Updates in Cervical Cancer

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Gynecologic Oncology

Ochsner Health System

Multidisciplinary Cancer Update
10/29/22

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Disclosures

- None

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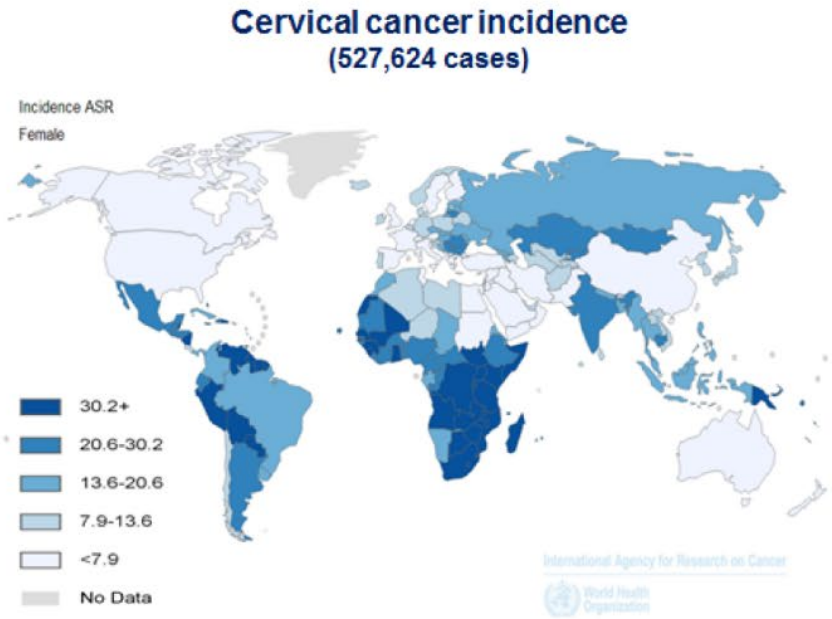
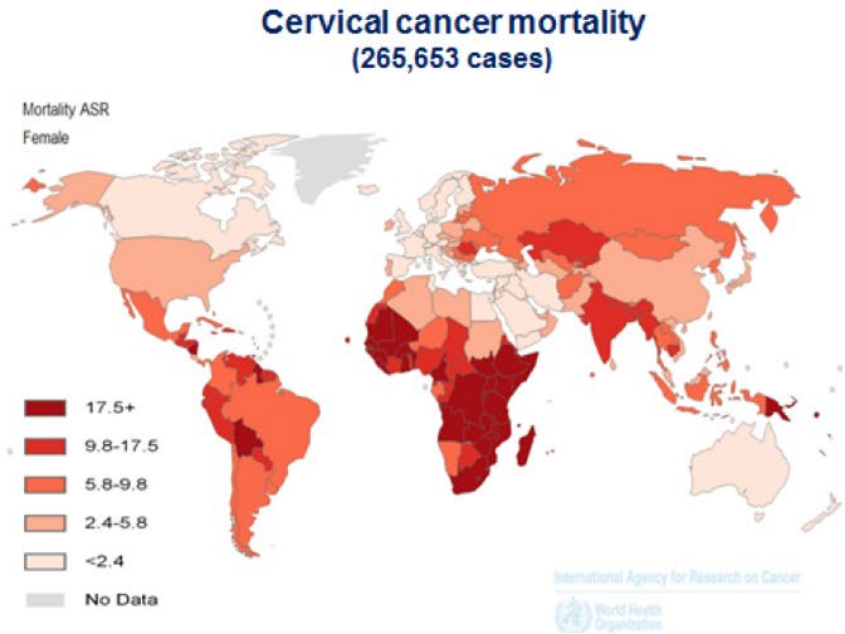
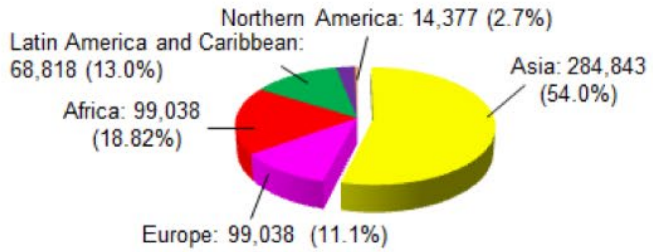
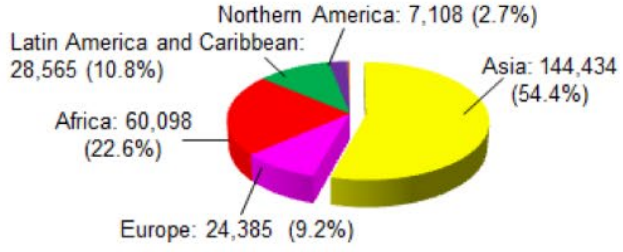
Cervical Cancer in an International Health Concern





Mortality: Incidence ratio: 50%





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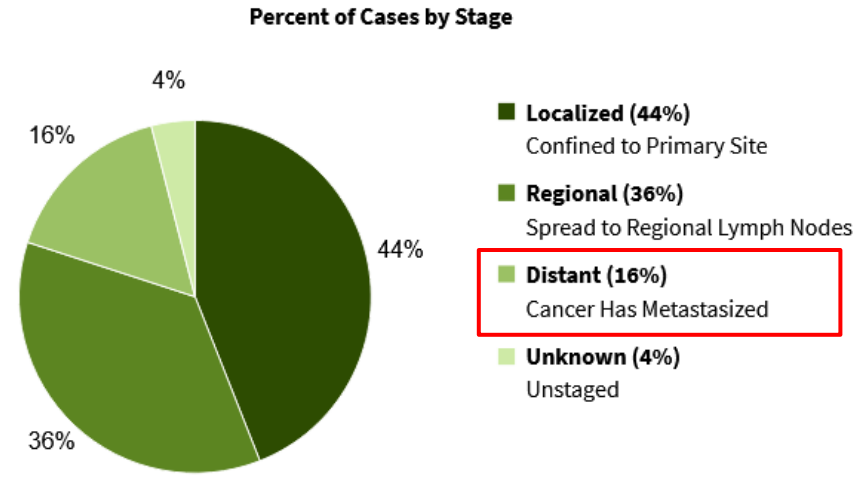
Jung HS et al. J Clin Med. 2015. 4(5): 1126

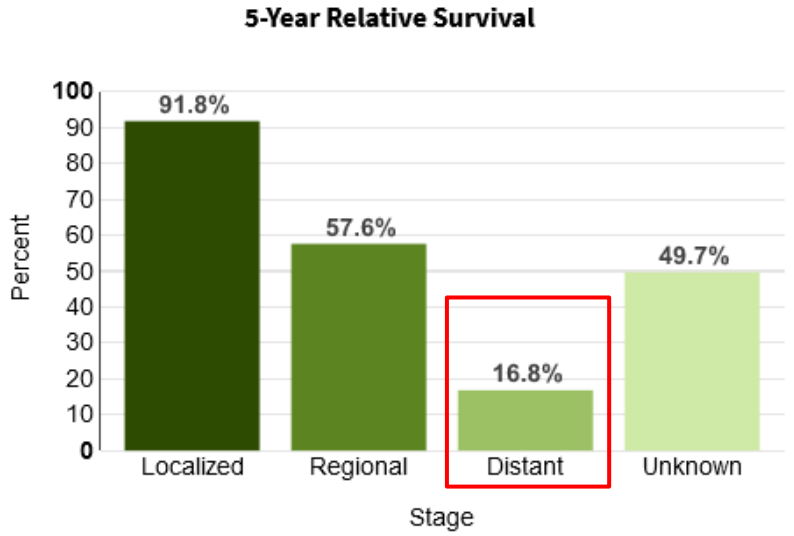
Selected New Cancer Cases and Deaths

Disease	New Cases	Deaths
Breast Cancer	281,550	43,600
Uterine Cancer	66,570	12,940
Ovarian Cancer	21,410	13,770
Cervical Cancer	14,480	4,290
Vulvar Cancer	6,120	1,550

Cervical Cancer

- Majority of Cervical Cancer cases present in early stage and are effectively treated using surgery and/or chemoradiation
- **Widely metastatic disease is still considered incurable**





