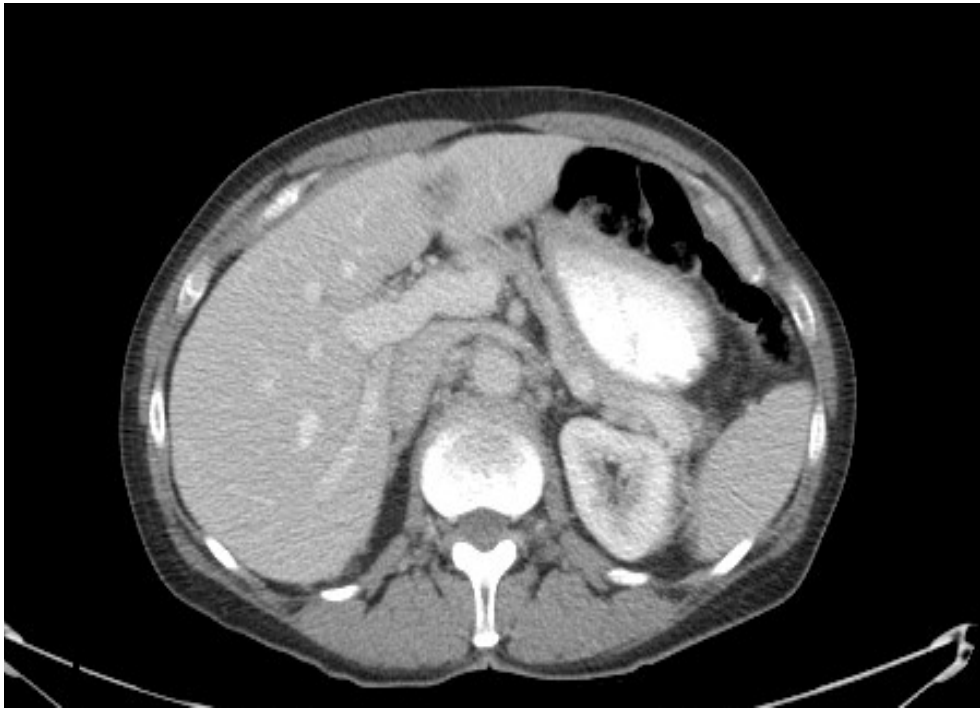
Case #1

- A 70 y.o. woman diagnosed in 8/13 with serous cancer of the ovary
- She was treated with neoadjuvant carbo/paclitaxel
- Optimal cytoreduction in 11/13 followed by 3 cycles of carbo/paclitaxel (2/14)
- Recurrent disease in 8/14 started on early phase trial CRLX101 + bevacizumab
- Progressive disease 9/15
- Started on Phase I trial of mirvetuximab soravtansine (IMGN853)

Initial Scan



After 2 cycles



- **Stayed on trial for 19 cycles**
- **PD on 2/1/17**

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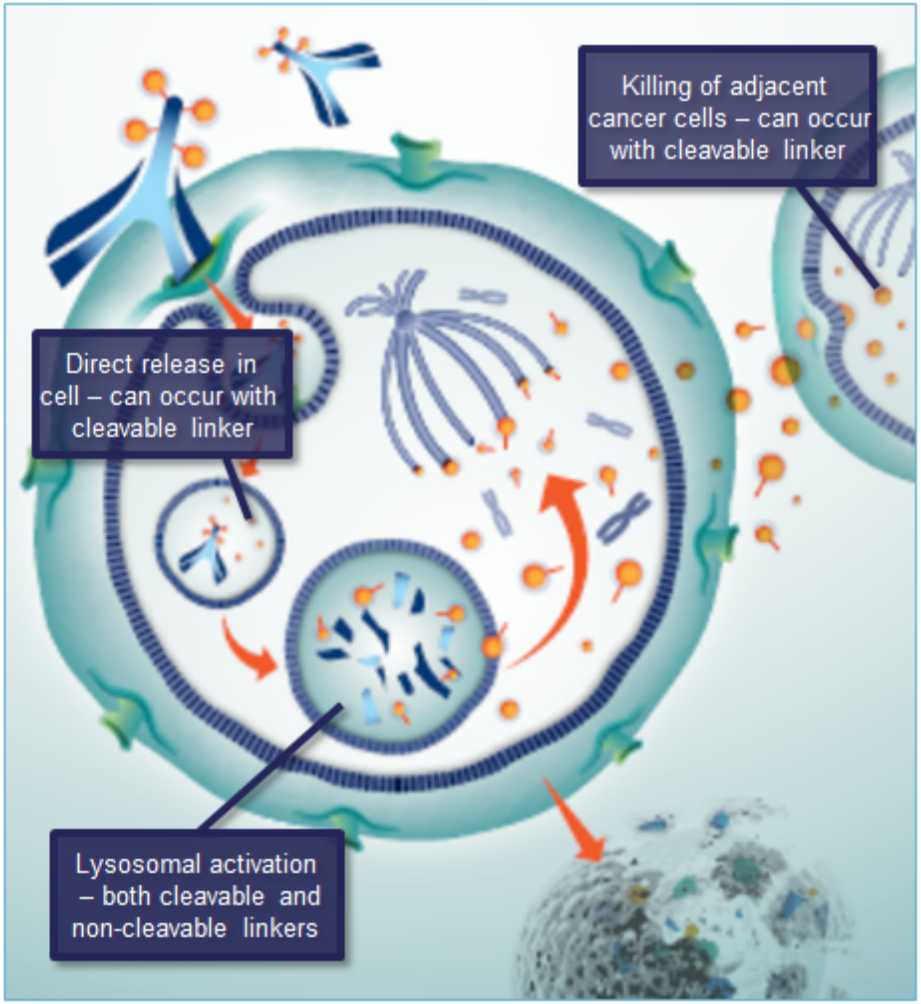
Disclosure

