Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Ovarian Cancer and Biomarkers

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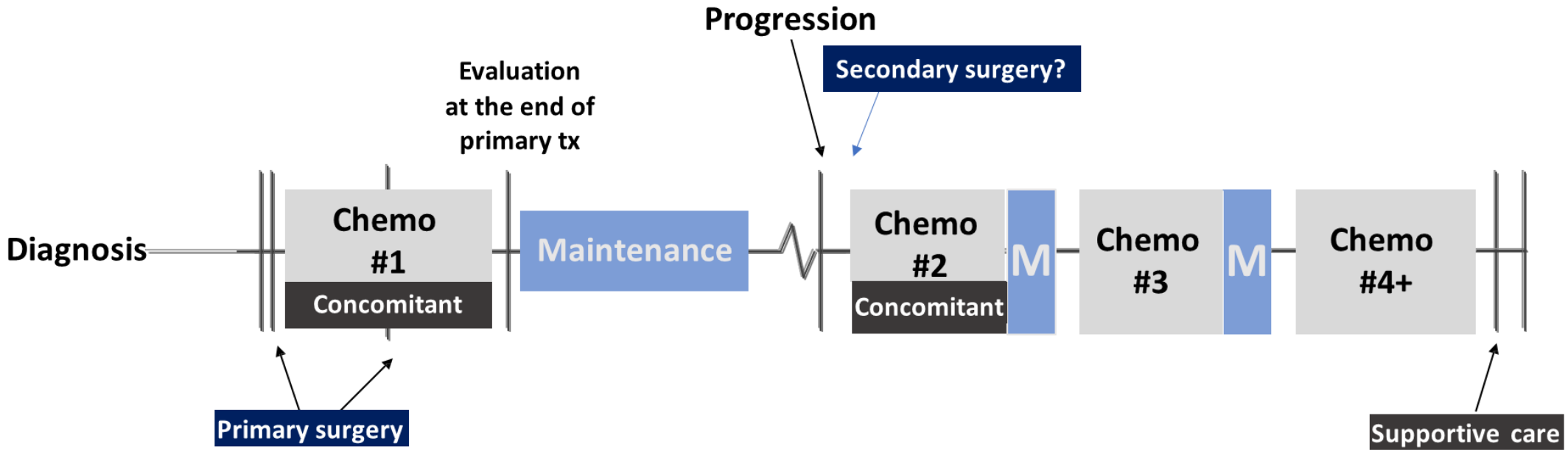
Disclosures

- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

OC treatment clinical landscape

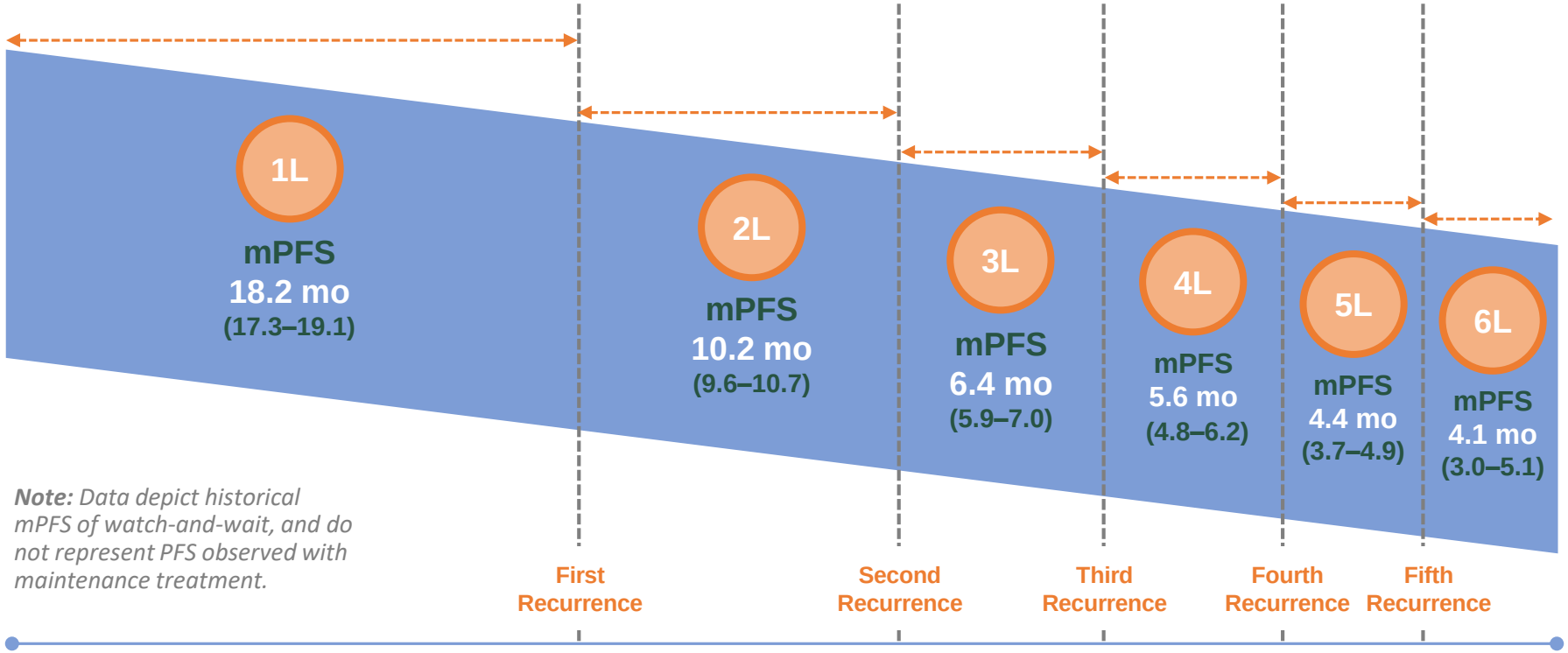
- Over recent decades, the 5-year OS of women with ovarian cancer has improved but largely due to more treatment lines rather than better first line therapy
- Platinum and paclitaxel are the main drugs that have been in standard use for >20 years
- Treatment of platinum-resistant ovarian cancer continues to be clinically challenging, has a poor outcome and the median PFS benefits are modest



Adapted from LaFargue C. et al. *Lancet Oncology* 2019; 20(1):e15-e28.

The Sad Reality: Poor Prognosis and Shorter Treatment Intervals

- Most ovarian cancers will recur, leading to poor prognosis and shorter treatment intervals
  - ~80% of advanced ovarian cancers will recur during or after 1L treatment
  - Median progression-free survival (mPFS) decreases after every recurrence*:



Note: *Data depict historical mPFS of watch-and-wait, and do not represent PFS observed with maintenance treatment.*

Response Rate to 2nd line cytotoxic chemotherapy: 15-25%.

*mPFS values measured from beginning of chemotherapy (ie, day of randomization) to the first disease progression and, thereafter, from one progression to the subsequent one or to death
L, line; mo, month; mPFS, median progression-free survival; PFS, progression-free survival.

Hanker LC, et al. *Ann Oncol*. 2012;23(10):2605-12.

Is immunotherapy ever going to be the future to treat OC?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[l]/Fallopian Tube/Primary Peritoneal Cancer[m]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens		Useful in Certain Circumstances
Cytotoxic Therapy	Cytotoxic Therapy[t]		Immunotherapy
Cyclophosphamide (oral)/bevacizumab[g,30]	Capecitabine	Oxaliplatin	Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase and no satisfactory alternative treatment options)[v,29]
Docetaxel[31]	Cyclophosphamide	Paclitaxel	
Etoposide, oral[32]	Doxorubicin	Paclitaxel, albumin bound	
Gemcitabine[33,34]	Ifosfamide	Pemetrexed	
Liposomal doxorubicin[33,34]	Irinotecan	Sorafenib/topotecan[39]	
Liposomal doxorubicin/bevacizumab[g,o,35]	Melphalan	Vinorelbine	
Paclitaxel (weekly)[36]			Hormone Therapy
Paclitaxel (weekly)/bevacizumab[g,o,35]			Fulvestrant (for low-grade serous carcinoma)
Topotecan[37,38]			Targeted Therapy (single agents)
Topotecan/bevacizumab[g,o,35]			Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[v]
Targeted Therapy (single agents)	Targeted Therapy (single agents)		Trametinib (for low-grade serous carcinoma)[28]
Bevacizumab[g,o,17,18]	Pazopanib (category 2B)[26]		
Niraparib[q,19]			
Olaparib[r,20]	Hormone Therapy		
Rucaparib[s,21]	Aromatase inhibitors (anastrozole, exemestane, letrozole)		
	Leuprolide acetate		
	Megestrol acetate		
	Tamoxifen		

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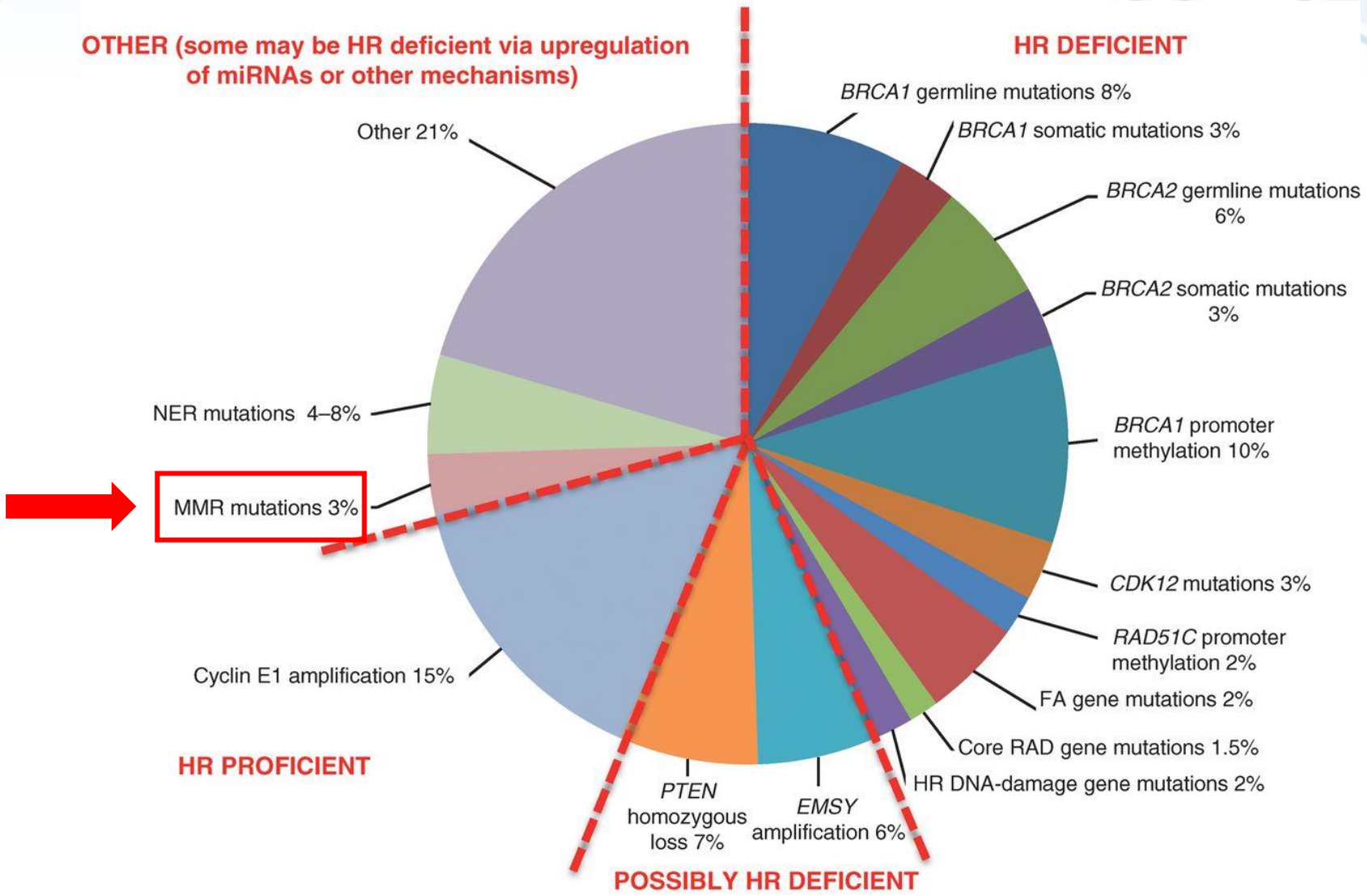
Mutational landscape of OC



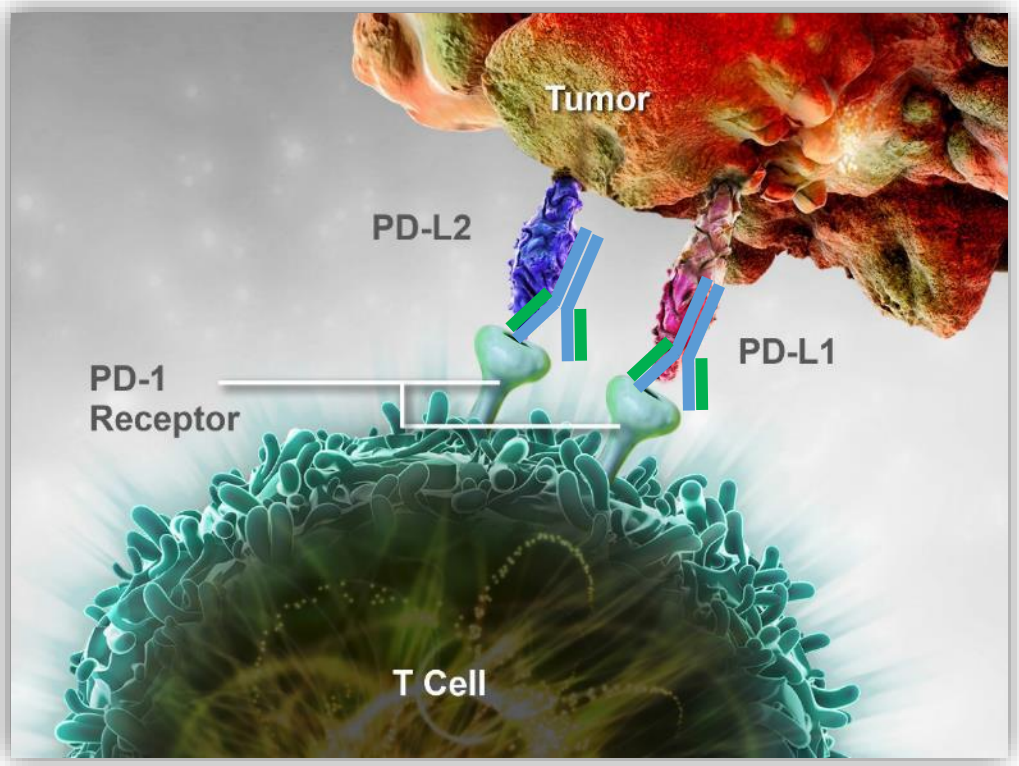
Konstantinopoulos et al., Cancer Discovery, 2015

TMB and MSI in OC

	N	n with TMB ≥ 7.6 muts/Mb	% n with TMB≥ 7.6 muts/Mb	n with MSI-H	n with MSI-H and TMB ≥ 7.6 muts/Mb	% MSI-H of TMB ≥ 7.6 muts/Mb
Clear cell	254	23	**9.06%**	4	3	**13.04%**
Endometrioid	140	29	**20.71%**	13	12	**41.38%**
Carcinoma Mixed	92	9	**9.78%**	2	2	**22.22%**
HG Serous	2655	208	**7.83%**	0	0	**0**

Feinberg J et al., SGO, 2018

Singe Agent ICB



Singe agent anti-PD1/PD-L1 in OC

Checkpoint inhibitor	Inclusion	Phase	patient number	# of prior therapies	ORR	Reference
Anti-PD1						
Nivolumab	Platinum resistant OC	2	20	≥ 4 (55%)	**10% CR 5% PR 30% SD**	Hamanishi et al 2015
Pembrolizumab (Keynote-28)	Recurrent OC	1b	26	≥ 3 (65%)	**4% CR, 8% PR, 23% SD**	Varga et al 2015
Pembrolizumab (Keynote-100)	Reccurent OC Cohort A: TFI of ≥ 3 to 12 months Cohort B: TFI of ≥ 3 months	2	376	A: 1-3 B: 4-6	**8% ORR (17.3% ORR CPS>10)**	Matulonis et al 2018
Anti-PD-L1						
Avelumab	Platinum resistant OC	1b	124	≥3 (58%)	**9.7% PR, 44% SD**	Disis et al 2016
Atezolizumab	Recurrent OC	1b	12	>6 (58%)	**25% ORR**	Infante et al 2016
BMS-936559	Recurrent OC	1	17	>1	**6% PR,18% SD**	Brahmer et al 2012

Marth et al., IJGC 2019

KEYNOTE-100: Phase 2 Two-Cohort Study of Pembrolizumab for Recurrent OC

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
Annals of Oncology 30: 1080–1087, 2019
doi:10.1093/annonc/mdz135
Published online 2 May 2019

ORIGINAL ARTICLE

Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study

U. A. Matulonis[1*], R. Shapira-Frommer[2], A. D. Santin[3], A. S. Lisyanskaya[4], S. Pignata[5], I. Vergote[6], F. Raspagliesi[7], G. S. Sonke[8], M. Birrer[9], D. M. Provencher[10], J. Sehouli[11], N. Colombo[12], A. González-Martín[13], A. Oaknin[14], P. B. Ottevanger[15], V. Rudaitis[16], K. Katchar[17], H. Wu[18], S. Keefe[19], J. Ruman[19] & J. A. Ledermann[20]

Patients (N = 376)

- Recurrent, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer
- ECOG PS 0 or 1
- Provision of a tumor sample for biomarker analysis

Key exclusion criteria:

- Mucinous histology
- No bowel obstruction within 3 months
- No active autoimmune disease
- No active CNS metastases and/or carcinomatous meningitis

Cohort A
- 1 - 3 prior lines
- PFI or TFI of 3 - 12 months

Total enrollment: n = 285

Pembrolizumab 200 mg IV Q3 weeks until PD, prohibitive toxicity, death, or completion of 2 years

Cohort B
- 4 - 6 prior lines
- PFI or TFI of ≥3 months

Total enrollment: n = 91

Primary endpoint:
ORR by RECIST v1.1 by BICR
- By cohort
- By PD-L1 expression

Secondary endpoints:
- DOR, DCR, PFS, OS, safety

PFI = platinum-free interval; TFI = treatment-free interval.

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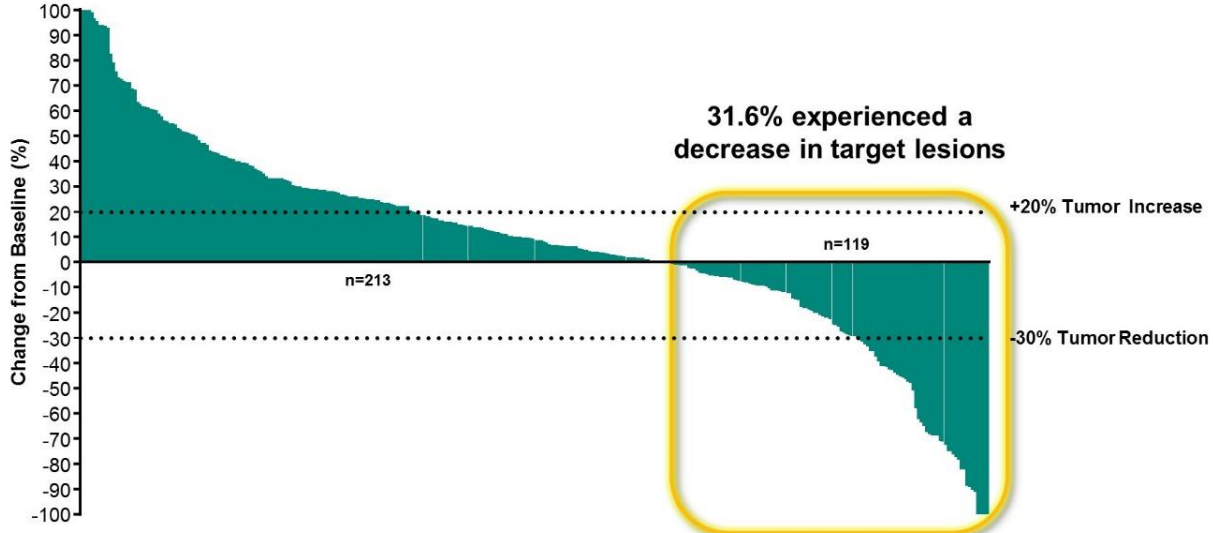
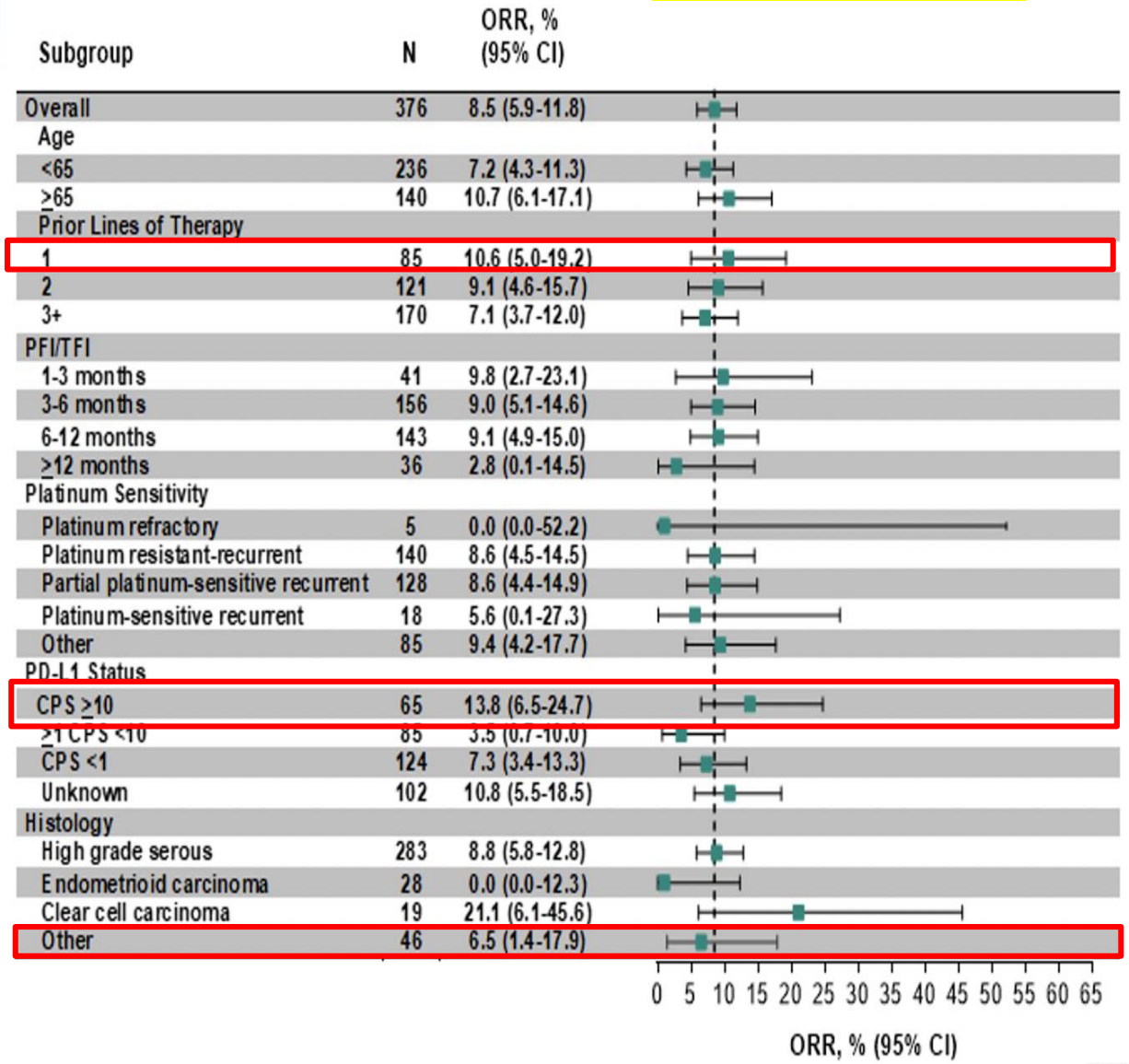
KEYNOTE-100

140 PRROC patients were treated with pembrolizumab monotherapy in KN100: ORR was 8.5%.

Best Change From Baseline in Tumor Size in Cohorts A + B: Based on RECIST v1.1 per BICR



Values higher than or equal to 100 are set to 100. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. BICR, Blinded Independent Central Review.
All Subjects as Treated Population. Database cut-off date: September 18, 2019.



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Matulonis U et al, ASCO2020

KEYNOTE-100

Antitumor Activity: Confirmed Objective Response Rate Based on RECIST v1.1 per BICR

	Cohort A 1 - 3 prior lines; PFI/TFI 3 - 12 months n = 285	Cohort B 4 - 6 prior lines; PFI/TFI ≥3 months n = 91	Cohorts A + B All-comers n = 376
ORR % (95% CI)	**8.1 (5.2 - 11.9)**	**9.9 (4.6 - 17.9)**	**8.5 (5.9 - 11.8)**
DCR % (95% CI)	22.1 (17.4 - 27.4)	22.0 (14.0 - 31.9)	22.1 (18.0 - 26.6)
Best overall response			
Complete response n (%)	5 (1.8)	2 (2.2)	7 (1.9)
Partial response n (%)	18 (6.3)	7 (7.7)	25 (6.6)
Stable disease n (%)	84 (29.5)	25 (27.5)	109 (29.0)
Progressive disease n (%)	165 (57.9)	49 (53.8)	214 (56.9)
Responders (n)	23	9	32
Time to response, median months (range)	2.1 (1.9 - 6.3)	2.1 (1.8 - 12.3)	2.1 (1.8 - 12.3)
Duration of response, median months (range)	8.3 (3.9 - 35.4+)	23.6 (3.3+ - 32.8+)	10.2 (3.3+ - 35.4+)

RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. BICR, Blinded Independent Central Review. DCR = CR + PR + SD ≥24 weeks.
Database cut-off date: September 18, 2019.

Antitumor Activity by PD-L1 Expression: Confirmed Response Rates Based on RECIST v1.1 per BICR

	Cohort A 1 - 3 prior lines; PFI/TFI 3 - 12 months		Cohort B 4 - 6 prior lines; PFI/TFI ≥3 months		Cohorts A + B All-comers	
	CPS ≥1 n = 101	CPS ≥10 n = 43	CPS ≥1 n = 49	CPS ≥10 n = 22	CPS ≥1 n = 150	CPS ≥10 n = 65
ORR % (95% CI)	**6.9 (2.8 - 13.8)**	**11.6 (3.9 - 25.1)**	**10.2 (3.4 - 22.2)**	**18.2 (5.2 - 40.3)**	**8.0 (4.2 - 13.6)**	**13.8 (6.5 - 24.7)**
DCR % (95% CI)	24.8 (16.7 - 34.3)	25.6 (13.5 - 41.2)	22.4 (11.8 - 36.6)	31.8 (13.9 - 54.9)	24.0 (17.4 - 31.6)	27.7 (17.3 - 40.2)
Best overall response						
Complete response n (%)	2 (2.0)	2 (4.7)	2 (4.1)	2 (9.1)	4 (2.7)	4 (6.2)
Partial response n (%)	5 (5.0)	3 (7.0)	3 (6.1)	2 (9.1)	8 (5.3)	5 (7.7)
Stable disease n (%)	32 (31.7)	12 (27.9)	14 (28.6)	6 (27.3)	46 (30.7)	18 (27.7)
Progressive disease n (%)	55 (54.5)	22 (51.2)	27 (55.1)	12 (54.5)	82 (54.7)	34 (52.3)

ECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. BICR, Blinded Independent Central Review. DCR = CR + PR + SD ≥24 weeks.
atabase cut-off date: September 18, 2019.

With 37.8m median follow-up, results confirm that pembrolizumab monotherapy in recurrent OC elicits modest antitumor efficacy:

- 8.5% ORR in all-comers (7CRs, 25 PRs).

