Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast & Gynecologic Cancers

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Disclosures

- Consulting Fees: AstraZeneca, GSK, Merck, Eisai, Roche
- Contracted Research: AstraZeneca, GSK
- I will be discussing non-FDA approved indications during my presentation.

Epidemiology

- Standard-of-care treatment usually involves Surgery, Chemotherapy & Radiation

- Application of immunotherapy is still in early stages

➔ Few indications in selected subgroup of patients

Est new cases

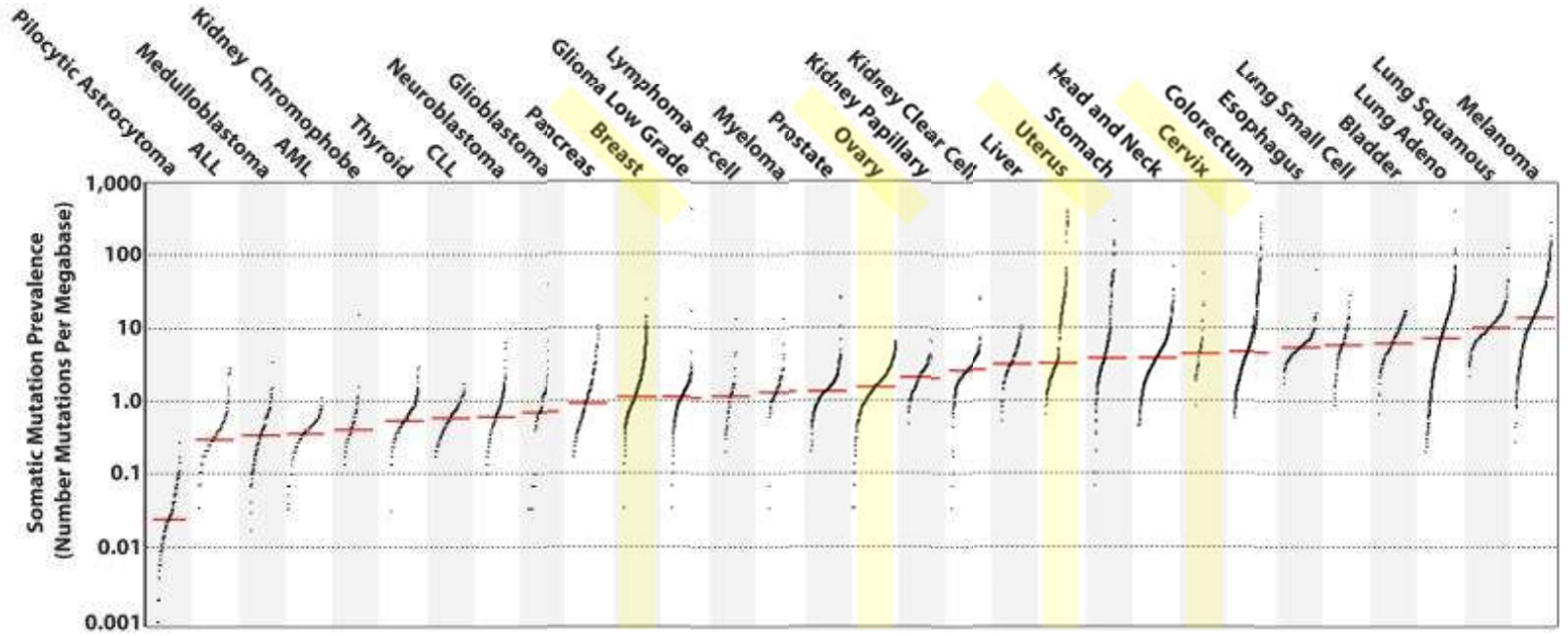
Female		
Breast	268,600	30%
Lung & bronchus	111,710	13%
Colon & rectum	67,100	7%
Uterine corpus	61,880	7%
Melanoma of the skin	39,260	5%
Thyroid	37,810	4%
Non-Hodgkin lymphoma	33,110	4%
Kidney & renal pelvis	29,700	3%
Pancreas	26,830	3%
Leukemia	25,860	3%
All sites	**891,480**	

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

Breast & Gynecological Cancers



Alexandrov, Nature 2013.

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Current FDA Approvals

Drug	Approved	Indication	Dose
HPV vaccination	2006 and many subsequent	Prevention of HPV infection	Depends on product
Pembrolizumab	2017/2020	MSI-H/dMMR/TMB-high **advanced cancer** with progression on previous treatment (includes especially **endometrial**)	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2018	Recurrent/metastatic **cervical cancer** with PD-L1 (CPS ≥1) and progression on previous therapy	200 mg Q3W or 400 mg Q6W
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

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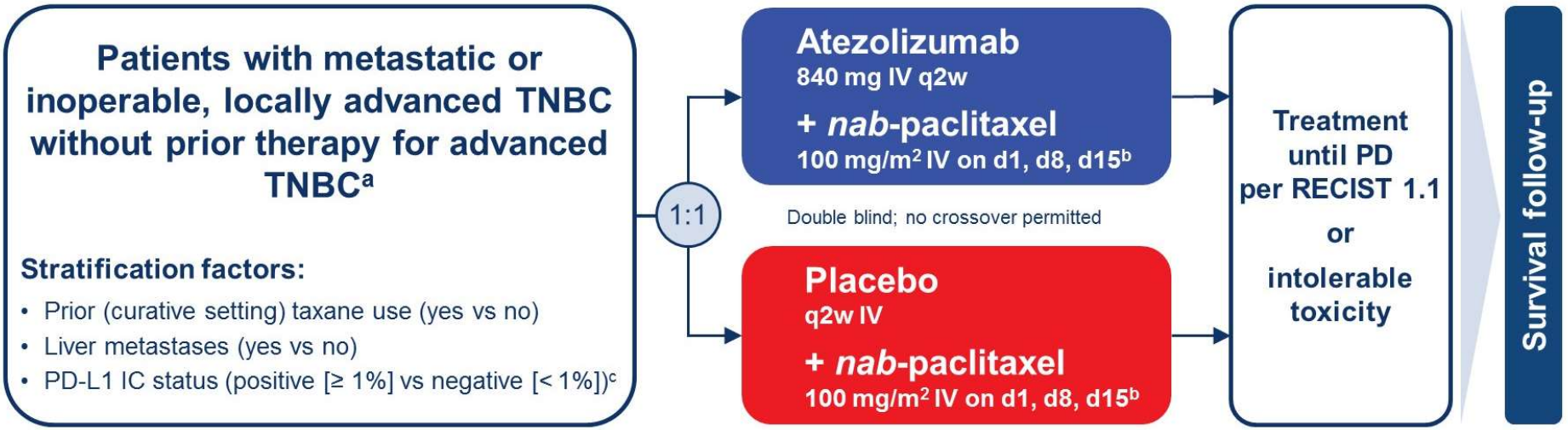
Breast Cancer – Focus on TNBC

Initial Trials

Trial	Checkpoint Inhibitor	Response	PFS	OS
KEYNOTE-012 (N=27)	Pembrolizumab	ORR 18.5%	1.9 months	11.2 months
KEYNOTE-028 (N=25)	Pembrolizumab	ORR 12%	1.8 months	8.6 months
KEYNOTE-086 Cohort A (N=170, 61.8% PD-L1+)	Pembrolizumab	ORR 4.7% (4.8% for PD-L1+, 4.7% for PD-L1-)	2 months	8.9 months
KEYNOTE-086 Cohort B (N=84)	Pembrolizumab	ORR 23.1%	2.1 months	-
Emens et al (N=115)	Atezolizumab	ORR 10% (12% for PD-L1+, 0% for PD-L1-)	1.4 months	8.9 months
JAVELIN (N=168)	Avelumab	ORR 4.8% (3.3% for PD-L1+, 2.4% for PD-L1-)	5.9 months	8.1 months
IMPASSION 130 (N=912)	Atezolizumab + nab-paclitaxel	ORR 56%	7.2 months (7.5 months for PD-L1+)	21.3 months (25 months for PD-L1+)