Advisory Committee	Roche Laboratories Inc

Mirvetuximab Soravtansine (IMGN853) – Antibody-Drug Conjugate Targeting Folate Receptor α



Target

- Folate receptor α (FRα) – highly expressed in ovarian and other solid tumors
- Distinct from homeostatic folate transporters

Antibody (Ab)

- A FRα-binding antibody

Linker

- Sulfo-SPDB cleavable linker - stable in the circulation, optimized to resist MDR, promote bystander cell killing

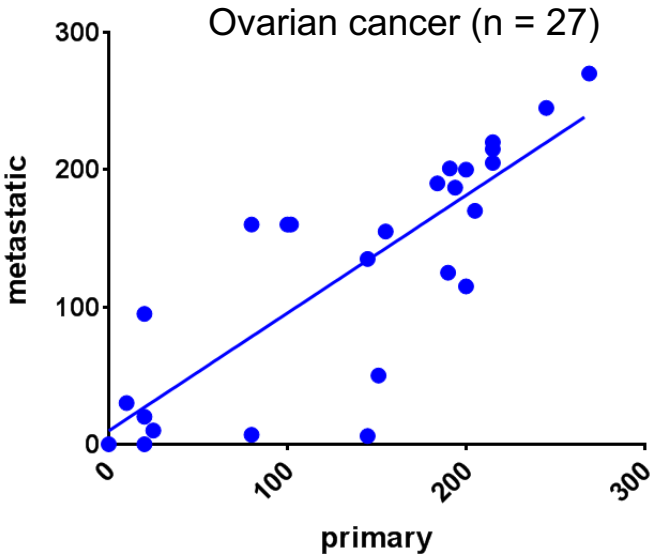
Anticancer agent payload

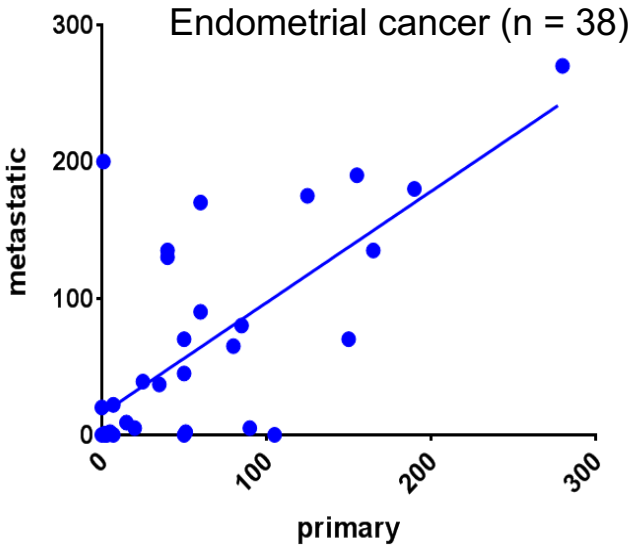
- DM4 – a potent tubulin-targeting agent

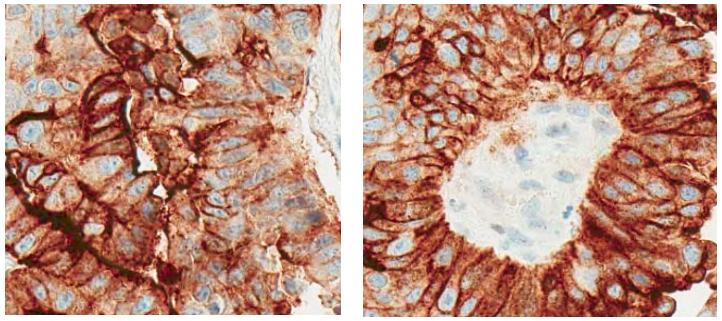
Mirvetuximab soravtansine exhibits linear PK with an elimination half-life of 4.8-5.8 days and no accumulation

ASCO 2016 Moore et al

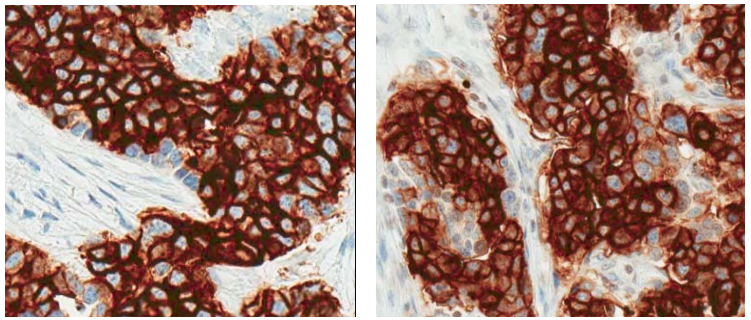
Correlation in FRα Expression Between Paired Primary and Metastatic Samples







