Merck Pfizer Alliance Strategy in gynecologic oncology

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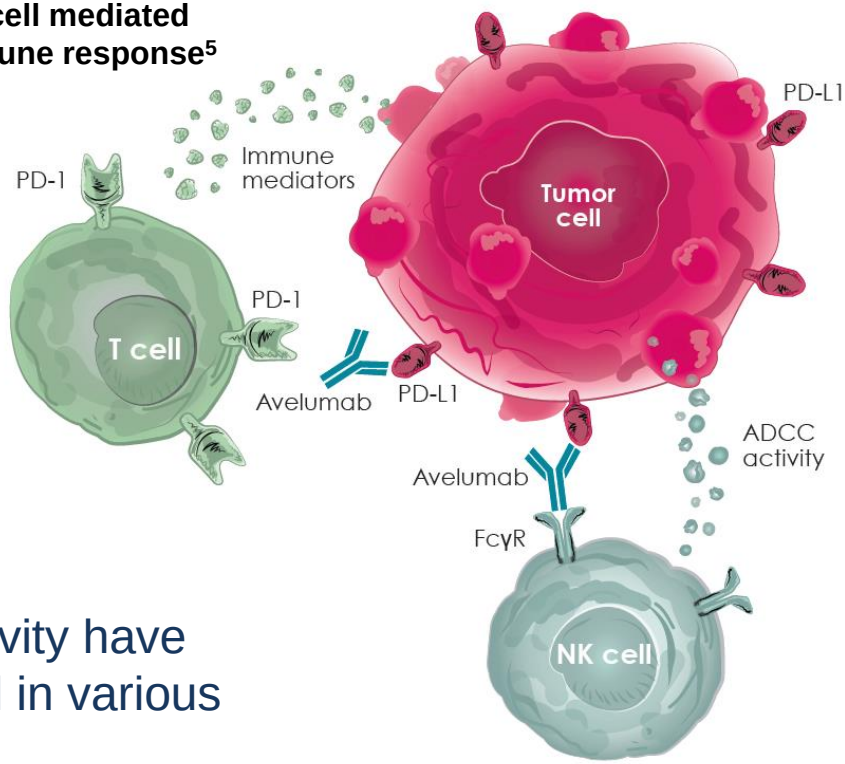
RO/AVEOV/1217/0001

Avelumab

Avelumab: proposed mechanism of action

- Fully human IgG1 anti-PD-L1 monoclonal antibody[1]
- Designed to bind PD-L1[1]
  - Designed to inhibit PD-1/PD-L1 interactions
  - Designed to leave PD-1/PD-L2 pathway intact
- ADCC may contribute to activity, as shown in preclinical models[2]
- Safety, pharmacokinetics and clinical activity have been investigated in a large Phase Ib trial in various advanced solid tumors[3]
- Half-life 3.9 days; >90% target occupancy at 10 mg/kg Q2W dose[4]

T-cell mediated immune response[5]



ADCC: antibody-dependent cell-mediated cytotoxicity; IgG: Immunoglobulin G; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; PD-L2: programmed death-ligand 2; Q2W: every 2 weeks

1. Grenga I et al. Clin Transl Immunol 2016;5:83; 2. Boyerinas B et al. Cancer Immunol Res 2015;3:1148–57; 3. Kelly K et al. ASCO 2016. Abstract 3055 (Poster); 4. Heery C et al. Lancet Oncol 2017;18:587–98; 5. Gulley JL et al. ASCO 2017. Abstract 9086 (Poster); 5. Bavencio US PI. March 2017.

