GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ESMO PRECEPTORSHIP IN IMMUNO-ONCOLOGY

LUGANO, MAY 4-5, 2018

Clinical development in ovarian cancer

C. Sessa, CH

DISCLOSURES

- Institutional financial interests: Clinical study grant from Pfizer International Inc, Pfizer AG, AstraZeneca AG, Basilea Pharmaceutica International Ltd.

CONTENT

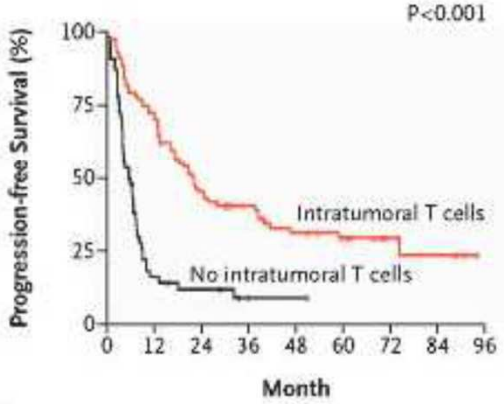
- Rationale for immunotherapy in ovarian cancer
- Clinical data with single agent immune checkpoint inhibitors
- Clinical data with combination with immune checkpoint inhibitors with
  - antiangiogenics
  - PARP inhibitors

ORIGINAL ARTICLE

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

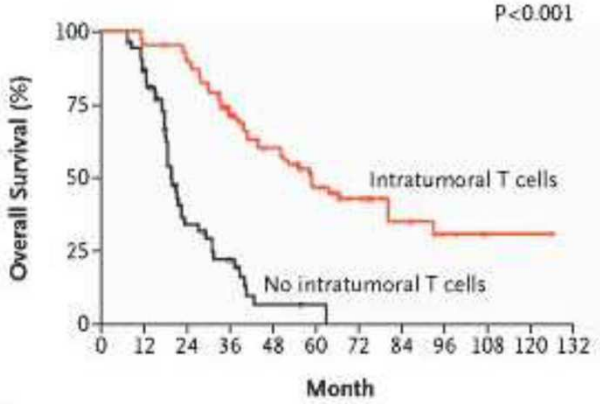
Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.

A



Intratumoral T Cells								
At risk	87	63	37	27	19	15	6	4
Events	24	23	4	6	1	0	1	0
Censored data	0	3	6	2	3	9	1	4
No Intratumoral T Cells								
At risk	55	8	5	1	1			
Events	44	2	2	0	0			
Censored data	3	1	2	0	1			

B



Intratumoral T Cells											
At risk	102	90	78	57	42	27	17	9	4	1	1
Events	12	10	16	8	11	2	2	1	0	0	0
Censored data	0	2	5	7	4	8	6	4	3	0	1
No Intratumoral T Cells											
At risk	72	48	14	8	2						
Events	21	29	5	5	1						
Censored data	3	5	1	1	1						

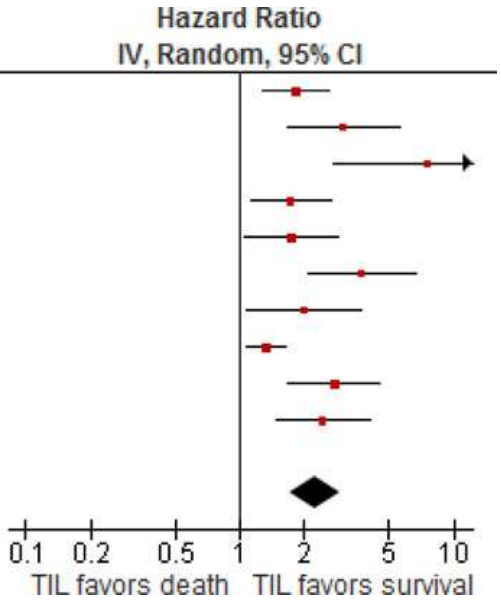
Prognostic significance of tumor-infiltrating T-cells in ovarian cancer: a meta-analysis

Forest plot of association of TILs with overall survival (10 studies)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Zhang(2003)	0.61	0.18	12.5%	1.84 [1.29, 2.62]
Sato(2005)	1.11	0.307	8.8%	3.03 [1.66, 5.54]
Hamanishi(2007)	2.031	0.518	4.8%	7.62 [2.76, 21.04]
Callahan(2008)	0.548	0.222	11.2%	1.73 [1.12, 2.67]
Han(2008)	0.563	0.258	10.1%	1.76 [1.06, 2.91]
Tomsova(2008)	1.308	0.296	9.1%	3.70 [2.07, 6.61]
Adams(2009)	0.694	0.315	8.6%	2.00 [1.08, 3.71]
Clarke(2009)	0.282	0.106	14.5%	1.33 [1.08, 1.63]
Leffers(2009)	1.02	0.251	10.3%	2.77 [1.70, 4.54]
Stumpf(2009)	0.895	0.258	10.1%	2.45 [1.48, 4.06]
Total (95% CI)			**100.0%**	**2.24 [1.71, 2.92]**

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 29.38$, df = 9 (P = 0.0006); $I^2 = 69\%$

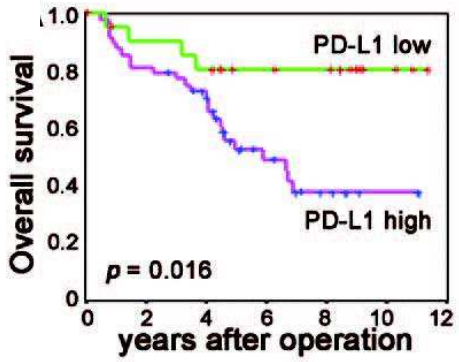
Test for overall effect: Z = 5.92 (P < 0.00001)



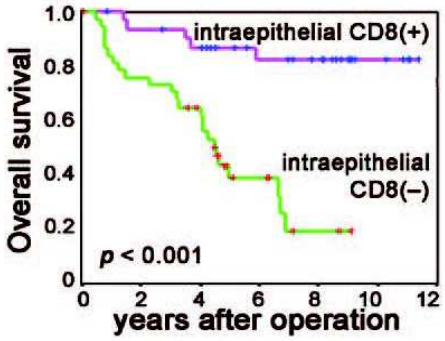
Hwang, 2012

PD-L1 and tumor infiltrating CD8$^+$ T lymphocytes are prognostic factors of human ovarian cancer

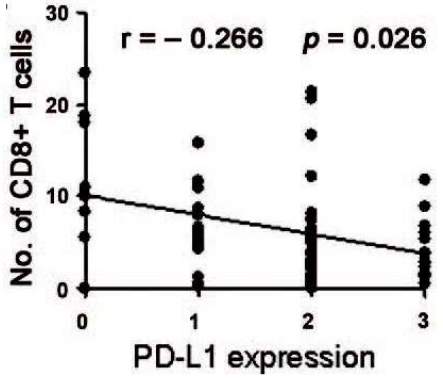
PD-L1 expression and intraepithelial CD8$^+$ T lymphocyte count are independent prognostic factors



Correlation between OS and PD-L1 expression



Correlation between OS and intraepithelial CD8$^+$ T lymphocyte count



Correlation between PD-L1 expression and intraepithelial CD8$^+$ T lymphocyte count

