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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast & Gynecologic Cancers

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AAEM™ AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Consulting Fees paid to institution only (no personal fees) from: Pfizer, Genentech/Roche, Lilly, Puma Biotechnology, Daiichi Sankyo, Mersana Therapeutics, Boehringer Ingelheim, AstraZeneca, Novartis, Silverback Therapeutics, Black Diamond
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- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy in breast and gynecologic cancers

- Standard-of-care treatment usually involves surgery, chemotherapy, radiation
- Immunotherapy has not been standard of care like other tumor types (melanoma, lung, bladder, etc.) and we are just getting approvals now.

Est new cases

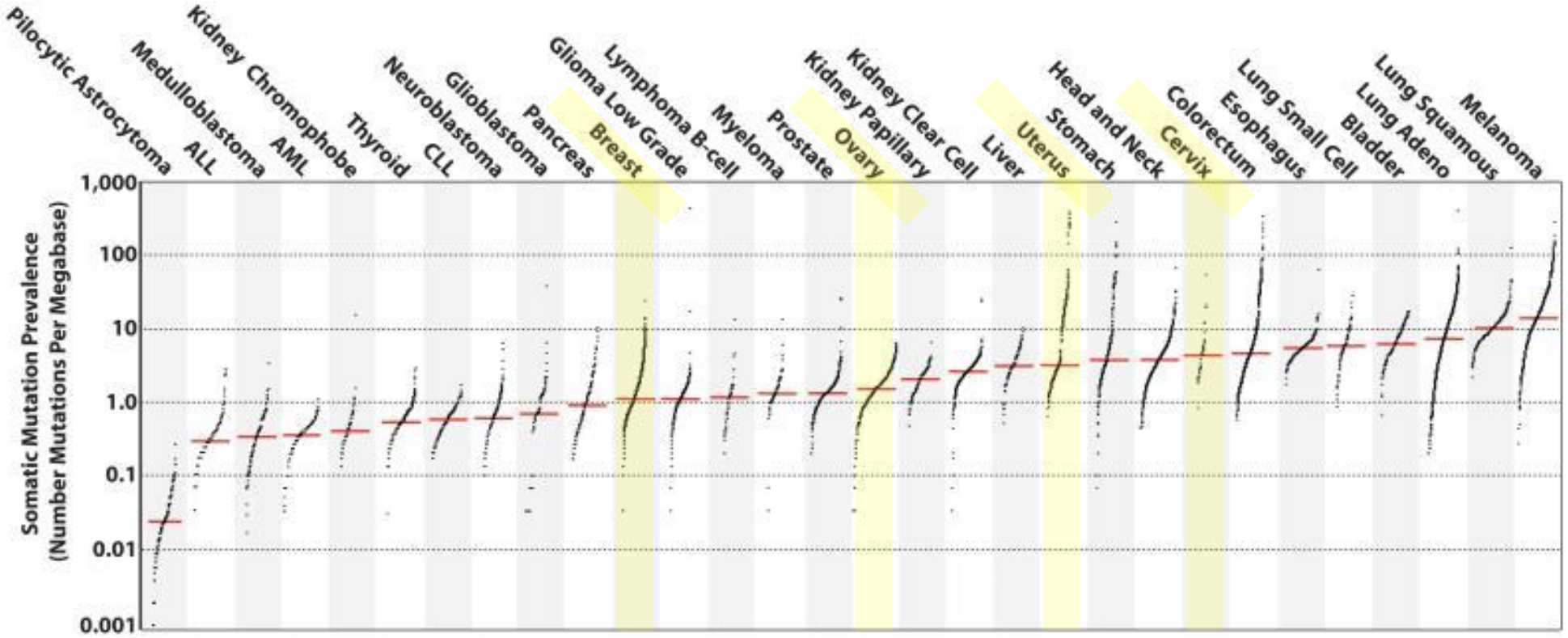
Female		
Breast	268,600	30%
Lung & bronchus	111,710	13%
Colon & rectum	67,100	7%
Uterine corpus	61,880	7%
Melanoma of the skin	39,260	5%
Thyroid	37,810	4%
Non-Hodgkin lymphoma	33,110	4%
Kidney & renal pelvis	29,700	3%
Pancreas	26,830	3%
Leukemia	25,860	3%
All sites	**891,480**	

Est deaths

Female		
Lung & bronchus	66,020	23%
Breast	41,760	15%
Colon & rectum	23,380	8%
Pancreas	21,950	8%
Ovary	13,980	5%
Uterine corpus	12,160	4%
Liver & intrahepatic bile duct	10,180	4%
Leukemia	9,690	3%
Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	7,850	3%
All sites	**285,210**	

American Cancer Society

Immunotherapy in breast and gynecological cancers

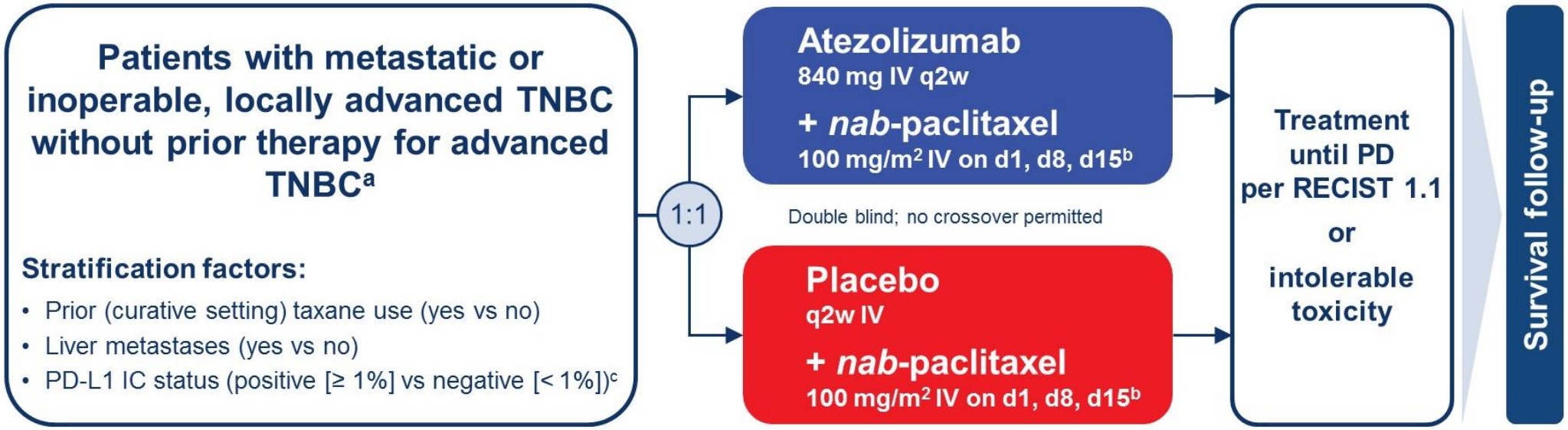


Alexandrov, Nature 2013.

Current approvals

Drug	Approved	Indication	Dose
HPV vaccination	2006 and many subsequent	Prevention of HPV infection	Depends on product
Pembrolizumab	2017	MSI-H/dMMR **advanced cancer** with progression on previous treatment (includes especially **endometrial**)	200 mg Q3W
Pembrolizumab	2018	Recurrent/metastatic **cervical cancer** with PD-L1 (CPS ≥1) and progression on previous therapy	200 mg Q3W
Atezolizumab + nab-paclitaxel or paclitaxel protein-bound	2019	Advanced/Metastatic **TNBC** with PD-L1 ≥1%	840 mg atezolizumab + 100 mg/m^2 paclitaxel
Pembrolizumab + lenvatinib	2019	**Endometrial cancer** – not MSI-H/dMMR, after progression on systemic therapy	Pembrolizumab 200 mg Q3W + lenvatinib 20 mg daily

