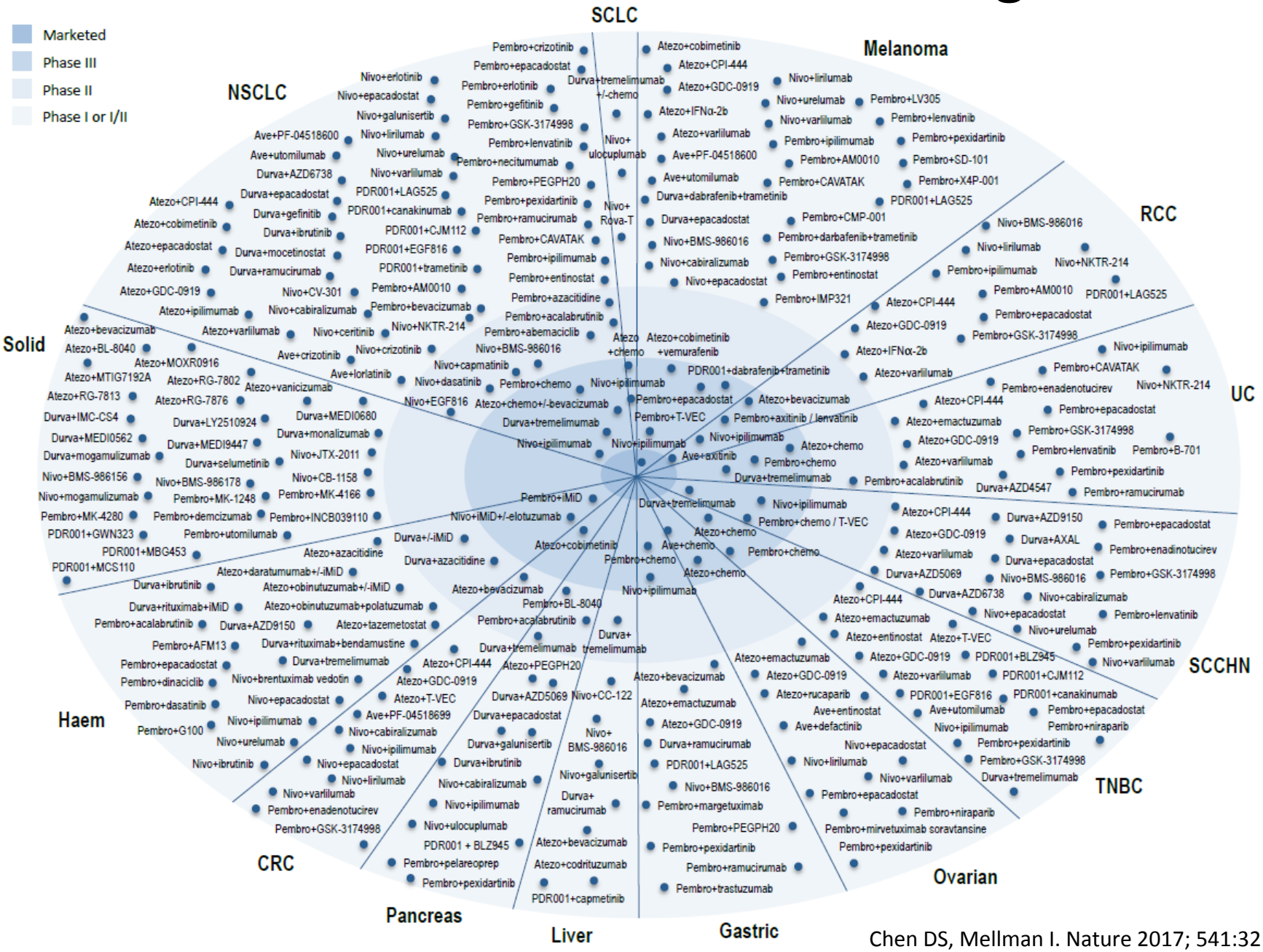
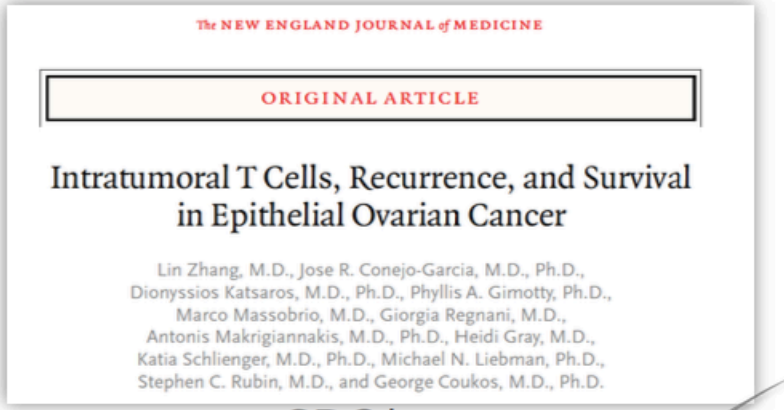