Trend toward increased ORR with higher PD-L1 expression:

- 11.6% ORR for PD-L:1 CPS≥10 in Cohort A
- 18.2% ORR for PD-L1 CPS≥10 in Cohort B

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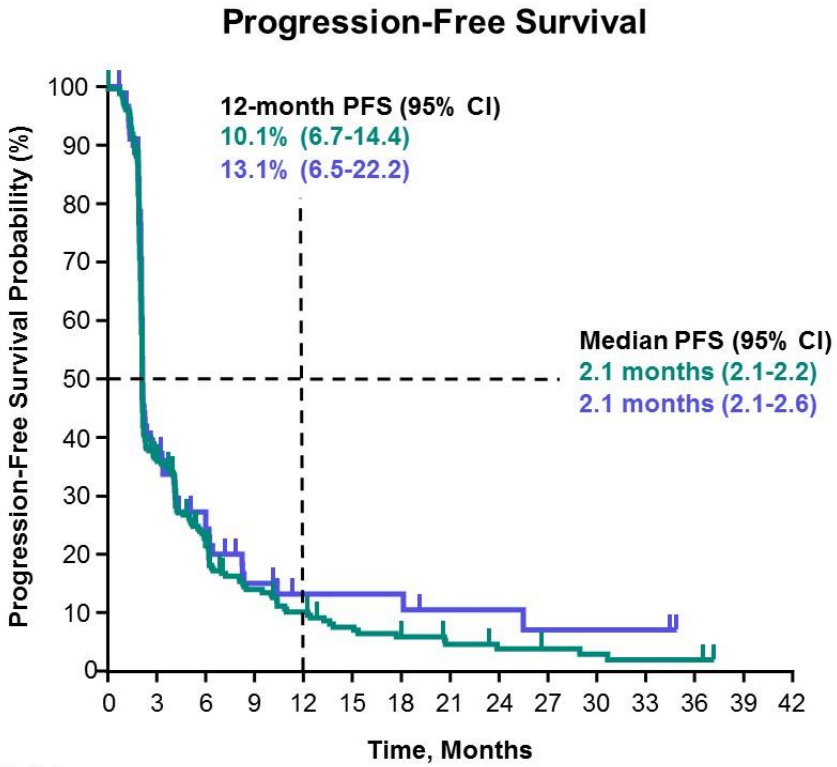
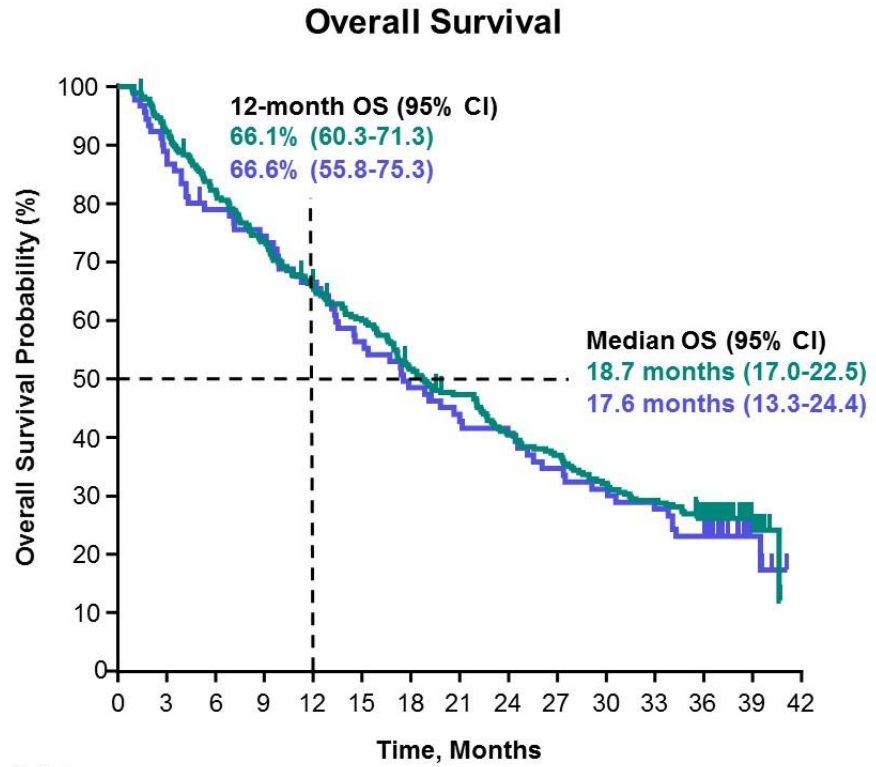
Matulonis U et al, ASCO2020

Progression-Free Survival and Overall Survival



No. at risk

Cohort A	285	98	55	30	21	14	11	7	5	4	3	2	2	0	0
Cohort B	91	33	19	9	5	5	5	3	3	2	2	2	0	0	0



No. at risk

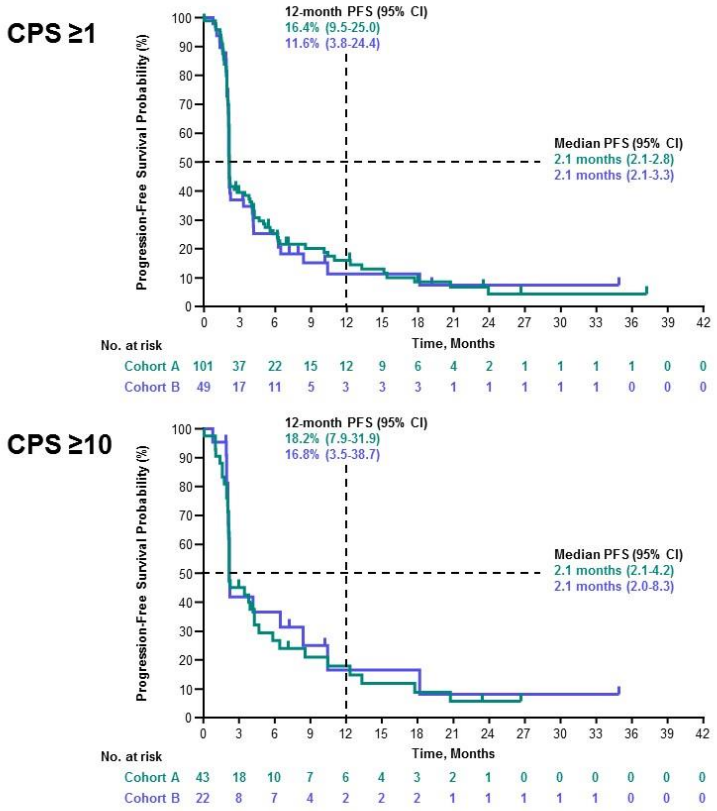
Cohort A	285	262	233	208	186	167	143	128	110	100	87	79	57	14	0
Cohort B	91	80	70	66	59	50	43	38	35	30	27	25	20	4	0

Progression-free survival based on RECIST v1.1 per BICR. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. BICR, Blinded Independent Central Review. All Subjects as Treated Population. Database cut-off date: September 18, 2019.

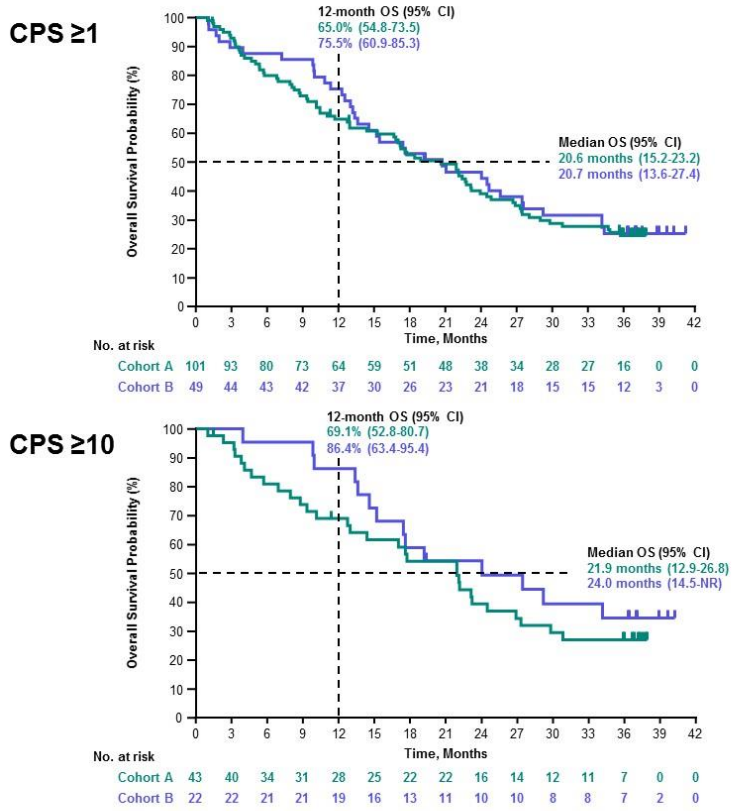
KEYNOTE-100 - Phase 2 Two-Cohort Study of Pembrolizumab for Recurrent OC

Progression-Free Survival and Overall Survival by PD-L1 Expression

Progression-Free Survival



Overall Survival

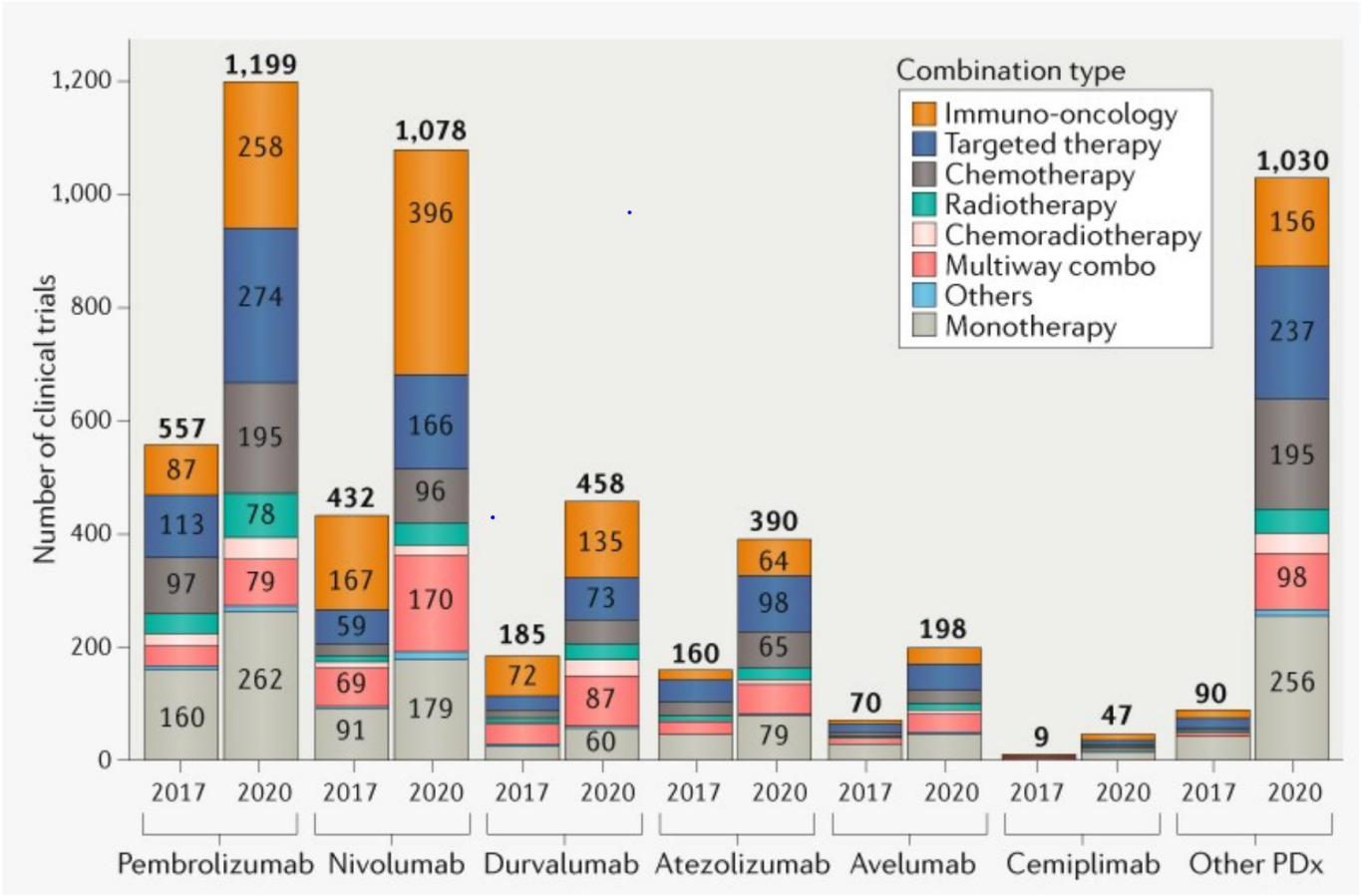


mPFS in CPS≥1 or CPS≥10 : 2.1m

mOS CPS≥1: 20.6m
mOS CPS≥10: 21.9m

Progression-free survival based on RECIST v1.1 per BICR. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. BICR, Blinded Independent Central Review.
All Subjects as Treated Population. Database cut-off date: September 18, 2019.

CHEMO + IO COMBINATION



Upadhaya S et al., Nat Rev Drug Disc 2021

RATIONALE FOR COMBINATION IN OC

Carboplatin/Paclitaxel: Combined PD-1 blockade in NSCLC- immunochemotherapy combination outperformed chemotherapy

Cisplatin: sensitize cells to T cell killing

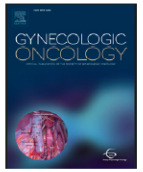
Doxorubicin + Oxaliplatin: Induce immunogenic cell death, which could, synergize with immunotherapy

Pegylated doxorubicin (PLD): Enhances the uptake of tumor antigens by myeloid DCs by promoting antigen processing and cross presentation to T cells

Low-dose Cyclophosphamide: Attenuate Tregs and improve vaccination and ACT efficacy combination with ICB- stimulates the generation of CD8+ TILs and improves ORR

Kandalaft L et al., Journal of Clinical Oncology 2019

Contents lists available at ScienceDirect
Gynecologic Oncology
journal homepage: www.elsevier.com/locate/ygyno



Pembrolizumab plus PLD in PRROC

Combined pembrolizumab and pegylated liposomal doxorubicin in platinum resistant ovarian cancer: A phase 2 clinical trial

Elizabeth K. Lee [a], Niya Xiong [b], Su-Chun Cheng [b], William T. Barry [b], Richard T. Penson [c], Panagiotis A. Konstantinopoulos [a,d], Mark A. Hoffman [e], Neil Horowitz [d,f], Don S. Dizon [g], Elizabeth H. Stover [a,d], Alexi A. Wright [a,d], Susana M. Campos [a,d], Carolyn Krasner [c,1], Stephanie Morrissey [d], Christin Whalen [d], Roxanne Quinn [d], Ursula A. Matulonis [a,d,*,2], Joyce F. Liu [a,d,*,2]

- **Open label, phase II study**
- **N=26 (single stage design with safety lead-in of n=6)**

Key Eligibility Criteria

- Recurrent EOC, fallopian tube or primary peritoneal cancer
- Received prior platinum-based therapy
- Platinum resistant (refractory excluded)
- Up to 2 prior lines of cytotoxic therapies for recurrent or persistent disease
- ECOG 0 or 1
- Presence of measurable disease per RECIST 1.1
- No prior immunotherapy

Intervention

Pembrolizumab 200 mg IV Q3W
PLD 40mg/m² IV Q4W

Primary objective

CBR (CR + PR+ SD ≥ 24w)

Matulonis U et al, SGO 2018

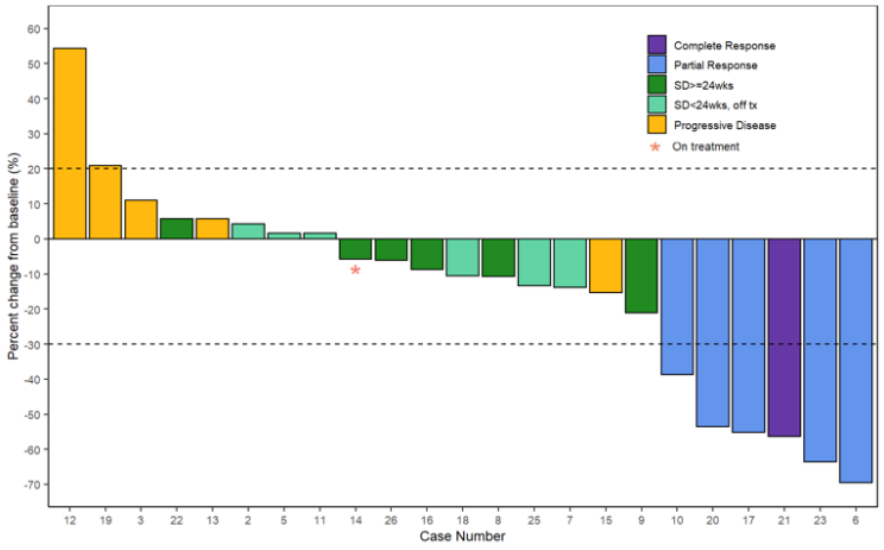
Pembrolizumab plus PLD

PRROC pts were treated with combination therapy in this MISP.

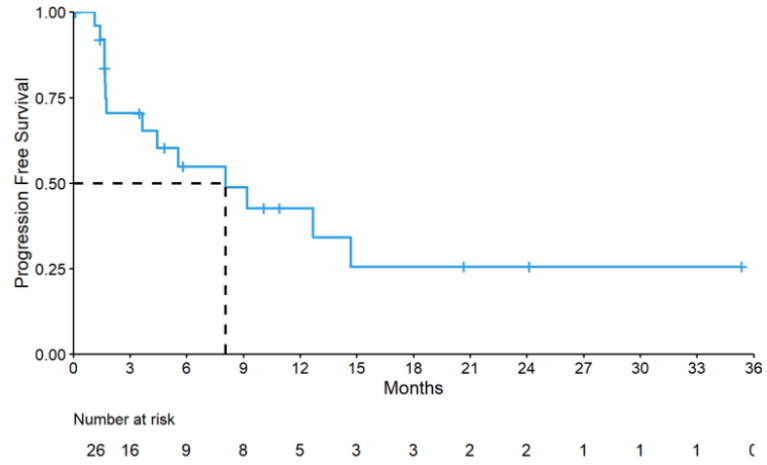
Best Overall Response – 26.1%
CBR: 52%

	Overall (n=26)
Best Overall Response	
Complete Response	1 (3.8%)
Partial Response	5 (19.2%)
SD ≥24 weeks	6 (23.1%)
SD <24 weeks	6 (23.1%)
Progressive Disease	5 (19.2%)
Unevaluable	3 (11.5%)

Waterfall Plot



Progression-Free Survival – 8.1 months

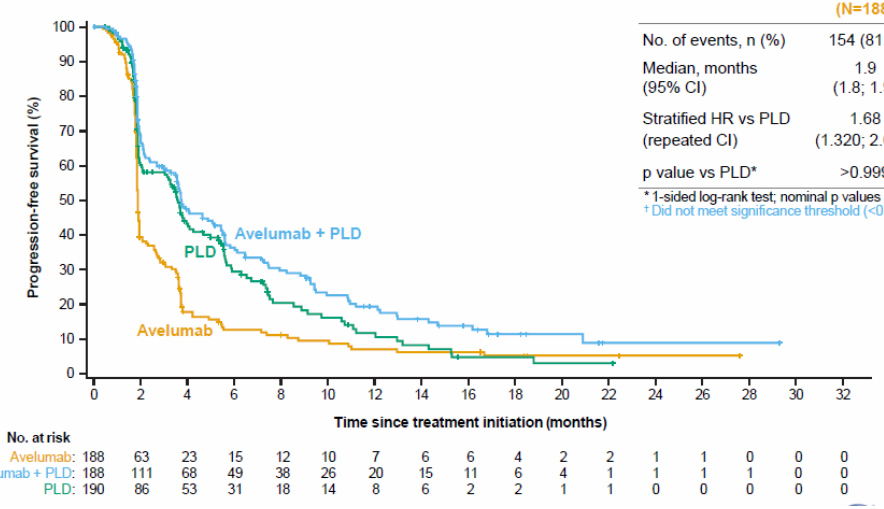


Lee EK et al., Gynegologic Ongology, 2020

IO in PRROC: JAVELIN Ovarian 200, the first ICB RP3 in PRROC was negative

Avelumab appeared to nominally improve on PLD monotherapy efficacy but not enough to result in a positive trial. Avelumab monotherapy activity in PRROC was minimal; ORR was 3.7%.

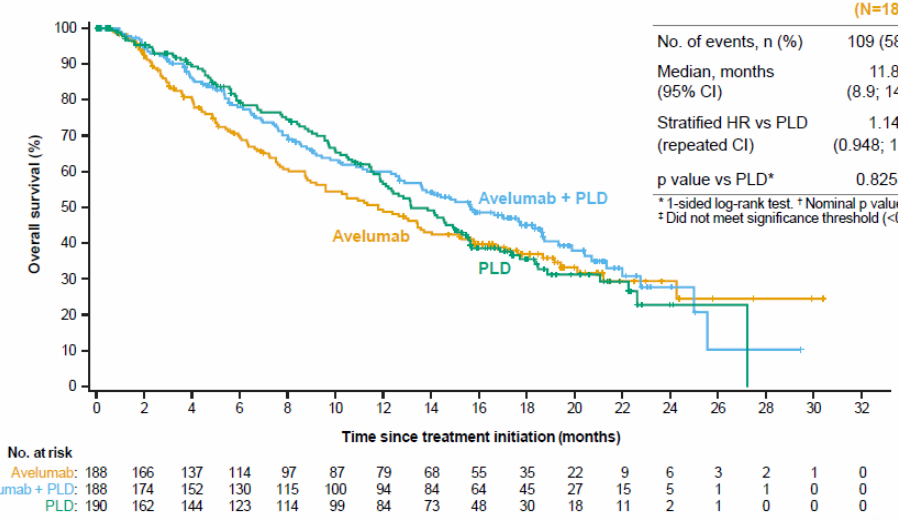
Progression-free survival by BICR



	Avelumab (N=188)	Avel. + PLD (N=188)	PLD (N=190)
No. of events, n (%)	154 (81.9)	134 (71.3)	125 (65.8)
Median, months (95% CI)	1.9 (1.8; 1.9)	3.7 (3.3; 5.1)	3.5 (2.1; 4.0)
Stratified HR vs PLD (repeated CI)	1.68 (1.320; 2.601)	0.78 (0.587; 1.244)	–
p value vs PLD*	>0.999	0.0301†	–

* 1-sided log-rank test; nominal p values (futility boundary was crossed at interim analysis)
† Did not meet significance threshold (<0.0002)

Overall survival



	Avelumab (N=188)	Avel. + PLD (N=188)	PLD (N=190)
No. of events, n (%)	109 (58.0)	102 (54.3)	104 (54.7)
Median, months (95% CI)	11.8 (8.9; 14.1)	15.7 (12.7; 18.7)	13.1 (11.8; 15.5)
Stratified HR vs PLD (repeated CI)	1.14 (0.948; 1.580)	0.89 (0.744; 1.241)	–
p value vs PLD*	0.8253†	0.2082‡	–

* 1-sided log-rank test. † Nominal p value (futility boundary was crossed at interim analysis)
‡ Did not meet significance threshold (<0.0103)

Possible reasons for failure:

1) Avelumab is a weak immune checkpoint inhibitor
   - ORR: 4% (1.5; 7.5);
2) PLD is not an optimal chemotherapy combination partner
   - ORR: 4 % (1.8; 8.1);
   - Combined Avelumab/PDL ORR: 13 %

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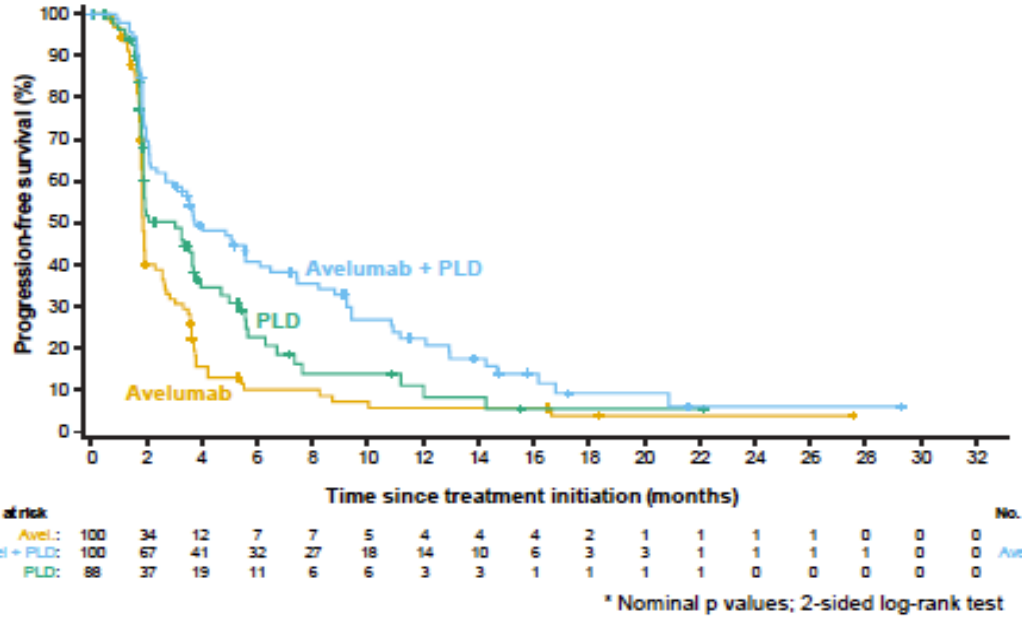
Pujade-Lauraine E et al, Lancet, 2021

JAVELIN Ovarian 200 Results: PFS in PD-L1+ subgroup exploratory analysis

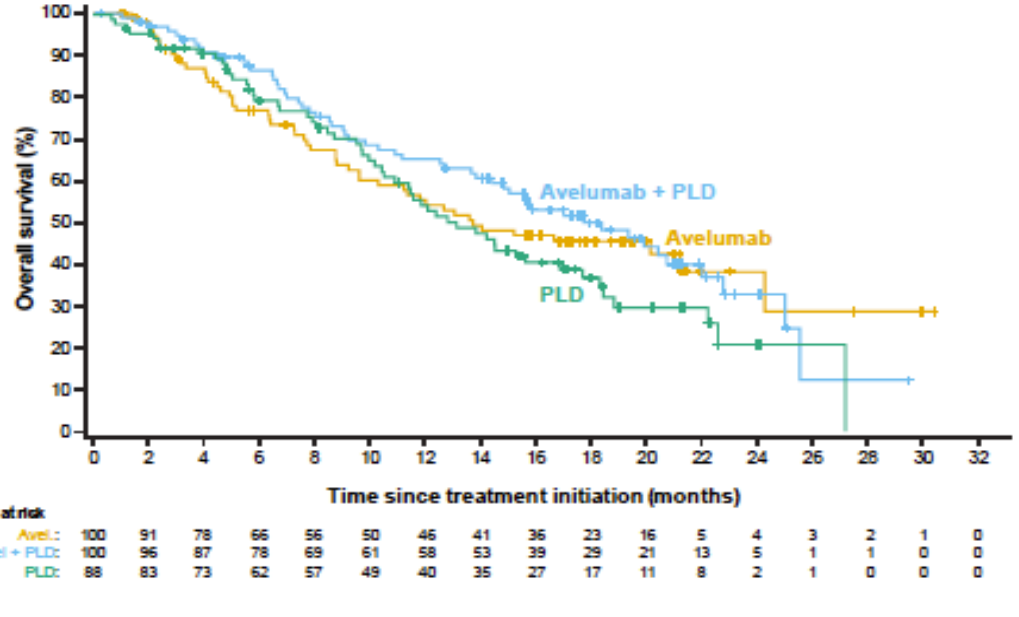
Progression-free survival

	Avelumab (N=100)	Avelumab + PLD (N=100)	PLD (N=88)
Median, mo	1.9	3.7	3.0
(95% CI)	(1.8; 2.3)	(2.7; 6.1)	(1.9; 3.7)
HR vs PLD	1.45	0.65	–
(95% CI)	(1.034; 2.043)	(0.457; 0.919)	
p value vs PLD*	0.0303	0.0143	–



Overall survival

	Avelumab (N=100)	Avelumab + PLD (N=100)	PLD (N=88)
Median, mo	13.7	17.7	13.1
(95% CI)	(9.6; 24.3)	(13.8; 22.0)	(10.5; 16.9)
HR vs PLD	0.83	0.72	–
(95% CI)	(0.567; 1.228)	(0.489; 1.048)	
p value vs PLD*	0.3580	0.0842	–



* Nominal p values; 2-sided log-rank test

PD-L1 status was evaluable in 508 patients (SP263 Ventana platform)
The cutoff: at least 1% of tumor cells expressing PD-L1 or more than 5% of immune cells expressing PD-L1

The HR of 0.65 for PFS and 0.72 for OS in PD-L1 + patients suggests that PD-L1 expression is a predictor of clinical benefit.

NRG-GY009: Phase II/III PLD With Atezolizumab and/or Bevacizumab in Platinum-Resistant Recurrent OC

Randomized Phase II/III Study (NCT02839707)

Enrollment Criteria

- Recurrent, platinum-resistant OC
- High-grade OC
- ≤2 prior regimens
- Measurable disease
- ECOG PS 0 or 1
- Mandatory submission of tumor tissue samples

RANDOMIZATION

1:1:1

- **Arm A** PLD + atezolizumab
- **Arm B** PLD + atezolizumab + bevacizumab
- **Arm C** PLD + bevacizumab

n = ~488

Primary Endpoint:	DLT, OS, PFS
Secondary Endpoints:	ORR, safety

Actual Study Start Date : May 12, 2017
Estimated Primary Completion Date : June 30, 2023
Estimated Study Completion Date : June 30, 2023

ENGOT European Network of Gynaecological Oncological Trial groups — GYNECOLOGIC CANCER INTERGROUP

ENGOT-ov34
AGO-OVAR 2.29

AGO AUSTRIA · GEICO · NSGO · BGOG · GINECO · SAKK

ENGOT model A
Sponsor AGO Study Group

- Epithelial ovarian, fallopian tube or primary peritoneal cancer
- 1st or 2nd relapse with TFI p < 6 months or 3rd relapse
- Prior Bevacizumab allowed
- Bev and atezolizumab specific exclusion criteria
- Archival and recent biopsy mandatory
- PS 0/1, life expectancy > 3 months

R 1:1 n=664

- PLD or Paclitaxel (qw)* + Bevacizumab + Placebo
- PLD or Paclitaxel (qw)* + Bevacizumab + Atezolizumab

* In arm 1 and 2 cohorts capping: 50% PLD and 50% Paclitaxel
PLD, pegylatiertes liposomales Doxorubicin; PS: Performance status

★ Mandatory Biopsy

- **Participating groups:** - AGO Germany (recruiting)
  - AGO Austria, BGOG, GEICO, GINECO, NSGO, SAKK
  Submission to Ethics Committee and Authority ~ Q4 2018
  → Recruitment start expected for 2019
- **Planned No. of patients:** - 664 patients in about 150 sites

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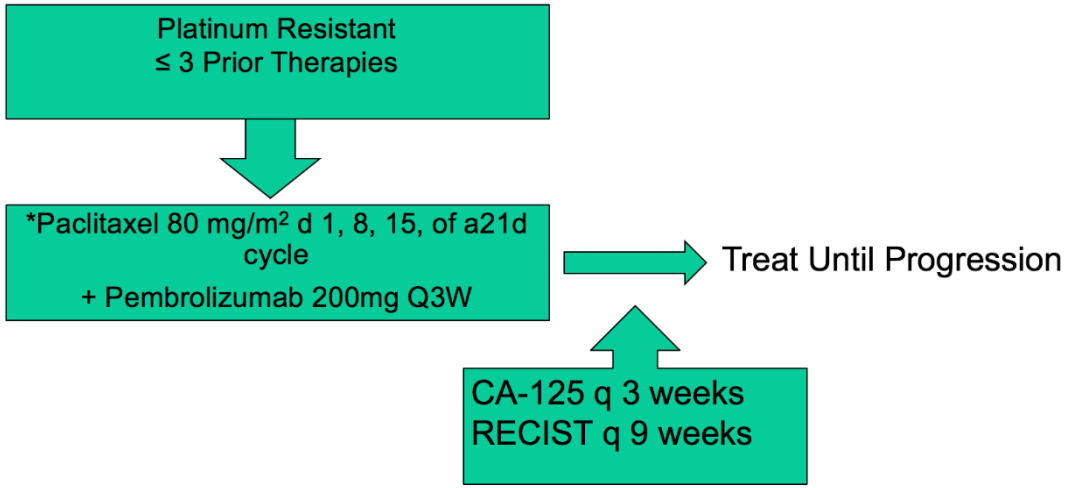
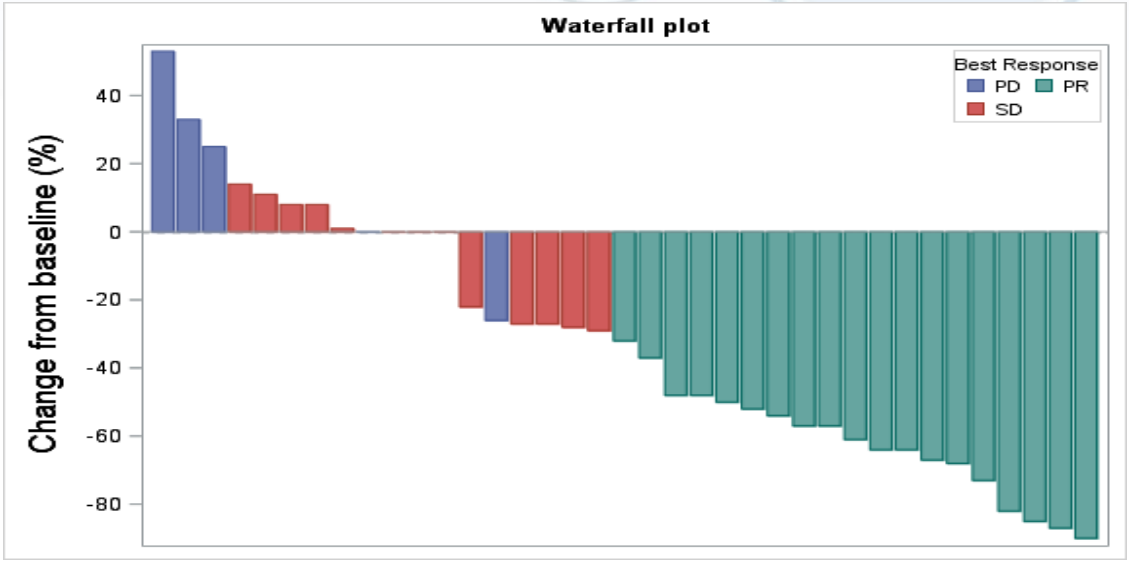
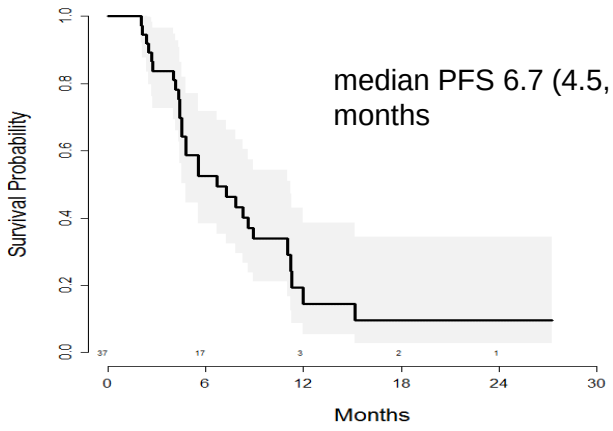
Phase II of weekly Paclitaxel with Pembrolizumab in PRROC

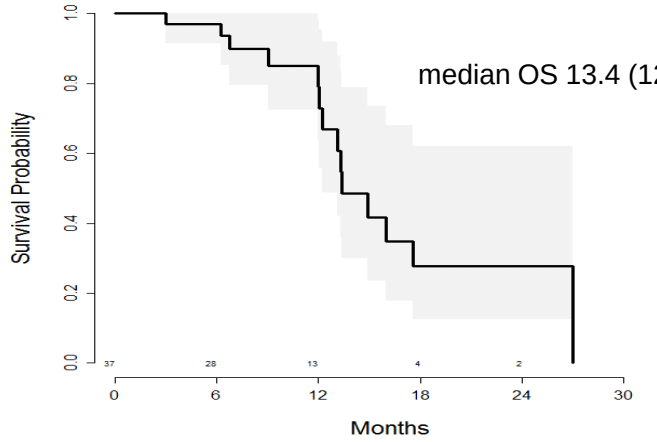


Best Response	N of Patients	% Evaluable (n=37)	% Treated (n=41)
CR	0	0	0
PR	19	**51.4%**	46.3%
SD	13	35.1%	31.7%
PD	5	13.5%	12.2%
Unassessed	4	NA	9.8%
DCR	32	86.5%	78%





median PFS 6.7 (4.5, 8.9) months



median OS 13.4 (12.1-27.0) mo

Wenham R et al, GCIG 2018

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AURELIA Results by Chemotherapy Subgroup

Weekly paclitaxel is the most active PRROC chemotherapy treatment with or without bevacizumab.