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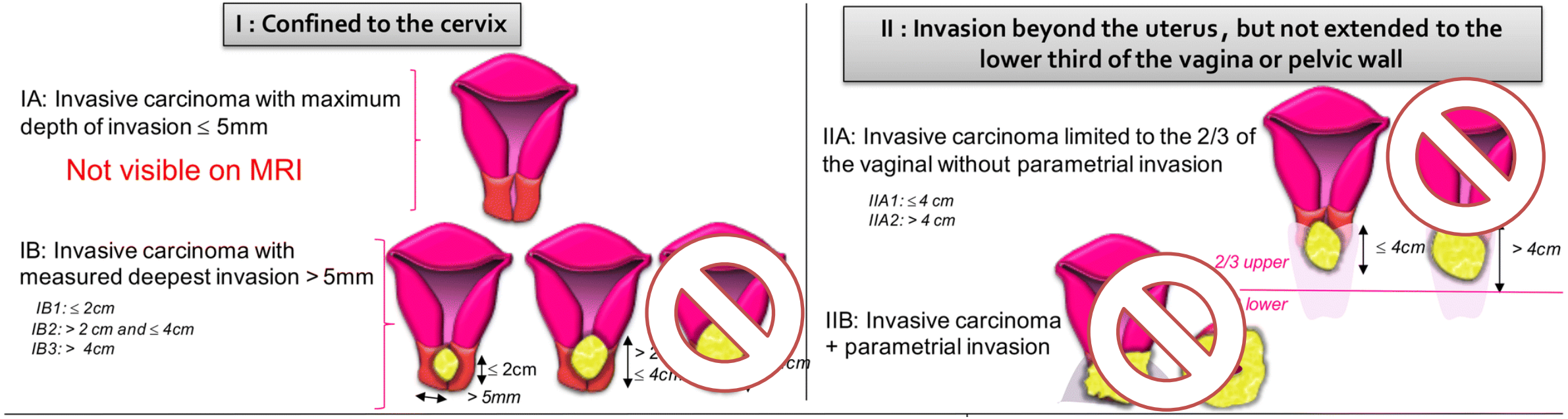
SEER 18 2010–2016, All Races, Females by SEER Summary Stage 2000

Early-stage Cervix Cancer

- Stage IA to IB1 (perhaps IIA1)
- Treated primarily surgically
- Fertility preservation considered
- 5-year survival >90%



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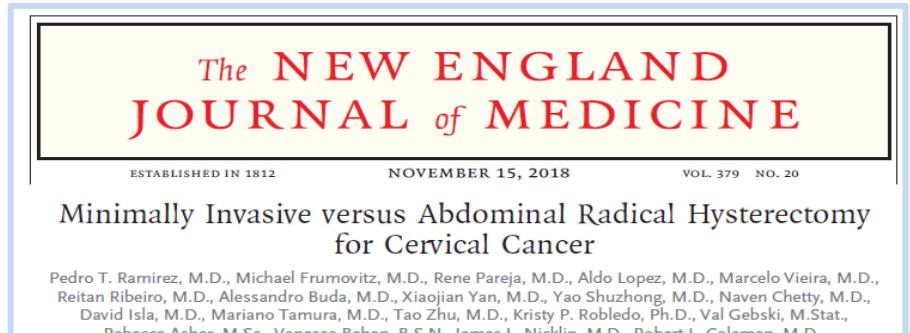
Mode of Surgery

- MIS employed for cervical cancer starting in early 2000s
- 2018 LACC RCT demonstrated MIS had inferior survival
  - DFS at 4.5 years - 86% versus 96.5%
  - DFS - 91.2% versus 97.1%
  - OS - 93.8% versus 99%
  - Rate of Cervical Cancer Death at 3 years - 4.4% versus 0.6%
- Meta-analysis confirm these findings
- ROCC/GOG43: Ongoing randomized non-inferiority trial of robotic vs open radical hysterectomy for early stage cervical cancer using



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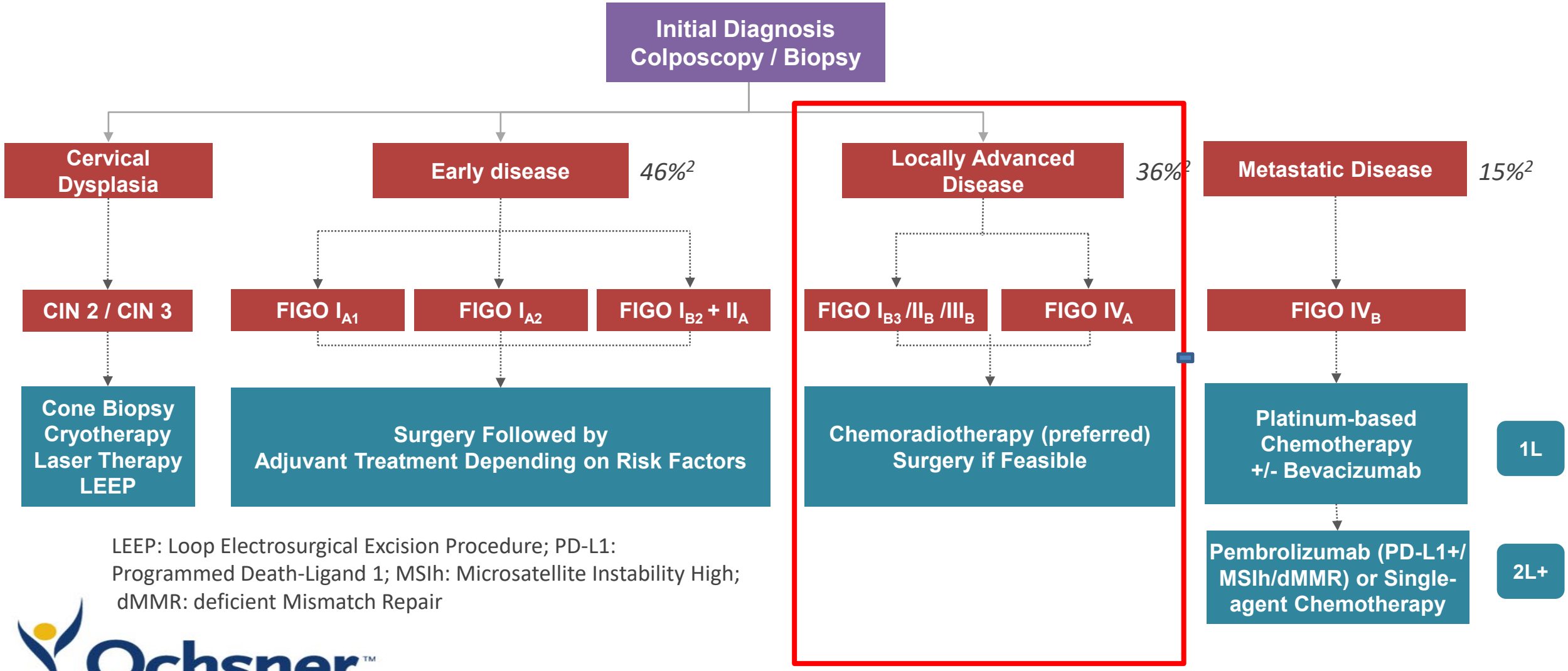
Cervical Cancer: Summary of Treatment



LEEP: Loop Electrosurgical Excision Procedure; PD-L1: Programmed Death-Ligand 1; MSIh: Microsatellite Instability High; dMMR: deficient Mismatch Repair

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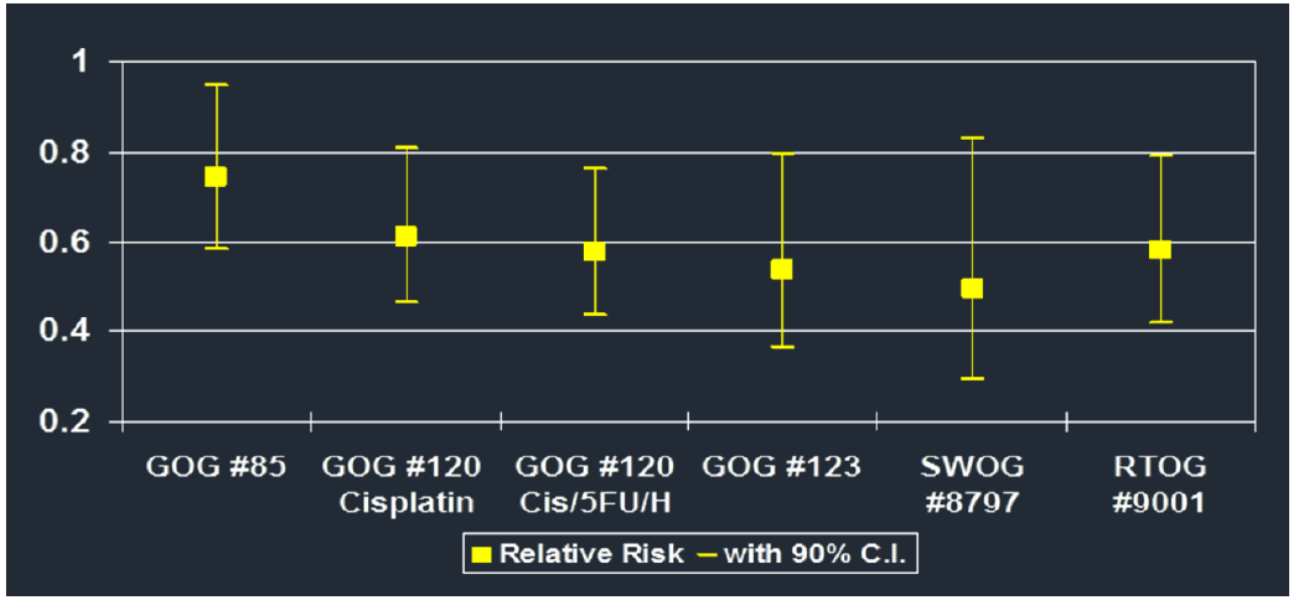
[1] NCCN Cervical Cancer Guidelines v2.2019

[2] SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD

Current Standard: Locally-advanced Disease (Is From 1999!)