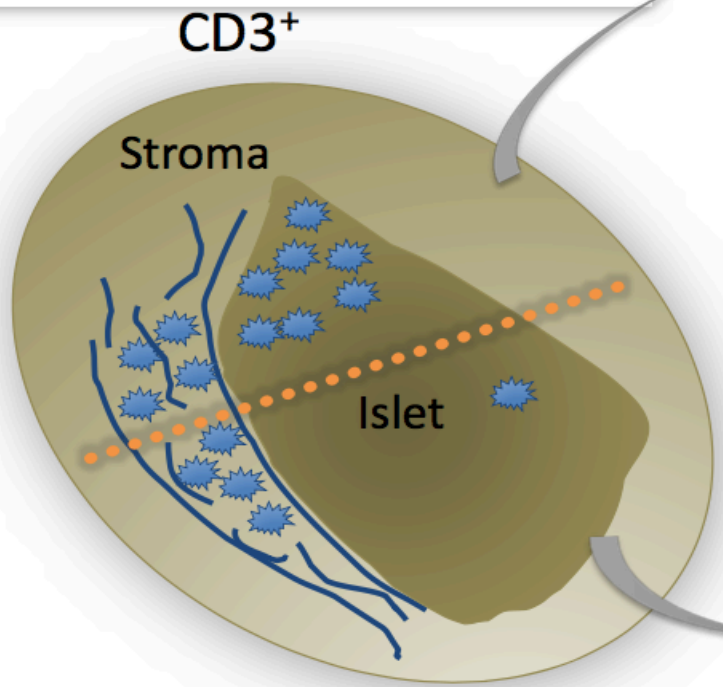
Over 1000 trials on clinicaltrials.gov!