Clinical Data – IMpassion130 PD-L1+ TNBC

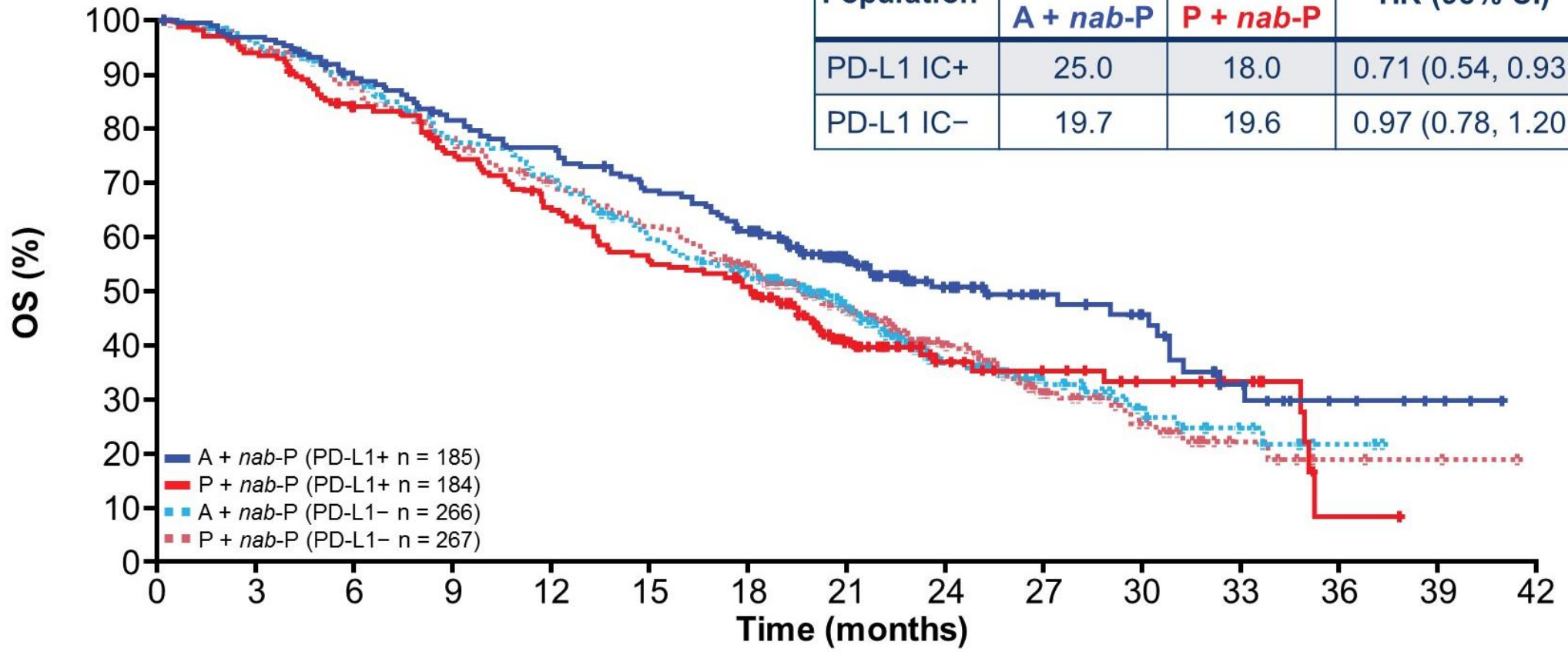


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

Clinical Data – IMpassion130 PD-L1+ TNBC

Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Schmid, ASCO 2019.

Performance of PD-L1 IHC assays - IMpassion 130

IMpassion-130: Atezolizumab + nab-paclitaxel demonstrated clinical benefit in PD-L1+ mTNBC vs placebo/nab-paclitaxel

- **PD-L1 expression on immune cells (IC) was evaluated using the VENTANA PD-L1 SP142 IHC assay with a ≥ 1% cutoff**

The SP 142 assay has been clinically validated and FDA-approved to identify patients with mTNBC for treatment with atezolizumab + *nab*-paclitaxel

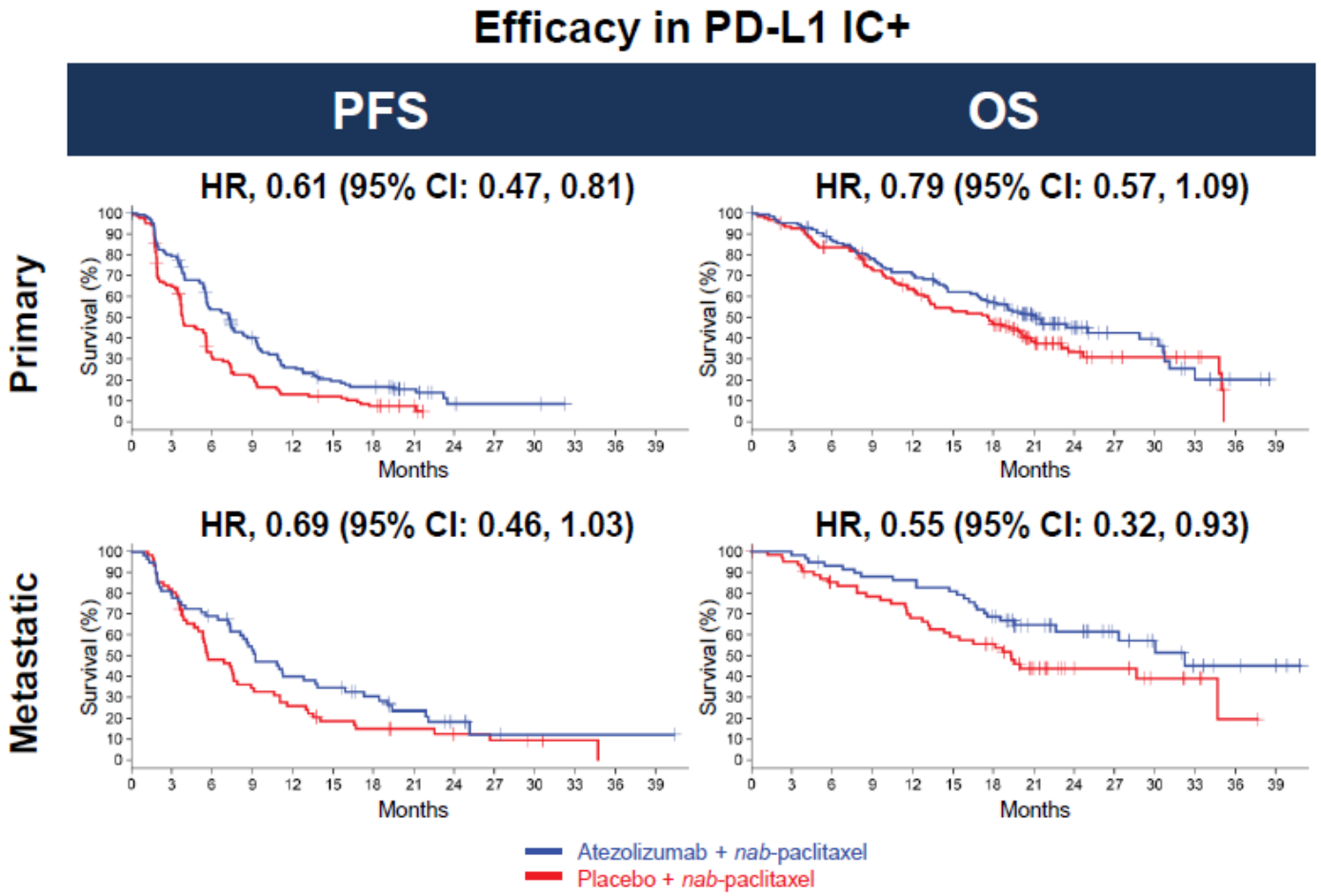
– Dako 22C3a and VENTANA SP263 are 2 other commercially available PD-L1 IHC assays approved for non-TNBC indications