- The findings of 5 trials demonstrated
  - an absolute improvement in survival of 8-18%
  - 30-50% improvement in survival with RT + chemotherapy
- GOG 120 current SOC: 2yr PFS: 67% v 47%

Keys et al. N Engl J Med. 1999, 340(15): 1154; Morris et al. N Engl J Med. 1999, 340(15):1137; Rose et al. N Engl J Med. 1999, 340(15): 1144. Vale C et al. J Clin Oncol. 2008, 26(35): 5802.

Despite HPV inducing an environment favorable to DNA damage inducing therapies, tx failure is still a problem

Study	Patients	Arms	Rec	Local Rec	Distant Rec	PFS	OS
GOG 24 & 56 (Stehman et al. 1991)	IIB-IVA (-PALN)	WPRT CB Hu/ Mis	49%			40-60%	
GOG 85 Whitney et al. 1999	IIB-IVA	Hu PF	53% 43%	30% 25%	21% 17.5%		57% 67%
GOG 120 Rose et al. 1999	IIB-IVA	P PFHu Hu	34% 34% 55%	19% 20% 30%	15% 14% 25%	58% 57% 35%	60% 61% 40%
RTOG 90-01 Morris et al. 1999	IB2-IVA	PF EFRT		19% 35%	14% 33%	67% 40%	73% 58%

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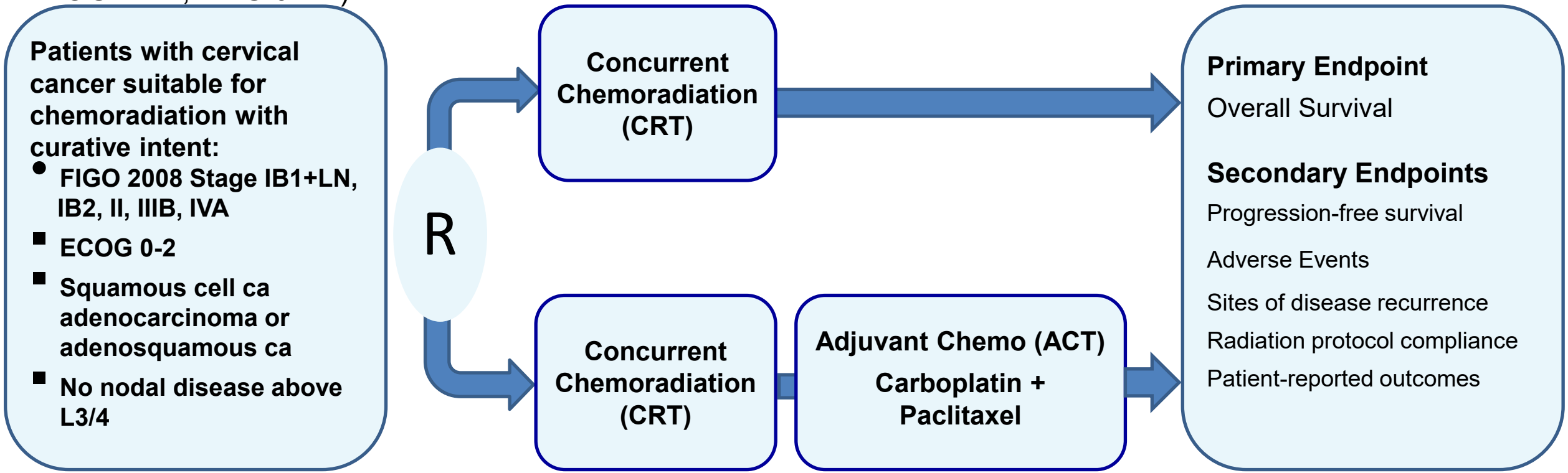
Stehman et al. Am J Obstet Gynecol 1988, 159(1): 87; Whitney et al. JCO 1999, 17(5): 1339; Morris et al. N Engl J Med. 1999, 340(15):1137; Rose et al. N Engl J Med. 1999, 340(15): 1144.

Adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone: The randomised phase 3 **OUTBACK Trial** (ANZGOG 0902, RTOG 1174, NRG 0274)

Study Schema



Stratification Factors

Pelvic or common iliac nodal involvement
Requirement for extended-field radiotherapy
FIGO 2008 stage: IB/IIA or IIB or IIIB/IVA
Age <60 or ≥60 years
Hospital/site

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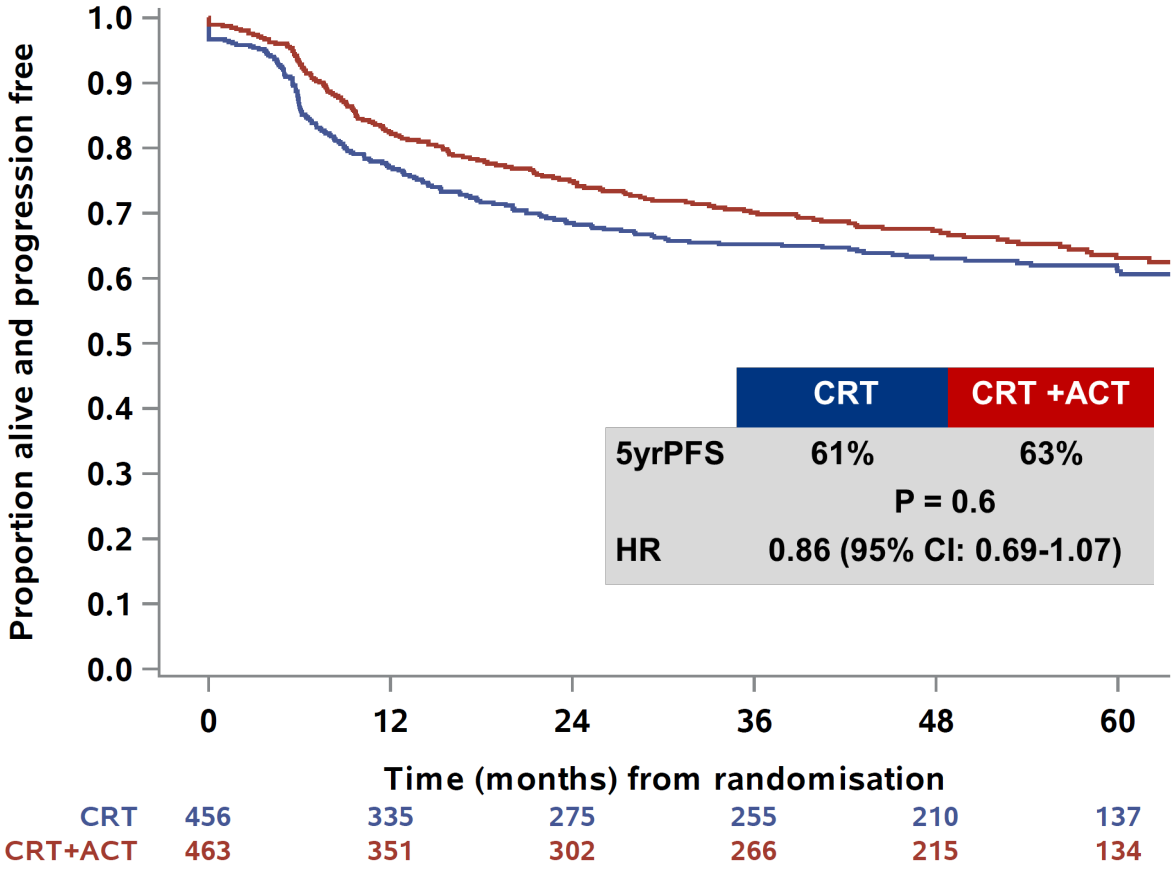
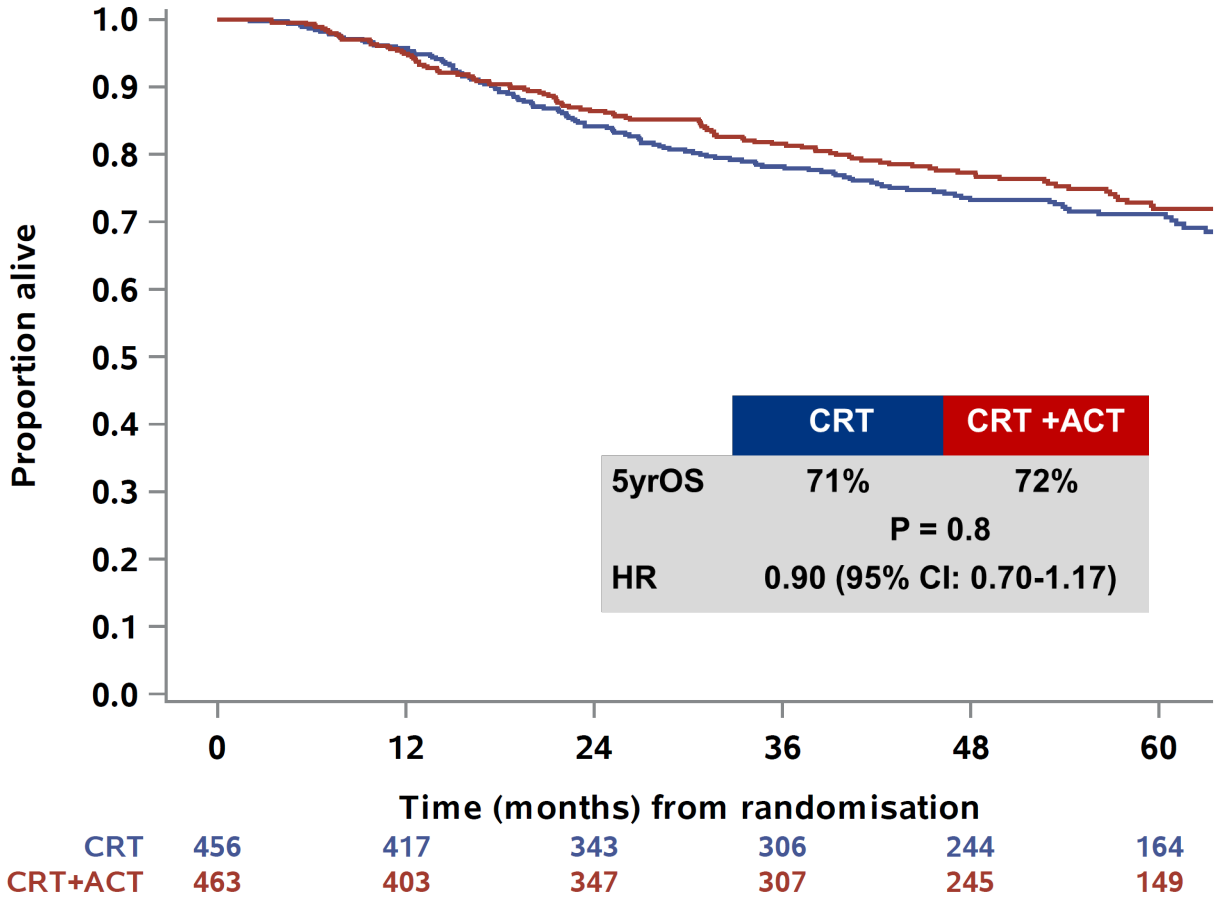
Progression-Free Survival