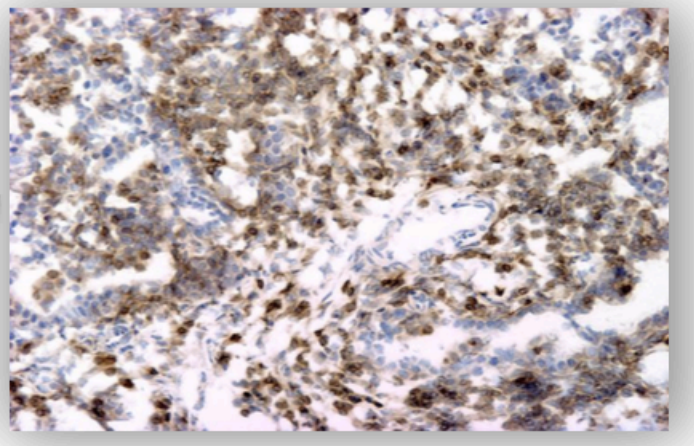
Chen DS, Mellman I. Nature 2017; 541:321-330

Is there a role for immunotherapy in ovarian cancer?

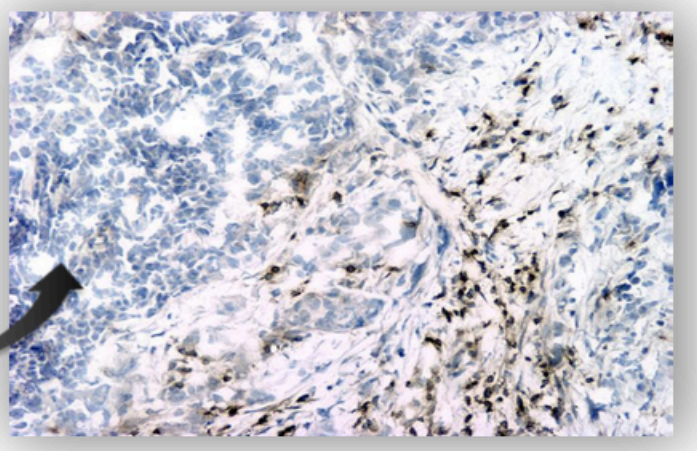




TIL Present
55%



TIL Absent
40%



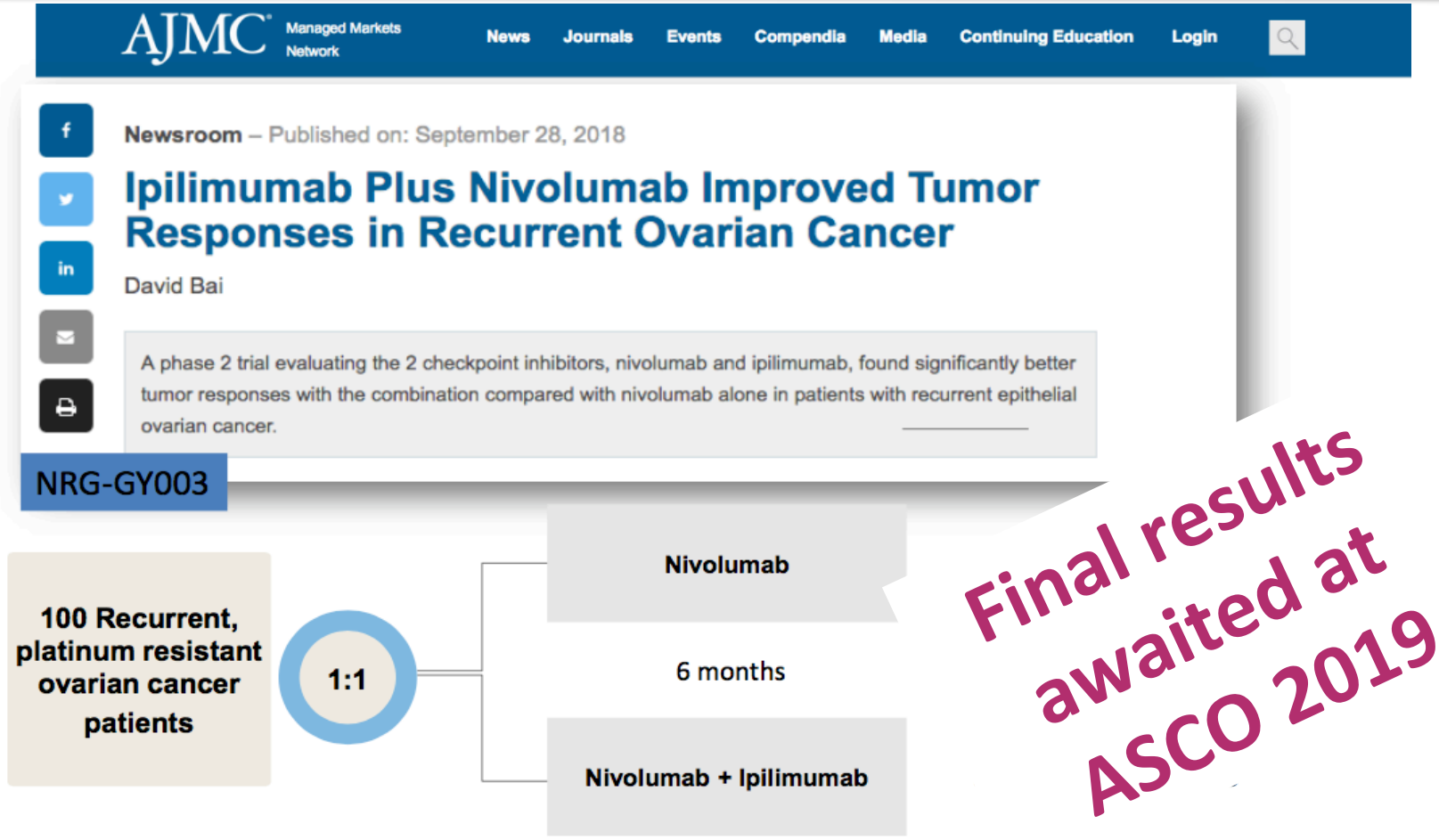
What are the results till now?

