HIGHLIGHTS OF GYNECOLOGIC MALIGNANCIES

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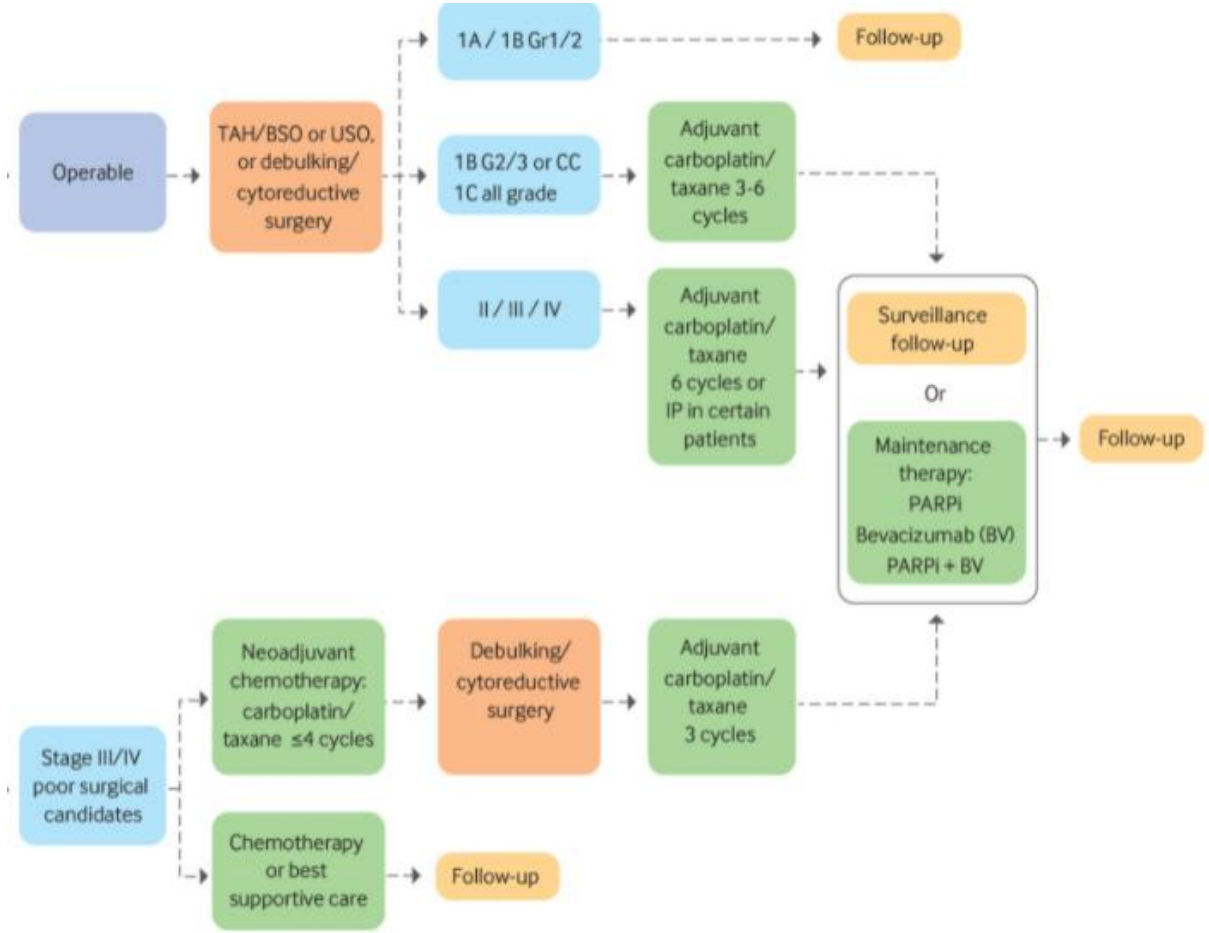
Disclosures

- I have nothing to disclose.

Objectives

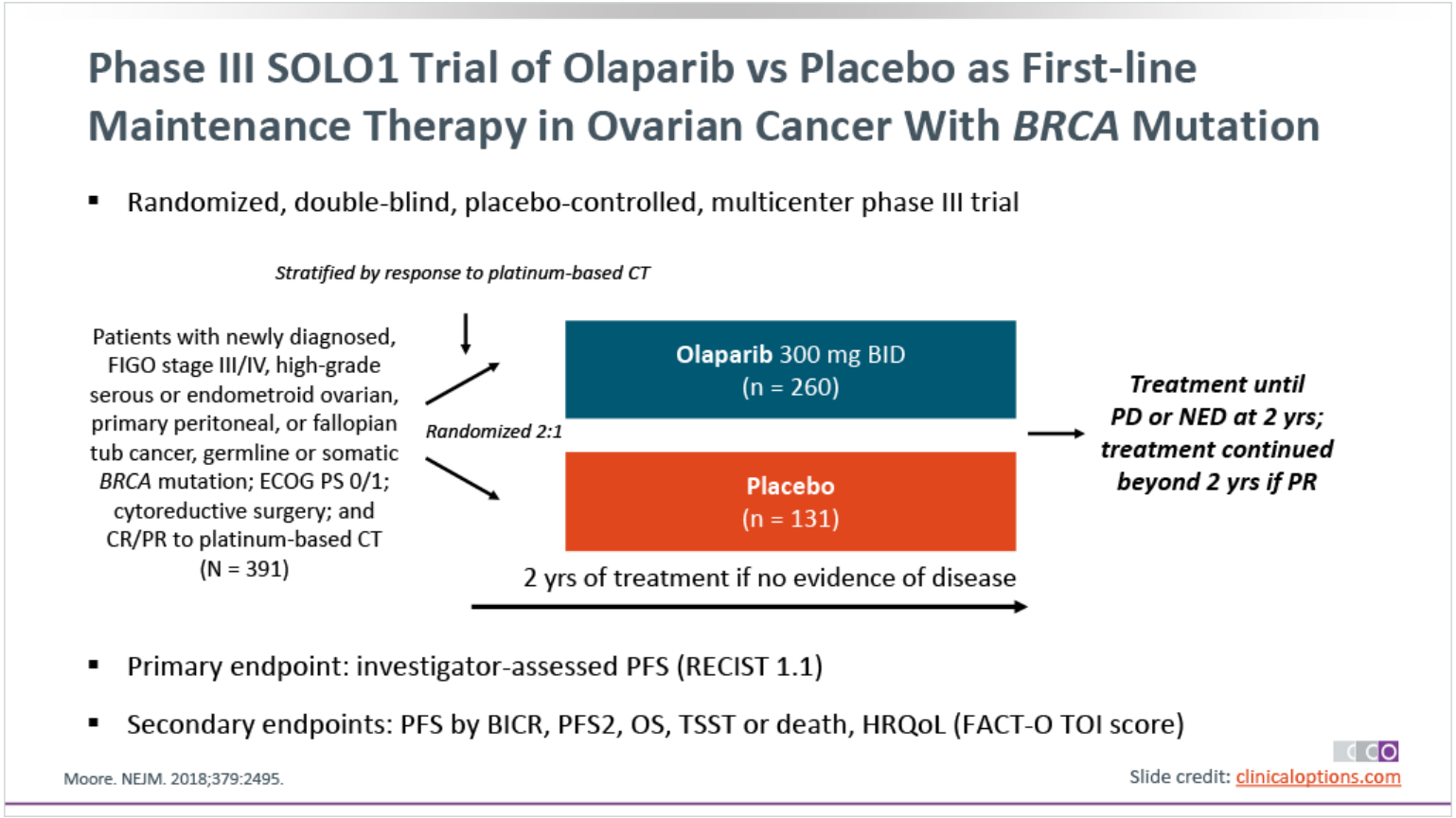
- Review practice changing publications and drug approvals impacting Gynecologic Oncology practice
- PARPi in high grade epithelial ovarian cancer as maintenance following initial therapy
- Chemoradiation versus chemotherapy in high risk endometrial cancer
- Checkpoint inhibitor therapy in MSI-H gynecologic cancers
- Adjuvant chemotherapy following definitive chemoradiation in cervical cancer
- Second line therapy in metastatic endometrial cancer
- Tissue agnostic, biomarker driven NTRK therapy in gynecologic malignancies