Primary Metastatic

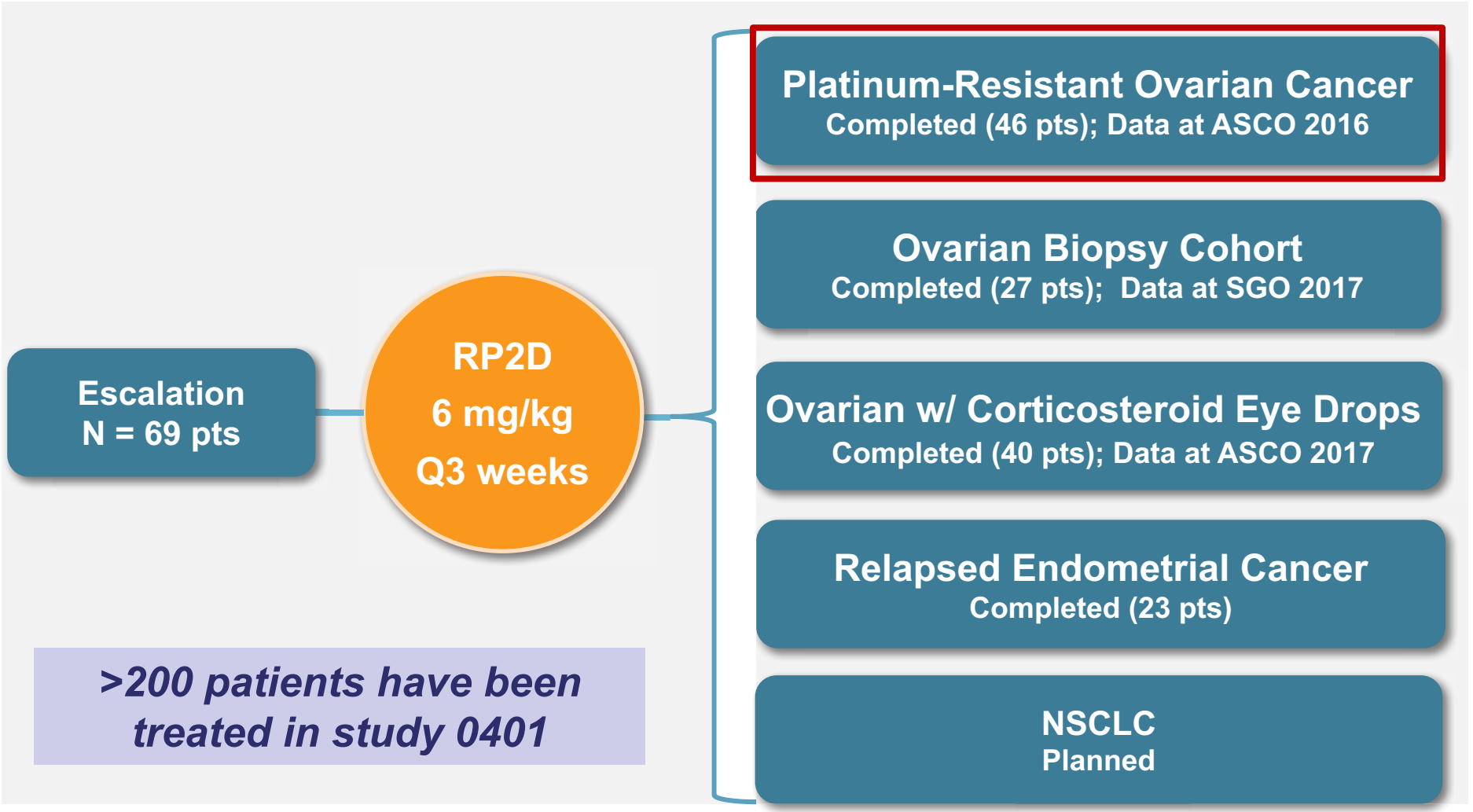


Primary Metastatic

Commercial samples, collected during same surgical procedure

Data suggest limited heterogeneity in FRα expression

Mirvetuximab 0401 FIH Phase I Trial
Platinum-Resistant Expansion

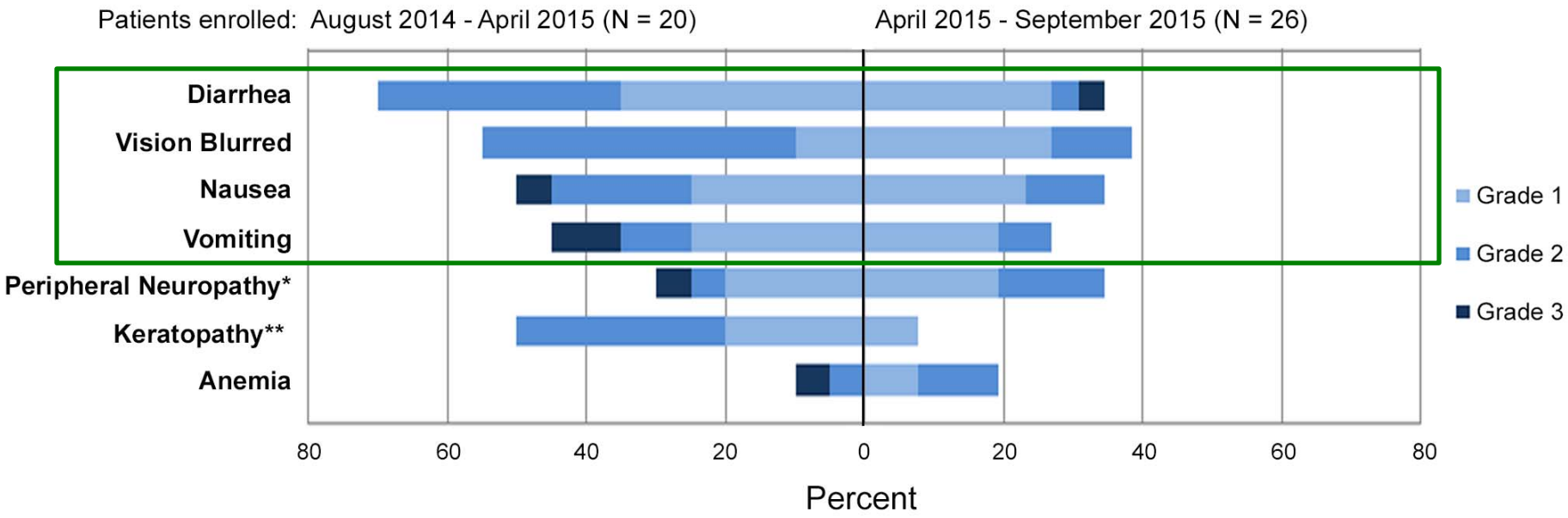


Baseline Demographics

	ASCO 2016 Cohort (n = 46)
Age	
Median	62.5
Min-Max	38 - 83
Number of Prior Systemic Therapies	
1-3	23 (50%)
4+	23 (50%)
Platinum Resistant	
Yes	46 (100%)
No	0 (0%)
Prior therapy with	
Platinum compounds	46 (100%)
Taxanes	46 (100%)
Bevacizumab	29 (63%)
PARP inhibitor	7 (15%)
FRα Expression	
Low	9 (20%)
Medium	14 (30%)
High	23 (50%)
Met Phase 3 FORWARD I Eligibility Criteria	16 (35%)