Hamanishi, 2007

ESMO

ARTICLE

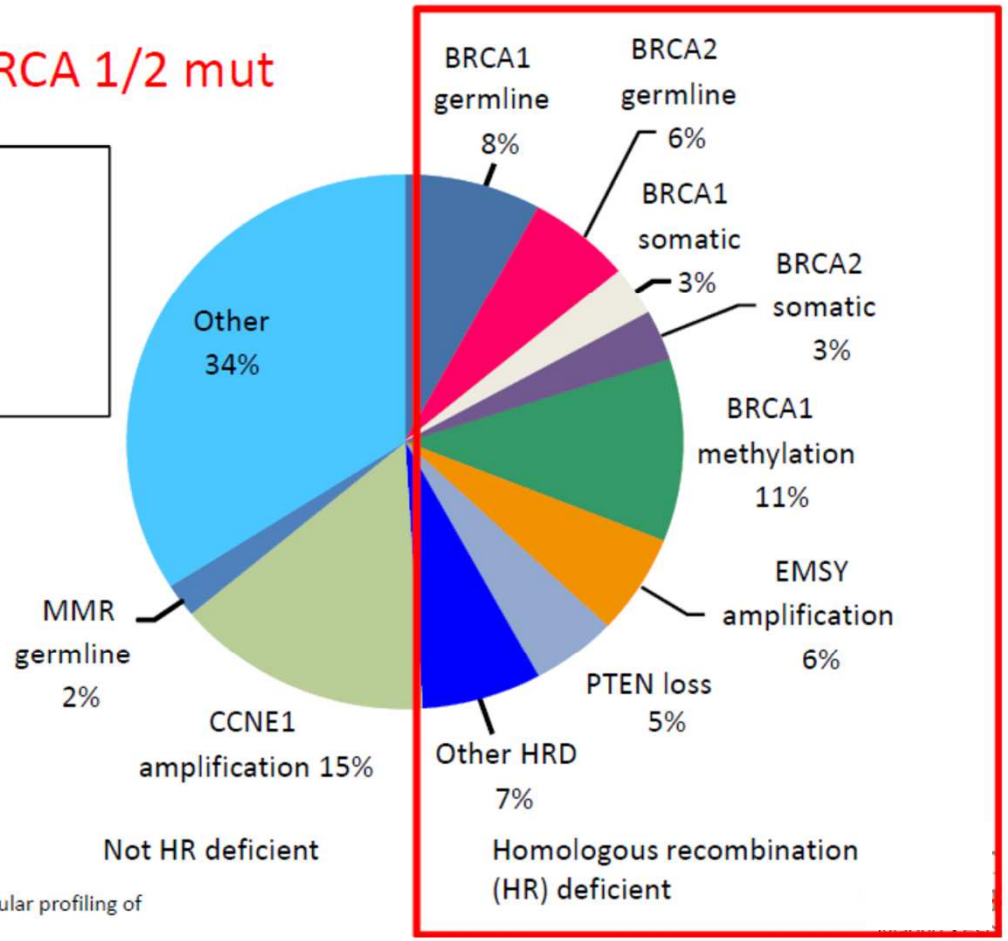
doi:10.1038/nature10166

Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*

20% HGSOC are BRCA 1/2 mut

- *BRCA1/2* germline mutation 14%
- *BRCA1/2* somatic mutation 6%
- Total 20%



Levine D. The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer. 2011

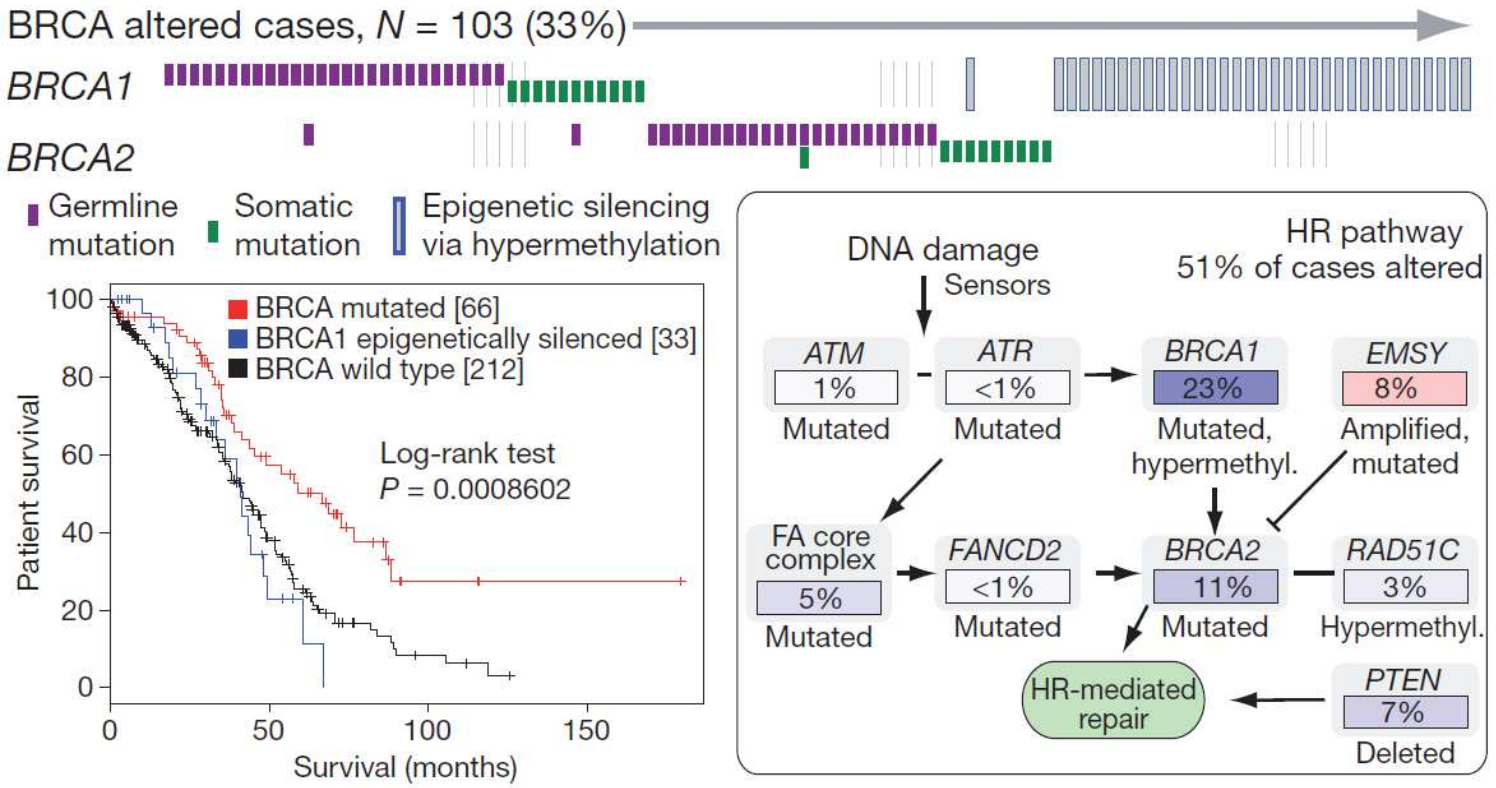
ARTICLE

doi:10.1038/nature10166

Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*

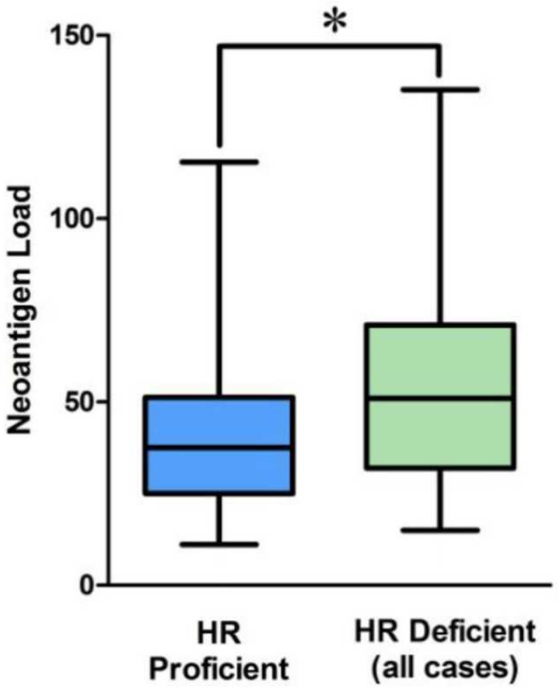
Genes alterations in the HR pathway



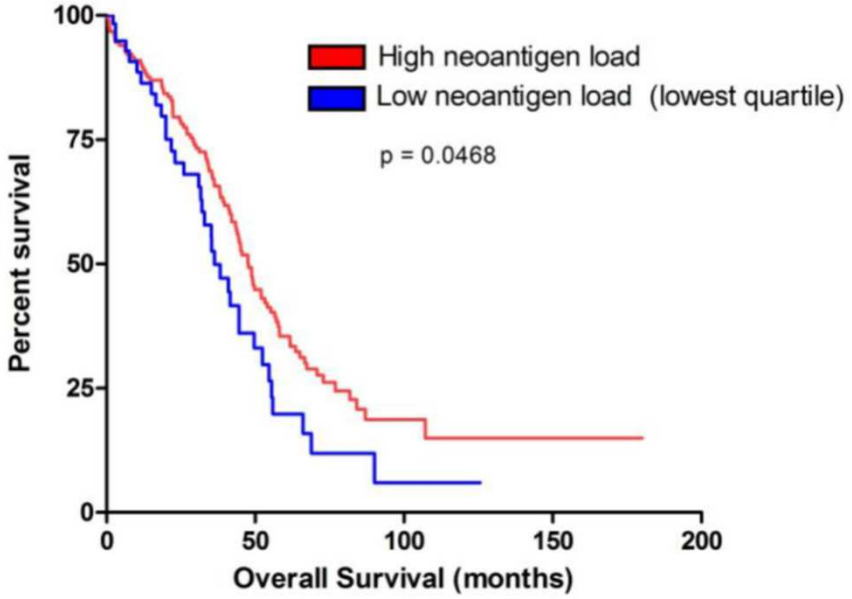
