Society for Immunotherapy of Cancer

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Immunotherapy for the Treatment of Microsatellite Instability – High 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

Society for Immunotherapy of Cancer

Disclosures

- Consulting Fees: Tesaoro for Niraparib
- Research Grant: Puma Biotechnology
- Area of research interest especially MSI-H and ovarian cancers

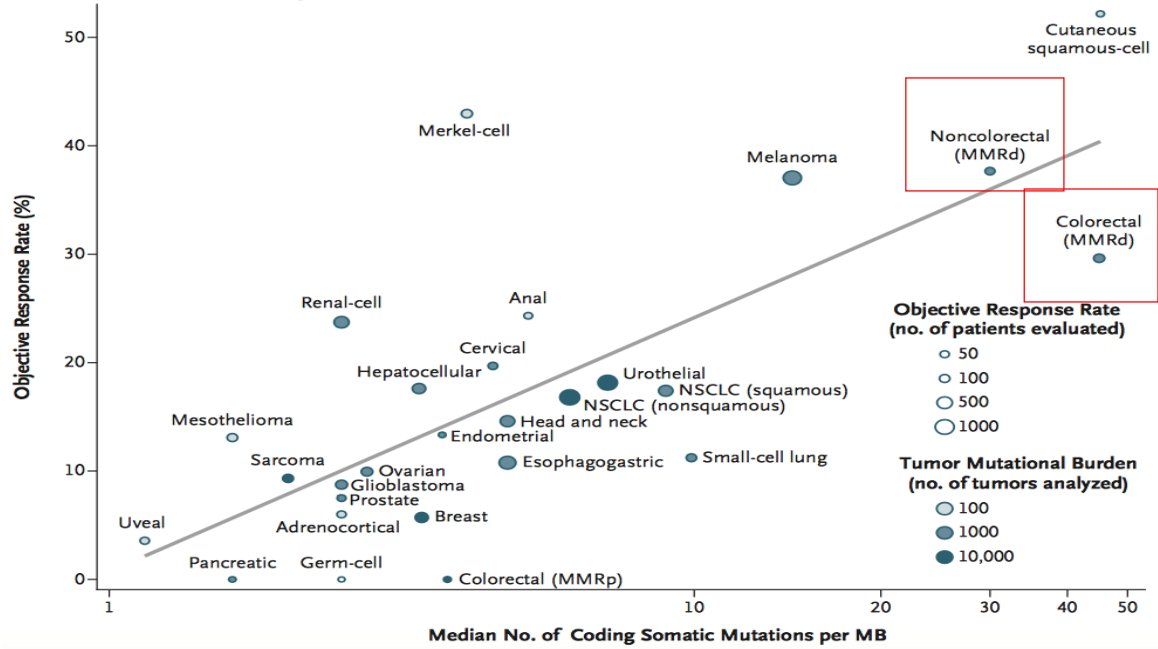
- I will be discussing non-FDA approved indications during my presentation.

DNA Mismatch Repair/Microsatellite Instability

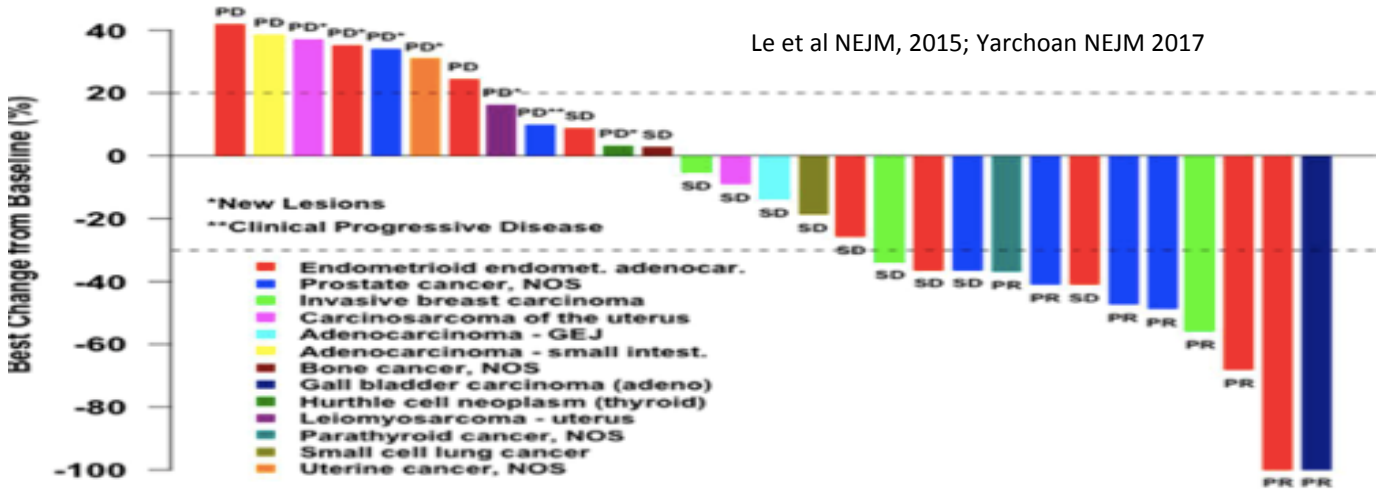
- The presence of microsatellite instability (MSI) represents phenotypic evidence of mismatch repair (MMR) dysfunction.
- MMR dysfunction can be caused by mutations in genes that code for MMR proteins (MLH1, MSH2, MSH6, PMS2)
- Diagnosed by IHC, PCR or NGS
- Mutations in MMR proteins can result from:
  - Hereditary causes (Lynch syndrome)
  - Somatic mutations
  - Silencing through promoter methylation

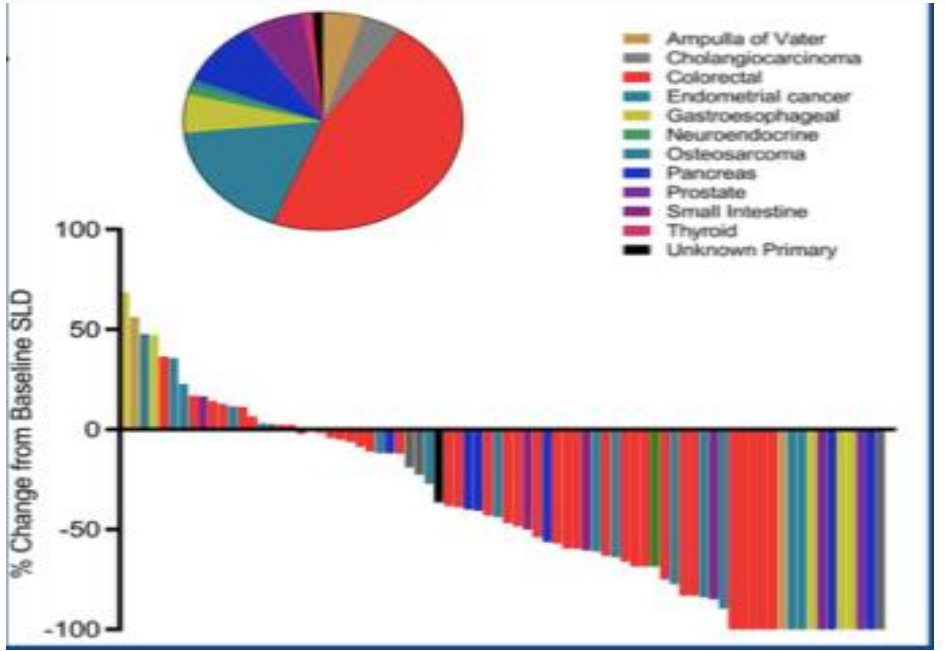
Microsatellite Instability

- Highly immunogenic tumors
- Increased somatic mutation and mutational burden
  - High NeoAgs burden
- Particularly sensitive to immunotherapy, PD1/PDL1 inhibitors
  - Rapid expansion of neoantigen-specific T cell clones that are reactive to tumor neoantigens