Moore et al ASCO 2016 – Moore et al JCO 28Dec2016

Investigator Experience – Improved Safety Profile

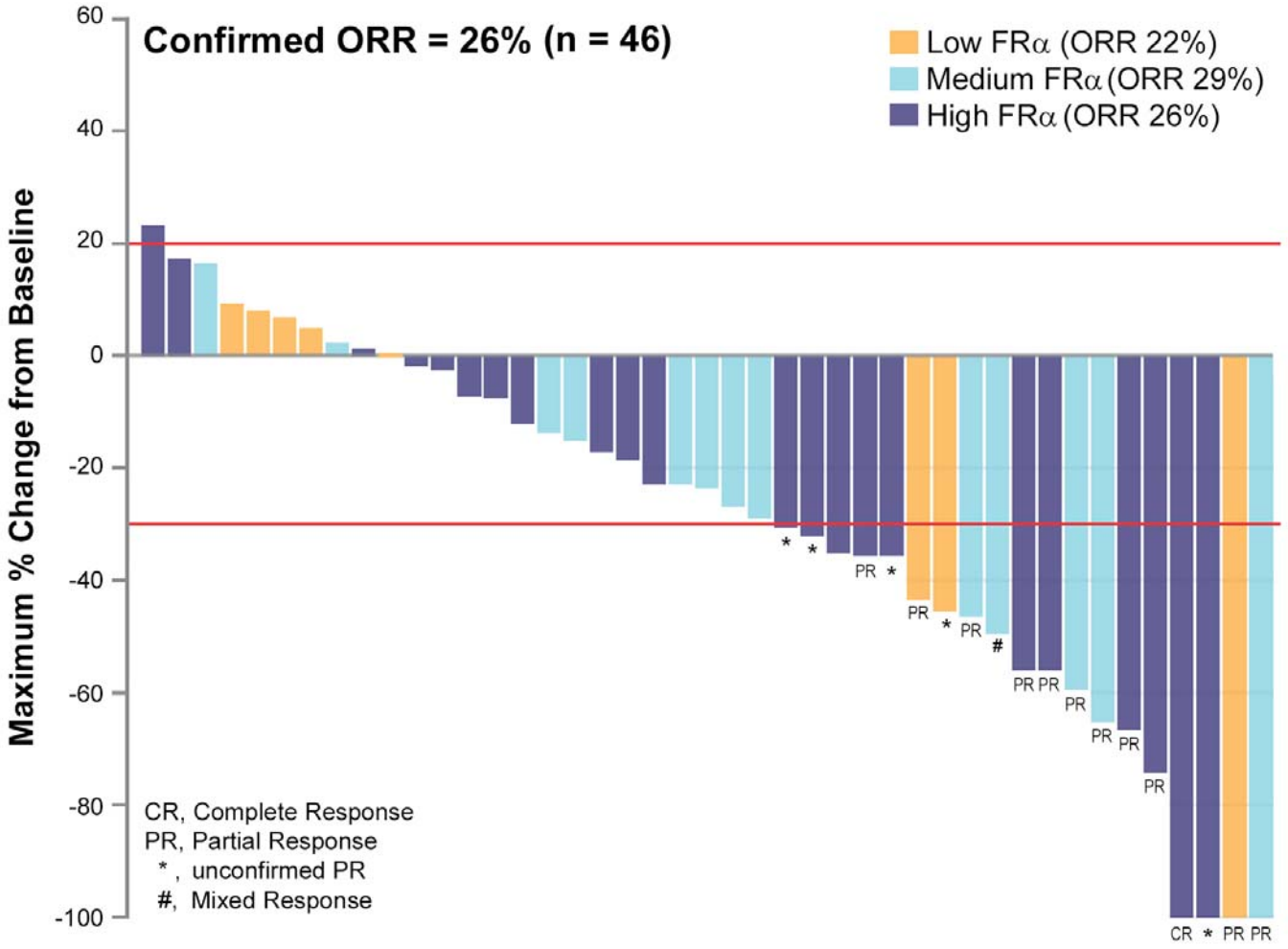


*Includes Neuropathy peripheral, Peripheral sensory neuropathy, Peripheral motor neuropathy, Paraesthesia, and Hypoesthesia
**Includes Corneal cyst, Corneal disorder, Corneal deposits, Corneal epithelial microcysts, Keratitis, Keratopathy, Limbal stem cell deficiency, and Punctate keratitis

- Ocular and GI adverse events decreased in frequency and grade in the subset of 26 patients enrolled following the initial 20-patient cohort analyzed
  - Improvement may be due to investigator experience, use of preservative-free lubricating eye drops, and other measures mandated in April 2015 to manage such symptoms

Moore et al ASCO 2016 – Moore et al JCO 28Dec2016

Maximum Percent Change in Target Lesions from Baseline



Note: Data is presented from 43 evaluable patients as post-baseline measurements were not available for 3 individuals.