Mina LA, 2019

Clinical Data – IMpassion130

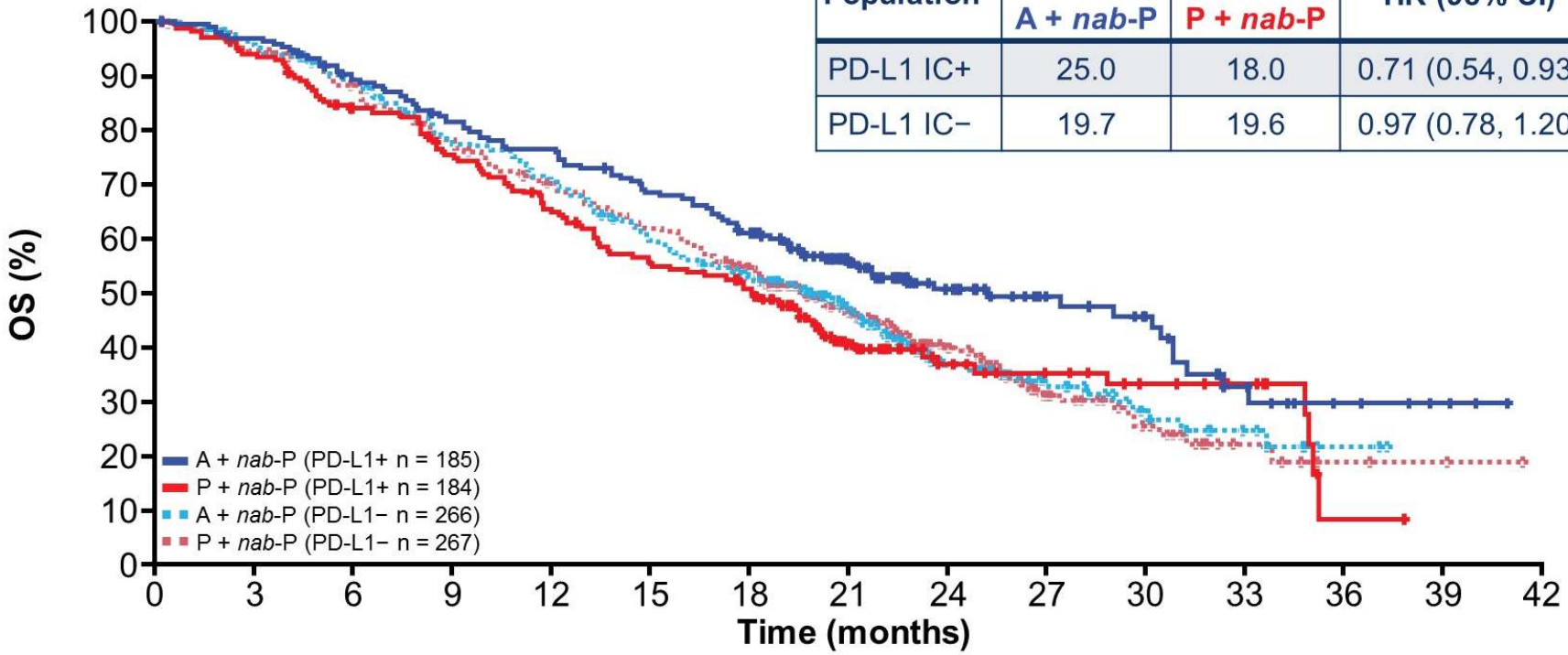


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

Clinical Data – IMpassion130

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.

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Ovarian Cancer

Keynote-100: Pembrolizumab in recurrent OC

ORR was 7.4% for cohort A (1-3 prior lines) and 9.9% for cohort B (4 to 6 lines).

CPS = [Total number of PD-L1+ cells (Tumor, lymphocytes, Macrophages) / total numer of cells] x 100

	Cohort A (285)	Cohort B (91)	Cohort A+B (376)
CPS < 1	107 **3.7%** (1.0-9.3)	34 **8.8%** (1.9-23.7)	141 **5.0%** (2.0-10.0)
CPS ≥ 1	147 **10.2%** (5.8-16.3)	50 **10%** (3.3-21.8)	197 **10.2%** (6.3-15.2)
CPS ≥ 10	60 **16.7%** (8.3-28.5)	22 **18.2%** (5.2-40.3)	82 **17.1%** (9.7-27.0)

Matulonis et al. Annal Oncol 2019; 30: 1080–1087,

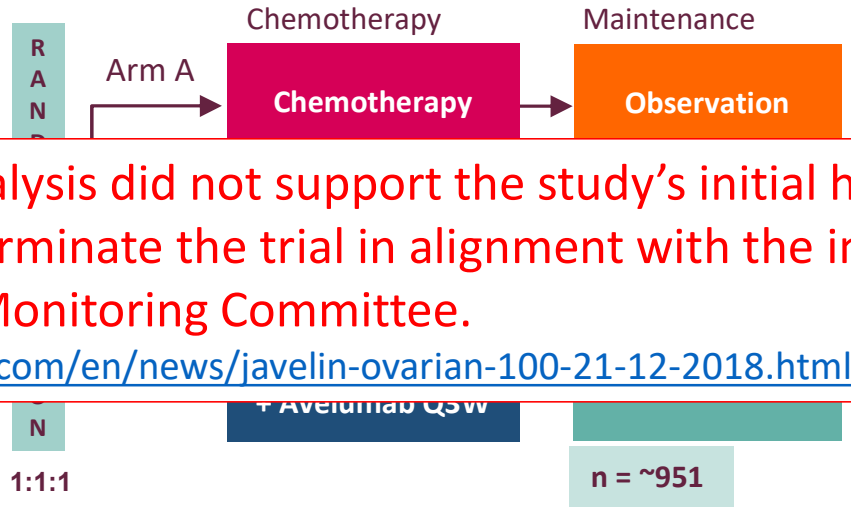
LS6

JAVELIN Ovarian 100 – First Line

Randomized Phase 3 Study (NCT02718417)

Enrollment Criteria

- ECOG PS 0 or 1
- Mandatory archival tissue



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

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.

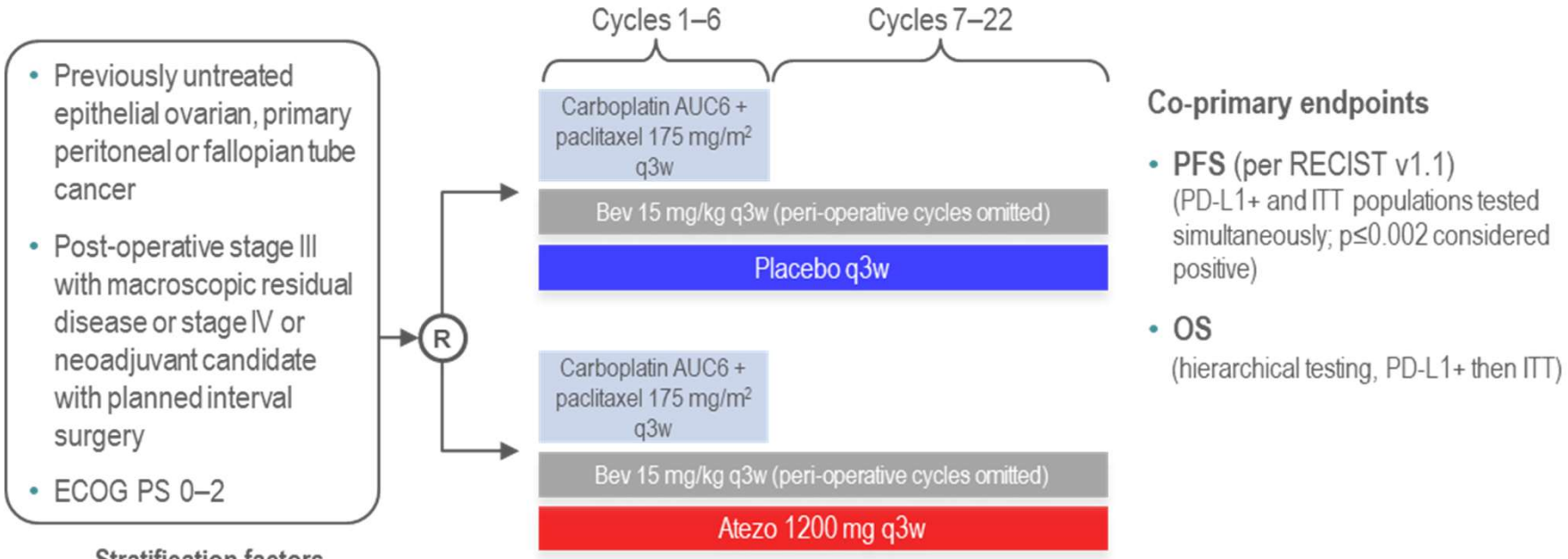
Clinicaltrials.gov. Accessed October 11, 2016.