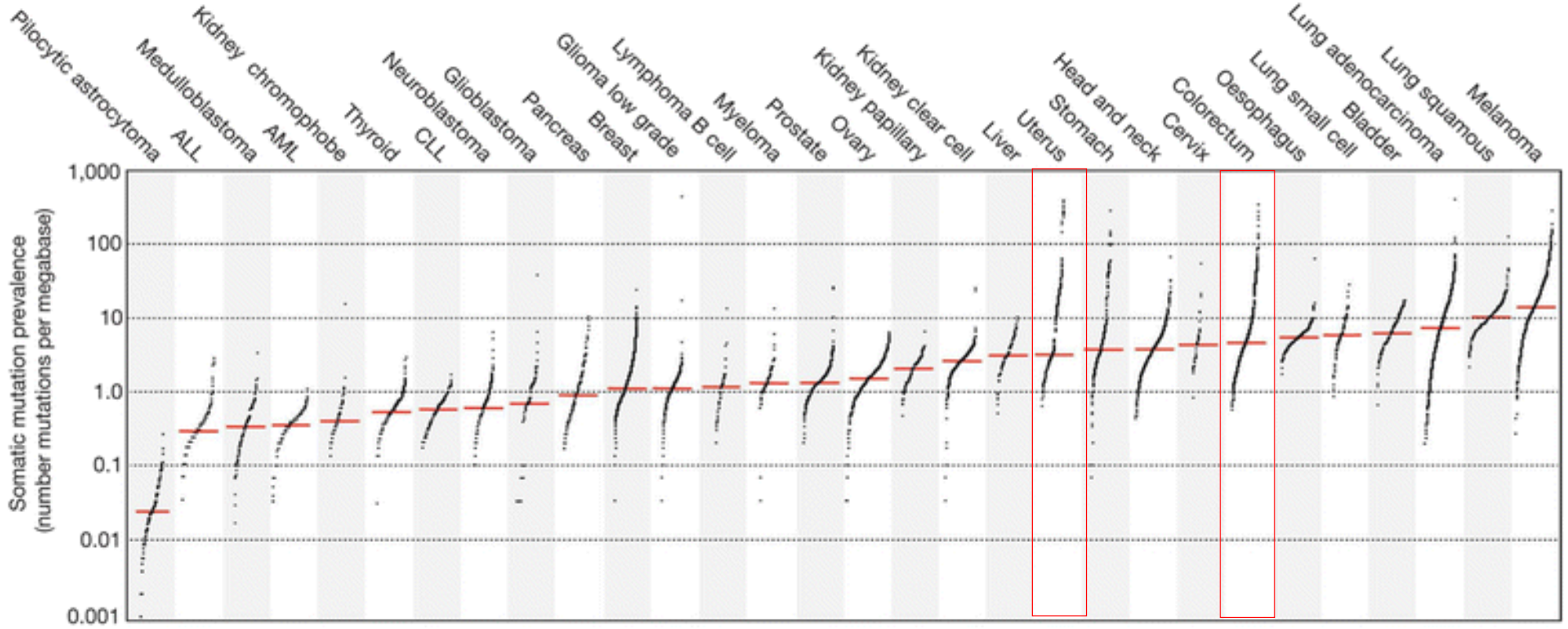


Le et al NEJM, 2015; Yarchoan NEJM 2017





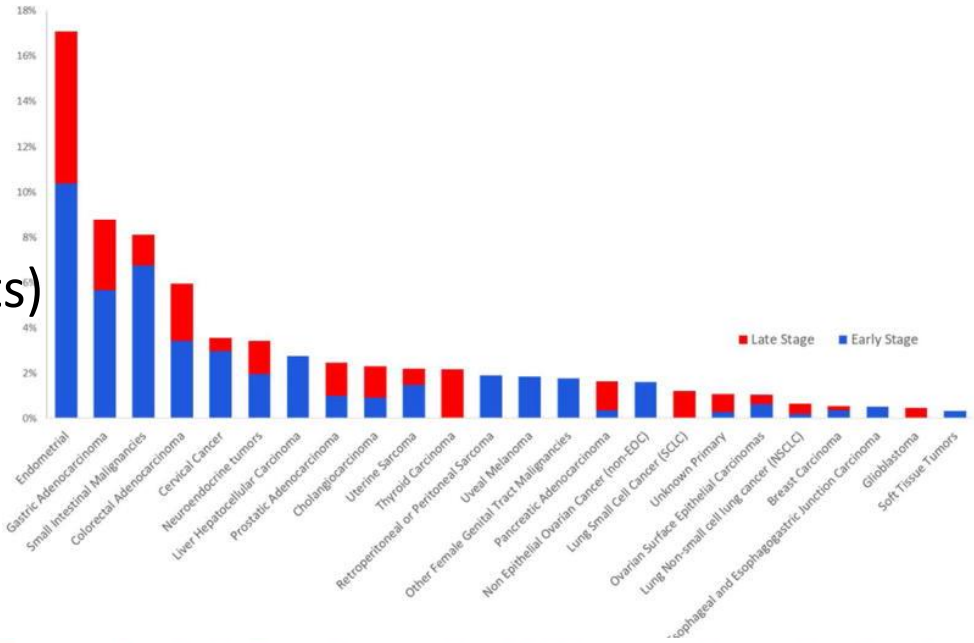
MSI-H/dMMR tumors have high TMB

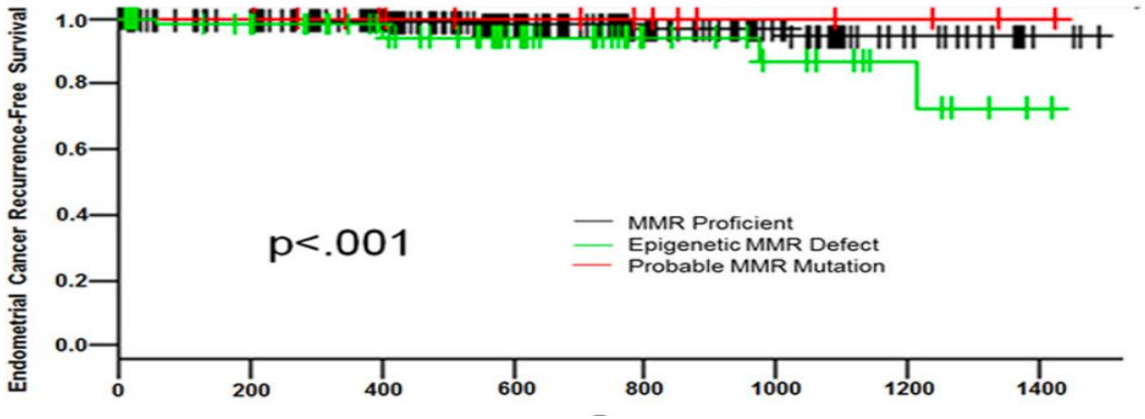


Alexandrov, Nature 2013.

Many tumors are MSI-high or MMR-deficient

- Endometrial cancer (30%)
- Colorectal/gastric cancer (20%, up to 5% of metastatic patients)
- Genitourinary, breast, thyroid, others (<5%)
- Also share histopathological characteristics, like immune cell infiltration, medullary histology, poorly differentiated
- Prognosis with MSI-H appears to be stage-specific
  - Localized, surgically-resected is favorable
  - Metastatic = not favorable
    - Trend toward lower response to chemotherapy stage in one study in MSI-H endometrial cancer
      - Epigenetic MMR defect
      - 48% vs. 3.4% in one study





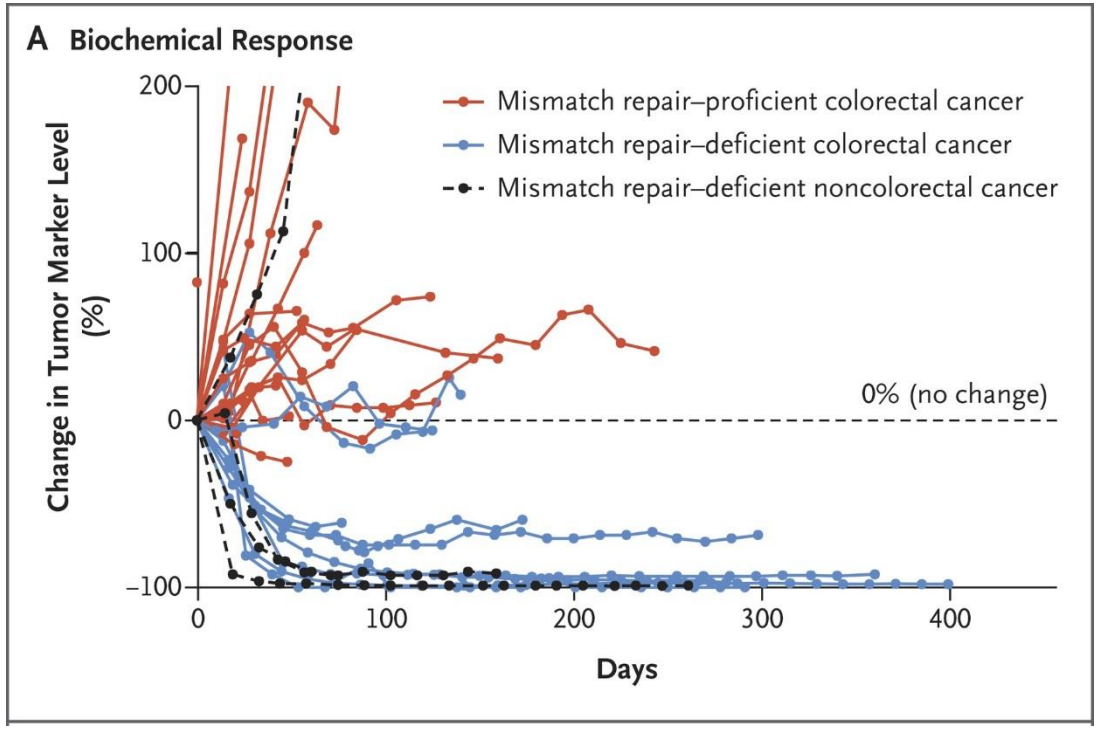
Le, Science 2017.