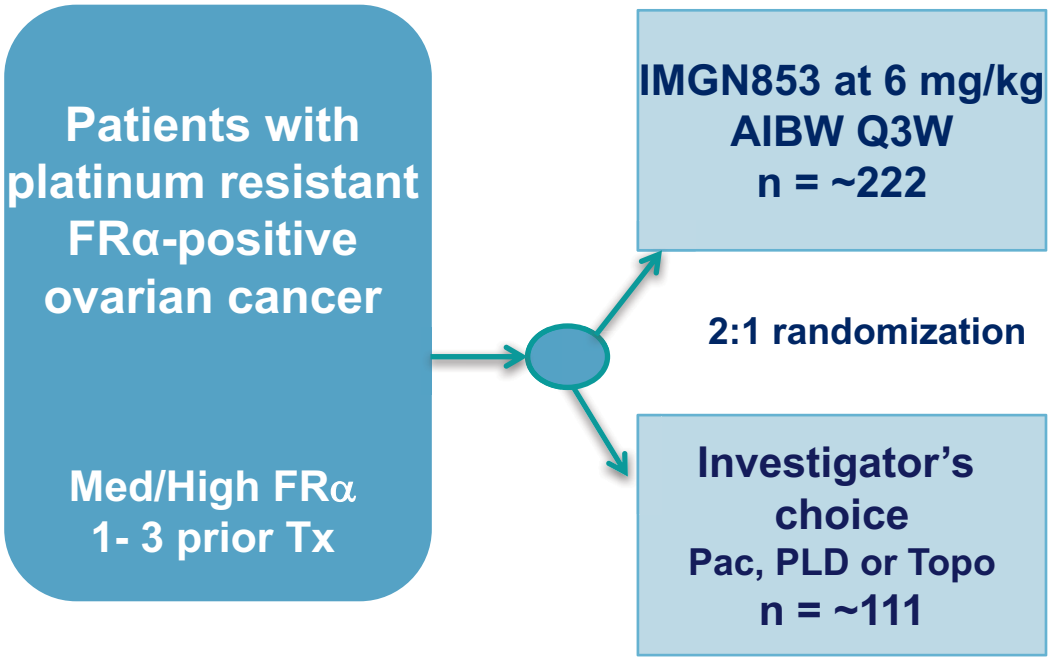
Moore et al ASCO 2016 – Moore et al JCO 28Dec2016

ORR by Number of Prior Lines and FRα Expression

Endpoint	All pts (n = 46)	1-3 priors (n = 23)	1-3 priors + med/high FRα expression (n = 16)	≥ 4 priors or low FRα expression (n = 30)
ORR (%) 95% CI	26 (14, 41)	39 (20, 62)	44 (20, 70)	17 (6, 35)
PFS (months) Median 95% CI	4.8 (3.9, 5.7)	6.7 (3.9, 8.7)	6.7 (3.9, 11.0)	4.2 (2.6, 5.6)
DOR (weeks) Median 95% CI	19.1 (16.1, 33.1)	19.6 (17.7, 44.1)	26.1 (17.7, -)	19.1 (13.0, 20.1)

Moore et al ASCO 2016 – Moore et al JCO 28Dec2016

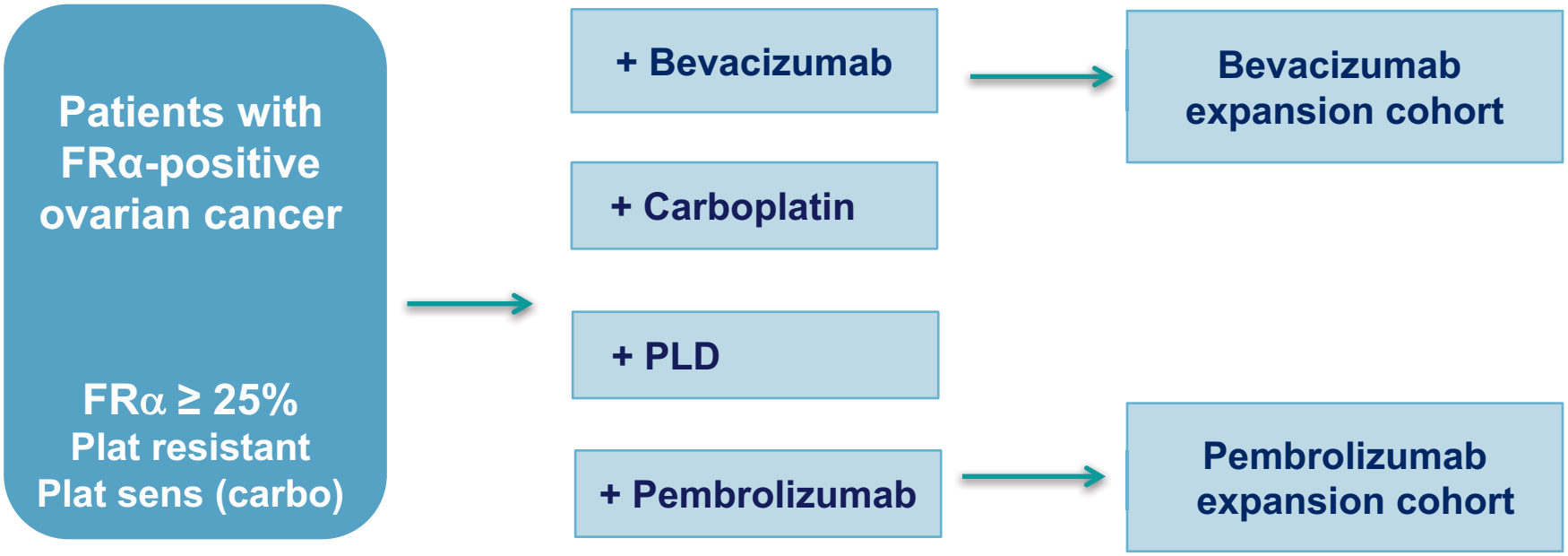
FORWARD I



- **Primary endpoint: PFS** (blinded independent central review)
  - **Entire population**
  - **Subset with high FRα** (~2/3 of patients in study)
- **Secondary endpoints: ORR, DOR, QoL and OS**