TCGA, Levine, 2011

Association and prognostic significance of BRCA status with neoantigen load, number of TIL and PD-1/PD-L1 expression in high grade serous ovarian cancer

HR deficient tumors has a higher neoantigen load than HR proficient tumors

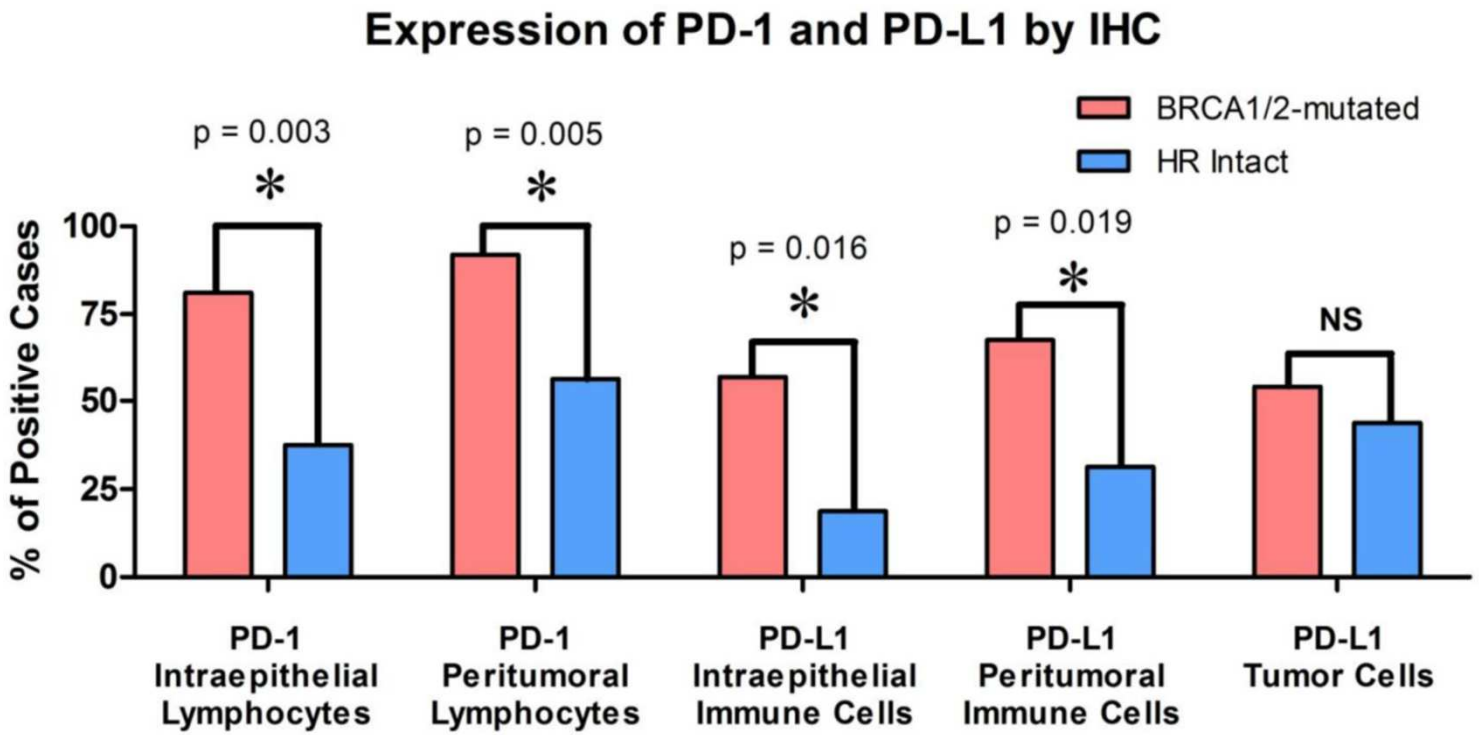


Tumors with a lower neoantigen load has a lower overall survival



Strickland, 2016

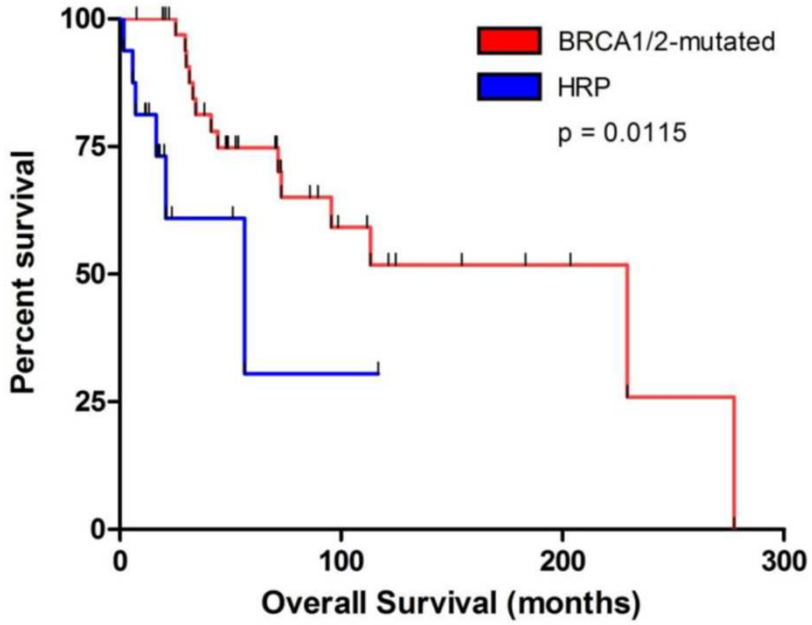
Association and prognostic significance of BRCA status with neoantigen load, number of TIL and PD-1/PD-L1 expression in high grade serous ovarian cancer