FDA-approved immunotherapies for MSI-high populations

Drug	Approved	Indication	Dose
Pembrolizumab	2017	Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment **MSI-H or dMMR colorectal cancer** with progression after 5FU, oxaplatin, and irinotecan	Adults: 200 mg Q3W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Nivolumab	2017	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaplatin, and irinotecan	≥40 kg: 240 mg Q2W or 480 mg Q4W <40 kg: 3 mg/kg Q2W
Ipilimumab + nivolumab	2018	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after 5FU, oxaplatin, and irinotecan	≥40 kg: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses, Then nivolumab 240 mg Q2W or 480 mg Q4W

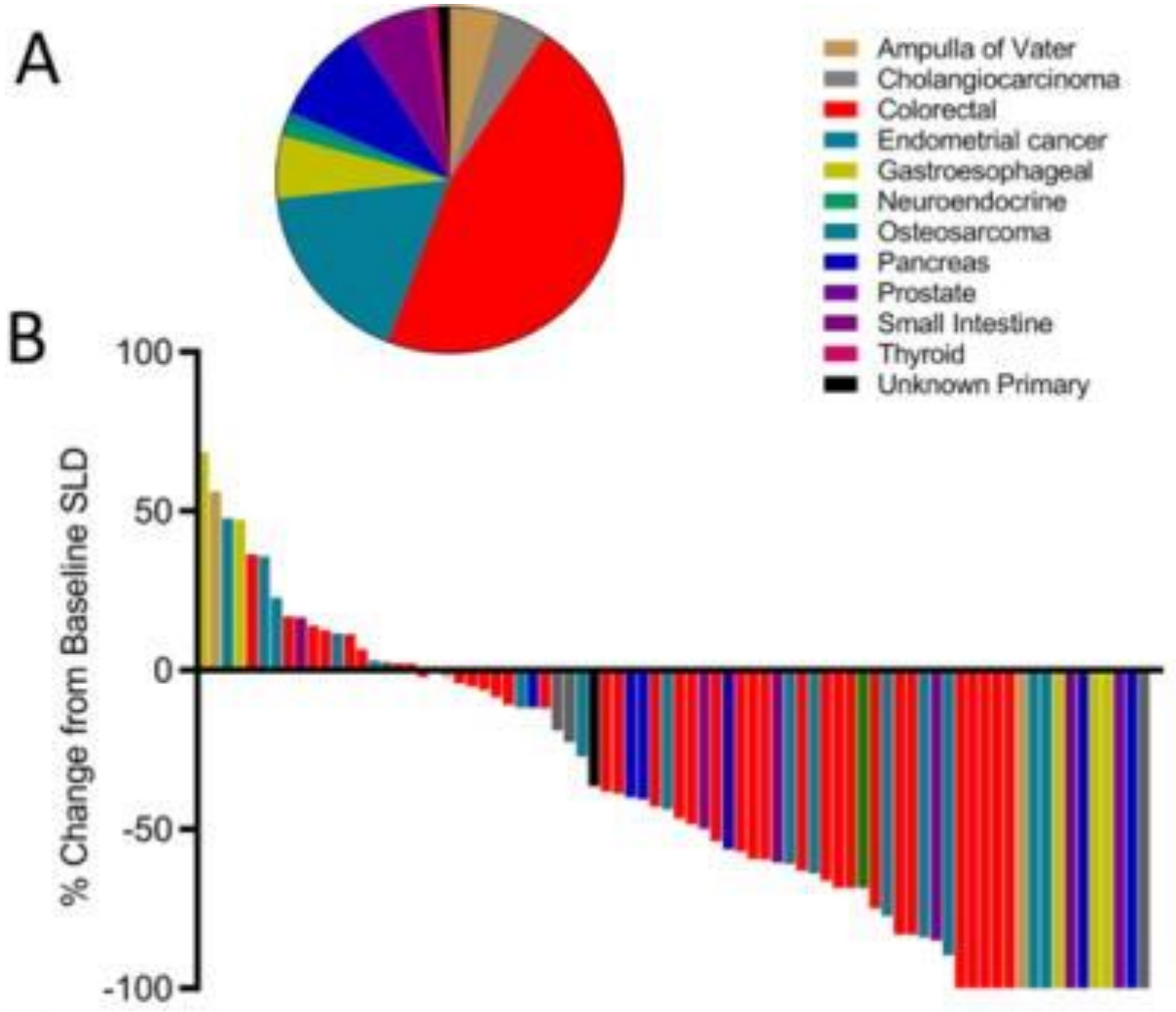
Clinical Data – pembrolizumab studies

- KEYNOTE-016: CRC only
  - no CR in MMR-proficient, 40% in dMMR
- KEYNOTE-164 and 158
  - ORR:
    - 27.9% for MSI-H CRC
    - 37.7% for MSI-H non-CRC
  - At 6 months OS:
    - 87% CRC
    - 73% non-CRC



Le, NEJM 2015.

Clinical Data – pembrolizumab studies



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

Le, Science 2017.

Table 23: MSI-H Trials

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

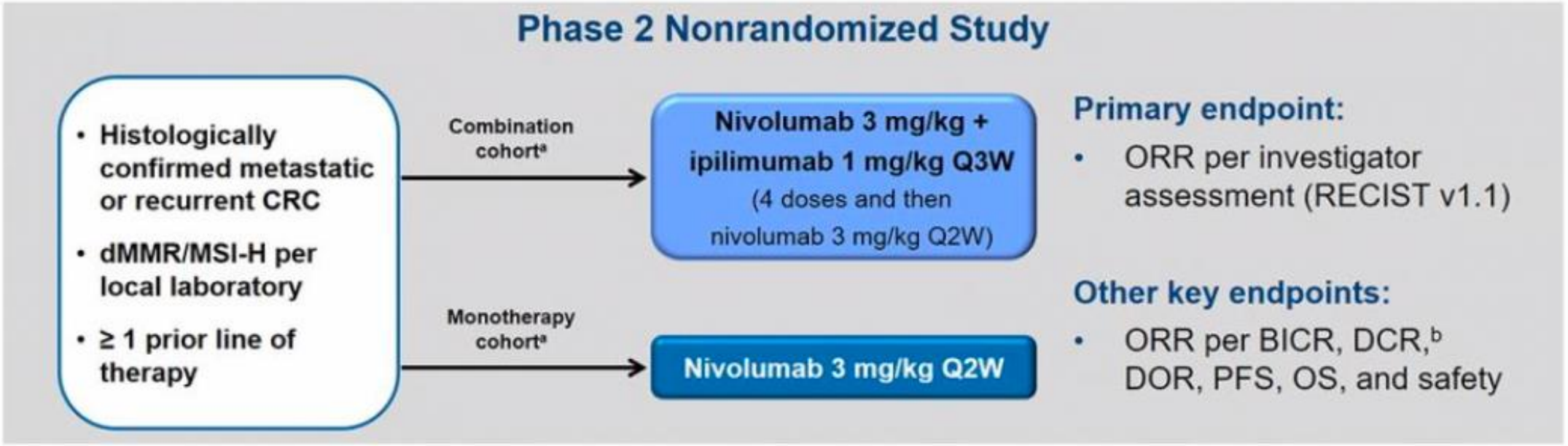
CRC = colorectal cancer

Table 24: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	n=149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4
Partial response rate	32.2
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