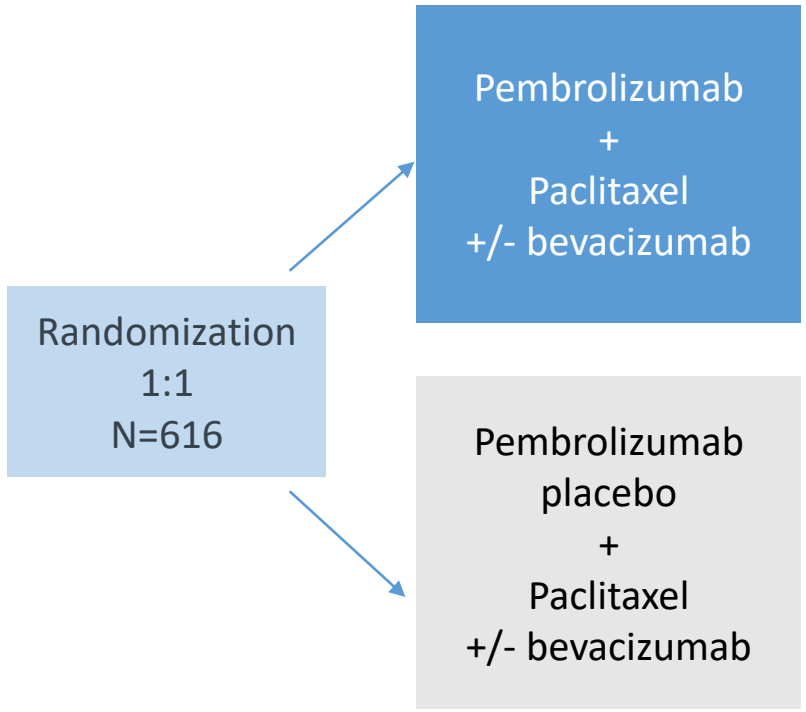
Combination	N/Lines of treatment	mPFS (CT +bev vs CT)	ORR (CT+bev vs CT)	mOS* (CT+bev vs CT)	mDoT CT+bev vs CT
Chemotherapy +/- bevacizumab10 mg/kg Q2W	361 PRROC (no refractory) up to 2L of prior treatment	6.7 vs 3.4 months HR: 0.48 (0.38, 0.60; *P* .001).	27.3% vs 11.8% (*P* .001)	16.6 vs 13.3 HR: 0.85 (0.66, 1.08); *P =0.*174; **NS**	6 cycles (1-24) vs 3 cycles (1-17) 1 cycle=4 w (except topotecan)
Paclitaxel 80mg/m^2 IV on days 1, 8, 15, and 22 every 4 weeks **+/-bevacizumab** 10 mg/kg Q2W	115 PRROC (no refractory) up to 2L of prior treatment	10.4 v 3.9 months HR: 0.46 (0.30, 0.71)	53.3% vs 30.2%	22.4 v 13.2 months Unadjusted HR: 0.65 (0.42,1.02) **NS**	
PLD 40 mg/m^2 IV on day 1 Q4W **+/- bevacizumab**10 mg/kg Q2W	126 PRROC (no refractory) up to 2L of prior treatment	5.4 v 3.5 months HR: 0.57 (0.39, 0.83)	13.7% vs 7.8%	13.7 m vs 14.1 m Unadjusted HR: 0.91 (0.62,1.36) **NS**	
Topotecan 4 mg/m^2 IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/m^2 on days 1 to 5 Q3W **+/- bevacizumab** 10 mg/kg Q2W or 15 mg/kg Q3W in patients receiving topotecan in a schedule Q3W	120 PRROC (no refractory) up to 2L of prior treatment	5.8 v 2.1 months HR:0.32 (0.21, 0.49)	17.0% vs 0.0%	13.8 v 13.3 m Unadjusted HR: 1.09 (0.72,1.67) **NS**	

Pujade-Lauraine E et al. JCO 2014

Keynote-B96/Engot-65 – ongoing clinical trial

Key Eligibility Criteria

- Platinum Resistant OC patients (refractory excluded)
- Up to 2L of prior therapy
- ECOG PS 0, 1
- Prior anti PD-1/PD-L1 allowed
- Prior PARPi allowed
- Prior bevacizumab allowed



Primary Endpoint: PFS

Stratification factors for randomization

- Bevacizumab use
- PD-L1 status
- Prior anti PD-1/PD-L1

Immune effects of NACT : Take home points

NACT

Immune Stimulation
- ↑ CD8, CD4
- ↓ FOXP3+
- ↑ CD8/FOXP3
- ↑ Mature DCs

Immune Suppression
- ↑ PD-L1 in tumor cells
- ↑ PD-L1 in immune cells
- ↑ PD-1 in T cells

Rationale for frontline CHEMO + IO combinations

Immune Effects of NACT : Current Study

Study	Paired samples	TILs	CD8+	CD4+	FOXP3+	CD20+	CD68+	CD163+	DCs	Granzyme	PD-1	PD-L1
Mesgagne et al.	n=83	↑ (stromal)										↑ (immune cells)
Polcher et al.	n=30		↑	↑	→					↑		
Lo et al.	n=26	↑ (CD3+)	↑	↑ (trend)	→	↑	→		→ (CD1a)	→	↑	
Bohm et al.	n=25		→	→ (but↑IFNγ and Th1 signature)	↓ (in good responders)						↑	↑
CHIVA STUDY	n=86		↑	↑	↓		→	→	↑			

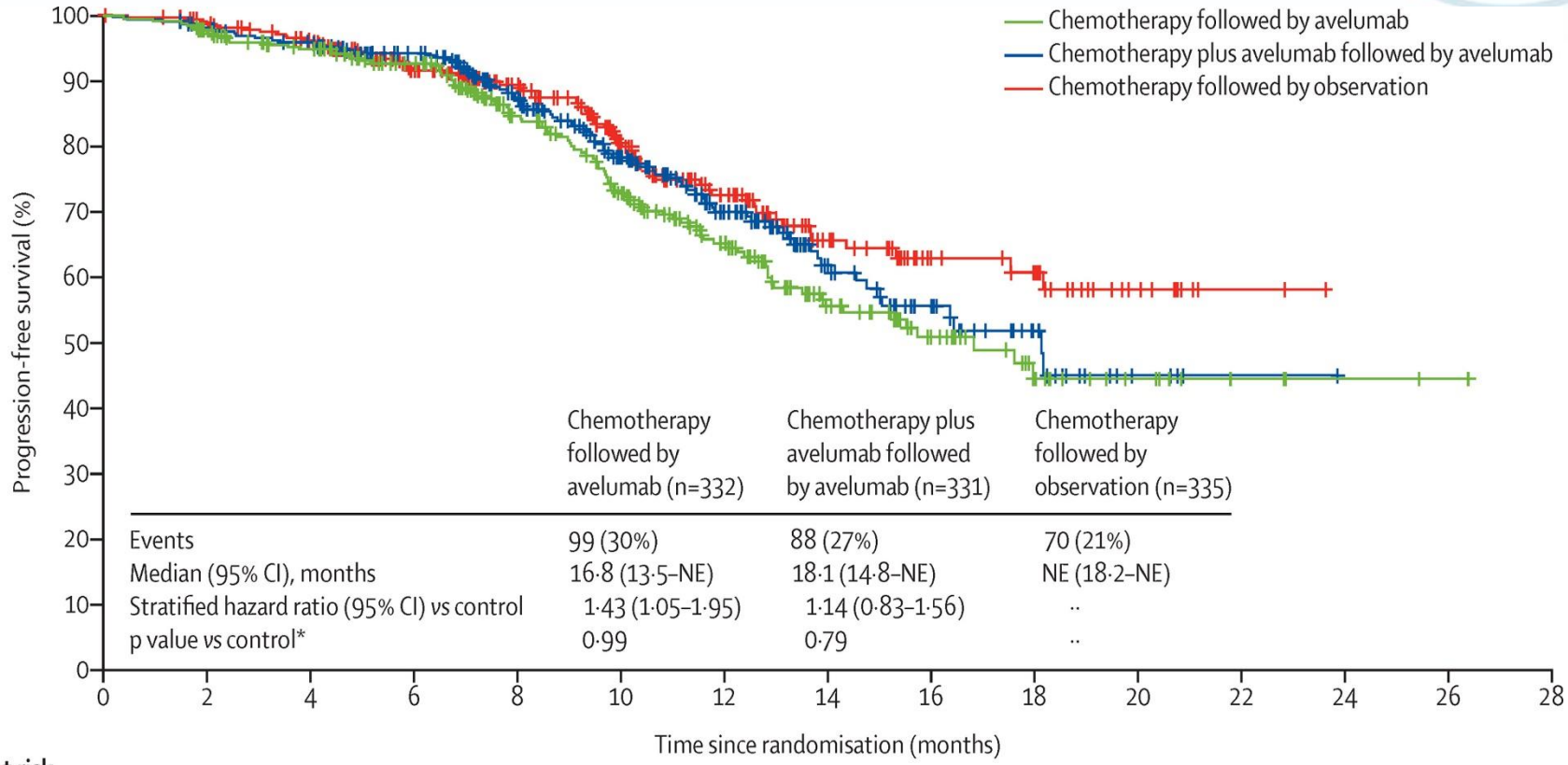
NOVEL FINDINGS FROM CHIVA: i) ↓ FOXP3+, ↑ CD8/FOXP3+ ratio
ii) ↑ Mature DCs
iii) No change in M1 / M2 and NK cells

Anti-PD-L1 in combination with chemotherapy

TRIAL	CONTROL ARM	EXPERIMENTAL ARM	N	PFS (HR 95%CI)	Reference
First Line					
Javelin 100	Cx: Q3W carboplatin+paclitaxel OR carboplatin + weekly paclitaxel	Cx + **avelumab** maintenance up to 2 yrs OR Cx & **avelumab** + avelumab maintenance up to 2 yrs	951	**1.43** (1.05-1.95) **1.14** (0.83-1.56)	Lederman JA et al SGO 2020
Imagyn050 GOG 3015	carboplatin+paclitaxel& bevacizumab + placebo & bevavizumab + placebo maint.	carboplatin+paclitaxel& bevacizumab + **atezolizumab** & bevacizumab + **atezolizumab** maint.	1301	**0.92** (0.79-1.07	Moore K et al ESMO 2020

Monk B et al, Lancet,2021
Moore K et al., JCO, 2021

Javelin-100



	Chemotherapy followed by avelumab (n=332)	Chemotherapy plus avelumab followed by avelumab (n=331)	Chemotherapy followed by observation (n=335)
Events	99 (30%)	88 (27%)	70 (21%)
Median (95% CI), months	16·8 (13·5–NE)	18·1 (14·8–NE)	NE (18·2–NE)
Stratified hazard ratio (95% CI) *vs* control	1·43 (1·05–1·95)	1·14 (0·83–1·56)	..
p value *vs* control*	0·99	0·79	..

Number at risk (number censored)

Chemotherapy followed by avelumab	332 (0)	303 (22)	280 (36)	252 (58)	186 (104)	143 (122)	100 (152)	58 (182)	36 (200)	18 (215)	10 (223)	4 (229)	2 (231)	1 (232)	..
Chemotherapy plus avelumab followed by avelumab	331 (0)	310 (15)	297 (21)	271 (42)	211 (84)	157 (118)	101 (160)	54 (198)	33 (214)	17 (228)	4 (239)	1 (242)	..	..	..
Chemotherapy followed by observation	335 (0)	313 (19)	294 (29)	241 (69)	190 (115)	136 (152)	90 (186)	55 (214)	32 (235)	26 (240)	10 (255)	2 (263)	..	..	..

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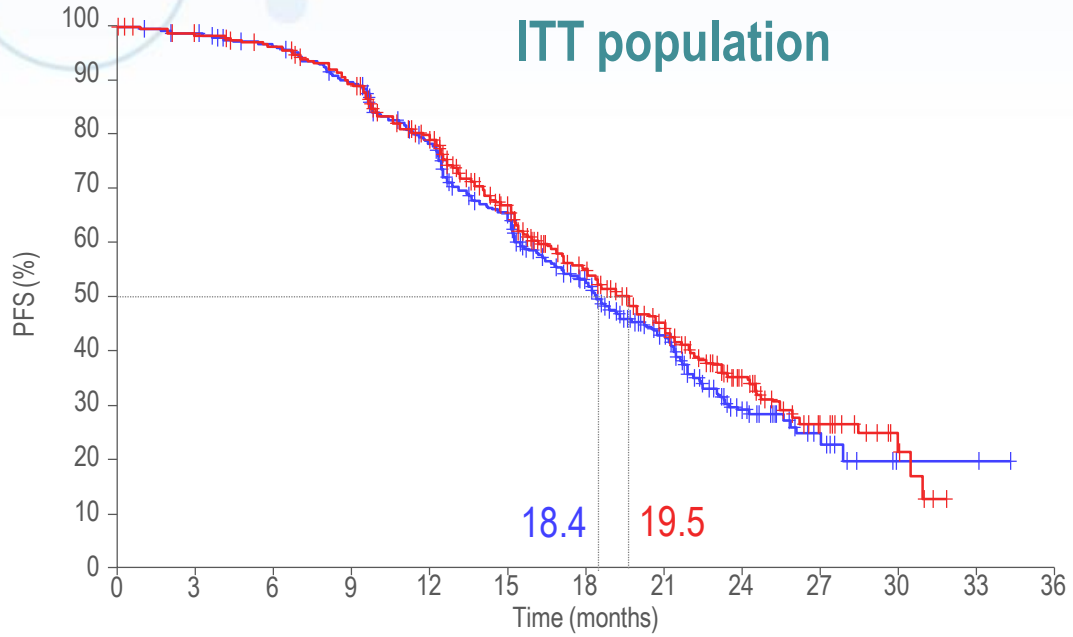
Monk B et al, Lancet,2021

Imagyn050/GOG 3015 phase 3 trial

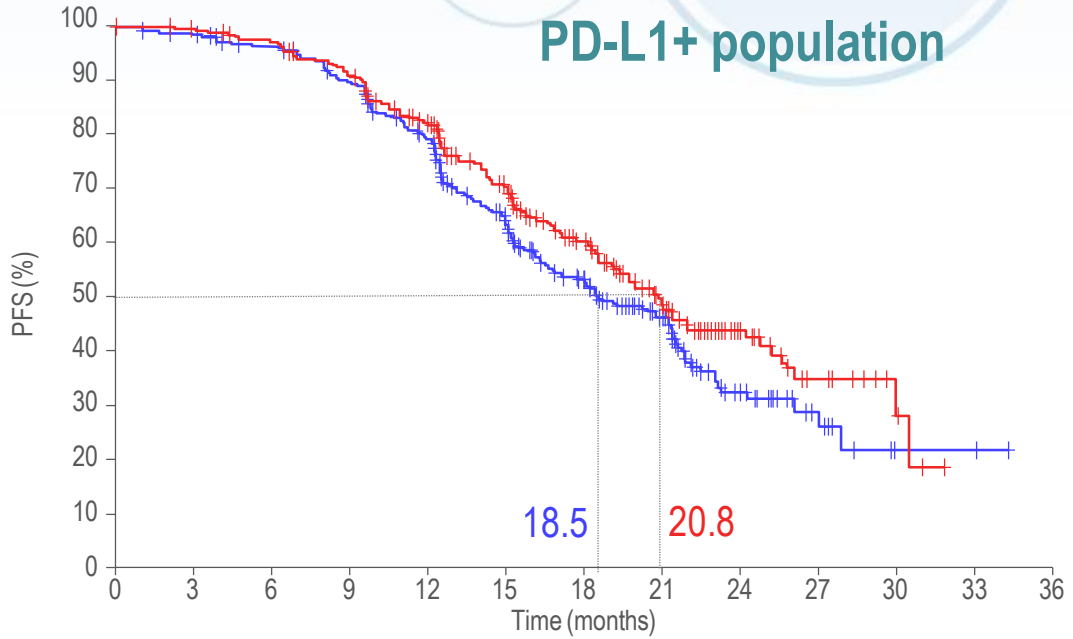
ITT population



Patients at risk

Placebo + CP + bev	650	627	604	556	474	344	216	131	42	11	3	2	NE
Atezo + CP + bev	651	617	597	549	473	348	218	128	55	20	6	NE	NE

PD-L1+ population



Patients at risk

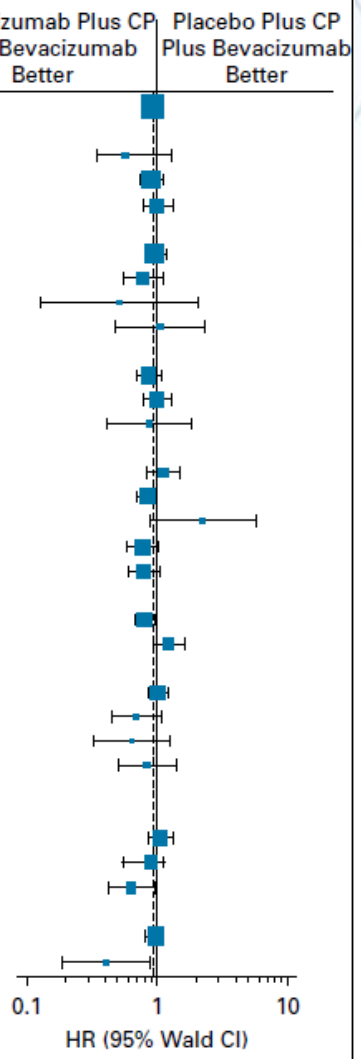
Placebo + CP + bev	393	379	366	336	288	209	127	82	27	9	2	2	NE
Atezo + CP + bev	391	374	362	335	294	218	136	74	32	13	4	NE	NE

PFS	ITT population		PD-L1+ population	
	Placebo + CP + bev (n=650)	Atezo + CP + bev (n=651)	Placebo + CP + bev (n=393)	Atezo + CP + bev (n=391)
Patients with events, n (%)	341 (52.5)	323 (49.6)	199 (50.6)	167 (42.7)
Median PFS, months (95% CI)	18.4 (17.2–19.8)	19.5 (18.1–20.8)	18.5 (16.6–21.4)	20.8 (19.1–24.2)
Stratified HR (95% CI)	0.92 (0.79–1.07)		0.80 (0.65–0.99)	
Stratified log-rank p-value	0.2785		0.0376	
2-year event-free rate (95% CI)	29.1 (23.9–34.3)	35.1 (30.0–40.3)	32.2 (25.4–39.0)	43.9 (37.2–50.5)

CI = confidence interval; HR = hazard ratio

- **Imagyn050/ GOG 3015 subgroup analysis**

Baseline Risk Factors	N	Placebo Plus CP Plus Bevacizumab (n = 650) n	Placebo Plus CP Plus Bevacizumab (n = 650) Median (months)	Atezolizumab Plus CP Plus Bevacizumab (n = 651) n	Atezolizumab Plus CP Plus Bevacizumab (n = 651) Median (months)	HR (95% Wald CI)
All patients	1,301	650	18.4	651	19.5	0.92 (0.79 to 1.07)
Age, years (by group)						
18-40	66	30	19.6	36	20.6	0.58 (0.35 to 1.30)
41-64	813	399	18.2	414	19.6	0.90 (0.74 to 1.10)
≥ 65	422	221	18.8	201	18.0	1.01 (0.78 to 1.32)
Race						
White	925	461	18.1	464	18.2	0.97 (0.82 to 1.16)
Asian	305	155	21.2	150	21.6	0.78 (0.55 to 1.10)
Black or African American	21	13	19.1	8	24.2	0.52 (0.13 to 2.07)
Other	50	21	18.2	29	19.7	1.06 (0.48 to 2.32)
Baseline ECOG PS						
0	708	353	18.4	355	20.2	0.87 (0.70 to 1.07)
1	529	266	18.7	263	18.3	1.00 (0.79 to 1.27)
2	64	31	18.2	33	17.1	0.87 (0.42 to 1.81)
Treatment approach						
Neoadjuvant	332	166	17.2	166	16.6	1.12 (0.85 to 1.47)
Primary surgery	969	484	18.4	485	19.8	0.84 (0.70 to 1.01)
No gross residual disease	72	41	22.1	31	19.3	2.27 (0.89 to 5.77)
Residual disease ≤ 1 cm	499	245	18.3	254	21.1	0.78 (0.60 to 1.01)
Residual disease > 1 cm	398	198	17.1	200	18.6	0.80 (0.61 to 1.05)
Disease stage						
Stage III	896	448	18.4	448	20.6	0.80 (0.67 to 0.97)
Stage IV	404	201	18.4	203	17.1	1.24 (0.95 to 1.63)
Histological type						
High-grade serous	993	489	19.0	504	19.3	1.01 (0.84 to 1.20)
High-grade nonserous	155	87	15.7	68	19.9	0.69 (0.45 to 1.07)
Clear cell	51	22	12.3	29	13.6	0.64 (0.33 to 1.24)
Low-grade serous	125	58	20.4	67	19.7	0.83 (0.50 to 1.38)
PD-L1 status						
PD-L1 IC status						
IC < 1%	517	257	18.3	260	17.4	1.06 (0.84 to 1.33)
IC ≥ 1% to < 5%	524	252	18.2	272	19.3	0.89 (0.55 to 1.13)
IC ≥ 5%	260	141	20.2	119	NE	0.64 (0.43 to 0.96)
PD-L1 TC status						
TC < 1%	1,228	610	18.4	618	19.2	0.96 (0.82 to 1.12)
TC ≥ 1%	73	40	15.0	33	NE	0.41 (0.19 to 0.90)



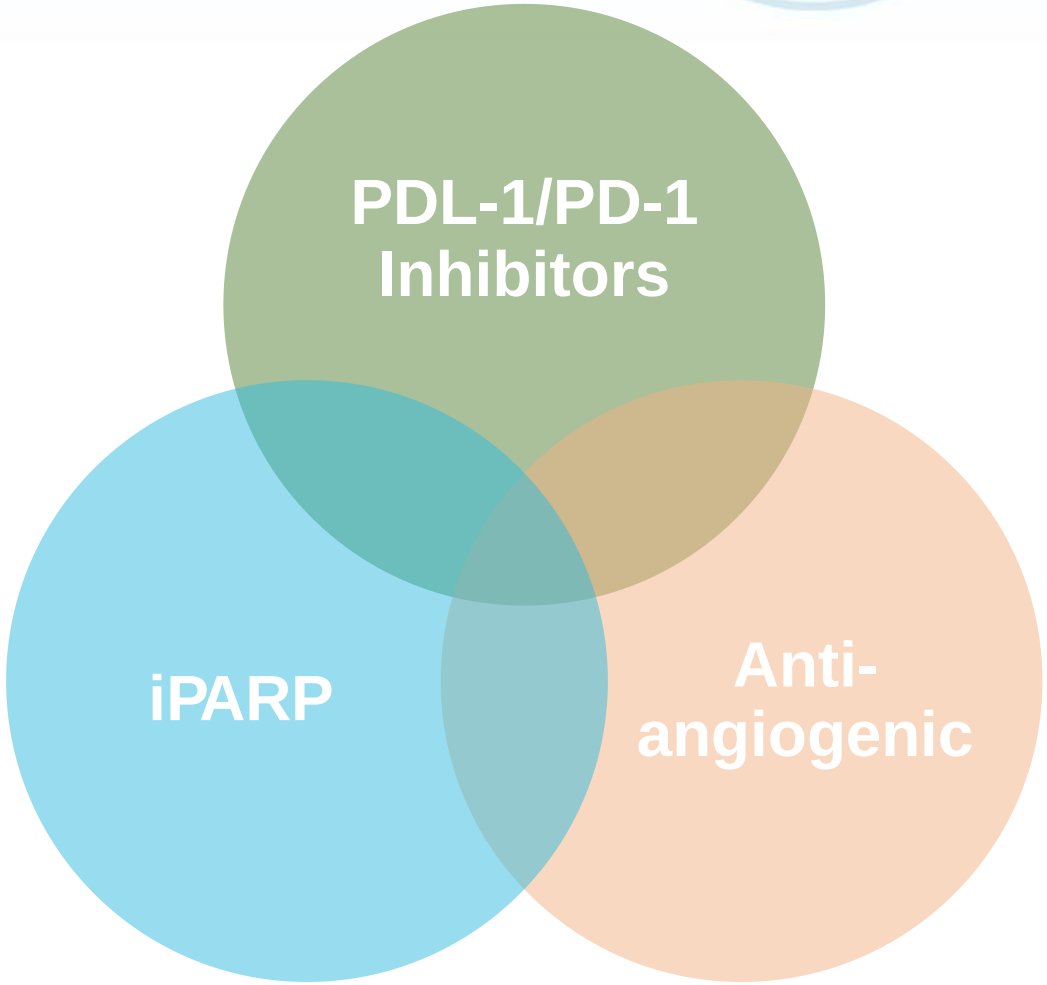
Moore K et al., JCO, 2021

NEW COMBINATIONS (CHEMO-FREE)

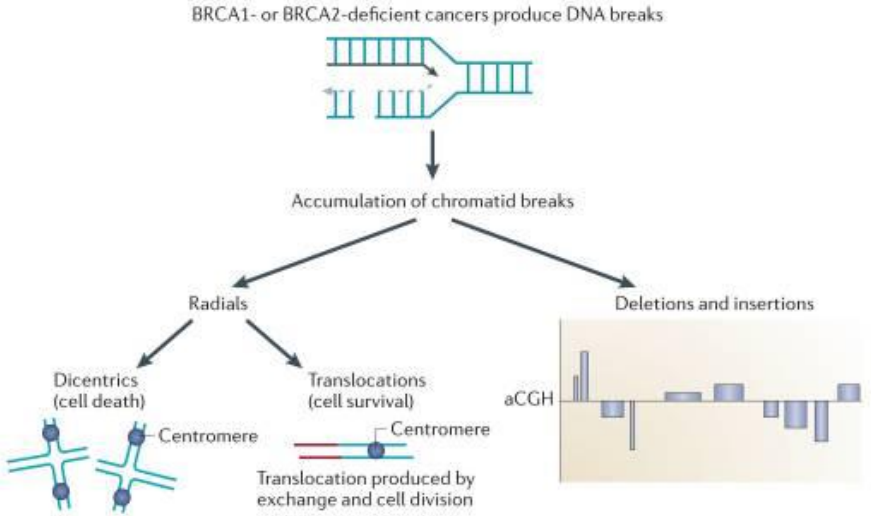
PARPi + antiangiogenic agents

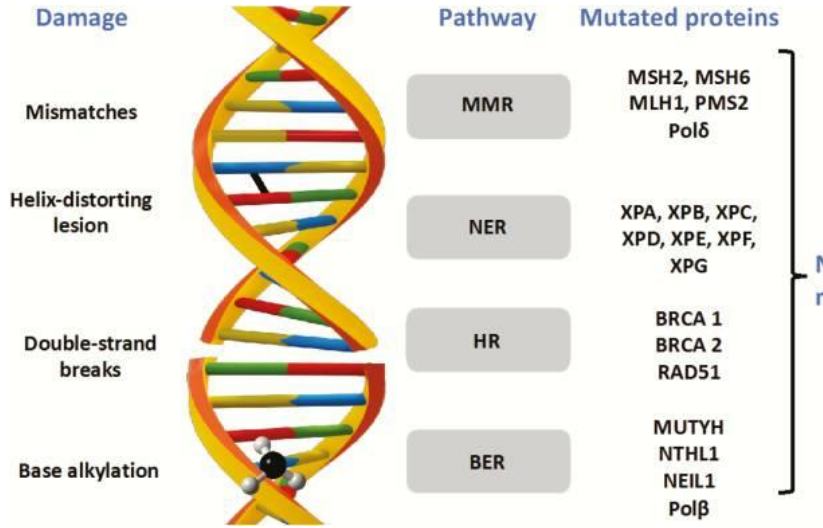
PARPi+ Immunotherapy

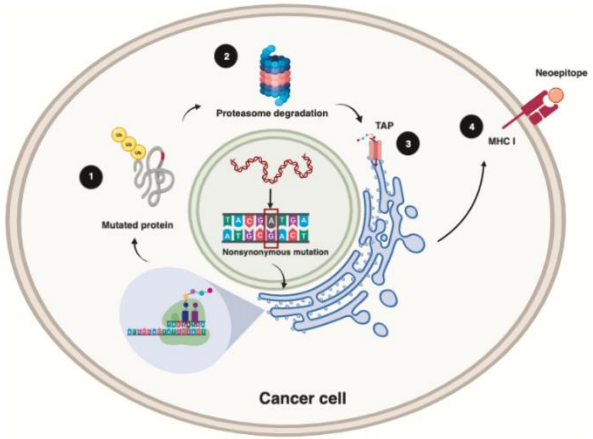
Immunotherapy + antiangiogenic agents



PARP Inhibitors in Combination with Immuno-Oncology Agents: Rationale







- BRCA mutated tumors:) have a high mutational load and a higher number of protein-coding mutations (neoepitopes) due to the inability of the cancer cell to repair DNA damage effectively