Consensus Approach to Initial Therapy of High Grade EOC

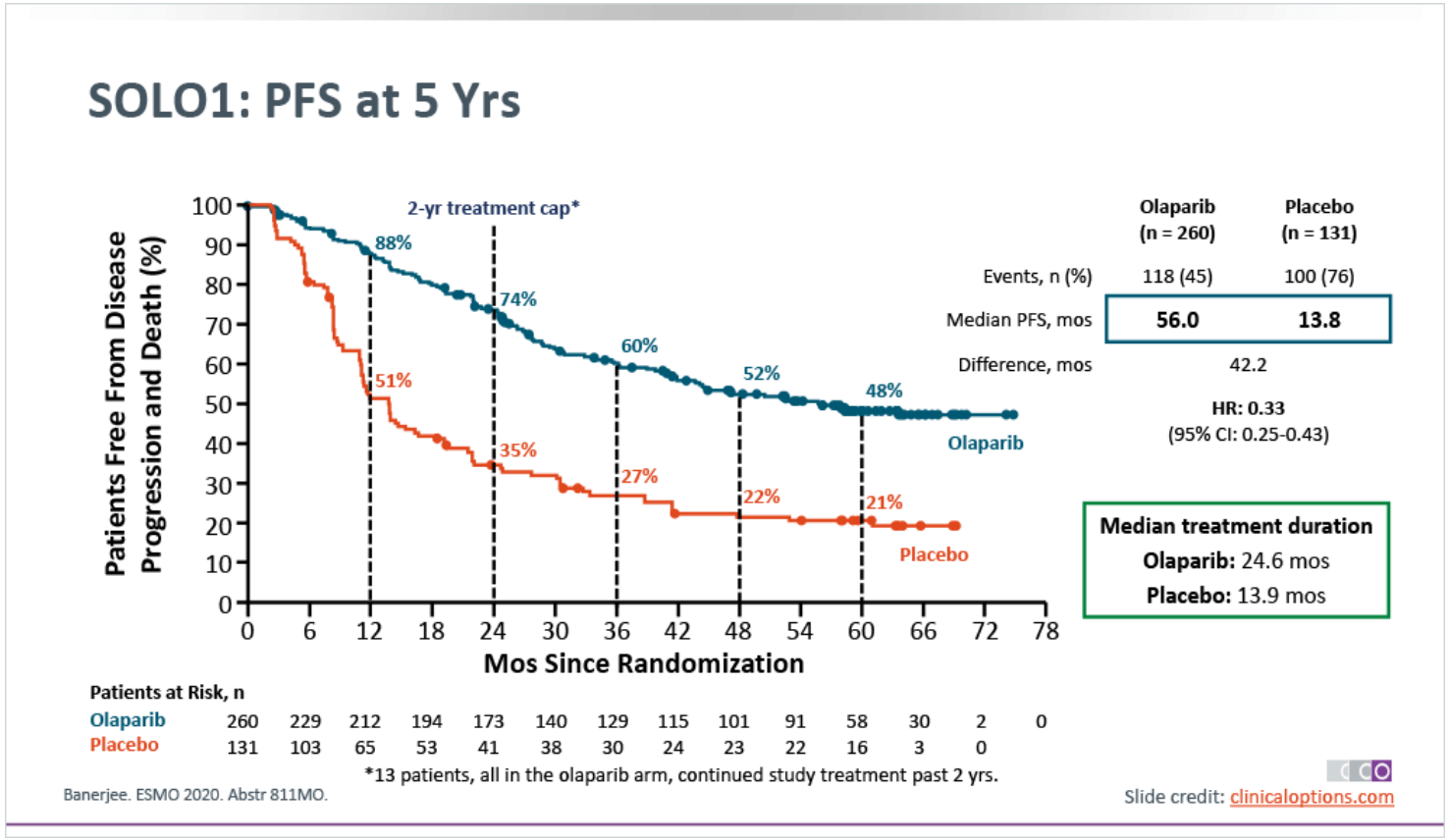


Lindsay Kuroki, and Saketh R Guntupalli BMJ 2020;371:bmj.m3773

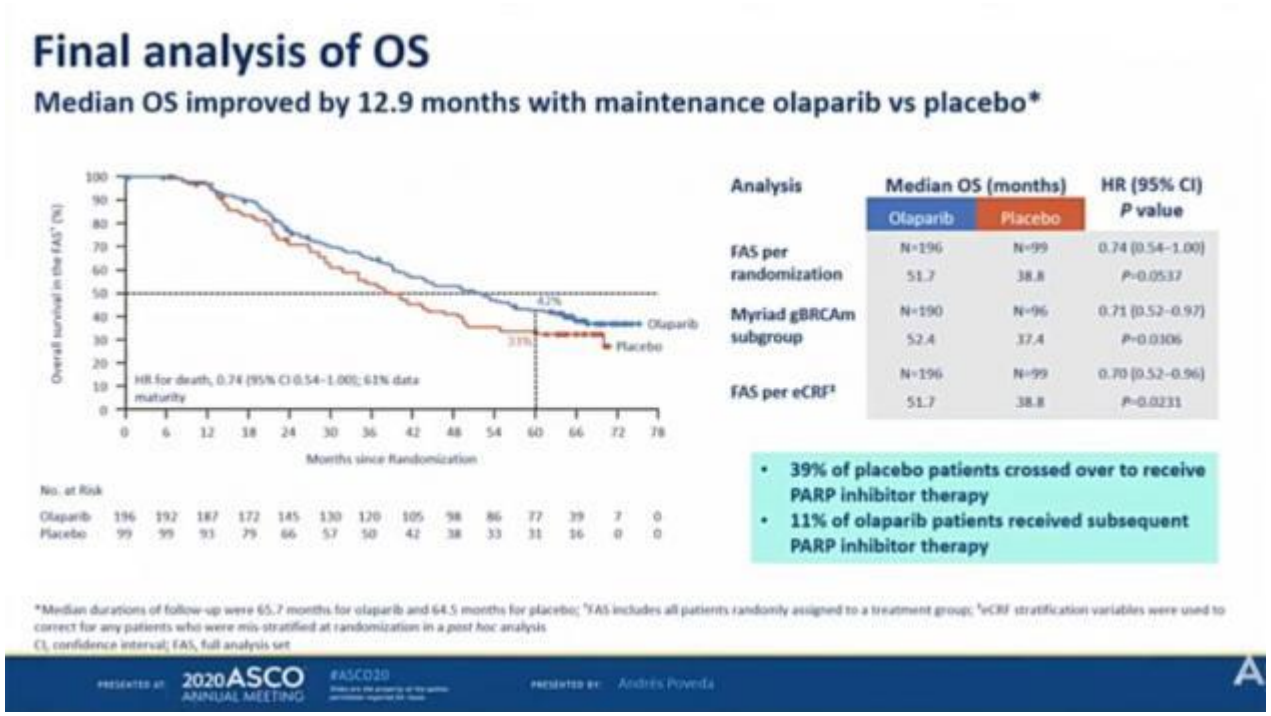
Olaparib Maintenance Therapy: SOLO-1



Olaparib Maintenance Therapy: SOLO-1



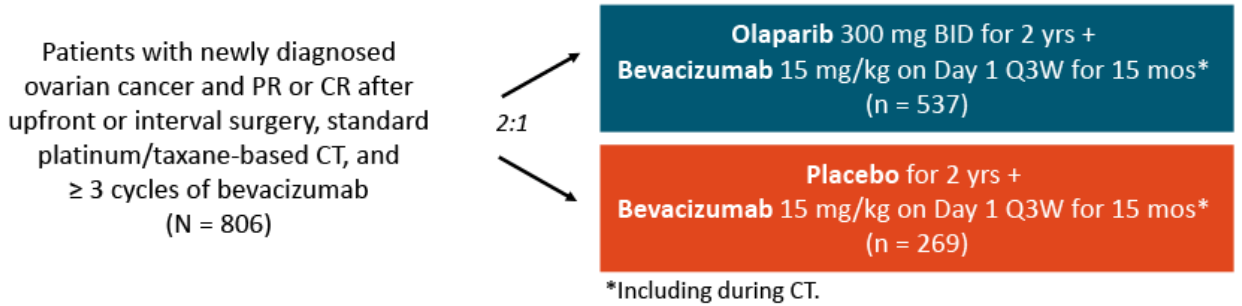
Olaparib Maintenance Therapy: SOLO-1



Olaparib Maintenance Therapy: PAOLA-1

PAOLA-1: Maintenance Olaparib + Bevacizumab After Initial Therapy for Ovarian Cancer

- Randomized, placebo-controlled phase III trial for patients with newly diagnosed, FIGO stage III-IV, high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer



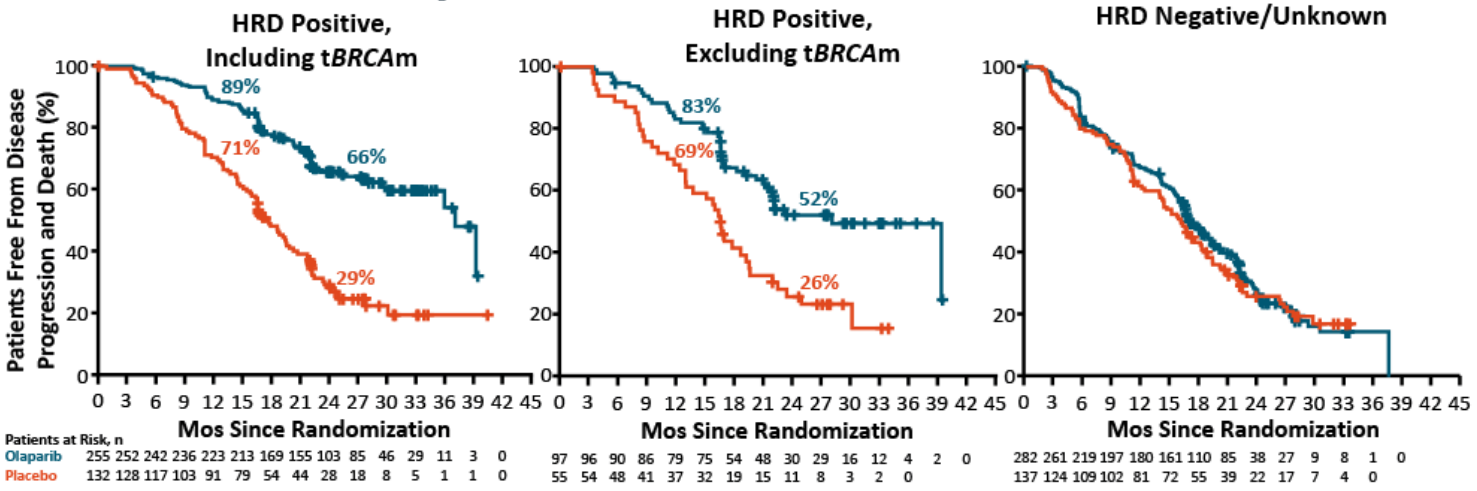
*Including during CT.

- Primary endpoint: investigator assessed PFS (RECIST v1.1)
- Secondary endpoints: TFST, PFS2, TSST, OS, HRQoL, AE
- Sensitivity analysis: PFS by BICR

Ray-Coquard. ESMO 2019. Abstr. LBA2.

Slide credit: clinicaloptions.com

Olaparib Maintenance: PAOLA-1



	O + B (n = 255)	P + B (n = 132)		O + B (n = 97)	P + B (n = 55)		O + B (n = 282)	P + B (n = 137)
Events, n (%)	87 (34)	92 (70)	Events, n (%)	43 (44)	40 (73)	Events, n (%)	193 (68)	102 (74)
Median PFS, mos	37.2*	17.7	Median PFS, mos	28.1*	16.6	Median PFS, mos	16.9	16.0
	HR: 0.33 (95% CI: 0.25-0.45)			HR: 0.43 (95% CI: 0.28-0.66)			HR: 0.92 (95% CI: 0.72-1.17)	

*Unstable due to lack of events; < 50% maturity.

Ray-Coquard. ESMO 2019. Abstr. LBA2. Ray-Coquard. NEJM. 2019;381:2416.