Overall Survival



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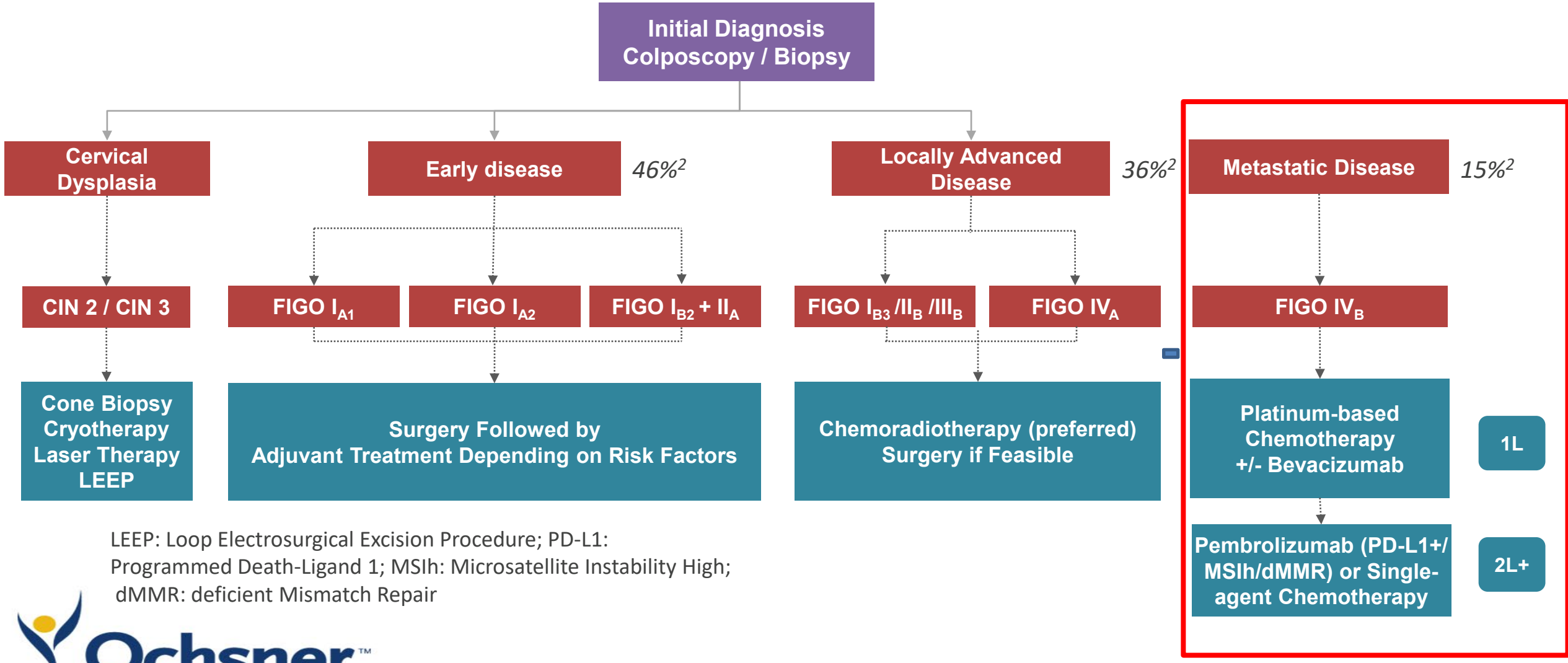
Cervical Cancer: Summary of Treatment



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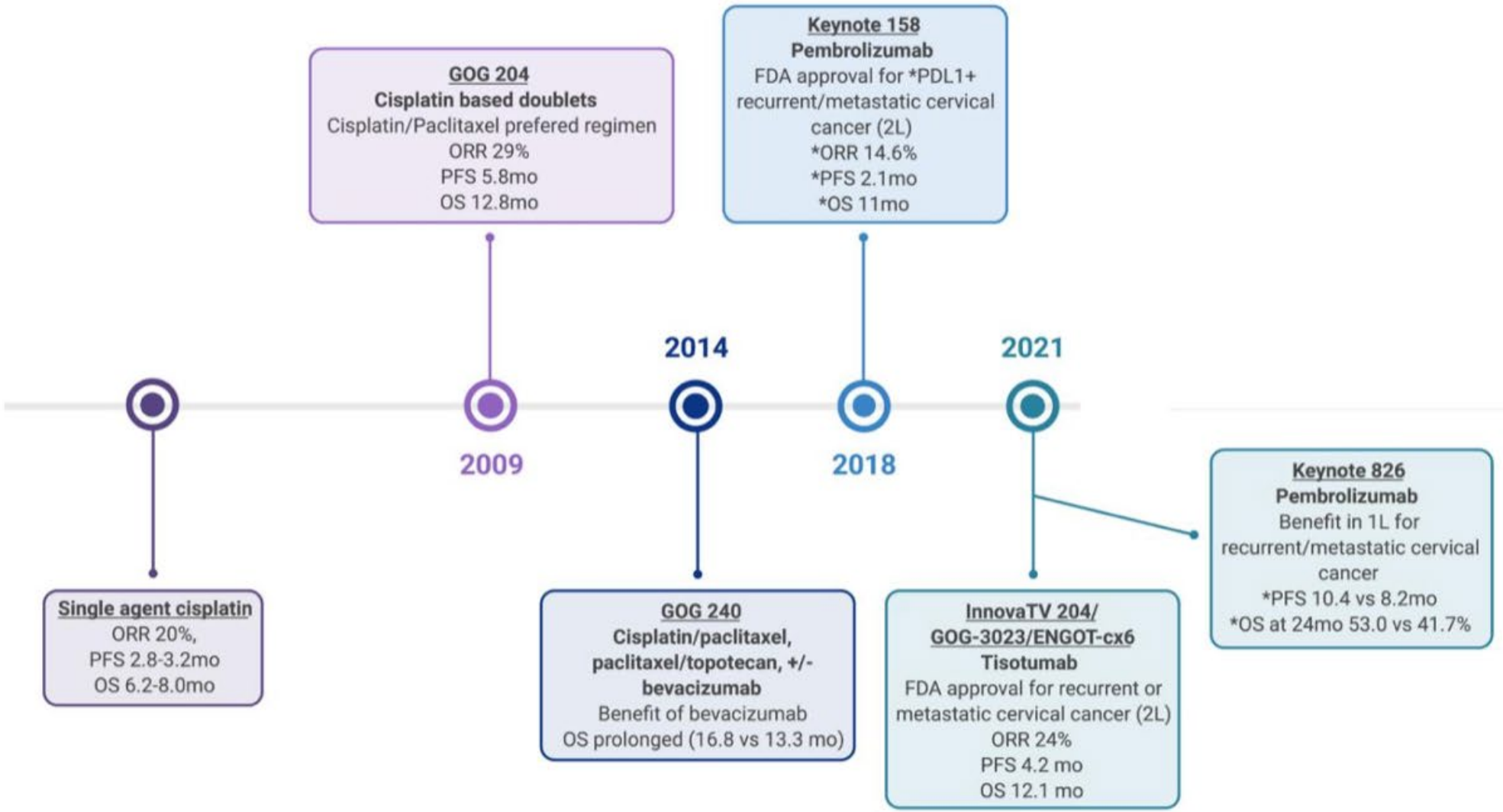