- *BRCA1/2* mutant and HR-deficient tumours are correlated with higher PD-L1 expression and CD8 T-cell infiltration that predict PD-(L)1 mAb response

Roy R., Nat.Rev.Cancer, 2012
Alvarado-Cruz I et al., Mutagenesis, 2020

PARP-I +IO Trials

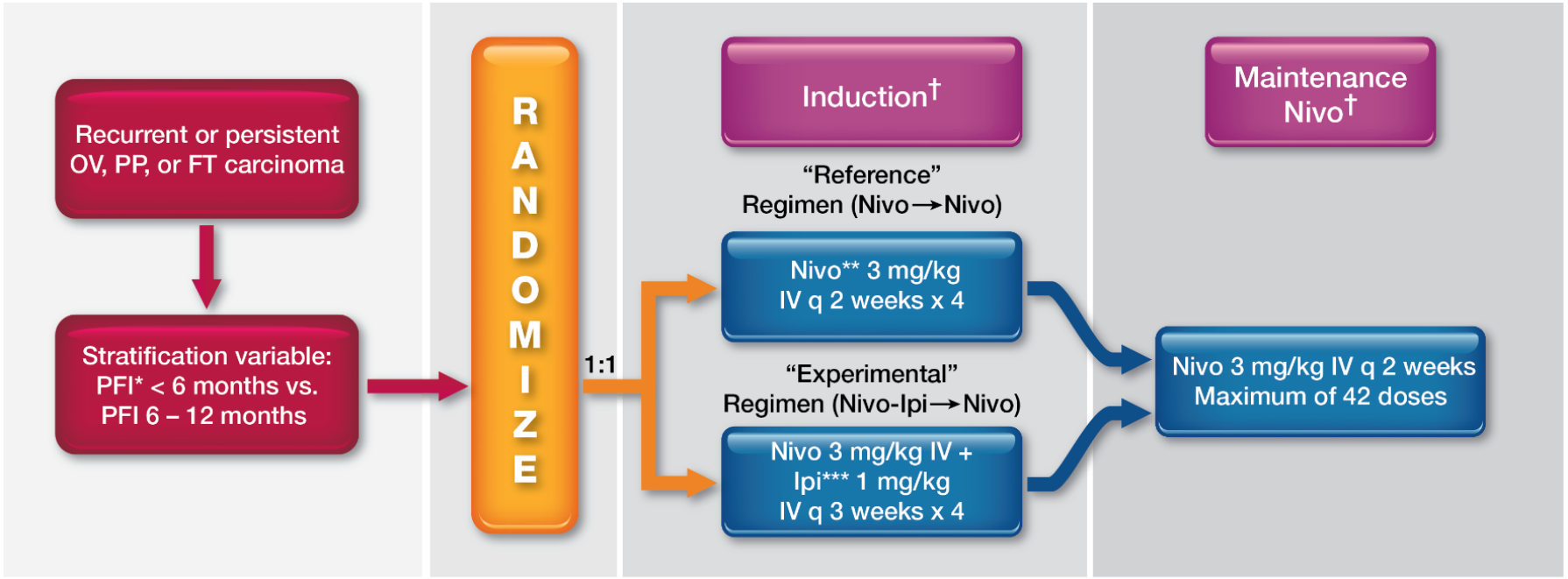
Combination Therapy	Inclusion	Phase	patient number	# of prior threapies	ORR	Reference
Durvalumab + olaparib	Recurrent OC	1	12	>1, 50%>4	17% PR 66% SD	Lee et al 2017
Durvalumab + cediranib			12		50% PR 25% SD	
Durvalumab + olaparib MEDIOLA	Platiunum sensitive BRCAmut	2	32	>1	19% CR 44% PR 9% SD	Drew et al 2018
Pembrolizumab+ niraparib TOPACIO	Platinum resistant OC	2	62	<5	25%ORR 42% SD; BRCAmut: 25% ORR, 38% SD	Konstantinopoulos et al 2018

Ongoing trials in 1L with ImmuneTx

	ATHENA	FIRST	ENGOT OV43	DUO-O
Sponsor	Clovis	Tessaro	Merck	Astra Zeneca
Group leader	GOG(NCRI)	GINECO (GOG??)	BGOG(leading) – unsure whether GOG will join as supporting groups	AGO(GOG)
ENGOT Model	C		C	C
Randomisation	Maintenance	Upfront	Upfront	Upfront
Bev in Standardarm	No	Optional	Optional	Yes
Exp. Arm	- **Ruca-Nivolu** - **Ruca** - **Nivolu**	- **Nira** - **Nira + O42**	**BRCA+: Ola +Pembro** **BRCA-: Pembro** **Pembro+Ola**	- **Durva** - **Durva+Ola**
NACT allowed	Yes	Yes	Yes	Yes
RT=0	CR/NED after CT	No	Yes	Yes
Endpoint	PFS	PFS	PFS+OS	PFS
MITO	6	A 8	C 10	B 10

IO+IO COMBINATION IN OC

Phase II Randomized Trial of Nivolumab With or Without Ipilimumab in Patients with Persistent or Recurrent Ovarian Cancer (NRG GY003)



* Platinum-Free Interval
** Nivolumab
*** Ipilimumab
† Protocol-directed therapy until progression or unacceptable toxicity

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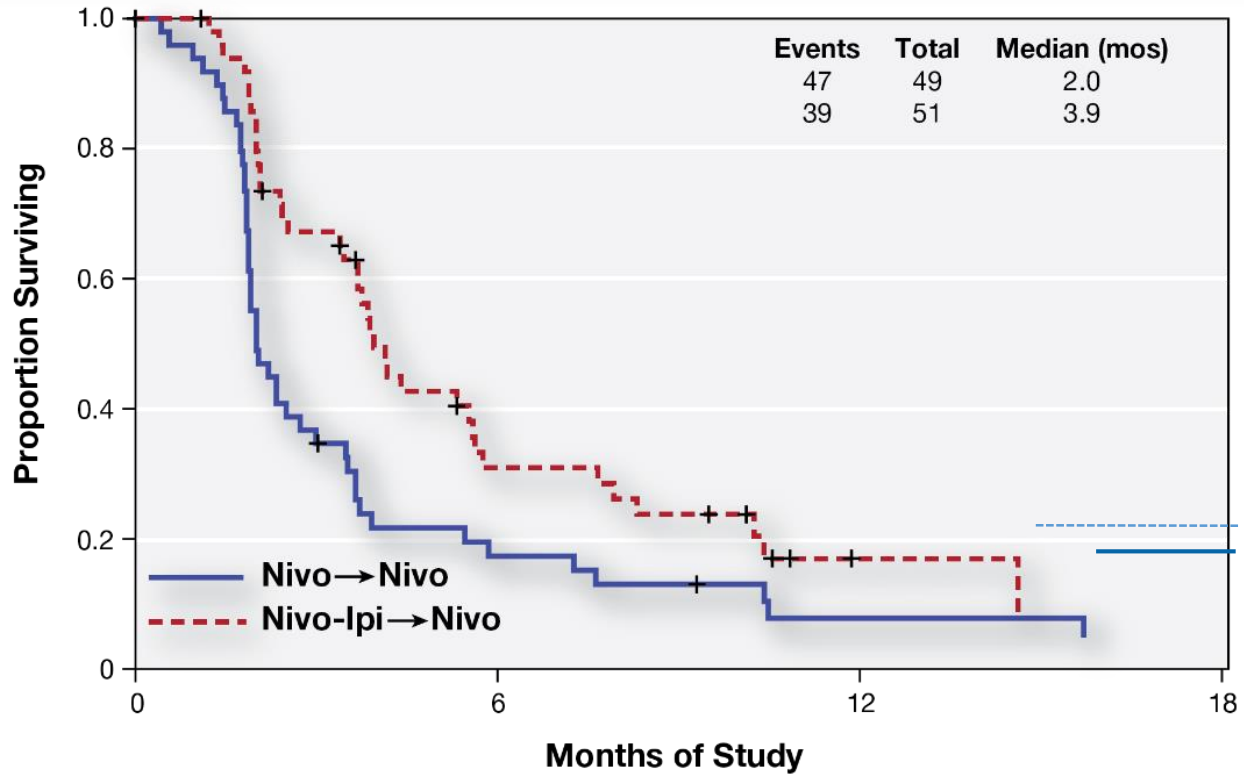
R.A. Burger et al, IGCS 2018

NRG GY003: PFS by Treatment Group



Nivo→Nivo	49	8	3	2
Nivo-Ipi→Nivo	51	13	2	1

		Nivo→Nivo (n=49)	Nivo-Ipi→Nivo (n=51)
Patients with event, n (%)		47 (95.9)	39 (76.5)
Median PFS, months		2.0	3.9
Stratified by PFI	HR (95% CI)	Reference	0.528 (0.339–0.821)
	Two-sided p-value (log-rank)		0.0041

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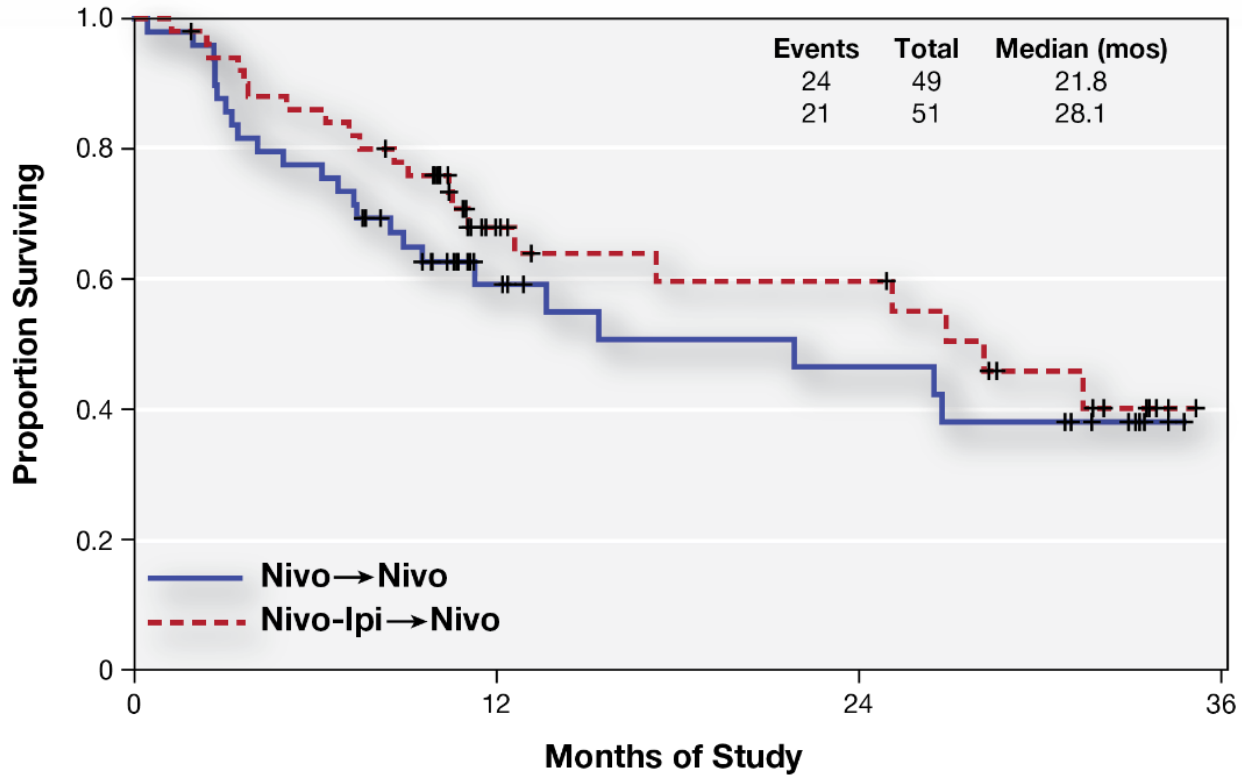
NRG GY003: OS by Treatment Group



Nivo→Nivo	49	17	11	0
Nivo-Ipi→Nivo	51	19	14	0

		Nivo→Nivo (n=49)	Nivo-Ipi→Nivo (n=51)
Patients with event, n (%)		24 (49.0)	21 (41.1)
Median OS, months		21.8	28.1
Stratified by PFI	HR (95% CI)	Reference	0.789 (0.439–1.418)
	Two-sided p-value (log-rank)		0.43

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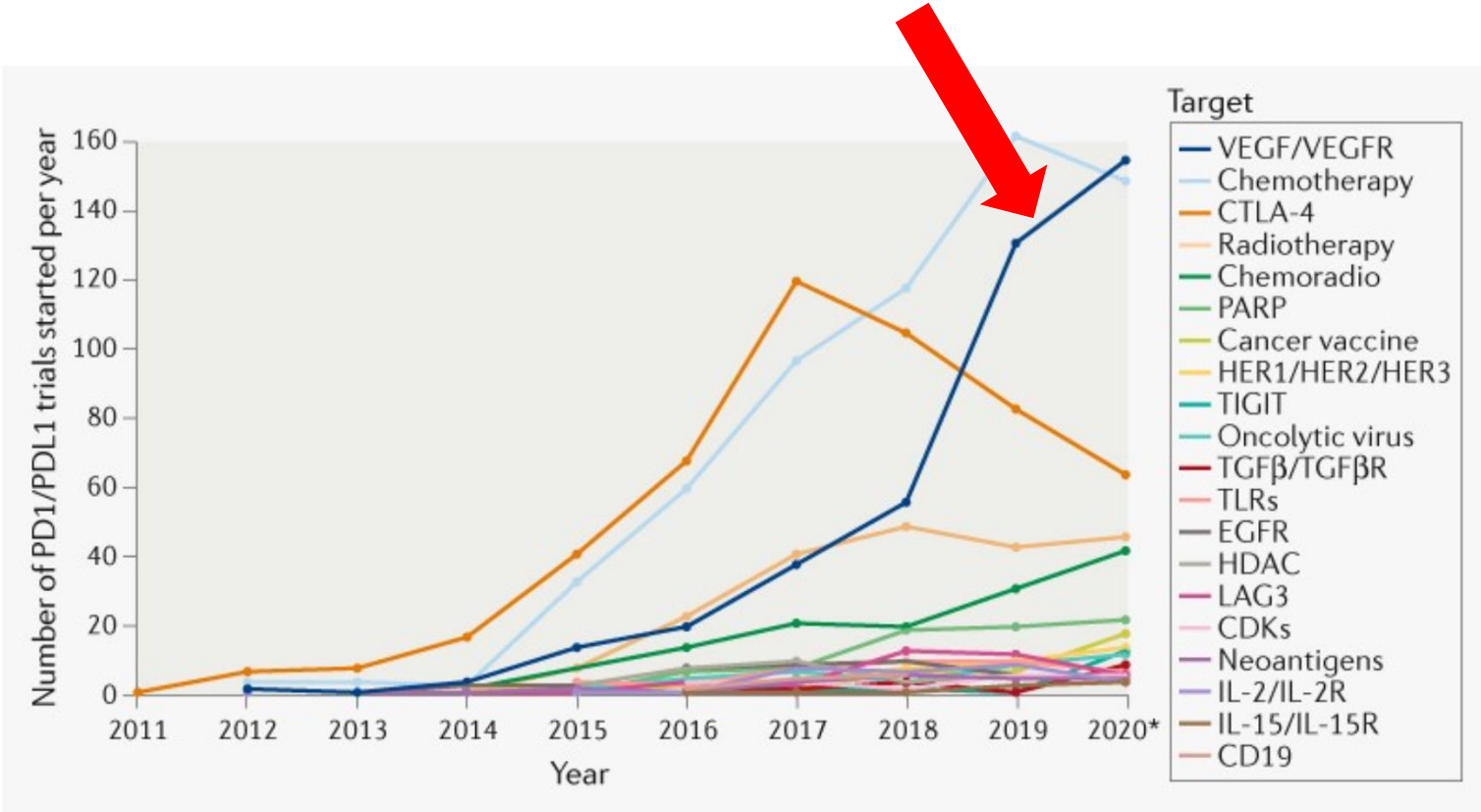
NRG GY003: Subgroup Analyses

	Statistic (95% CI)		
Characteristic	Response*	PFS**	OS**
Age: > vs ≤ median	0.653 (0.244-1.748)	1.002 (0.638-1.574)	1.499 (0.818-2.747)
PS: > 0 vs 0	1.210 (0.422-3.471)	0.843 (0.519-1.368)	1.295 (0.681-2.465)
Prior cytotoxic regimens: >1 vs 1	0.676 (0.220-2.079)	1.021 (0.602-1.730)	1.150 (NA***)
PFI: ≥ 6 vs < 6 months	1.900 (0.709-5.091)	0.662 (0.418-1.047)	**0.518 (0.273-0.984)**
Cell type: clear cell vs other	**5.205 (1.370-19.774)**	0.562 (NA)	1.674 (NA)

* Logistic regression, odds ratio, adjusted for treatment group
** Cox proportional hazards model, hazard ratio, adjusted for treatment group and PFI
*** Not available, insufficient number of events

ICB + anti-VEGF/VEGFR COMBINATION



Upadhaya S et al., Nat Rev Drug Disc 2021

Rationale for Combining Cancer Immunotherapy with Anti-VEGF

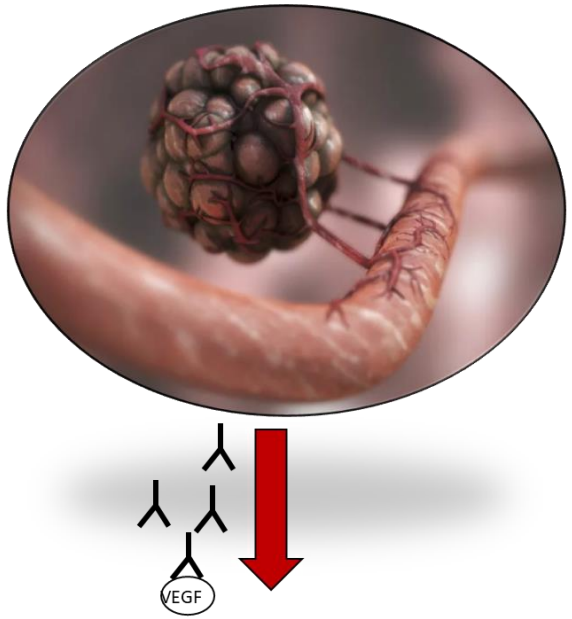
VEGF

Tumor neovascularization

Angiogenesis → Tumor growth

Lymphangiogenesis → Metastasis

Hypoxic/acidic microenvironment
Interstitial fluid pressure ↑
Adhesion molecules on EC ↓
Decrease T cell transmigration



Immunomodulation

Promotes immunosuppression
- T reg expansion
- MDSC expansion
- TAM expansion
- DC maturation ↓

T cell inhibition
- Effector function ↓
- Trafficking ↓
- T cell apoptosis by FasL on EC

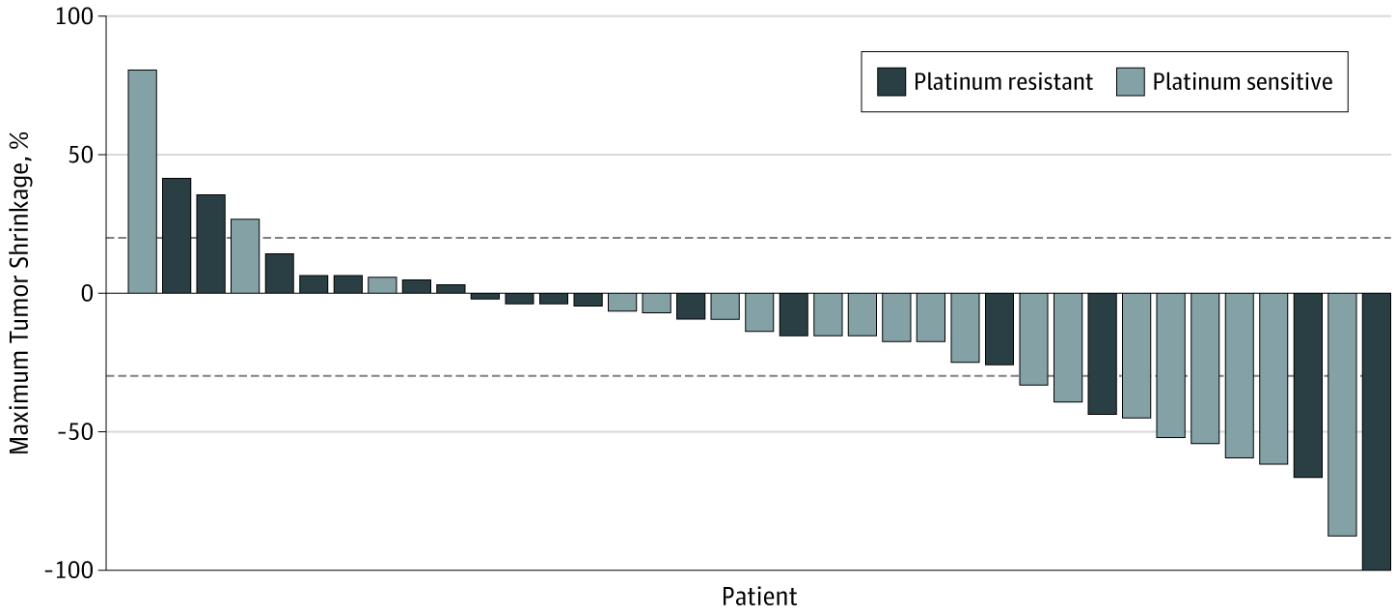
Tumor vessel "normalization"
Decrease local immunosuppression
Increase T cell infiltration to TME

Maj E et al 2016
Yang J el al 2018
Alaoui-Lasmaili et al 2018

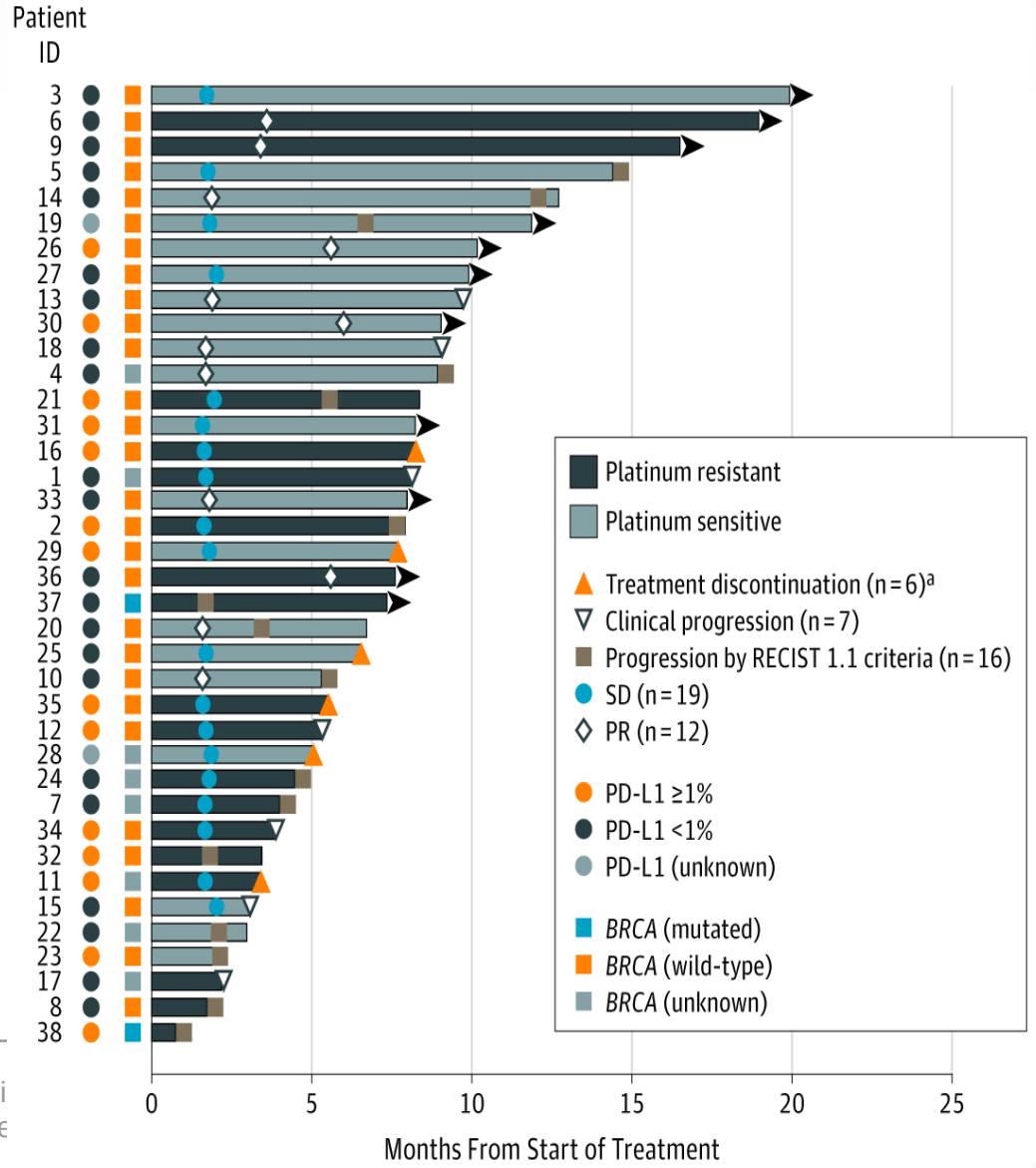
Credit: EQUINOX GRAPHICS

From: **Assessment of Combined Nivolumab and Bevacizumab in Relapsed Ovarian Cancer: A Phase 2 Clinical Trial**

JAMA Oncol. 2019;5(12):1731-1738. doi:10.1001/jamaoncol.2019.3343



ORR: 29% Median PFS: 8.1 months



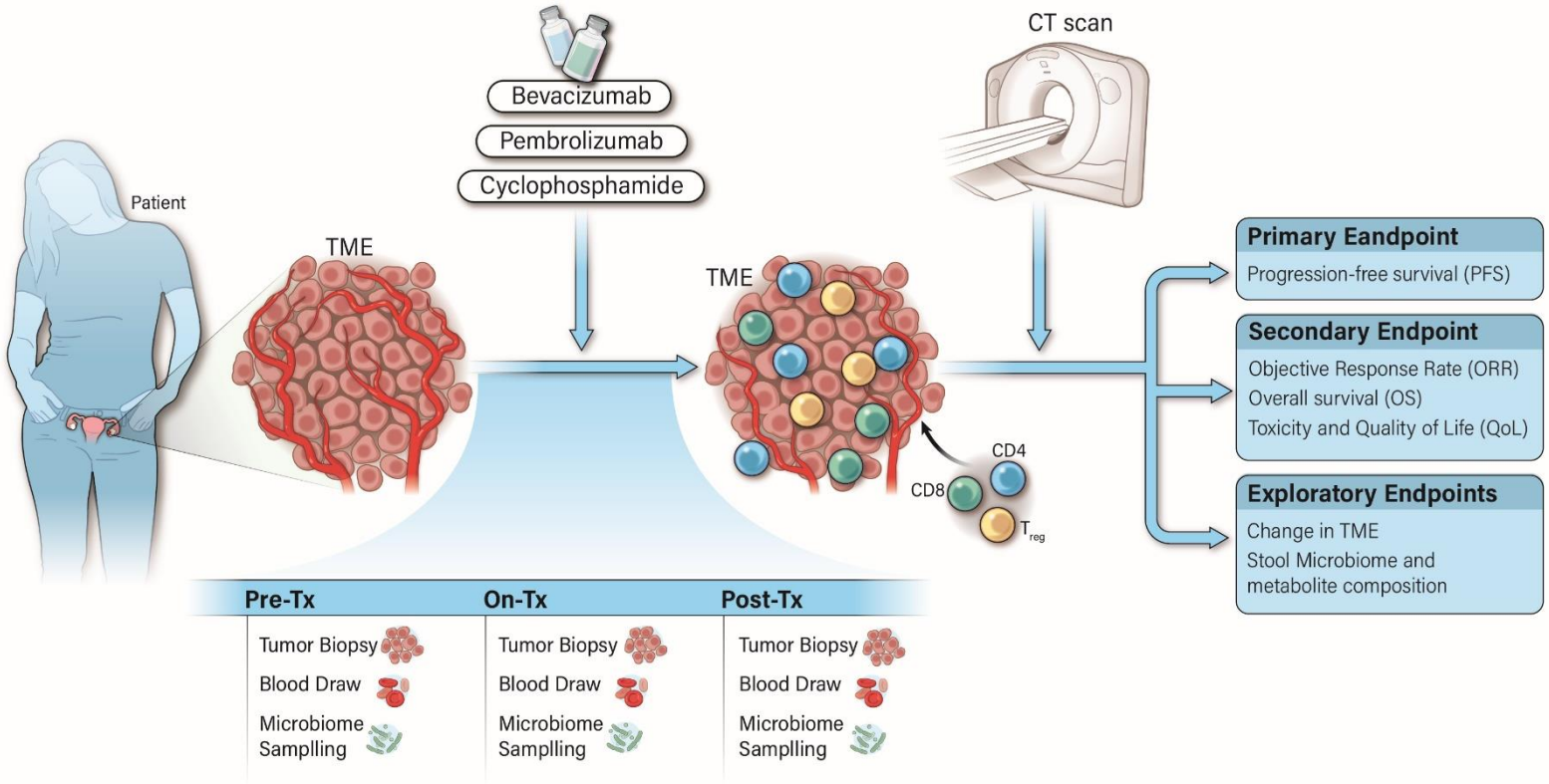
Research

JAMA Oncology | Original Investigation

Efficacy and Safety of Pembrolizumab in Combination With Bevacizumab and Oral Metronomic Cyclophosphamide in the Treatment of Recurrent Ovarian Cancer

A Phase 2 Nonrandomized Clinical Trial

Emese Zsiros, MD, PhD; Sarah Lynam, MD; Kristopher M. Attwood, PhD; Chong Wang, MA; Shanmuga Chilakapati, PhD; Eduardo Cortes Gomez, MS; Song Liu, PhD; Stacey Akers, MD, MBA; Shashikant Lele, MD; Peter J. Frederick, MD; Kunle Odunsi, MD, PhD