Anti-PD-L1 antibodies with an intact Fc region may attach both to PD-L1 on tumor cells and to Fcγ receptors on immune cells

Variable region[1]

Designed to bind to PD-L1

Intact Fcγ region[1]

Capable of binding to Fcγ receptors on NK cells (and other immune cells)

Binding may induce ADCC

Avelumab: fully human IgG1 anti-PD-L1 monoclonal antibody with an intact Fcγ region

Other PD-1/PD-L1 inhibitors that are marketed or under investigation do not appear to induce ADCC:[2]

- IgG4 antibodies, e.g. nivolumab, pembrolizumab, do not mediate a robust ADCC response
- Other IgG1 antibodies have been specifically engineered to eliminate ADCC activity, e.g. atezolizumab, durvalumab

ADCC: antibody-dependent cell-mediated cytotoxicity; IgG: immunoglobulin G; NK: natural killer; PD-1: programmed death-1; PD-L1: programmed death-ligand 1

1. DiLillo DJ, Ravetch JV. Cancer Immunol Res 2015;3:704–13; 2. Boyerinas B et al. Cancer Immunol Res 2015;3:1148–57

JAVELIN clinical trial program

JAVELIN clinical trial program: Phases I/II

Phase	Trial ID	Indication	Design*	PD-L1+†	Primary endpoint	Enrollment target	Primary completion
I	JAVELIN Solid Tumor JPN NCT01943461	Solid tumors and gastric	Avelumab monotherapy	No	DLT	57	Oct 2014
II	JAVELIN Merkel 200 NCT02155647	MCC	Avelumab monotherapy	No	BOR, DR	200	Part A (2L+) complete; Part B (1L) Mar 2019
I	JAVELIN Hodgkin's NCT02603419	Hodgkin's lymphoma	Avelumab monotherapy	No	TO, PK	70	Sept 2017
Ib/II	JAVELIN Lung 101 NCT02584634	NSCLC	Avelumab + crizotinib/ PF-06463922	No	DLT, OR	130	Jan 2018
Ib	JAVELIN Renal 100 NCT02493751	Advanced RCC	Avelumab + axitinib	No	DLT	55	Apr 2018
Ib	COMBO NCT02994953	Advanced solid tumors	Avelumab + NHSIL12	No	DLT, safety	30	April 2018
I	JAVELIN Solid Tumor NCT01772004	Advanced solid tumors	Avelumab monotherapy	No	DLT, BOR	1,706	May 2018
Ib/II	JAVELIN Medley NCT02554812	CRC, NSCLC, melanoma, SCCHN, TNBC	Avelumab + utomilumab/ PF-04518600/ PD-0360324	No	DLT, OR	549	Dec 2019
Ib/II	JAVELIN PARP Medley NCT03330405	NSCLC, BC, Ovarian, Urothelial, CRPC	Avelumab + talazoparib	Yes in NSCLC cohort	DLT, OR	296	March 2020

PF-04518600 is an investigational anti-OX40 immunotherapy mAb. PF-05082566 (proposed name utomilumab) is an investigational 4-1BB agonist mAb. PF-06463922 is an investigational small-molecule inhibitor of ALK/ROS1

*Trial designs are subject to change; †Indicates primary analysis on enriched PD-L1 expressors; ‡Only enrolling for escalation revised dosing regimen cohort

Visit ClinicalTrials.gov for the latest trial status.

JAVELIN clinical trial program: Phase III

Trial ID	Indication	Design*	PD-L1+†	Primary endpoint	Enrollment target	Primary completion
JAVELIN Gastric 300 NCT02625623	Gastric 3L	Avelumab vs physician's choice BSC	No	OS	376	Aug 2017
JAVELIN Lung 100 NCT02576574	NSCLC 1L	Avelumab vs platinum-based doublets	Yes	PFS	1,095	Apr 2019
JAVELIN Lung 200 NCT02395172	NSCLC 2L	Avelumab vs docetaxel	Yes	OS	792	Jan 2018
JAVELIN Ovarian 200 NCT02580058	Ovarian (platinum-resistant/refractory)	Avelumab vs avelumab + doxo vs doxo	No	OS, PFS	550	Mar 2018
JAVELIN Renal 101 NCT02684006	RCC 1L	Avelumab + axitinib vs sunitinib	No	PFS	583	Jun 2018
JAVELIN Gastric 100 NCT02625610	Gastric 1L (switch maintenance)	Avelumab vs chemotherapy/BSC	No	OS, PFS	666	Mar 2019
JAVELIN Bladder 100 NCT02603432	Urothelial bladder 1L (switch maintenance)	Avelumab + BSC vs BSC	No	OS	668	Jul 2019
JAVELIN Ovarian 100 NCT02718417	Ovarian 1L (platinum sensitive)	Carbo/pac vs carbo/pac with avelumab maintenance vs carbo/pac + avelumab with avelumab maintenance	No	PFS	951	Sep 2019
JAVELIN Head and Neck 100 NCT02952586	Locally advanced SCCHN	Avelumab + SOC CRT vs SOC CRT	No	PFS	640	Apr 2021