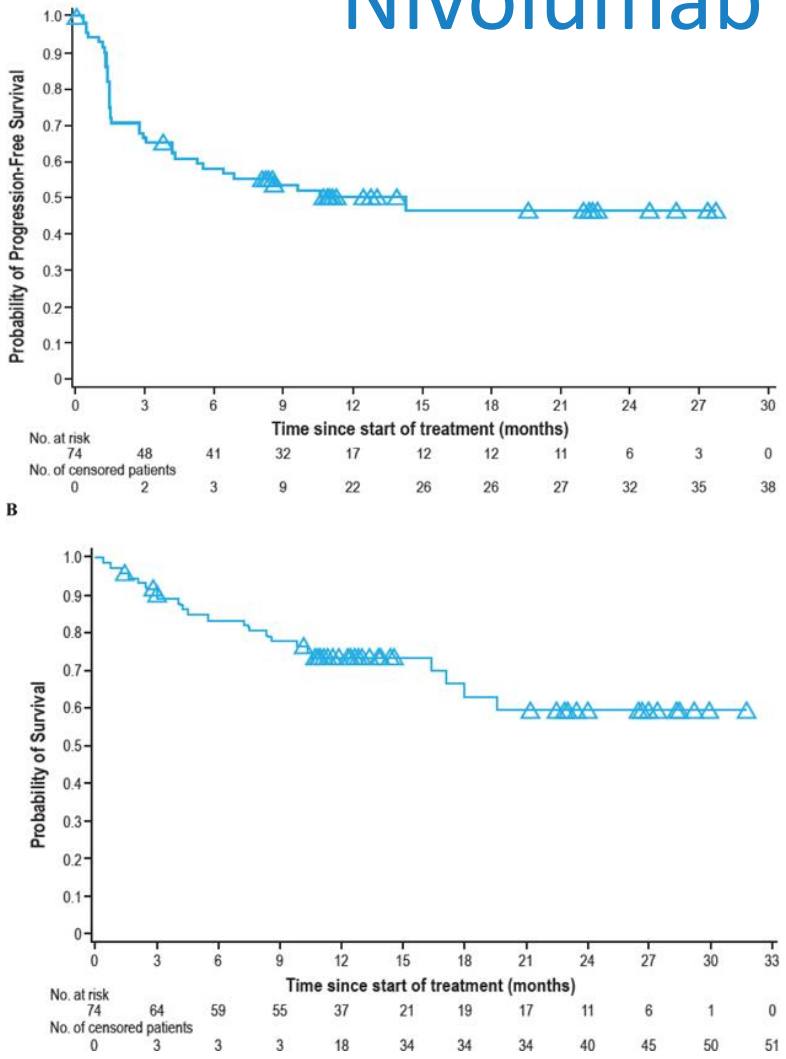
NR = not reached

CheckMate 142



- Median follow-up in the combination therapy cohort (N = 119) was 13.4 months (range, 9–25)[c]
- Results of the monotherapy cohort (N = 74) with a similar median follow-up of 13.4 months (range, 10–32) are also presented[1,c]

Clinical Data – CheckMate 142
Nivolumab monotherapy



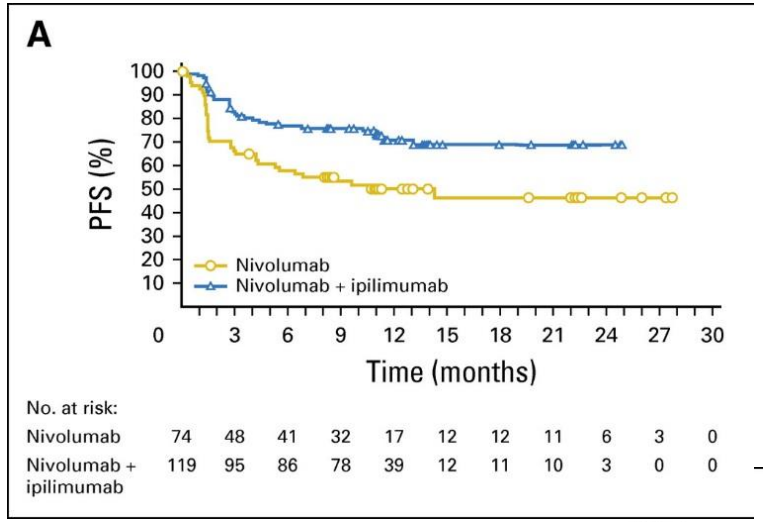
- mCRC with MSI-H, progressed after ≥1 therapy
- Nivolumab 3 mg/kg Q2W
- At 12 months: 31% ORR
- 68.9% disease control >12 weeks
- Median DOR not reached

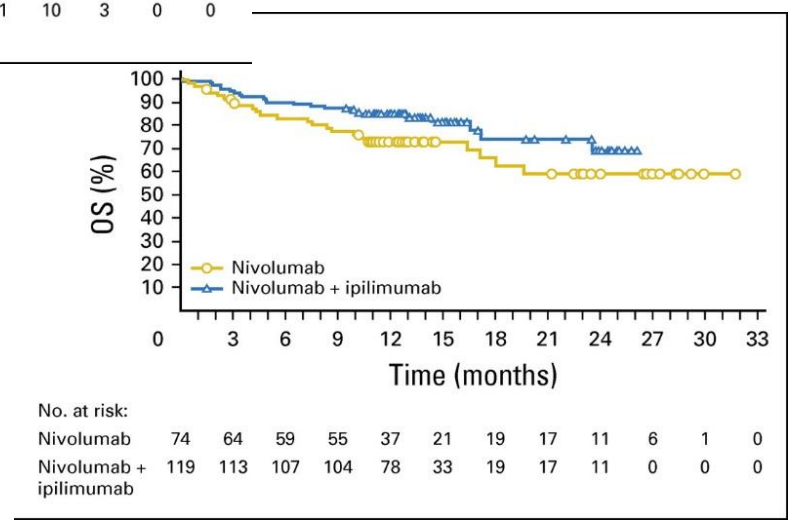
Overman, Lancet Oncol 2017.

Clinical Data – CheckMate 142

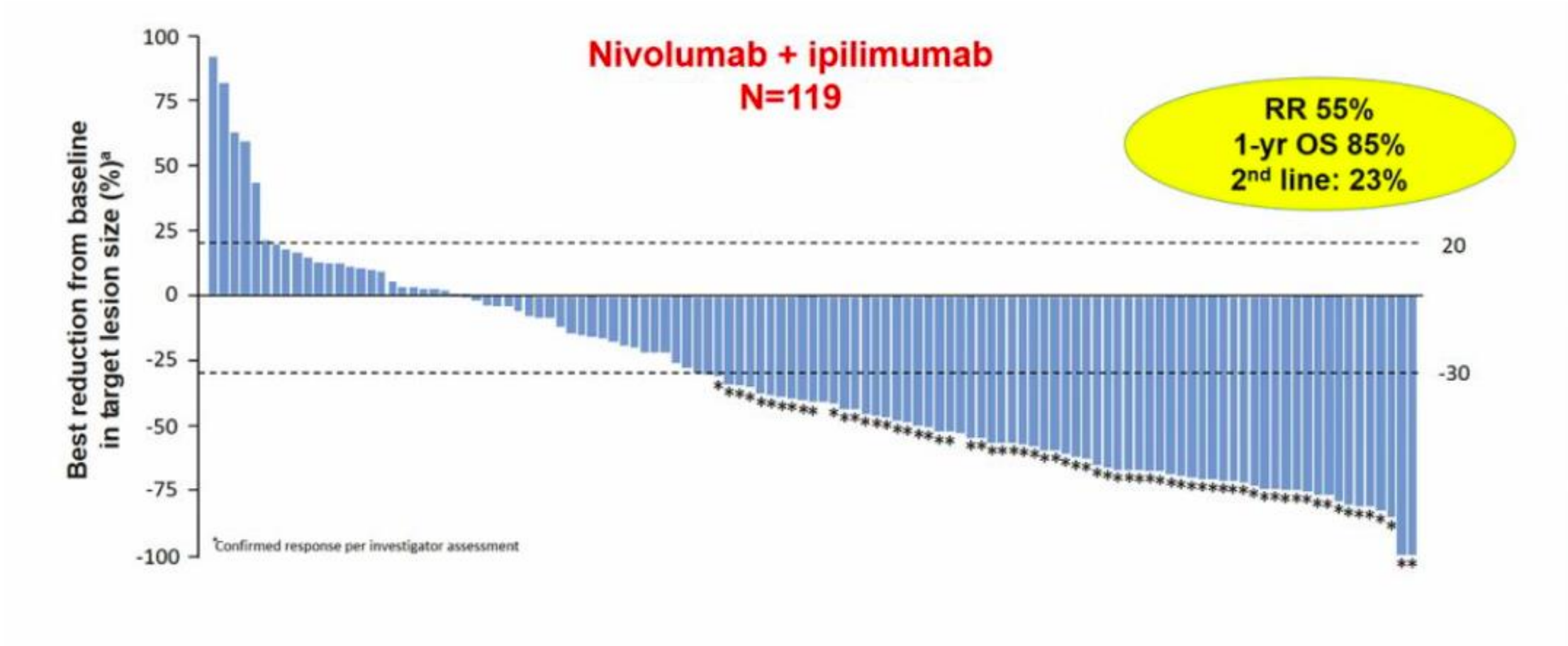
Nivolumab + Ipilimumab

- MSI-H/dMMR mCRC
- Nivolumab 3mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), then nivolumab 3 mg/kg Q2W
- At 13.4 months: 55% ORR
- PFS: 76% (9 months); 71% (12 months)