Slide 12

LS6 need to add ref

Lheureux, Stephanie, 12/7/2020

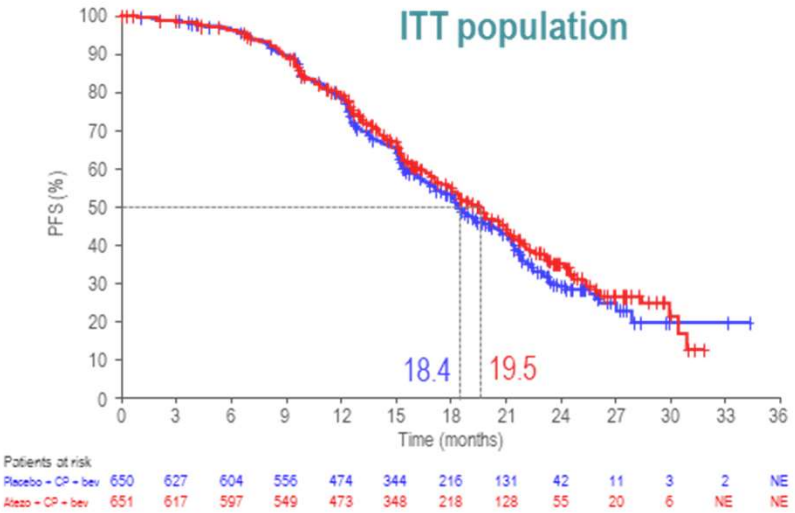
IMagyn050 Study – First Line

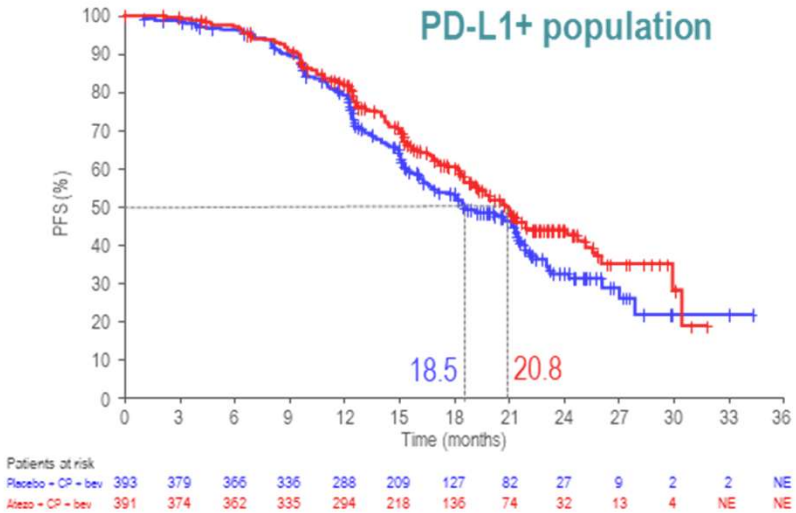


NCT03038100

Moore K, ESMO 2020.

Clinical Data: Progression Free Survival



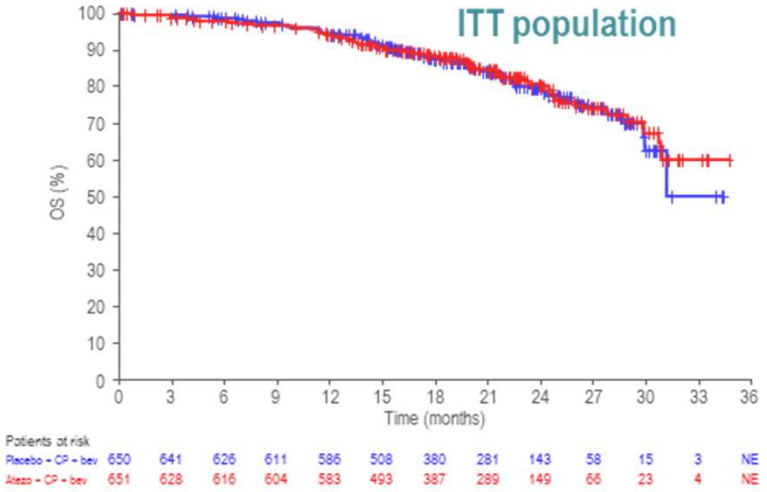


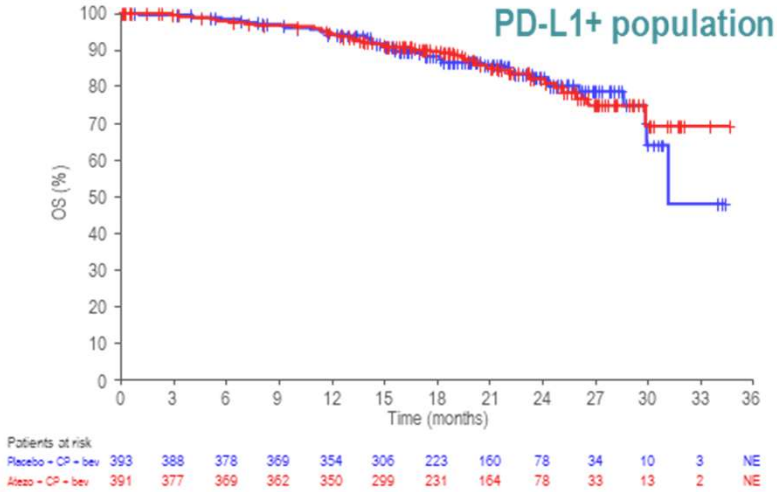
PFS	ITT population		PD-L1+ population	
	Placebo + CP + bev (n=650)	Atezo + CP + bev (n=651)	Placebo + CP + bev (n=393)	Atezo + CP + bev (n=391)
Patients with events, n (%)	341 (52.5)	323 (49.6)	199 (50.6)	167 (42.7)
Median PFS, months (95% CI)	18.4 (17.2–19.8)	19.5 (18.1–20.8)	18.5 (16.6–21.4)	20.8 (19.1–24.2)
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

Moore K, ESMO 2020.

Overall Survival: First interim Analysis





OS	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 (%)	110 (16.9)	109 (16.7)	59 (15.0)	57 (14.6)
Median OS, months (95% CI)	NE	NE	31.2 (30.0–NE)	NE
Stratified HR (95% CI)	0.96 (0.74–1.26)		0.98 (0.68–1.41)	
Stratified log-rank p-value	0.7887		0.9083	
2-year event-free rate (95% CI)	79.4 (75.4–83.3)	80.6 (76.8–84.5)	82.5 (77.8–87.3)	82.1 (77.2–87.0)

[a]Information fraction: 41% (ITT population) and 37% (PD-L1+ population). NE = not estimable

Moore K, ESMO 2020.

PD-L1 Status and Clinical Data

IMagyn050 PD-L1 analyses

Co-primary endpoint:

PD-L1 IC positive — IC ≥1%

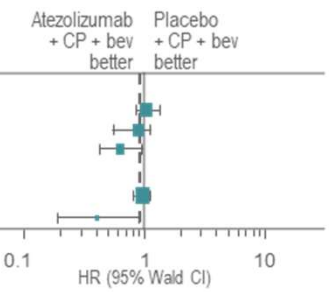
Exploratory analysis:

PD-L1 IC negative	IC <1%	PD-L1 TC negative	TC <1%
IC positive-low	IC ≥1–<5%	TC positive	TC ≥1%
IC positive-high	IC ≥5%		

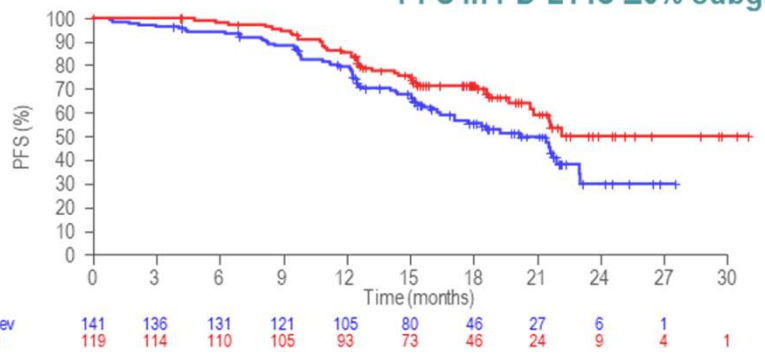
ITT population

PD-L1 status	Total n	Placebo + CP + bev (n=650) n	Placebo + CP + bev (n=650) Median (months)	Atezolizumab + CP + bev (n=651) n	Atezolizumab + CP + bev (n=651) Median (months)	HR (95% Wald CI)
PD-L1 IC status						
IC <1%	517 (40%)	257	18.3	260	17.4	1.06 (0.84–1.33)
IC ≥1% to <5%	524 (40%)	252	18.2	272	19.3	0.89 (0.55–1.13)
IC ≥5%	260 (20%)	141	20.2	119	NE	0.64 (0.43–0.96)
PD-L1 TC status						
TC <1%	1228 (94%)	610	18.4	618	19.2	0.96 (0.82–1.12)
TC ≥1%[a]	73 (6%)	40	15.0	33	NE	0.41 (0.19–0.90)

[a]PD-L1 TC ≥1% and IC ≥1%: n=67. PD-L1 TC ≥1% and IC <1%: n=6



PFS in PD-L1 IC ≥5% subgroup



	Placebo + CP + bev (n=141)	Atezo + CP + bev (n=119)
Patients with events, n (%)	66 (46.8)	39 (32.8)
Median PFS, months	20.2	NE
(95% CI)	(17.1–21.9)	(20.8–NE)
Unstratified HR (95% CI)	0.64 (0.43–0.96)	
Unstratified log-rank p-value	0.0278	

Moore K, ESMO 2020.