Best Response	Platinum -sensitive n=10 (%)	Platinum-resistant n=30 (%)	Total n=40 (%)
Complete response	**0**	**3 (10%)**	**3 (7.5%)**
Partial response	**6 (60%)**	**10 (33.3%)**	**16 (40%)**
Stable disease only			
≥ 24 weeks	3 (30%)	8 (26.7%)	**11 (27.5%)**
< 24 weeks	1 (10%)	7 (23.3%)	**8 (20%)**
Progressive disease	0	2 (6.7%)	**2 (5%)**
Objective response rate (irCR + irPR)	**6 (60%)**	**13 (43.3%)**	**19 (47.5%)**
Total clinical benefit (irCR + irPR + irSD)	**10 (100%)**	**28 (93%)**	**38 (95%)**
Median DOR * (months, range)	11.5 (11.6-21.3)	5.8 (0.9-26.5)	**5.9 (0.9-26.5)**

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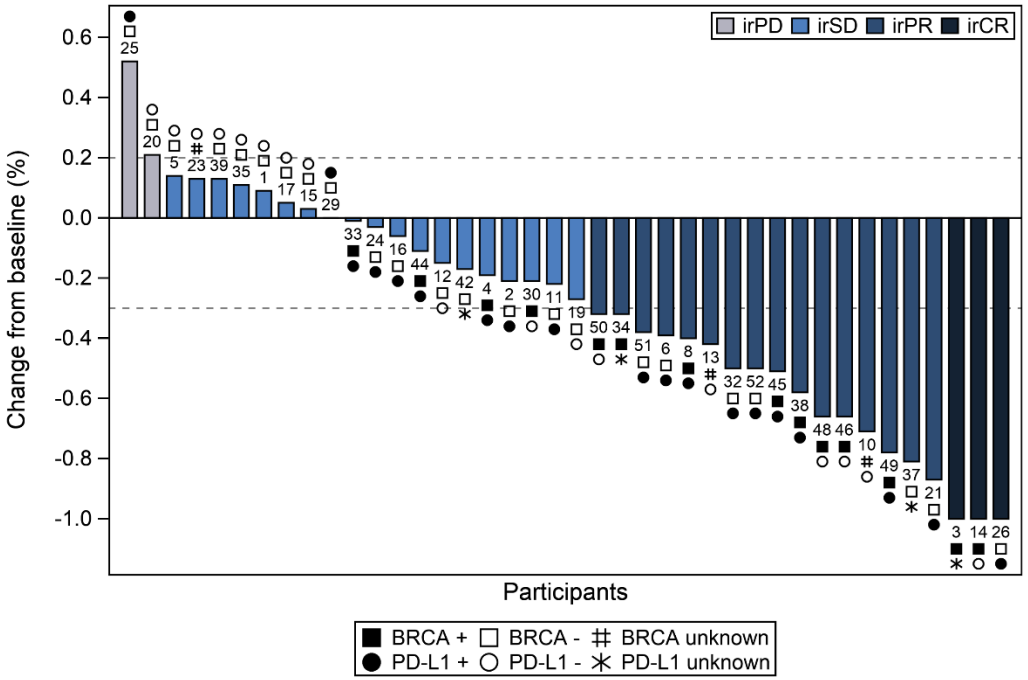
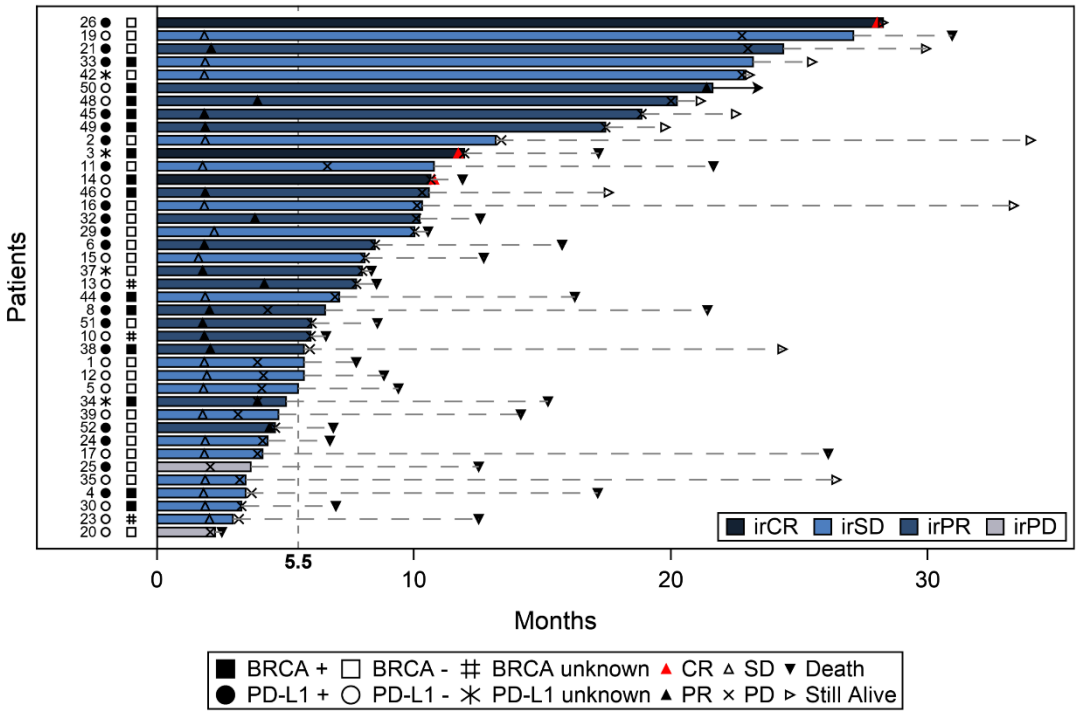
Pembrolizumab+ Bevacizumab + oral Cytoxan in recurrent OC





25% of the patients had PFS> 12 months

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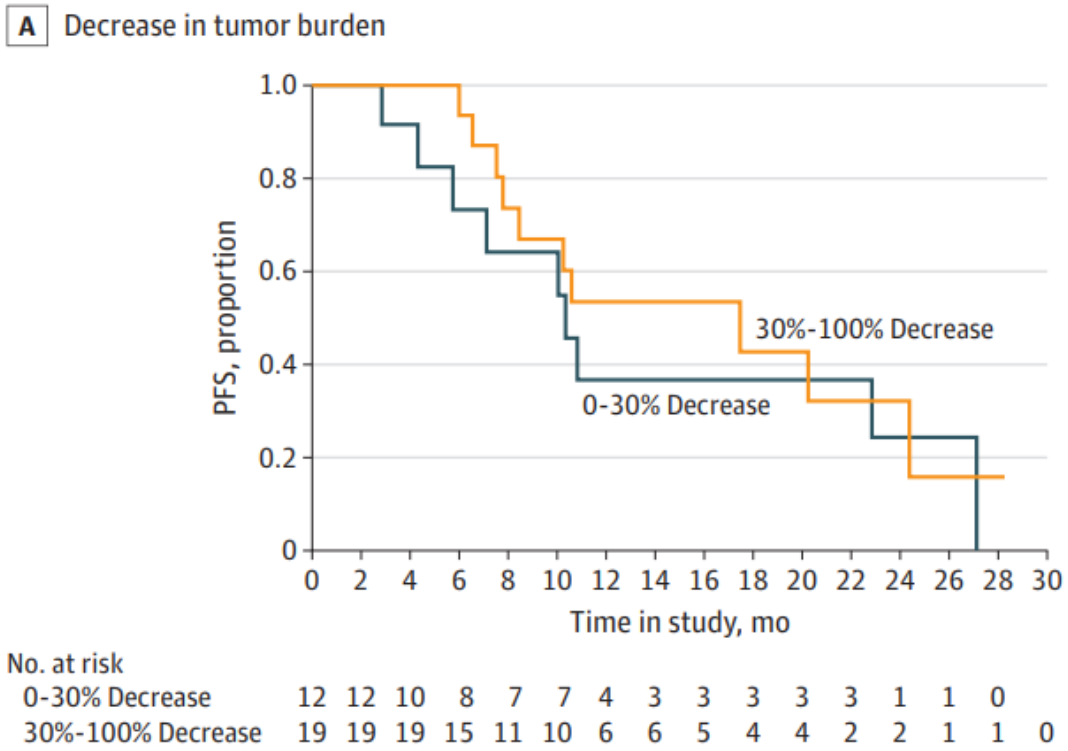
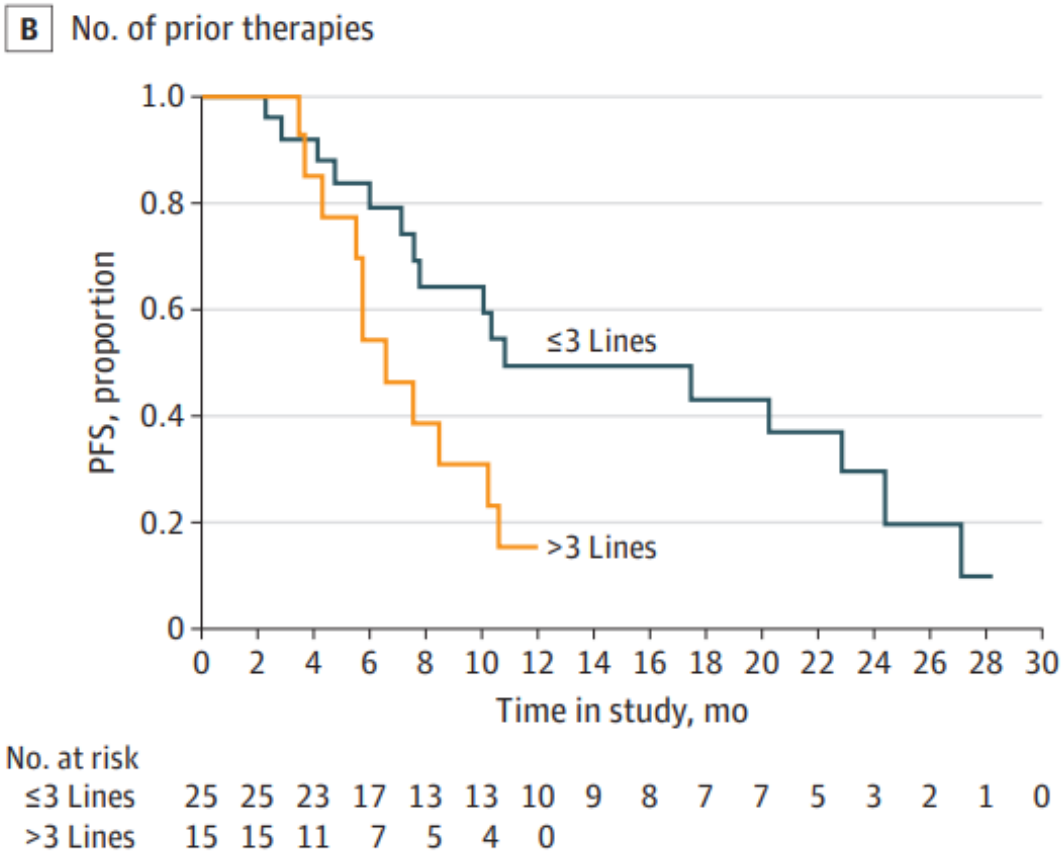
Zsiros E. et al., Jama Oncology 2021

No significant difference in PFS between patients with 0% to 30% decrease in tumor burden vs. those with more than 30% to 100% decrease in tumor burden, (log-rank P = .47).



Among patients with 3 or fewer prior lines of chemotherapy, median 6-month PFS median PFS, **10.8** (90% CI, 7.6-24.4) months. Among patients with more than 3 prior lines of chemotherapy, median PFS, 6.5 (90% CI, 4.3-10.2) months (P = .03).



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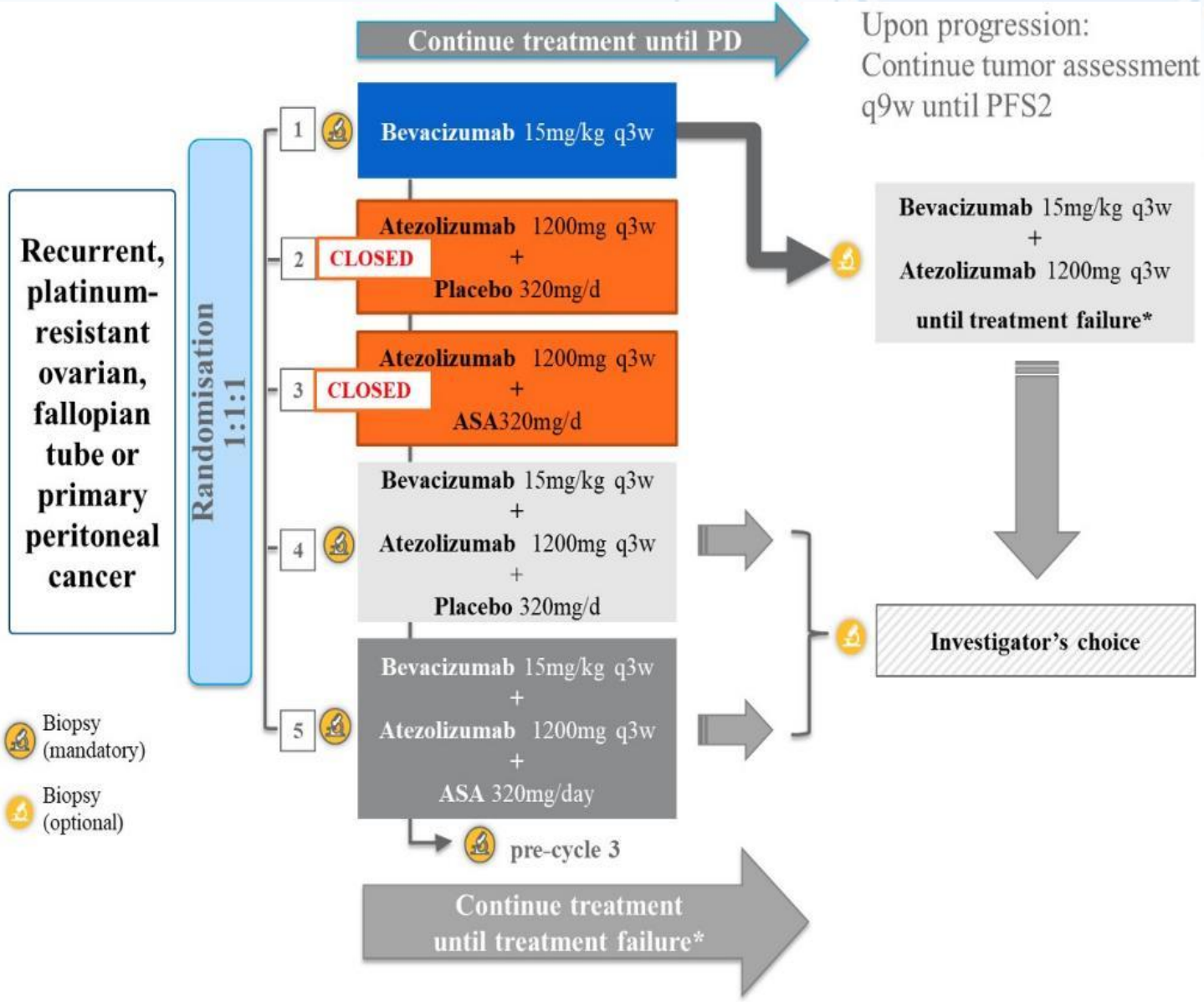
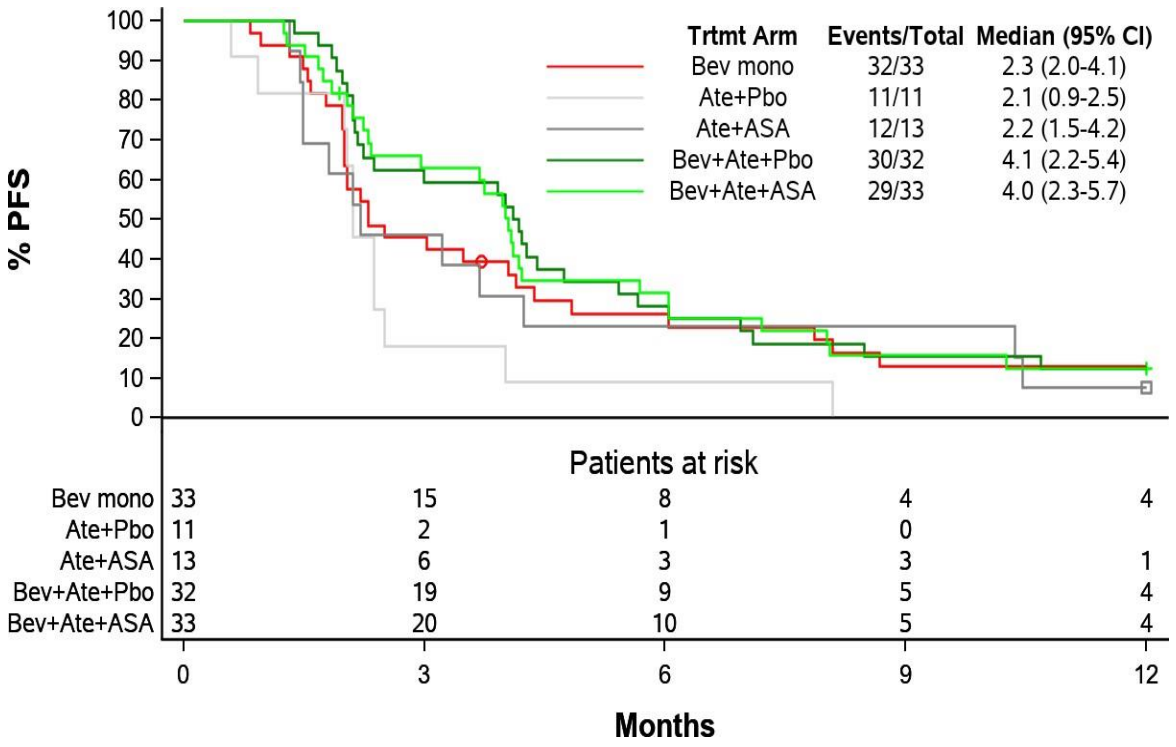
Zsiros E. et al., Jama Oncology 2021

Principal results of the EORTC-1508 trial: A phase II randomized, multicenter study of bevacizumab vs atezolizumab and bevacizumab with acetylsalicylic acid or placebo in recurrent platinum-resistant ovarian, fallopian tube or primary peritoneal adenocarcinoma



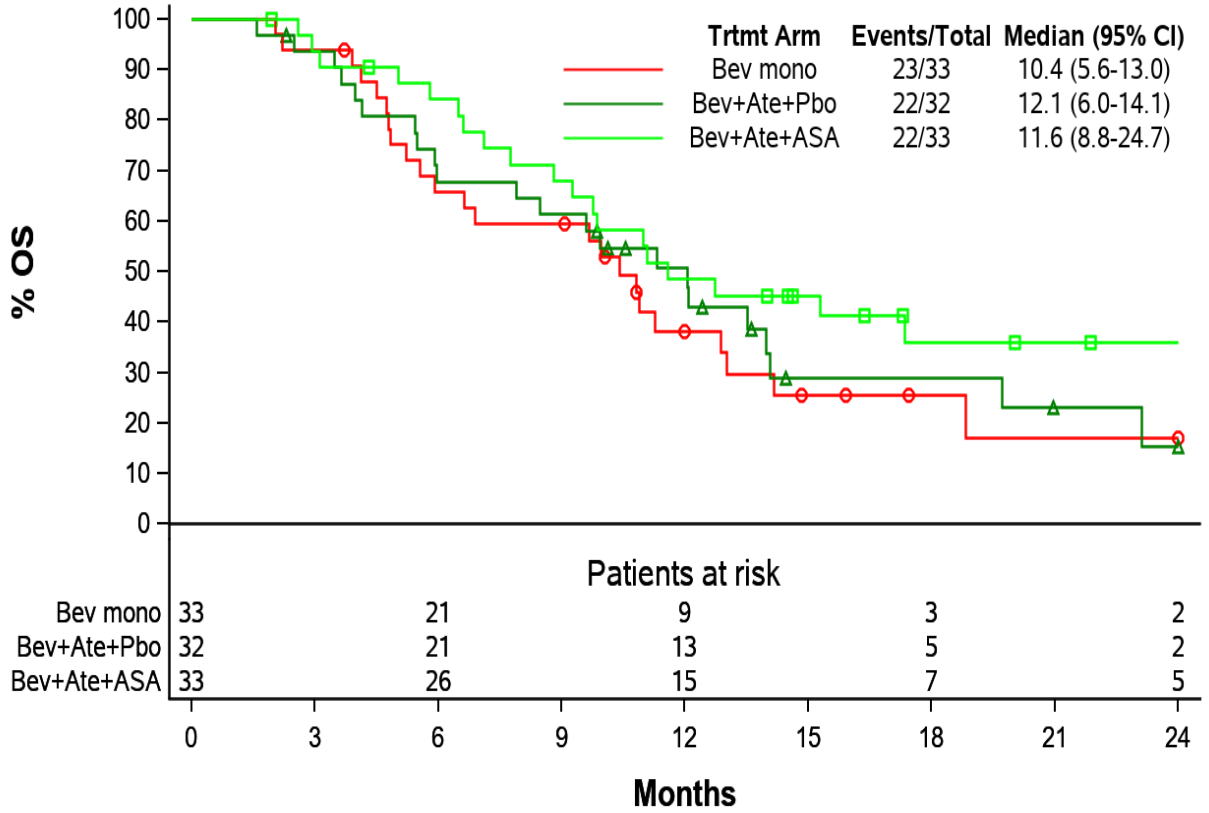
Banerjee S et a;., ESMO 2021

Progression-Free Survival



Ate+Pbo and Ate+ASA arms recruitment closed Jan 2019

Overall Survival (Arm 1,4,5)



Banerjee et al. ESMO 2021

Society for Immunotherapy of Cancer

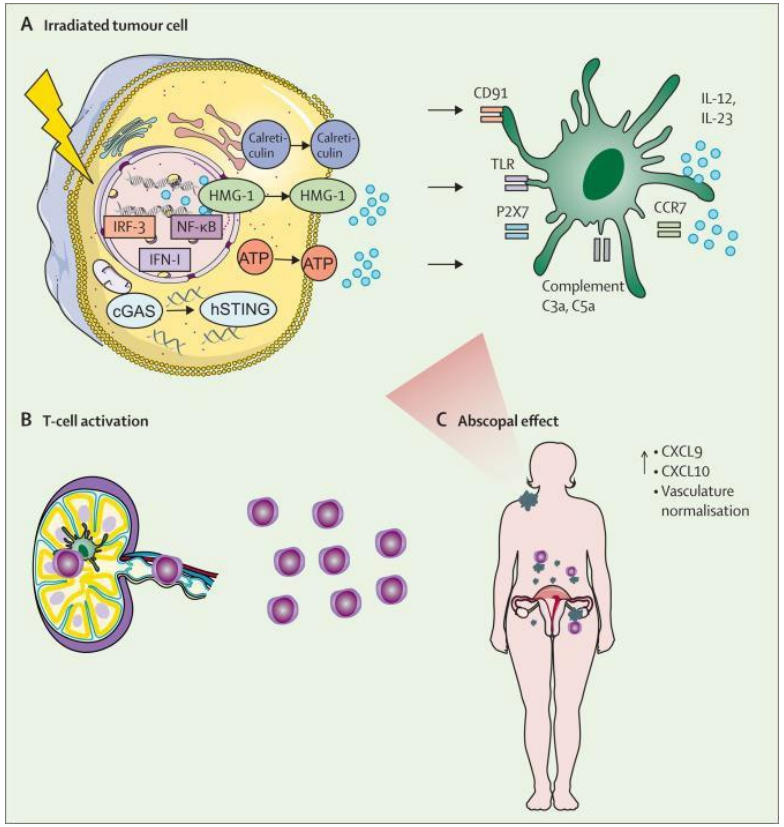
Advances in radioimmunotherapy 2

Rational combinations of immunotherapy with radiotherapy in ovarian cancer

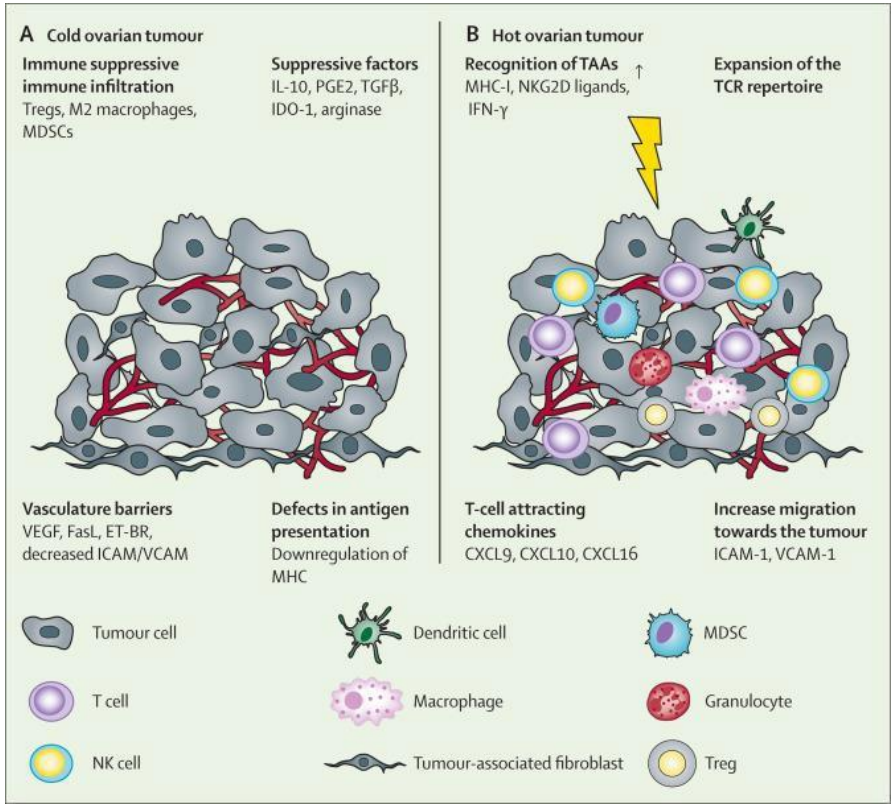
Fernanda G Herrera, Melita Irving, Lana E Kandalaft, George Coukos

RADIATION + ICB

Priming and Activating the immune system



Reprogramme the tumour microenvironment



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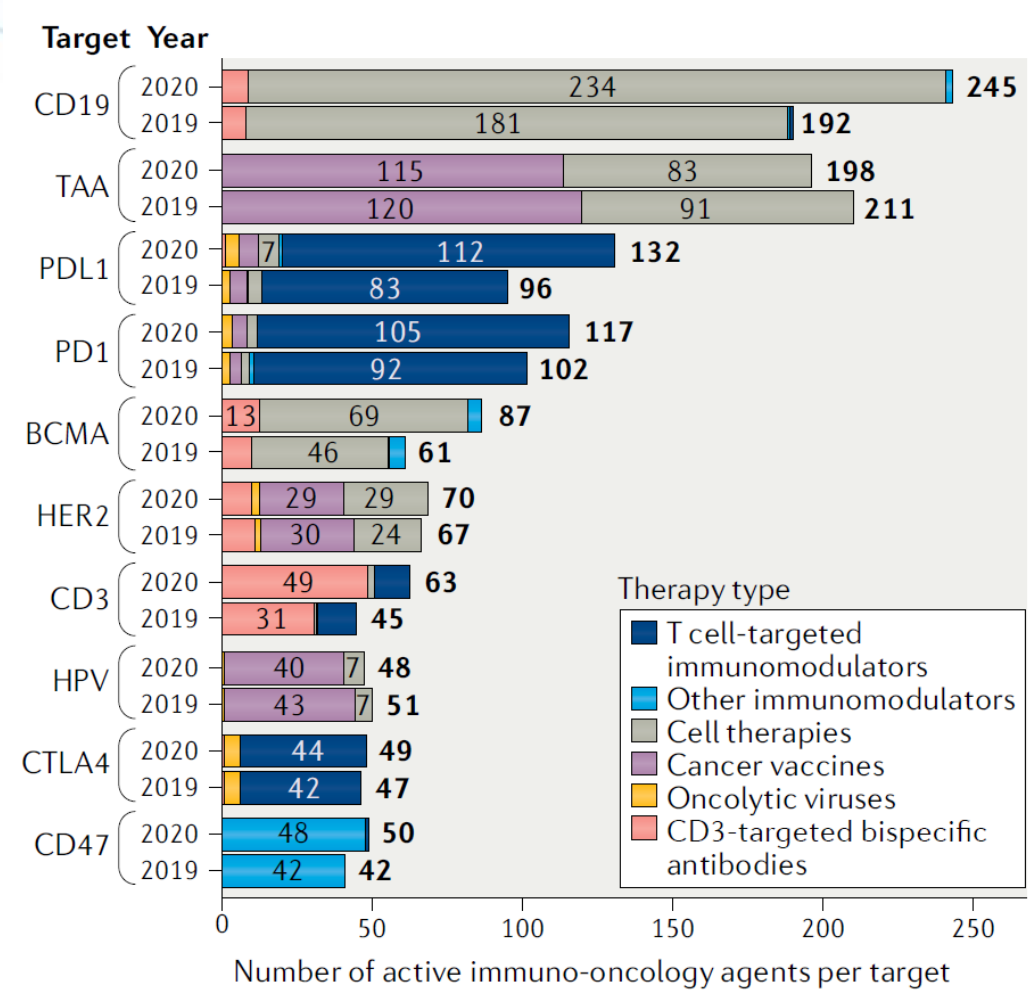
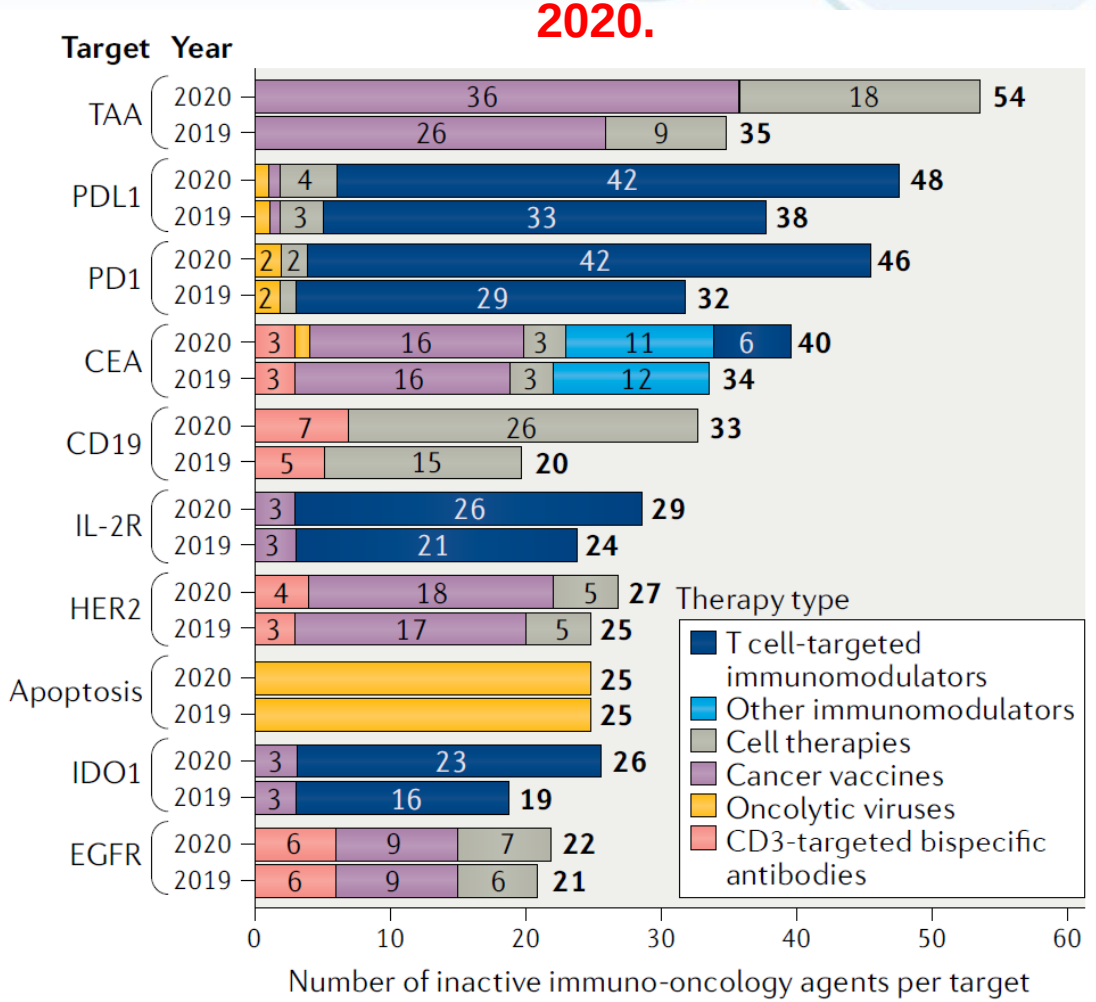
F. Herrera, M. Irving, L E Kandalaft and G Coukos, The Lancet Oncology, September 2019

THE LANCET Oncology

What is the in future?