Slide credit: clinicaloptions.com

OLAPARIB maintenance

Table 3. Efficacy results from SOLO-1 and PAOLA-1 trials

Trial name	Patient population	Maintenance treatment arms	PFS in indicated population	Companion diagnostic
SOLO-1	*BRCA*m newly diagnosed advanced ovarian cancer	Olaparib vs. placebo	*BRCA*m population PFS NR vs. 13.8 months HR: 0.30 (0.23, 0.41)	BRACAnalysis CDx and FoundationOne CDx
PAOLA-1	Newly diagnosed advanced ovarian cancer	O+B vs. P+B	HRD-positive population PFS 37.2 vs. 17.7 months HR: 0.33 (0.25, 0.45)	Myriad myChoice CDx

Abbreviations: *BRCA*m, *BRCA* mutated; CDx, companion diagnostic; HR, hazard ratio; HRD, homologous recombination deficient; NR, not reached; O+B, olaparib plus bevacizumab; P+B, placebo plus bevacizumab; PFS, progression-free survival.

Both trials demonstrated that BRCAm patients treated with Olaparib monotherapy and HRD positive patients Treated with O+B had a clinically meaningful improvement in PFS.

Olaparib Maintenance: Safety

Table 4. Safety results from SOLO-1 and PAOLA-1 trials

Trial name	Patient population	Maintenance treatment arms	Median time on therapy (months)	Discontinuations because of AE	All grade AEs	Grade 3–4 AEs	On treatment deaths
SOLO-1 (*n* = 391)	*BRCA*m newly diagnosed advanced ovarian cancer	Olaparib vs. placebo	O: 24.6 P: 13.9	O: 12% P: 2%	O: 99% P: 92%	O: 30% P: 5%	No deaths because of AEs while on study drug or within 30 days after last dose in either arm
PAOLA-1 (*n* = 806)	Newly diagnosed advanced ovarian cancer	O+B vs. P+B	O+B: 17.3 P+B: 15.6	O+B: 20% P+B: 6%	O+B: 99% P+B: 96%	O+B: 57% P+B: 50%	O+B: 1 death because of aplastic anemia/ pneumonia P+B: 4 deaths (2 myocardial infarction, 1 intestinal perforation, 1 cardiovascular failure)

Abbreviations: AE, adverse event; B, bevacizumab; *BRCA*m, *BRCA* mutated; O, olaparib; O+B, olaparib plus bevacizumab; P, placebo; P+B, placebo plus bevacizumab.

Niraparib

Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391-2402.
Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154-2164.

NIRAPARIB Maintenance: PRIMA

PRIMA: Maintenance Niraparib vs Placebo in Ovarian Cancer at High Risk of Recurrence After 1L Platinum

- Randomized, double-blind, placebo-controlled phase III trial (active, not recruiting, as of 10/2020)

Stratified by neoadjuvant CT (yes vs no), best response to first platinum (CR vs PR), tissue HRD test (deficient vs proficient/not determined)

Patients with newly diagnosed, ovarian cancer* with response to 6-9 cycles 1L chemo; high risk of recurrence; neoadjuvant chemo allowed (N = 733)

Randomized 2:1

Niraparib 300 mg QD† x 28-day cycles (n = 487)

Placebo QD x 28-day cycles (n = 246)

Treatment for 36 mos or until PD

*Stage III w/residual tumor after debulking surgery, inoperable stage III disease, or any stage IV disease.

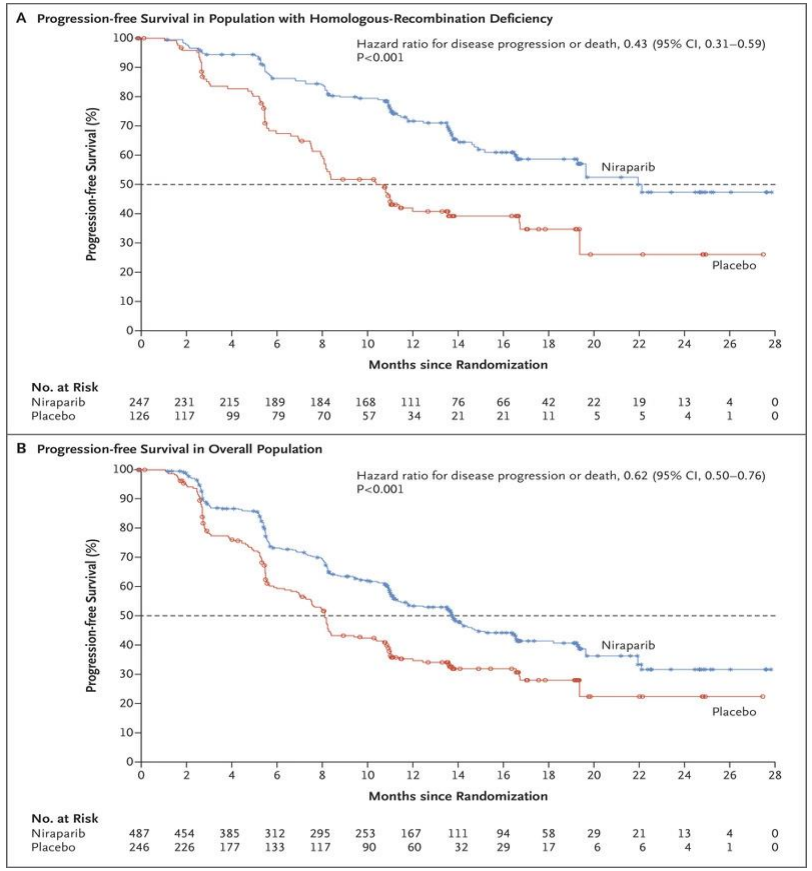
†Dosing amended in November 2017 to 200 mg QD if < 77 kg body weight, platelets < 150,000/mm³, or both.

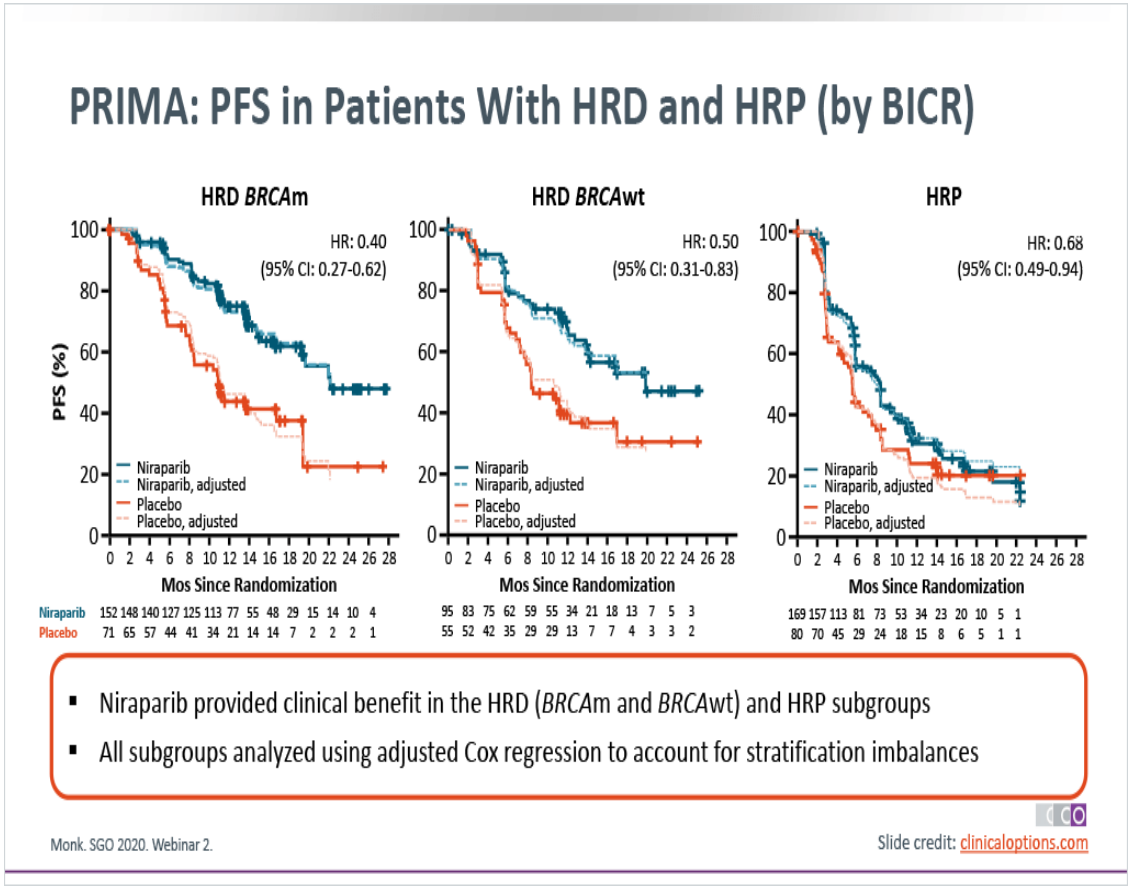
- Primary endpoint: PFS (HRD+ and overall population)
- Secondary endpoints: OS, PFS2, QoL PROs, safety

Gonzalez-Martin. NEJM. 2019;381:2391. Mirza. ASCO 2020. Abstr 6050.