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*Trial designs are subject to change; †Indicates primary analysis on enriched PD-L1 expressors. Visit ClinicalTrials.gov for the latest trial status. Accessed June 2017

Alliance Strategy in gynecologic oncology – Ovarian cancer

OVARIAN Cancer – a need for new treatment options

- Majority of OC patients present with advanced disease[1]
- Despite surgery and current chemotherapy options 5-year survival rates remain low at 45%
- Clinical trials of cytotoxic and targeted agents have not yielded major improvements in cure rates[3-10]
- Novel therapies are urgently needed to improve clinical outcomes
  - Immunotherapy is a promising novel approach for OC

1. Greene FL et al.. *AJCC Cancer Staging Manual, 6th edition*. New York: Springer; 2002. 2. American Cancer Society. Cancer Facts & Figures, 2015. 3. Bookman MA et al. *J Clin Oncol.* 2009;27:1419-1425. 4. McGuire WP et al. *N Engl J Med.* 1996;334:1-6. 5. Ozols RF et al. *N Engl J Med.* 2006;354:34-43. 6. Katsumata N et al. *Lancet Oncol.* 2013;14:1020-1026. 7. Burger RA et al. *N Engl J Med.* 2011;365:2473-2483. 8. Armstrong DK et al. *N Engl J Med*. 2006;354:34-43. 9. Aghajanian C. *J Clin Oncol.* 2012;30:2039-2045. 10. Huang L et al. *Cancer.* 2008;112:2289-2300.

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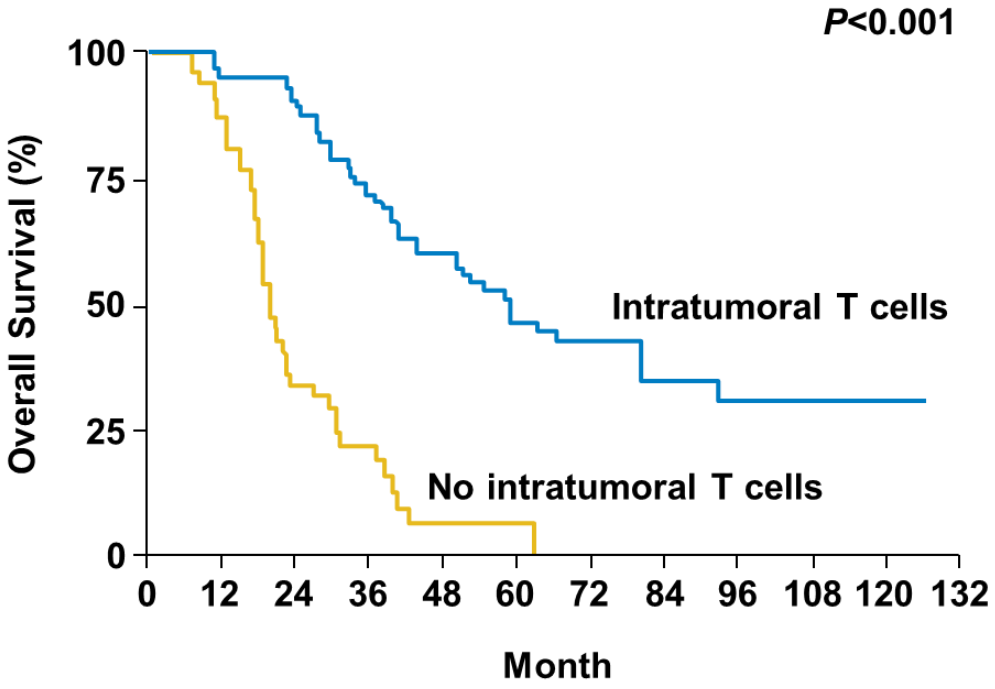
Ovarian Cancer is an immunogenic tumour[1-4]