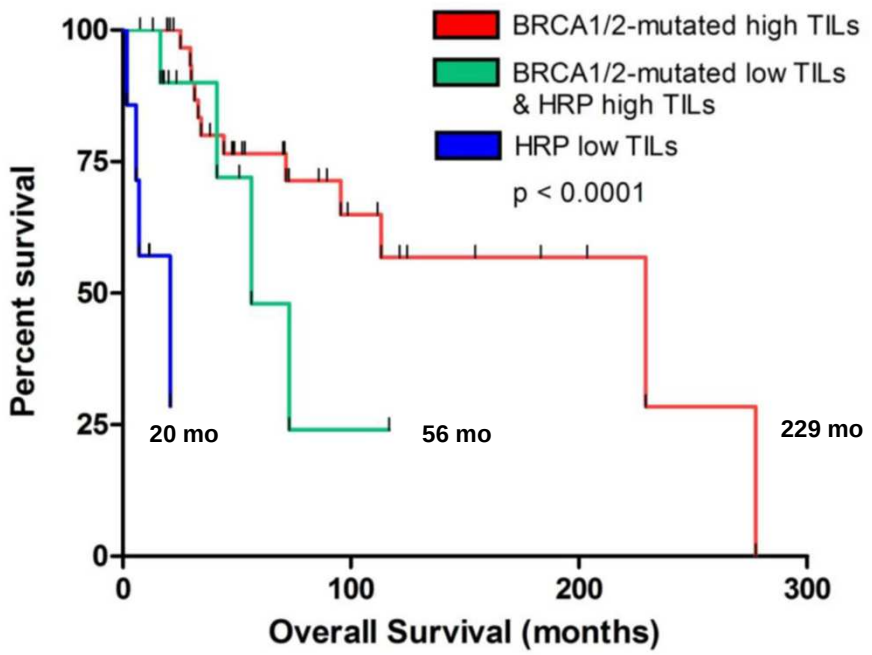


Strickland, 2016

Association and prognostic significance of BRCA status with neoantigen load, number of TIL and PD-1/PD-L1 expression in high grade serous ovarian cancer

Association between survival, number of CD3+ TIL and BRCA mutation status





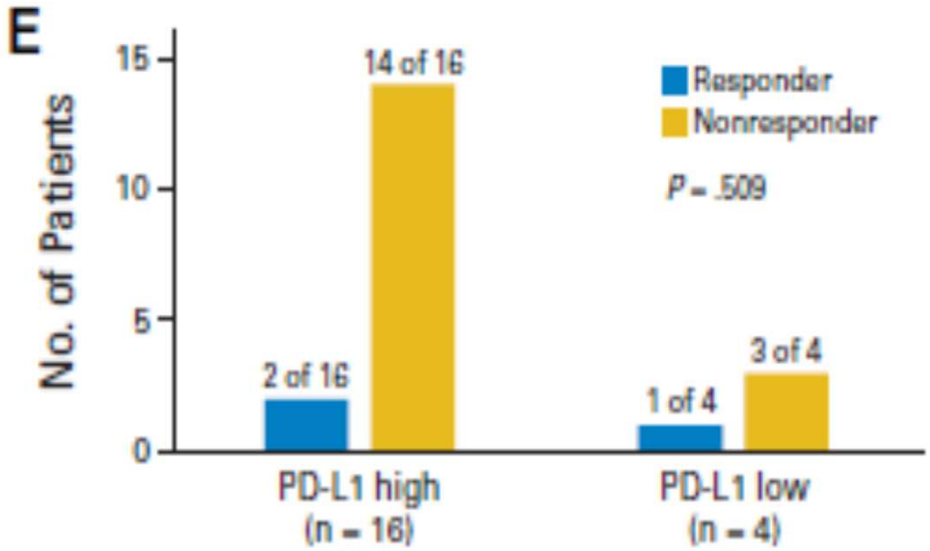
Strickland, 2016

Single agent activity of immune checkpoint inhibitors in advanced ovarian cancer

	Nivolumab Anti-PD1	Pembrolizumab Anti-PD1	Avelumab Anti-PD-L1	Atezolizumab Anti-PD-L1
No of patients	20	26	24	12
No of prior CTs	≥ 4 (55%)	≥ 3 (65%)	≥ 3 (58%)	> 6 (58%)
PD-L1+	80% (IHC)	100% (IHC)	77%	83%
ORR (%)	15	115	9.7	25
Duration	4 (20%) >24 wks	7 (30%) >24 wks	16.1% 24 wks	mPFS >12 mo

Safety and antitumor activity of Nivolumab in platinum-resistant ovarian cancer

Relationship between PD-L1 expression on tumor cells and objective response to nivolumab