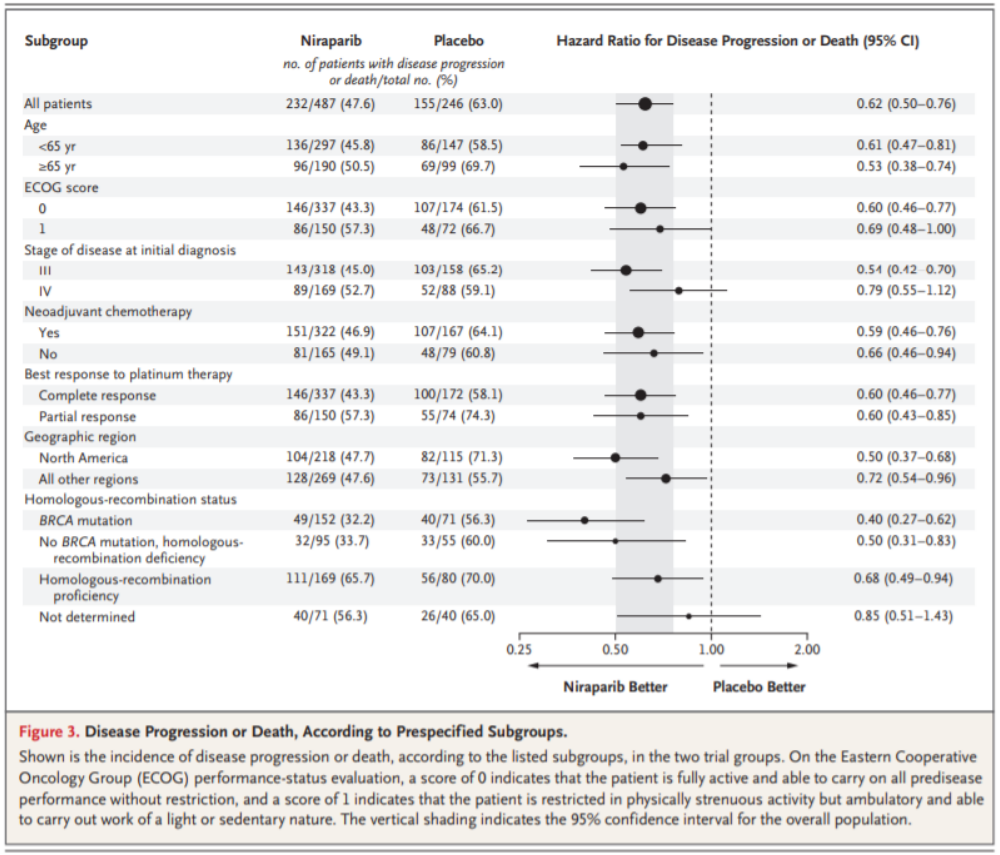
Slide credit: clinicaloptions.com

Niraparib Maintenance: PRIMA





Niraparib Maintenance: PRIMA



Subgroup	Niraparib	Placebo
	no. of patients with disease progression or death/total no. (%)	
All patients	232/487 (47.6)	155/246 (63.0)
Age		
<65 yr	136/297 (45.8)	86/147 (58.5)
≥65 yr	96/190 (50.5)	69/99 (69.7)
ECOG score		
0	146/337 (43.3)	107/174 (61.5)
1	86/150 (57.3)	48/72 (66.7)
Stage of disease at initial diagnosis		
III	143/318 (45.0)	103/158 (65.2)
IV	89/169 (52.7)	52/88 (59.1)
Neoadjuvant chemotherapy		
Yes	151/322 (46.9)	107/167 (64.1)
No	81/165 (49.1)	48/79 (60.8)
Best response to platinum therapy		
Complete response	146/337 (43.3)	100/172 (58.1)
Partial response	86/150 (57.3)	55/74 (74.3)
Geographic region		
North America	104/218 (47.7)	82/115 (71.3)
All other regions	128/269 (47.6)	73/131 (55.7)
Homologous-recombination status		
BRCA mutation	49/152 (32.2)	40/71 (56.3)
No *BRCA* mutation, homologous-recombination deficiency	32/95 (33.7)	33/55 (60.0)
Homologous-recombination proficiency	111/169 (65.7)	56/80 (70.0)
Not determined	40/71 (56.3)	26/40 (65.0)

Figure 3. Disease Progression or Death, According to Prespecified Subgroups.

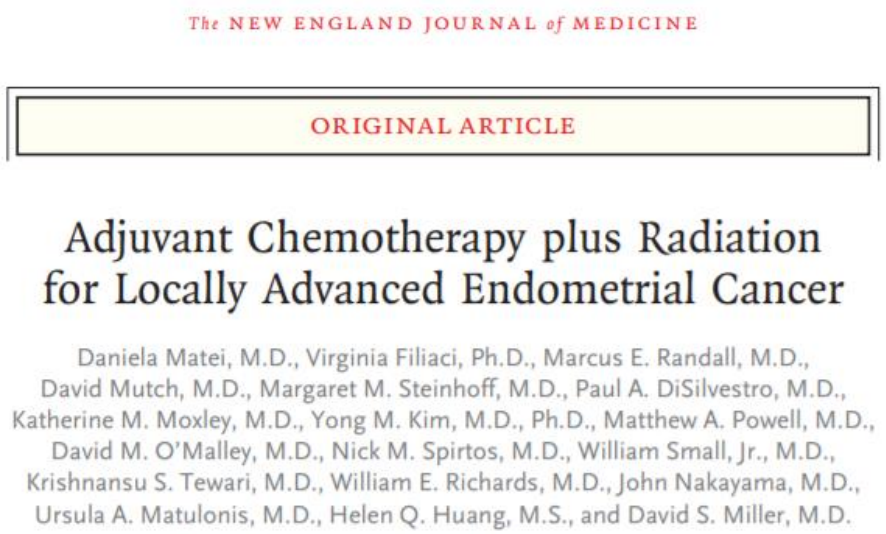
Shown is the incidence of disease progression or death, according to the listed subgroups, in the two trial groups. On the Eastern Cooperative Oncology Group (ECOG) performance-status evaluation, a score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. The vertical shading indicates the 95% confidence interval for the overall population.

PARPi Approved for Maintenance After Initial Therapy

Agent	FDA Approved	Indication	Biomarker	Dose
Olaparib	12/19/18	Maintenance in tBRCA positive patients after response to initial therapy	Germline or somatic BRCA mutation	300 mg BID for 2 years
Olaparib	5/8/20	Maintenance in combination with bevacizumab after response to initial therapy including bevacizumab	tBRCA or HRD positive	300 mg BID for 2 years, Bevaciumab 15 mg/kg every 21 days x 15 cycles
Niraparib	4/29/20	Maintenance after response to initial therapy	None	200 mg per day if <77 kg OR platelets <150; 300 mg per day if >77kg AND platelets>150

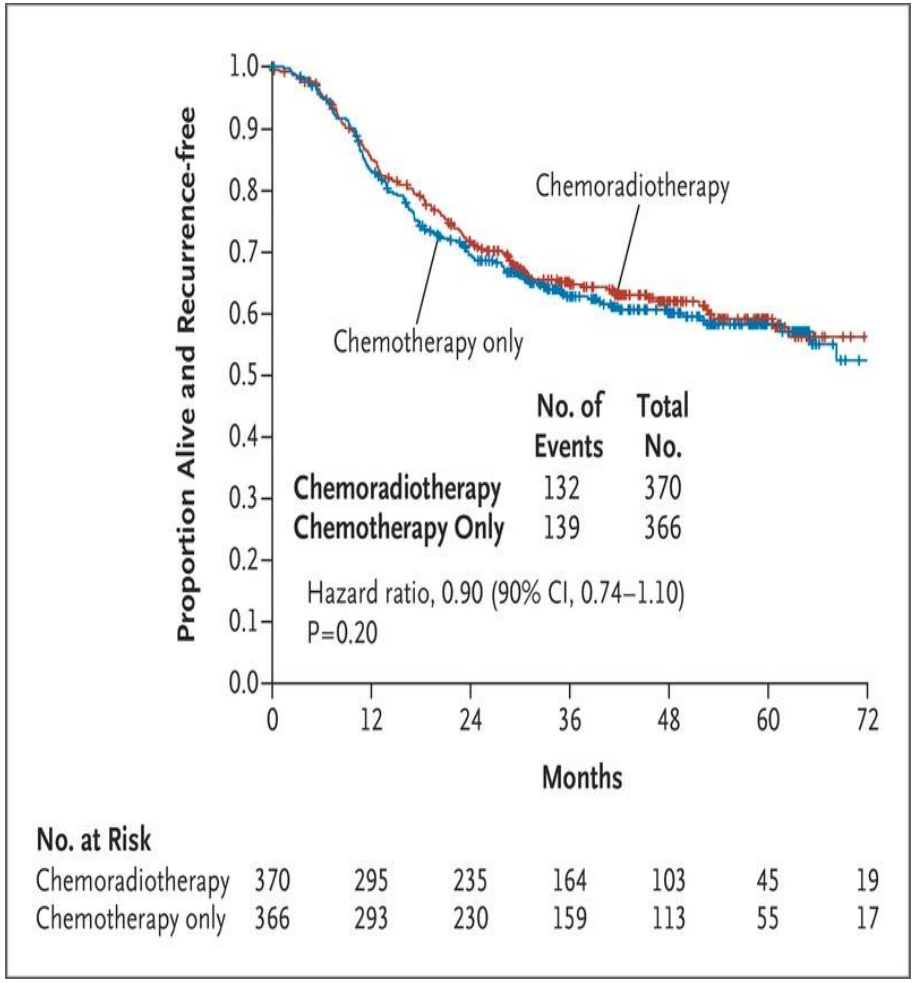
ENDOMETRIAL CANCER, CERVICAL CANCER

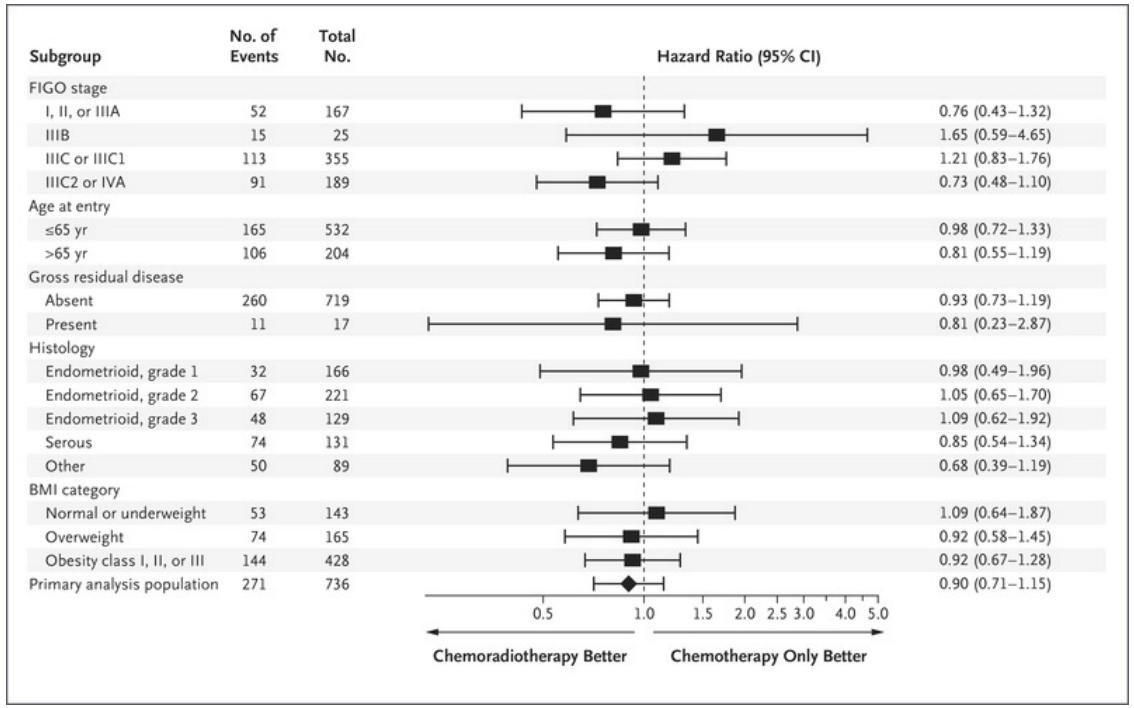
Does Adjuvant Chemoradiotherapy Extend Relapse-Free Survival in Stage III or IV Endometrial Cancer?