	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	15	9.7	25
Duration	4 (20%) >24 wks	7 (30%) >24 wks	16.1% 24 wks	mPFS >12 mo

Single CPIs are not sufficient!

Hamanishi et al. J Clin Oncol 2015; Varga et al. J Clin Oncol 2015: 33 (suppl; abstr 5510); Disis ML, et al. J Clin Oncol. 2016;34 (suppl): Abstract 5533; Infante et al. Ann Oncol 2016: 27 (Supple 6) Abstract 871P

How about combo?

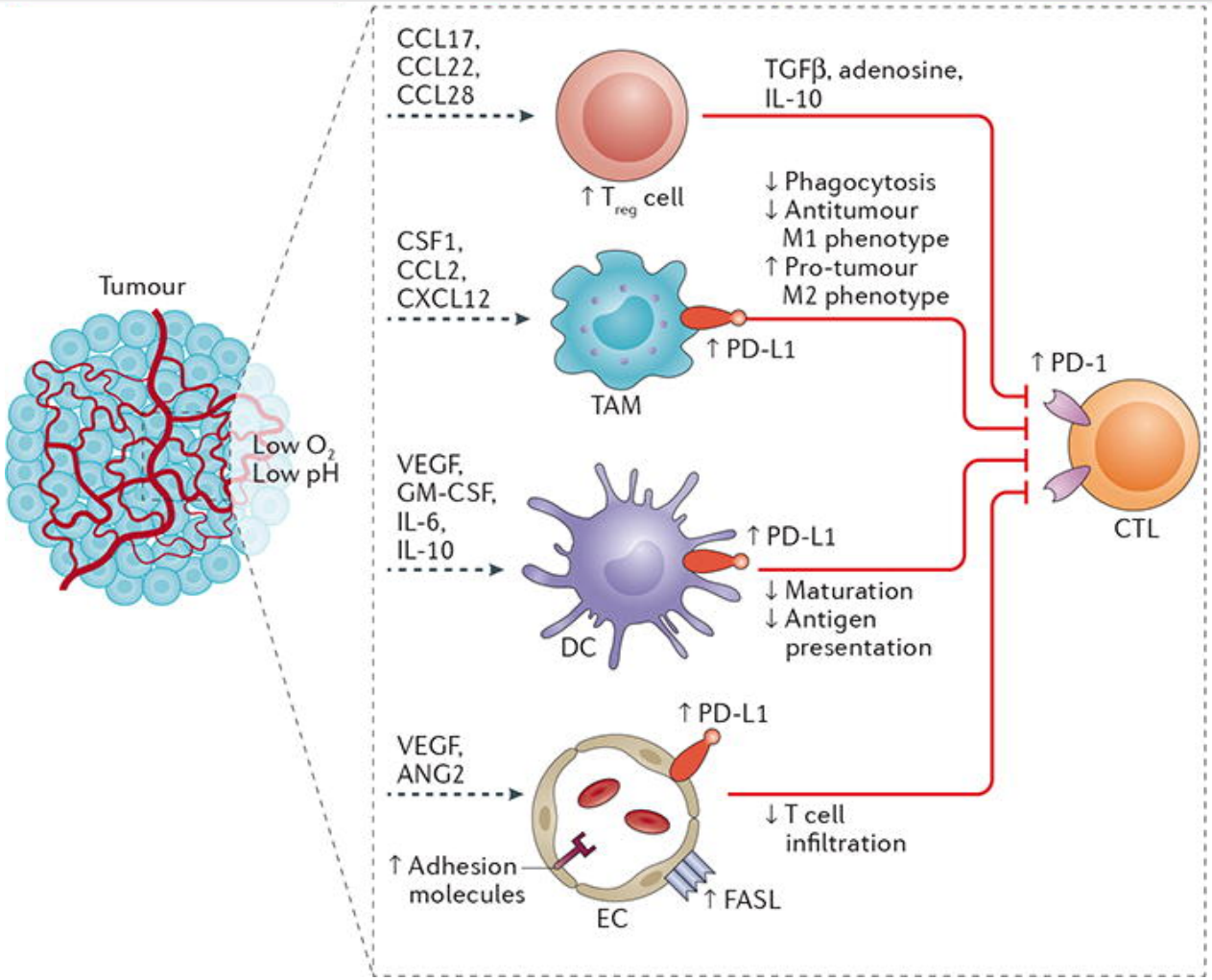


Burger R, et al. NRG oncology phase 2 randomized trial of nivolumab with or without ipilimumab in patients with persistent or recurrent ovarian cancer. Abstract presented at IGCS 2018; Kyoto, Japan.