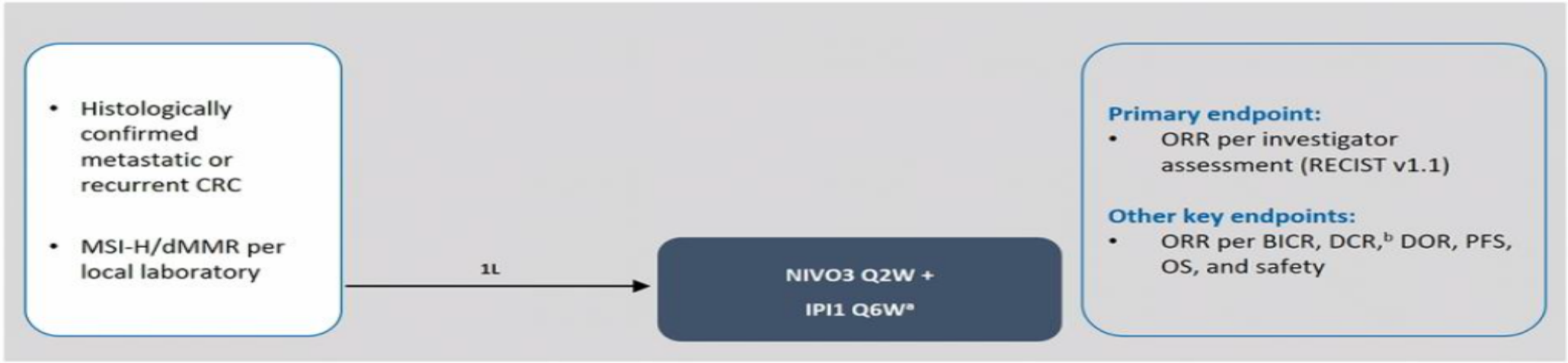


Overman, J Clin Oncol 2018.



First Line metastatic MSI-H CRC

Nivo + Ipi: First Line MSI-H CRC



Heinz-Josef Lenz, ESMO 2018

ORR 60%, CBR 84% with durable deep responses

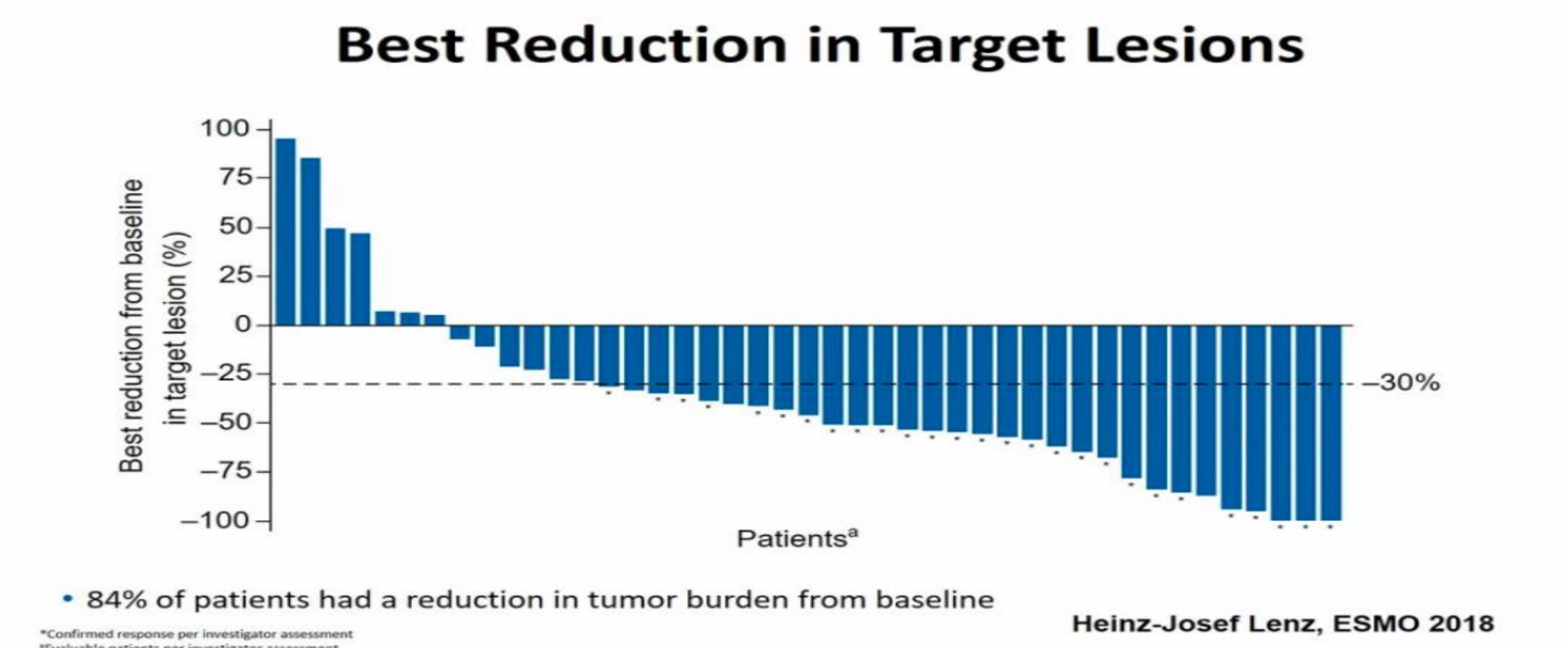
Response and Disease Control

Investigator-assessed	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
ORR[a], n (%) [95% CI]	27 (**60**) [44.3–74.3]
Best overall response, n (%)* CR PR SD PD Not determined	 3 (**7**) 24 (53) 11 (24) 6 (13) 1 (2)
DCR[b], n (%) [95% CI]	38 (**84**) [70.5–93.5]

- Responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutation status, or diagnosis of Lynch syndrome
  - The ORR and DCR in patients with a *BRAF* mutation (n = 17) were 71% and 88%, respectively

*Percentages may not add up to 100% because of rounding
[a]Patients with CR or PR divided by the number of treated patients; [b]Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients

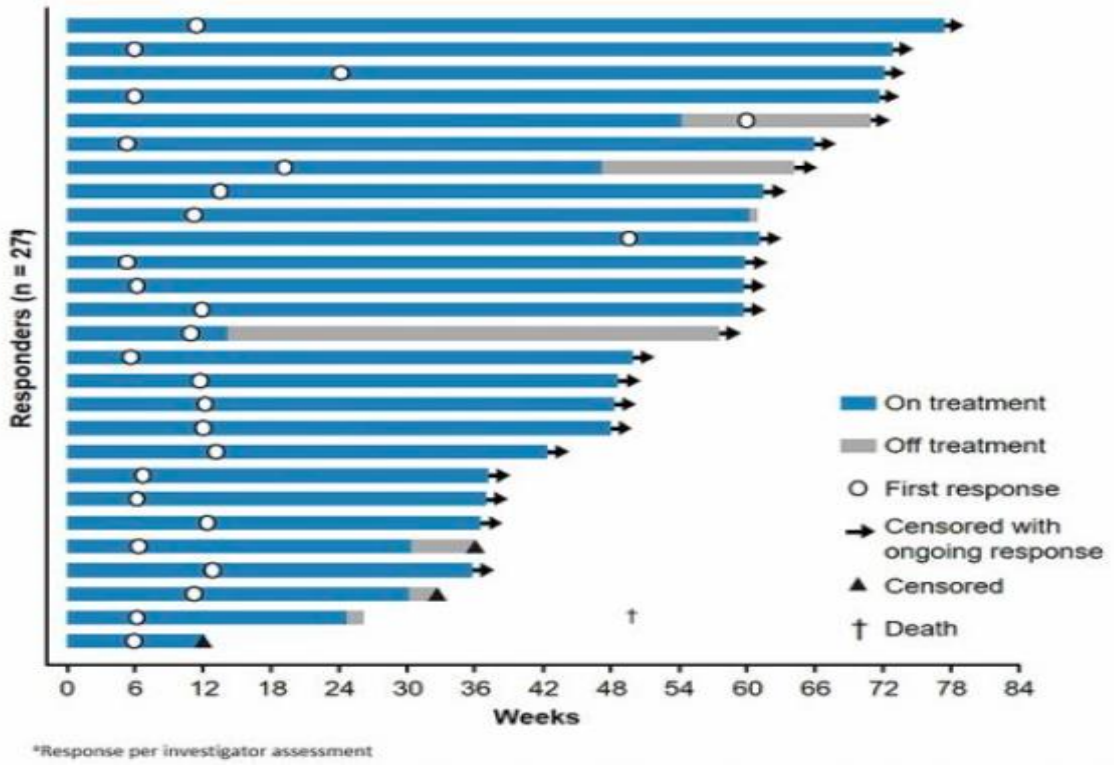
>80% of patients had decreased Tumor burden and benefit from therapy