- Phase III GOG 258
  - Open label trial of 736 patients, 6/09-6/14
  - Adjuvant chemoradiotherapy: cisplatin 50 mg/m2 days 1 and 29 with volume-directed EBRT (4500 cGy in 25 fractions) followed by carboplatin AUC 5-6 plus paclitaxel 175 mg/m2 every 3 weeks for 4 cycles with growth factor support
  - Versus adjuvant carboplatin AUC 6 plus placlitaxel 175 mg/m2 every 3 weeks for 6 cycles.

Adjuvant CRT versus CT: GOG 258



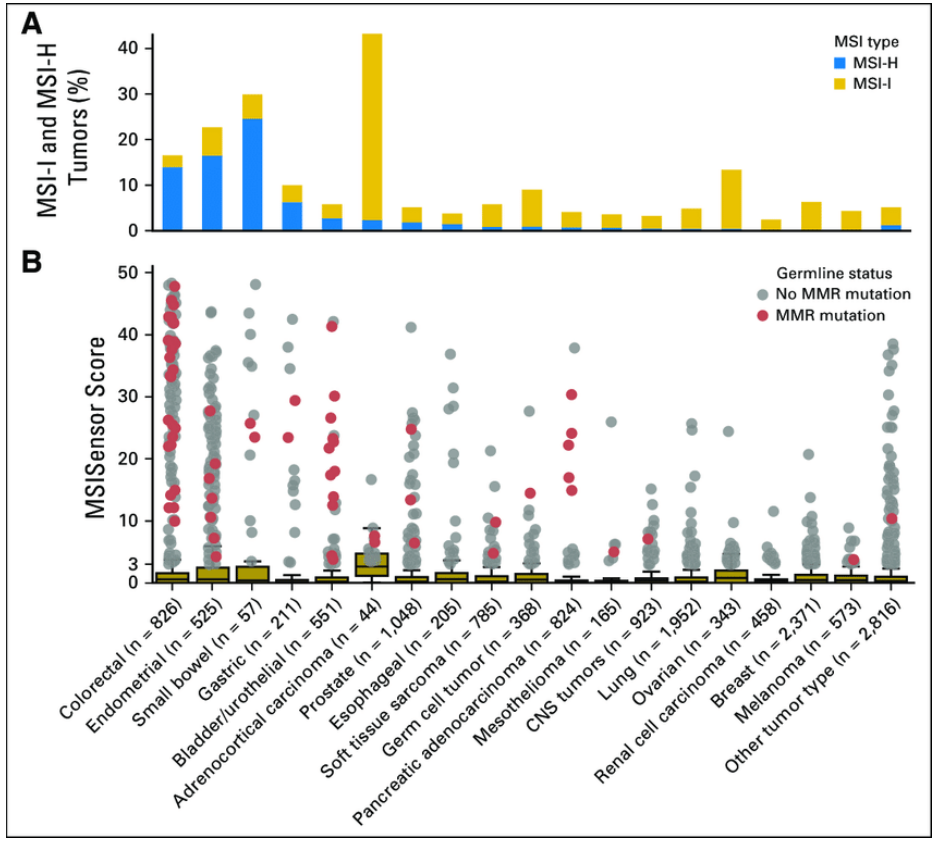


dMMR in Gynecologic Malignancies

Mismatch repair proteins correct genetic errors.

dMMR leads to genomic instability, with accumulation of errors and a high tumor mutation burden associated with infiltrating lymphocytes that are sensitive to PD-1/PD-L1 blockade

dMMR common in endometrial cancer: 25-30% of endometrioid endometrial carcinoma



Latham A, J Clin Oncol 2018

Pembrolizumab in dMMR/MSI-H

Table 1 Clinical response to pembrolizumab in microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers

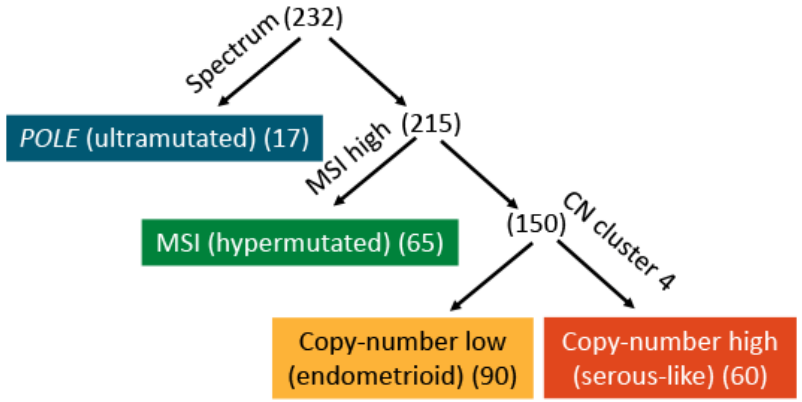
Cancer type[11]	*n* (%)	Overall response rate (% (95% CI))	Duration of response (range, months)
Total	149 (100%)	39.6% (31.7–47.9)	1.6[a]–22.7[a]
Colorectal	90 (60.4%)	36% (26–46%)	1.6[a]–22.7[a]
Noncolorectal	59 (39.6%)	46% (33–59%)	1.9[a]–22.1[a]
Endometrial	14 (9.4%)	36% (13–65%)	4.2[a]–17.3[a]
Biliary	11 (7.4%)	27% (6–61%)	11.0[a]–19.6[a]
Gastric or GE junction	9 (6.0%)	56% (21–86%)	5.8[a]–22.1[a]
Pancreatic	6 (4.0%)	83% (36–100%)	2.6[a]–9.2[a]
Small intestinal	8 (5.4%)	38% (9–76%)	1.9[a]–9.1[a]
Breast	2 (1.3%)	PR, PR	7.6–15.9
Prostate	2 (1.3%)	PR, SD	9.8[a]
Bladder	1 (0.7%)	NE	NA
Esophageal	1 (0.7%)	PR	18.2[a]
Sarcoma	1 (0.7%)	PD	NA
Thyroid	1 (0.7%)	NE	NA
Retroperitoneal adenocarcinoma	1 (0.7%)	PR	7.5[a]
Small cell lung	1 (0.7%)	CR	8.9[a]
Renal cell	1 (0.7%)	PD	NA

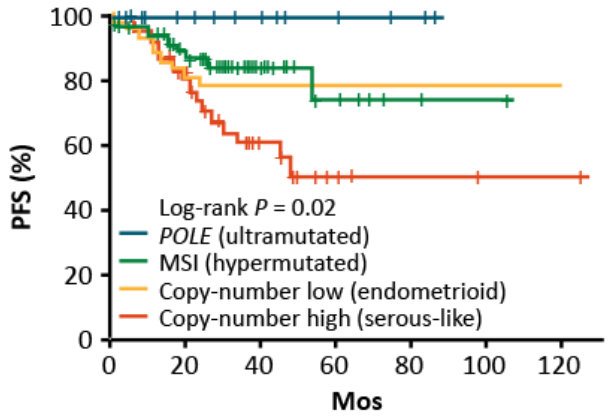
CI, confidence interval; CR, complete response; GE, gastroesophageal; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Ongoing response.

Keytruda package insert, 2019

Endometrial Cancer: Molecular Classification

The "Modern" Molecular Classification: TCGA Classification





- **POLE (ultramutated malignancies):**
  - Their hallmark are mutations in the exonuclease domain of POLE
  - POLE encodes the catalytic subunit of DNA polymerase epsilon which plays a relevant role in DNA repair.
- **MSI-High: Tumors that harbor a high rate of mutations resulting from impaired DNA MMR pathway:**
  - A DNA repair system that corrects errors such as single-base mismatches or short insertions and deletions that spontaneously occur during DNA replications
  - The most implicated genes are: MLH1, MSH2, MSH6, PMS2

Cancer Genome Atlas Research Network. Nature. 2013;497:67.

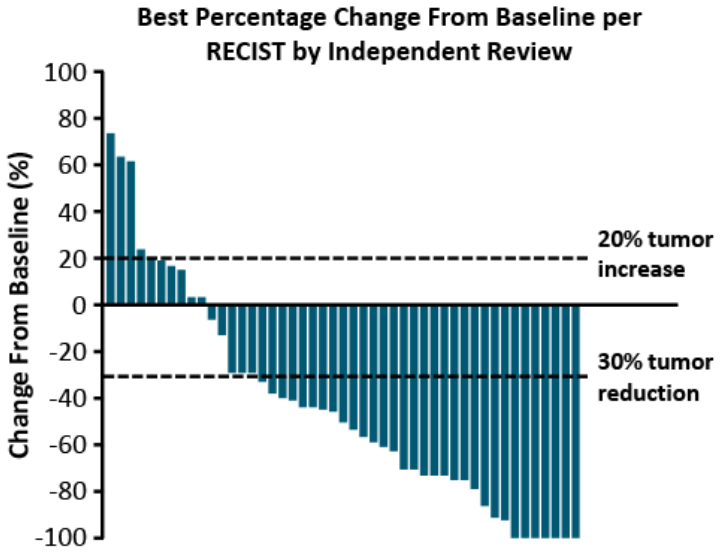
Slide credit: clinicaloptions.com

dMMR Endometrial Cancer: Pembrolizumab

KEYNOTE-158: Antitumor Activity in Patients With MSI-H Advanced EC

Confirmed Objective Response per RECIST v1.1 by IRC	MSI-H EC, N = 49 (Cohorts D + K)	EC, N = 107 (Cohort D, biomarker unselected)
ORR, % (95% CI)	57.1 (42.2-71.2)*	11.2 (5.9-18.8)
Best overall response n (%)		
CR	8 (16.3)	0
PR	20 (40.8)	12 (11.2)
Stable disease	8 (16.3)	26 (24.3)
Progressive disease	11 (22.4)	56 (52.3)

*ORR 45.5% in cohort D (n = 11)and 60.5% in Cohort K (n = 38)



O'Malley ESMO 2019. Abstr 3394. Marabelle. JCO. 2020;38:1.

