Role of Systemic therapy in Gynecological Cancers

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Endometrial Cancer

Guideline Recommendations for the Management of Newly Diagnosed EC

- Surgery is the first treatment for EC[1]
- Total hysterectomy bilateral salpingo-oophorectomy
    - Sentinel lymph node mapping vs lymph node dissection

Stage I Endometrioid Cancer[1,2]

- Manage with surgery ± RT
    - Frail and comorbidities: External RT and/or vaginal brachytherapy is recommended
    - Consider hormone therapy for fertility-sparing option

Stage II Cancers[1,2]

- Surgery (to remove uterus, connective tissue, upper part of vagina, both fallopian tubes and ovaries) + external RT and/or vaginal brachytherapy

Stage IIIA-IIIC (Cancer Spread to Lymph Nodes)[1,2]

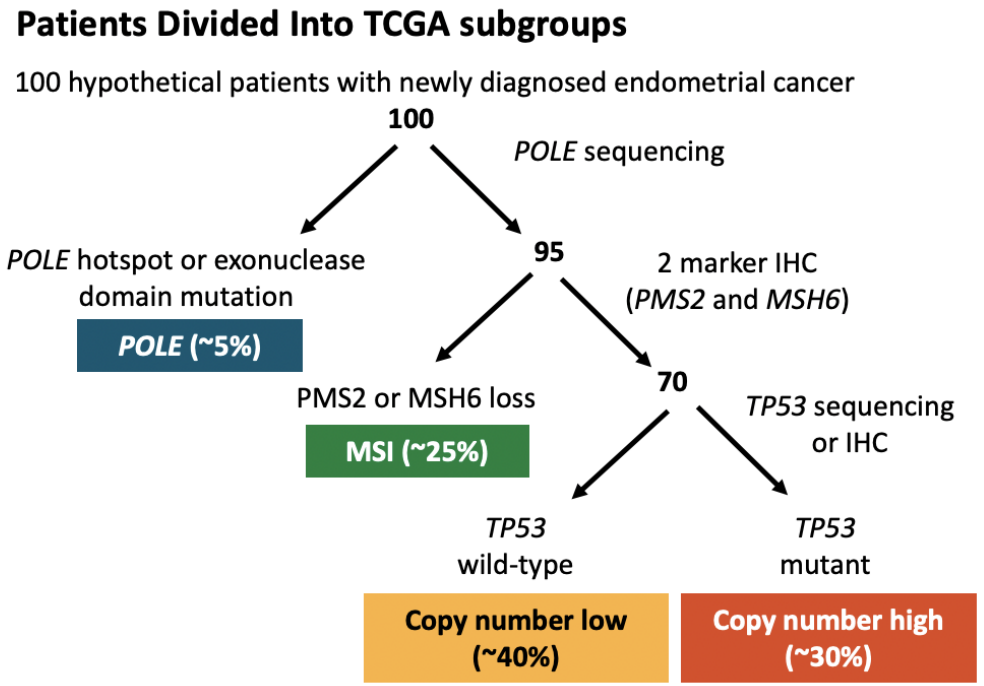
- Surgery, platinum-based chemotherapy* ± RT
    - Frail and comorbidities: External RT and/or vaginal brachytherapy is recommended
- High grade: omentectomy ± peritoneal biopsies

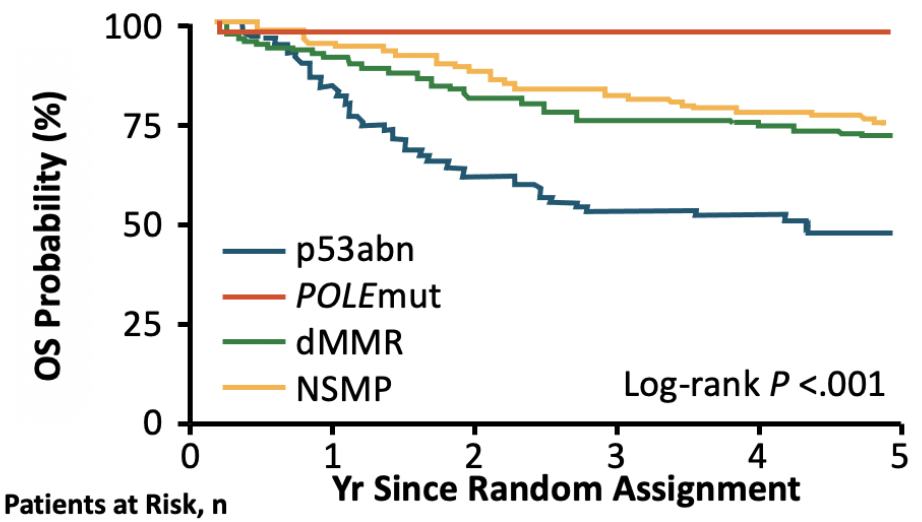
Stage IVA-IVB (Spread Into Bladder or Lymph Nodes Outside Pelvis)[1,2]

- Hysterectomy to prevent excessive bleeding ± RT
- Hormone therapy in endometrioid type (progestin, tamoxifen, LHRH agonist, aromatase inhibitors)
- Combination chemotherapy
- Targeted therapy (lenvatinib, bevacizumab, everolimus/letrozole, temsirolimus)
- Immunotherapy (pembrolizumab)

1. cancer.org/cancer/endometrial-cancer/treating/by-stage.html. 2. Concin. Int J Gynecol Cancer. 2021;31:12.

TCGA Molecular Classification and Outcomes





Patients at Risk, n

p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
dMMR	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

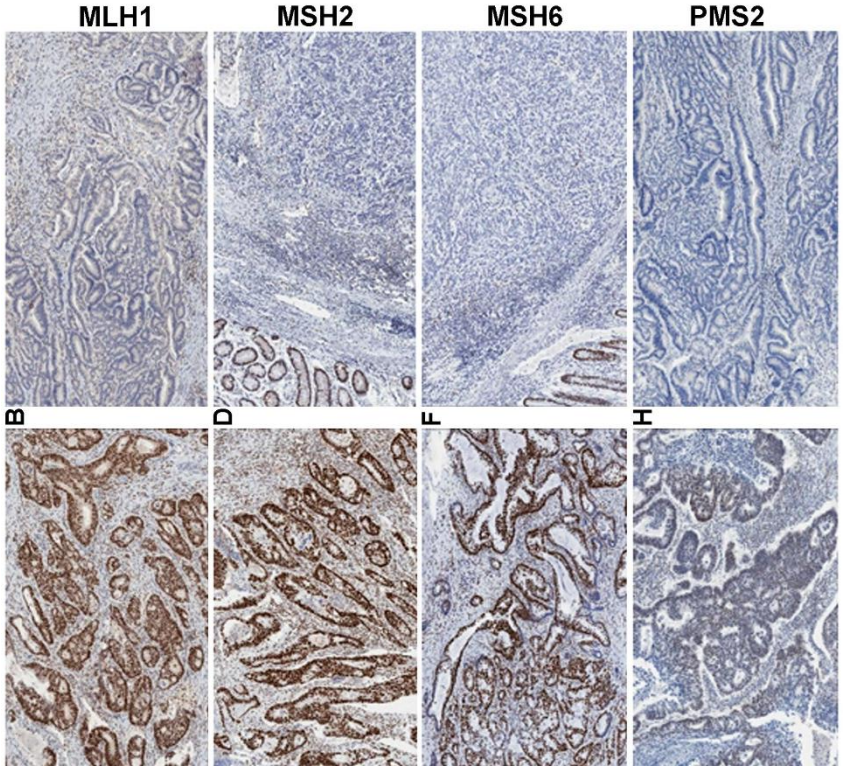
- 410 patients with successful molecular testing
  - 23% *p53*abn: *p53* abnormal
    12% *POLE*mut: *POLE* ultramutated
    33% dMMR: mismatch repair deficient
    32% NSMP: no specific molecular profile

- Prognostic value of molecular classification of high-risk endometrial cancer for benefit from chemotherapy

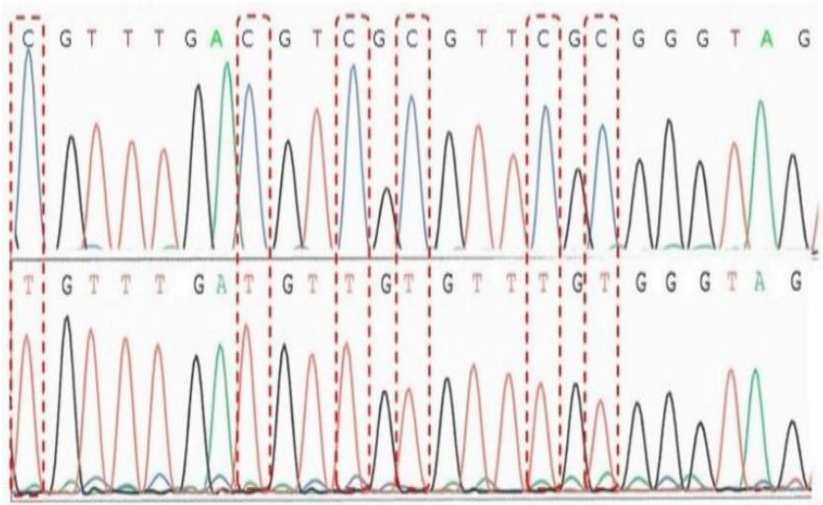
MacKay. Oncotarget. 2017;8:84579. León-Castillo. JCO. 2020;38:3388.

Recommendations for Molecular Testing to Inform Treatment Decisions in Endometrial Cancer

- Testing for *MLH1* promoter methylation status is recommended



- dMMR testing by IHC to test for MLH1, MSH2, MSH6, and PMS2 protein loss



ACOG Practice Bulletin No. 147: Lynch syndrome. Obstet Gynecol. 2014;124:1042. Cho. Int J Gynecol Pathol. 2019;38:S11. Concin. Int J Gynecol Cancer. 2021:12. Crosbie. Genet Med. 2019;21:2390. Ryan. Genet Med. 2019;21:2167. Takeda. Genes (basel). 2016;7:86. Richman. Int J Oncol. 2015; 47:1189.

Slide credit: clinicaloptions.com

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

Recommendations as per risk category

Risk group	Molecular classification unknown	Molecular classification known*†
Low	**Observation alone (Leve III A)**	**Observation alone (Leve I A)**

Based on the GOG 99 and PORTEC 1 studies

Stelloo E, Nout RA, Osse EM, et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer—combined analysis of the PORTEC cohorts. Clin Cancer Res 2016;22:4215–24.

Recommendations as per risk category

Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion

Adjuvant brachytherapy can be recommended (Level I A)
Omission of Adj BT esp for pts <60 (Level II, A)

Recommendations as per risk category

High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma

pN0 after lymph node staging

Adjuvant brachytherapy can be recommended (Level II B)
EBRT for Substantial LVSI
Adjuvant Chemo especially for G3 and/or LVSI (Level II C)
Omission of any adjuvant therapy (Level IV C)

Recommendations as per risk category

High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma

cN0/pNx (lymph node staging not performed)

Substantial LVSI + ->EBRT
Adjuvant BT alone if High grade, LVSI –ve, Stage II
Additional Adjuvant Chemo especially for G3 and/or LVSI (Level II C)

Recommendations as per risk category

High	▶ Stage III–IVA with no residual disease ▶ Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	▶ Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ▶ Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ▶ Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease

Adjuvant chemotherapy in Endometrial Cancer

- Stage I /II – Clear Cell , Serous
- III & IV A–All Histology

- Chemotherapy→RT
  - 4 cycles of Paclitaxel (175 mg/m^2)+ Carboplatin AUC 5-6
  - Followed by RT

PORTEC 3

- Adjuvant Chemo radiotherapy compared to RT alone
- Improved FFS and PFS in
  - Stage III
  - Serous Histology
- Toxicity higher in CTRT arm during treatment. No significant difference at 5 years

	PORTEC 3	GOG 258
Comparison	CTRT vs RT	CTRT vs CT
Inclusion Criteria	IA G3+ LVSI, IBG3 II, IIIA, IIIC, III B (if para involved) Stage I-III with clear cell and Serous histology	Stage III, IVA –any histology Stage I/II –Clear Cell/Serous
Stage III	FFS – CTRT-70.9% RT-58.4%	RFS –(most pts stage III) CTRT-59% CT-58%
Recurrence Sites		
Vaginal	CTRT-2.1% RT-2.1%	CTRT-2% CT-7%
Pelvic and PA Nodal Rec	(Pelvic)CTRT-5.5 RT-8.5	CTRT-11% CT-20%
Distant	CTRT-22% RT-29%	CTRT-27% CT-21%

Evidences

PORTEC 3

- Combined CTRT (two cycles of cisplatin during radiotherapy followed by four cycles of carboplatin-paclitaxel) compared with RT alone,
- 5% overall survival benefit at 5 years and a 7% failure-free survival benefit was seen in the combined therapy group compared with radiotherapy alone.