Top immuno-oncology targets for active and deprioritized agents in the drug development pipeline from 2019 and 2020.





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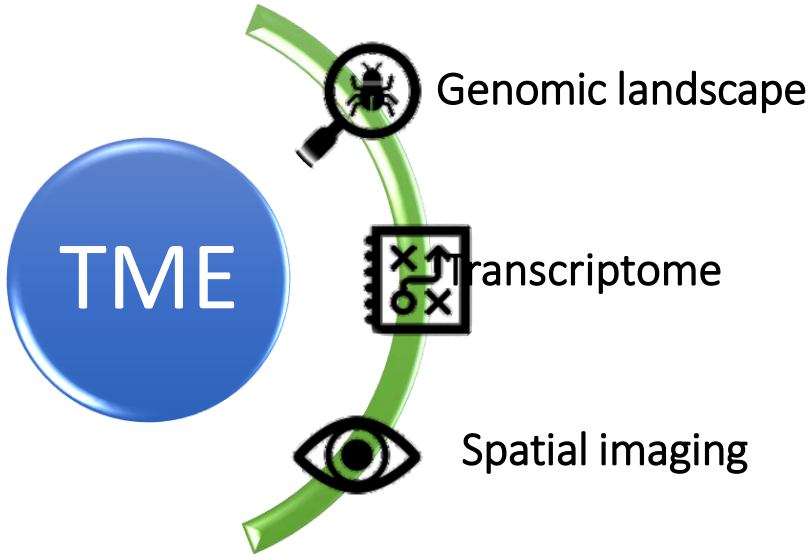
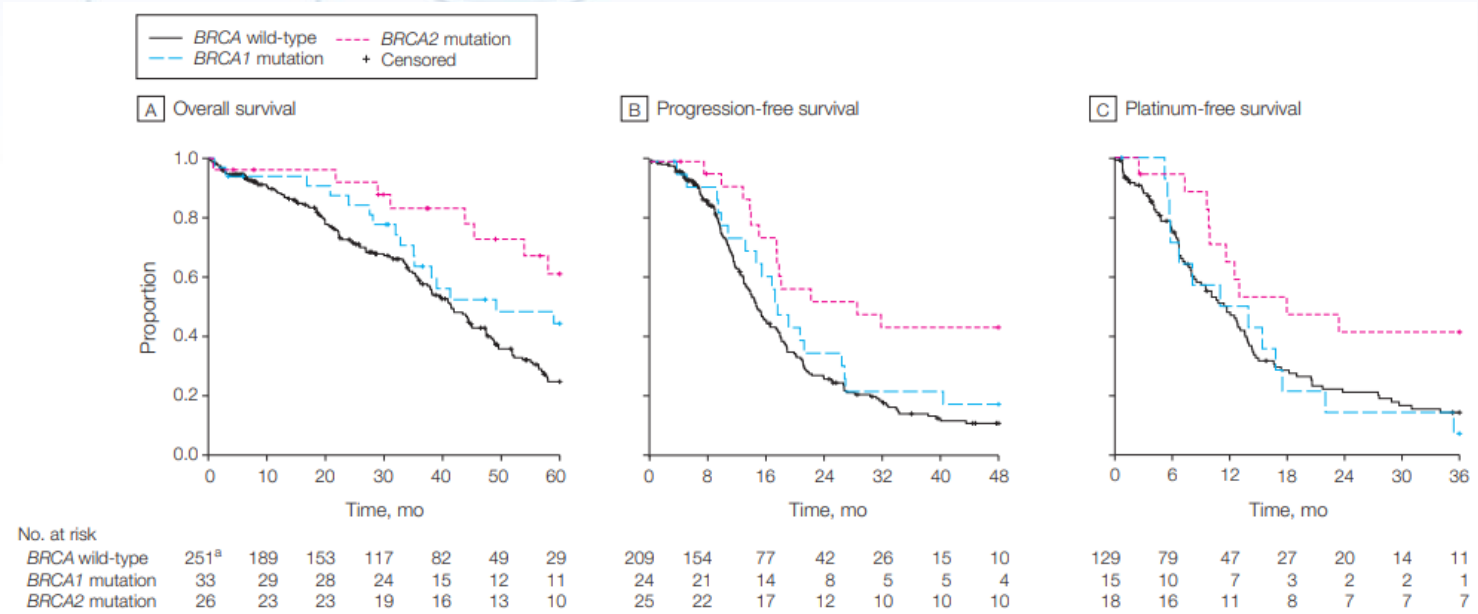
Upadhaya S et al., Nat Rev Drug Disc 2021

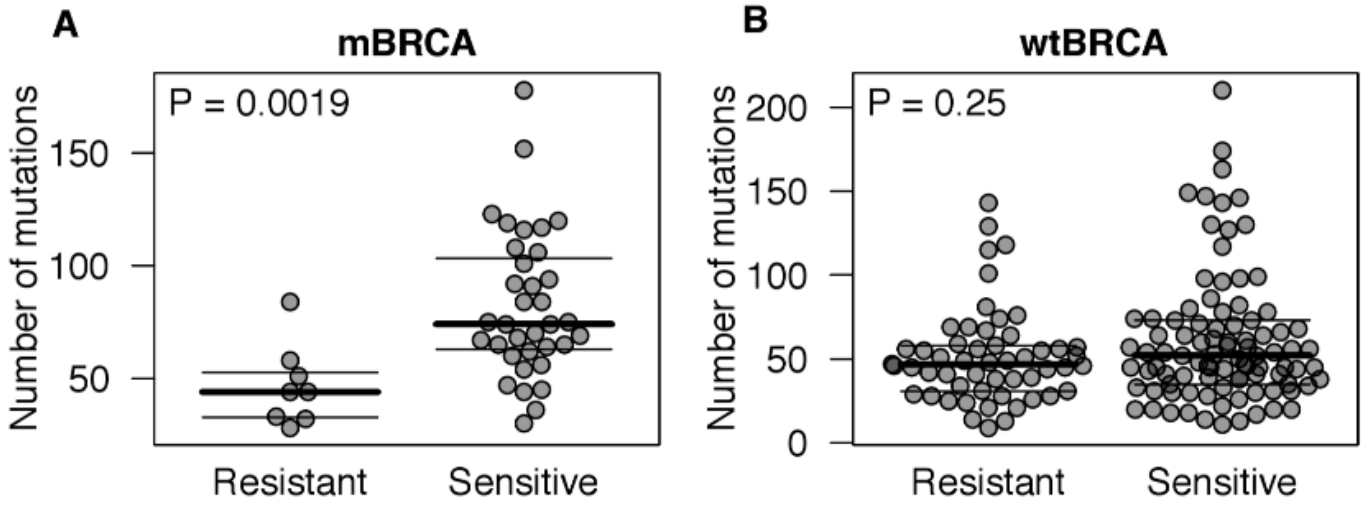
BIOMARKERS FOR RESPONSE TO ICB THERAPY

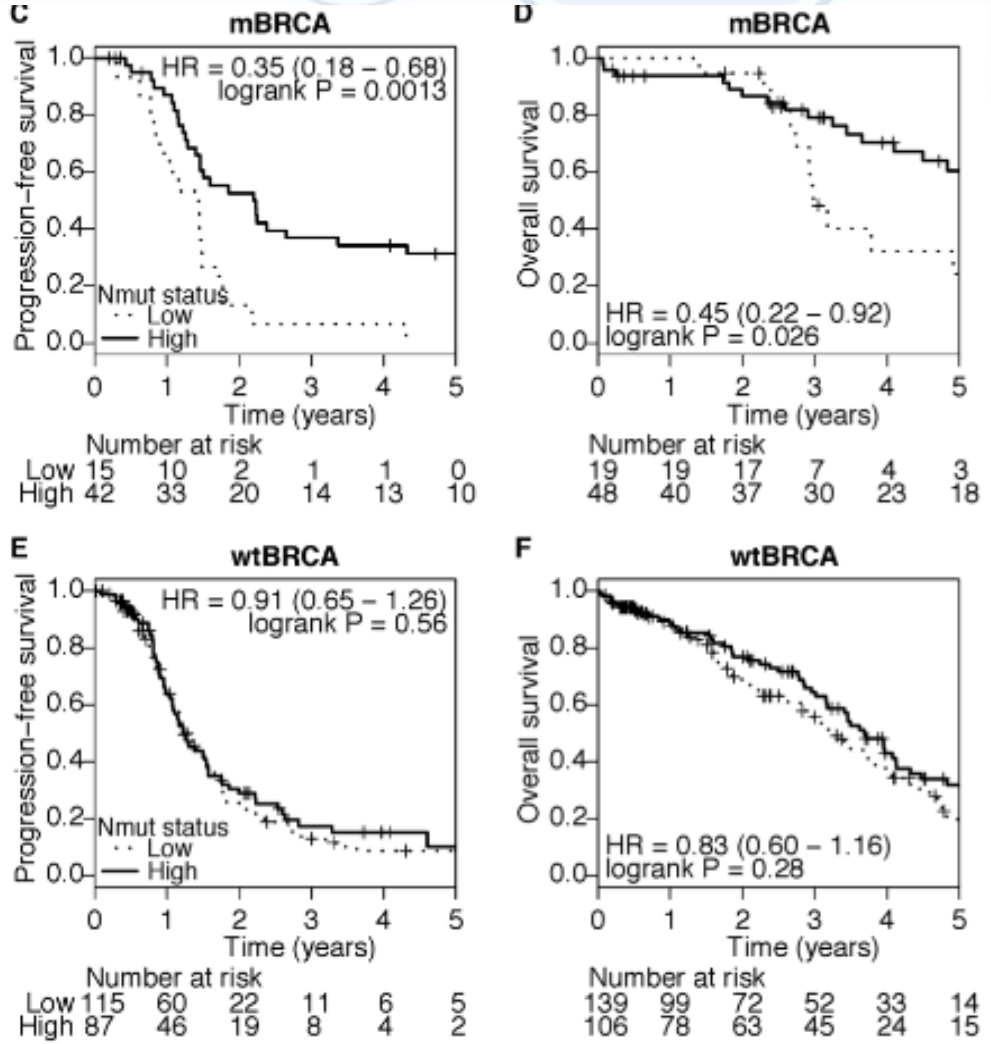
- **Clinically Applicable Biomarkers**
- BRCA mutation
- MSI and TMB
- PD-L1 staining
- **Tissue based biomarkers**
- TILs
- B cells and tertiary lymphoid structures
- **New genomic biomarkers**
- **Transcriptomic signatures**
- **Host factors**



mBRCA as a marker for improved clinical outcome





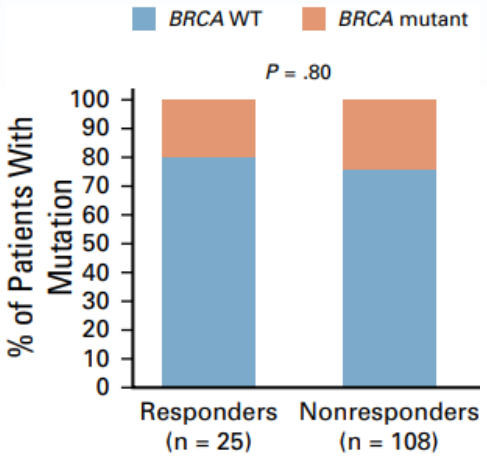


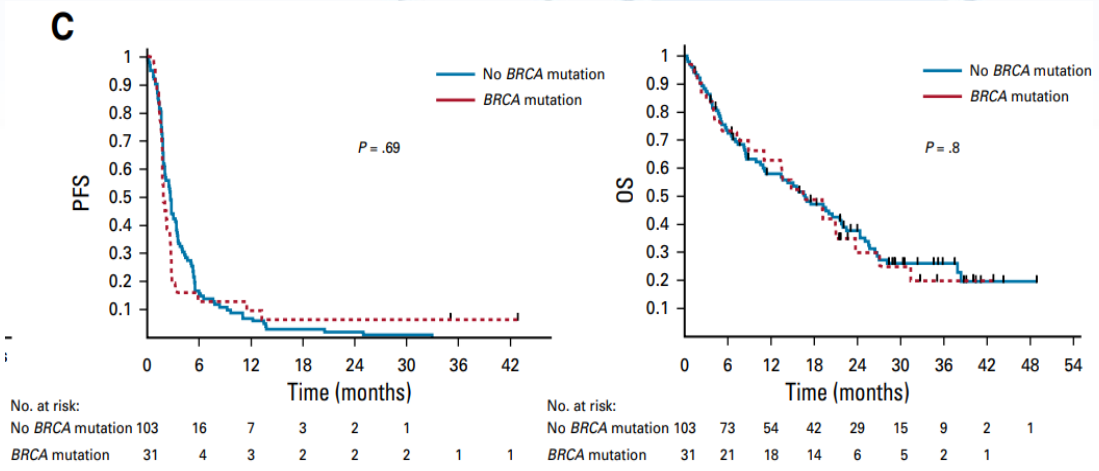
Yang et al., JAMA 2011
Birkbak et al, Plos One, 2013

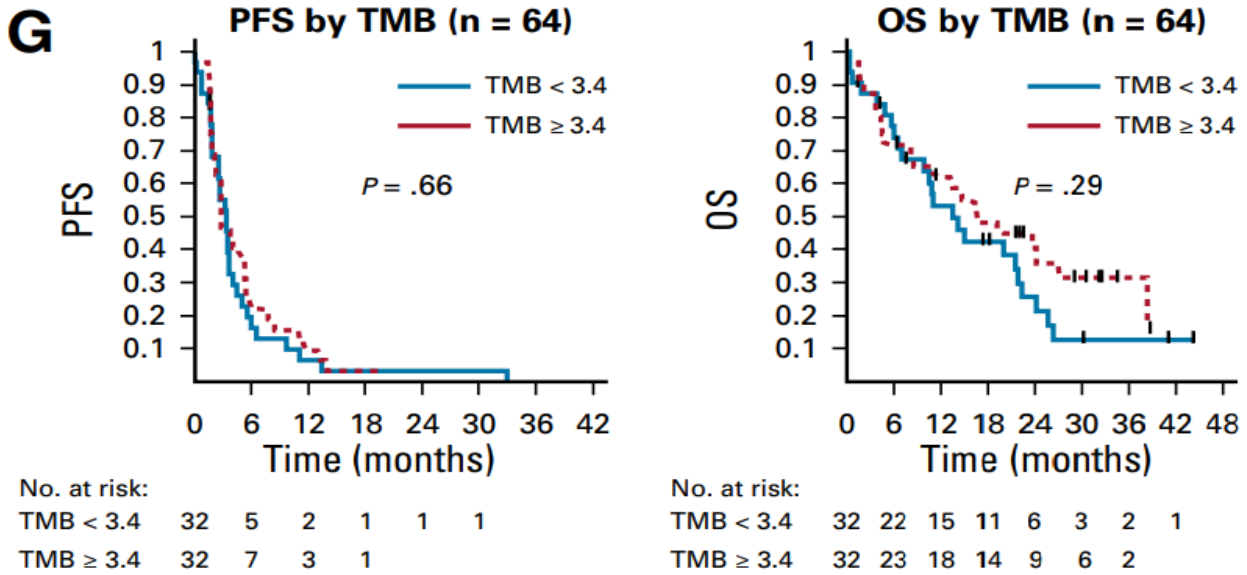
TMB and HRD markers may not predict response to ICB

Patients with recurrent ovarian cancer treated with ICI from January 2013 to April 2019 (N = 143; 27 treated off protocol)

- **Excluded (n = 9);** missing *BRCA* testing data
- ***BRCA* status known (n = 134)**
  - Wild-type (n = 103; 76%)
  - Mutated (n = 31; 24%)
    - ***BRCA* mutations**
      - g*BRCA1* (n = 12)
      - g*BRCA2* (n = 9)
      - s*BRCA1* (n = 4)
      - s*BRCA2* (n = 6)
- **Genomic Analysis**
  - LST and FGA (n = 73; WES, n = 20; IMPACT, n = 53)
  - TMB (n = 64; all IMPACT)







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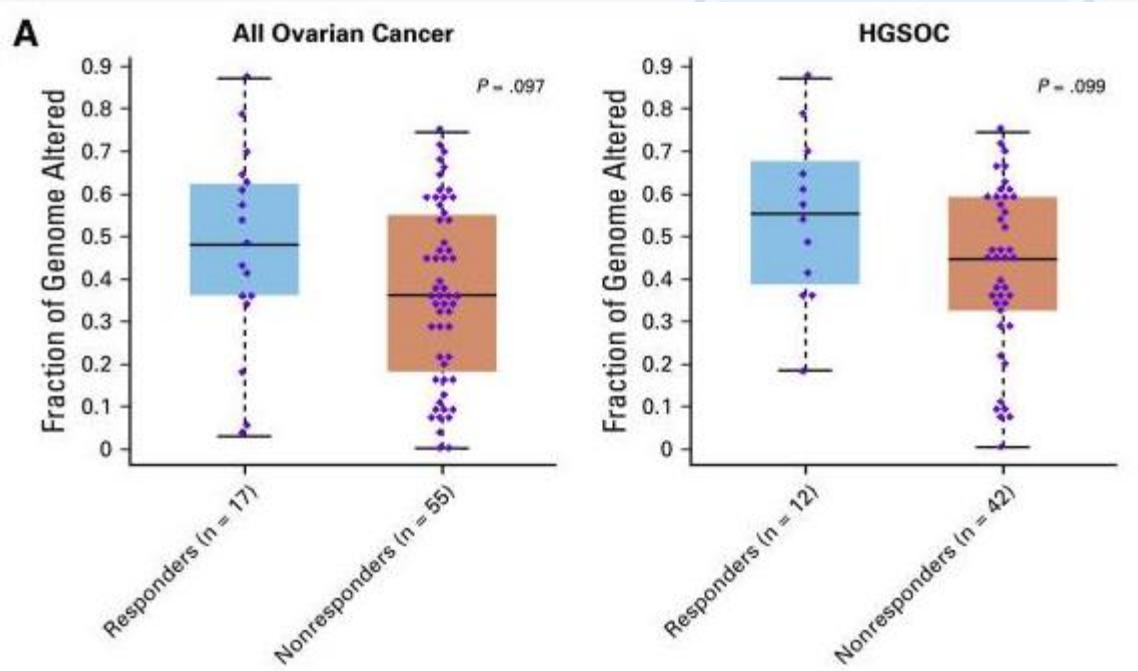
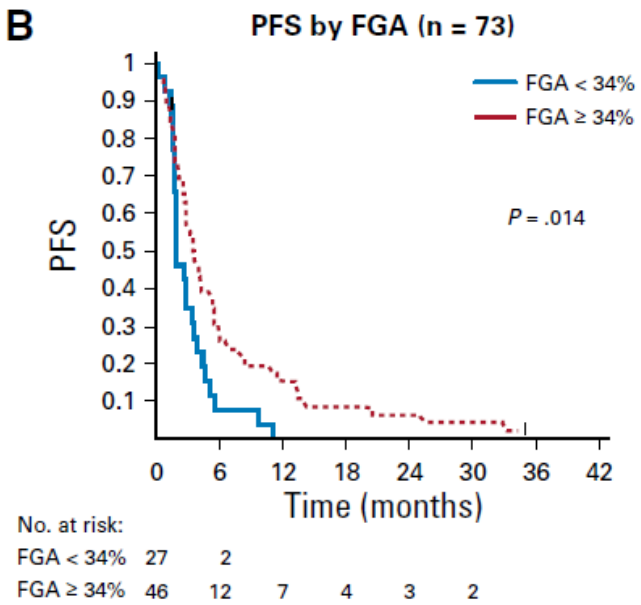
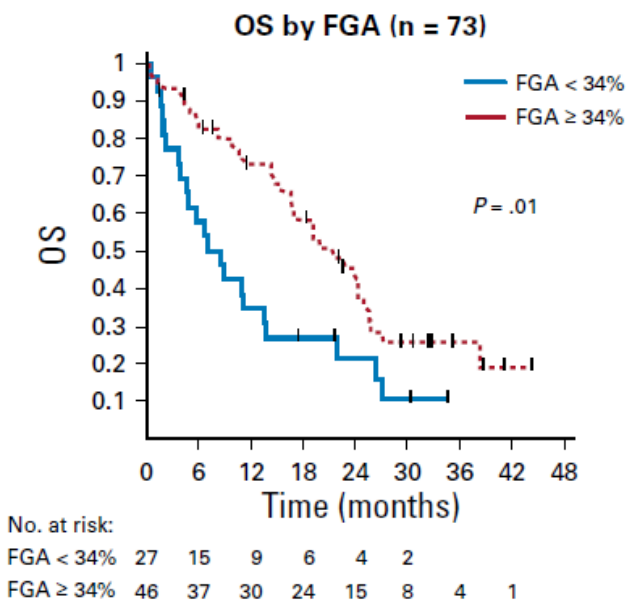
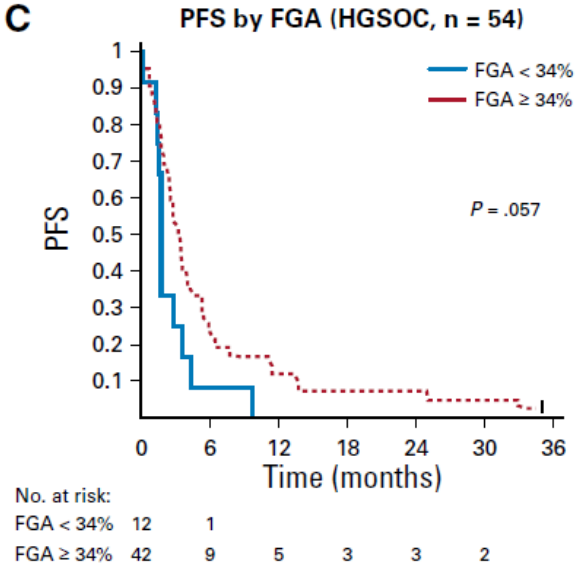
Liu Y. et al, JCO 2021

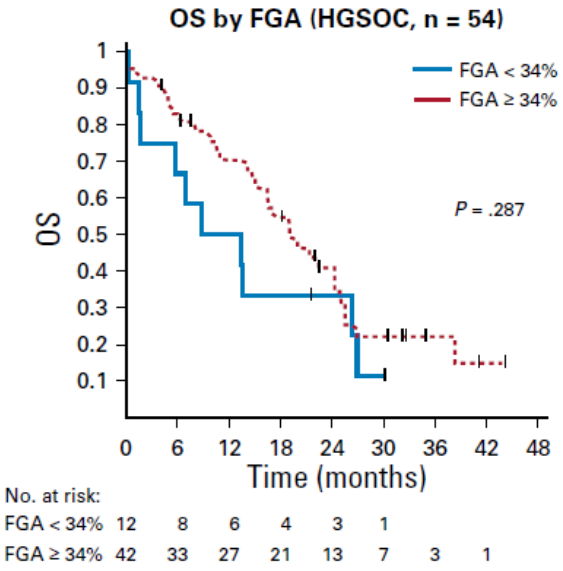
Fraction of Genome Altered as a potential biomarker for ICB response











Liu Y. et al, JCO 2021

TILS in OC as a prognostic marker

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

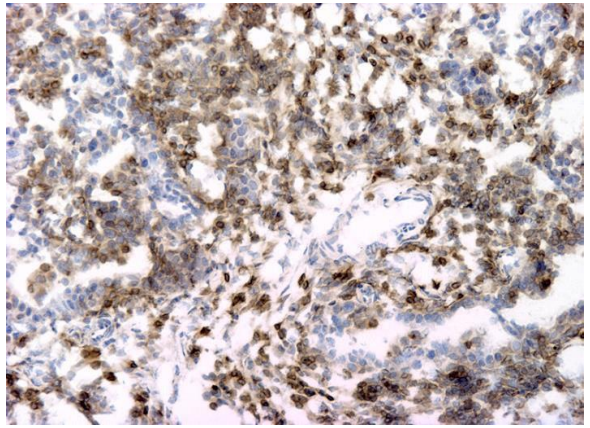
Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and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

HOT TME

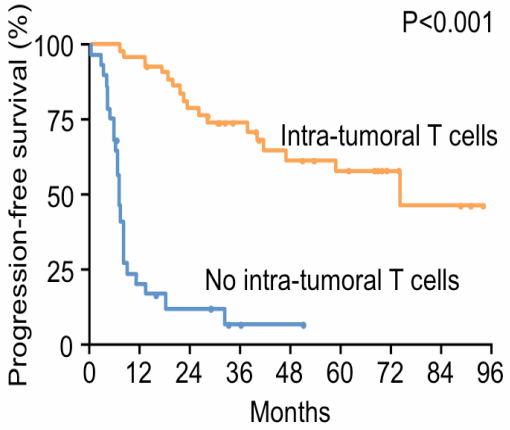
CD3+

Immune inflamed

TILs present
55%

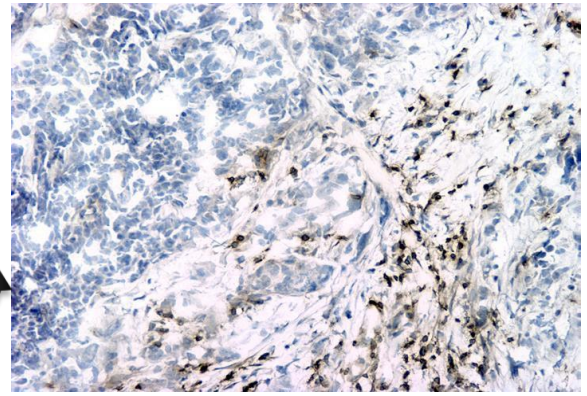


At 96 months:
50% in remission

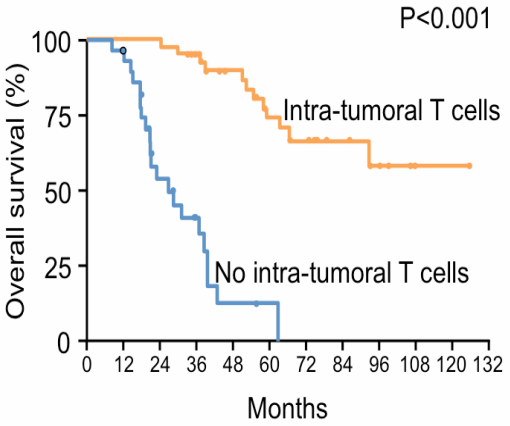


COLD TME

TILs absent
or excluded
45%



At 96–132 months:
>60% alive



Immune exclusion

Immune ignorance

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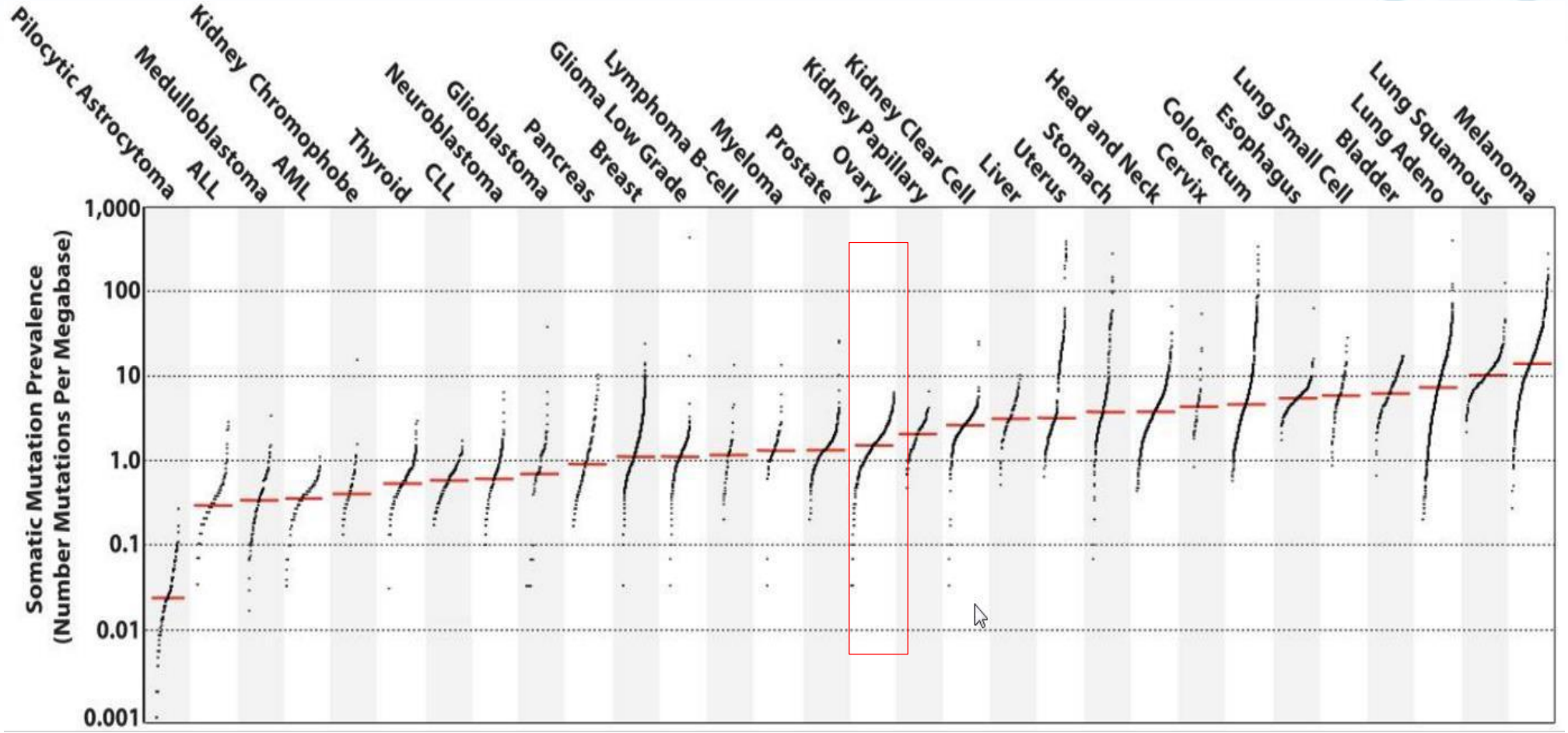
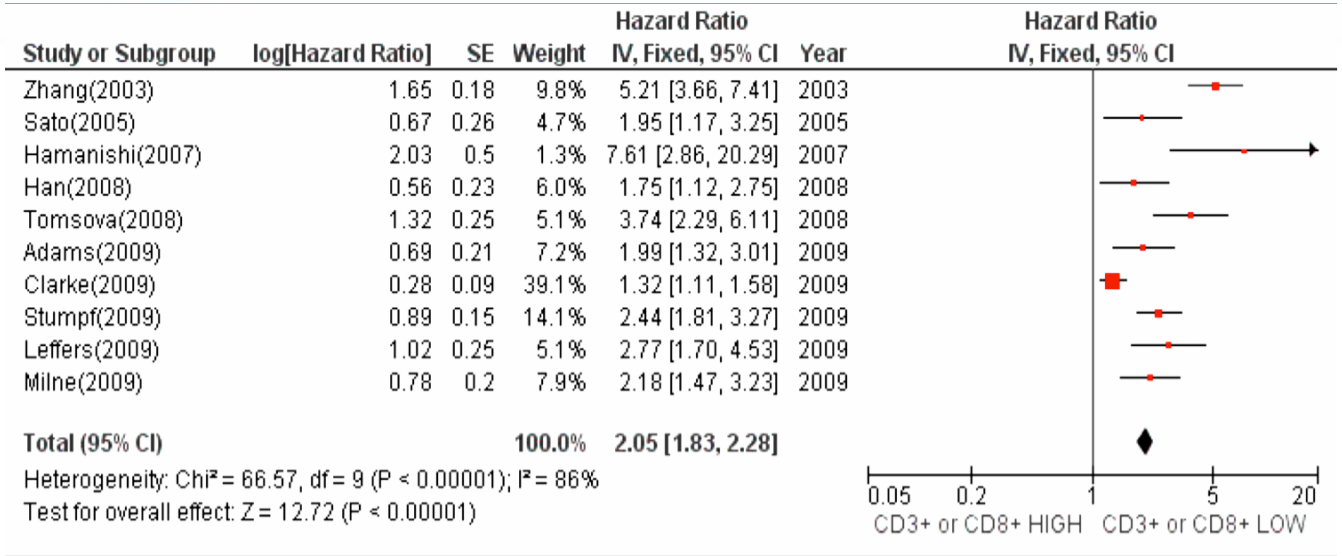
Zhang, et al. *N Engl J Med* 2003

Is there neo-epitope specific recognition in Ovarian Cancer ?