Heinz-Josef Lenz, ESMO 2018

Durable response with mDoR was not reached

Characterization of Response



- Median time to response was 2.6 months (range, 1.2–13.8 months)
- Responses were durable:
  - Median DOR was not reached
  - 82% of responders had ongoing responses at data cutoff
  - 74% of responders have already had responses lasting ≥6 months
  - Most responders (96%) were alive at data cutoff

Heinz-Josef Lenz, ESMO 2018

In development for MSI-high

- Other tissue-agnostic markers:
  - Microbiome
  - POLE mutation
  - Mutational signatures beyond TMB
  - GEP immune signature (IFN-g signature)

Resistance in MSI-H tumors

- Loss of β2 Microglobulin, a critical component of the antigen presentation machinery and MHC class I expression.
  - Gurjao C, Liu D, Hofree M, et al. Intrinsic Resistance to Immune Checkpoint Blockade in a Mismatch Repair Deficient Colorectal Cancer. Cancer Immunol Res. 2019 Jun 19. pii: canimm.0683.2018. doi: 10.1158/2326-6066.CIR-18-0683. [Epub ahead of print]
- Other mechanisms are similar to causes of resistance to ICI in any cancer type

Immunotherapy for the Treatment of Breast & Gynecologic Cancers

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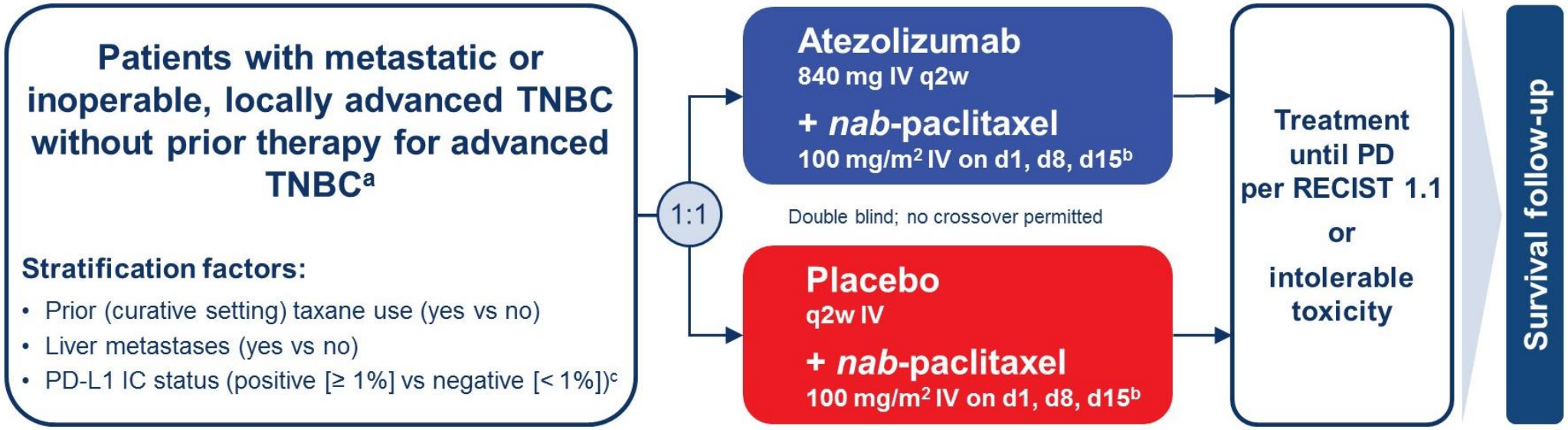
Current approvals

Drug	Approved	Indication	Dose
Atezolizumab + nab-paclitaxel	2019	Advanced/Metastatic **TNBC** with PD-L1 ≥1%	840 mg atezolizumab + 100 mg/m^2 nab-paclitaxel
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

Clinical Data – IMpassion130 PD-L1+ TNBC

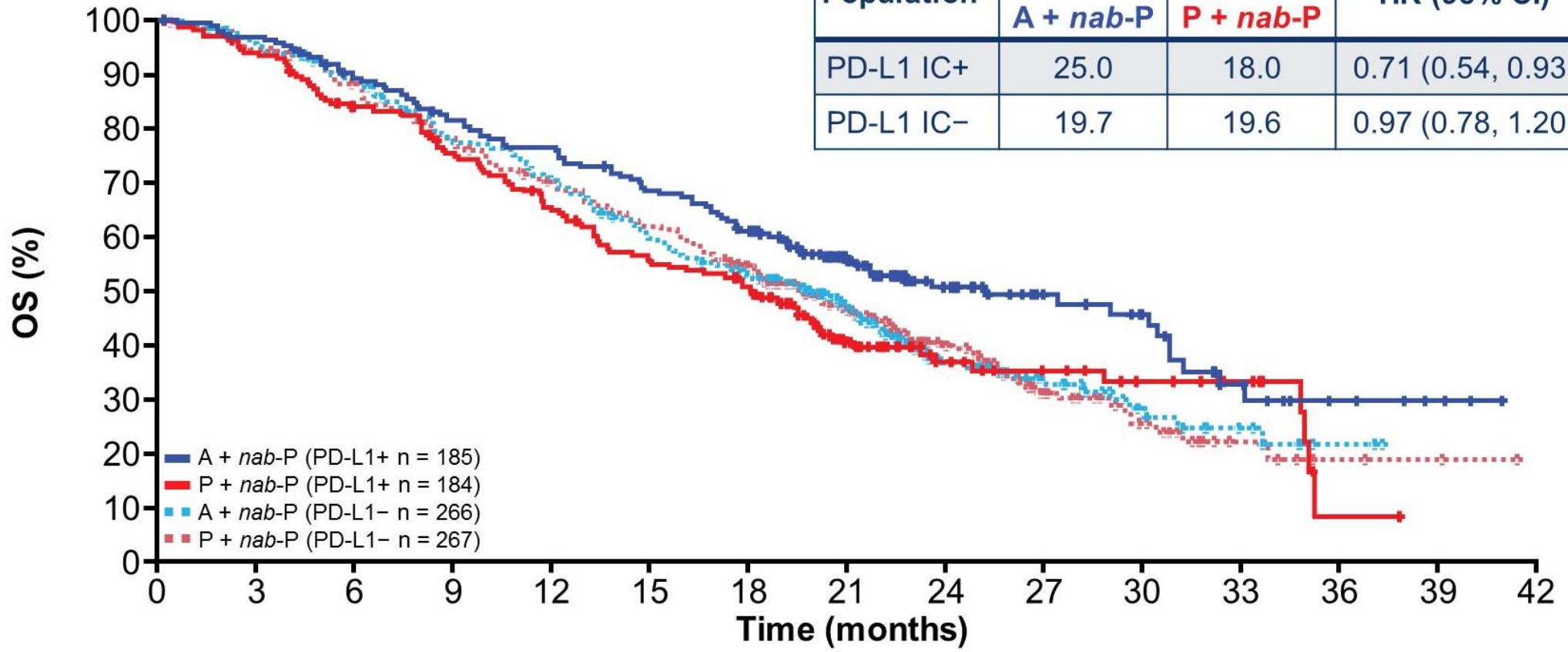


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

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)

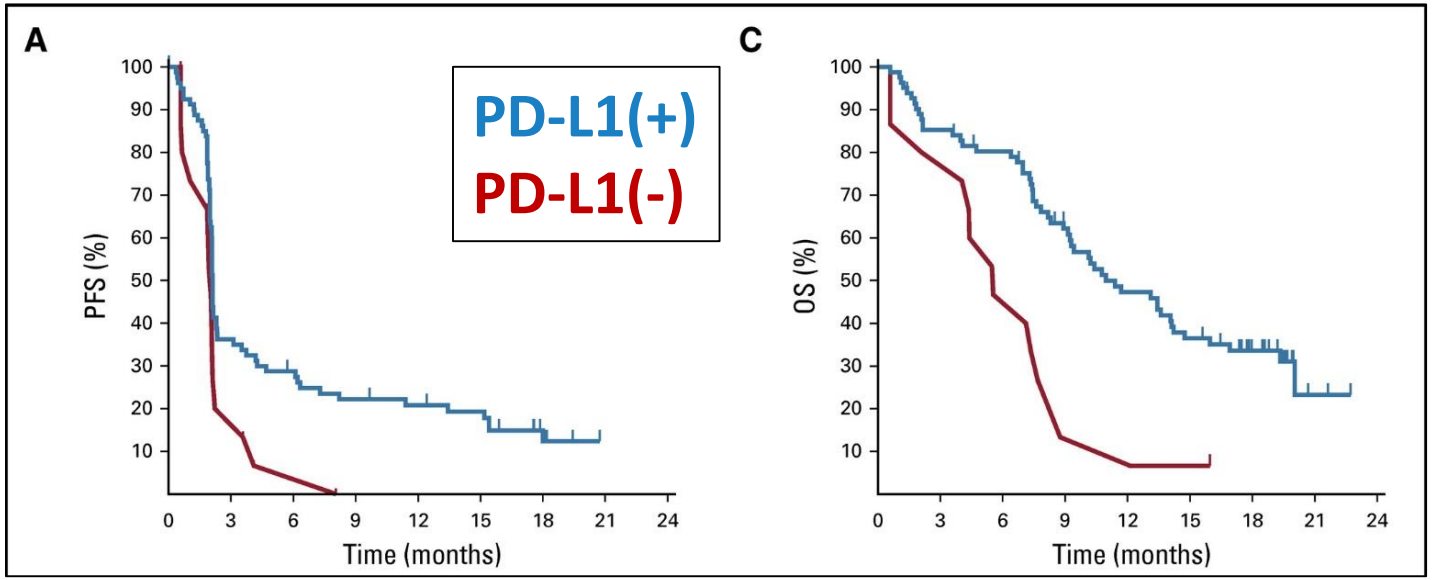


Schmid, ASCO 2019.