How can we improve these results?

- **Check-point inhibitors combinations**
  - Anti-angiogenics
  - PARP inhibitors
- **A new option: T-cell therapy**
- **Better patients selection**
  - More efficient biomarkers
  - Immunophenotypes
  - Stroma and microbiome characterization

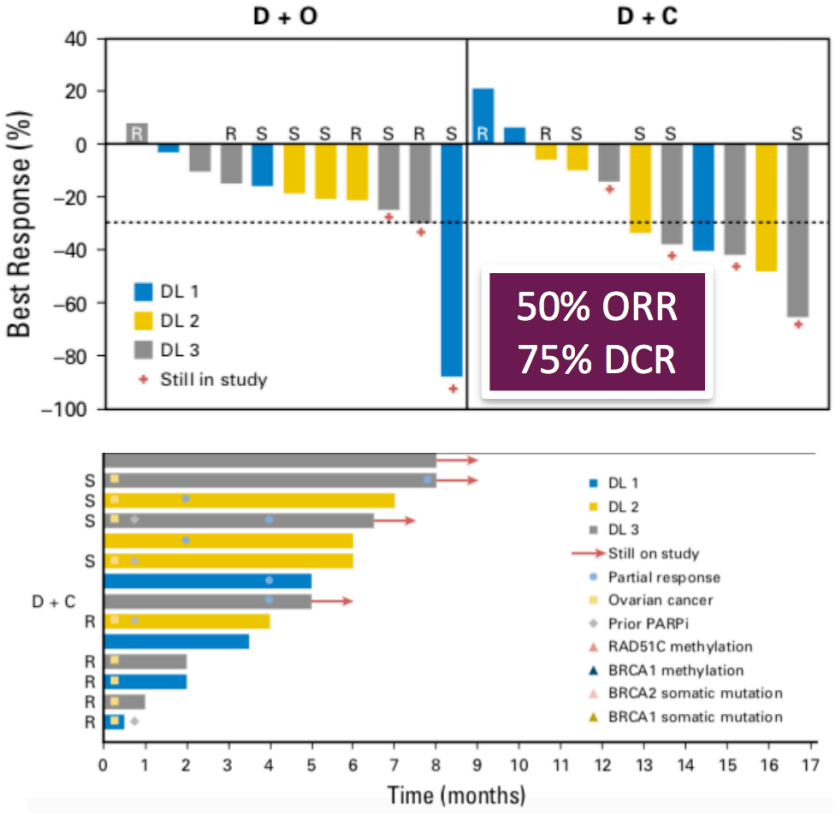
Rationale for combining anti-VEGF and CPI



Dai Fukumura et al. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nature Reviews Clinical Oncology* volume 15, 325–340 (2018).

Phase I of durvalumab and cediranib

- RP2D Durvalumab 1500 mg /28 days + intermitent cediranib 20 mg (5 days on / 2 days off)
- Continuous cediranib was not tolerated due to hypertension, diarrea and pulmonay embolism (2 of 8 each)