ORR (%)	12.3	5.9
95% CI	5.1-23.7	0.1-28.7

Hamanishi, 2015

Pathway of treatment in high grade ovarian cancer

Surgery

First-line therapy

- Primary cytoreductive surgery
- Standard chemotherapy
- Interval debulking

Maintenance therapy

Recurrent disease

- Chemo-sensitive
- Chemo-resistant

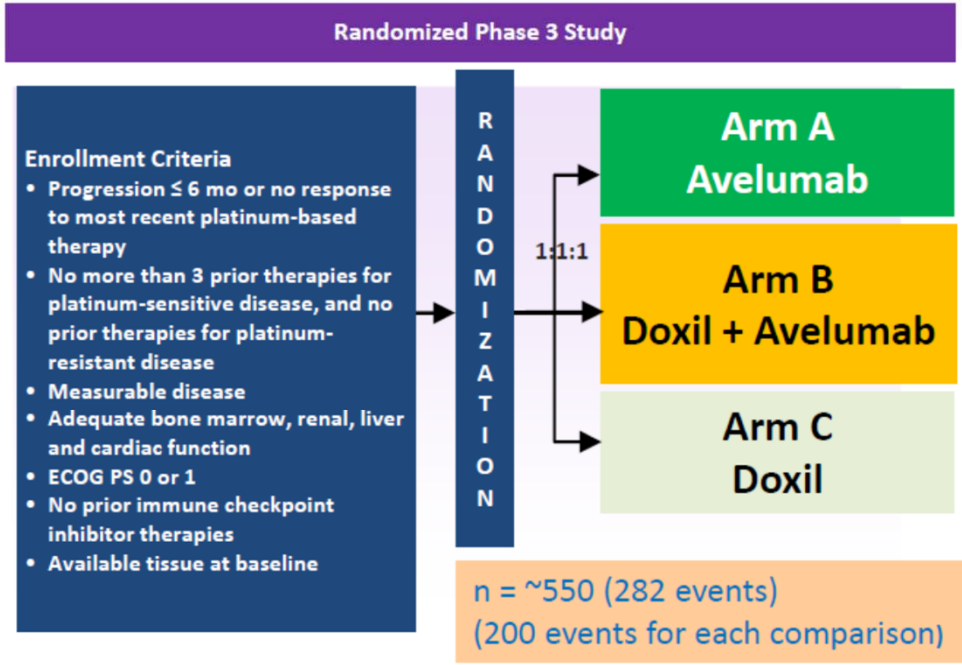
Anti VEGF therapy

PARP inhibitors

Immunotherapy

JAVELIN 200

Avelumab (anti-PDL1) in Platinum Resistant/Refractory Ovarian Cancer



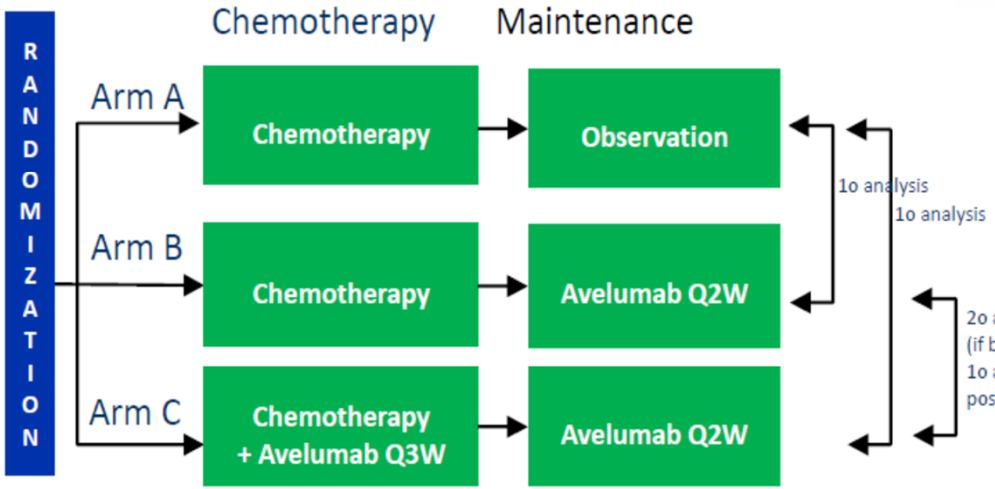
Stratification: Platinum refractory vs resistant, #prior therapies, bulky disease.

Primary Endpoint:	OS
Secondary Endpoints:	ORR, PFS, Duration of response, PROs, Safety

Confidential

JAVELIN 100

Enrollment Criteria
- **Previously untreated**
- **Stage II-IV**
- **Prior debulking surgery or plan for neoadjuvant chemotherapy**
- **ECOG PS 0 or 1**
- **Mandatory archival tissue**



1:1:1

Chemotherapy: Choice of carboplatin q3w, paclitaxel, OR carboplatin + weekly paclitaxel as per JGOG 3016. Maintenance avelumab up to 2 years.

Patients whose tumor 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

Outcomes

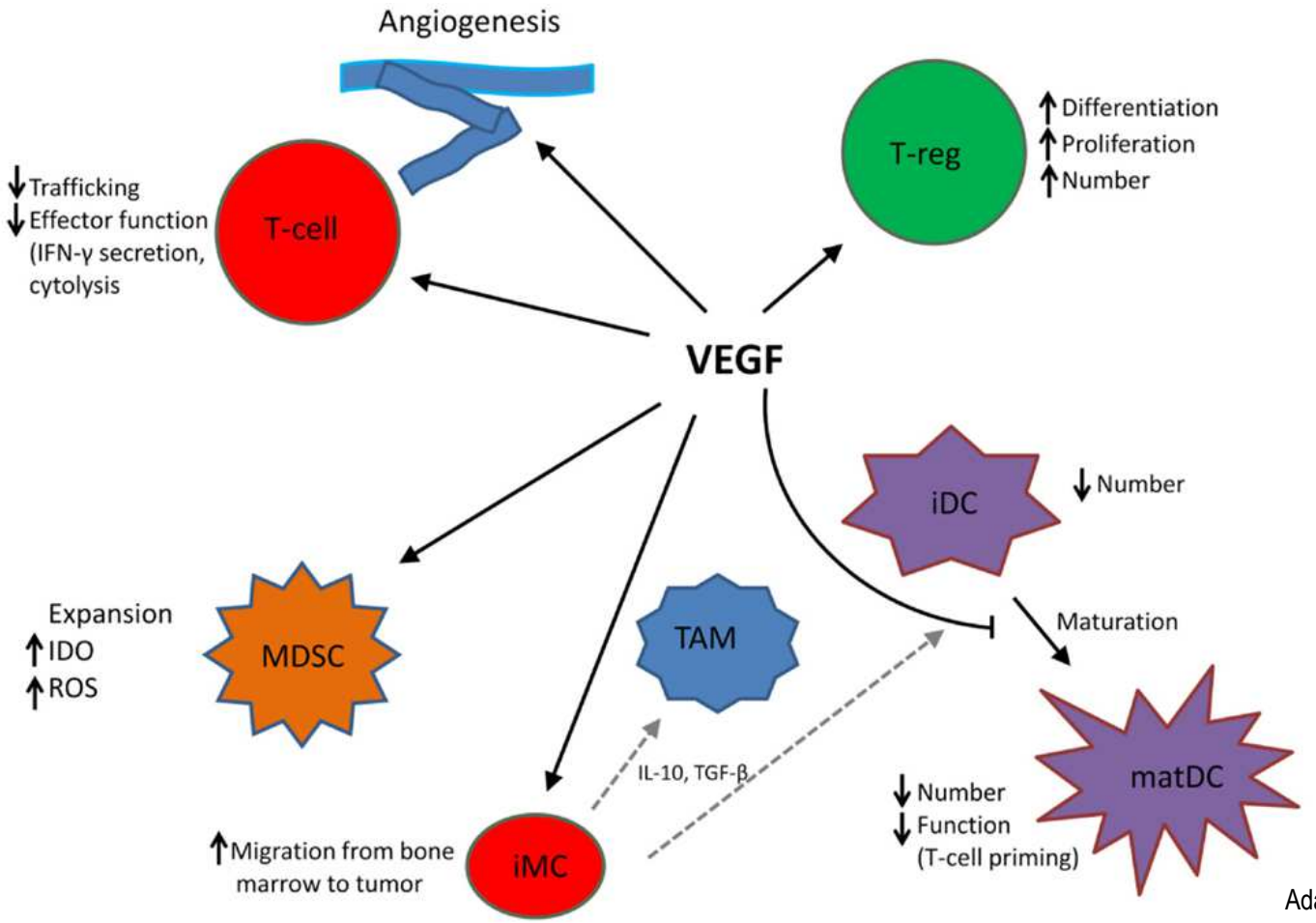
- Anticipated start: Feb 2016
- Target PFS: HR=0.65
- Arm A mPFS: 23 mo
- Arms B and C mPFS: 35.4 mo
- Accrual rate = 40 pts/mo
- Accrual duration = 27 mo.
- IA of PFS for efficacy or futility = ~30 mo. 2/3 of events
- Expected PFS readout at 41 mo