CHUV
UNIL | Université de Lausanne
LUDWIG CANCER RESEARCH

Not all TILs are created equal



Meta-analysis of intraepithelial TIL impact in ovarian cancer:
10 studies; 1,782 patients

Hwang et al, Gynecol Oncol 2011

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-03301-0 OPEN

Sensitive and frequent identification of high avidity neo-epitope specific CD8+ T cells in immunotherapy-naive ovarian cancer

Sara Bobisse[1], Raphael Genolet[1], Annalisa Roberti[2], Janos L. Tanyi[2], Julien Racle[1,3], Brian J. Stevenson[3], Christian Iseli[3], Alexandra Michel[1], Marie-Aude Le Bitoux[1], Philippe Guillaume[1], Julien Schmidt[1], Valentina Bianchi[1], Denarda Dangaj[1], Craig Fenwick[4], Laurent Derré[5], Ioannis Xenarios[3], Olivier Michielin[1,3], Pedro Romero[1], Dimitri S. Monos[6], Vincent Zoete[1,3], David Gfeller[1,3], Lana E. Kandalaft[1,2], George Coukos[1] & Alexandre Harari[1]

Liu et al. Journal for ImmunoTherapy of Cancer (2019) 7:156
https://doi.org/10.1186/s40425-019-0629-6

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Efficient identification of neoantigen-specific T-cell responses in advanced human ovarian cancer

Song Liu[1*†], Junko Matsuzaki[2*†], Lei Wei[1†], Takemasa Tsuji[2†], Sebastiano Battaglia[2†], Qiang Hu[1], Eduardo Cortes[1], Laiping Wong[1], Li Yan[1], Mark Long[1], Anthony Miliotto[2], Nicholas W. Bateman[3], Shashikant B. Lele[4], Thinle Chodon[2], Richard C. Koya[2], Song Yao[5], Qianqian Zhu[1], Thomas P. Conrads[3,6,7], Jianmin Wang[1], George L. Maxwell[3,6], Amit A. Lugade[2] and Kunle Odunsi[2,4*]

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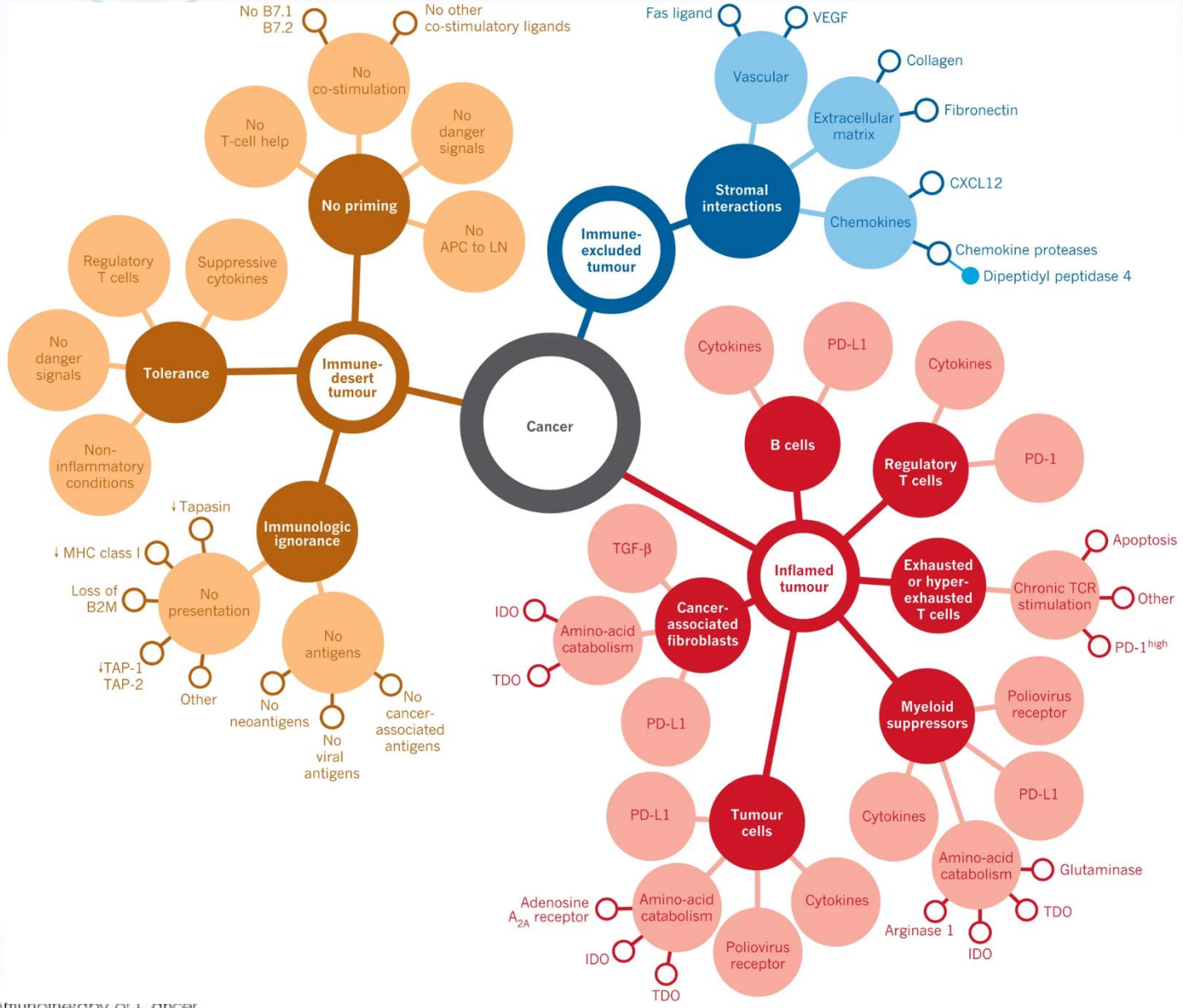
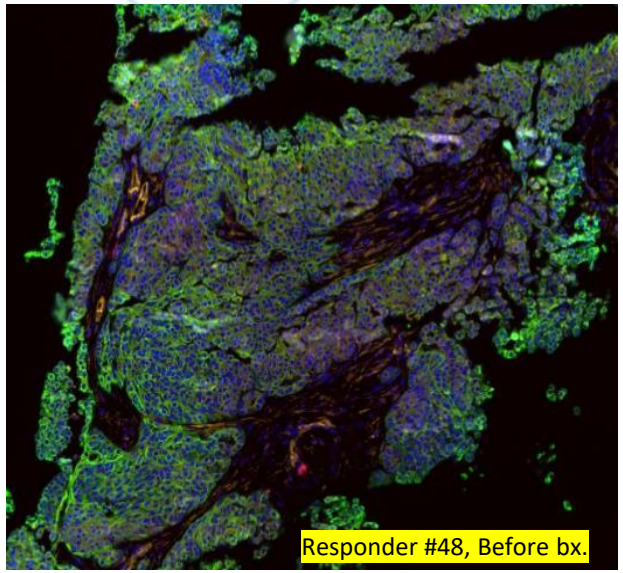
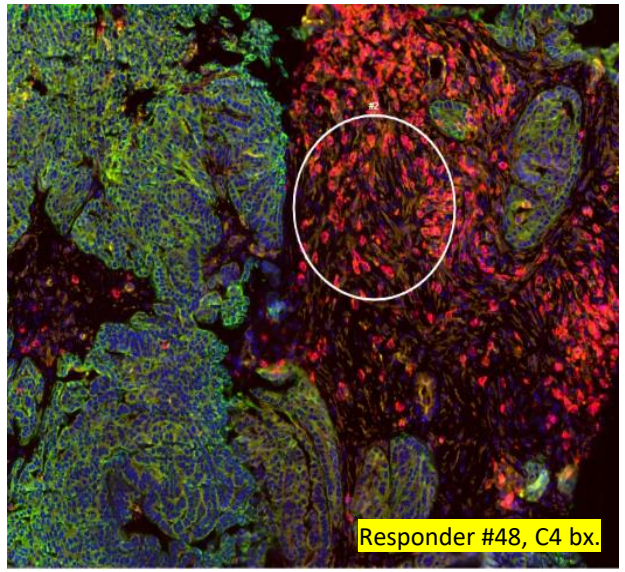
Cancer-immune phenotypes: consistent with most solid tumors

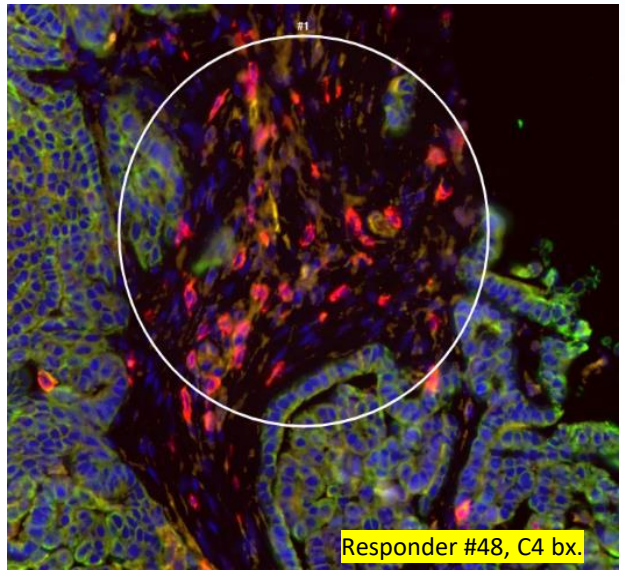


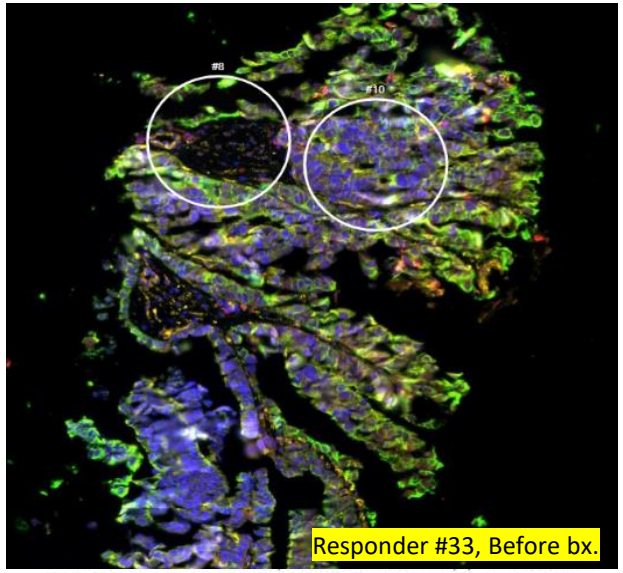
Chen DS et al, Nature, 2017

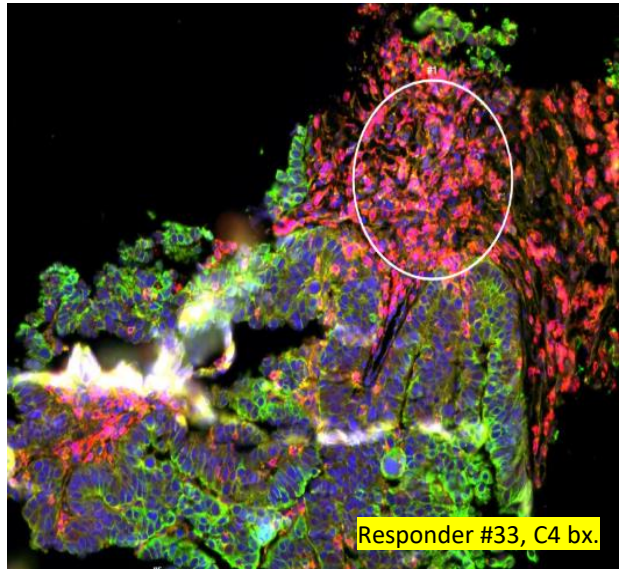
CHANGESIN OC TME with PEMBRO + BEV + Oral Cytoxan

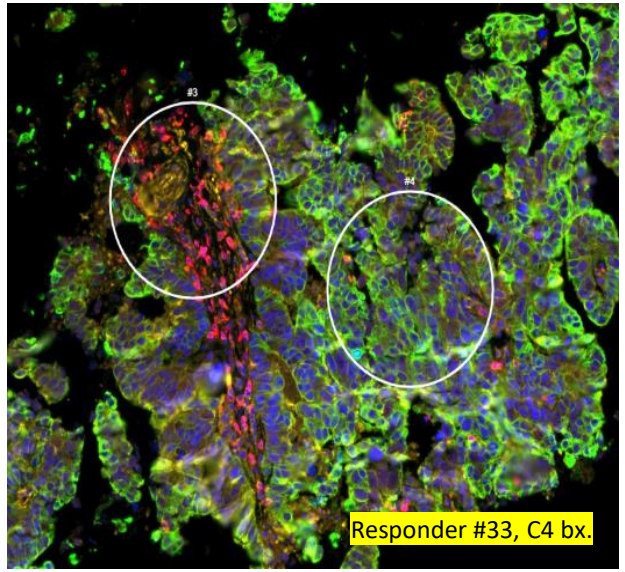












Nanostring DSP:
Green: OC cells (PanCK)
Blue: nuclei (DNA)
Yellow: vasculature (CD31)
Red: CD3+ T cells

NCT02853318

ZSIROS et al, manuscript in preparation

Article

B cells and tertiary lymphoid structures promote immunotherapy response

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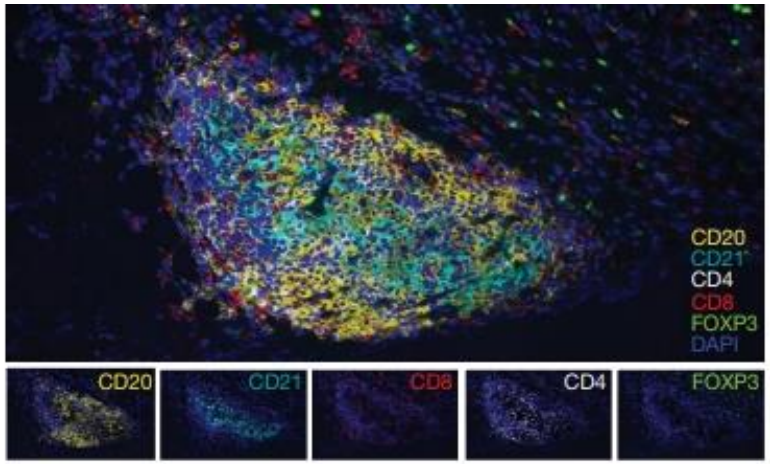
Published online: 15 January 2020

Beth A. Helmink[1,24]*, Sangeetha M. Reddy[2,24], Jianjun Gao[3,24], Shaojun Zhang[4,24], Rafet Basar[5,24], Rohit Thakur[1], Keren Yizhak[6], Moshe Sade-Feldman[6,7], Jorge Blando[8], Guangchun Han[4], Vancheswaran Gopalakrishnan[1], Yuanxin Xi[9], Hao Zhao[8], Rodabe N. Amaria[10], Hussein A. Tawbi[10], Alex P. Cogdill[1], Wenbin Liu[8], Valerie S. LeBleu[11], Fernanda G. Kugeratski[11], Sapna Patel[10], Michael A. Davies[10], Patrick Hwu[10], Jeffrey E. Lee[1], Jeffrey E. Gershenwald[1], Anthony Lucci[1], Reetakshi Arora[4], Scott Woodman[10], Emily Z. Keung[1], Pierre-Olivier Gaudreau[1], Alexandre Reuben[12], Christine N. Spencer[13], Elizabeth M. Burton[1], Lauren E. Haydu[1], Alexander J. Lazar[4,14,15], Roberta Zapassodi[16], Courtney W. Hudgens[14], Deborah A. Ledesma[14], SuFey Ong[17], Michael Bailey[17], Sarah Warren[17], Disha Rao[18], Oscar Krijgsman[18], Elisa A. Rozeman[18], Daniel Peeper[18], Christian U. Blank[18], Ton N. Schumacher[18], Lisa H. Butterfield[19], Monika A. Zelazowska[20], Kevin M. McBride[20], Raghu Kalluri[11], James Allison[6], Florent Petitprez[21,22,23], Wolf Herman Fridman[21,22], Catherine Sautès-Fridman[21,22], Nir Hacohen[6,7], Katayoun Rezvani[5,25], Padmanee Sharma[3,8,25], Michael T. Tetzlaff[14,15,25], Linghua Wang[4,25] & Jennifer A. Wargo[1,4,25]*



Article

IgA transcytosis and antigen recognition govern ovarian cancer immunity

https://doi.org/10.1038/s41586-020-03144-0
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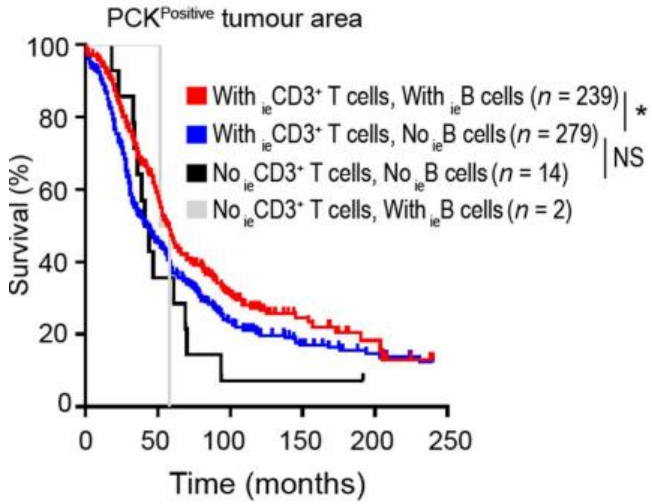
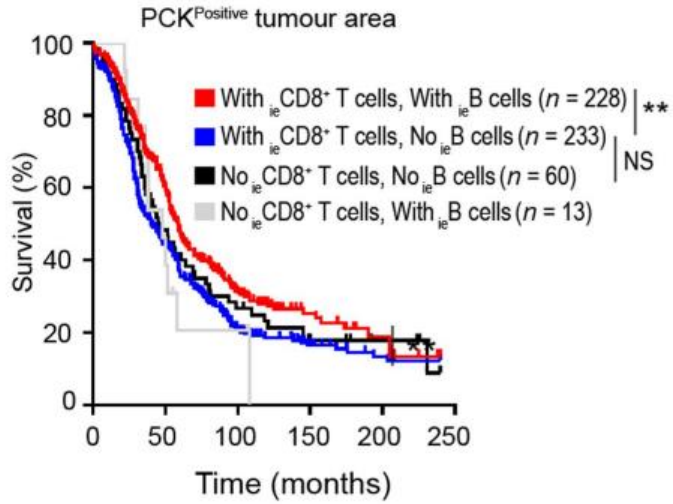
Open access

Subir Biswas[1], Gunjan Mandal[1], Kyle K. Payne[1], Carmen M. Anadon[1], Chandler D. Gatenbee[2], Ricardo A. Chaurio[1], Tara Lee Costich[1], Carlos Moran[3], Carly M. Harro[1], Kristen E. Rigolizzo[1], Jessica A. Mine[1], Jimena Trillo-Tinoco[1], Naoko Sasamoto[4], Kathryn L. Terry[4], Douglas Marchion[4], Andrea Buras[5], Robert M. Wenham[5], Xiaoqing Yu[6], Mary K. Townsend[7], Shelley S. Tworoger[7,8], Paulo C. Rodriguez[1], Alexander R. Anderson[2] & Jose R. Conejo-Garcia[1]✉





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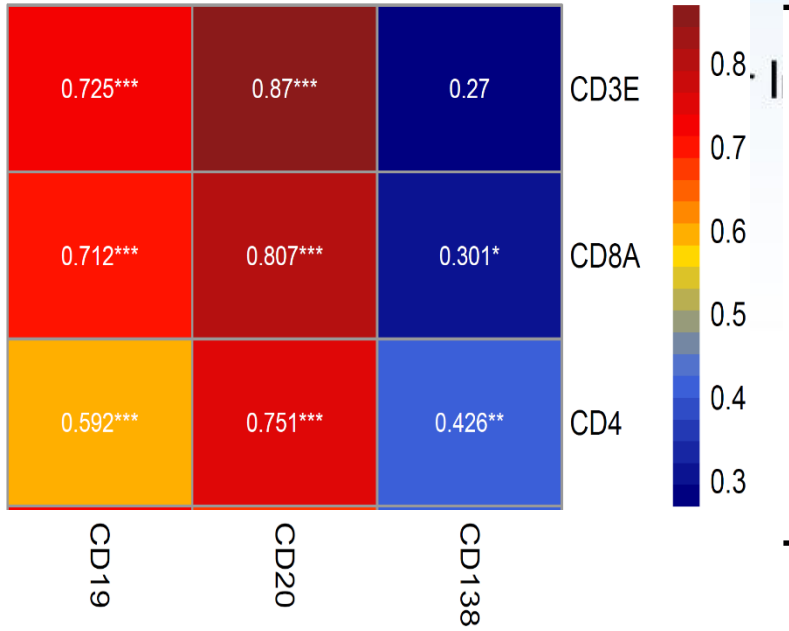
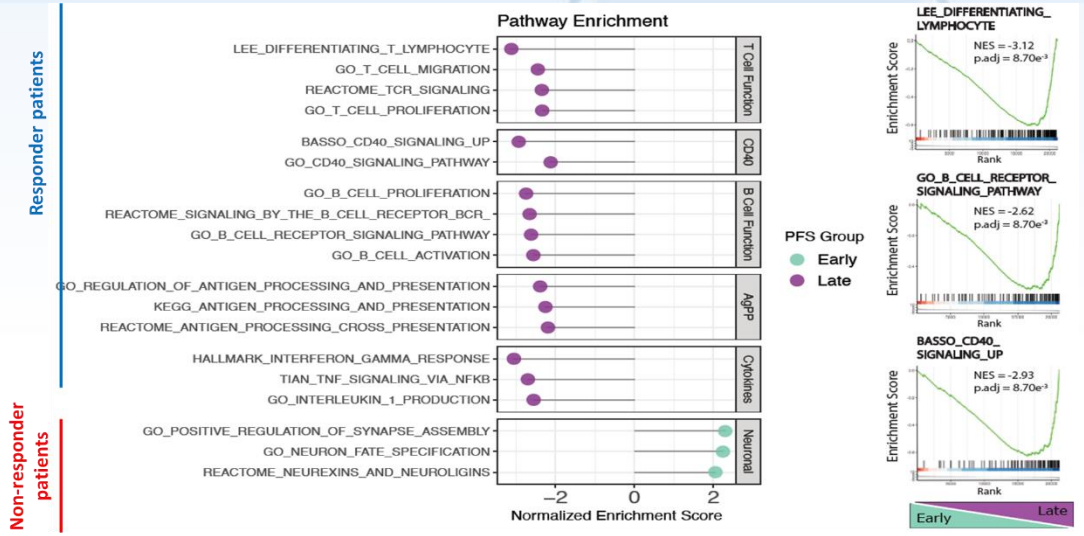


Marker	CellType	Estimate	p value
CD19	b-cell	0.72	0.03
CD20	b-cell	0.76	0.03
CD3D	t-cell	0.68	0.01
CD3E	t-cell	0.65	0.01
CD3G	t-cell	0.68	0.04
CD4	t-cell	0.54	0.01
CD8A	t-cell	0.60	0.03
CD8B	t-cell	0.68	0.03

Correlation with PFS



NCT02853318

FUTURE TRIAL

Recurrent OC
(serous, clear cell, endometrioid)

Platinum-sensitive or resistant
≤ 3 prior lines of treatment

→

Research specimen collection (baseline)
- Tumor biopsy
- Blood
- Stool sample

QoL Questionnaires

→ :1

Cohort 1 (n=40)
Pembrolizumab 200 mg every 3 weeks +
Bevacizumab 15 mg/kg every 3 weeks

Cohort 2 (n=40)
Pembrolizumab 200 mg every 3 weeks +
Bevacizumab 15 mg/kg every 3 weeks +
CDX-1140 1.5 mg/kg IV every 3 weeks

→

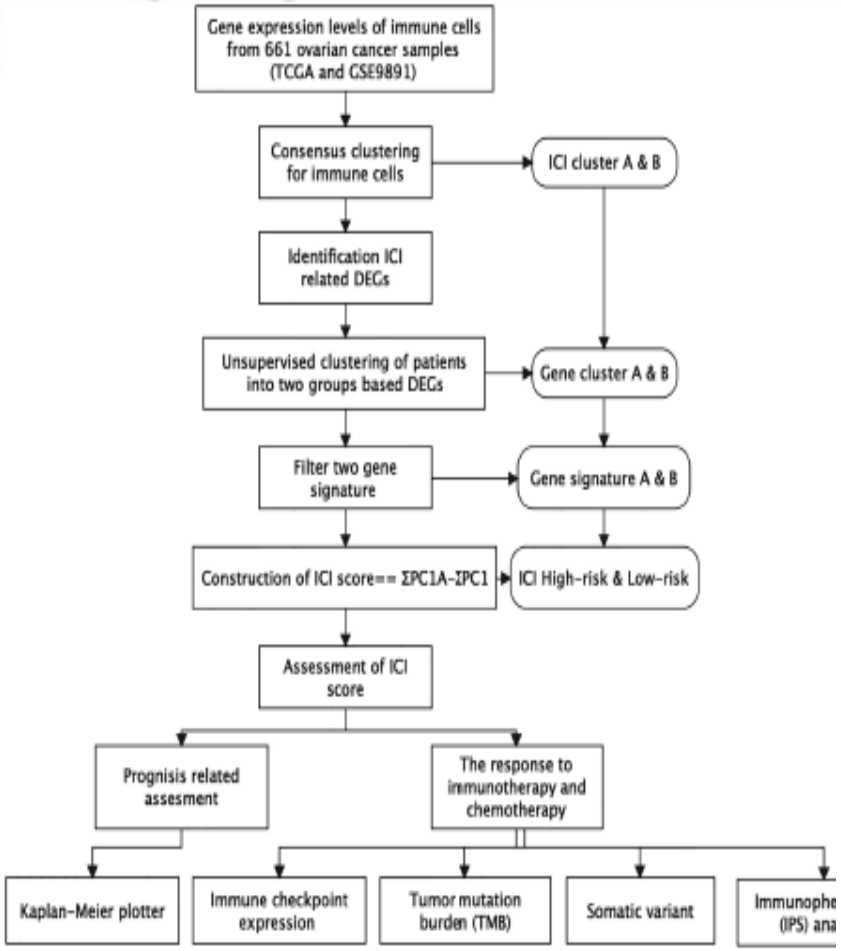
Treatment until disease progression or unacceptable toxicity

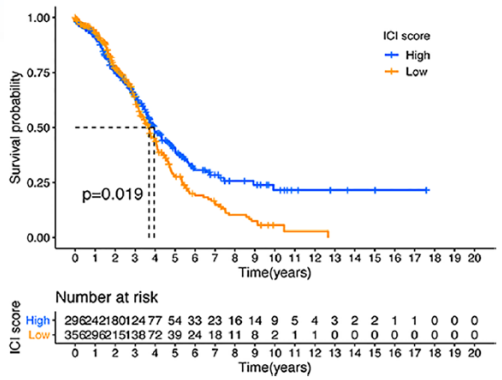
Research specimen collection (C2D1, C4D1, C7D1 and at the end of treatment):
- Blood
- Stool sample
- QoL questionnaires

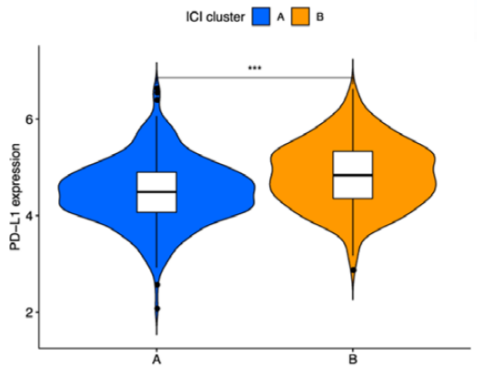
Tumor biopsy:
C4D1: after 3 cycles of treatment (mandatory) and at the end of treatment (optional)

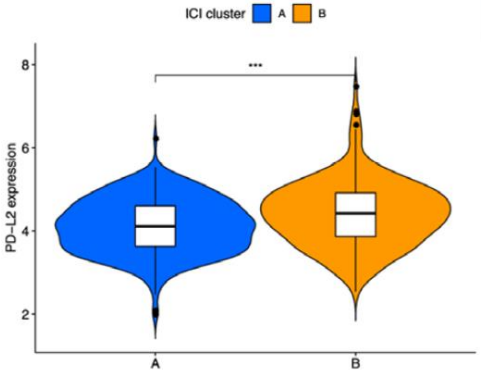
Zsiros – Unpublished data

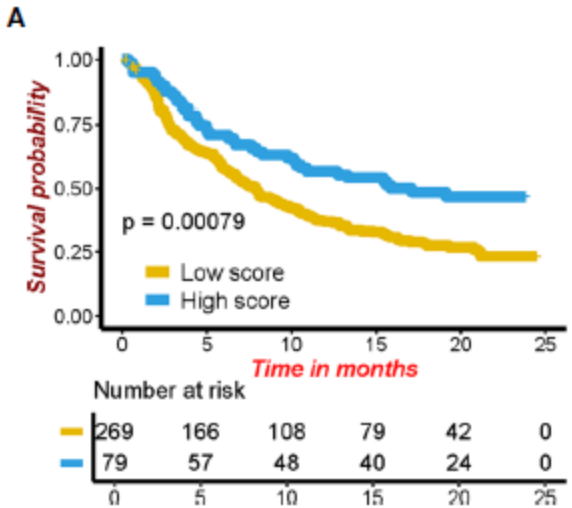
Immune Cell Infiltration Score to predict prognosis and response to ICB?