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Cervical Cancer

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Checkpoint inhibitor in Cervical Cancer

	Lheureux et al.[1]	KEYNOTE-028[2]	KEYNOTE-158[3] (Cohort E)[b]	Checkmate 358[4]
Phase(s)	2	1b	2	1/2
Population	Metastatic or recurrent cervical cancer with progression after prior platinum chemotherapy	PD-L1+ advanced cervical squamous cell cancers after failure of prior systemic therapy	Advanced cervical cancer with progression on or intolerance to ≥1 line of prior therapy, PD-L1+ (CPS ≥1)	HPV-associated tumors, including recurrent or metastatic cervical, vaginal, vulvar cancers
Patients, n	42[a]	24	77[d]	24
Treatment	Ipilimumab	Pembrolizumab	Pembrolizumab	Nivolumab
ORR, %	8.8[c]	12.5[c]	14.3	ITT: 20.8[c] Cervical cancer pts: 26.3%
DCR, %	32.3	25.0	—	70.8
mDOR	—	19.3 wk	NR (range: 4.1–18.6+ mo)	NR
PFS	mPFS: 2.5 mo	6-mo PFS: 13.0%	—	mPFS: 5.5 mo
OS	—	6-mo OS: 66.7%	—	NR
Safety	Manageable toxicities	≥Gr 3 TRAEs: 20.8%	Serious AEs: 39%	Gr 3/4 TRAEs: 12.5%
Follow-up	—	48.9 wk	11.7 mo	31 wk

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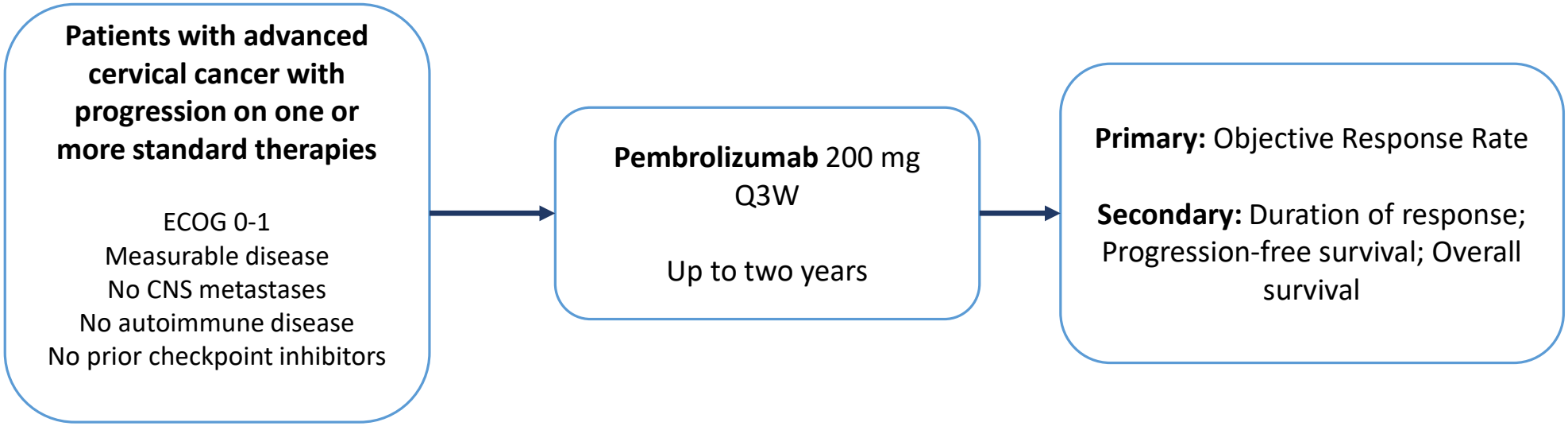
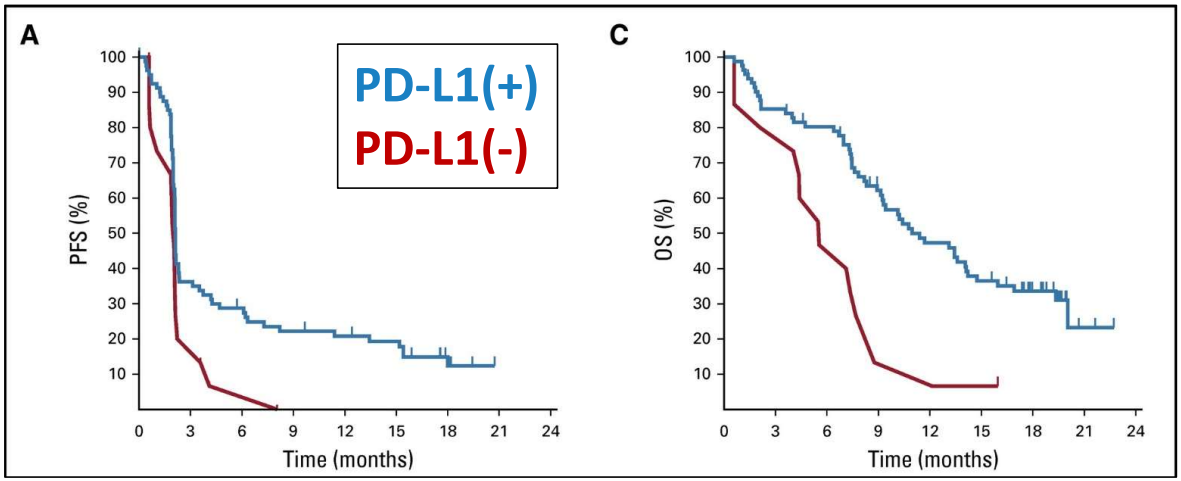
Clinical Data – KEYNOTE-158



Clinical Data – KEYNOTE-158

- 82/98 pts were PD-L1(+)
- Follow-up 10 months: ORR – 14.6% (all in PD-L1(+) patients)
- Median duration of response not reached
- mOS: 9.4 mths in total population; 11.0 mths in PD-L1(+)



PD-L1 positive: Combined Positive Score (CPS) ≥ 1

Cheol Chung, J Clin Oncol 2019.