Slide credit: clinicaloptions.com

Pembrolizumab in Advanced Cervical Cancer

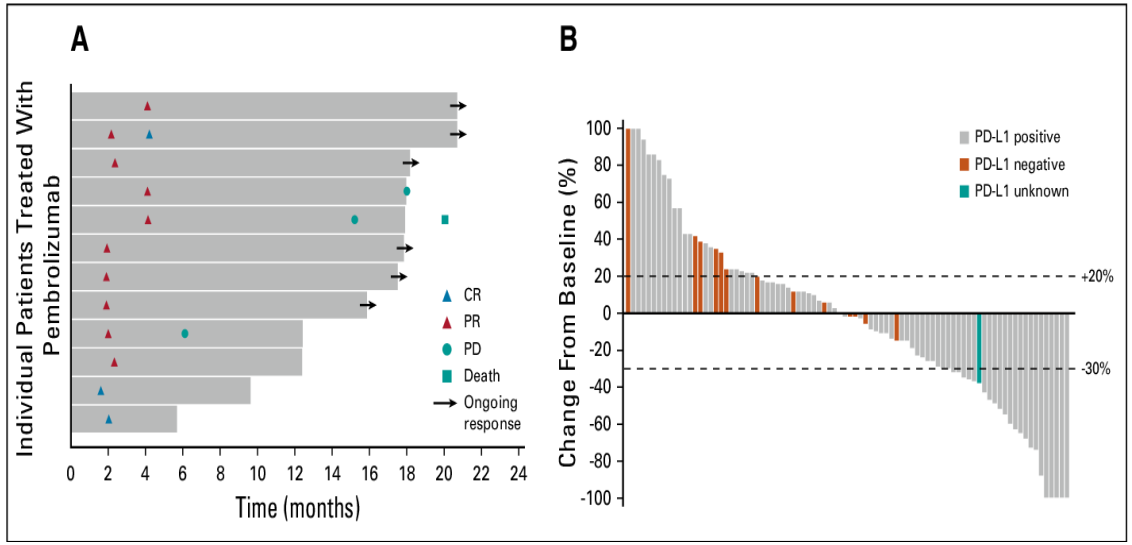
Approved for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1, CPS >=1

KEYNOTE-158, Chung H, JCO 2019

N= 98 patients with advanced cervical cancer

ORR 12%, CR 3 PR 9

All responses seen in patients with PD-L1 positive tumors, ORR 4 14.6%



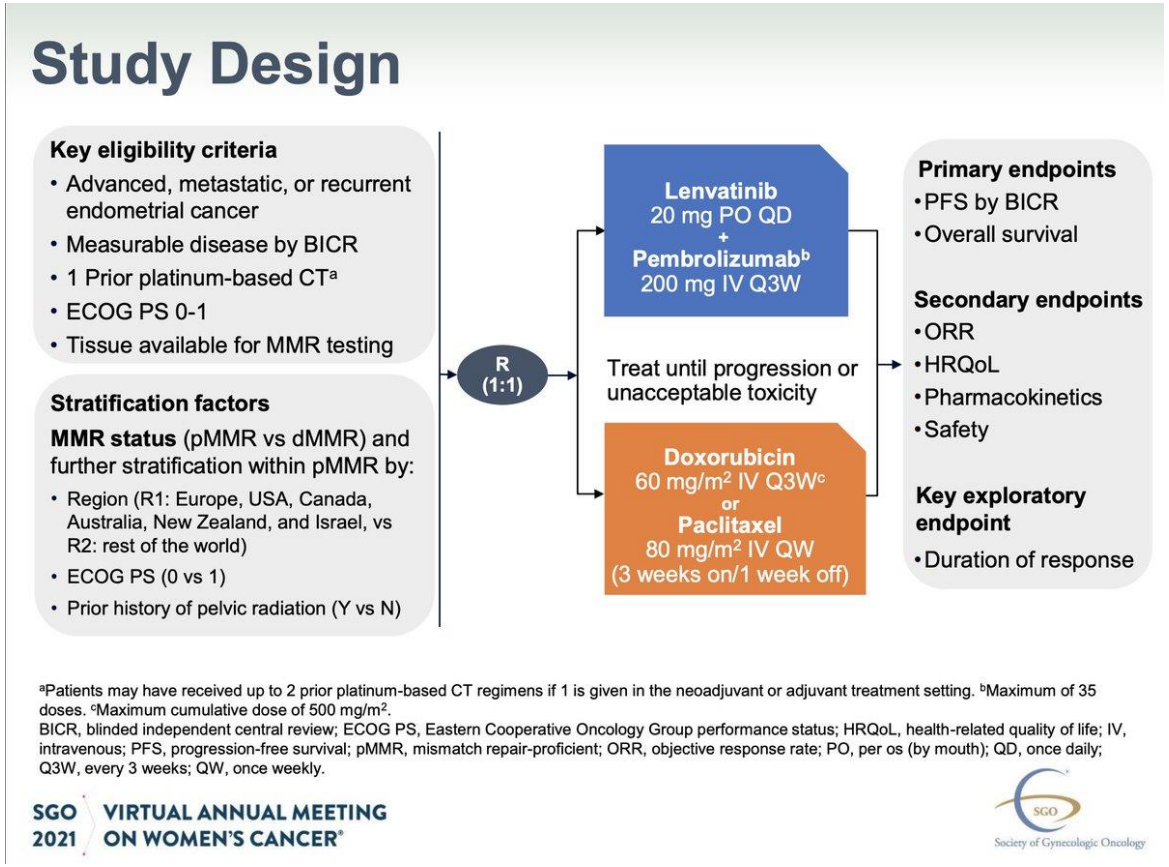
Approved Checkpoint Inhibitors in dMMR/MSI-H Tumors

- Pembrolizumab: approved 4/2017
  - Indication: adult and pediatric patients with unresectable of metastatic solid tumors that are MSI-high or mismatch repair deficient (dMMR) that have progressed following prior treatment and who have no satisfactory alternatives
  - Targets PD-1/PD-L1 pathway: pooled analysis of 5 independent trials, each with different eligibility criteria, n = 149, 15 cancer types
    - ORR 39%, duration of response 6 months in 78%
    - ARs: fatigue, pruritis, diarrhea, decreased appetite, rash, fevers, cough, dyspnea, musculoskeletal pain, constipation, nausea, IRAEs
- Dostarlimab: approved 8/17/21
  - Indication: adult patients with dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment
  - GARNET trial: n = 209 patients with dMMR recurrent or advanced solid tumors
    - ORR 41.6%, CR 9%, duration of response longer than 6 months in 95% of patients, median response duration 34.7 months
- Pembrolizumab: approved 6/16/20: Indication: unresectable or metastatic solid tumors, TMB>= 10mut/Mb
  - KEYNOTE 158: cohort of 102 patients with TMB-H: ORR 29%, 50% of responses lasted greater than 2 years

Endometrial Cancer: Second Line Therapy

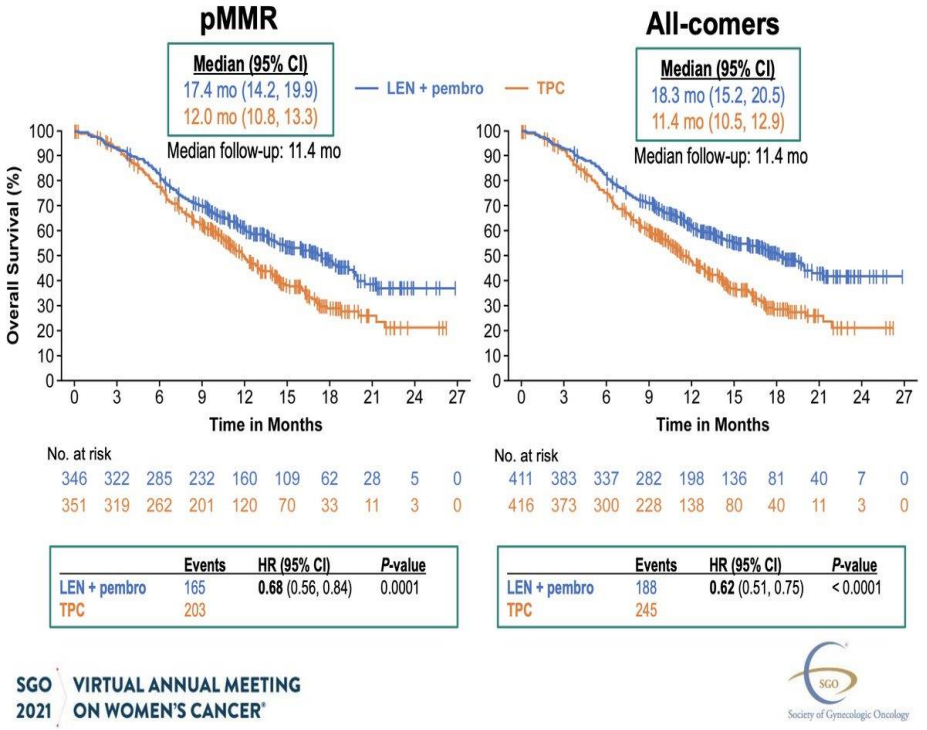
- Advanced endometrial cancer that is not MSI-H or dMMR
- Disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Endometrial Cancer, 2nd line: KEYNOTE 775