- Have not shown direct overlap at all with SP142

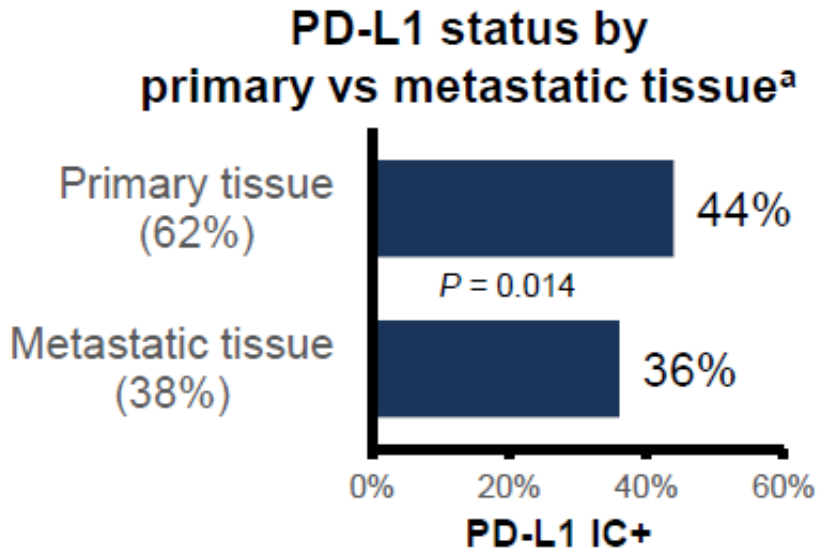
IC= Immune cells

Rugo et al. ESMO 2019, Abstract 6571

PD-L1 status in primary vs metastatic breast tissue

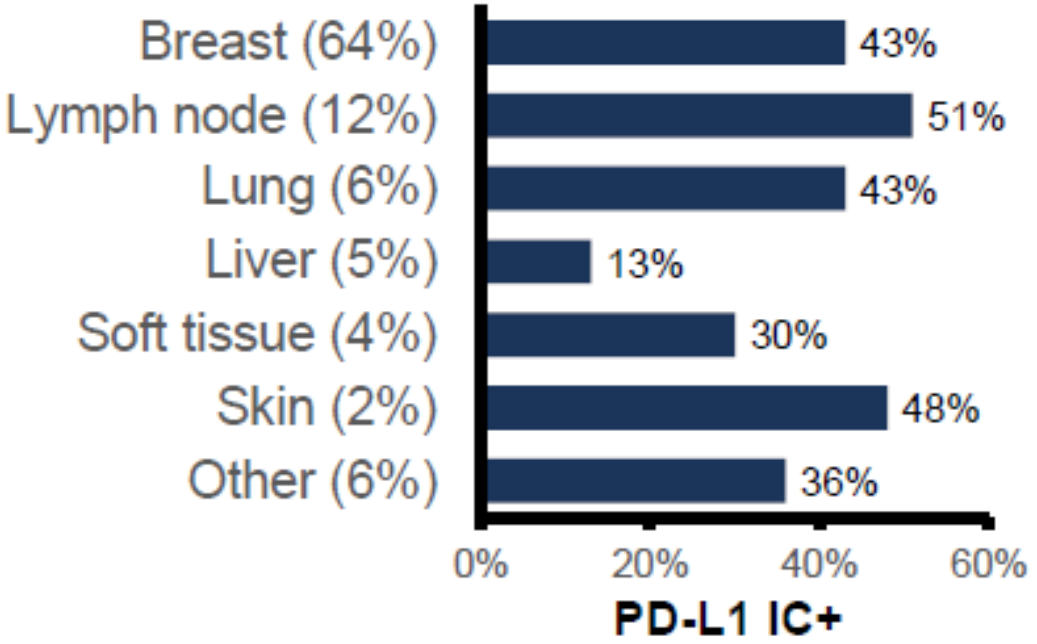


- Median time of sample collection to randomization: 61 days



Rugo et al. ESMO 2019, Abstract 6571

PD-L1 status by anatomic location

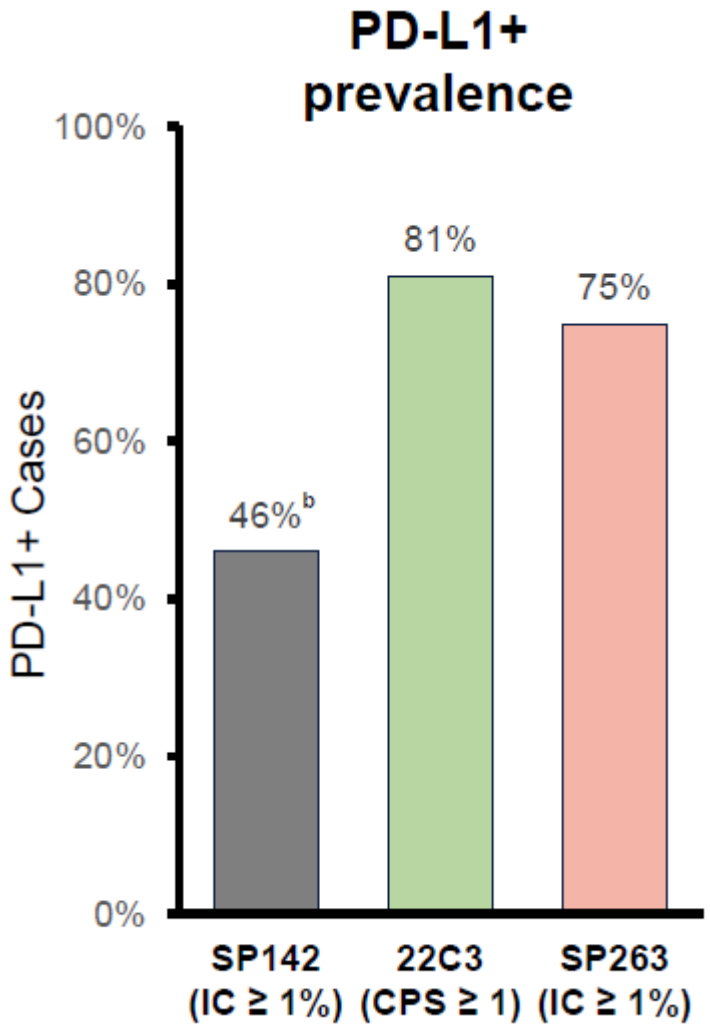


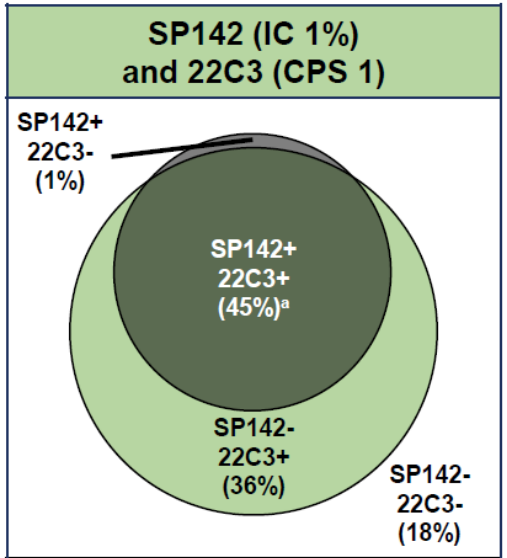
PD-L1 status evaluated by Ventana SP 142 assay

Hence evaluating PD-L1 expression from primary tumors or certain metastatic sites may be more informative

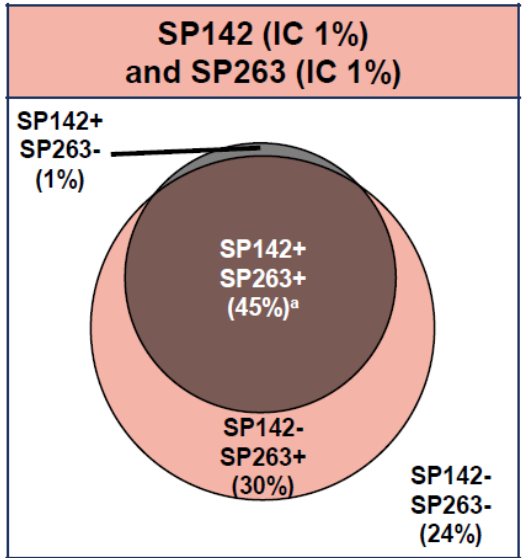
Rugo et al. ESMO 2019, Abstract 6571

PD-L1 IHC assays: Prevalence and analytical concordance





OPA[c]	64%
PPA	98%
NPA	34%



OPA[c]	69%
PPA	98%
NPA	45%

Overall agreement between SP142 and 22C3 and SP263 assays but the analytical concordance was subpar (<90%)

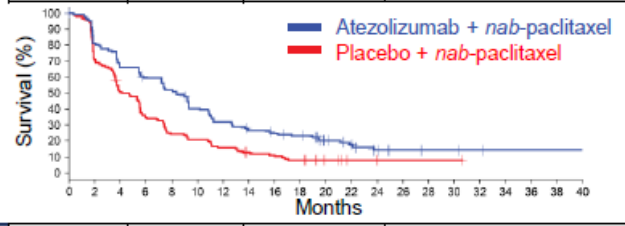
22C3 (CPS ≥ 1) and SP263 (IC ≥ 1%) PD-L1 assays identified a larger patient population of which SP142+ (IC ≥ 1%) is a subgroup

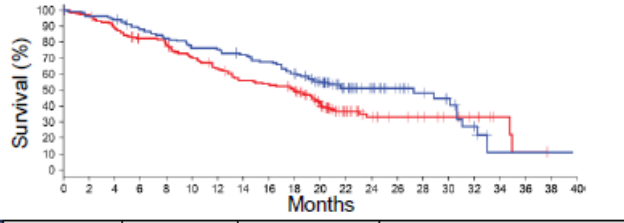
NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.
[a] > 97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT (Schmid, *New Engl J Med* 2018).
[c] ≥ 90% OPA, PPA ***and*** NPA required for analytical concordance.

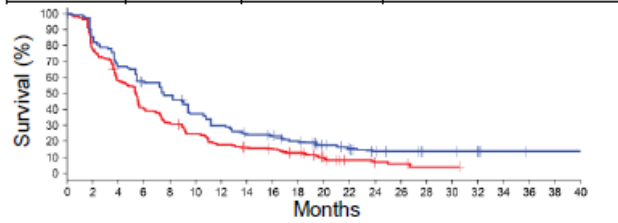
Rugo et al. ESMO 2019, Abstract 6571

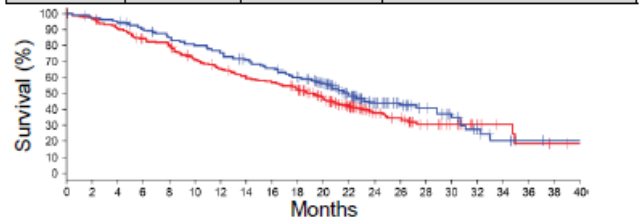
Clinical outcomes in PD-L1 + populations

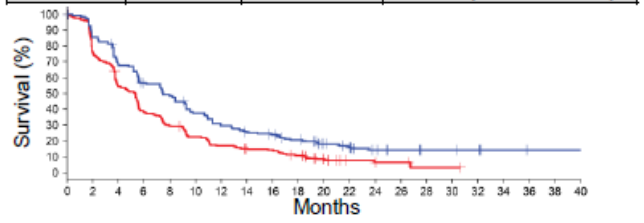
Population	PFS				OS			
	Median PFS, mo			HR (95% CI)	Median OS, mo			HR (95% CI)
	A + nP	P + nP	Δ		A + nP	P + nP	Δ	
SP142 **IC ≥ 1%: 46%** **(285/614)**	8.3	4.1	4.2	0.60 (0.47, 0.78)	27.3	17.9	9.4	0.74 (0.54, 1.01)
22C3 **CPS ≥ 1: 81%** **(497/614)**	7.5	5.4	2.1	0.68 (0.56, 0.82)	21.6	19.2	2.4	0.78 (0.62, 0.99)
SP263 **IC ≥ 1%: 75%** **(460/614)**	7.5	5.3	2.2	0.64 (0.53, 0.79)	22.0	18.7	3.3	0.75 (0.59, 0.96)