Rationale for IO

- Presence of intratumoral T cells associated with better clinical outcome
- Spontaneous antitumor immune response can be detected in the form of tumor-reactive T cells and antibodies
- Strong immunosuppressive environment present in OC



1. Turner TB et al. *Gynecol Oncol*. 2016;142:349-356. 2. Coukos G et al. *Ann Oncol*. 2016;27(suppl 1):i11-i15. 3. Mandai M et al. *Int J Clin Oncol.* 2016;21:456-461. 4. Zhang L et al. *N Engl J Med.* 2003;348:203–213.

Avelumab, an anti-PD-L1 antibody, in patients with previously treated, recurrent or refractory ovarian cancer: a phase Ib, open-label expansion trial

Disis et al. Poster Presentation at the 51st ASCO Annual Meeting, May 29-June 2, 2015; Chicago, Illinois. Abstract No. 5509.

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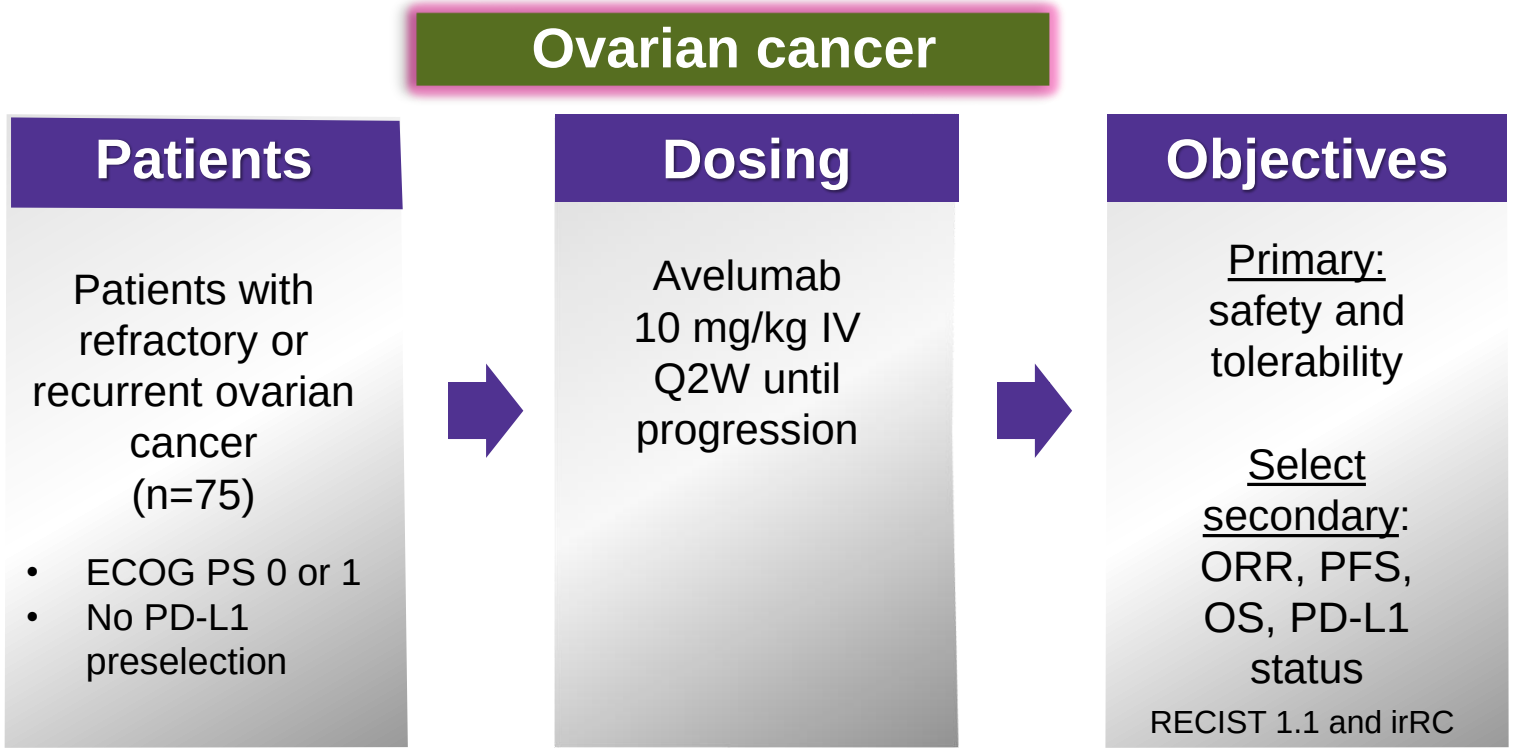
Study design