Endometrial Cancer, 2nd line: KEYNOTE 775

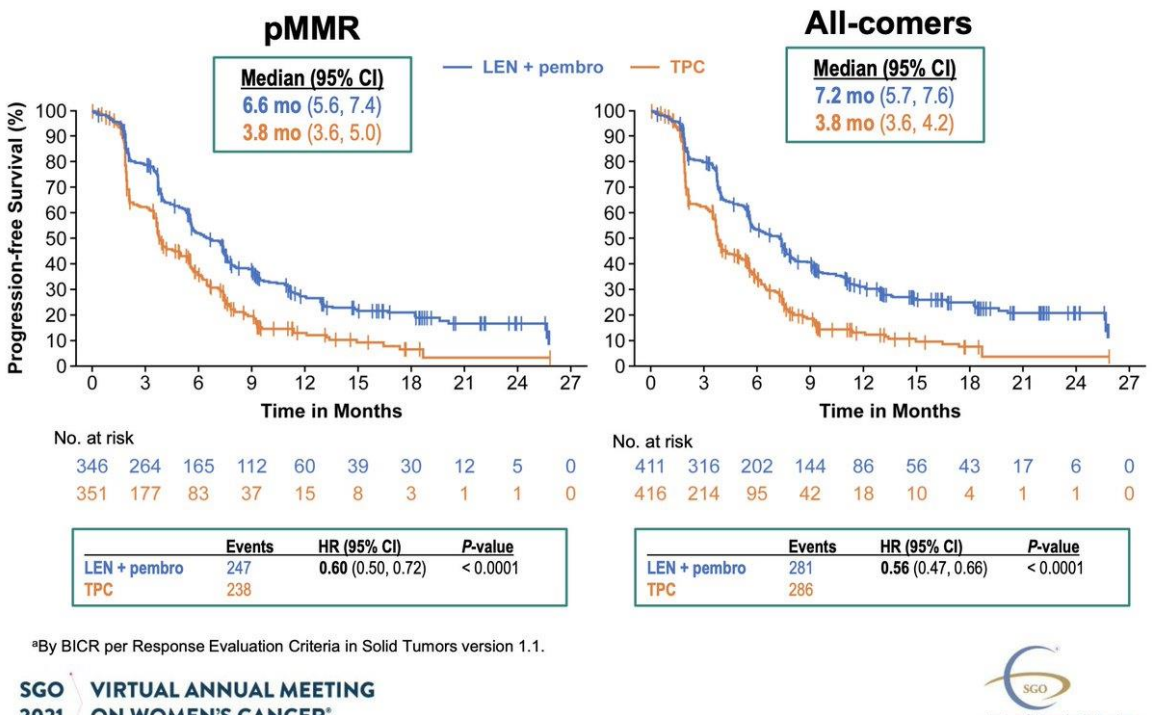
Overall Survival



SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

Society of Gynecologic Oncology

Progression-free Survival[a]

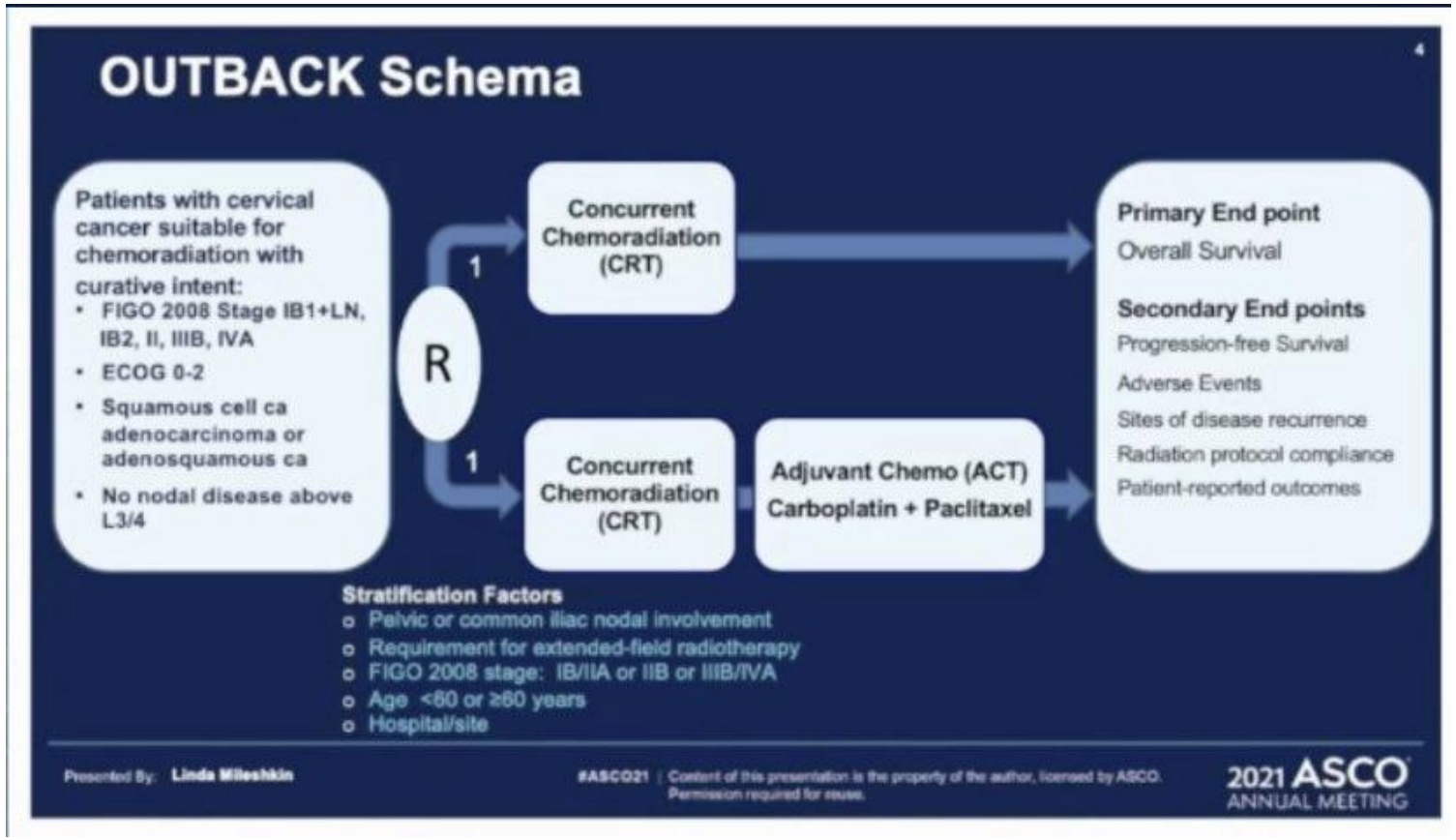


[a]By BICR per Response Evaluation Criteria in Solid Tumors version 1.1.

SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

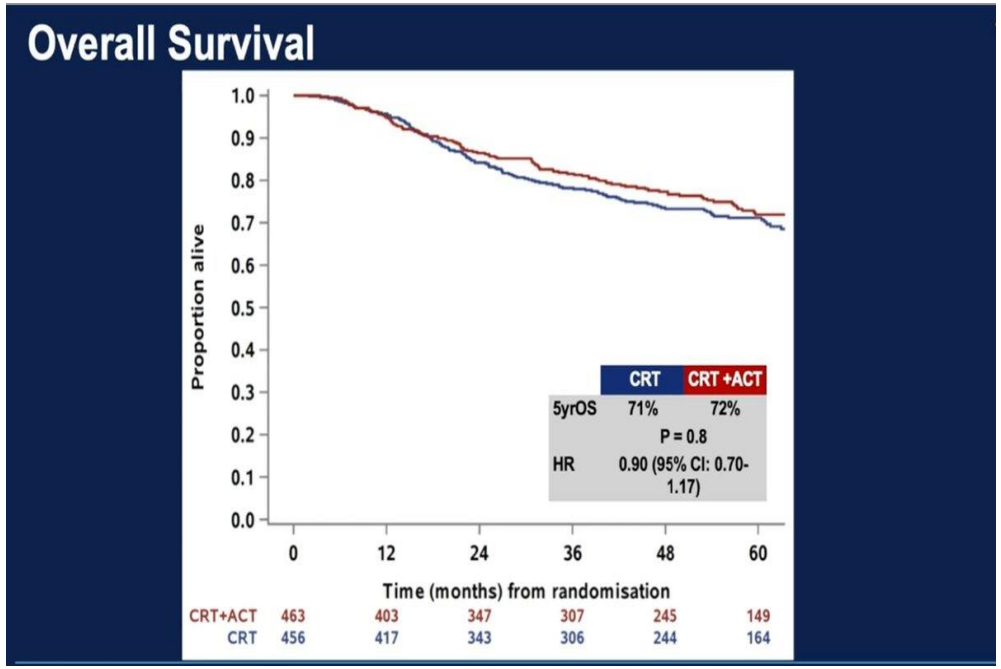
Society of Gynecologic Oncology

Cervical Cancer: Adjuvant Chemotherapy to Improve Cure?



Mileskin, L ASCO 2021

Cervical Cancer: OUTBACK trial



- PFS at 5 years 63 v 61%
- Similar pattern of recurrence in both arms
- Questions that remain:
  - Would different drugs be better, less toxic?
  - Should only higher risk patients receive extra treatment?

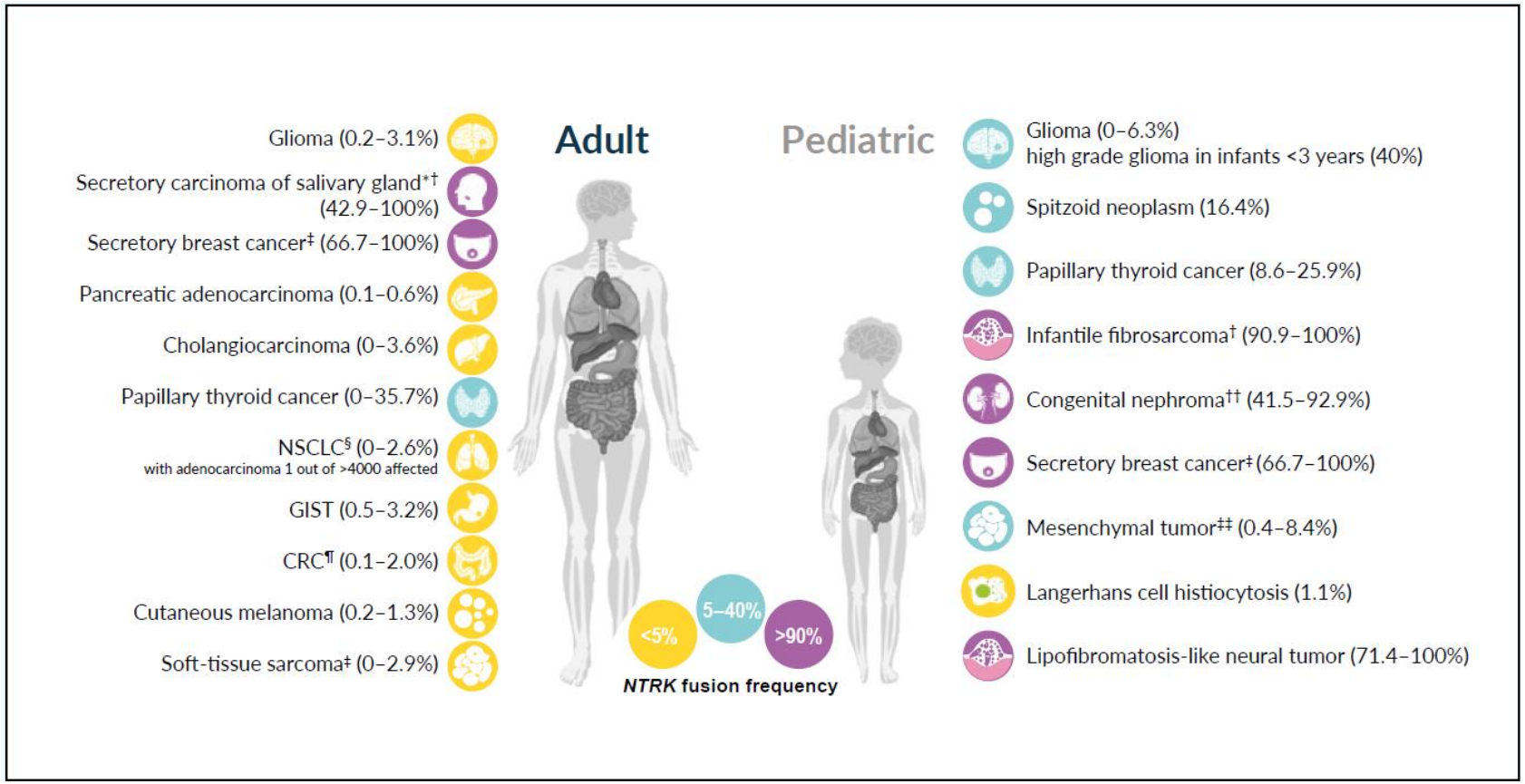
Mileshkin L et al, JCO 2021.