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Slide from K. Moore OncLive, updates in cervix cancer 2022

GOG 240

Carcinoma of the cervix
- Primary stage IVB
- Recurrent/persistent
- Measureable disease
- GOG PS 0-1
- No prior chemotherapy for recurrence

(N = 452)

RANDOMIZE

1:1:1:1

Stratification factors:
- **Stage IVB vs recurrent/ persistent disease**
- **Performance status**
- **Prior cisplatin Rx as radiation-sensitizer**

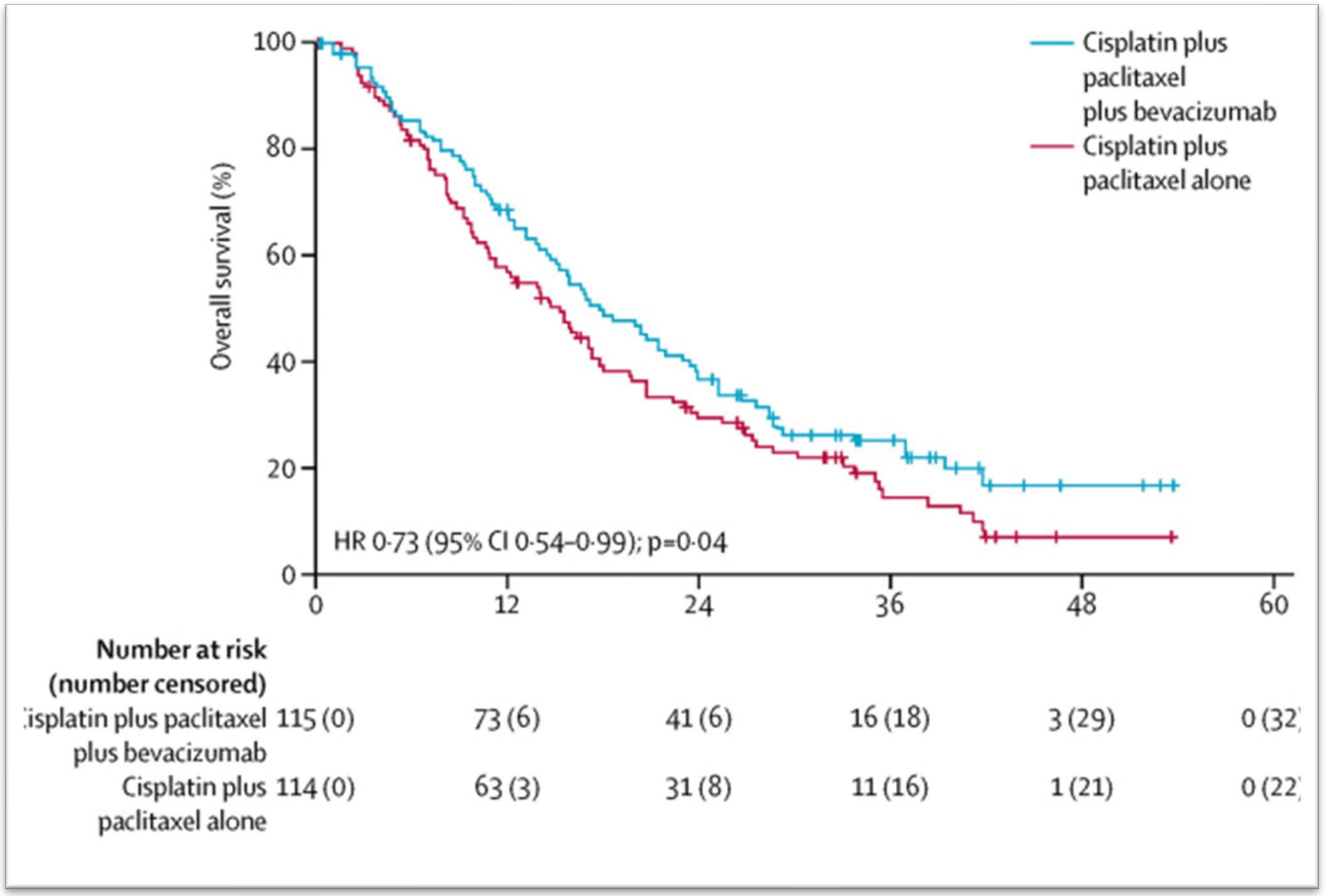
Activated: 4/6/09 Closed to accrual: 1/3/12	United States, Canada & Spain

I	Paclitaxel 135 or 175 mg/m² IV Cisplatin 50 mg/m² IV	Chemo alone
II	Paclitaxel 135 or 175 mg/m² IV Cisplatin 50 mg/m² IV Bevacizumab 15 mg/kg IV	q 21 d Rx to PD, toxicity, CR
III	Paclitaxel 175 mg/m² IV Topotecan 0.75 mg/m² d1-3	Chemo alone
IV	Paclitaxel 175 mg/m² IV Topotecan 0.75 mg/m² d1-3 Bevacizumab 15 mg/kg IV	Chemo + bevacizumab

National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed 15 January 2018.

Metastatic Disease

- Platinum based combination chemo + bevacizumab (GOG 240)
  - OS 17 v. 13 months
  - PFS 8 v. 6 months
  - ORR 49 v. 36%
  - Bleeding 5 v. 1%
  - VTE 9 v. 2%
  - GI fistula 3 v 0%
  - QOL equivalent



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N Engl J Med. 2014;370(8):734
Lancet. 2017;390(10103):1654-63

Evolution of 1L metastatic Cervical Cancer Treatment

Design	N	ORR (%)	PFS (months)	P-value	OS (months)	P-value	Reference
Bev + PC or TP vs. PC or TP	227 225	48 36	8.2 5.9	0.0002	17.0 13.3	0.0004	GOG 240 Study Tewari et al., NEJM.2014
PC vs. Carbo/Pacli	121 123	-- --	6.9 6.21	0.053	18.3 17.5	0.032	JCOG 0505 Study Kitagawa et al., JCO.2012
PC VC GC TC	103 108 112 111	29.1 25.9 22.3 23.4	5.82 3.98 4.7 4.57	 0.06 0.04 0.19	12.87 9.99 10.28 10.25	 0.71 0.90 0.89	GOG 204 Study Monk et al., JCO.2009
PC Cisplatin	130 134	36 19	4.8 2.8	0.001	9.7 8.8	NS	GOG 169 Study Moore et al., JCO.2004
TC Cisplatin	147 146	27 13	4.6 2.9	0.014	9.4 6.5	0.021	GOG 179 Study Long et al., JCO.2005

Addition of bevacizumab significantly increased rates of grade 3 or higher gastrointestinal or genitourinary fistula (6% vs. 0%, P=0.002), in addition to thromboembolic events (8% vs. 1%, P=0.001)

GC: gemcitabine/cisplatin; NS: not stated; PC: paclitaxel/cisplatin; TC:Topotecan/cisplatin; VC: vinorelbine/cisplatin