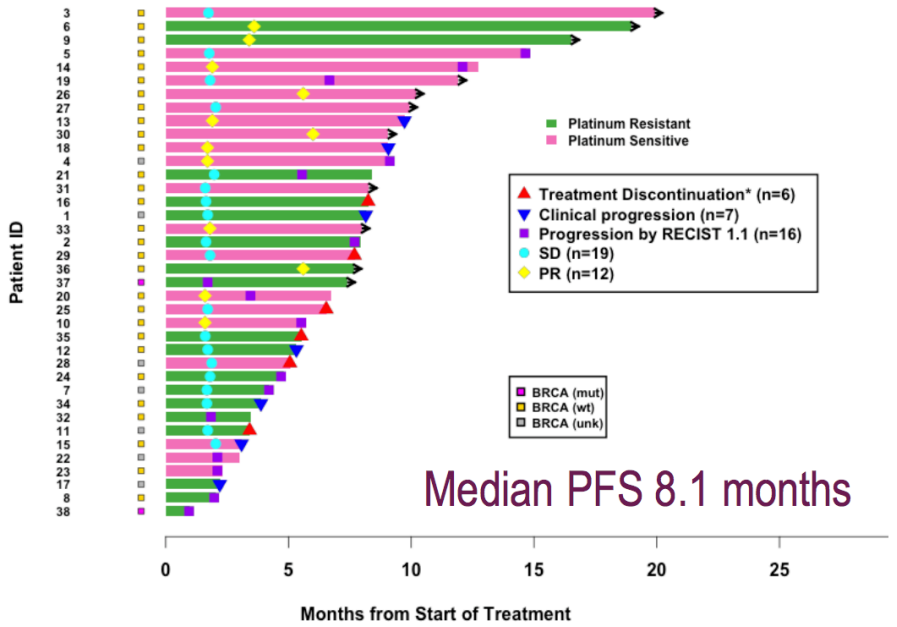


J Clin Oncol. 2017 Jul 1;35(19):2193-2202. Lee JM et al. Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study. J Clin Oncol. 2017 Jul 1;35(19):2193-2202.

Phase II of nivolumab and bevacizumab

Best Overall Response	Platinum-Sensitive (N=20)		Platinum-Resistant (N=18)		Overall (N=38)	
	N	%	N	%	N	%
Unevaluable	-	-	1	5.6	1	2.6
Partial response						
Confirmed	8	40.0	3	16.7	11	28.9
Unconfirmed	1	5.0				
Stable disease						
>24 weeks	6	30.0	3	16.7	9	23.7
<24 weeks	3	15.0	7	38.9	10	26.3
Progressive disease	2	10.0	4	22.2	6	15.8
Overall confirmed response rate	8	40.0	3	16.7	**11**	**28.9**
Total clinical benefit rate (CBR)	15	75.0	6	33.3	**21**	**55.3**

Durable responses or prolonged stable disease (including in platinum-resistant patients)



Joyce Liu et al. - A phase 2 trial of combination nivolumab and bevacizumab in recurrent ovarian cancer. 937PD- Poster Presentation, ESMO Congress 2018.