RARE MOLECULAR BIOMARKERS

NTRK Fusion

- Larotrectinib: accelerated approval 11/26/18
  - 3 multicenter, open-label, single-arm trials: LOXO-TRK-14001, SCOUT, and NAVIGATE
  - ORR 75%, CR 22% PR 53%, duration of response exceeded 6 months in 73%, 12 months in 39%
  - ARs >+20%: fatigue, nausea, dizziness, vomiting, increased AST/ALT, cough, constipation, diarrhea
  - Approved dose: 100 mg BID
- Entrectinib: approved 8/15/2019
  - Tissue agnostic, NTRK 1,2,3 fusion
  - 3 trials: ALKA-372-001, STARTRK-1, STARTRK-2
  - ORR 57%, CR 7%, duration of response 6 months 68%
  - ARs: CHF, CNS effects, skeletal fractures, hepatotoxicity, hyperuricemia, QT prolongation, vision disorders.

NTRK Fusion Frequency



NTRK Fusions in Gynecologic Malignancy

Am J Surg Pathol. Author manuscript; available in PMC 2019 Sep 27.
Published in final edited form as:
Am J Surg Pathol. 2018 Jun; 42(6): 791–798.
doi: 10.1097/PAS.0000000000001055

PMCID: PMC6764747
NIHMSID: NIHMS945057
PMID: 29553955

NTRK Fusions Define a Novel Uterine Sarcoma Subtype with Features of Fibrosarcoma

Sarah Chiang, MD,[1,*] Paolo Cotzia, MD,[1] David M. Hyman, MD,[2] Alexander Drilon, MD,[3] William D. Tap, MD,[4] Lei Zhang, MD,[1] Jaclyn F. Hechtman, MBBS, MD, FRCPA,[1] Kay J. Park, MD,[1] Ryma Benayed, PhD,[1] Marc Ladanyi,

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Gynecol Oncol Rep. 2019 May; 28: 141–144.
Published online 2019 Apr 23. doi: 10.1016/j.gore.2019.04.006

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PMID: 31080864

NTRK-1 fusion in endocervical fibroblastic malignant peripheral nerve sheath tumor marking eligibility for larotrectinib therapy: A case report

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NTRK Inhibitor Response

Table 2 Clinical response to TRK inhibitors in *NTRK* fusion–positive cancers

	Larotrectinib[22]			Entrectinib[24]		
Cancer type	*n* (%)	Overall response rate (% (95% CI))	Duration of response (range, months)	*n* (%)	Overall response rate (% (95% CI))	Duration of response (range, months)
Total	55 (100%)	75% (61–85%)	1.6[a]–33.2[a]	54 (100%)	57% (43–71%)	2.8–26.0[a]
Appendix	1 (1.8%)	SD	NA		NA	
Breast	1 (1.8%)	PD	NA	6 (11.1%)	83% (36–100%)	4.2–14.8[b]
Cholangiocarcinoma	2 (3.6%)	SD, NE	NA	1 (1.9%)	PR	9.3
Colorectal	4 (7.3%)	25% (NA)	5.6[b]	4 (7.4%)	25% (NA)	4.8 [b]
Gastrointestinal stromal tumor	3 (5.5%)	100% (29–100%)	9.5–17.3[a,b]		NA	
Gynecologic	NA			2 (3.7%)	PR	20.3 [b]
Infantile fibrosarcoma	7 (12.7%)	100% (59–100%)	1.4[a]–10.2[a]		NA	
Lung	4 (7.3%)	75% (19–99%)	8.2–20.3[a]	10 (18.5%)	70% (35–93%)	1.9 [b]–20.1 [b]
Melanoma	4 (7.3%)	50% (NA)	1.9–17.5[a]		NA	
Neuroendocrine		NA		3 (5.6%)	PR	5.6 [b]
Pancreas	1 (1.8%)	0% (NA)	NA	3 (5.6%)	PR, PR	7.1–12.9
Salivary gland	12 (21.8%)	83% (52–98%)	7.7–27.9[a]	7 (13.0%)	86% (42–100%)	2.8–16.5 [b]
Soft tissue sarcoma	11 (20.0%)	91% (59–100%)	3.6–33.2[a]	13 (24.1%)	46% (19–75%)	2.8–15.1
Thyroid	5 (9.1%)	100% (48–100%)	3.7–27.0[a]	5 (9.3%)	20% (NA)	7.9

CI, confidence interval; NA, not applicable; NE, not evaluable; *NTRK*, neurotrophic receptor tyrosine kinase gene; PD, progressive disease; PR, partial response; SD, stable disease; TRK, tropomyosin receptor kinase.
[a]Ongoing response. [b]Value at data cutoff.

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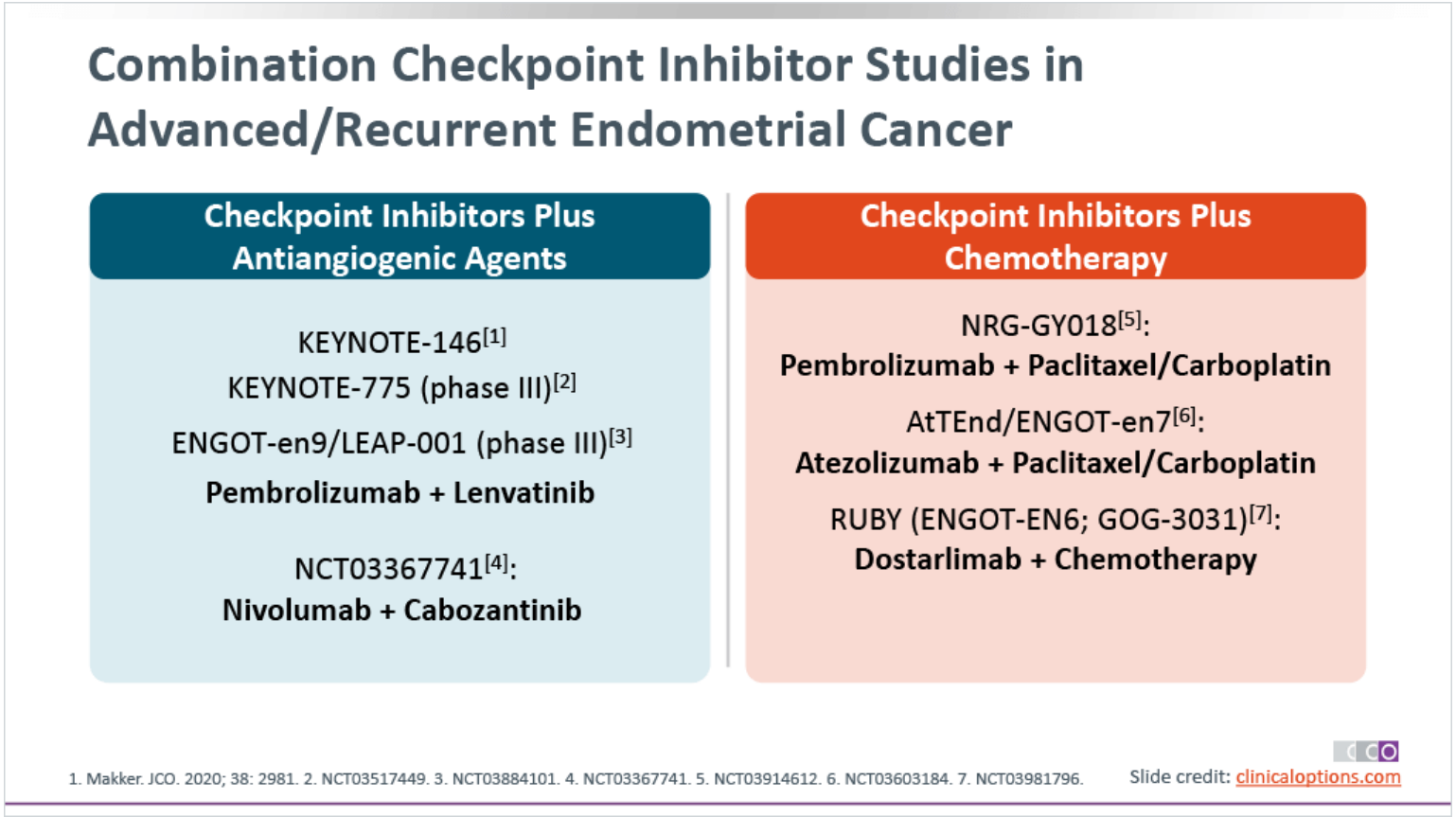
Future Directions



Future Directions

- Overcome PARPi resistance in ovarian cancer
- Later line role of her2 targeted therapies in high grade serous endometrial cancer after Herceptin-based regimens
- PARPi in high grade serous endometrial carcinoma
- Targeting HPV driven GYN malignancies
- Novel ADCs