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Endometrial Cancer

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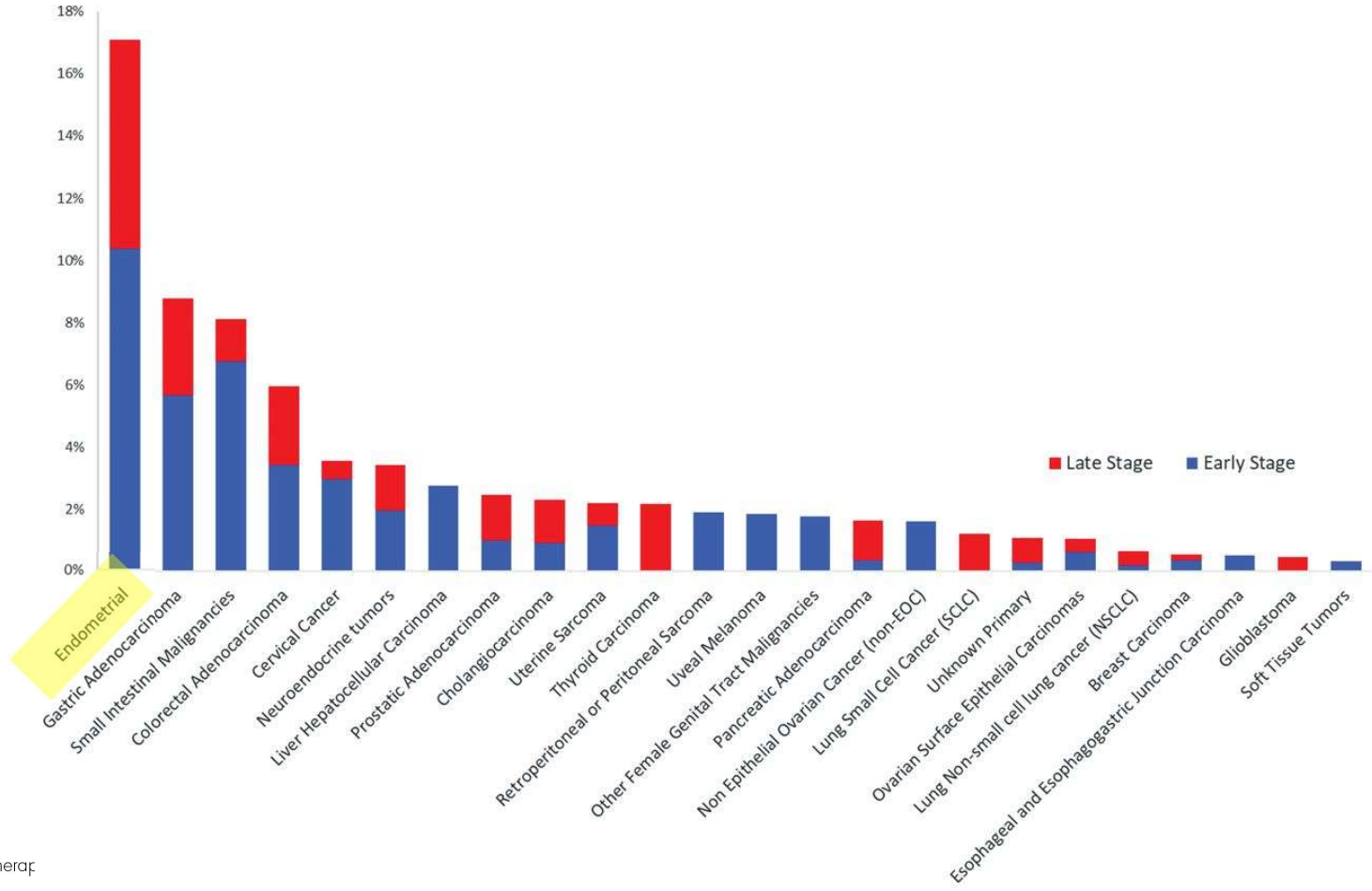
Mismatch Repair Deficiency across tumors



Le, Science 2017.

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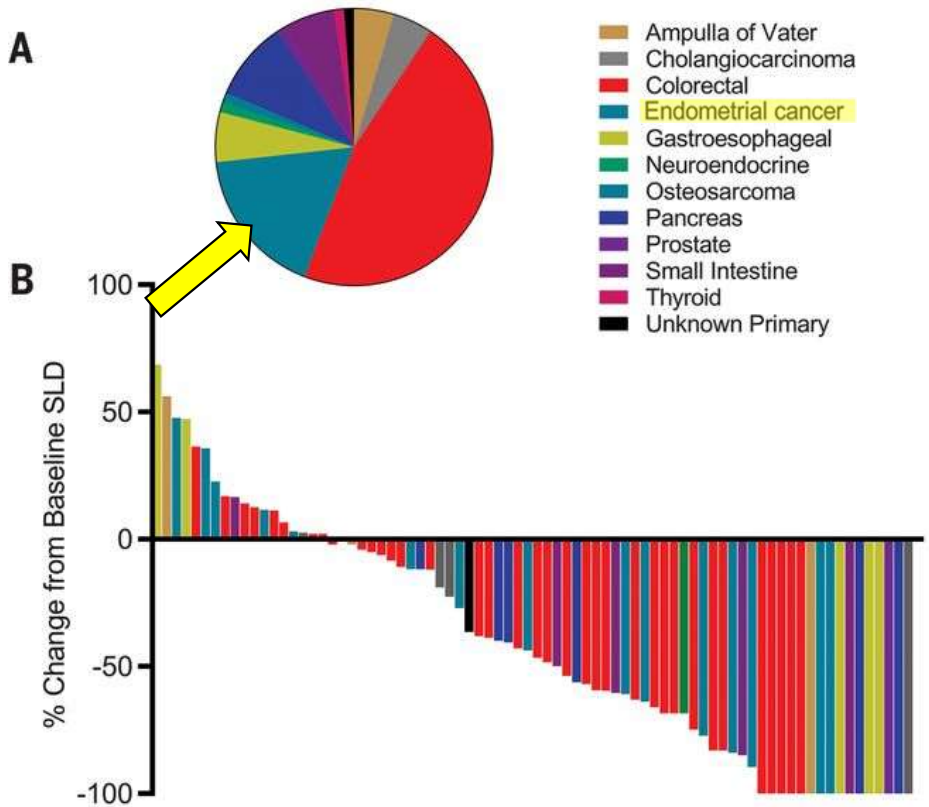
Pembrolizumab in MSI-High cancers



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

Le, Science 2017.

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Checkpoint inhibition in Endometrial Cancer

Study	Drug	N	Patient Selection	ORR(%)
Le et al. (2017)	Pembro	15	MMRd EC	53%
Ott et al. (2017)	Pembro	24	PDL1+	13%
Fleming et al. (2017)	Atezo	15	All	13%
Hasegawa et al. (2018)	Nivo	23	All	23%
Oaknin (2019)	Dostarlimab	125	All	29.6% d-MMR 48.8% p-MMR 20,3%
Antill (2019)	Durvalumab	70	All	d-MMR 43% p-MMR 3%
Konstantinopoulos (2019)	Avelumab	31	All	d-MMR 27% p-MMR 6%

Le et al. NEJM. 2015; 372:2509-20; Ott et al. J Clin Oncol. 2017; 35(22):2535-41; Fleming et al. J Clin Oncol 35, 2017 (suppl; abstr 5585); Hasegawa et al. J Clin Oncol 36, 2018 (suppl: abstr 5594) , Le Science 2017; Oaknin, SGO 2019; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019