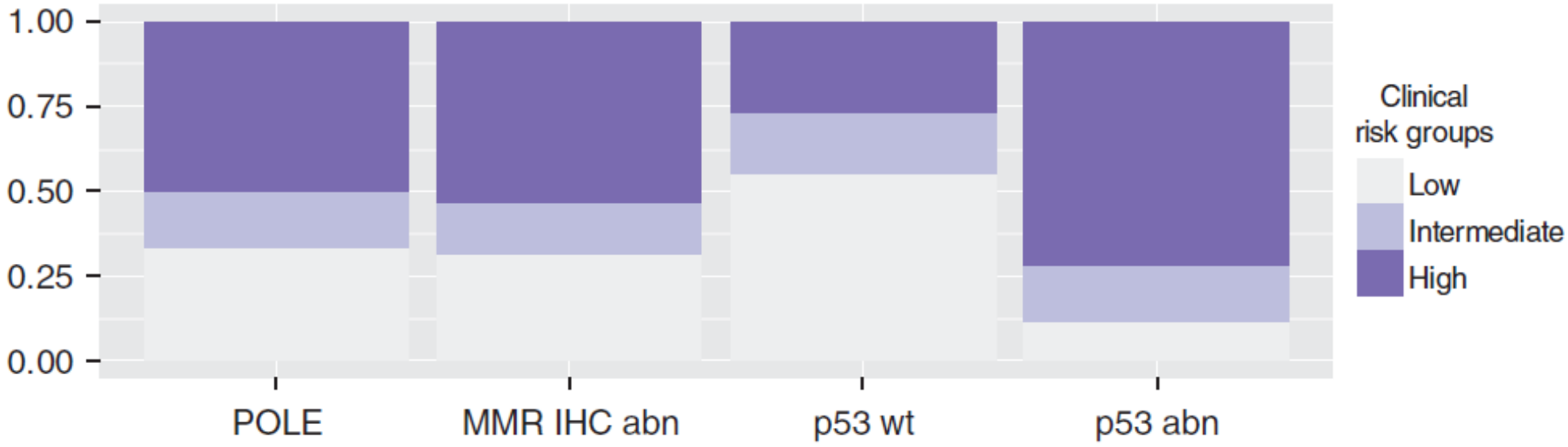
GOG 258

- Same CTRT schedule vs 6# C+P alone with no difference
- Chemo alone arm had increased Pelvic and Para-aortic recurrence

GOG 249

- No increase in Recurrence free survival in vaginal cuff brachytherapy followed by three cycles of paclitaxel and carboplatin chemotherapy compared to Pelvic RT alone

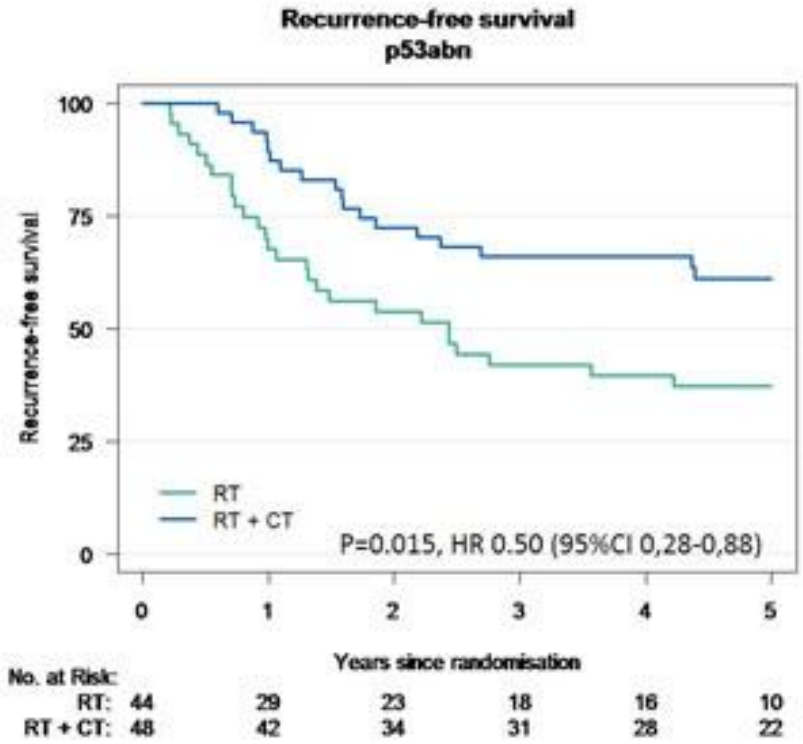
Molecular subtypes and Clinical risk groups

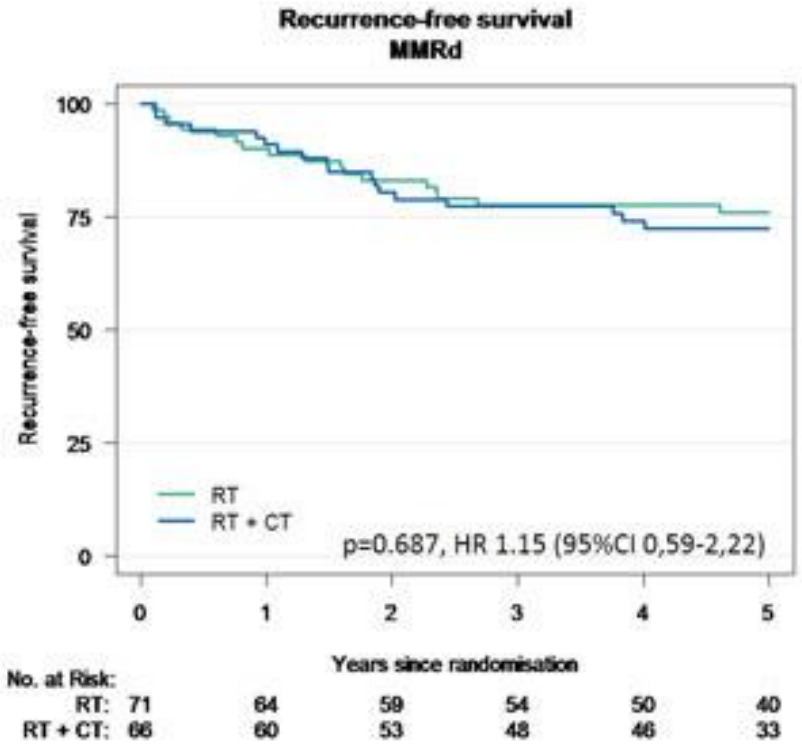


Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on adjuvant therapy

Mol Type (n)	Events	5 yr RFS estimate %	HR (95%CI)	P value HR
p 53 abn (92)				
RT	28	37.2	1	
CTRT	20	61.1	0.5 (0.28-0.88)	**0.017**
POLE mut (52)				
RT	1	96.6	1	
CTRT	0	100	0.02(<0.01- >10^4)	0.632
MMRd (137)				
RT	17	75.8	1	
CTRT	18	72.4	1.15 (0.59-2.22)	0.687
NSMP (129)				
RT	19	68.9	1	
CTRT	17	81.2	0.71 (0.37-1.37)	0.311

Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: Impact on adjuvant therapy



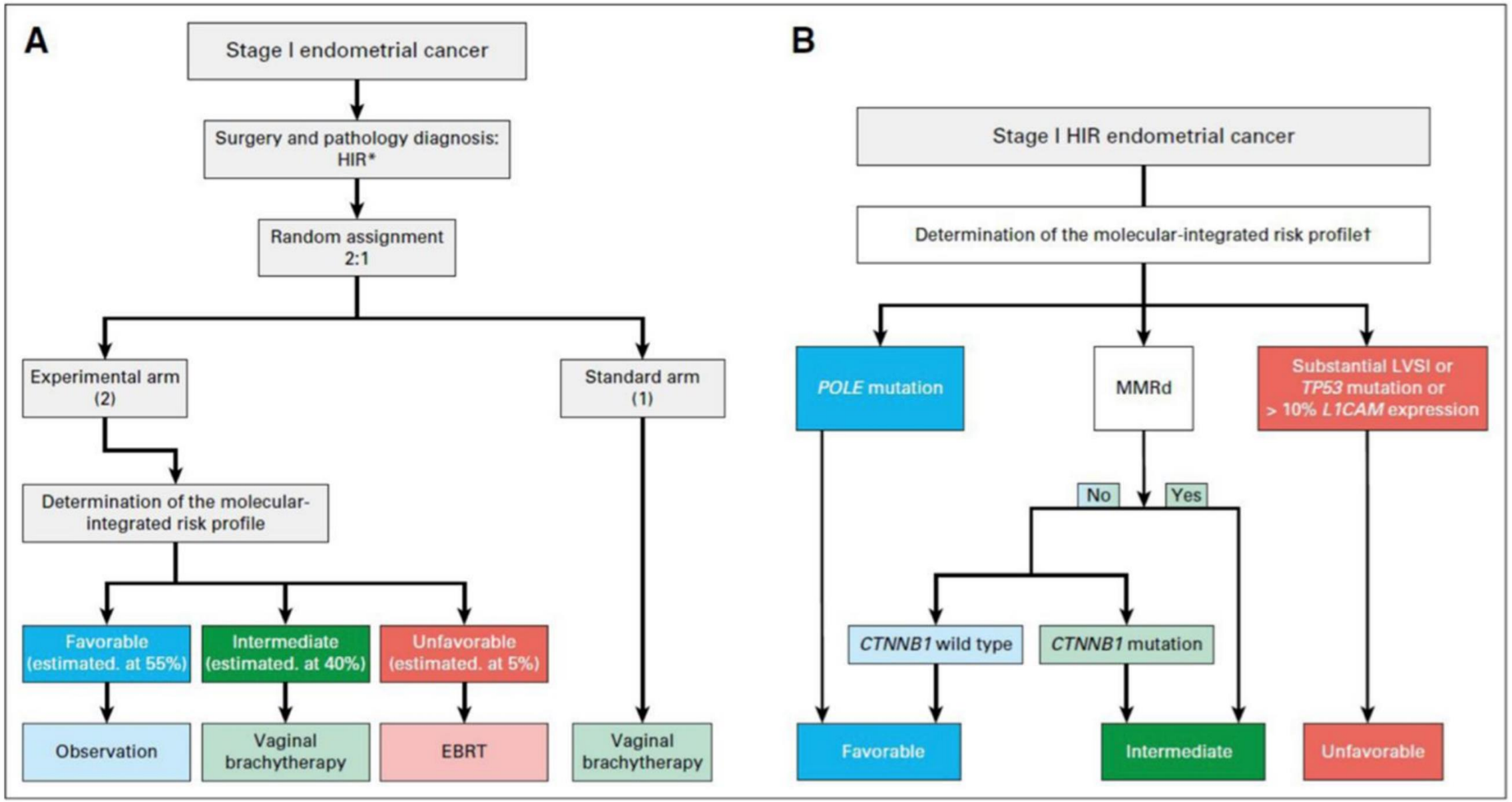


Recommendations as per risk category

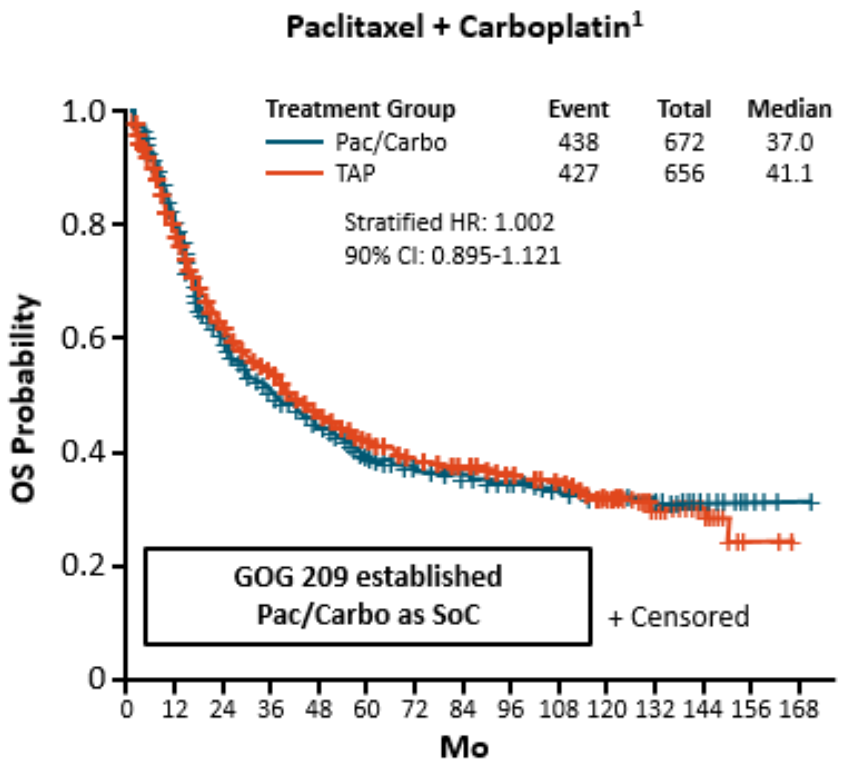
High	▶ Stage III–IVA with no residual disease ▶ Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	▶ Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ▶ Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ▶ Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease

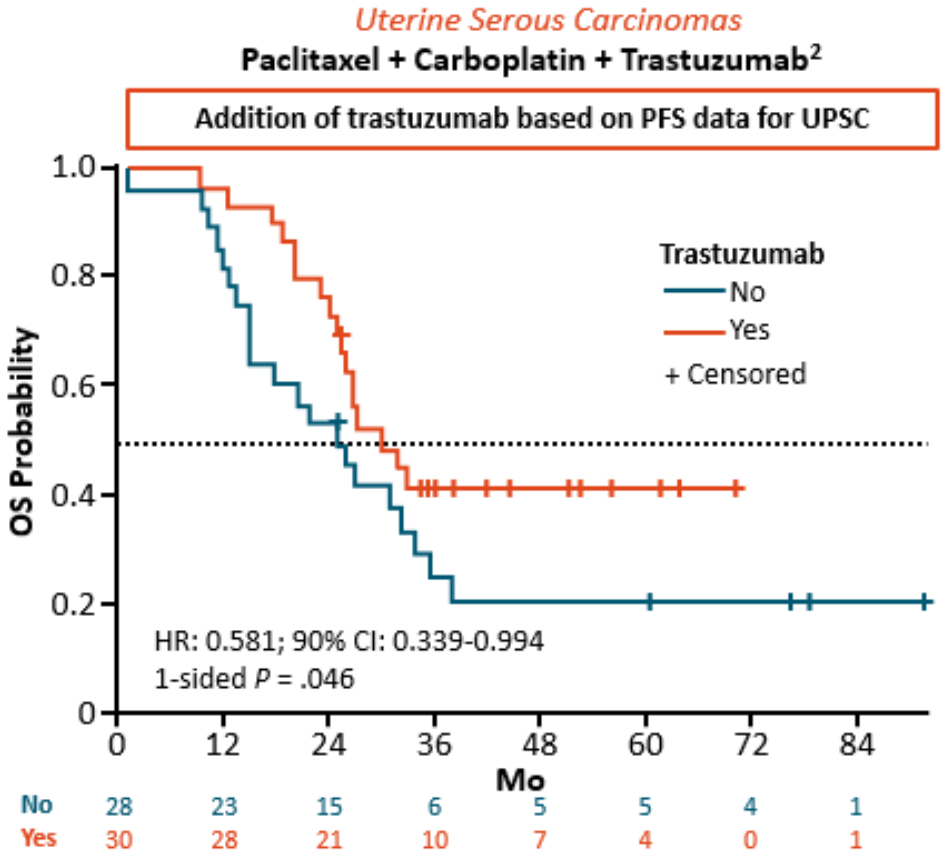
EBRT with concurrent and adjuvant chemotherapy (I, A) Alternatively sequential chemotherapy and radiotherapy is recommended (I, B)
Chemo alone (I, B)

Study design of the PORTEC-4a trial



Advanced/Recurrent Endometrial Cancer





1. Miller. JCO. 2020;38:3841. 2. Fader. Clin Cancer Res. 2020;26:3928.

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

- Prospective, open-label phase II study in patients with MSI-H/dMMR solid tumors (N = 233)

Efficacy Summary	MSI-H EC (N = 49) (Cohorts D + K)
ORR, % (95% CI)	57.1 (42.2-71.2)*
Best overall response n (%)	
▪ CR	8 (16.3)
▪ PR	20 (40.8)
▪ SD	8 (16.3)
▪ PD	11 (22.4)
Median PFS, mo (95% CI)	25.7 (4.9-NR)
Median OS, mo (95% CI)	NR (27.2-NR)
Median DoR, mo (range)	NR (2.9-27.0+)

FDA Approval May 2017
First FDA approval based on a biomarker regardless of tumor type

Ongoing phase III NRG-GY018 trial is directly comparing carboplatin + paclitaxel with placebo or pembrolizumab in patients with recurrent or primary advanced EC (estimated N = 810); primary endpoint: PFS (NCT03914612)

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

Study 309/KEYNOTE-775: Lenvatinib + Pembrolizumab After Platinum in Advanced EC

- Confirmatory, randomized, open-label phase III study

FDA Accelerated Approval September 2019
FDA Full Approval July 2021
For patients with recurrent/advanced endometrial cancer who are not MSI-H or dMMR

Stratified by MMR status (pMMR vs dMMR), within pMMR by region, ECOG PS 0 vs 1, prior history of pelvic radiation

Patients with advanced, metastatic, or recurrent EC with measurable disease after 1 previous platinum-based CT*; ECOG PS 0/1; tissue available for MMR testing (N = 827)

→ Lenvatinib 20 mg PO QD + Pembrolizumab 200 mg IV Q3W (n = 411)

→ Doxorubicin 60 mg/m^2 IV Q3W or Paclitaxel 80 mg/m^2 IV QW 3 wk on/1 wk off (n = 416)

→ *Until PD or unacceptable toxicity*

Primary endpoints: PFS by BICR, OS

Secondary endpoints: ORR, health-related quality of life, pharmacokinetics, safety

Key exploratory endpoint: DoR

2 prior regimens allowed if 1 regimen was in neoadjuvant/adjuvant setting.

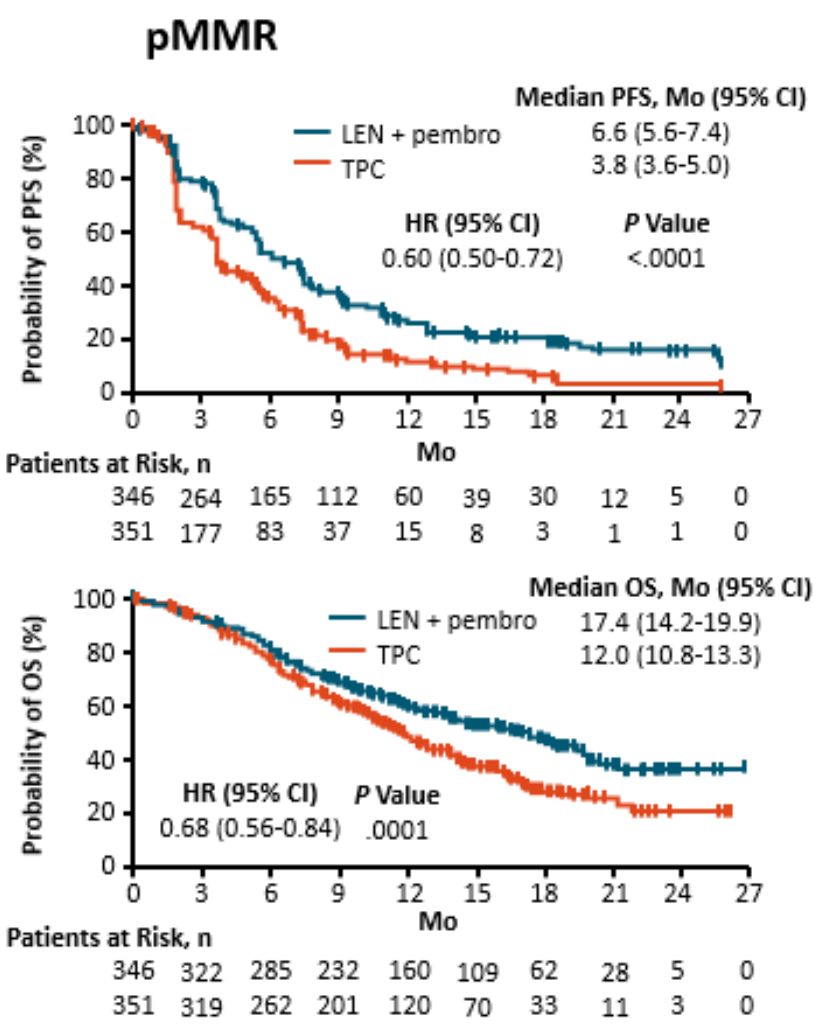
Makker. NEJM. 2022;386:437.

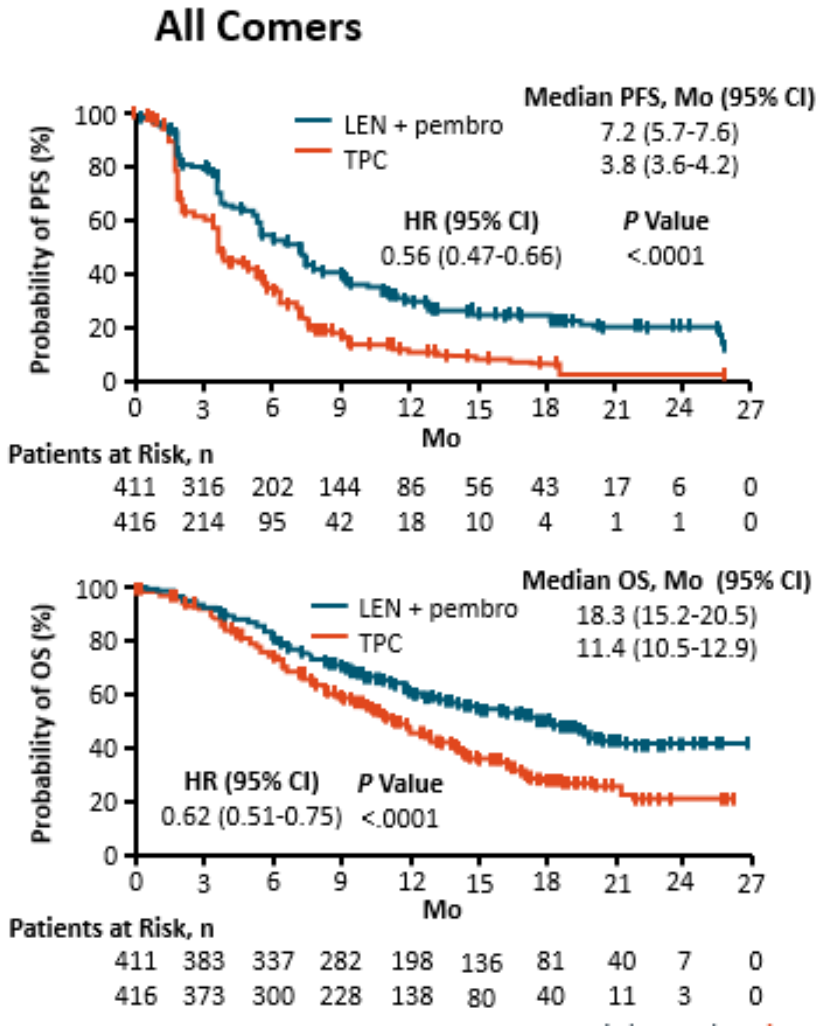
Study 309/KEYNOTE-775: Responses

Parameter	pMMR		Overall	
	Lenvatinib + Pembrolizumab (n = 346)	Doxorubicin or Paclitaxel (n = 351)	Lenvatinib + Pembrolizumab (n = 411)	Doxorubicin or Paclitaxel (n = 416)
ORR, % (95% CI)	30.3 (25.5-35.5)	15.1 (11.5-19.3)	31.9 (27.4-36.6)	14.7 (11.4-18.4)
	P <.0001		*P* <.0001	
Best overall response, %				
▪ CR	5.2	2.6	6.6	2.6
▪ PR	25.1	12.5	25.3	12.0
▪ SD	48.6	39.6	47.0	40.1
▪ PD	15.6	30.8	14.8	29.6
▪ Not evaluable/assessed	0.6/4.9	2.0/12.5	1.2/5.1	1.9/13.7
Median DoR, mo (range)	9.2 (1.6-23.7)	5.7 (0-24.2)	14.4 (1.6-23.7)	5.7 (0-24.2)
Median time to response, mo (range)	2.1 (1.5-9.4)	3.5 (1.0-7.4)	3.1 (1.5-16.3)	2.1 (1.0-7.4)

Makker. NEJM. 2022;386:437.