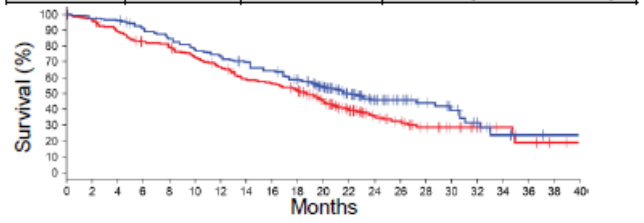








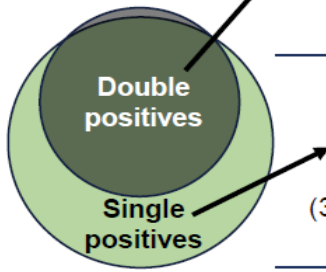




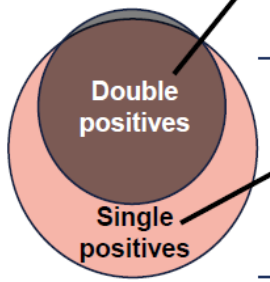
Rugo et al. ESMO 2019, Abstract 6571

Clinical outcomes in BEP subpopulations

BEP: Biomarker evaluable population (N=614)



Population	Median PFS, months			HR (95% CI)
	A+nP	P+nP	D	
SP142+ 22C3+ (45%; 279/614)	8.3	3.9	4.4	0.60 (0.46, 0.78)
SP142- 22C3+ (36%; 218/614)	7.3	5.6	1.7	0.81 (0.61, 1.09)
SP142- 22C3- (18%, 111/614)	5.5	5.6	-0.1	1.00 (0.66, 1.51)

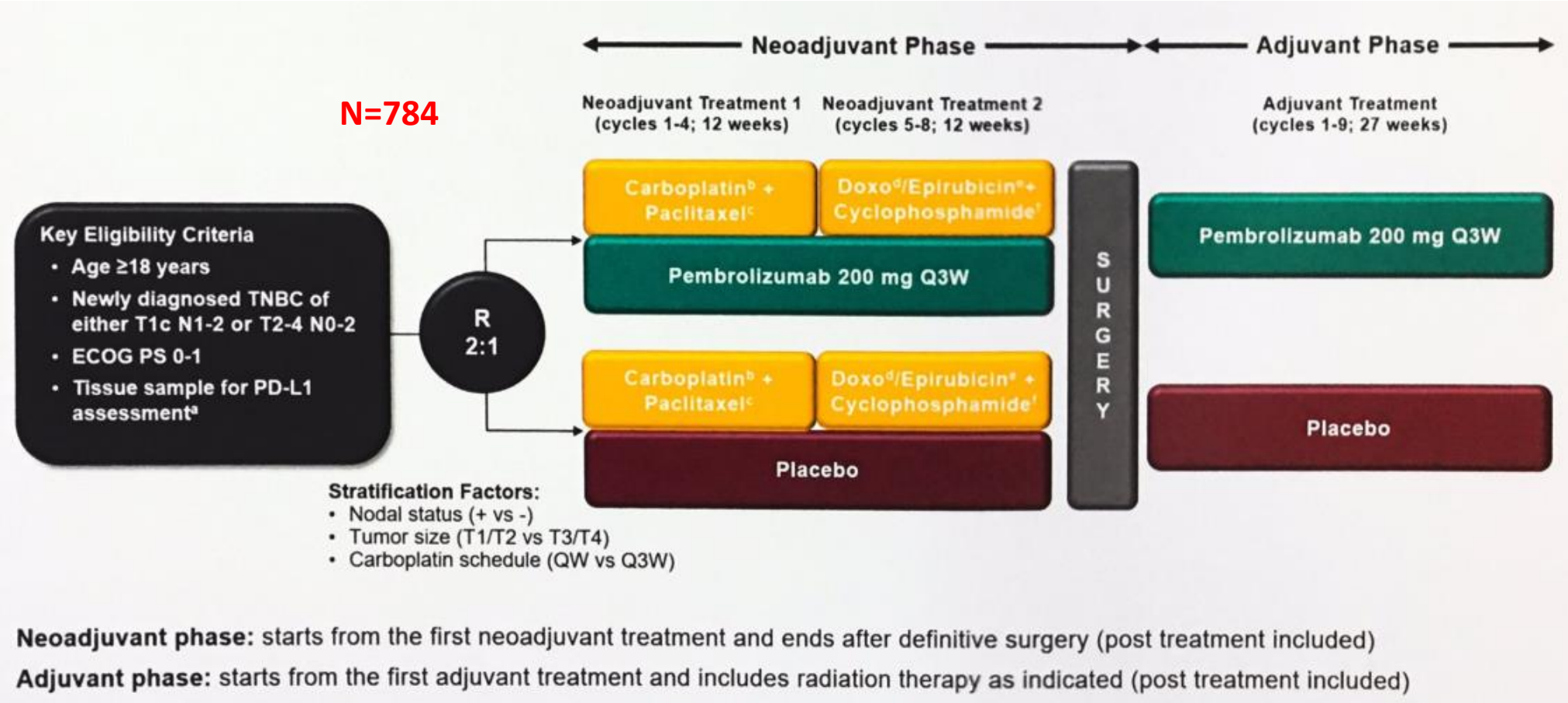


Population	Median PFS, months			HR (95% CI)
	A+nP	P+nP	D	
SP142+ SP263+ (45%; 278/614)	8.3	4.1	4.2	0.61 (0.47, 0.79)
SP142- SP263+ (30%; 182/614)	7.0	5.4	1.6	0.68 (0.49, 0.94)
SP142- SP263- (24%; 147/614)	5.5	6.9	-1.4	1.13 (0.79, 1.61)

Clinical benefit in 22C3+ and SP263+ subgroups driven by the SP142+ subgroup

Rugo et al. ESMO 2019, Abstract 6571

KEYNOTE-522: Neoadjuvant Pembrolizumab + chemo for TNBC

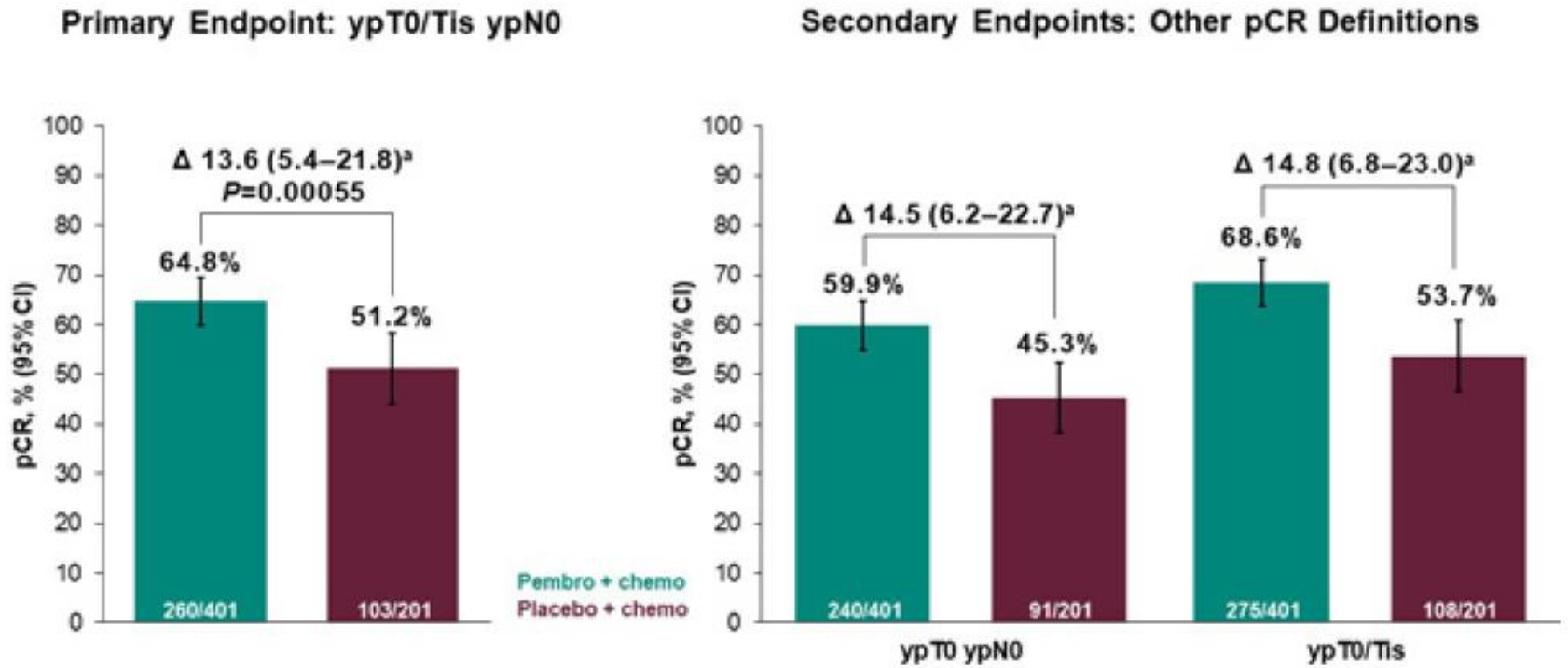


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

KEYNOTE-522: Primary and secondary endpoints

13% improvement in pCR rate with addition of pembro to standard chemo (64.8% vs 51.2%, p 0.00055)