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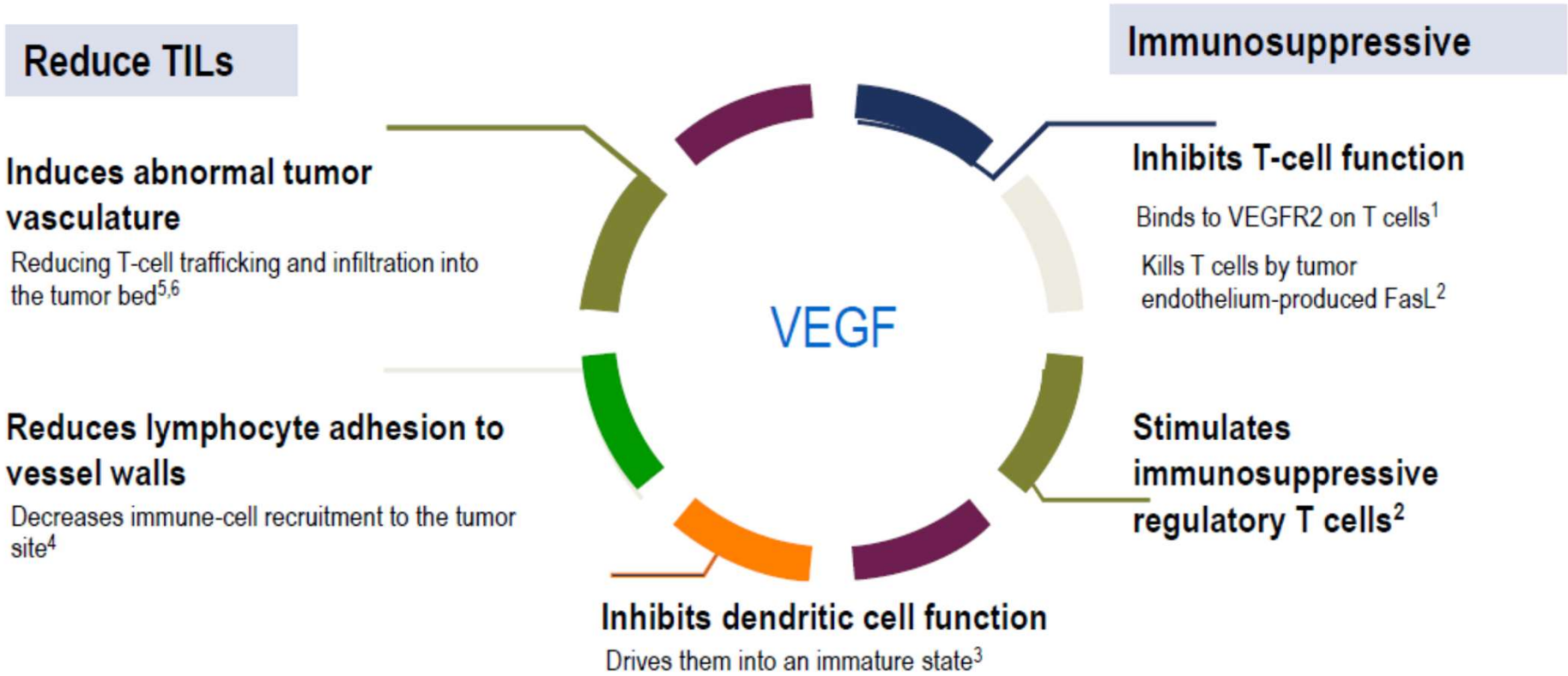
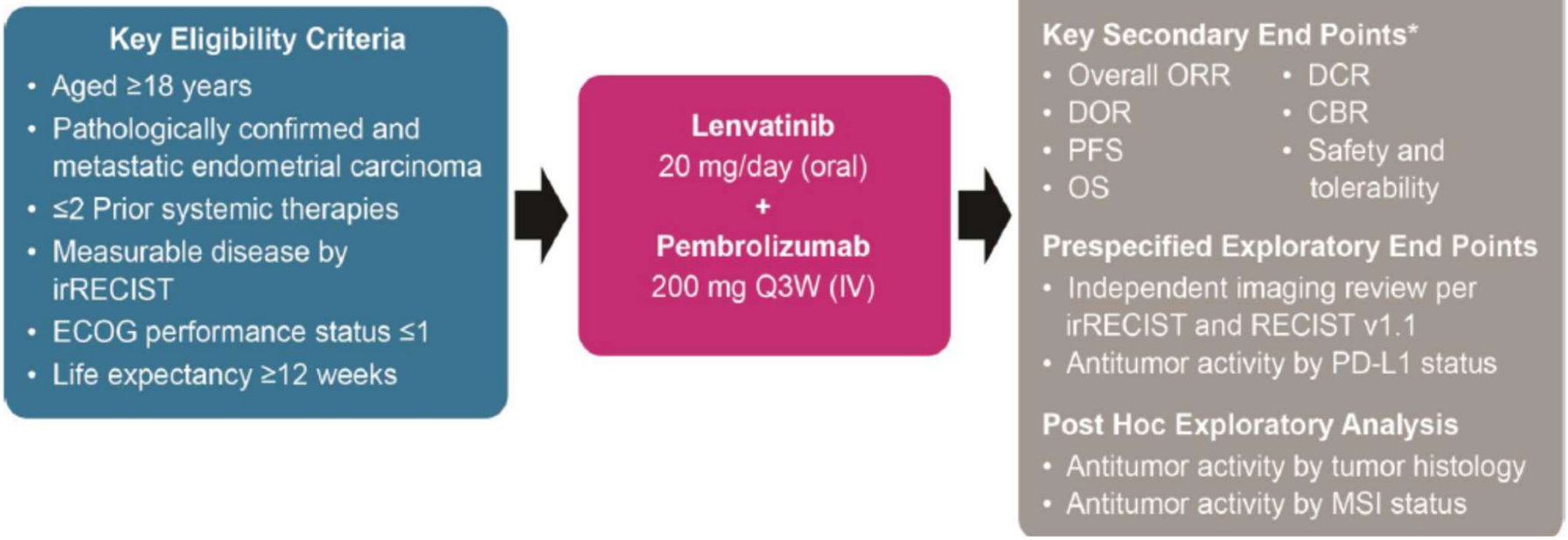
Rationale for Combination



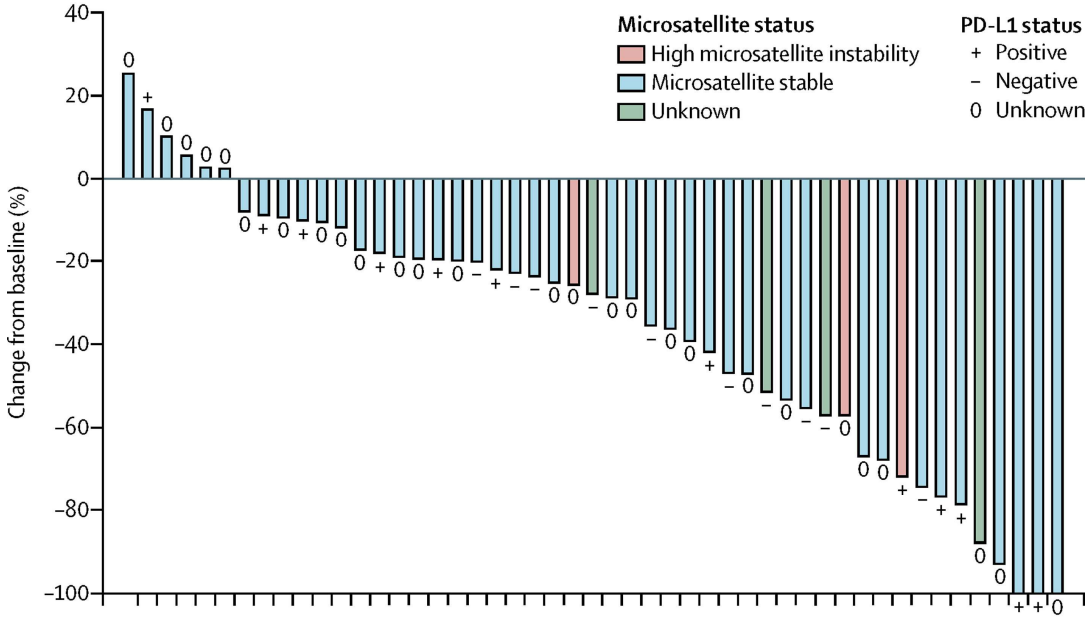
1. Gavalas NG, et al. *Br J Cancer*. 2012;107(11):1869-1875. 2. Terme M, et al. *Cancer Res*. 2013;73(2):539-549. 3. Coukos G, et al. *Br J Cancer*. 2005;92(7):1182-1187 4. Bouzin C, et al. *J Immunol*. 2007;178(3):1505-1511. 5. Shrimali RK, et al. *Cancer Res*. 2010;70(15):6171-6180. 6. Chen DS, et al. *Immunity*. 2013;39(1):1-10.

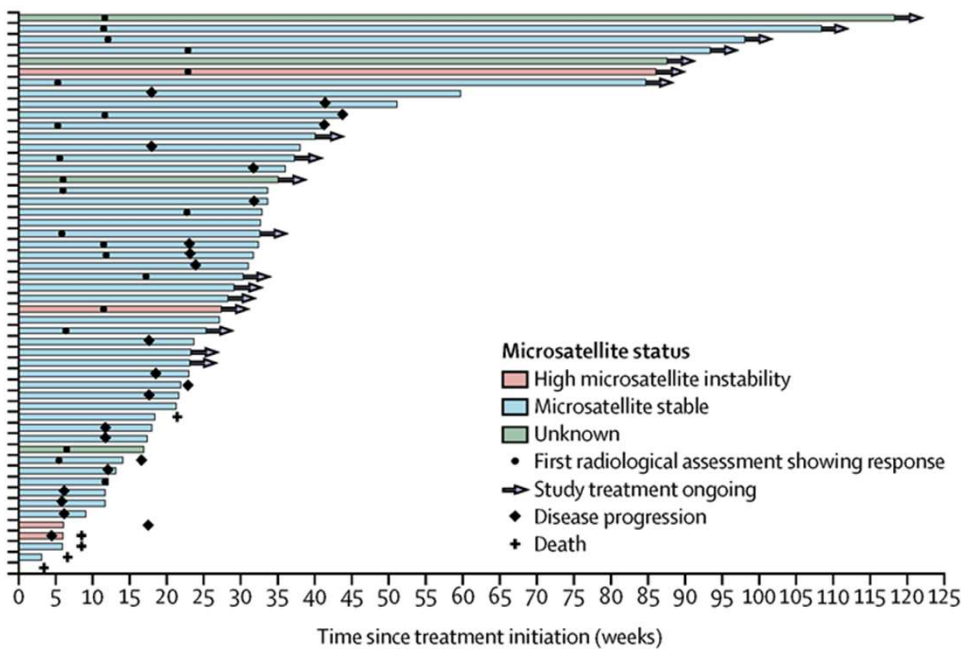
Phase 2, Open Label, Single arm



Makker V, Lancet Oncology 2019

Clinical Data: Response & Duration





Grade 3 treatment-related AE occurred in 36 pts (68%).