Study 309/KEYNOTE-775: PFS and OS Benefit





Makker. NEJM. 2022;386:437.

Study 309/KEYNOTE-775: TEAEs

TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 351)	
	Any Grade	Grade ≥3*	Any Grade	Grade ≥3*
Hypertension	64.0	37.9	5.2	2.3
Hypothyroidism	57.4	1.2	0.8	0
Diarrhea	54.2	7.6	20.1	2.1
Nausea	49.5	3.4	46.1	1.3
Decreased appetite	44.8	7.9	21.1	0.5
Vomiting	36.7	2.7	20.9	2.3
Weight decrease	34.0	10.3	5.7	0.3
Fatigue	33.0	5.2	27.6	3.1
Arthralgia	30.5	1.7	8.0	0

TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 351)	
	Any Grade	Grade ≥3*	Any Grade	Grade ≥3*
Proteinuria	28.8	5.4	2.8	0.3
Anemia	26.1	6.2	48.7	14.7
Constipation	25.9	0.7	24.7	0.5
UTI	25.6	3.9	10.1	1.0
Headache	24.9	0.5	8.8	0.3
Asthenia	23.6	5.9	24.5	3.9
Neutropenia	7.4	1.7	33.8	25.8
Alopecia	5.4	0	30.9	0.5

general disorder [1.5%], and infections [0.7%]), and 4.9% of patients in the TPC arm suffered grade 5 AEs (including cardiac disorder [1%], general disorder [1.3%], infections [1.5%], and subdural hematoma [0.3%]).

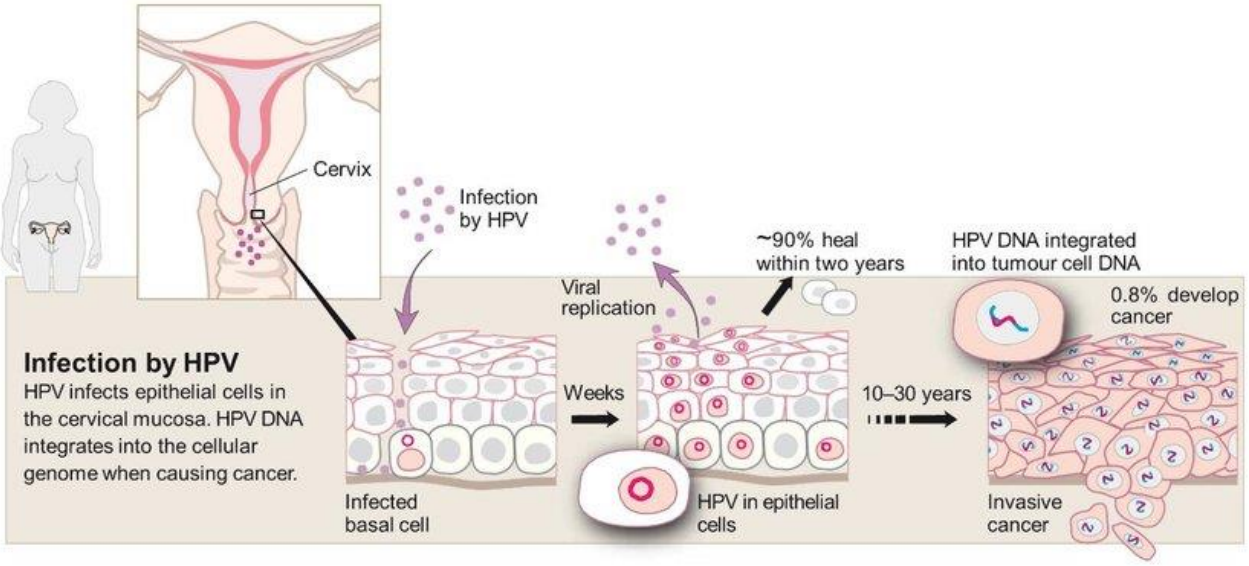
Makker. NEJM. 2022;386:437.

Systemic Therapy in Cervical Cancer

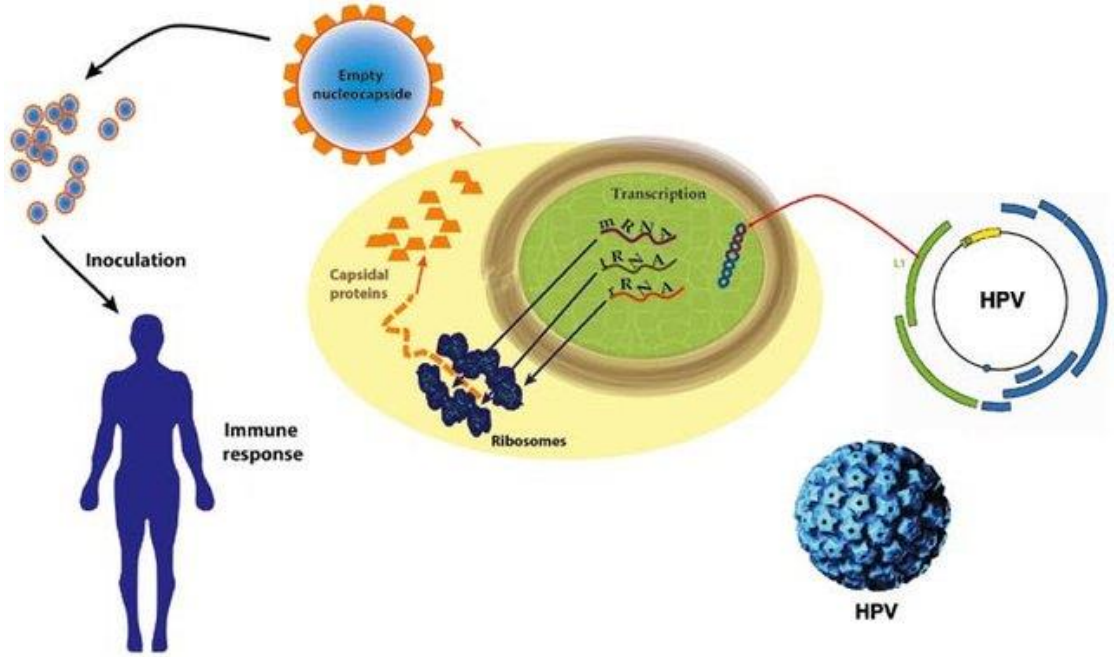
i) Concurrent
ii) Neoadjuvant
iii) Adjuvant
iv) Palliative

Cancer of the Cervix: Tumorigenesis and Prevention

- HPV infection and tumorigenesis[1]



- HPV vaccination and preventive measures[2]



1. Stark. Acta Facultatis Medicae Naissensis. 2018;35:5. 2. Boda. Int J Oncol. 2018;52:637.

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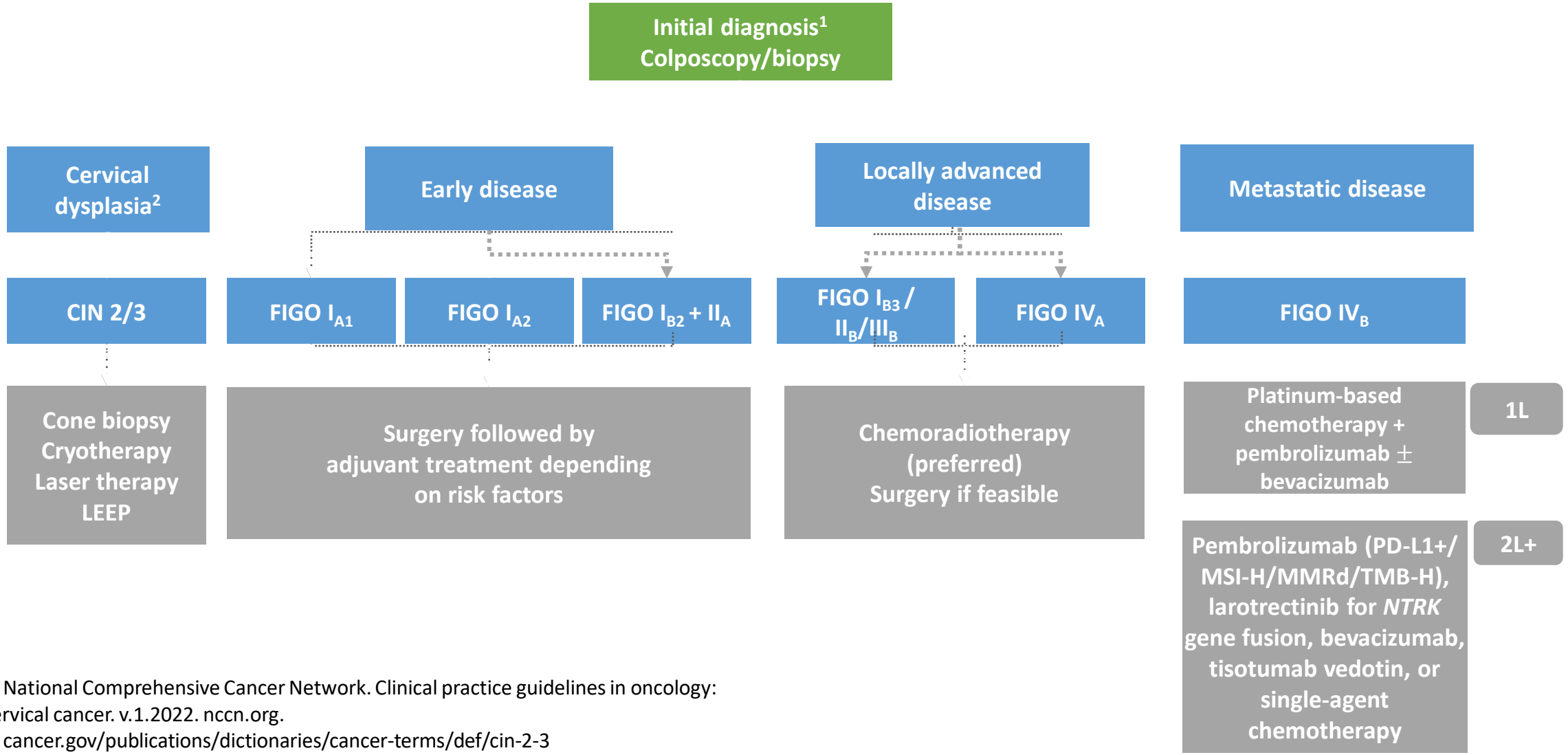
Cervical Cancer: Summary of Available Treatment Options



1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: cervical cancer. v.1.2022. nccn.org.
2. cancer.gov/publications/dictionaries/cancer-terms/def/cin-2-3
3. SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD.
4. Tisotumab vedotin PI. 5. Pembrolizumab PI.

Concurrent Chemotherapy

- Concurrent chemoradiation in locally advanced CA Cervix had been investigational until the late 1990s.

- A series of five randomized trials in a variety of disease stages matured around then:

GOG 85	Whitney et al, JCO 1999
RTOG – 9001[1]	Morris M et al, NEJM 1999
GOG 120	Rose PG et al, NEJM 1999
SWOG 8797/GOG 109[2]	Peters WA et al, Gynecol Oncol 1999
GOG 123[3]	Keys HM et al, NEJM 1999

- Collectively, 1894 women were analysed and cisplatin based chemoRT was compared to RT alone (RTOG 9001, GOG 123, SWOG 87-97) and to hydroxyurea (GOG 85 and 120). All showed a significant reduction in the risk of recurrence and death with cisplatin-based chemoRT.
- Meta-analysis: GREEN/Cochrane showed benefit.