Pac: paclitaxel; PLD: pegylated liposomal doxorubicin; Topo: topotecan; AIBW = adjusted ideal body weight

FORWARD II



- **Enable mirvetuximab soravtansine to move up into earlier lines of therapy**

*Preclinical combination data – Ponte et al, Neoplasia 2016

Case #2

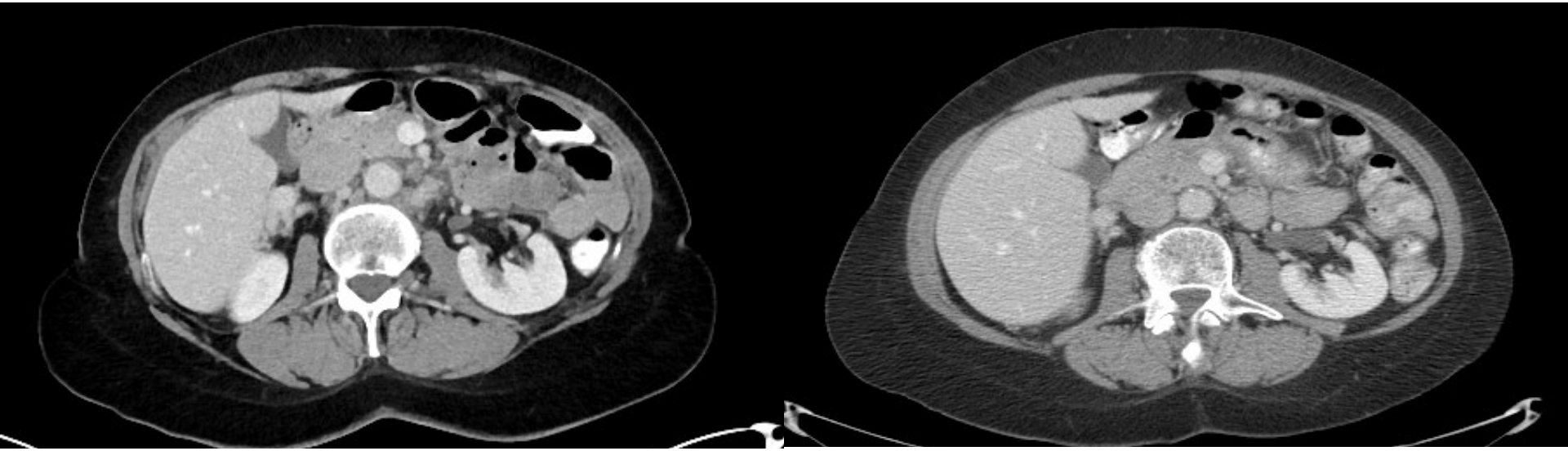
- A 68 y.o diagnosed with fallopian tube cancer
- 1/15 robotic surgery for 4x2x2 pelvic mass with optimal debulking IIIC
- She was treated with carbo/paclitaxel 2/15 finished 6/15 Scan showed PE
- CA125 increased 1/16; 2/16 scan showed enlarging para-aortic LNs
- Started on Phase II trial of single agent Pembro