Cervical Cancer

Clinical Data – KEYNOTE-158

- 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(+)



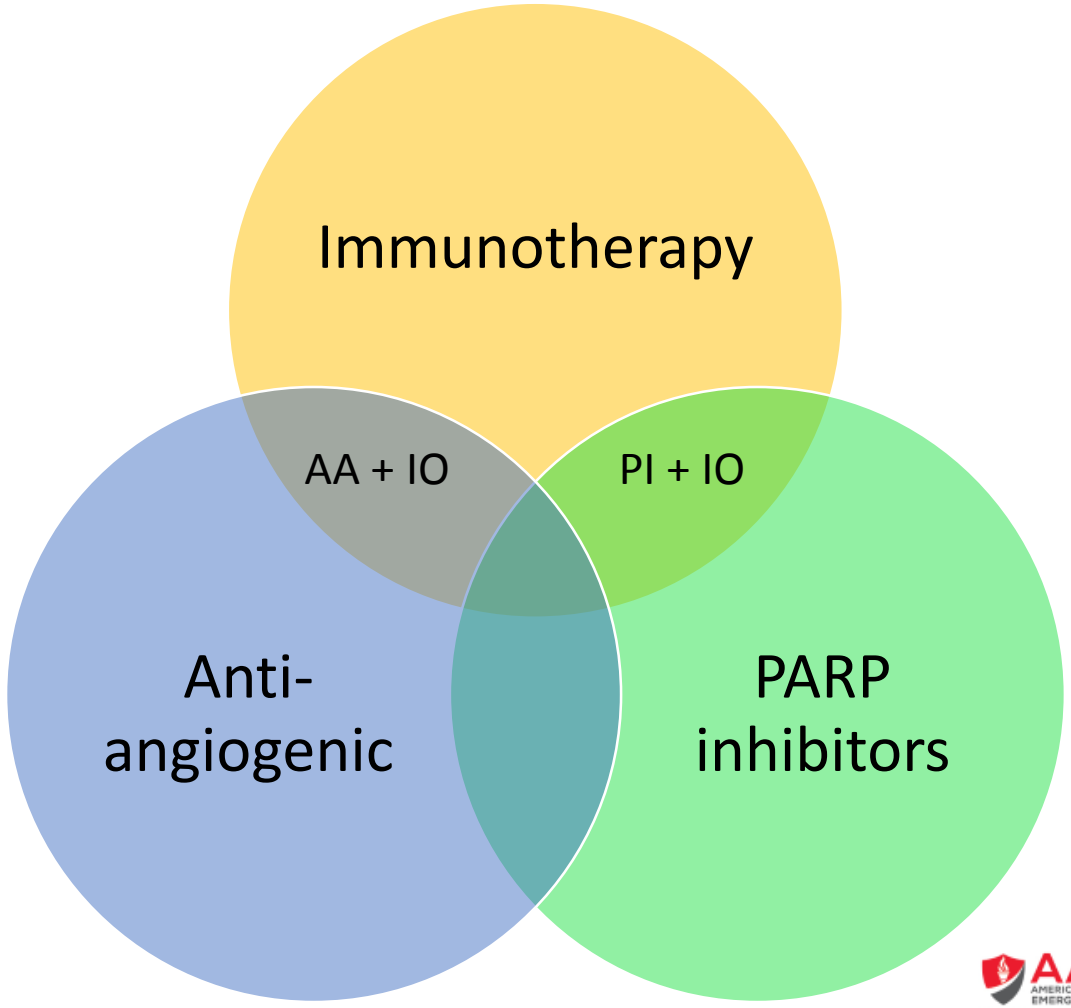
Cheol Chung, J Clin Oncol 2019.

Future Directions

In development: 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			

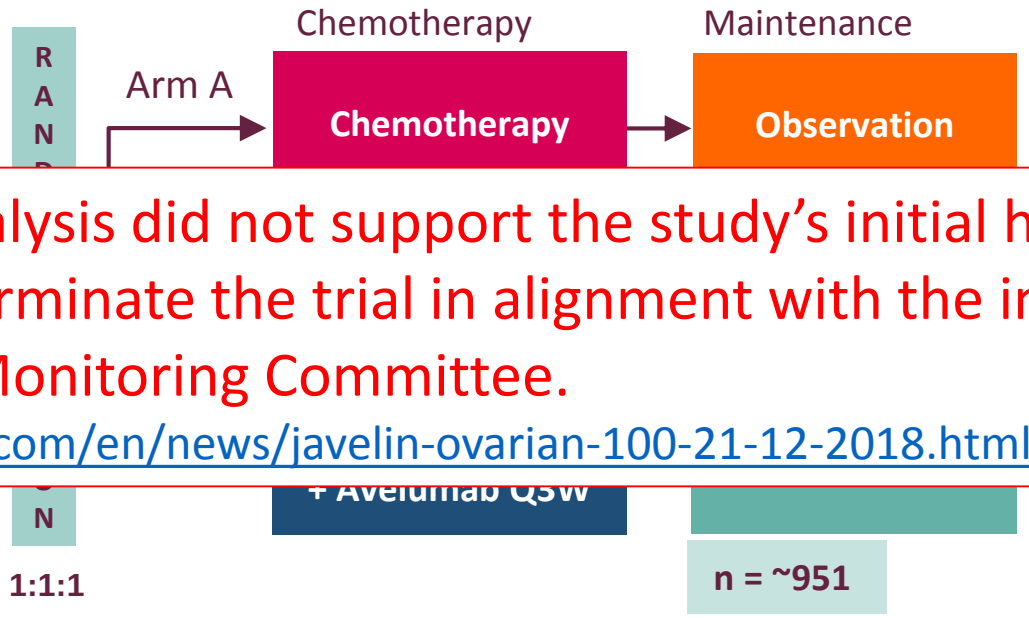
In development: Therapeutic strategies in ovarian cancer