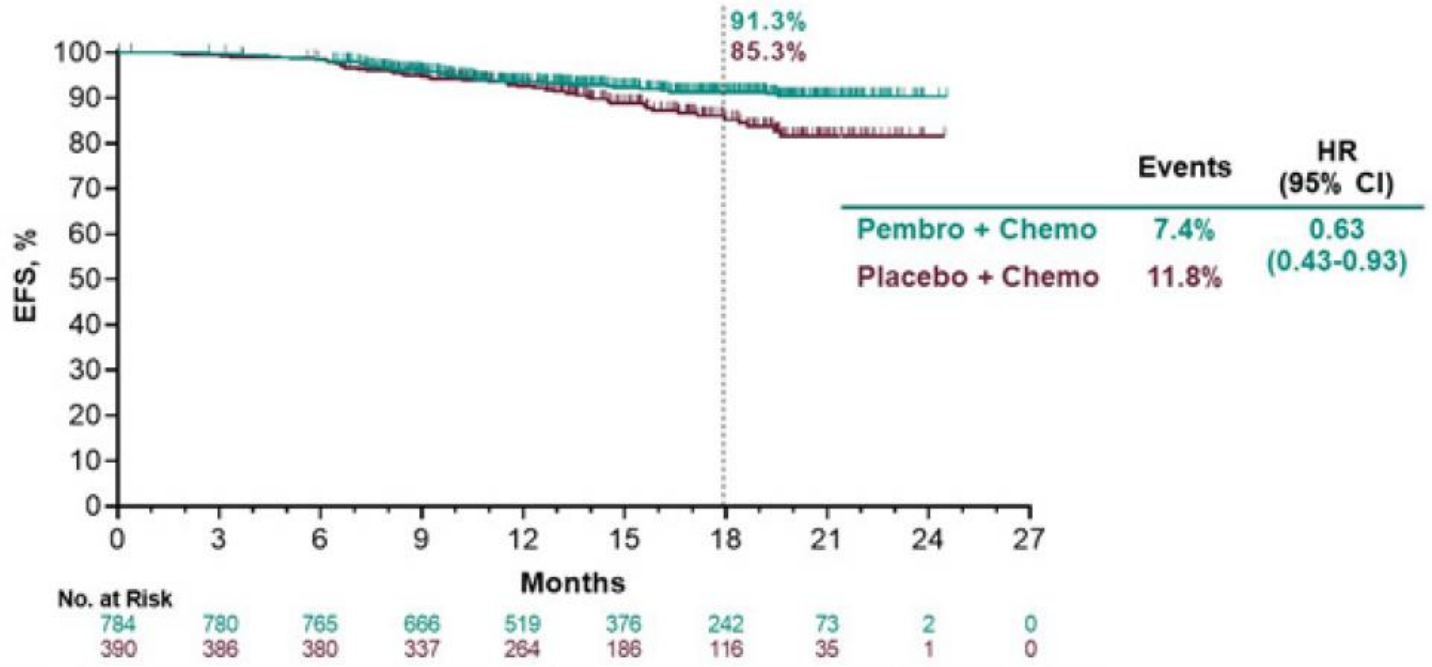


[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors.
Data cutoff date: September 24, 2018.

pCR rates were higher in the pembro group in both PD-L1 positive and negative subgroups

KEYNOTE-522: Event-free survival

Median follow up:
15.5 months



Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors.
Data cutoff April 24, 2019.

Favorable trend in EFS observed in pts treated with pembro+chemo as neoadjuvant therapy followed by adjuvant pembro

If this trends holds up, this regimen is likely to become SOC for neoadjuvant TNBC

Clinical Data – KEYNOTE-158

Patients with advanced cervical cancer with progression on one or more standard therapies

ECOG 0-1
Measurable disease
No CNS metastases
No autoimmune disease
No prior checkpoint inhibitors

→

Pembrolizumab 200 mg Q3W

Up to two years

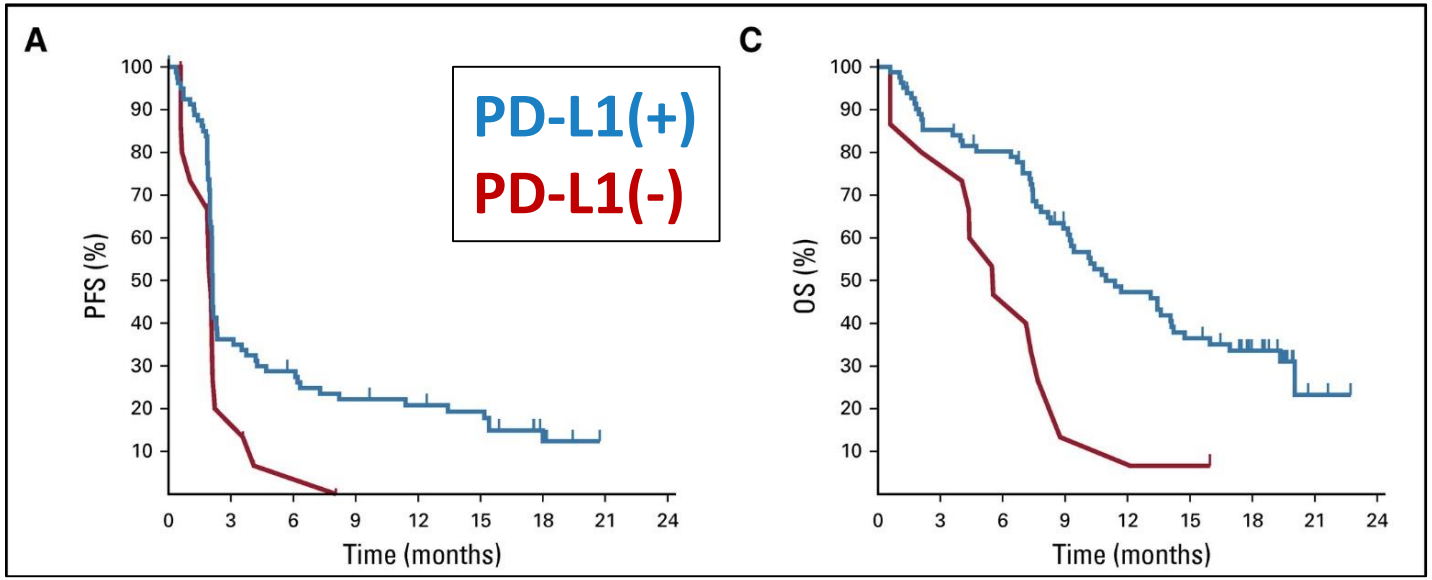
→

Primary: Objective response rate

Secondary: Duration of response; Progression-free survival; Overall survival

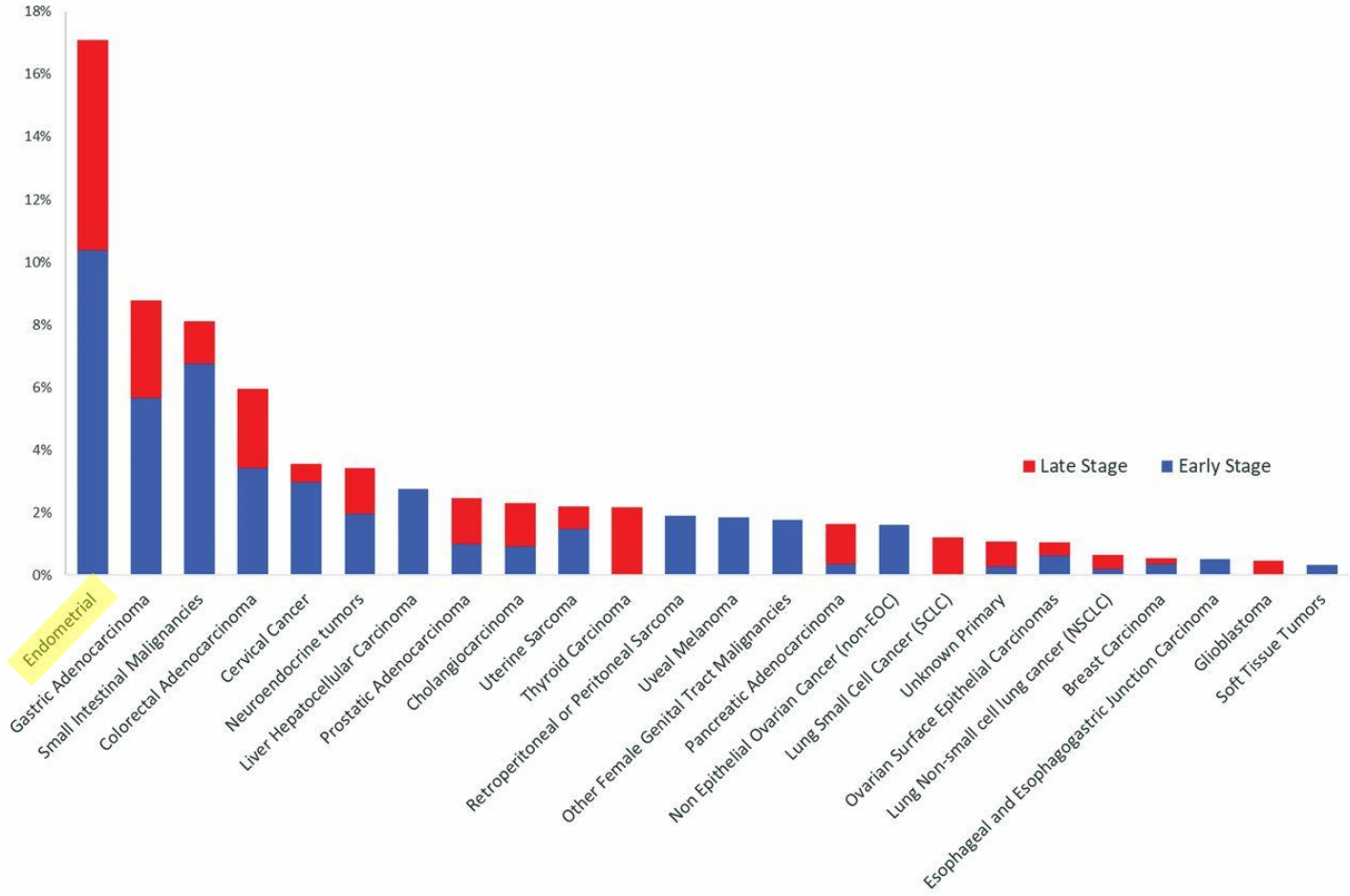
Clinical Data – KEYNOTE-158
Cervical Cancer