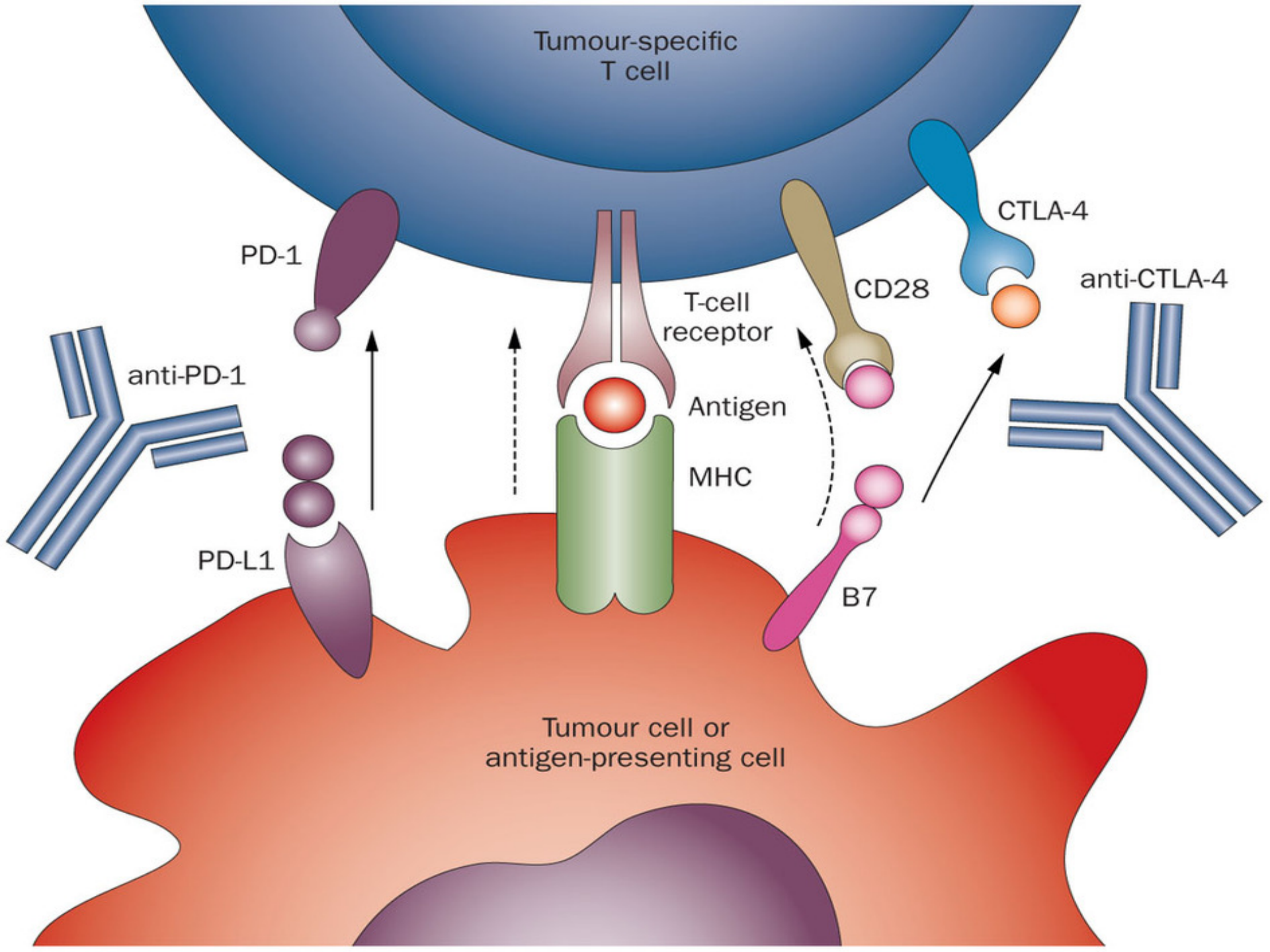
Tumor metrics

- After 3 cycles -43%
- After 6 cycles -52.7%
- After 9 cycles -62.81%
- Presently on cycle 13 essentially NED; no toxicities

Initial Scan

After 8 cycles




Tumour-specific
T cell
PD-1
T-cell
receptor
CD28
CTLA-4
anti-CTLA-4
anti-PD-1
Antigen
MHC
PD-L1
B7
Tumour cell or
antigen-presenting cell

Selected trials of PD-1/PD-L1 and CTLA-4 immune checkpoint blockade in ovarian cancer

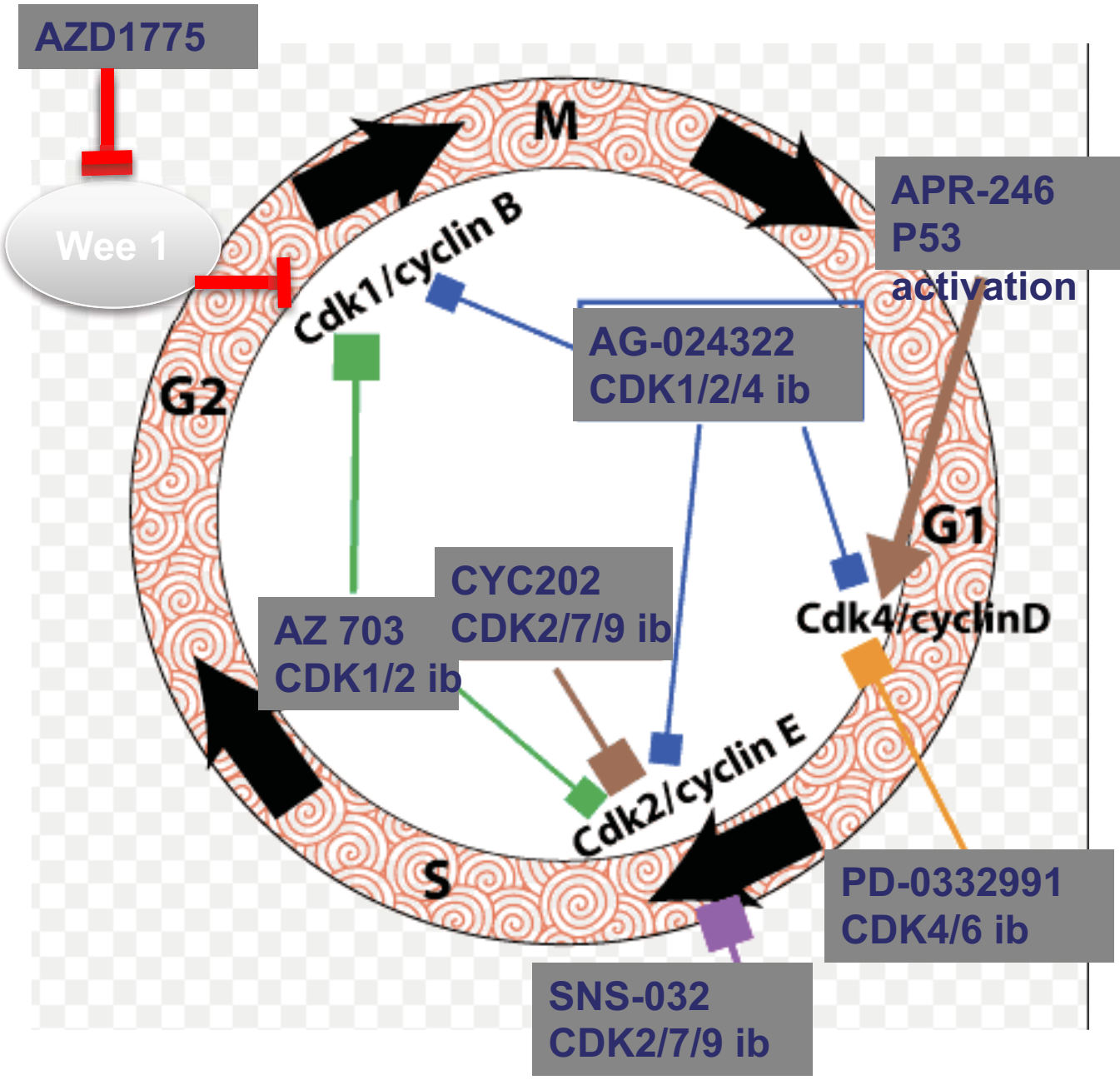
Target	Antibody	IgG subclass	Study setting	Phase	No.	CR	PR	SD	ORR (%)	DCR (%)	Median PFS (wk)	≥G3 AE (%)	Trial identifier	Ref.
PD-1	Nivolumab	Human IgG4	Relapsed platinum resistant EOC	II	20	2	1	6	15.0	45.0	14.0	40.0	UMIN000005714	[62]
	Pembrolizumab	Humanized IgG4	Advanced EOC	I	26	1	2	6	11.5	34.6	NA	3.8	NCT02054806	[63]
PD-L1	BMS-936559	Human IgG4	Advanced EOC	I	17	0	1	3	6.0	23.5	NA	9.0	NCT0072966	[64]
	Avelumab	Human IgG1	Relapsed platinum resistant EOC	I	124	0	12	55	9.7	54.0	11.3	6.5	NCT01772004	[65]
CTLA-4	Ipilimumab+GM-CSF	Human IgG1	Advanced EOC	I	9	0	1	3	11.1	44.4	NA	22.2	NCT01611558	[67]