Disis et al. Poster Presentation at the 51st ASCO Annual Meeting, May 29-June 2, 2015; Chicago, Illinois. Abstract No. 5509.

Most common treatment-related AEs, >5%

Patients experiencing event (n=75)	Treatment-related AEs, all grades*, n (%)
Any event	52 (69.3)
Fatigue	12 (16.0)
Chills	9 (12.0)
Nausea	8 (10.7)
Diarrhea	8 (10.7)
Infusion-related reaction	6 (8.0)
Rash	6 (8.0)
Vomiting	6 (8.0)
Constipation	4 (5.3)
Hypothyroidism	4 (5.3)

* Most common treatment-related AEs were grade 1 or 2

Disis et al. Poster Presentation at the 51st ASCO Annual Meeting, May 29-June 2, 2015; Chicago, Illinois. Abstract No. 5509.

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Clinical activity: best overall response

Best overall response by RECIST 1.1, unconfirmed*	Ovarian (n=75) n (%)	95% CI
Complete response (CR)	0	
Partial response (PR)	8 (10.7)	
Stable disease (SD)	33 (44.0)	
Progressive disease (PD)	26 (34.7)	
Objective response rate (ORR)	**8 (10.7)**	**4.7, 19.9**
Disease control rate (DCR)†	41 (54.7)	

Median duration of F/U: 5 months (range, 3-15 mos)

* There were 8 patients (10.7%) with “missing” and/or “not evaluable” information.
† DCR is defined as responses plus stable disease.

Disis et al. Poster Presentation at the 51st ASCO Annual Meeting, May 29-June 2, 2015; Chicago, Illinois. Abstract No. 5509.

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Conclusions

- Avelumab has an acceptable safety profile
  - 8% of patients (n=6) experienced grade 3/4 treatment-related AE
  - No treatment-related death seen in this cohort
- Clinically active in heavily pretreated, unselected ovarian cancer
  - ORR of 10.7%, based on 8 PRs by RECIST (2 additional PRs by irRC)
    - 62.5% ongoing
    - Patients with clear cell histology (2 of 2) responded
  - SD: 44.0% additional patients
  - DCR: 54.7%
- Largest reported dataset of patients with refractory or recurrent ovarian cancer treated with anti-PD-(L)1 therapy

Disis et al. Poster Presentation at the 51st ASCO Annual Meeting, May 29-June 2, 2015; Chicago, Illinois. Abstract No. 5509.