Treatment-related adverse events led to dose interruptions in 39 pts (74%) and dose reduction in 28 pts (53%).

Makker V, Lancet Oncology 2019

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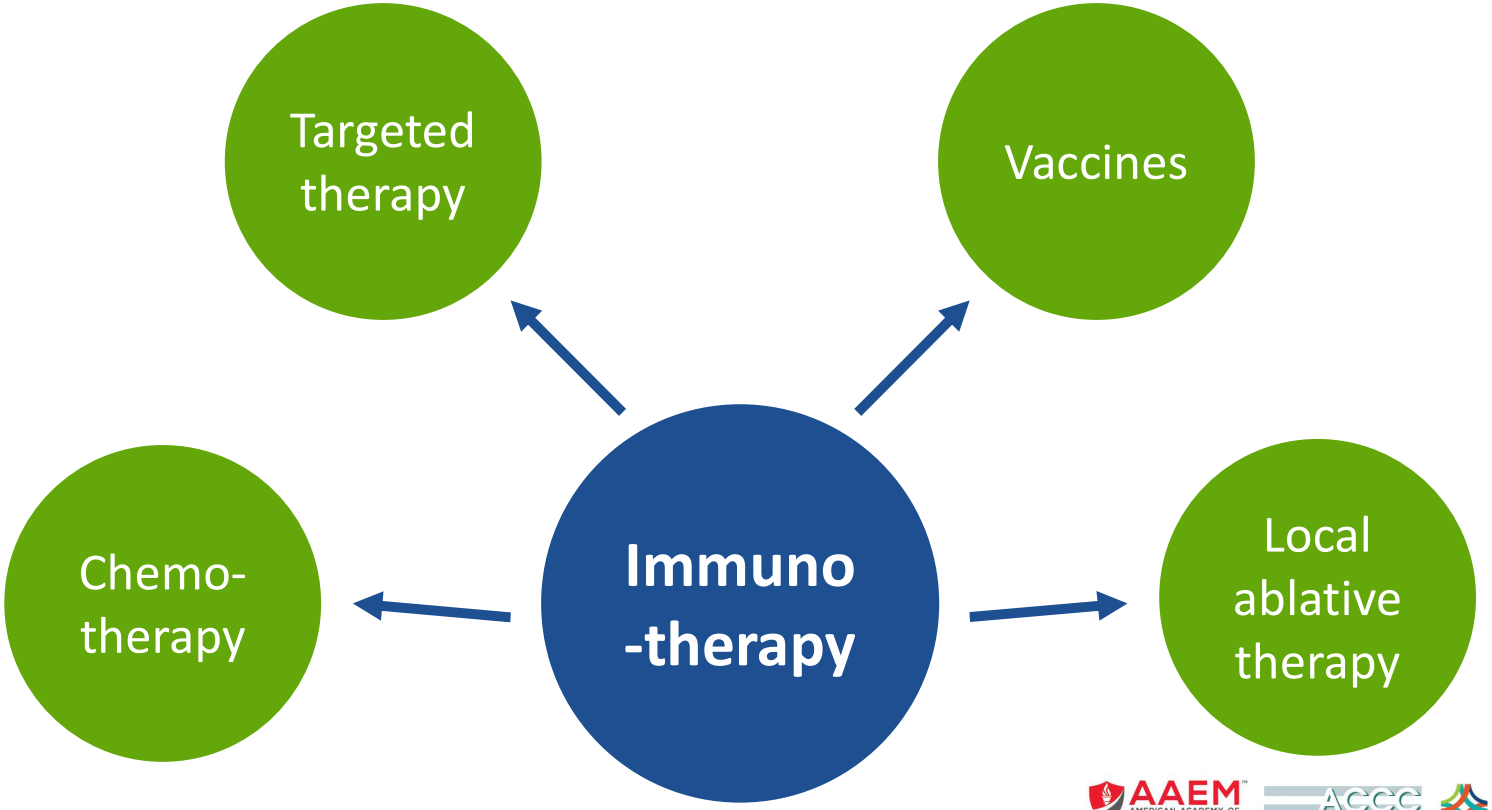
Future Directions

In development: Breast cancer immunotherapy

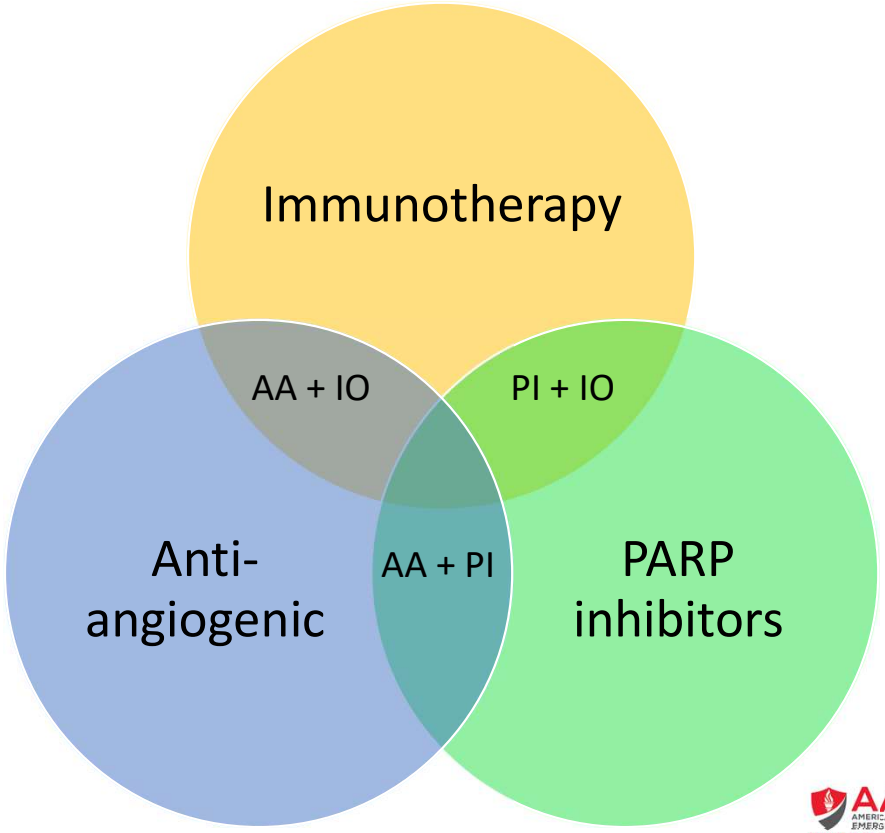


Adams, JAMA Oncol 2019.

In development: Breast cancer

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 > 300 trials on going			

In development: OC Therapeutic Strategies



First line: Clinical trials in Ovarian Cancer

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
ATHENA	St III/IV ovarian,– maintenance treatment 1st line	• Rucaparib + nivolumab • Rucaparib +placebo • Placebo + nivolumab • Placebo	Active, Not 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

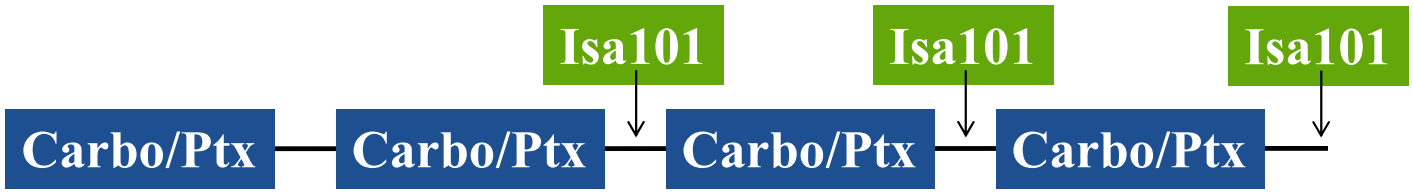
Cervical cancer immunotherapy opportunities:

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

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

In development: HPV peptide therapeutic vaccination

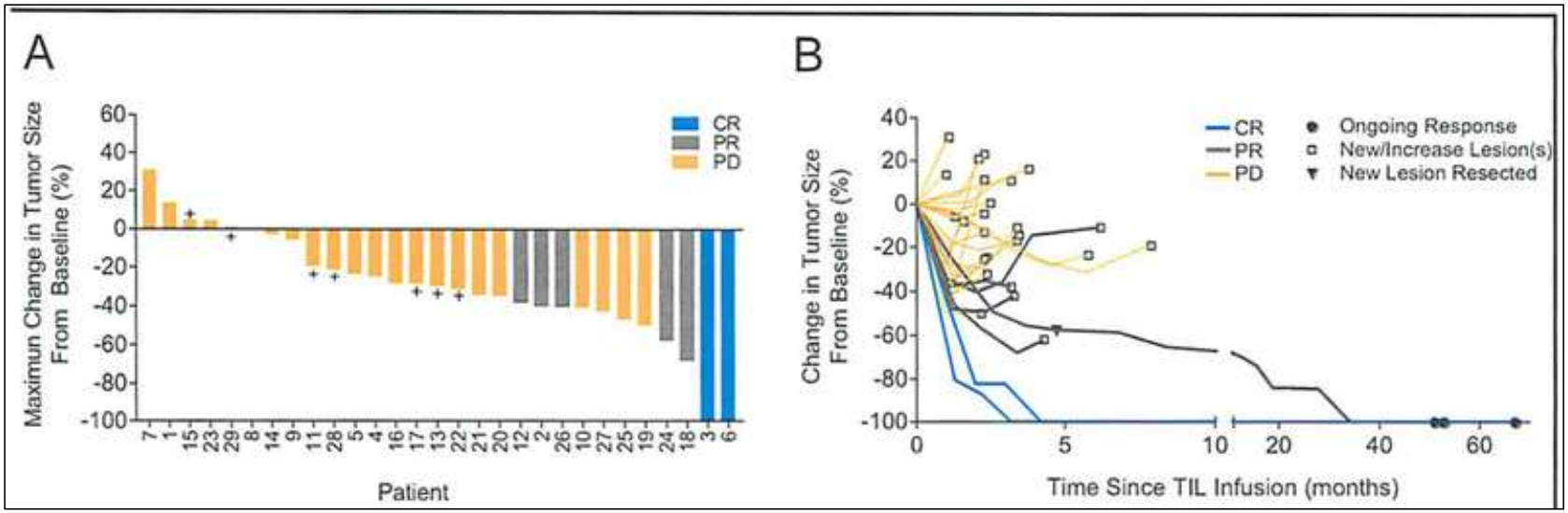
- Advanced cervical cancer
- ISA101 vaccine = 13 overlapping HPV16 (E6&7) synthetic long peptides
- N = 60 patients at 4 dose levels
- mOS not reached at two highest dose levels



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 - Triple-negative subtype shows promise
- For Ovarian Cancer, combinations on going – results awaited
- Cervical Cancer and HPV-associated cancers present unique treatment options
- Endometrial Cancer: MSI Subgroup benefit of single agent – MSS require combination

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

Case Study 1

A 35 years old woman with metastatic cervical cancer, squamous type, has just progressed on carboplatin-paclitaxel-bevacizumab. She was previously treated with chemoradiation and brachytherapy.

What is your proposed treatment option?

A. Clinical Trial
B. Pembrolizumab
C. Pembrolizumab only if PD-L1 positive
D. Standard chemotherapy

Case Study 1

- Discussion with the patient about clinical trial or pembrolizumab only if PD-L1 positive and if patient can get access to immune therapy.
- Importance of early palliative care consultation

- Patient was started on pembrolizumab and developed diarrhea grade 2 and abdominal cramp.
- Options:

  A: Steroids per os

  B: Steroids IV

  C: Investigations with lab and CT

  D: Hold pembrolizumab

Case Study 1

- Hold pembrolizumab - Investigations with imaging & complete lab including thyroid function
- IV hydration and steroids

Immune-mediated AEs and infusion reactions‡		
Hypothyroidism	11 (11.2)	0
Hyperthyroidism	9 (9.2)	0
Infusion-related reaction	3 (3.1)	0
Colitis	2 (2.0)	0
Hepatitis	2 (2.0)	2 (2.0)
Severe skin reactions	2 (2.0)	2 (2.0)
Adrenal insufficiency	1 (1.0)	1 (1.0)
Myositis	1 (1.0)	0
Pneumonitis	1 (1.0)	0
Uveitis	1 (1.0)	0

	No. (%)*	
AE	Any Grade	Grade 3-4
Treatment-related AEs of any grade†		
Any	64 (65.3)	12 (12.2)
Hypothyroidism	10 (10.2)	0
Decreased appetite	9 (9.2)	0
Fatigue	9 (9.2)	0
Diarrhea	8 (8.2)	1 (1.0)
AST increased	7 (7.1)	2 (2.0)
Asthenia	7 (7.1)	1 (1.0)
Pyrexia	7 (7.1)	1 (1.0)
Hyperthyroidism	7 (7.1)	0
Arthralgia	6 (6.1)	1 (1.0)
Nausea	6 (6.1)	0
Pruritus	6 (6.1)	0
Rash	6 (6.1)	0
Vomiting	6 (6.1)	0
Abdominal pain	5 (5.1)	0
ALT increased	3 (3.1)	3 (3.1)

Case Study 2

A 58 years old woman with newly diagnosed endometrial cancer, endometrioid type, grade 1, ER and PR positive, MSI high/ loss MLH-1. She is not a surgical candidate.

What is your suggested treatment option?

A. Clinical Trial
B. Pembrolizumab
C. Pembrolizumab + Levatinib
D. Standard chemotherapy
E. Hormonal therapy

Case Study 2

- Few standard options
  - Hormonal therapy
  - Chemotherapy
  - On going trial to assess immune therapy as first line

- At Recurrence: Pembrolizumab if patient received prior platinum chemotherapy (if access)

- Testing Microsatellite Instability
  - **MMR protein IHC**
    ➔ Antibodies recognizing the 4 MMR proteins: MLH1, MSH2, MSH6, and PMS2
  - **PCR Testing**

Case Study 2

- Her sister who is 62 years old came to see you as well as she was recently diagnosed with disease progression after chemo for her endometrial cancer; serous type.

She would like to get the same therapy with pembrolizumab as her sister given the benefit observed with her sister

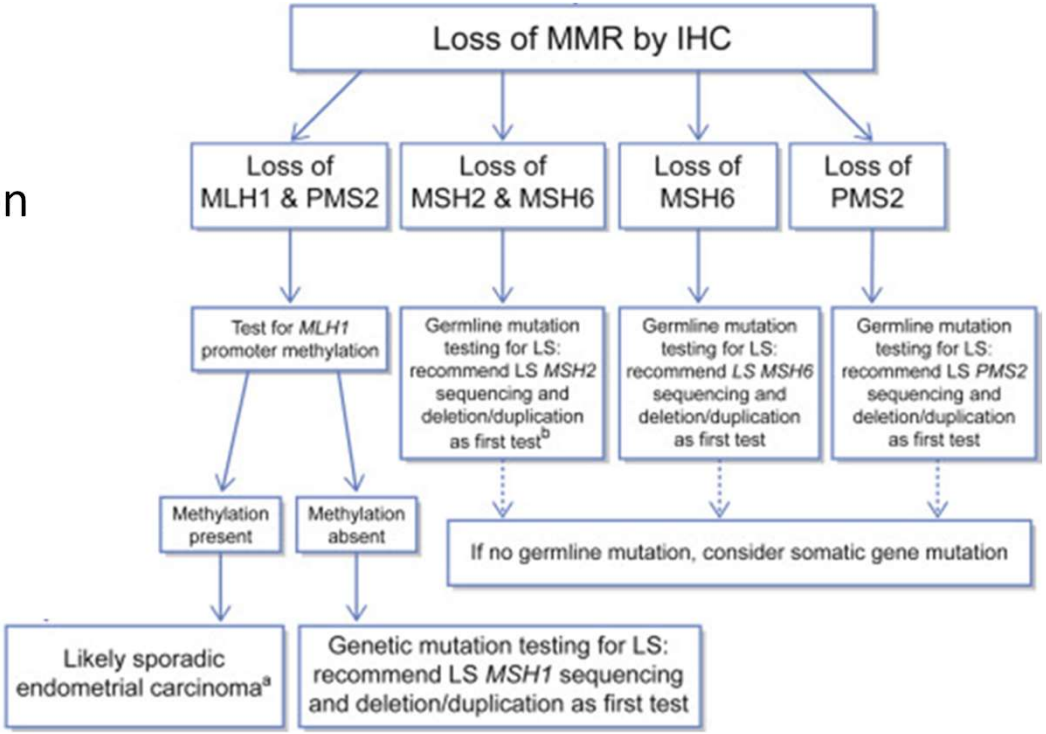
Do you think this is a good option?

A. Yes
B. No
C. Need genetic testing

Case Study 2

- In her sister:

MLH-1 loss ➔ Test for Promotor Methylation



- In her case: Serous endometrial cancer

MSI negative

➔Suggestion of the combination: pembrolizumab + levatinib