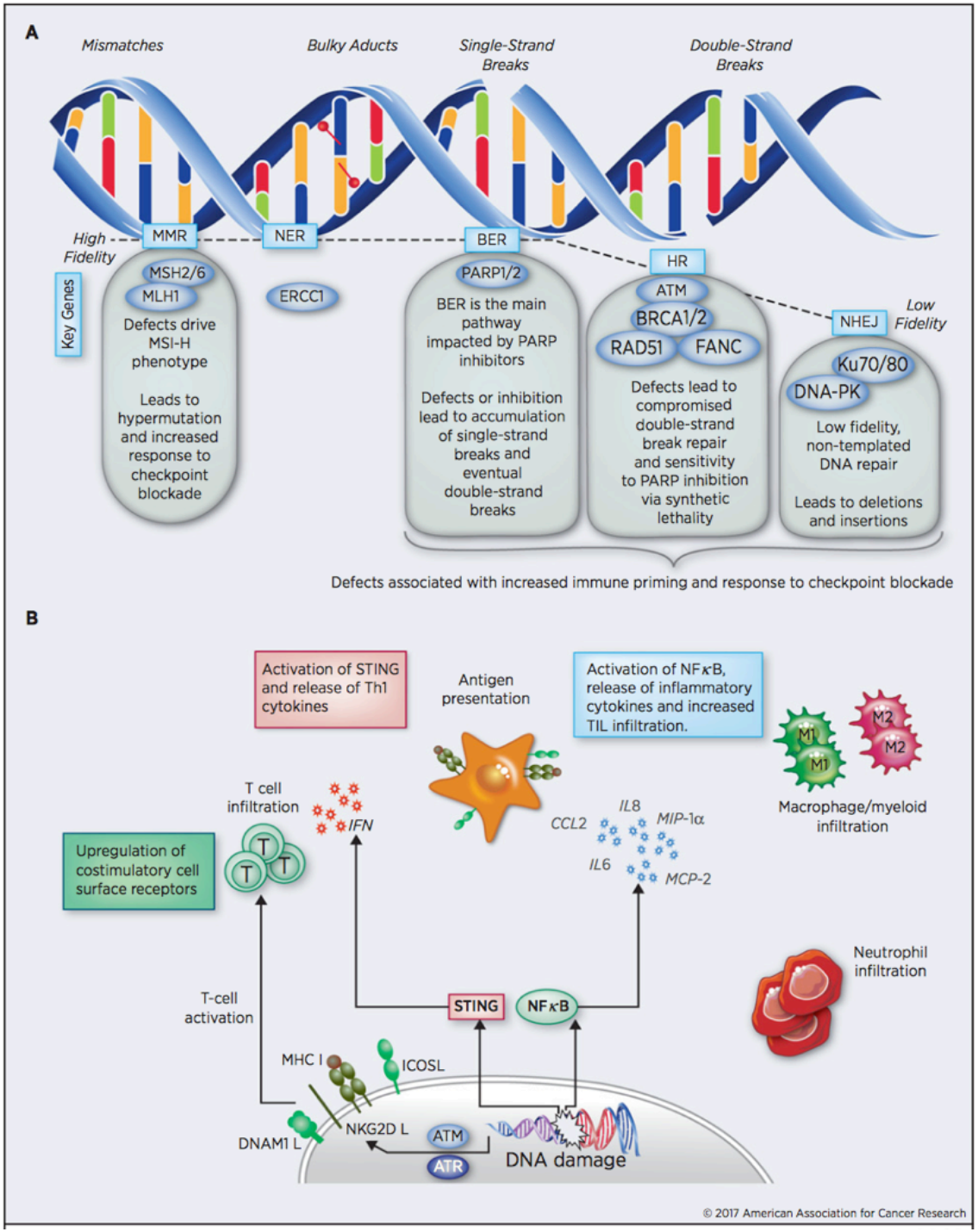
Bev + CPIs ongoing trials

Trial	Setting	Patients' selection	Arms
GOG3015/ ENGOT OV39	Front line	Stage III or IV PDS or IDS any residual Stratification PDL1 0 vs 1+	Carbo-Tax +Bev Carbo-Tax +Bev+Atezo
ATALANTE/ ENGOT OV29	Recurrence	1 or 2 previous CT lines PFI>6 months Stratification PDL1	Carbo combo +Bev Carbo combo +Bev+ Atezo
EORTC-1508	Recurrence	Platinum resistant Any num of platinum lines Max 2 lines non-platinum Biopsy required	Bev + aspirin Bev + Atezo + aspirin Bev + Atezo + placebo Atezo + aspirin Atezo + placebo

How can we improve these results?

- **Check-point inhibitors combinations**
  - Anti-angiogenics
  - PARP inhibitors
- **A new option: T-cell therapy**
- **Better patients selection**
  - More efficient biomarkers
  - Immunophenotypes
  - Stroma and microbiome characterization

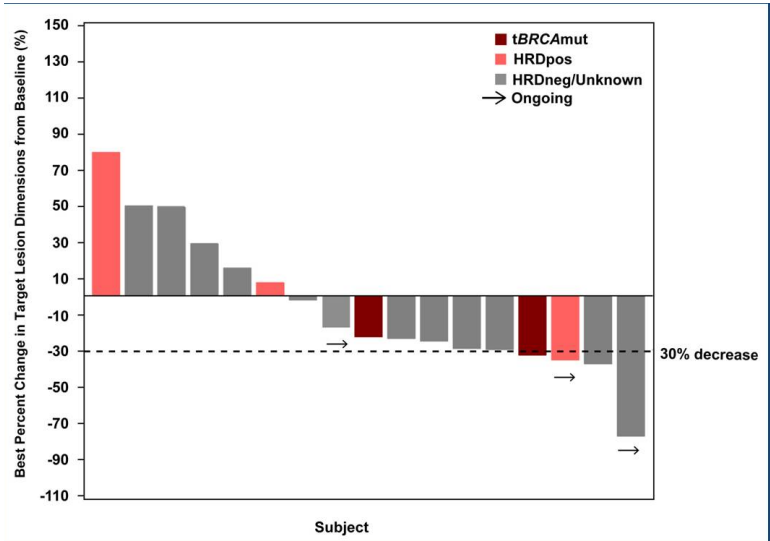
Rationale for CPIs and PARPIs



Ross A et al. Development of PARP and Immune-Checkpoint Inhibitor Combinations. Clinical Cancer research review
Published OnlineFirst November 29, 2018; DOI: 10.1158/0008-5472