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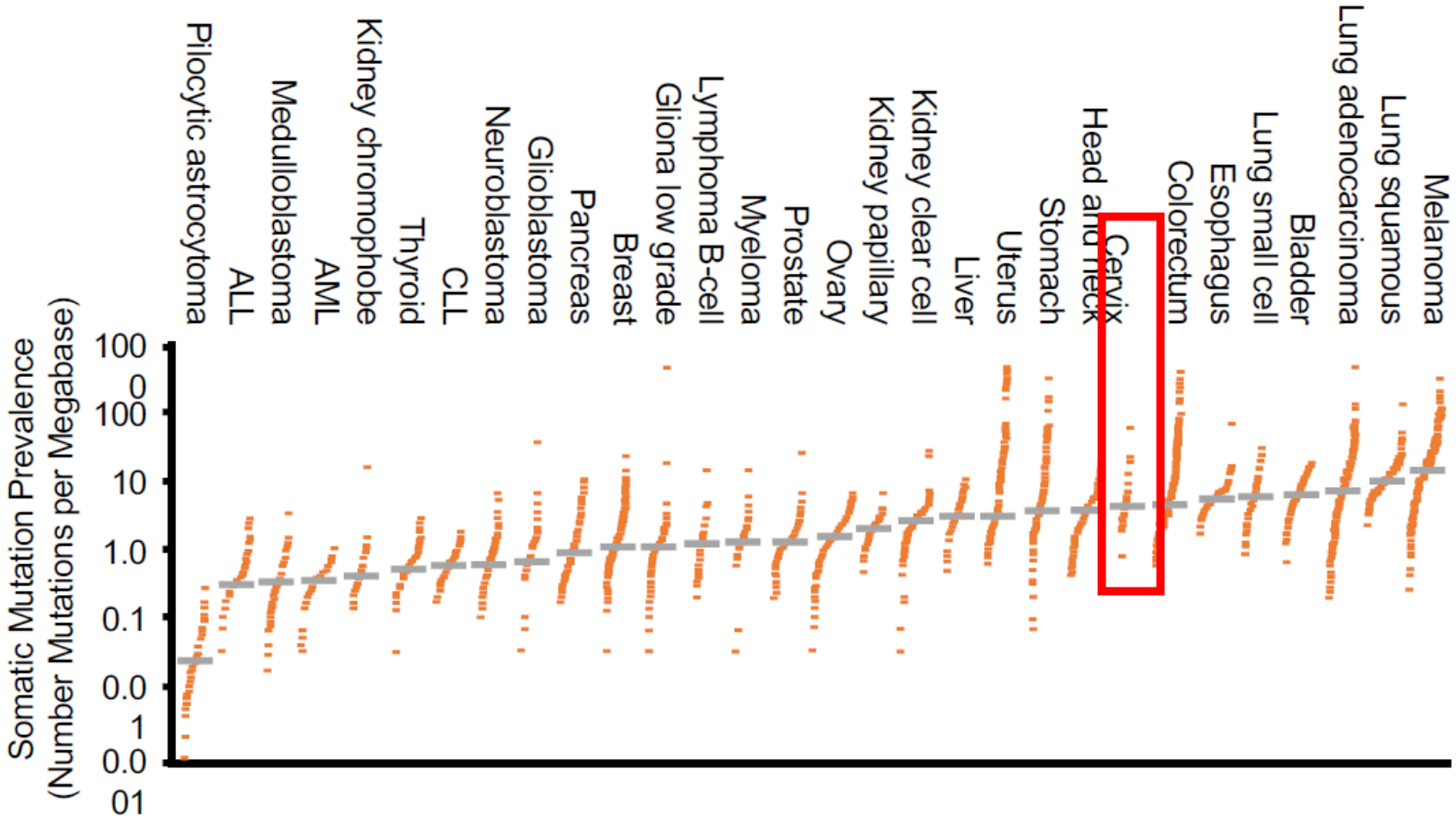
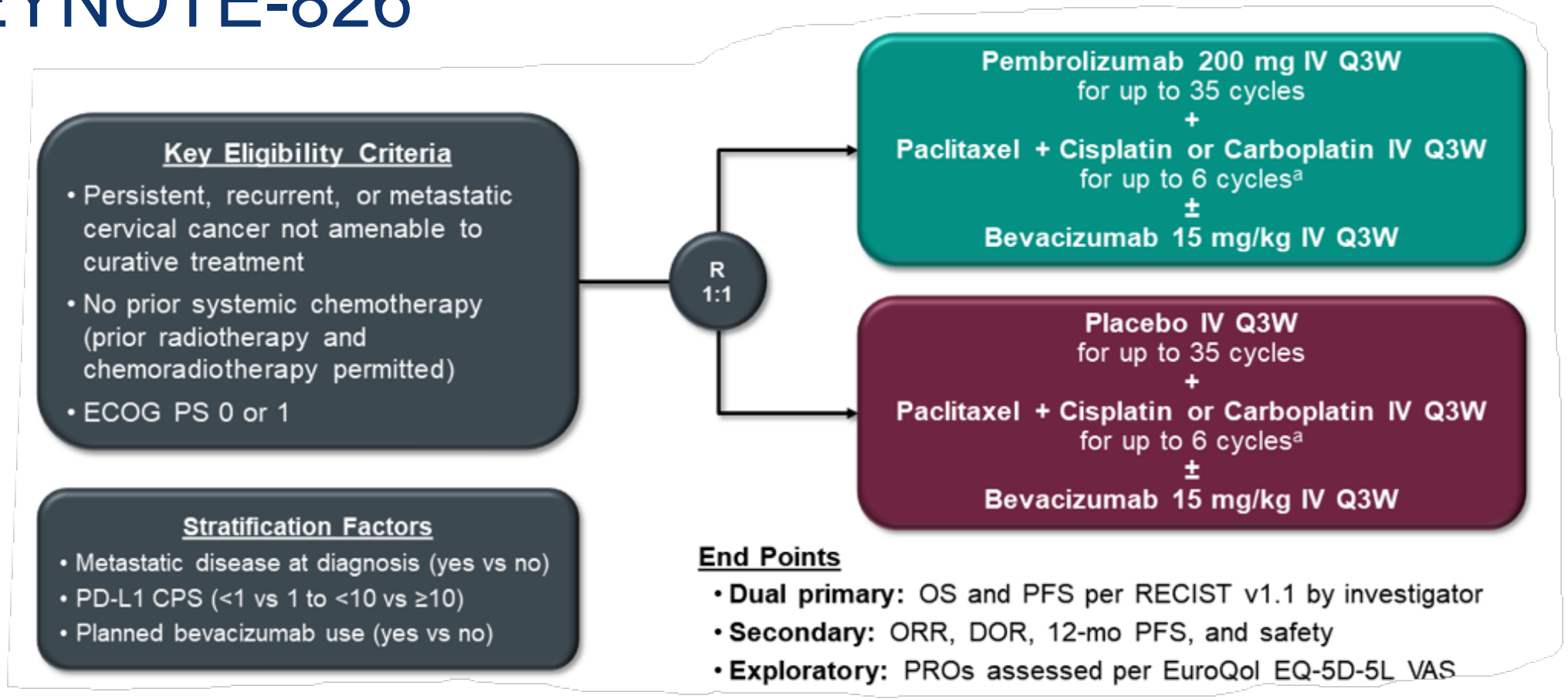
Mutational Burden Compared with Other Tumors



Alexandrov LB, et al. *Nature*. 2013;500(7463):415-421.