AE, adverse events; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DCR, disease control rate includes patients with complete response, partial response and stable disease; EOC, epithelial ovarian cancer; GM-CSF, granulocyte-macrophage colony-stimulating factor; IgG, Immunoglobulin G; NA, data not available at the time of review; NCT, National Clinical Trial; ORR, overall response rate; PD-1, programmed cell-death 1; PD-L1, programmed cell-death ligand 1; PFS, progression free survival; PR, partial response; SD, stable disease; UMIN, University Hospital Medical Information Network.

Selected ongoing trials of immune checkpoint inhibitors in gynecological cancers

Type of malignancy	Combination	Treatment	Study population	Phase	Trial identifier
Ovarian cancer	aPD-1+TLRa+CTX	Durvalumab+motolimod+ pegylated liposomal doxorubicin	Recurrent platinum resistant	I/II	NCT02431559
	aPD-1+aCD27	Nivolumab+varlilumab	Recurrent previous platinum based therapy	I/II	NCT02335918
	aPD-1+aCSF1R	Pembrolizumab+PLX3397	Advanced	I/II	NCT02452424
	aPD-L1+Bev	Atezolizumab+bevacizumab	Recurrent platinum resistant	II	NCT02659384
	aPD-1+PARPi	Pembrolizumab+niraparib	Recurrent platinum resistant	I/II	NCT02657889
	aCTLA-4	Ipilimumab	Recurrent	I	NCT00039091
	aCTLA-4+PARPi	Tremelimumab+olaparib	Recurrent *BRCA1/2* mutation+	I/II	NCT02571725
	aCTLA-4+PARPi aCTLA-4+VEGFi	Tremelimumab+olaparib, tremelimumab+cediranib	Recurrent platinum resistant	I/II	NCT02484404
Endometrial cancer	aPD-1+CTX	Pembrolizumab+carboplatin+ paclitaxel	Advanced/recurrent	II	NCT02549209
	aPD-1+JAK1i aPD-1+PI3Kδi	Pembrolizumab+INCB039110, pembrolizumab+INCB050465	Advanced	I/II	NCT02646748
	aPD-1	Pembrolizumab	Advanced	II	NCT02628067
Cervical cancer	CTX/brachytherapy+aPD-1; CTX/brachytherapy followed by aPD-1	Pembrolizumab brachytherapy cisplatin	Advanced	II	NCT02635360
	CTX/EBRT followed by aCTLA-4	Ipilimumab external beam RT cisplatin	Stage IB–IVa	II	NCT01711515
	aPD-1±aCTLA-4	Nivolumab±ipilimumab	Advanced	I/II	NCT02488759
	aPD-1	Nivolumab	Advanced	II	NCT02257528

aCD-27, agonist monoclonal antibody for CD27; aCSF1R, small-molecule receptor tyrosine kinase inhibitor of CSF1R; aCTLA-4, anti-cytotoxic T-lymphocyte-associated antigen 4; aPD-1, anti-programmed cell-death 1; aPD-L1, anti-programmed cell-death ligand 1; CTX, chemotherapy; JAK1i, inhibitor of Janus-associated kinase 1; NCT, National Clinical Trial; PI3Kδi, poly (ADP-ribose) polymerase inhibitor; PI3Kδi, inhibitor of the delta isoform of phosphoinositide-3 kinase; TLRa, agonist of Toll-like receptor 8; VEGFi, inhibitor of vascular endothelial growth factor.



Cell Cycle Checkpoint Inhibitors

An international, biomarker-directed, randomized, phase II trial of AZD1775 plus paclitaxel and carboplatin (P/C) for the treatment of women with platinum-sensitive, ***TP53***-mutant ovarian cancer.

- 121 pts with confirmed *TP53* mutations were randomized
- PFS was greater with AZD1775/P/C compared with P/C alone (RECIST: HR 0.55, *P*= 0.030, median 42.86 vs 34.86 weeks).
- ORRs were 81.4% vs 75.8% (*P*= 0.459)
- Most common adverse events (AEs) were nausea (78.0% vs 60.0% for AZD1775/P/C vs P/C, respectively), diarrhea (74.6% vs 36.7%), alopecia (54.2% vs 66.7%) and fatigue (54.2% vs 55.0%).

Oza et al ASCO 2015

Phase II study with Wee1 inhibitor AZD1775 plus carboplatin in patients with p53 mutated ovarian cancer refractory or resistant (<3 months) to standard first line therapy –

- Bone marrow toxicity, fatigue, diarrhea, nausea and vomiting were the most common adverse events.
- Out of 24 pts enrolled, 22 pts were evaluable for study endpoints.
- As best response (RECIST 1.0), 6 pts (27%) showed confirmed partial response (PR) with a median progression-free survival (PFS) of 10.9 months.
- Nine pts (41%) had stable disease and 7 pts (32%) had progressive disease as best response, with a median PFS of 5.3 and 1.3 months, respectively.

Leijen et al ASCO 2015