Updates:

1. Eifel PJ, et al. J Clin Oncol, 2004
2. Monk BJ, et al. Gynecol Oncol 2005
3. Stehman FB, et al. Am J Obstet Gynecol 2007

Updated data of GOG 123 (2007)

- At 72 months, 71% of patients receiving CT+RT were predicted to be alive and disease-free when adjusting age and for tumor size compared to 60% of those receiving RT alone.

- The adjusted death HR 0.63 (95% CI: 0.43–0.91, $p<0.015$) favoring CT+RT.

Cisplatin-ineligible patients

Treatment with **carboplatin plus RT** resulted in:

- A similar overall response rate compared with cisplatin plus RT (90 versus 88 percent, respectively; p = 0.31).
- No difference in survival outcomes at three years.
- OS rate was 88 and 94 percent (HR 1.80, 95% CI 0.49-6.54).
- No difference in the incidence of serious (grade 3/4) toxicity.

Nam EJ, Lee M, Yim G et al. Comparison of carboplatin- and cisplatin-based concurrent chemoradiotherapy in locally advanced cervical cancer patients with morbidity risks.
Oncologist. 2013;18(7):843.

Neoadjuvant Chemotherapy in Cervical Cancer

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

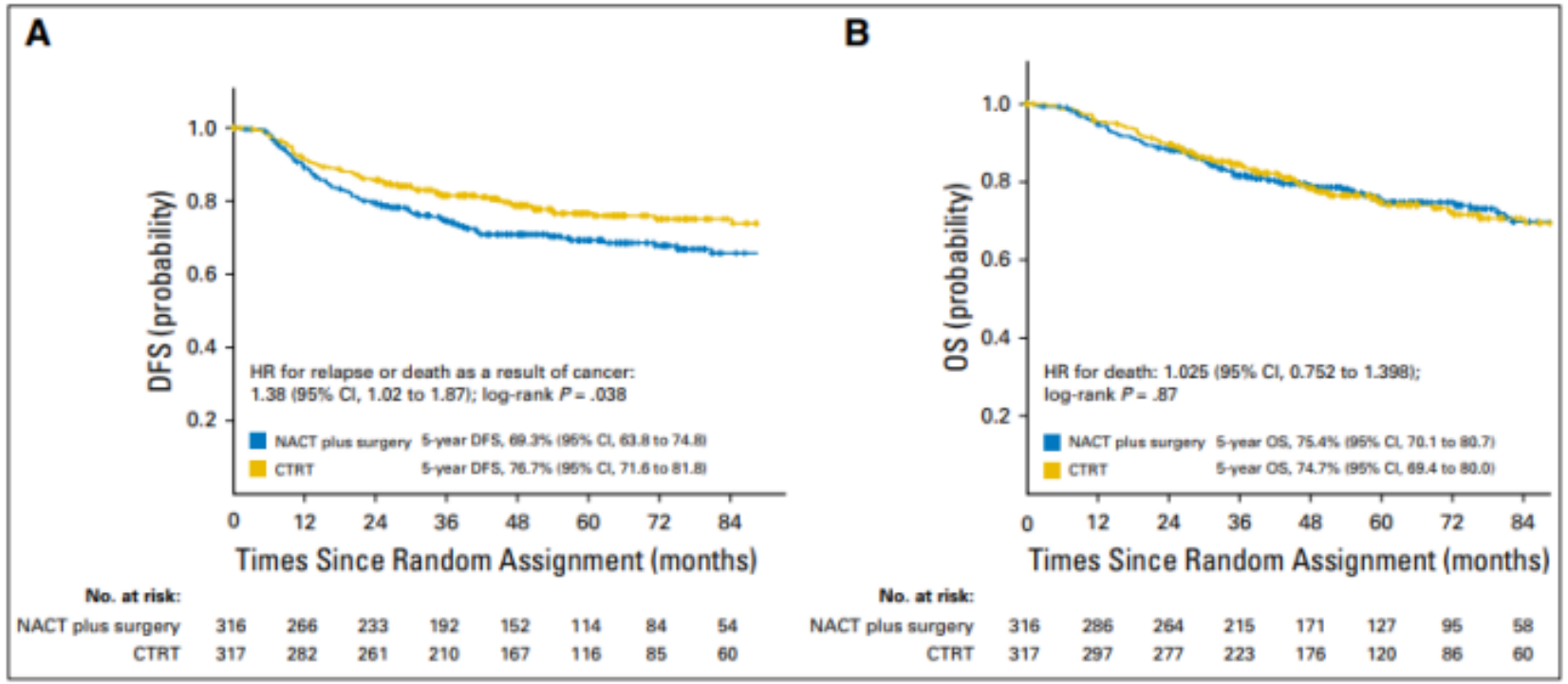
Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

Sudeep Gupta, Amita Maheshwari, Pallavi Parab, Umesh Mahantshetty, Rohini Hawaldar, Supriya Sastri (Chopra), Rajendra Kerkar, Reena Engineer, Hemant Tongaonkar, Jaya Ghosh, Seema Gulia, Neha Kumar, T. Surappa Shylasree, Renuka Gawade, Yogesh Kembhavi, Madhuri Gaikar, Santosh Menon, Meenakshi Thakur, Shyam Shrivastava, and Rajendra Badwe

- Single-center, phase III, randomized controlled trial
- NACT - paclitaxel and carboplatin Q3W f/b RH or standard Cisplatin based CCRT Q1W for 5 weeks.
- September 2003 and February 2015,

- 5-year DFS (Primary outcome):
  - NACT f/b Sx: 69.3% ; CCRT : 76.7% (HR, 1.38; 95% CI, 1.02 to 1.87; P = .038),
- 5-year OS (Sec outcome):
  - NACT f/b Sx: 75.4%; CCRT: 74.7%, (HR, 1.025; 95% CI, 0.752 to 1.398; P = .87).
- Delayed toxicities at 24 months or later (Sec outcome) :

  NACT f/b Sx versus CCRT:
  - rectal (2.2% v 3.5%, respectively),
  - bladder (1.6% v 3.5%, respectively)
  - vaginal (12.0% v 25.6%, respectively).



Limitations:

- Over representation of stage IIB cases
- > 20% cases needed adjuvant treatment.
- Not powered for OS as primary end point

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Original Article

Neoadjuvant Chemotherapy in Locally Advanced Cervical Carcinoma – a Role in Patients with Para-aortic Lymph Node Involvement? A 10-year Institutional Experience

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Available online 6 January 2022, Version of Record 10 June 2022.

Results

- NACT and extended-field RT had a lower risk of death compared with extended-field RT alone

- HR 0.27, 95% CI: 0.08–1.00; *P* = 0.05.

- Three-year OS rates were 83.3% (95% CI 66.1–100) and 64.6% (95% CI 44.6–84.6), respectively.

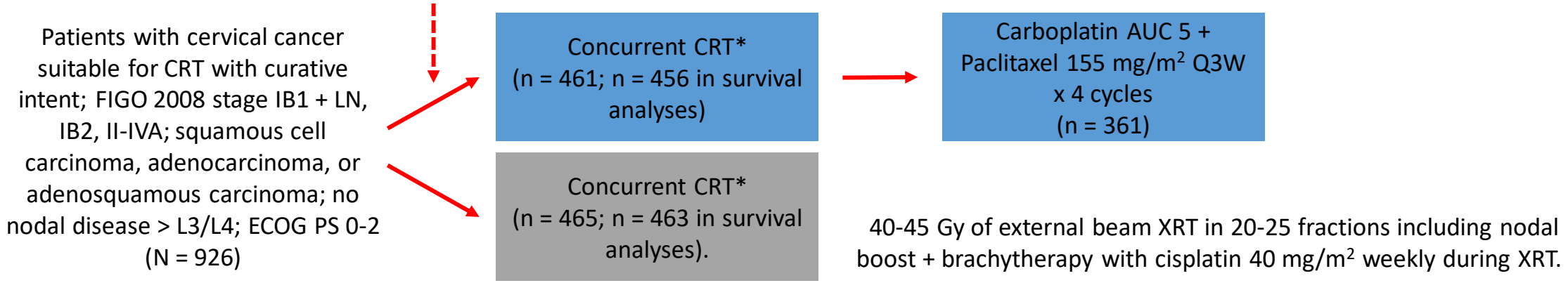
Other Indications of NACT in Cervical Cancer

- Stage IVB disease (Bladder/ Rectal Involvement)

- Fistula formation can be prevented with NACT

Adjuvant chemotherapy-OUTBACK: Study Design

- International, randomized phase III trial (median follow-up: 5 yr)



Primary endpoint: OS

Study protocol amended in 2016 to increase sample size from N = 780 to 900 due to nonadherence with adjuvant CT and lower event rate than anticipated (80% power and 2-sided $\alpha = 0.05$ to detect 8% absolute improvement in OS at 5 yr [72% to 80%])

Secondary endpoints: PFS, patterns of disease recurrence, radiation protocol compliance, PROs, safety

Mileshkin. ASCO 2021. Abstr LBA3. NCT01414608.

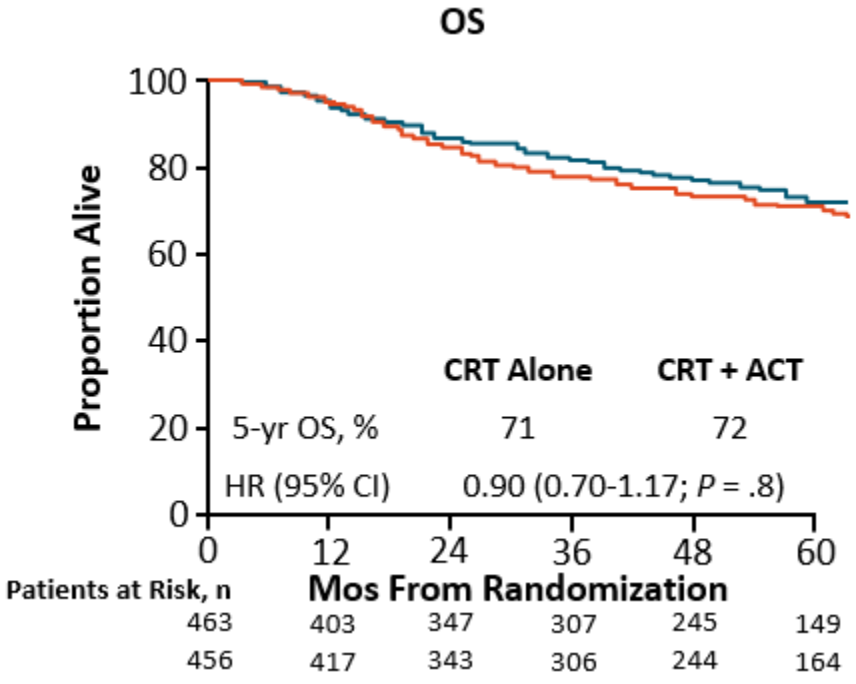
OUTBACK: Baseline Characteristics

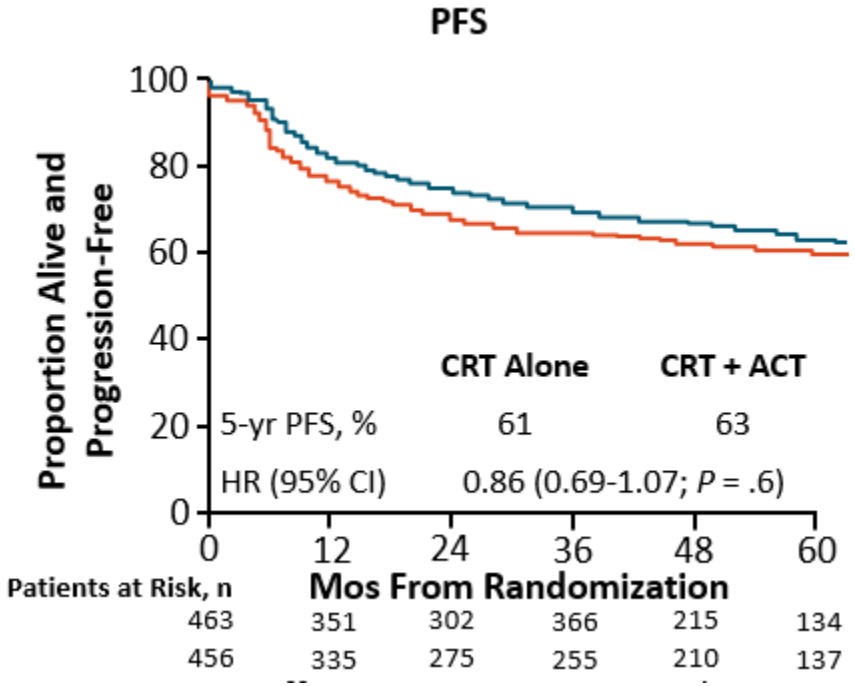
Characteristic	CRT Alone (n = 456)	CRT + ACT (n = 463)
Median age, yrs (range)	45 (22-88)	46 (21-99)
ECOG PS, n (%)		
▪ 0	344 (75)	337 (73)
▪ 1	94 (21)	117 (25)
▪ 2	18 (4)	9 (2)
Race, n (%)		
▪ White	326 (72)	337 (73)
▪ Black	68 (15)	53 (11)
▪ Asian	22 (5)	31 (7)
▪ Aboriginal/Pacific Islander	11 (2)	13 (3)
▪ Other	28 (6)	29 (6)
Region, n (%)		
▪ Australia and New Zealand	84 (18)	81 (17)
▪ USA and Canada	366 (80)	373 (81)
▪ Rest of world	6 (1)	9 (2)
Tobacco smoking, n (%)		
▪ Never	237 (52)	224 (48)
▪ Current/ex-smoker/unknown	219 (48)	239 (52)