KEYNOTE-826



Colombo et al. NEJM 2021

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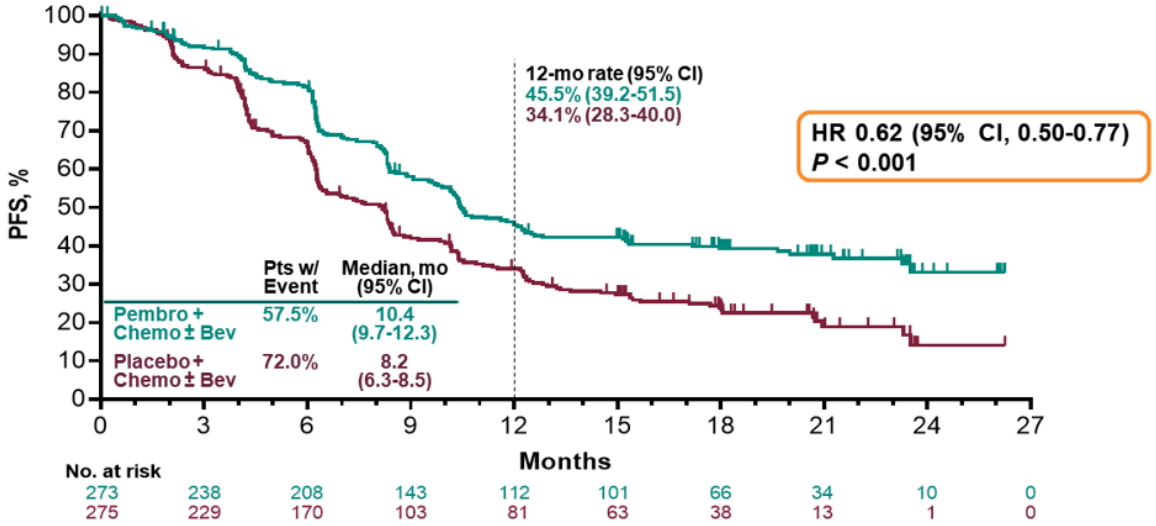
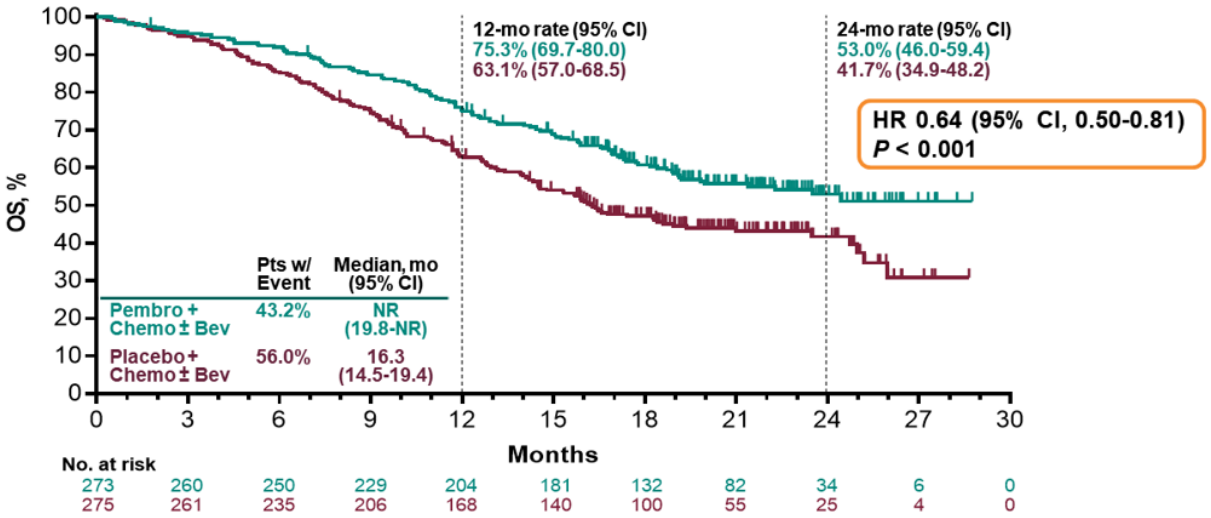
KEYNOTE-826: PFS & OS PD-L1+





Colombo et al. NEJM 2021

Evolution of 1L metastatic Cervical Cancer Treatment

Design	N	ORR (%)	PFS (months)	P-value	OS (months)	P-value	Reference
TC+/- BEV or TC +/-Bev + Pembro	**309 307**	**50.8% 65.9%**	**8.2 10.4**	**<0.001**	**16.5 24.4**	**P<0.001**	**Keynote 826: Colombo et al, NEJM 2021**
Bev + PC or TP vs. PC or TP	227 225	48 36	8.2 5.9	0.0002	17.0 13.3	0.0004	GOG 240 Study Tewari et al., NEJM.2014
PC vs. Carbo/Pacli	121 123	-- --	6.9 6.21	0.053	18.3 17.5		
PC VC GC TC	103 108 112 111	29.1 25.9 22.3 23.4	5.82 3.98 4.7 4.57	 0.06 0.04 0.19	12.87 9.99 10.28 10.25		
PC Cisplatin	130 134	36 19	4.8 2.8	0.001	9.7 8.8		
TC Cisplatin	147 146	27 13	4.6 2.9	0.014	9.4 6.5	0.021	Long et al., JCO.2005

On October 13,2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) 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.

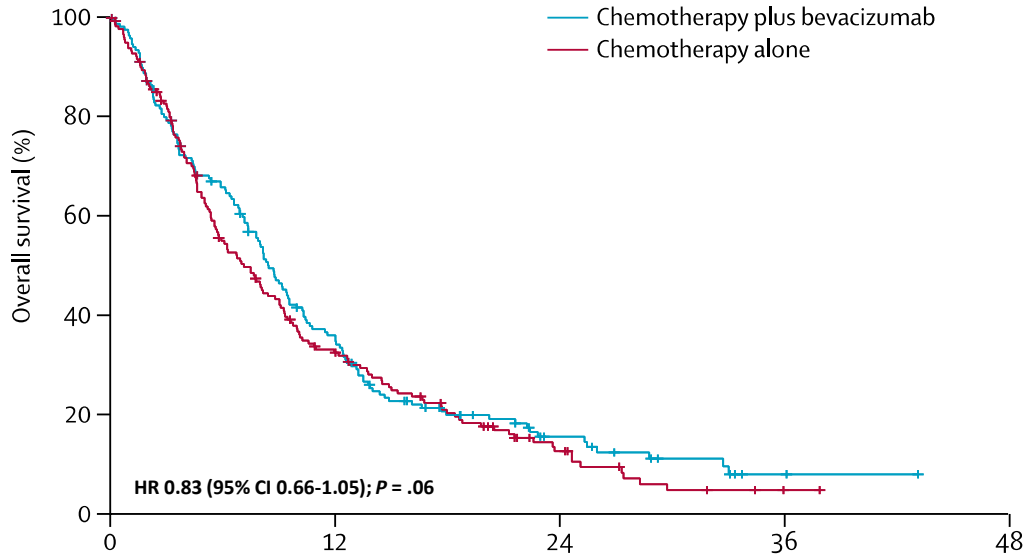
Addition of bevacizumab significantly increased rates of grade 3 or higher gastrointestinal or genitourinary fistula (6% vs. 0%, P=0.002), in addition to thromboembolic events (8% vs. 1%, P=0.001)

GC: gemcitabine/cisplatin; NS: not stated; PC: paclitaxel/cisplatin; TC:Topotecan/cisplatin; VC: vinorelbine/cisplatin

What Happens Post 1st Line Metastatic? GOG 240 Mature Post-Progression OS

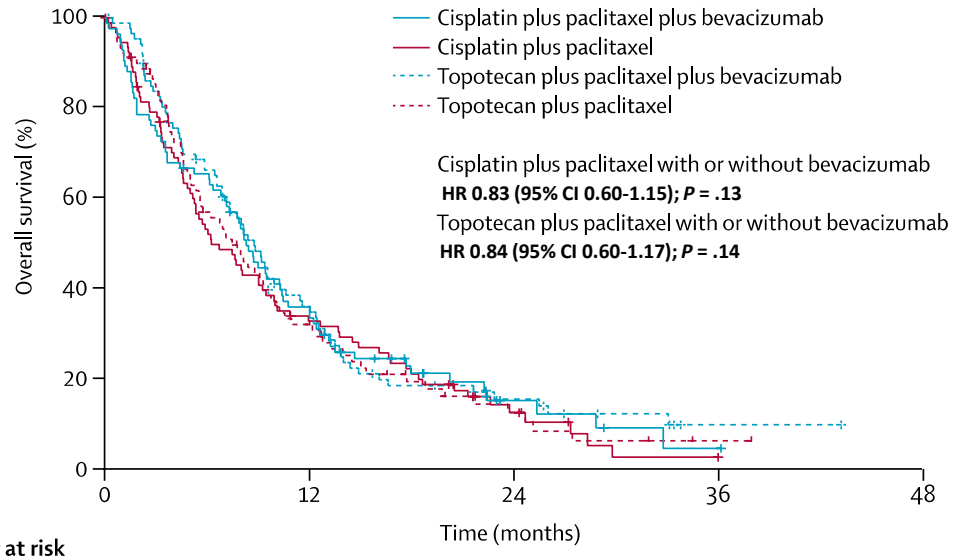
Varies between 6.2 months to 8.7 months

ITT



Number at risk (number censored)					
Chemotherapy plus bevacizumab	172 (0)	56 (7)	15 (20)	2 (27)	0 (29)
Chemotherapy alone	181 (0)	52 (12)	14 (21)	1 (27)	0 (28)

All 4 Arms



Number at risk (number censored)					
Cisplatin plus paclitaxel	92 (0)	28 (4)	7 (9)	0 (12)	0 (12)
Cisplatin plus paclitaxel plus bevacizumab	85 (0)	27 (3)	5 (13)	1 (14)	0 (15)
Topotecan plus paclitaxel	89 (0)	24 (8)	7 (12)	1 (15)	0 (16)
Topotecan plus paclitaxel plus bevacizumab	87 (0)	29 (4)	10 (7)	1 (13)	0 (14)

Tewari KS, et al. *Lancet*. 2017;390(10103):1654-1663.