- 82/98 were PD-L1(+)
- @10 months: ORR – 14.6% (all in PD-L1(+) patients)
- mOS: 9.4 mo in total population; 11.0 mo in PD-L1(+)



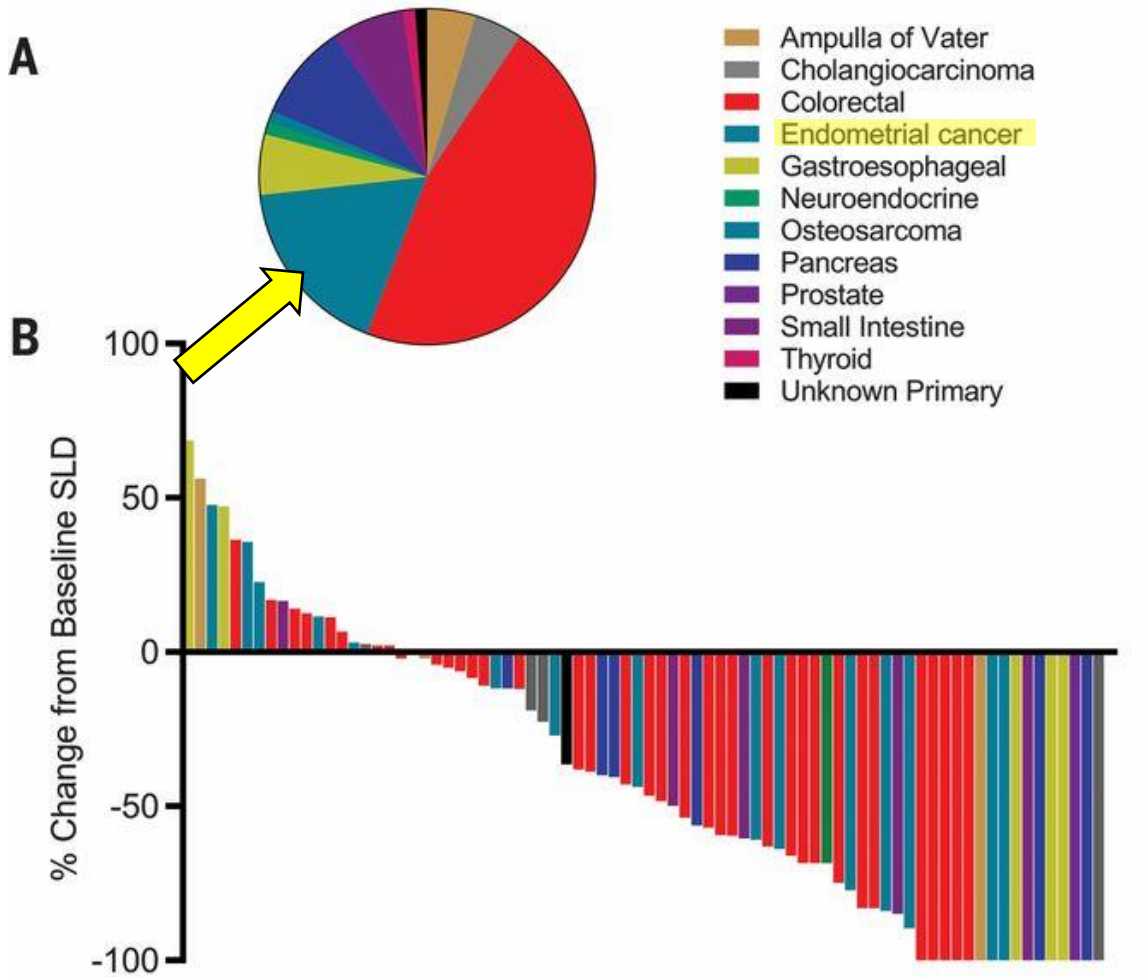
Cheol Chung, J Clin Oncol 2019.

Clinical Data – Pembrolizumab in MSI-high endometrial cancer



Le, Science 2017.

Clinical Data – pembrolizumab in MSI-high cancers



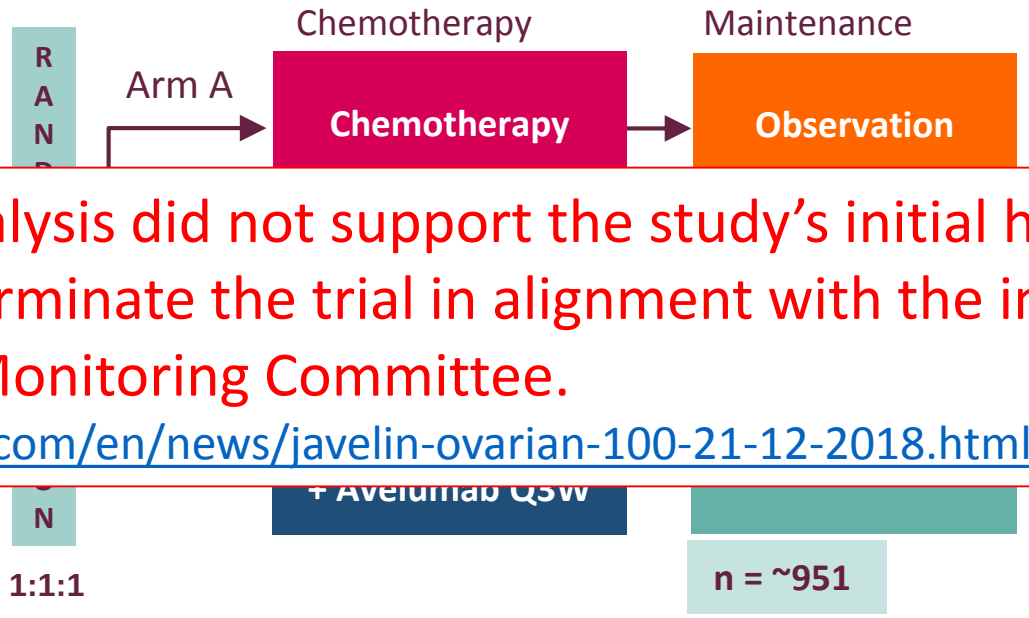
- NCT01876511
- 12 cancer types with dMMR
- ORR: 53%
- CR: 21%

Le, Science 2017.