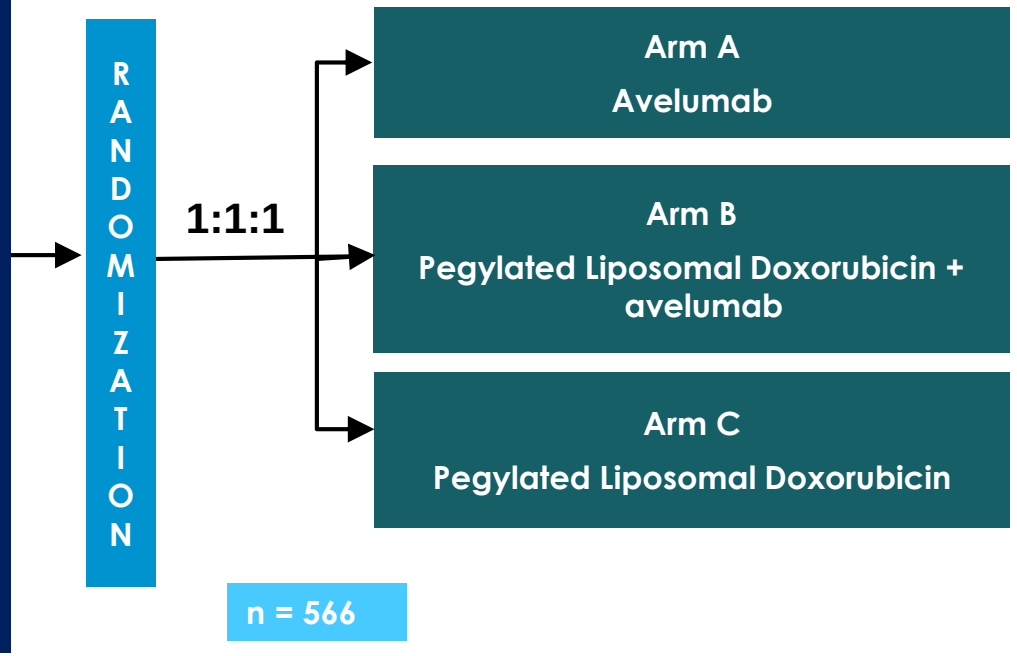
Tretment of recurrent/refractory Ovarian cancer

JAVELIN Ovarian 200: Avelumab in platinum Resistant/Refractory ovarian cancer

Randomized Phase III Study

Enrollment Criteria

- Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer
- Platinum resistant/refractory disease (resistant: progression ≤6 mo from last dose of platinum-based therapy; refractory: no response/progression to most recent platinum-based therapy)
- Up to 3 lines of systemic anticancer therapy for PS* disease, most recently platinum-containing, and no prior therapy for PR** disease
- Mandatory tumor sample – Archived or De novo (unless medically contraindicated)



Primary endpoint:	OS, PFS by BICR
Secondary endpoints:	ORR, PFS by investigator assessment, duration of response, PROs, safety