Phase 1/2 of pembrolizumab and niraparib

Response	All (%)	t*BRCA*mut (%)	HRDpos* (%)	t*BRCA*wt (%)	HRDneg (%)
ORR	11/47 (23%)	2/8 (25%)	4/16 (25%)	9/37 (24%)	7/26 (27%)
DCR	30/47 (64%)	5/8 (63%)	11/16 (69%)	24/37 (65%)	15/26 (58%)



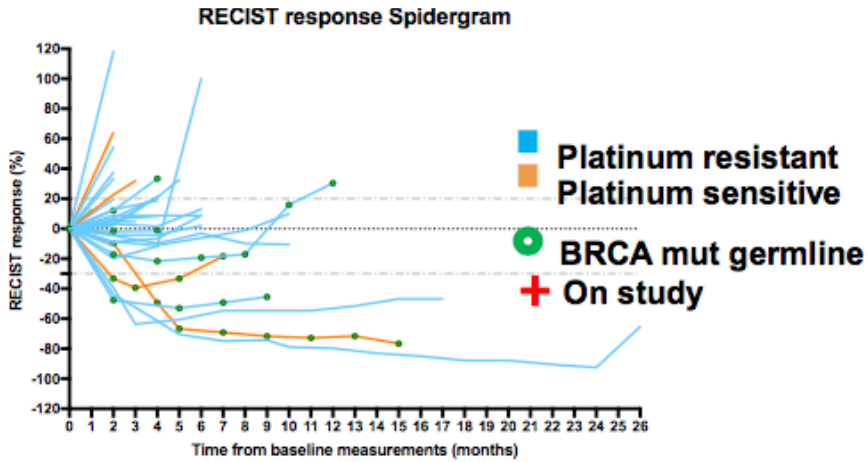
- Evaluable platinum-refractory patients (n=17): ORR, 24%; DCR, 59%
- Biomarker-negative patients:
  - t*BRCA*wt: ORR, 23%; DCR, 54%
  - HRDneg: ORR, 25%; DCR, 50%
- 2 of 4 responders still on treatment

TOPACIO/Keynote-162: A phase 1/2 study of niraparib + pembrolizumab: results from the platinum-resistant ovarian cancer (PROC) cohort. Presented by Panagiotis Konstantinopoulos at 2018 ASCO Annual Meeting.

Phase II of durvalumab and olaparib

- Phase I RP2D was D 1500 mg iv/4w and Ola 300mg BID (Lee et al. JCO 2017)
- 35 patients included in Phase II
  - 6 PS (17%) and 29 PR (83%)
  - 40% had ≥ 4 prior lines
  - gBRCA mut 6 (17%)

Characteristics	Total (n=35)
Complete Response (CR)	0
Partial Response (PR)	5 (14%)
Stable Disease (SD)	20 (57%)
Progression of Disease (PD)	10 (29%)
Disease Control Rate (CR+PR+SD ≥6months)	13 (37%)



- 3 / 5 PR were gBRCA mut
- 4 / 29 were HRD+ (1PR in a sBRCA mut)
- Study did not meet primary objetive for further development (6/35 responders)

Jung-Min Lee et al. - A phase 2 study of durvalumab, a PD-L1 inhibitor and olaparib in recurrent ovarian cancer (OvCa). 936PD − Poster Presentation at ESMO Congress 2018.

CPIs + Bev + PARPIs?

TRIAL	Setting	Patient selection	Arms
AGO / DUO-O ENGOT Ov46	Front line	tBRCAnon-mut* PDS or IDS Any residual LGSOC excluded	CP-Bev-placebo-placebo CP-Bev-Durvalumab-placebo CP-Bev-Durvalumab-Olaparib
BGOG /ENGOT Ov43	Front line	tBRCA non-mut*, Any histotype PDS or IDS Any residual Bev optional	CP-Placebo-Placebo CP- Pembro-Placebo CP- Pembro-Olaparib
GINECO/ FIRST ENGOT Ov44	Front line	PDS (high risk) or IDS Bev optional Mucinous excluded	CP-Placebo-Placebo CP-Placebo-Niraparib CP-TSR042-Niraparib
ATHENA GOG3020 / ENGOT Ov45	Maintenance after front line	Stage III-IV and high grade PDS or IDS Response to platinum	Rucaparib-Nivolumab Rucaparib-Placebo Nivolumab-Placebo Placebo-Placebo

González Martín A., Poster Discussion Gynaecological Cancer, ESMO Congress 2018