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

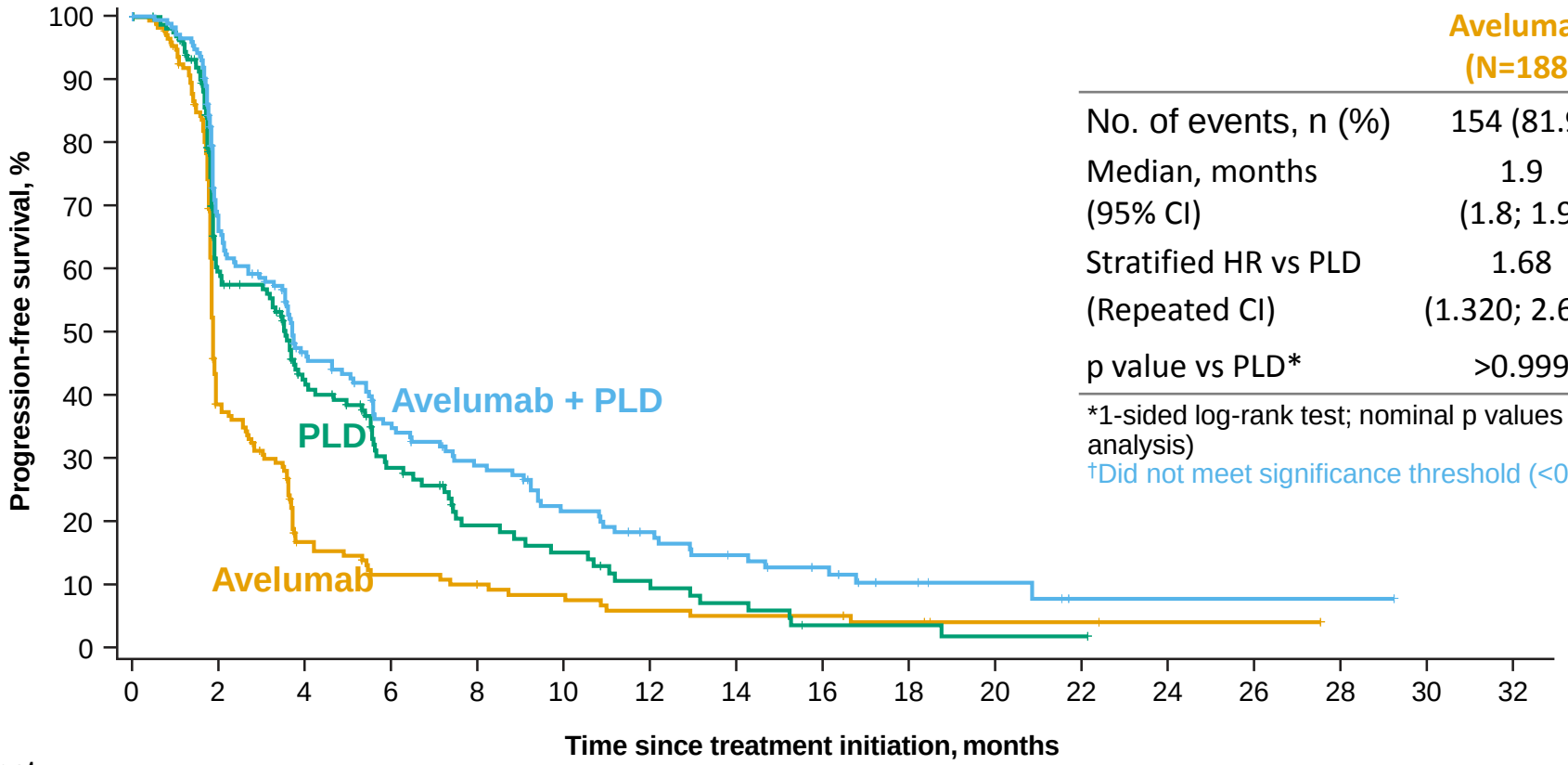
Primary Endpoint:	**PFS**
Secondary Endpoints:	**Maintenance PFS, OS, ORR, duration of response, pCR, PROs, safety**, PK

- 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.

JAVELIN Ovarian 200 Results



	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)

Number at risk																
Avelumab:	188	63	23	15	12	10	7	6	6	4	2	2	1	1	0	
Avelumab + PLD:	188	111	68	49	38	26	20	15	11	6	4	1	1	1	1	0
PLD:	190	86	53	31	18	14	8	6	2	2	1	1	0			

Pujade-Lauraine, SGO Women's Cancer 2019.

Clinical trials in ovarian cancer – AA + 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 – PI + 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 – PI + AA + 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

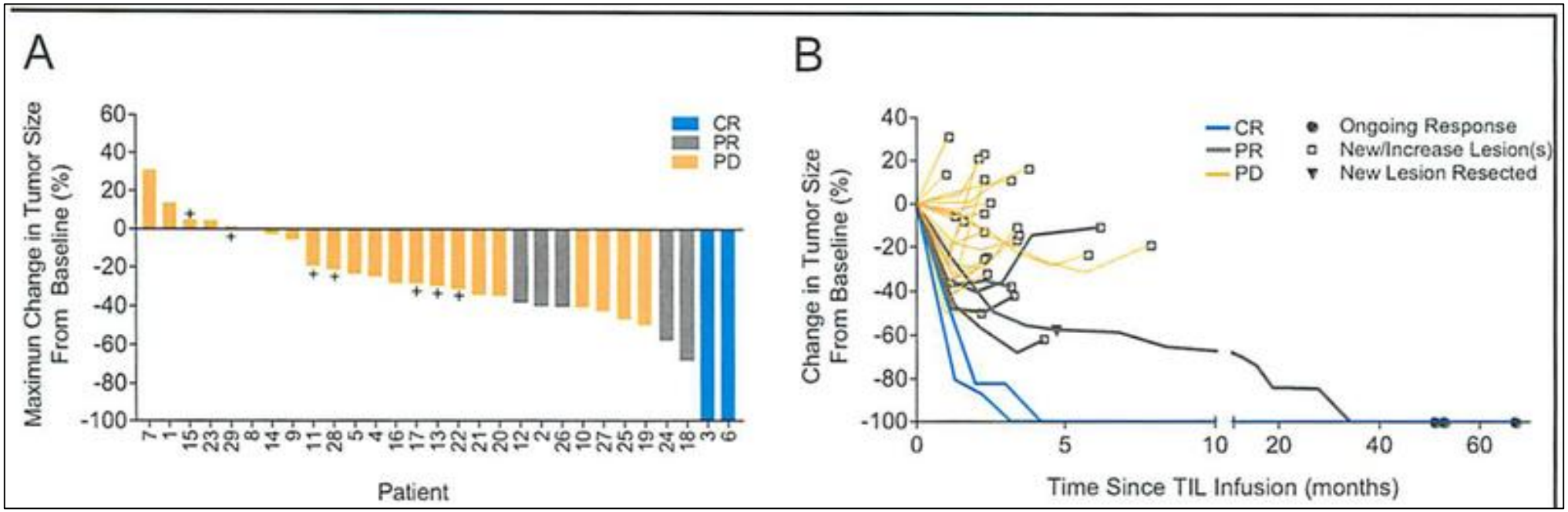
Cervical cancer immunotherapy opportunities:

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

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

In development: 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.

Break Through Designation
TIL in recurrent cervical cancer

Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma.

- 27 efficacy evaluable patients
- ORR was 44% (1 CR, 9 PR, 2 uPR)
- DCR was 89% at 3.5-month median study follow-up with 11/12 patients maintaining their response

ASCO 2019

Break Through Designation MSS/pMMR Endometrial Cancer-2nd line Pembrolizumab+Lenvatinib

- KN-146
- N=54
- 13 months follow up
- ORR 40%
- Toxicity is a concern? (>50%)
  - Can we find better less toxic alternative to Lenvatinib

Makkar et al, The Lancet Oncology, 2019

Conclusions

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

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Case Studies

Case Study 1

- 50 year old woman with history of abnormal pap smear with atypical glandular cells of endometrial origin in Jan. 2018 with no follow up then in July 2018, she presented with shortness of breath. Work up includind CT PE showed evidence of bilateral PE. At that time, she reported vaginal bleeding. CT abdomen/pelvis was c/w extensive pelvic adenopathy (largest 5.5 on left nd 4 cm on right), left adnexal mass and cervical mass extending to upper vagina and lower endometrium.
- What would be your next step:
  - She underwent IR biopsy of the pelvic adenopathy
  - Results: high grade adenocarcinoma, P53+, ER+, PAX8+, CDX2-, TTF1-, P16+
    - Endometrioid cell type
    - Mulerian origin
      - Cervical vs. endometrial
      - ?HPV status

Case Study 1

- Treatment course

1. Neo-adjuvant chemoRT with weekly cisplatin
   - Post-Tx PET/CT scan showed persistent disease with new para-aortic adenopathy
2. Next Step:
3. Chemotherapy: Carboplatin/Taxol
   - Could not be tolerated
4. Next step
   - Tumor for MMR status, genomic profiling
   - IHC: loss of PMS2/MLH1 expression
5. Next step

Case Study 1

5. Next step
   A. Somatic vs. germline: MLH1 promoter methylation
   B. Immunotherapy with PD1 inhibitor pembrolizumab
      - Major treatment response with resolution of adenopathy, decrease in size of adnexal masses and normalization of CA-125 (450s at start) then continued with stable disease (durable major partial response)
      - Still on treatment and currently received 12 cycles
6. Question: CA-125 is rising but CT scan stable, what would you do?

Case Study 2

- 61 yr old woman with fatigue and vaginal bleeding. CT scan showed pelvic and retro-peritoneal adenopathy and 5-6cm pelvic mass in the lower uterine segment extending to the cervix. On exam friable 6-7 cm cervical mass extending to bilateral parametria and upper vagina was noted.
- Next step:
  - She underwent exam under anasthesia, biopsies, cystoscopy and proctoscopy
  - Results: moderately differentiated squamous cell carcinoma
  - Pelvic MRI and PET/CT scan: multiple hypermetabolic pulmonary nodules, large cervical mass, retroperitoneal/pelvic and inguinal adenopathy
- Next step

Case Study 2

- Primary chemotherapy: Regimen?
  - Cisplatin/Taxol/bevacizumab. Received 9 cycles
  - Initial response then disease progression with increased size of cervical mass and adenopathy
- Next step?
  - Immunotherapy with pembrolizumab?
- What test do you need?
  - PDL1 testing: what do you do at your site PDL1 or CPS
    - What is the difference?
  - CPS for her came back 25
- Started immunotherapy with pembrolizumab.
  - Stable disease, s/p 6 cycles thus far