Stratification:
- - weekly vs Q3W taxol
- - residual vs no residual disease vs neoadjuvant
- - Region – North America vs other

n = ~951 (388 PFS events) 272 events within each of the 2 main comparisons

Primary endpoint:	**PFS from randomization (A vs B, A vs C)**
Secondary endpoints:	**PFS from randomization (B vs C)** **Maintenance PFS, OS, ORR, duration of response, PROs, safety, PK**

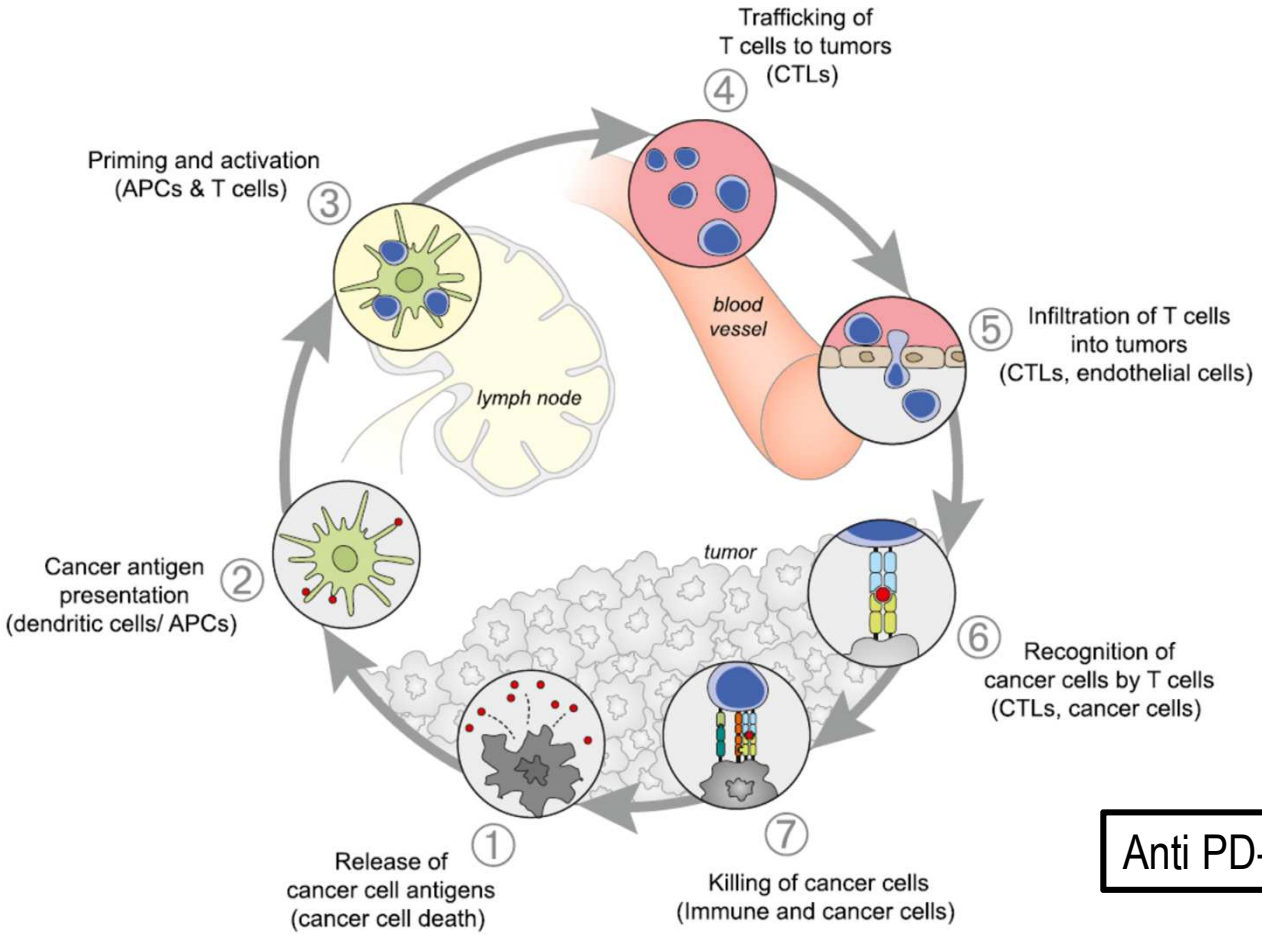
VEGF modulates the functions of T cell, MDSC and stroma in the tumor microenvironment



Adapted from Olt, 2015

Cancer Immunity cycle

Dual targeting with antiangiogenics and anti PD-L1



Anti VEGF

Anti PD-L1

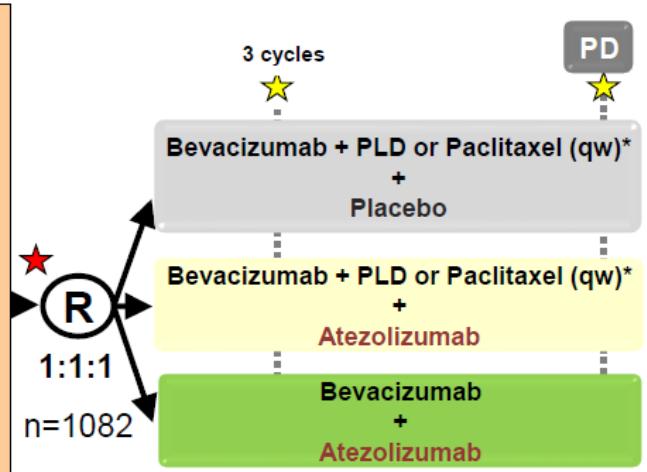
Chen, 2013

ENGOT – OV34 AGO-OVAR 2.29

Atezolizumab in combination with bevacizumab +/- CT versus CT-Bevacizumab in recurrent OvCa: a randomised Phase III trial

ENGOT model A
Sponsor AGO Study Group

- epithelial ovarian, fallopian tube or primary peritoneal cancer
- **1st or 2nd relapse: TFI p < 6 months**
- **OR 3rd / 4th relapse**
- **Prior Bevacizumab allowed**
- Bev and atezolizumab specific exclusion criteria
- Archival **and** recent biopsy mandatory
- PS 0/1, life expectancy 3 months +