JAVELIN Ovarian 100

Randomized Phase 3 Study (NCT02718417)

Enrollment Criteria



Dec 21, 2018: Planned interim analysis did not support the study's initial hypothesis, and therefore a decision was made to terminate the trial in alignment with the independent Data Monitoring Committee.

https://www.emdgroup.com/en/news/javelin-ovarian-100-21-12-2018.html

- ECOG PS 0 or 1
- Mandatory archival tissue

Primary Endpoint:	**PFS**
Secondary Endpoints:	**Maintenance PFS, OS, ORR, duration of response, pCR, PROs, safety**, PK

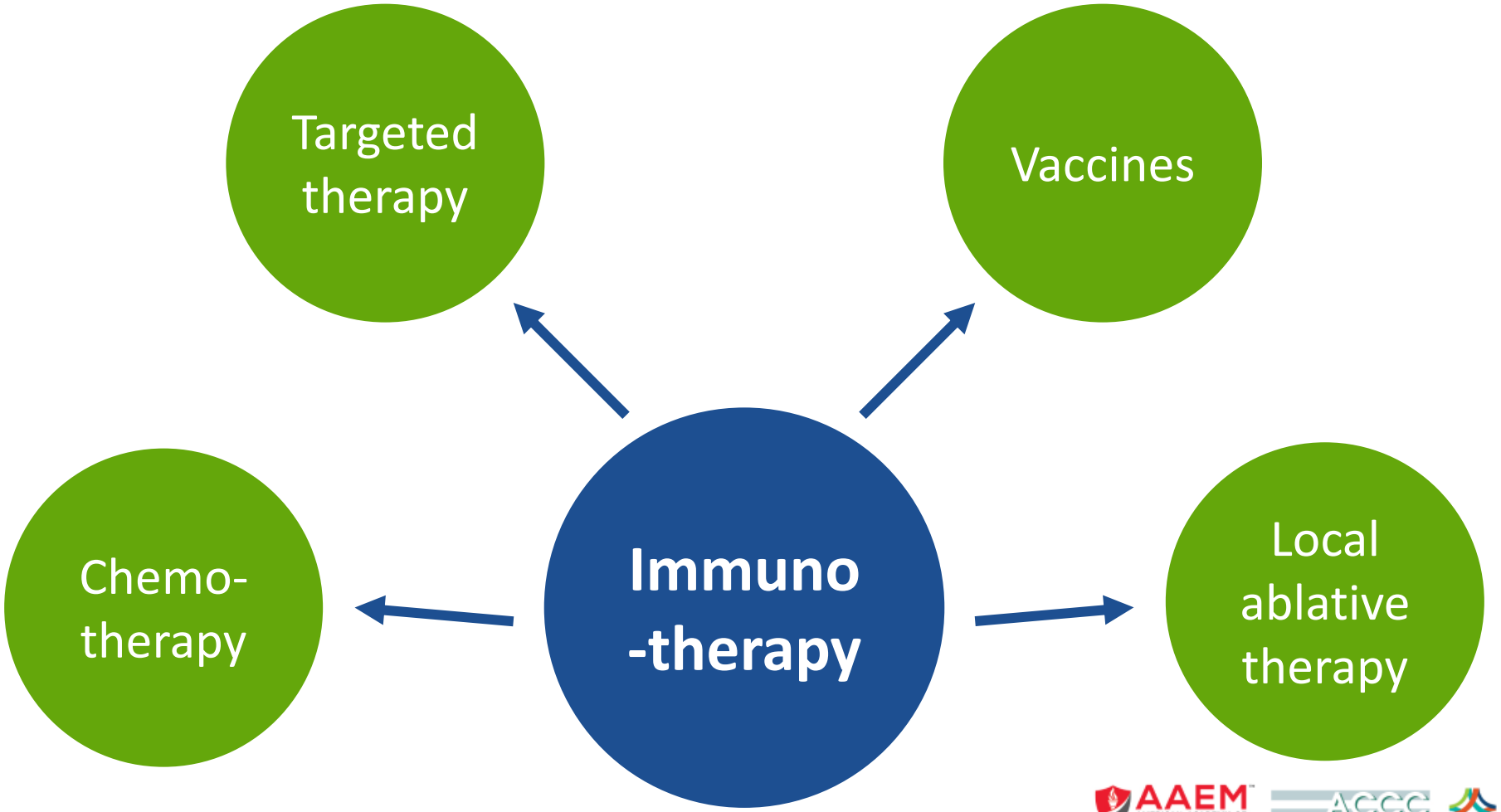
- Patients with SD or better will be allowed to continue to maintenance
- Chemotherapy: Choice of Q3W carboplatin-paclitaxel OR carboplatin + weekly paclitaxel
- Maintenance avelumab up to 2 years

ORR, overall response rate; OS, overall survival, pCR, pathological complete response; PFS, progression-free survival, PK, pharmacokinetics; PROs, patient-reported outcomes; SD, stable disease.

Clinicaltrials.gov. Accessed October 11, 2016.

Future Directions

In development: Breast cancer immunotherapy

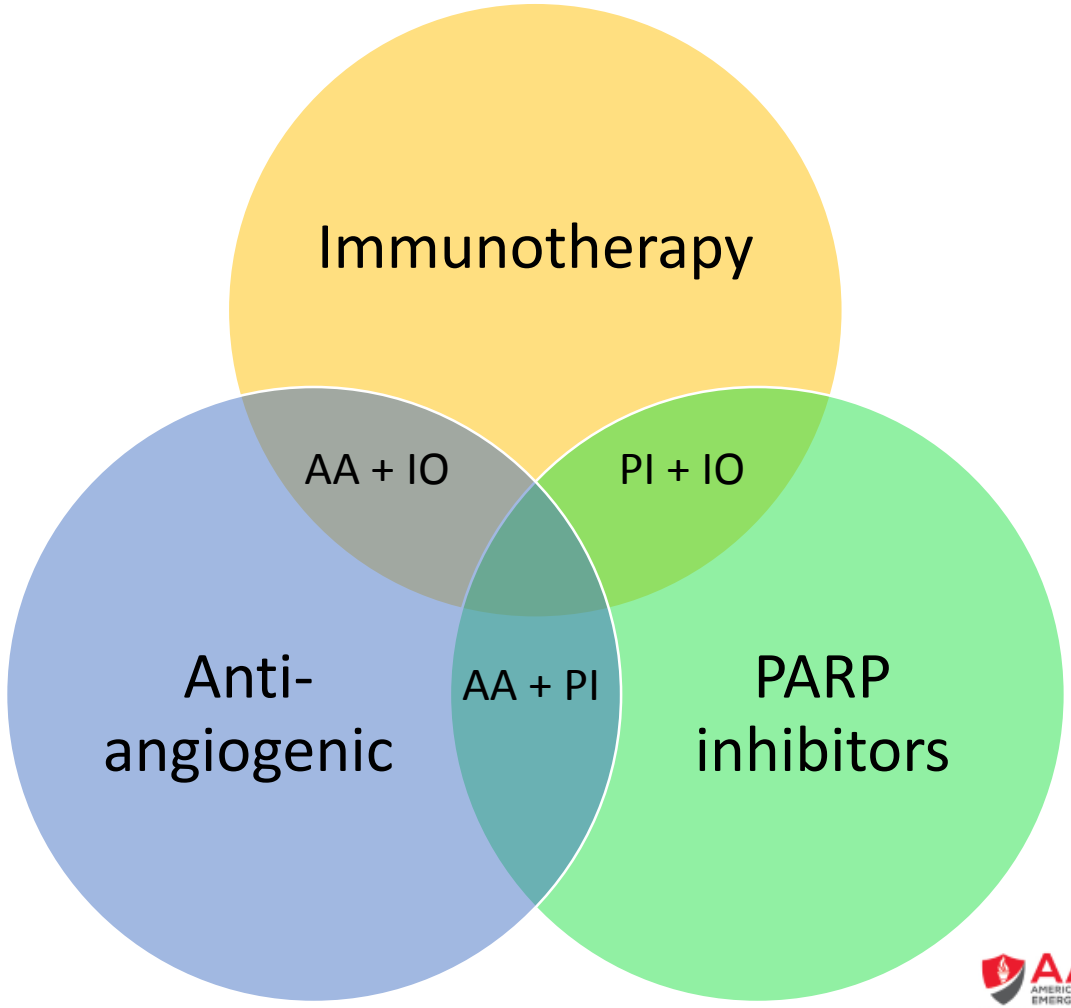


Adams, JAMA Oncol 2019.

Next Directions: Breast cancer immunotherapy

Trial	Population	Arms	Status
NCT03199885	1st line HER2+ metastatic breast cancer	• Pertuzumab + trastuzumab + paclitaxel + atezolizumab • Pertuzumab + trastuzumab + paclitaxel + placebo	Recruiting
KEYNOTE-756	Neoadjuvant ER+/HER2- breast cancer	• Pembrolizumab + chemo → pembrolizumab + endocrine therapy • Placebo + chemo → placebo + endocrine therapy	Recruiting
NCT03804944 /CBCV	Postmenopausal ER+/HER2- newly diagnosed breast cancer	• Hypofractionated RT • Hypofractionated RT + pembrolizumab • Hypofractionated RT + Ftl-3 ligand • Hypofractionated RT + Ftl-3 ligand + pembrolizumab	Planned
And many more			

In development: Therapeutic strategies in ovarian cancer



Clinical trials in ovarian cancer – Angiogenesis inhib + IO

Trial	Population	Arms	Status
IMaGYN050	Neo-adjuvant St III/IV ovarian, peritoneal, fallopian tube	• Bevacizumab + chemo + placebo • Bevacizumab + chemo + atezolizumab	Recruiting
ATALANTE	Recurrent, Pt-sensitive ovarian	• Bevacizumab + chemo + placebo → placebo • Bevacizumab + chemo + atezolizumab → atezolizumab	Recruiting
NRG-GY009	Recurrent, Pt-resistant ovarian	• PLD + atezolizumab • PLD + atezolizumab + bevacizumab • PLD + bevacizumab	Scheduled interim monitoring