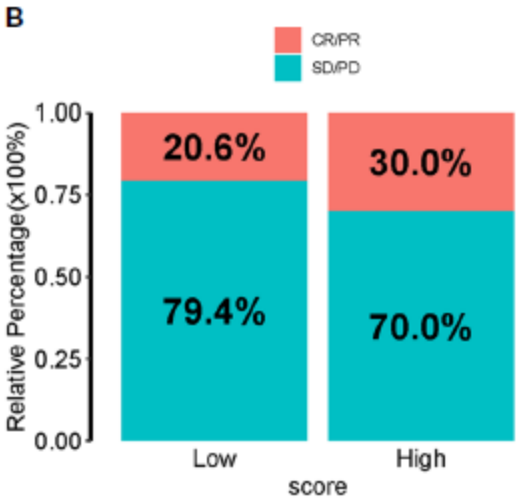


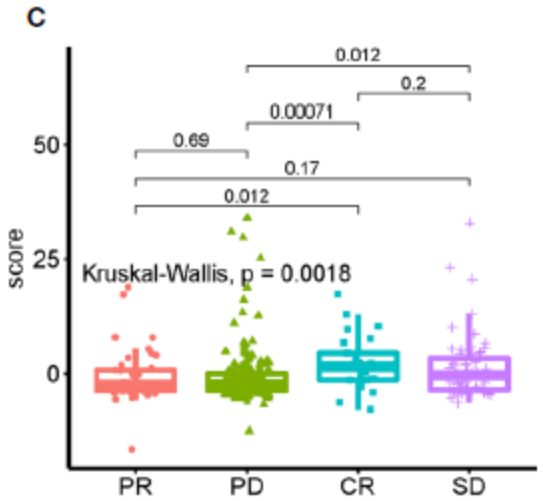












Liu J. et al., Frontiers in Immunology, 2021

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PD-L1 staining conundrum

COMBINED POSITIVE SCORE - CPS Definition

This scoring method evaluates the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) relative to all viable tumor cells.

CPS Calculation

$$\text{CPS} = \frac{\text{\# of PD-L1–positive cells}}{\text{Total \# of PD-L1–positive + PD-L1–negative tumor cells}} \times 100$$

Although the result of the CPS calculation can exceed 100, the maximum score is defined as CPS 100.

A minimum of 100 viable tumor cells in the PD-L1–stained slide is required for the specimen to be considered adequate for PD-L1 evaluation.

TUMOR PROPORTION SCORE - TPS Definition

This scoring method evaluates the percentage of viable tumor cells showing partial or complete membrane staining at any intensity.

TPS Calculation

$$\text{TPS (\%)} = \frac{\text{\# of PD-L1–positive tumor cells}}{\text{Total \# of PD-L1–positive + PD-L1–negative tumor cells}} \times 100$$

PD-L1 expression level in advanced NSCLC is determined by the TPS, which is reported as a percentage on a scale of 0% to 100%.

A minimum of 100 viable tumor cells in the PD-L1–stained slide is required for the specimen to be considered adequate for PD-L1 evaluation.

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https://www.keytrudahcp.com/biomarker-testing

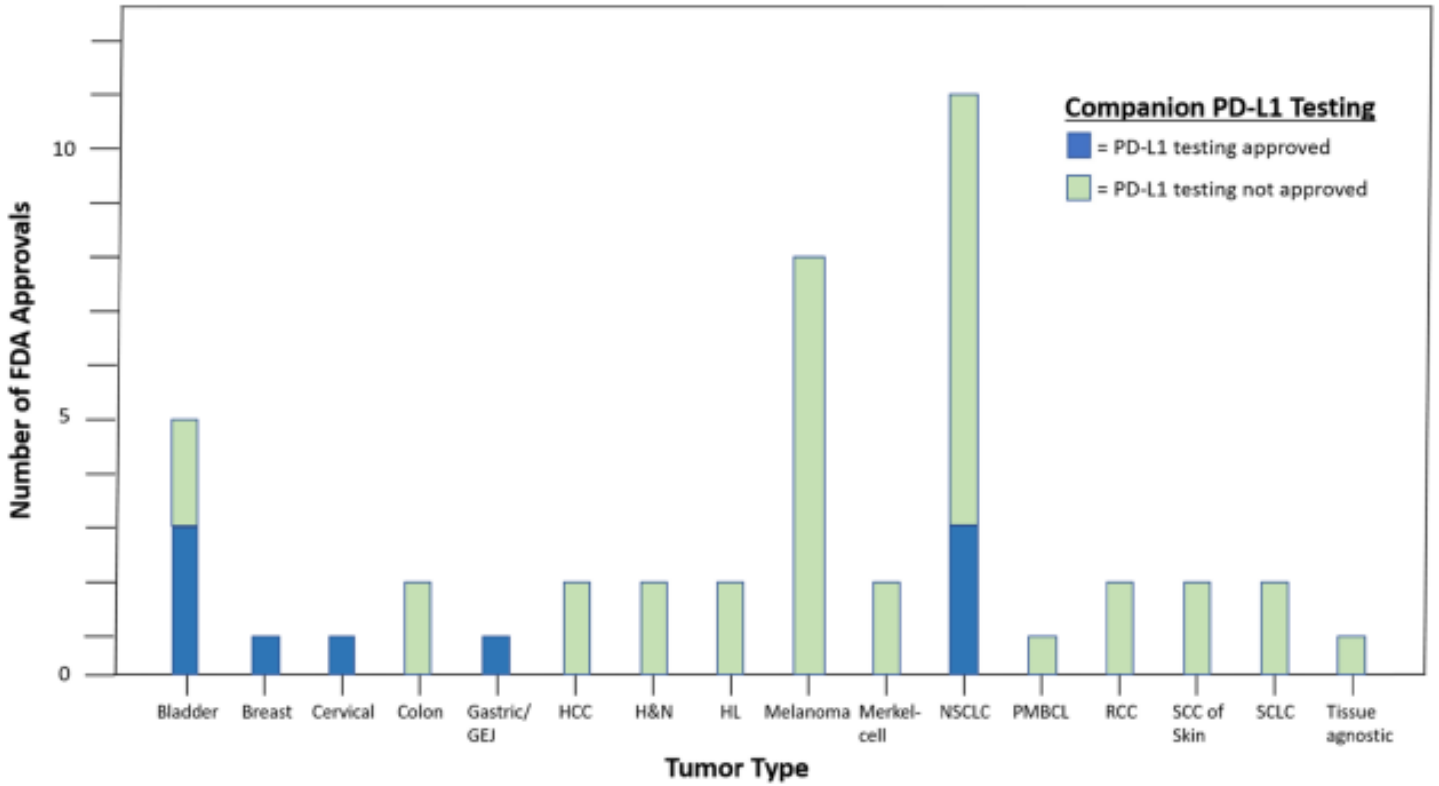
Companion PD-L1 testing

Different cut-offs

TPS > 1%: Advanced Non-Small Cell Lung Cancer (NSCLC) uses, Ovarian cancer MISP studies

CPS>1% : Advanced Cervical Cancer
Metastatic or Unresectable, Recurrent Head and Neck Squamous Cell Carcinoma (HNSCC)

CPS> 10%: Advanced Esophageal or GEJ Carcinoma
Advanced TNBC or High-Risk Early-Stage Triple-Negative Breast Cancer (TNBC)



Ovarian cancer: KN-100, Javelin studies, MISP studies – PD-L1 expression is NOT predictive biomarker to ICB response

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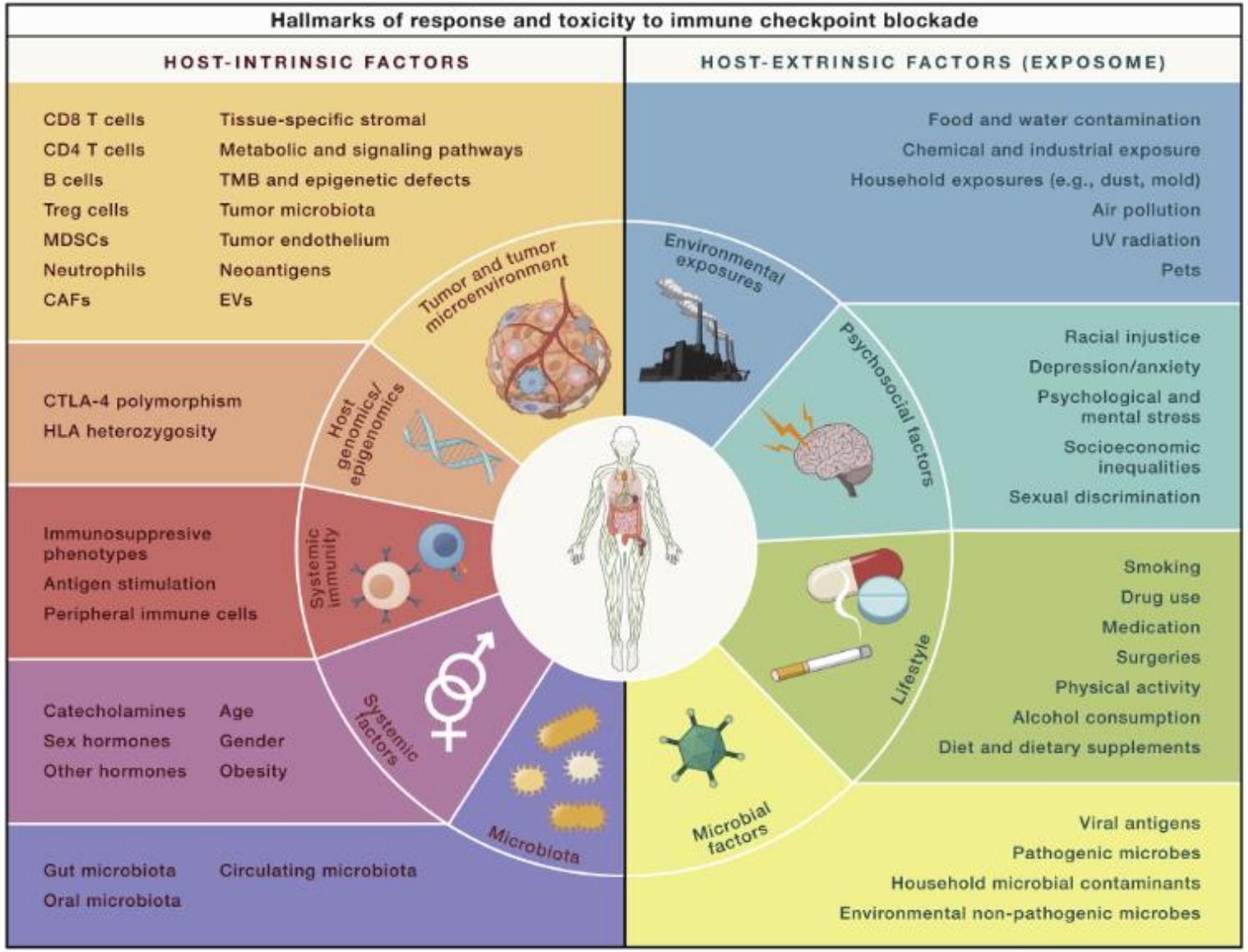
Davis A. et al, Journal of Immunotherapy of Cancer, 2019

HOST FACTORS



Morad et al., Cell, 2021

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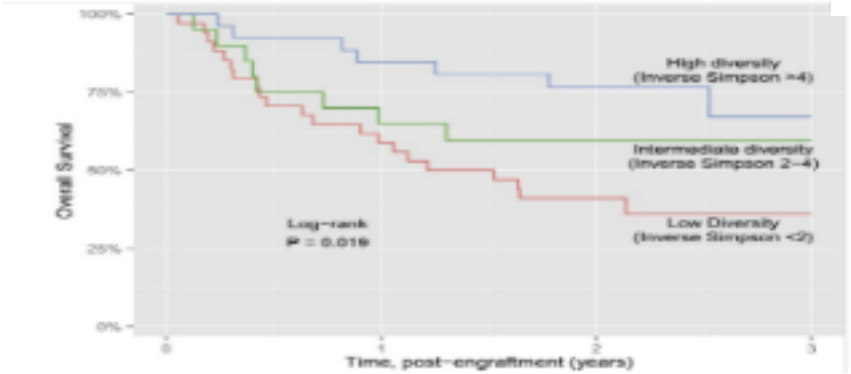
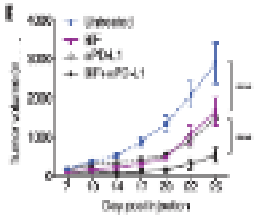
Early studies supported a role for gut microbes in shaping response to ICB

Diversity and composition of the gut microbiome are associated with differential outcomes to stem cell transplant (in patients) and immune checkpoint blockade (in mice)

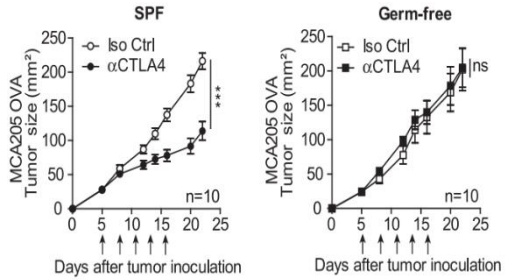


Taur…Pamer Blood 2014

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

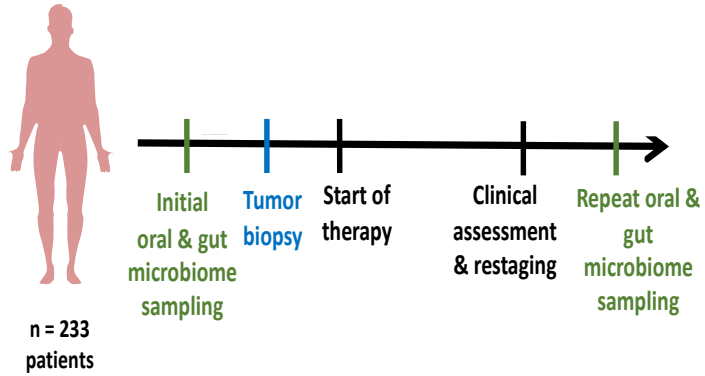


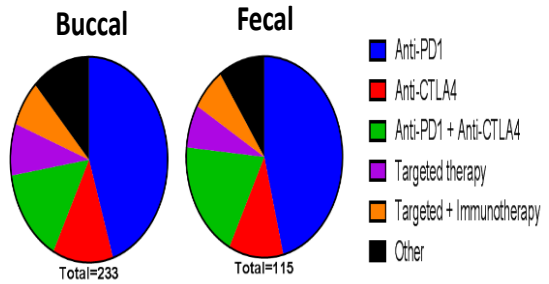
Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

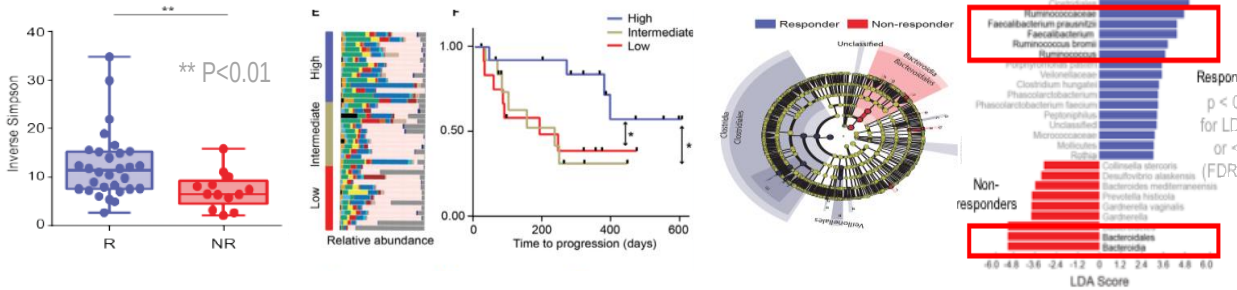


Sivan…Gajewski Science 2015, Vetizou…Zitvogel Science 2015

Diversity and composition of the gut microbiome are associated with differential outcomes to immune checkpoint blockade in patients with melanoma







Responders to anti-PD-1 had a higher diversity of gut bacteria associated with prolonged PFS (along with additional compositional differences)

Routy…Zitvogel et al, Science 2018

and many more studies now published…

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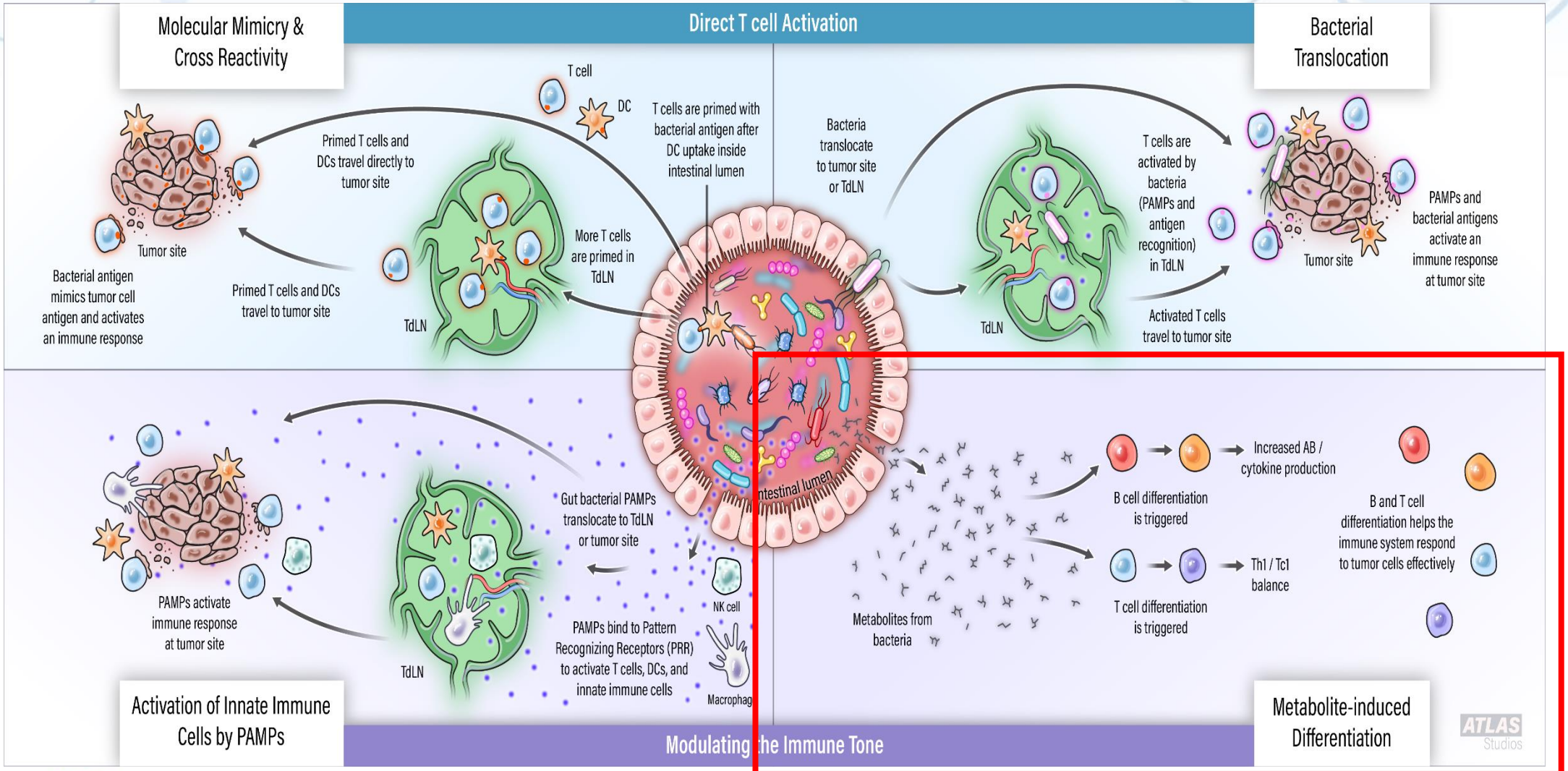
Bacterial metabolites as an important modulators of immune system



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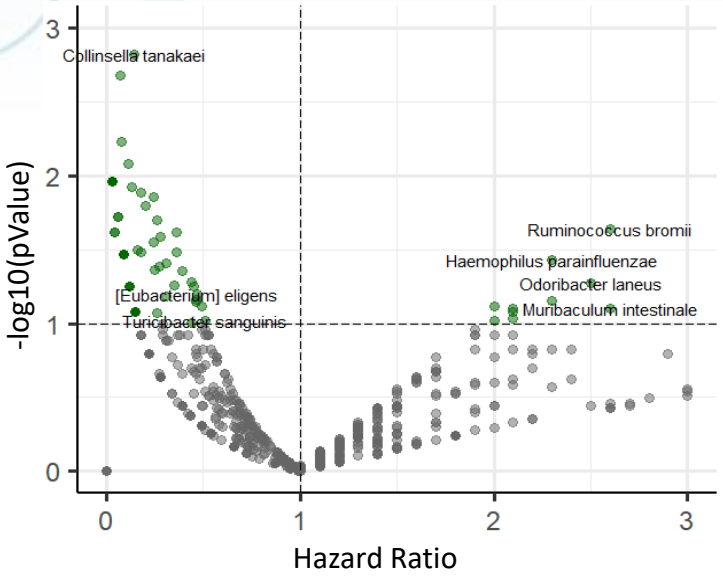
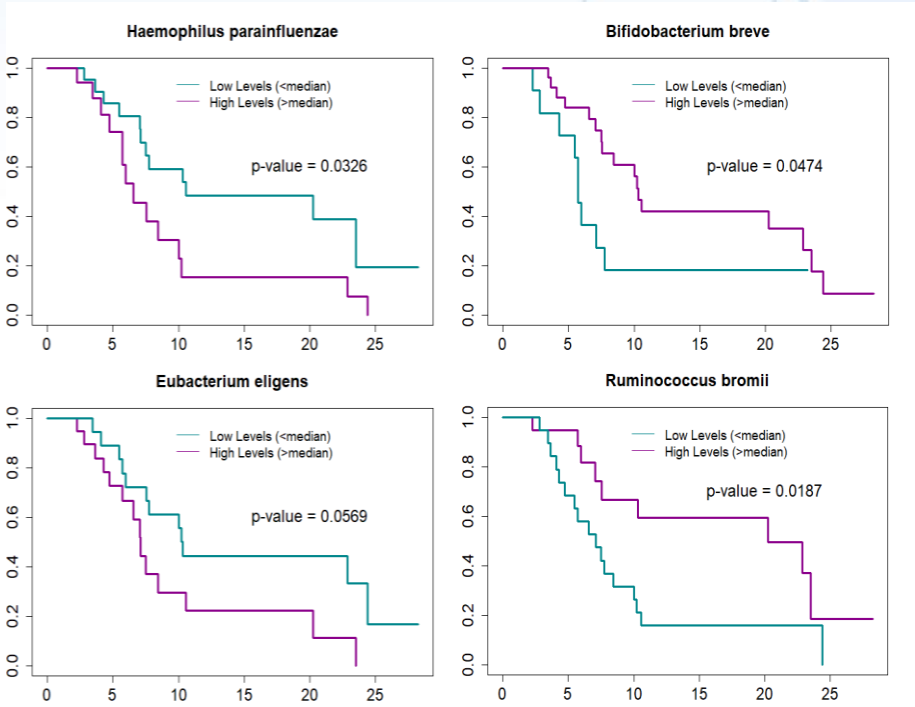
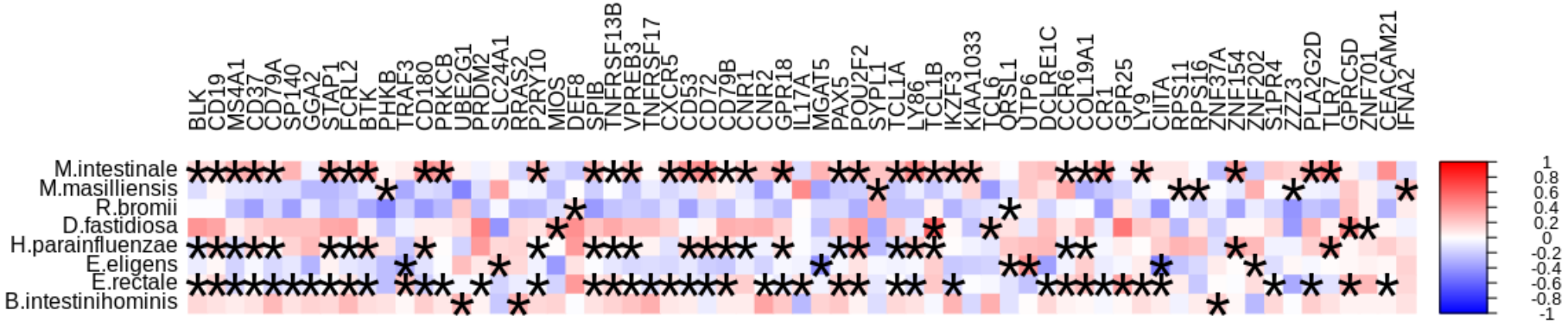
Chilakapati SR. et al., 2020

Stool microbiome analysis from NCT02853318







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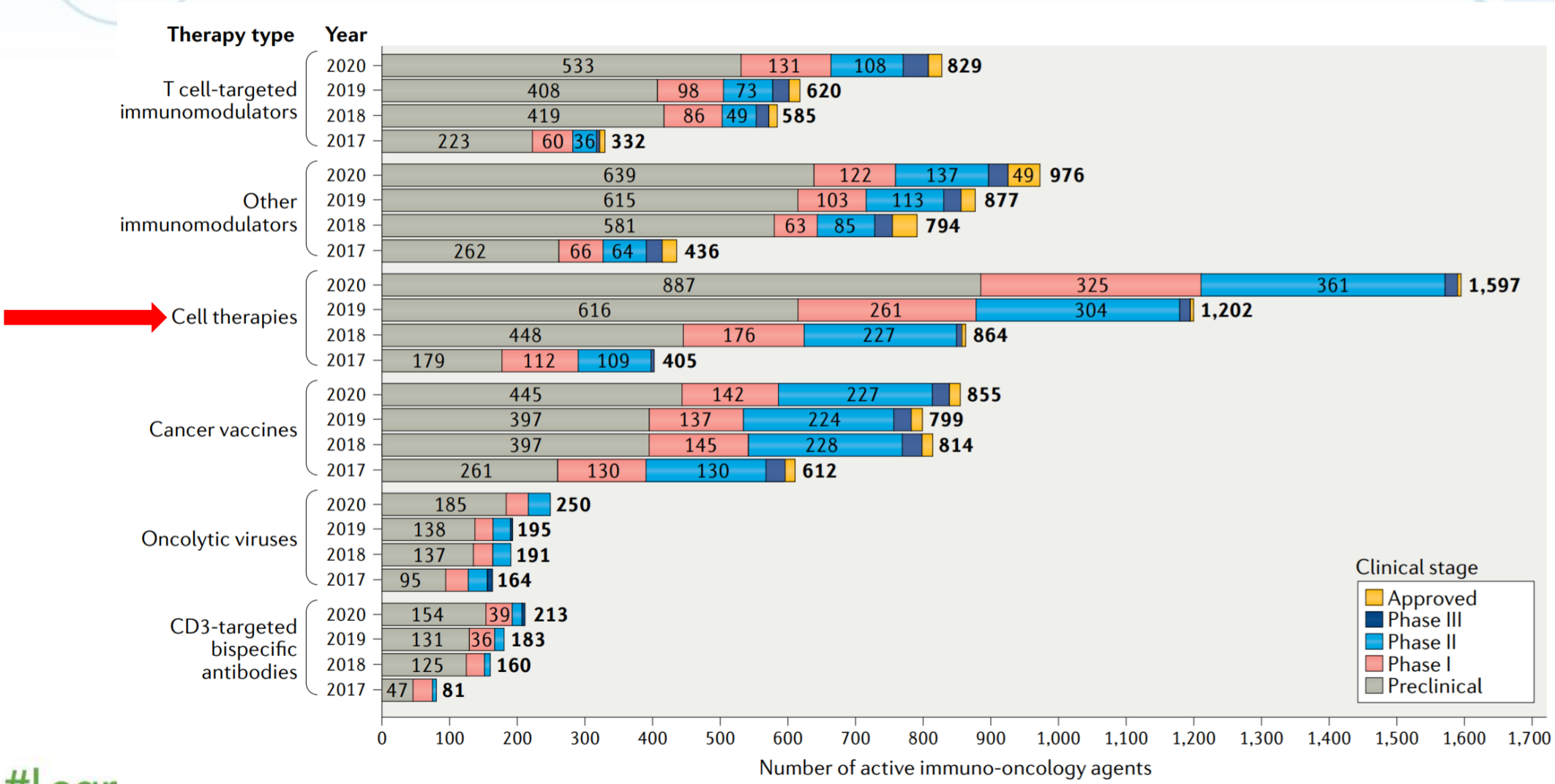
Rosario and Zsiros et al, manuscript in preparation

The Future: IO Drug Development



Upadhaya S, Nat.Rev. Drug Discovery, 2020

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Biostatisticians:
Kris Attwood
Katy Wang

Patients and their families