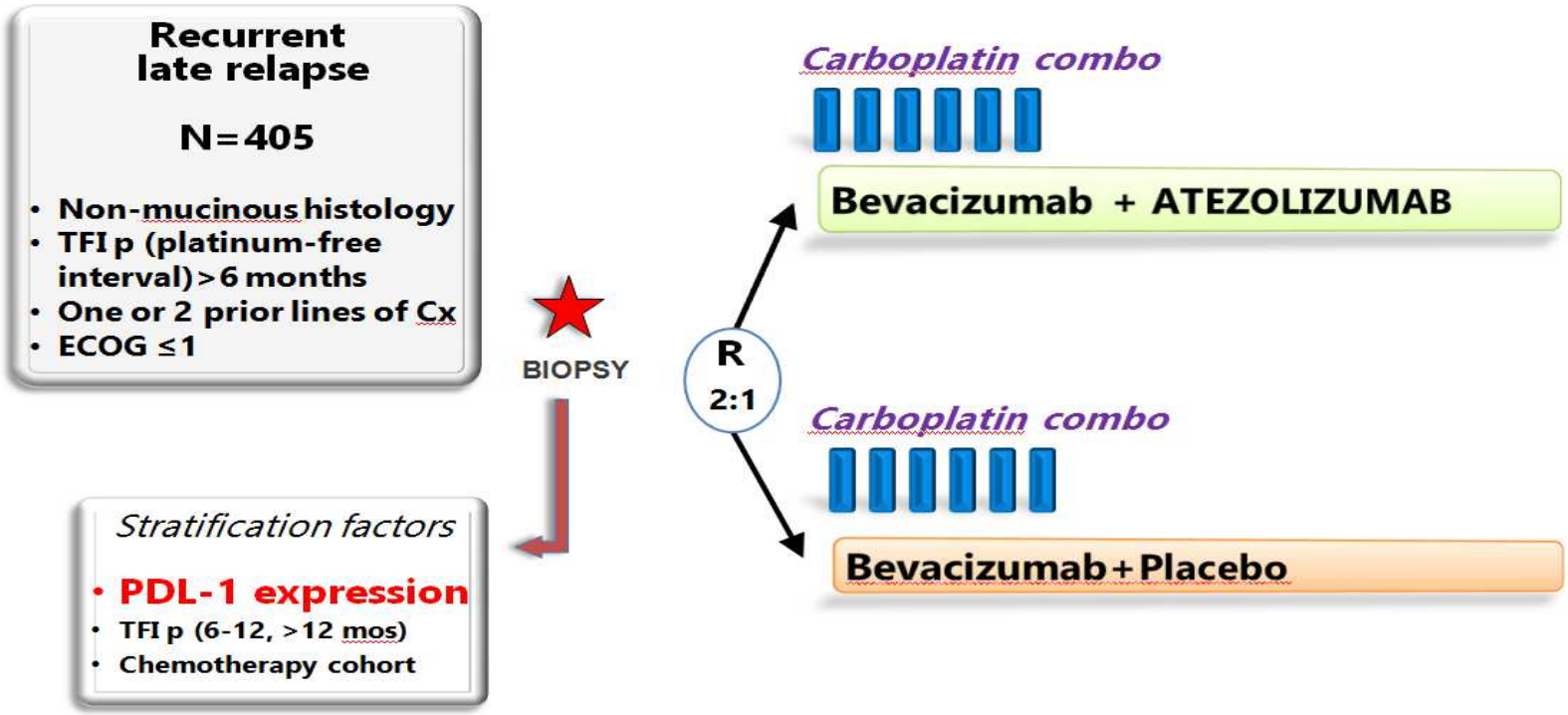
* In arm 1 and 2 cohorts caping: 50% PLD and 50% paclitaxel

PLD, pegylated liposomal doxorubicin; PS: performance status

★ Mandatory Biopsy ☆ Optional biopsy

ALANTE DESIGN

PI: J.E. Kurtz



Chemotherapy-based schedule options (investigator's choice): carboplatin AUC5 + PLD(30mg/m² q 4wks) or paclitaxel (175mg/m² q3wks) or gemcitabine (1000 mg/m² D1&D8 q3wks) . BEV 15mg/kg q3 wks or 10mg/kg q2 wks. ATEZO/PLACEBO: 1200mg, I.V q3wks or 800mg q2wks.*

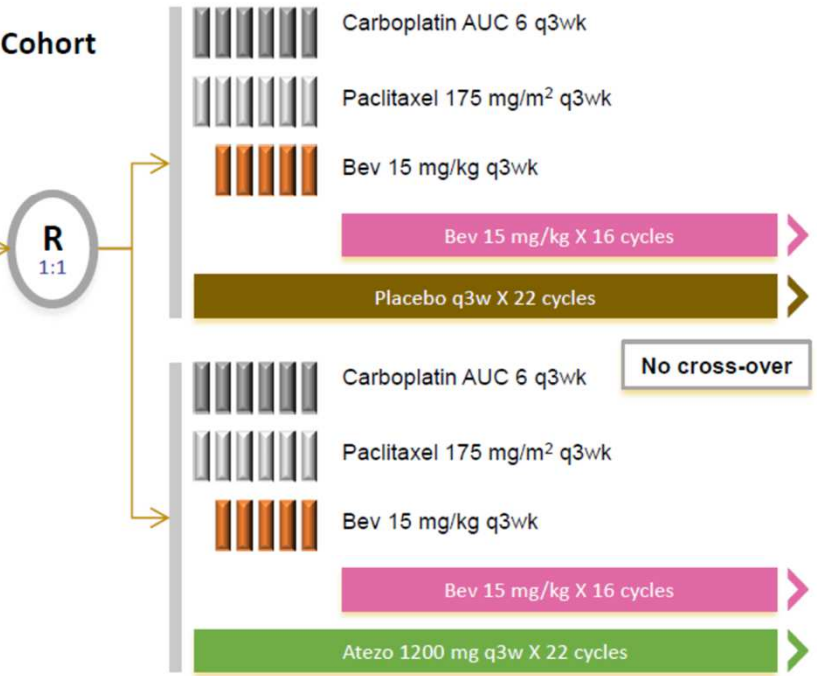
ENGOT Ov-39 Trial
IMaGYN 050
Study Design

Study Design in Primary Surgery Cohort

- **Previously untreated ovarian, fallopian tube, or peritoneal cancer**
- **Post-operative Stage III w/macroscopic residual disease, Stage IV**
- **ECOG PS 0-2**

Stratification variables

- Stage/debulking status
- ECOG PS
- PDL1 IC0 vs IC1+
- Adjuvant/Neo-adjuvant



Niraparib plus pembrolizumab in platinum resistant ovarian cancer

Topacio study

Platinum status	Response	All (%)	tBRCAmut (%)	HRD pos (%)	tBRCAwt	HRD neg (%)
All	ORR	15/60 (25)	5/11 (45)	7/21 (33)	10/43 (23)	7/30 (23)
Platinum resistance/ refractory	ORR	11/46 (24)	2/7 (29)	4/15 (27)	9/34 (26)	7/24 (29)

The addition of pembrolizumab to niraparib in tBRCAwt and HRD neg led to ORR similar to PARPi efficacy in tBRCAmut population

HRD status does not correlate with response in platinum resistant refractory disease