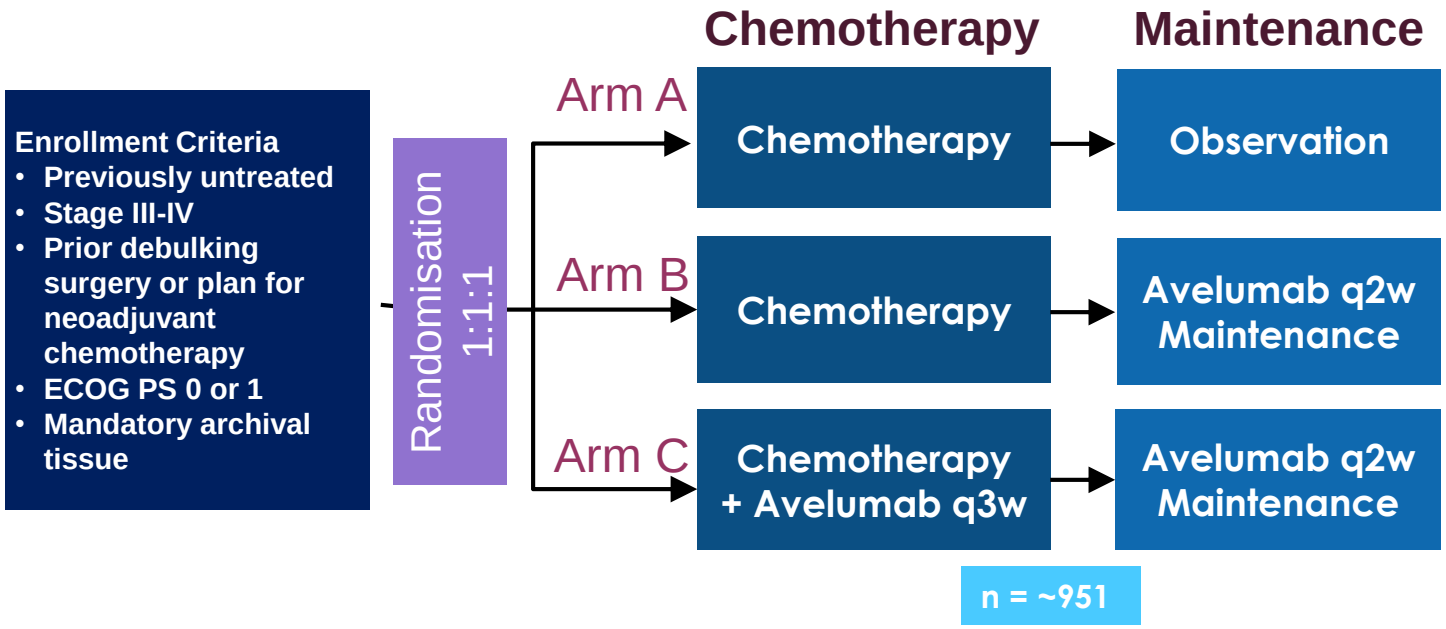
* Platinum sensitive disease
** Platinum resistant disease

NCT02580058

First-line treatment of Ovarian cancer

JAVELIN Ovarian 100: Avelumab Platinum Combo + Maintenance (1L)

Randomized Phase III Study



Patients whose tumour was **not** progressing as per RECIST 1.1 criteria (CR, PR, or SD) will be allowed to continue onto the maintenance portion of the study

Primary endpoint:	PFS
Secondary endpoints:	Maintenance PFS, OS, ORR, duration of response, PROs, safety, PK

- Chemotherapy: Choice of Q3W carboplatin-paclitaxel, OR carboplatin + weekly paclitaxel as per JGOG 3016.
- Maintenance avelumab up to 2 years.