Clinical trials in ovarian cancer – PARP + IO

Trial	Population	Arms	Status
JAVELIN Ovarian 100 PARP	Untreated St III/IV ovarian	• Chemo + avelumab → avelumab + talazoparib • Chemo → talazoparib • Chemo + bevacizumab → bevacizumab	Discontinued in 3/2019: - Poor outcomes in JAVELIN ovarian 100 in unselected patients - Approval of PARP inhibitor in frontline maintenance
ATHENA	St III/IV ovarian, peritoneal, fallopian tube – only previous treatment 1st line Pt	• Rucaparib + nivolumab • Rucaparib +placebo • Placebo + nivolumab • Placebo	Recruiting
ANITA	Recurrent ovarian, peritoneal, fallopian tube	• Chemo + placebo → Niraparib + placebo • Chemo + atezolizumab → Niraparib + atezolizumab	Recruiting

Clinical trials in ovarian cancer – PARP + angiogenesis inhibitors + IO

Trial	Population	Arms	Status
FIRST	Newly diagnosed ovarian	• Chemo + placebo ± bevacizumab → placebo ± bevacizumab • Chemo + placebo ± bevacizumab → niraparib + placebo ± bevacizumab • Chemo + anti-PD-1 ± bevacizumab → niraparib + anti-PD-1 ± bevacizumab	Recruiting
ENGOT-ov46/DUO-O	Newly diagnosed ovarian	• Chemo + placebo + bevacizumab → bevacizumab + placebo • Chemo + bevacizumab + durvalumab → bevacizumab + durvalumab + placebo • Chemo + bevacizumab + durvalumab → bevacizumab + durvalumab + olaparib	Recruiting
ENGOT-ov43	1st line ovarian	• Pembrolizumab + olaparib ± bevacizumab • Pembrolizumab + placebo ± bevacizumab • Placebo ± bevacizumab	Recruiting

Cervical cancer immunotherapy

Cervical cancer is primarily the result of persistent infection with high-risk types of HPV

HPV DNA is present in the majority of cervical cancer

HPV-associated tumors elicit an innate host immune response to the viral antigen
But…

HPV-associated cancers are excellent evaders of host immunity

Cervical cancers with cytotoxic T-cell infiltration enjoy a better prognosis

Why?
Evidence of some successful innate immune attack on the tumor

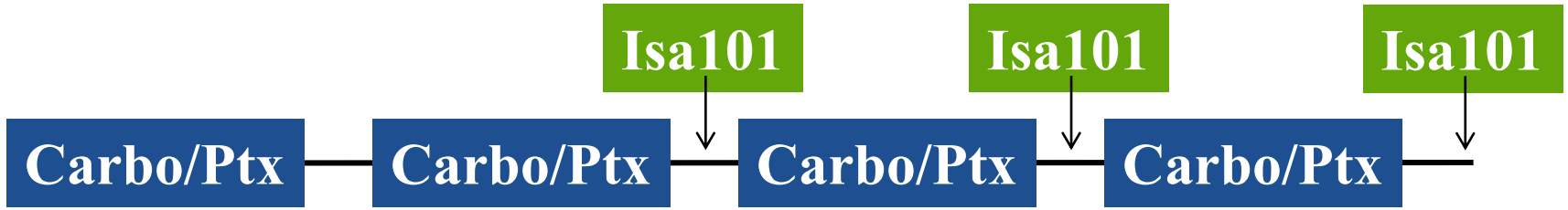
Cervical cancer immunotherapy opportunities:

- Inhibit the tumor-induced immunosuppression
- Stimulate HPV-targeted immune response

Jun-Han, BioDrugs 2010.
Piersma, Cancer Res 2007.

In development: HPV peptide therapeutic vaccination

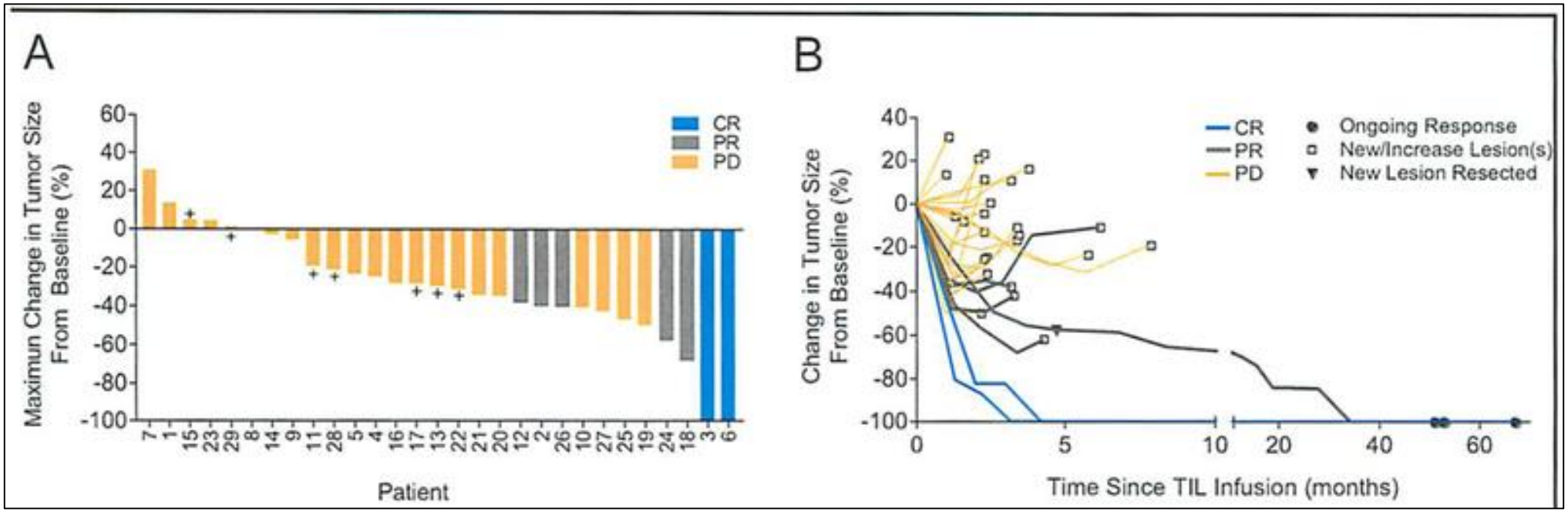
- Advanced cervical cancer
- ISA101 vaccine = 13 overlapping HPV16 (E6&7) synthetic long peptides
- N = 60 patients at 4 dose levels
- mOS not reached at two highest dose levels



Melief, ASCO-SITC 2017.

In development: Cell therapies in HPV-associated cancers

- TIL treatment of HPV+ cancers, ~half cervical cancer
- 28% ORR in cervical, 18% non-cervical



Stevanovic, Clin Cancer Res 2019.

Conclusions

- Immunotherapy in breast cancer shows promise in certain subtypes
- For ovarian cancer, combinations seem to be the way to go
- Cervical cancer and HPV-associated cancers present unique treatment options

Case Studies

Case Study 1

- Mrs. A is a healthy 52 year old female who palpated a lump in her right breast. She is evaluated by mammogram which shows a 2.5 cm mass and an enlarged 1.5 cm axillary lymph node.
- Biopsy of the breast and LN reveals triple negative breast cancer w/ ER0%, PR 0%, Her-2 1+ by ICH and ratio of 1.3 by FISH
- CT C/A/P and bone scan reveals several 1-2 cm liver lesions and enlarged mediastinal and hilar adenopathy, bone scan reveals lesions with the sacrum and bilateral ribs.
- Biopsy of the liver confirms TN metastatic breast cancer.

Case Study 1

What would you do next?

- A) start a bone modifying agent
- B) start single agent chemotherapy
- C) Start combination chemotherapy
- D) Test for PD-L1
- E) Both A and D

Case Study 1

- Correct answer is: E

- Ms. A should undergo testing for PD-L1 via Ventana's SP142 assay on immune cells.
- Bone modifying agent should be started due to presence of bone mets and utility in preventing fracture.

Case Study 1

What would you give her for systemic treatment?

a) Capecitabine
b) Gemcitabine/carboplatin
c) Nab-paclitaxel if PD-L1 +

Case Study 1

- Correct answer: C

- The addition of atezolizumab to nab-paclitaxel shows an improvement of overall survival for pts with TNBC that express PD-L1 via SP142 assay.

Case Study 2

You see Ms. C as a new consultation. She was diagnosed with a G2 , stage II endometrial cancer 18 months ago and was treated with surgery and 6 cycles of carboplatin/taxol. She was having belly pain and CT A/P at an outside facility showed enlarged lymph nodes in her abdomen and some strand peritoneal thickening.

Case Study 2

- What would you do next?
- A) Get a surgical opinion re: removing all the lymph nodes and debulking again
- B) Start doxorubicin chemotherapy
- C) Molecular profiling to include MSI status
- D) hospice, endometrial patients don’t respond well to chemotherapy

Case Study 2

- Correct answer is: C

- Molecular profiling to include MSI – status. Broad molecular profiling may be useful here as endometrial carcinomas also show an up to 40% PI3k mutation rate and drugs can be used off-label or on study to treat.

Case Study 2

- Molecular profiling shows MSI-H, p53 mutation, and an ARID1a amplification.

- How would you treat her:
- A) pembrolizumab
- B) Doxil
- C) carboplatin/taxol
- D) clinical trial with combination immunotherapy
- E) A or D

Case Study 2

- Answer: E

- Immunotherapy would likely be most appropriate for this patient – either with pembrolizumab which is approved or a combination immunotherapy clinical trial.