Characteristic	CRT Alone (n = 456)	CRT + ACT (n = 463)
Nodal involvement, n (%)		
▪ None	225 (49)	231 (50)
▪ Pelvic only	144 (32)	149 (32)
▪ Common iliac only	33 (7)	31 (7)
▪ Pelvic and common iliac	44 (10)	44 (10)
▪ Unknown	10 (2)	8 (2)
Extended field planned, n (%)		
▪ No	397 (87)	404 (87)
▪ Yes	59 (13)	59 (13)
FIGO 2008 stage, n (%)		
▪ IB1 (all node+), IB2, IIA	152 (33)	154 (33)
▪ IIB	196 (43)	197 (43)
▪ IIIB or IVA	108 (24)	112 (24)
Histology, n (%)		
▪ Squamous	358 (79)	383 (83)
▪ Adenocarcinoma	79 (17)	68 (15)
▪ Adenosquamous	19 (4)	12 (3)
Median max tumor diameter, cm (range)	5.0 (0-11)	5.0 (0-12)

Mileshkin. ASCO 2021. Abstr LBA3.

OUTBACK: OS and PFS



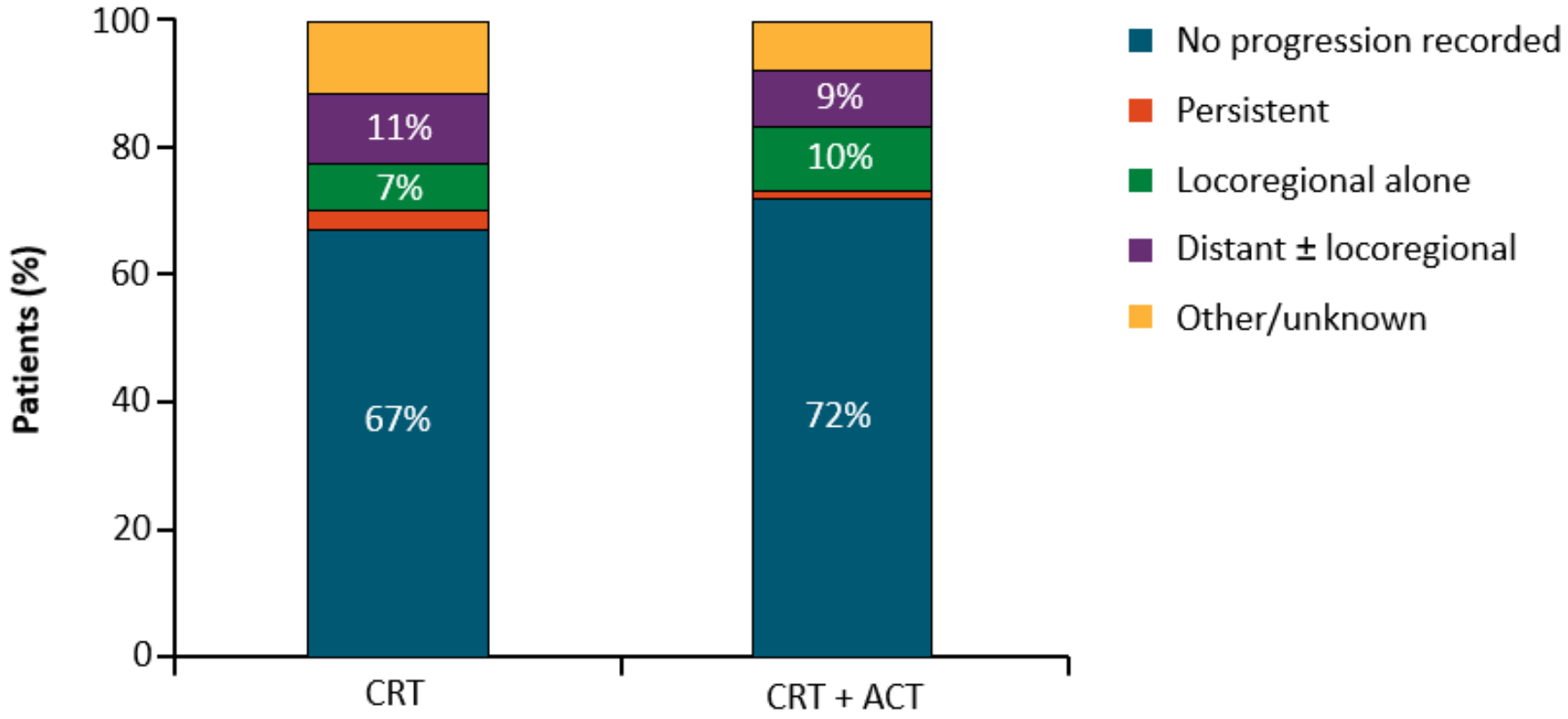


- No significant improvement in 5-yr rates for OS or PFS with CRT + ACT vs CRT alone
- Sensitivity analyses found no significant differences in OS or PFS in CRT + ACT arm for those who did vs did not complete CRT

- Treatment effects consistent across subgroups except for those aged < vs ≥60 yr, where younger patients had greater OS and PFS benefit with CRT + ACT (interaction *P* = .01 and .03, respectively)

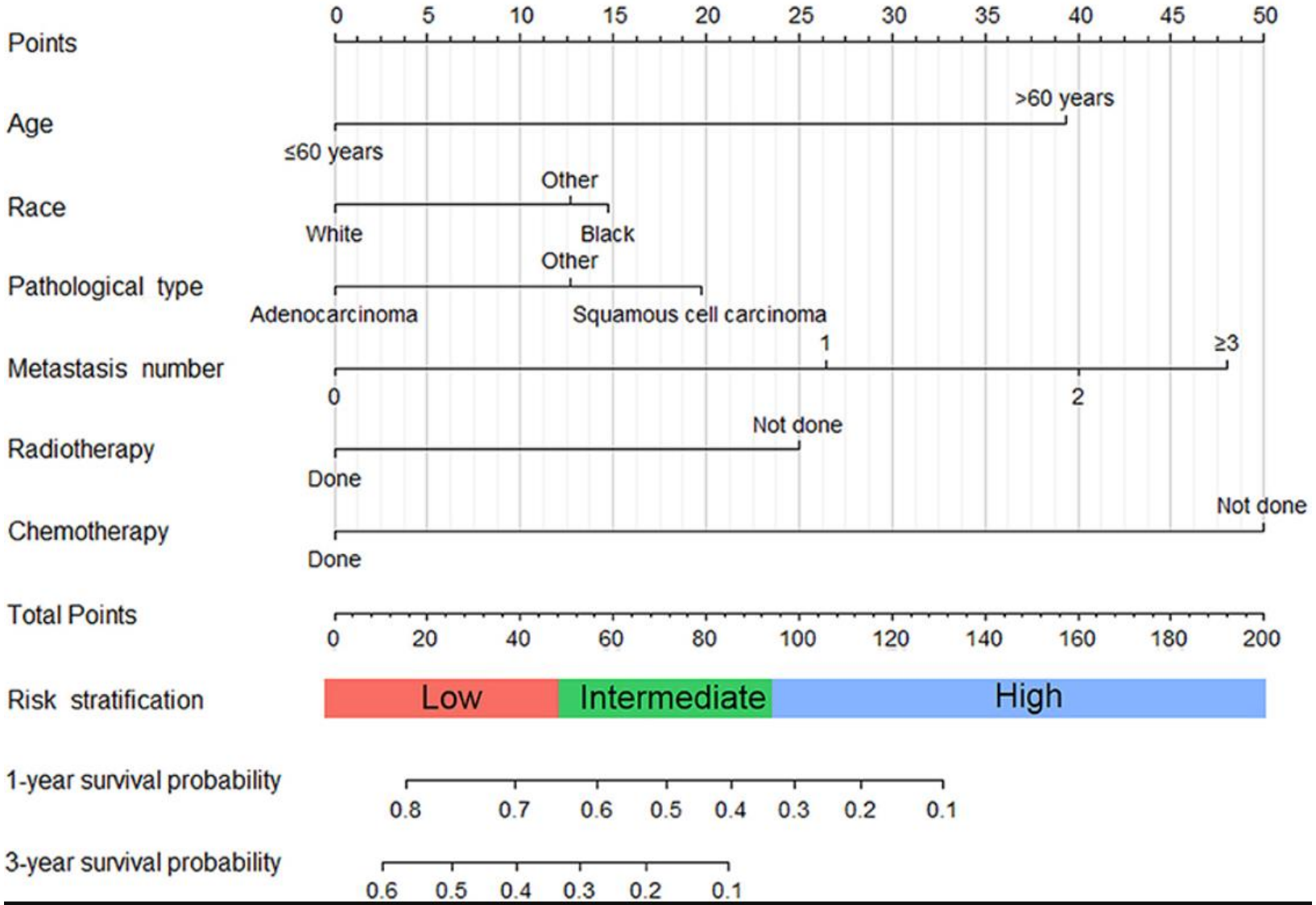
Mileshkin. ASCO 2021. Abstr LBA3. Reproduced with permission.

OUTBACK: Disease Recurrence



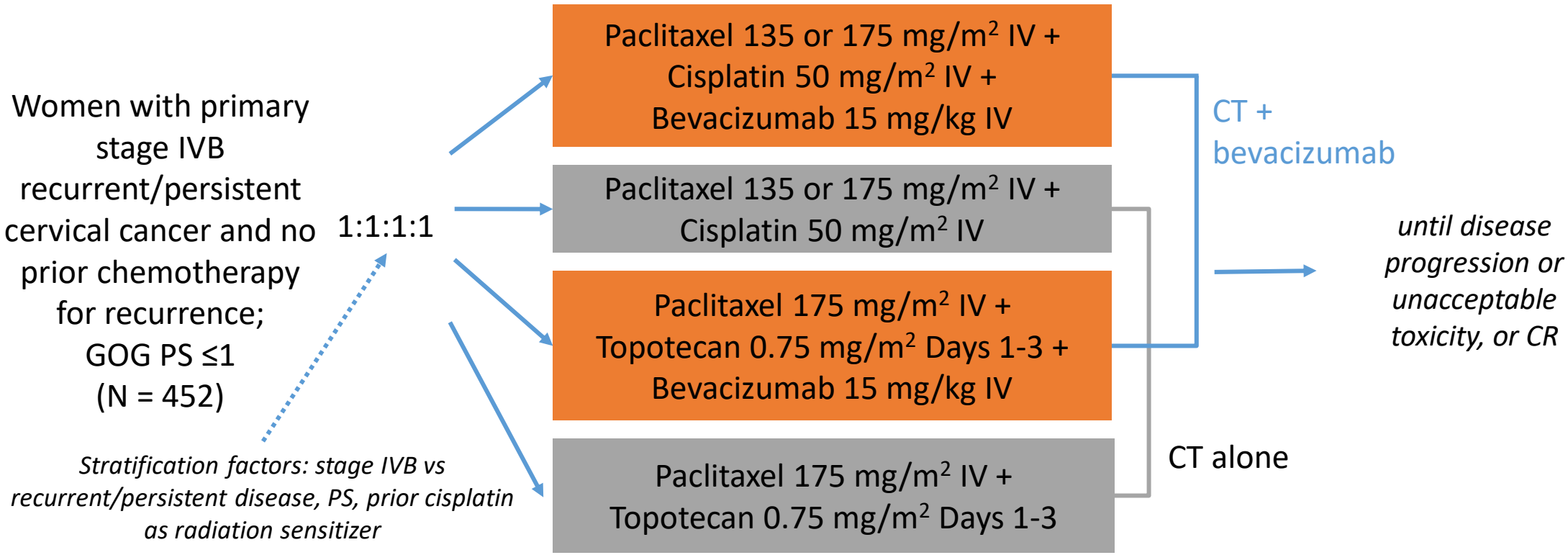
Mileshkin. ASCO 2021. Abstr LBA3. Reproduced with permission.