NCT02718417

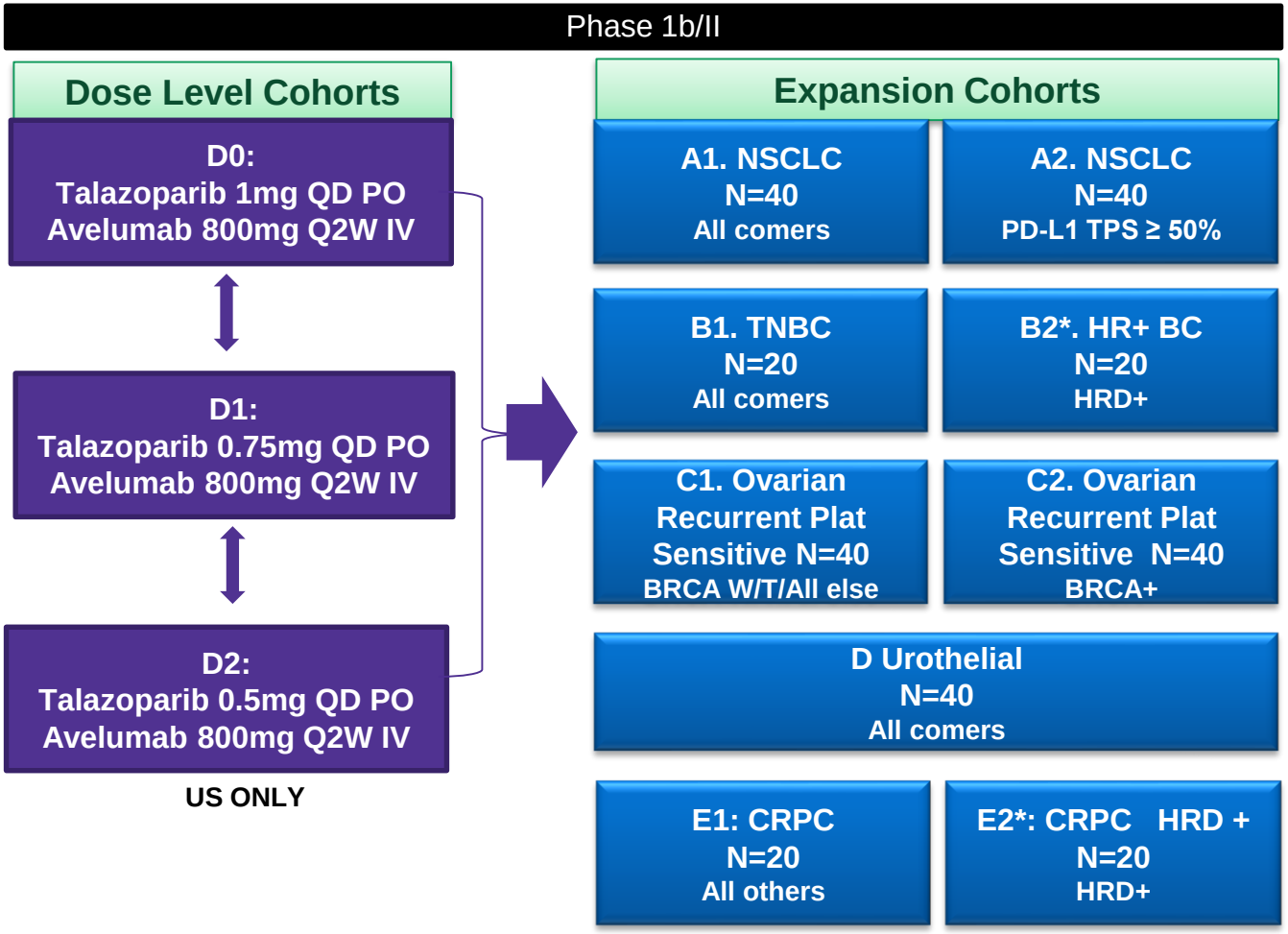
Combination strategy

JAVELIN PARP MEDLEY – B9991025

- Avelumab + Talazoparib Combination

Eligibility:

- Advanced solid tumors including NSCLC, breast, ovarian, bladder, Prostate
- PARP refractory excluded
- PD-1/PD-L1 naïve
- ECOG 0 and 1
- Prior platinum eligibility varies by tumor type



*Require prospective selection for enrollment

NCT03330405

Australia, Belgium, Canada, Czech Republic, Denmark, Hungary, Korea, Poland, Russia, Spain, UK, US

Summary

- OC is a leading cause of death for gynaecological cancers
- 5y survival rate less than 50% - the lowest of gynae malignancies
- Despite optimal upfront surgery and frontline CHT ~ 70% of pts relapse in first 3 years
- Novel therapies are urgently needed to improve clinical outcomes
  - Immunotherapy is a promising novel approach for OC
  - PARPi
  - Combination strategies

http://eco.iarc.fr/eucan/, Ledermann JA el al. Annals of Oncology 24 (Suppl 6): vi24-32, 2013