Kostantinopoulos, SGO, 2018

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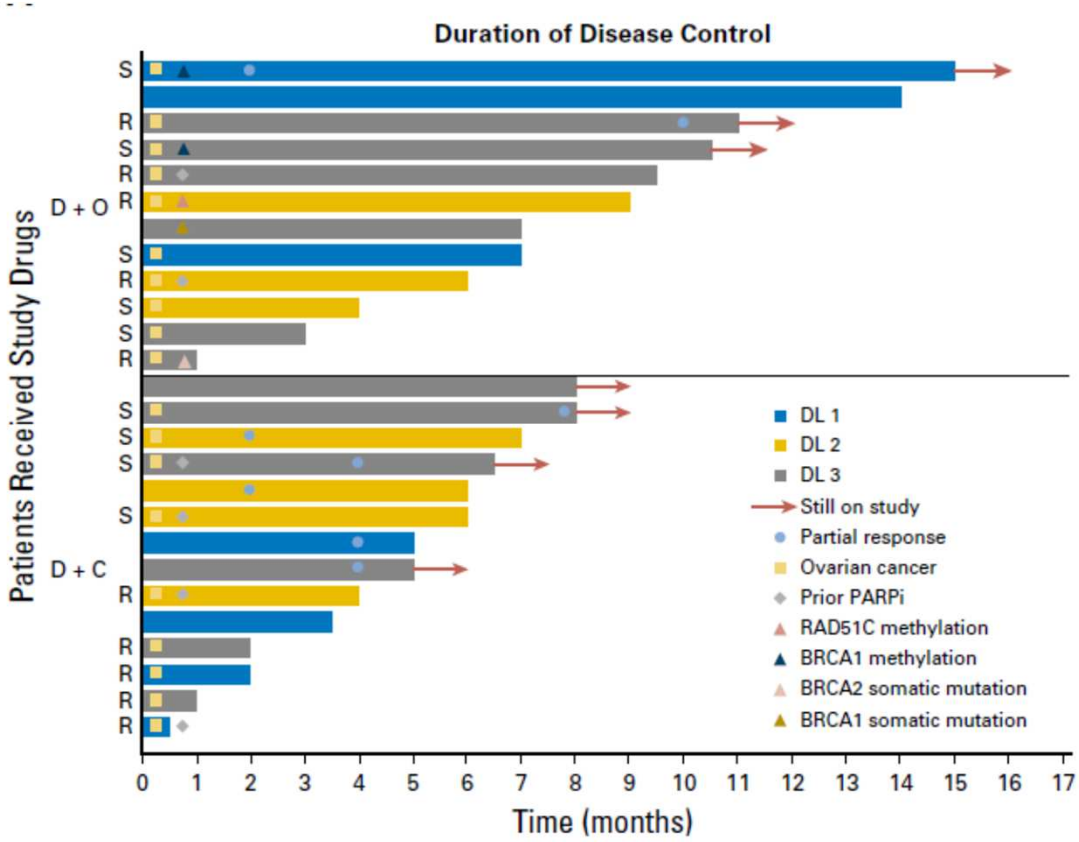
Phase I study of Durvalumab with Olaparib or Cediranib in women's cancer



No association between clinical response and:

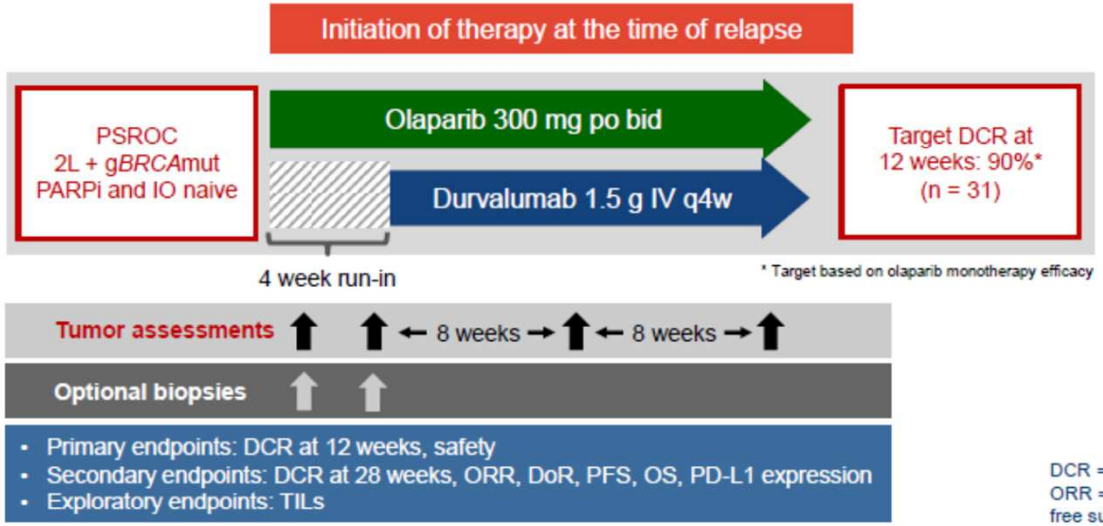
- Degree of TIL infiltrate, carcinoma cell PD-L1 labeling, TIL PD-L1 labeling
- HRD phenotype

Lee, 2017

Olaparib plus durvalumab in patients with platinum-sensitive recurrent Ovarian cancer

MEDIOLA study (phase II) - results in patients with germline *BRCA*-mutation

Study design



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

Objective:

- Efficacy and safety of PARP-inhibitor olaparib in combination with anti-PD-L1 durvalumab in patients with platinum-sensitive relapsed ovarian cancer (PSROC)

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

An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline *BRCA*-mutated (*gBRCA*m) platinum-sensitive relapsed (PSR) ovarian cancer (OC) **Drew Y et al.**, SGO 2018, late-breaking abstract

Frauenheilkunde Innsbruck

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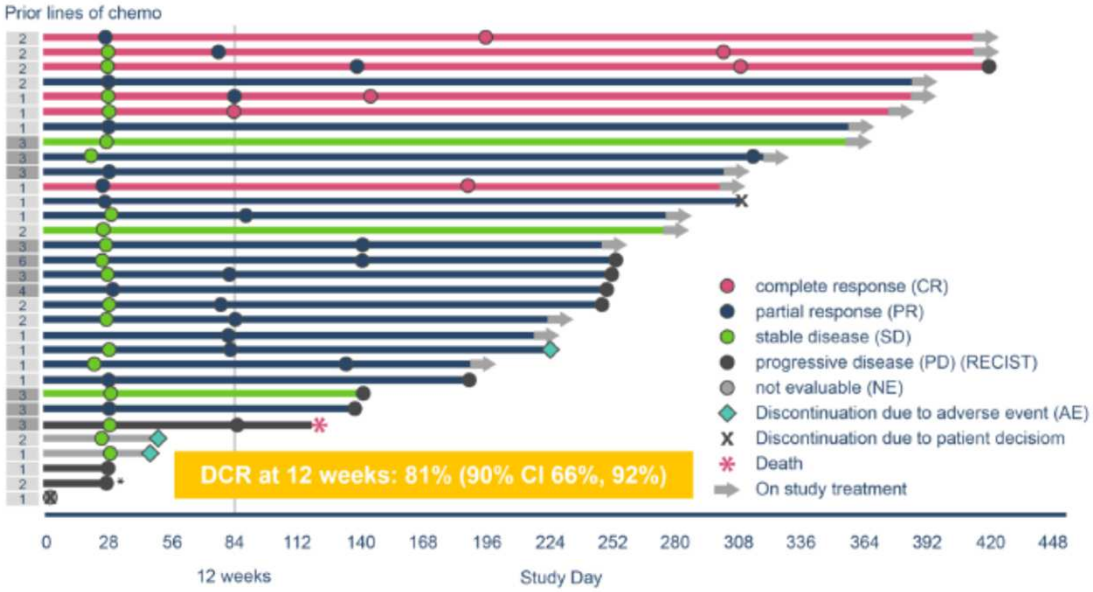
Olaparib plus durvalumab in patients with platinum-sensitive recurrent Ovarian cancer

Time to progression or treatment discontinuation (n=32)



* Patient later achieved a PR after receiving durvalumab + olaparib combination
AE = adverse event
CR = complete response
NE = not evaluable
PD = progressive disease
PR = partial response
SD = stable disease

An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline *BRCA*-mutated (*gBRCA*m) platinum-sensitive relapsed (PSR) ovarian cancer (OC) **Drew Y et al.**, SGO 2018, late-breaking abstract

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Clinical development of immune checkpoint inhibitors in Ovarian Cancer

What we know

- Good rationale for further development in combination
- Limited antitumor activity of single agent, however also in resistant disease and with long term responders

What we should do

- Assess antitumor activity in randomized clinical trials
- Incorporate translational endpoints in clinical trials
- Adapt study design to
    - Stage of clinical course
    - HRD and BRCA status
    - Upcoming results from ongoing studies

THANKS FOR YOUR ATTENTION