Nomogram to predict Survival in advanced Cervical Cancer



GOG 240: Paclitaxel + Cisplatin or Topotecan ± Bevacizumab in Recurrent/Persistent Cervical Cancer

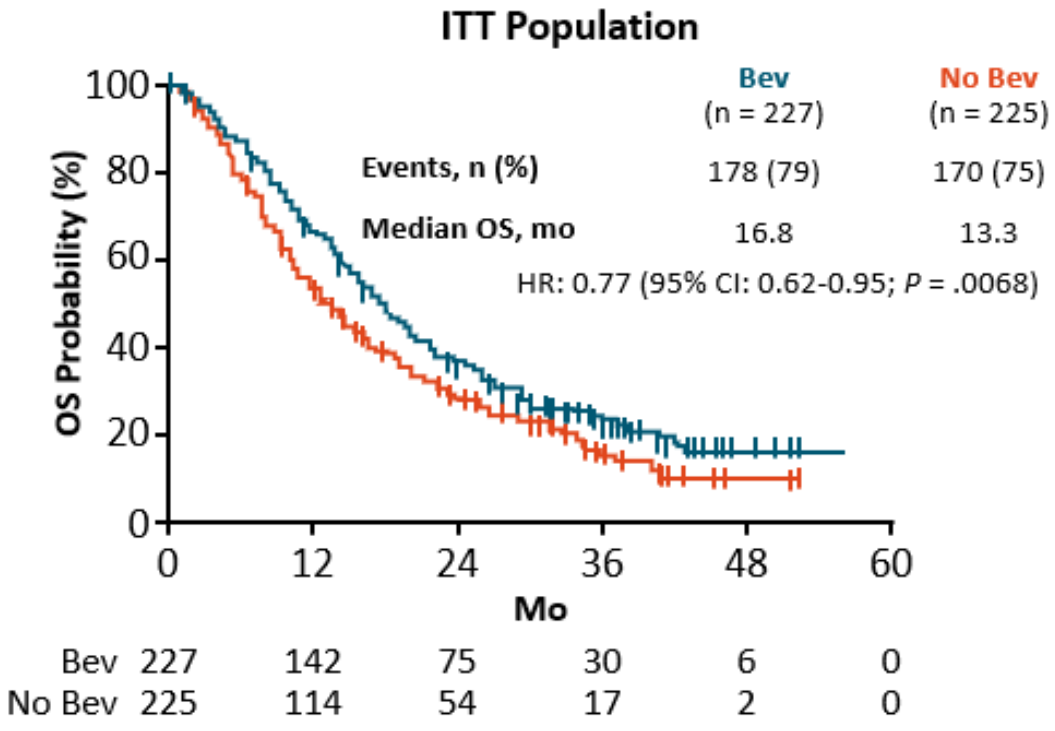
- Randomized, open-label phase III study

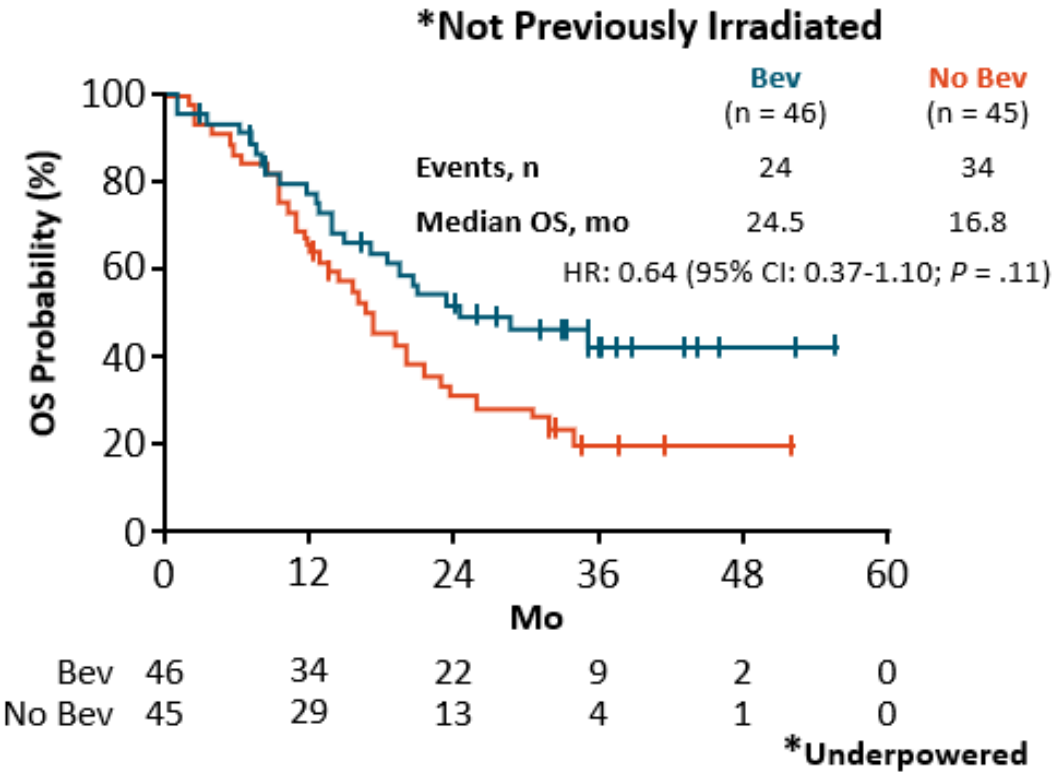


- Primary endpoints: OS, safety
- Secondary endpoints: PFS, ORR
- Tertiary endpoints: HRQoL, plasma markers of angiogenesis, cell-free DNA

Tewari. Lancet. 2017;390:1654. NCT00803062.

Paclitaxel + Cisplatin or Topotecan ± Bevacizumab in Cervical Cancer (GOG 240): Mature OS Results





Tewari. Lancet. 2017;390:1654.

Rationale for Immunotherapy in Cervical Cancer: Cervical Cancer Immunosuppression

Immunosuppression ↔ Invasion

- HPV E6 and E7 induce cascade of cytokines and T-cell signaling (1,2)
- ↑ IL-6
  - Myelo/monocyte infiltration (3)
  - Activated fibroblast inflammation (4)
  - Disables antigen presentation (5)
- Tregs and MDSC infiltration (6)
- PD-L1 upregulation (7)
- All worse with hypoxia, TGF-β, ROS

Smola. Ther Adv Vaccines. 2017;5:69.

Additional Molecular Testing in Cervical Cancer

- NCCN guidelines recommend testing for molecular biomarkers in patients with recurrent progressive or metastatic cervical cancer[2]
  - PD-L1 (CPS ≥1%)
  - MMR/MSI
  - *NTRK* gene fusion testing
  - TMB testing through validated and/or FDA-approved assay

NCCN. Clinical practice guidelines in oncology: cervical cancer. v.1.2022. nccn.org.

KEYNOTE-826: Pembrolizumab + CT vs Placebo + CT in Cervical Cancer: Study Design

International, randomized, double-blind phase III trial

Stratified by metastatic disease (yes vs no), PD-L1 CPS (<1 vs 1 to <10 vs ≥10), planned bevacizumab (yes vs no)

Adults with persistent, recurrent, or metastatic cervical cancer; no prior systemic chemotherapy; ECOG PS 0-1 (N = 548)

→ Pembrolizumab* 200 mg IV Q3W + CT† IV Q3W ± Bevacizumab 15 mg/kg IV Q3W

→ Placebo* IV Q3W + CT† IV Q3W ± Bevacizumab 15 mg/kg IV Q3W

Treatment until death, radiographic progression, unacceptable toxicity, or study completion

FDA Approval October 2021
Pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test

≤35 cycles pembrolizumab/placebo. †CT: ≤6 cycles: paclitaxel 175 mg/m^2 + (cisplatin 50 mg/m^2 or carboplatin AUC 5 mg/mL/min).

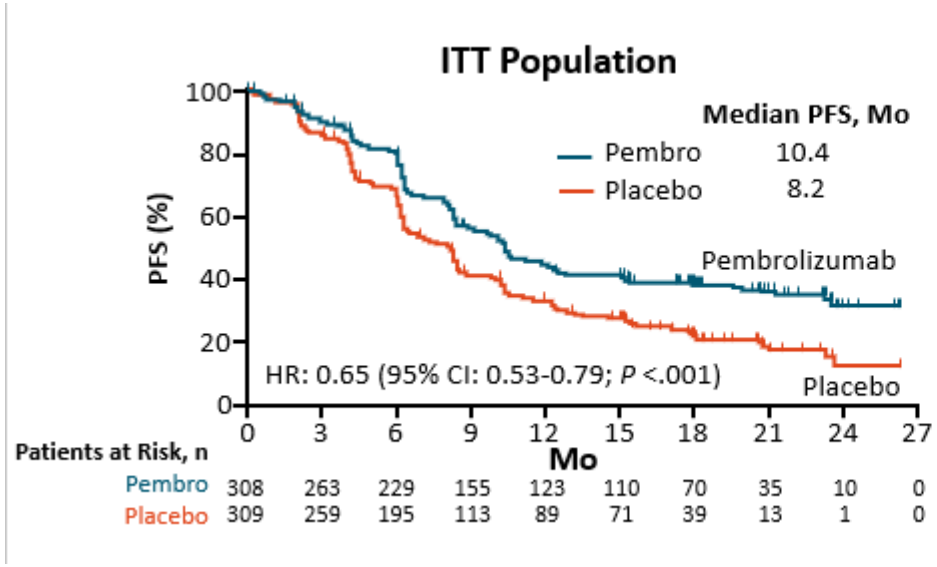
Dual primary endpoints: OS and PFS

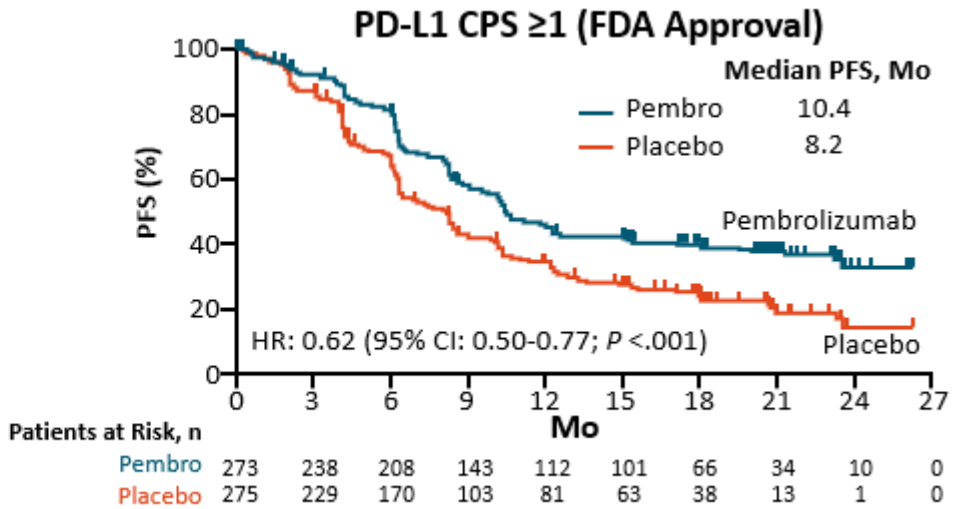
Secondary endpoints: ORR, DoR, 12-mo PFS, safety

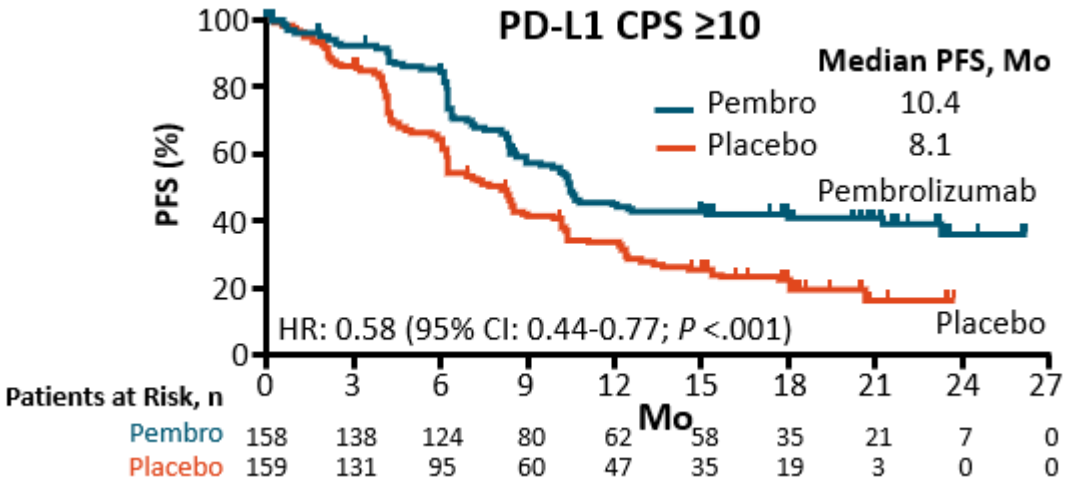
Exploratory endpoints: PROs assessed per EuroQol EQ-5D-5L VAS

Colombo. NEJM. 2021; 385:1856. Pembrolizumab PI.

KEYNOTE-826: PFS

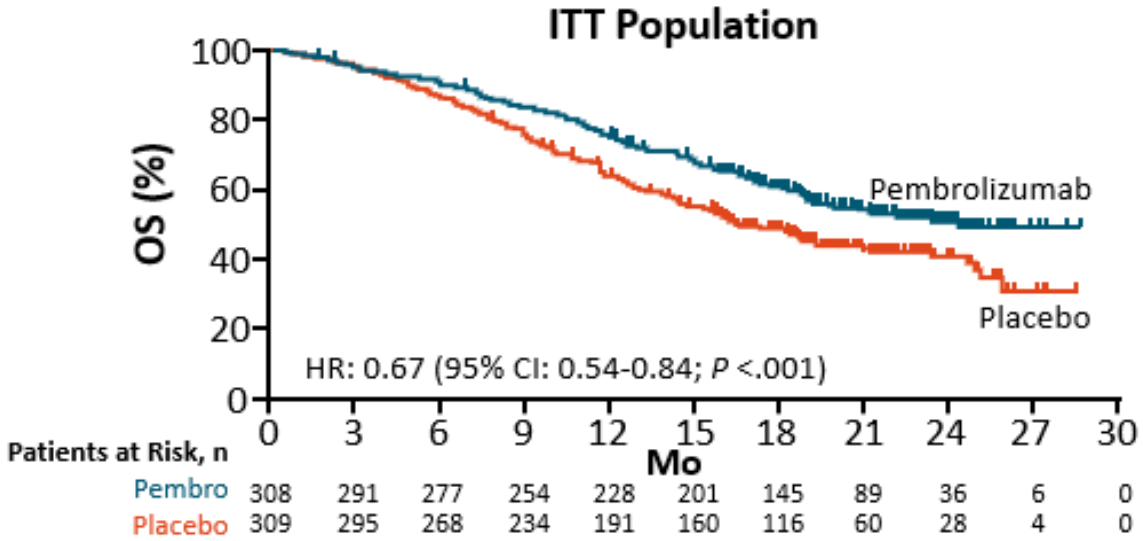


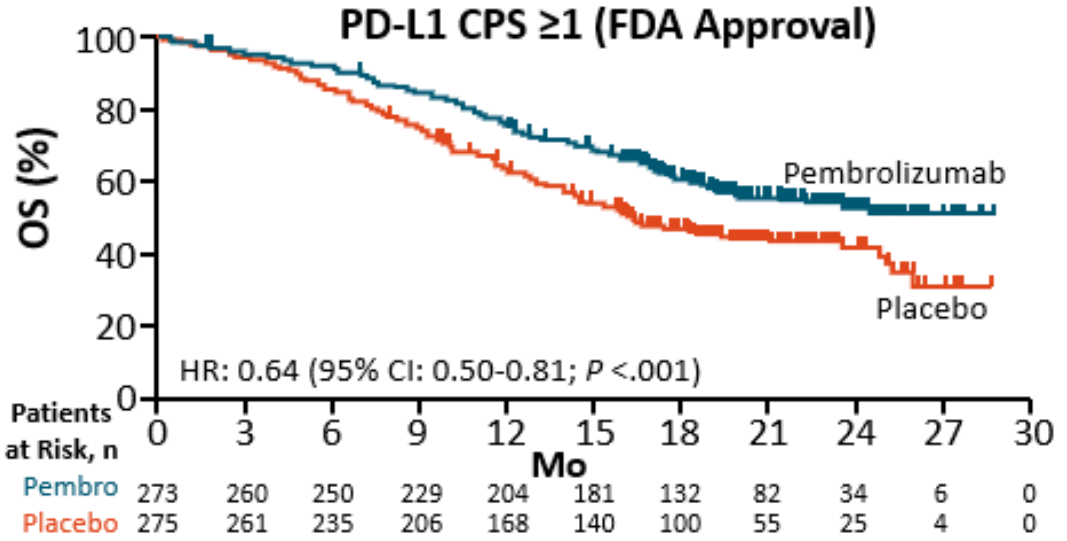


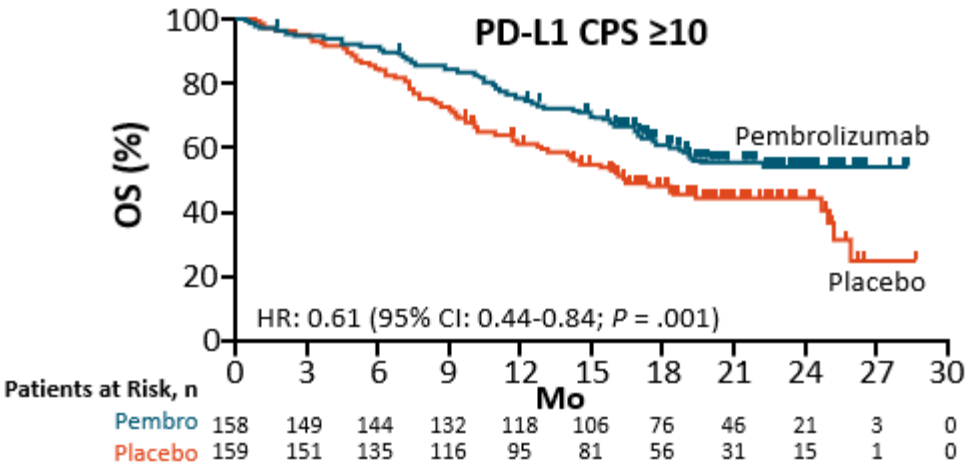


Colombo. NEJM. 2021; 385:1856.

KEYNOTE-826: OS

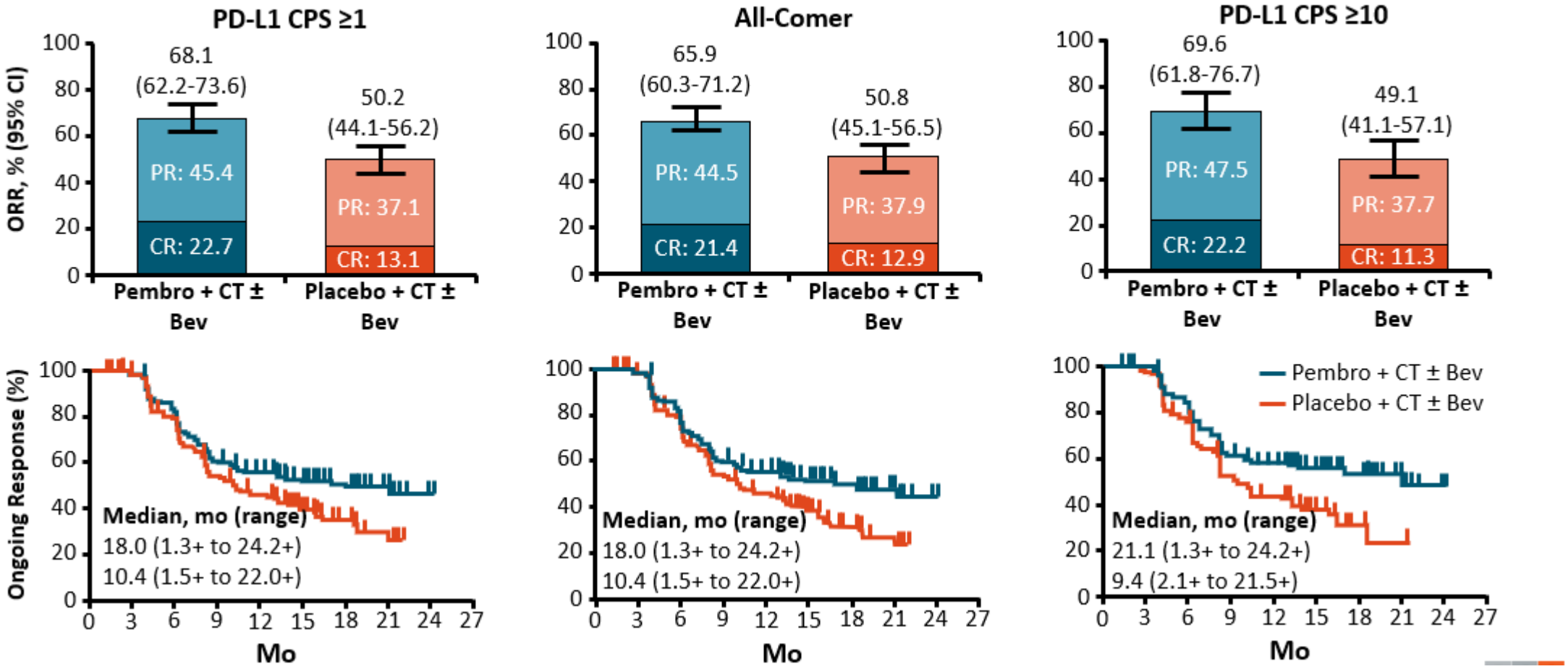






Colombo. NEJM. 2021; 385:1856.

KEYNOTE-826: ORR and DoR



Colombo. NEJM. 2021; 385:1856.

Carcinoma Vagina

- Primary vaginal cancer is rare, representing only 1–2% of all gynecological cancers.
- Strongly associated with HPV
- SCC: most prevalent histology (80%), followed by adenocarcinomas (15%).
- Other factors that negatively affect prognosis include tumor size >4 cm, older age, and possibly tumor location outside of the upper third of the vagina.

- Two prognostic factors, high-risk HPV DNA and low MIB-1 index, have been found to have a favorable prognostic value
- In general, surgery has a limited role in treating vaginal cancer due to the proximity of the cancer to normal tissues such as the bladder, rectum, and urethra.
- The general recommendation is that surgery might be considered in small stage I tumors.
- Radiation therapy is the treatment of choice in most patients with vaginal cancer, especially in patients with advanced-stage disease

CT RT

- CT RT (Cisplatin based) has been adopted in treating vaginal cancer
- Data extrapolated in patients with locally advanced cervical cancer.

THANK YOU