KEYNOTE-158 (NCT02628067): Phase II basket study, single-agent pembrolizumab, cervical cancer cohort

- Advanced cervical squamous cell carcinoma with progression on/intolerance to ≥1 prior line of standard therapy
- ECOG PS 0/1

Primary endpoint: IRC-assessed ORR (RECIST v1.1)

Secondary endpoints: DoR, IRC-assessed PFS, OS, safety

84% PD-L1-positive; 77/98 (79%) had CPS ≥1
65% ≥2 prior therapies for recurrent/metastatic CC)

Response	All patients (n=98)	PD-L1 positive (n=82)	PD-L1-negative (n=15)	Adenocarcinoma Histology, all PDL1+	Bev-exposed
ORR (95% CI)	12.2%	14.6% (8–24)	0% (0–22)	1/6=17%	2/41=5%
CR	3%	4%	0%		
PR	9%	11%	0%		
SD	18%	18%	20%		

- Median time to response: 2.1 months (range 1.6–4.1)
- Median DoR: not reached (range 3.7+–18.6+)
- 6/12 responses ongoing at data cut-off

Pembrolizumab 200 mg q3w for 2 years or until PD, intolerable toxicity, patient withdrawal or investigator decision

Published in: Hyun Cheol Chung; Willeke Ros; Jean-Pierre Delord; Ruth Perets; Antoine Italiano; Ronnie Shapira-Frommer; Lyudmila Manzuk; Sarina A. Piha-Paul; Lei Xu; Susan Zeigenfuss; Scott K. Pruitt; Alexandra Leary; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.18.01265

Regimen for 2L+ Metastatic Cervical Cancer

Design	N	ORR (%)	PFS (months)	OS (months)
Topotecan	45	12.5	2.1	6.6
Vinorelbine	44	13.7	NS	NS
Pemetrexed	**29**	**15**	**3.1**	**7.4**
Pemetrexed	**43**	**13.9**	**2.3**	**8.05**
Docetaxel	**27**	**8.7**	**3.8**	**7.0**
Gemcitabine	22	4.5	2.1	6.5
Bevacizumab	46	10.9	3.4	7.29
Pembrolizumab	**77**	**14.3**	**--**	**--**

[1] Yu et al., Am J Hematol Oncol 2015;11:27-31

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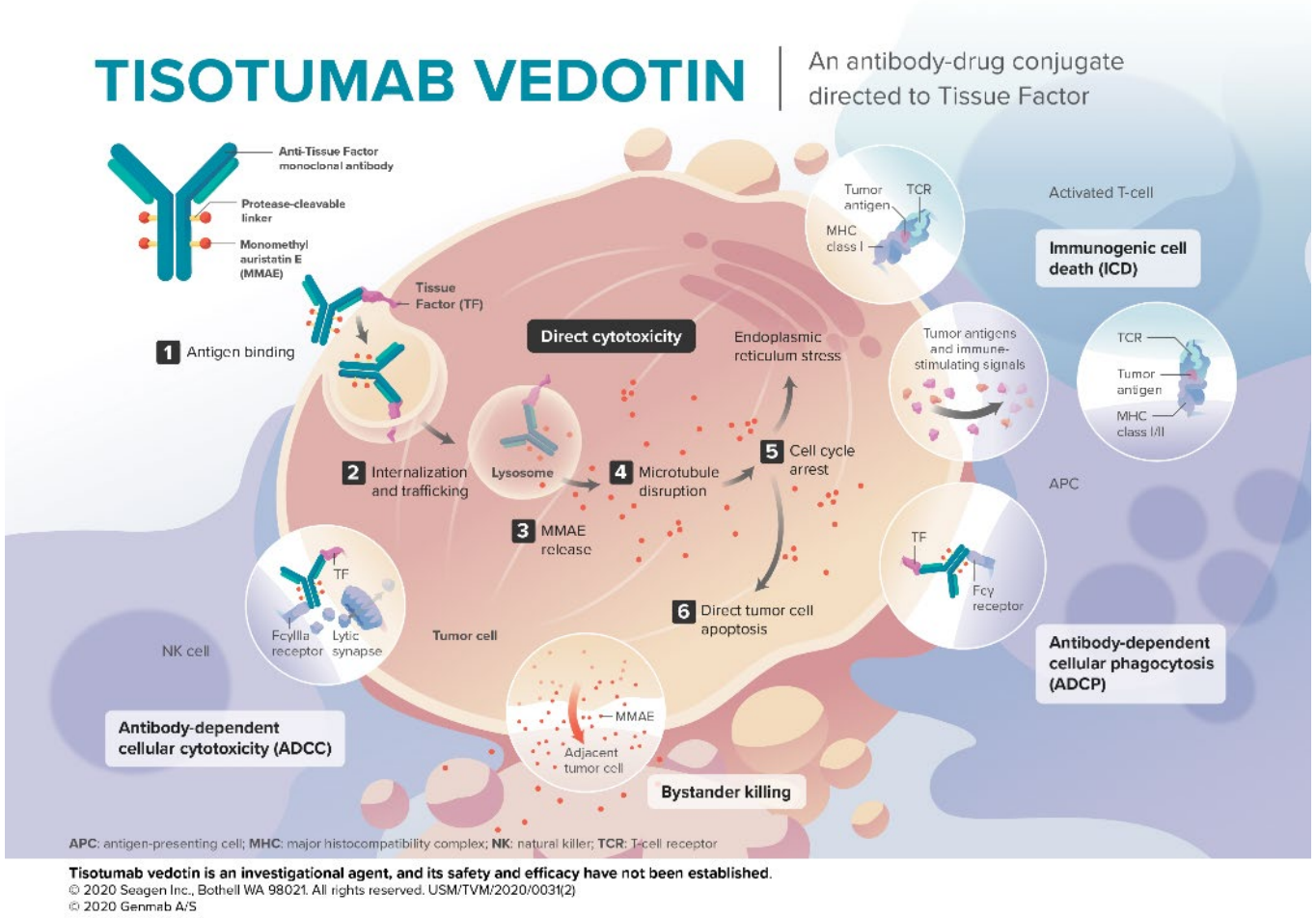
On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Tisotumab Vedotin

- Tisotumab vedotin is an investigational antibody-drug conjugate directed to tissue factor (TF) and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]
- TF is highly prevalent in cervical cancer and other solid tumors, and is associated with cancer pathophysiology and poor prognosis[3-5]
  - TF is co-opted by tumor cells to promote tumor growth, angiogenesis, and metastasis[6]
  - In normal physiology, TF's primary role is to initiate the coagulation cascade after vascular injury[6]
- Tisotumab vedotin has multiple antitumor effects[1,2,7]



Tisotumab vedotin is an investigational agent, and its safety and efficacy have not been established.

1. Breij EC et al. *Cancer Res.* 2014;74(4):1214-1226. 2. De Goeij BE et al. *Mol Cancer Ther.* 2015;14(5):1130-1140. 3. Pan L et al. *Mol Med Rep.* 2019;19:2077-2086. 4. Cocco E et al. *BMC Cancer.* 2011;11:263. 5. Zhao X et al. *Exp Ther Med.* 2018;16:4075-4081. 6. Forster Y et al. *Clin Chim Acta.* 2006;364:12-21 7. Alley SC et al. American Association for Cancer Research Annual Meeting; March 29 – April 3, 2019; Atlanta, GA, USA; Abstract #221.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action; TF, tissue factor.

Coleman RL, et al. Presented at ESMO Congress 2020, virtual. Abstract LBA24.

innovaTV 204 Study Design

innovaTV 204 (NCT03438396) is a pivotal phase 2 single-arm, multicenter (United States and Europe) study evaluating tisotumab vedotin in patients with previously treated recurrent and/or metastatic cervical cancer

Key Eligibility Criteria

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] with bevacizumab (if eligible)
- Received ≤2 prior systemic regimens[b]
- ECOG PS 0-1

Enrolled: 102[c]
Treated: 101*

Tisotumab vedotin
2.0 mg/kg IV Q3W

Until PD or unacceptable toxicity

Tumor responses assessed using computed tomography (CT) or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

Primary Endpoint

- ORR[d] per RECIST v1.1, by independent imaging review committee (IRC)

Secondary Endpoints

- ORR[d] per RECIST v1.1, by investigator
- DOR, TTR, and PFS by IRC and investigator
- OS
- Safety

Exploratory Endpoints

- Biomarkers
- HRQoL

*Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin and to provide ≥80% power to exclude an ORR of ≤11%[e]

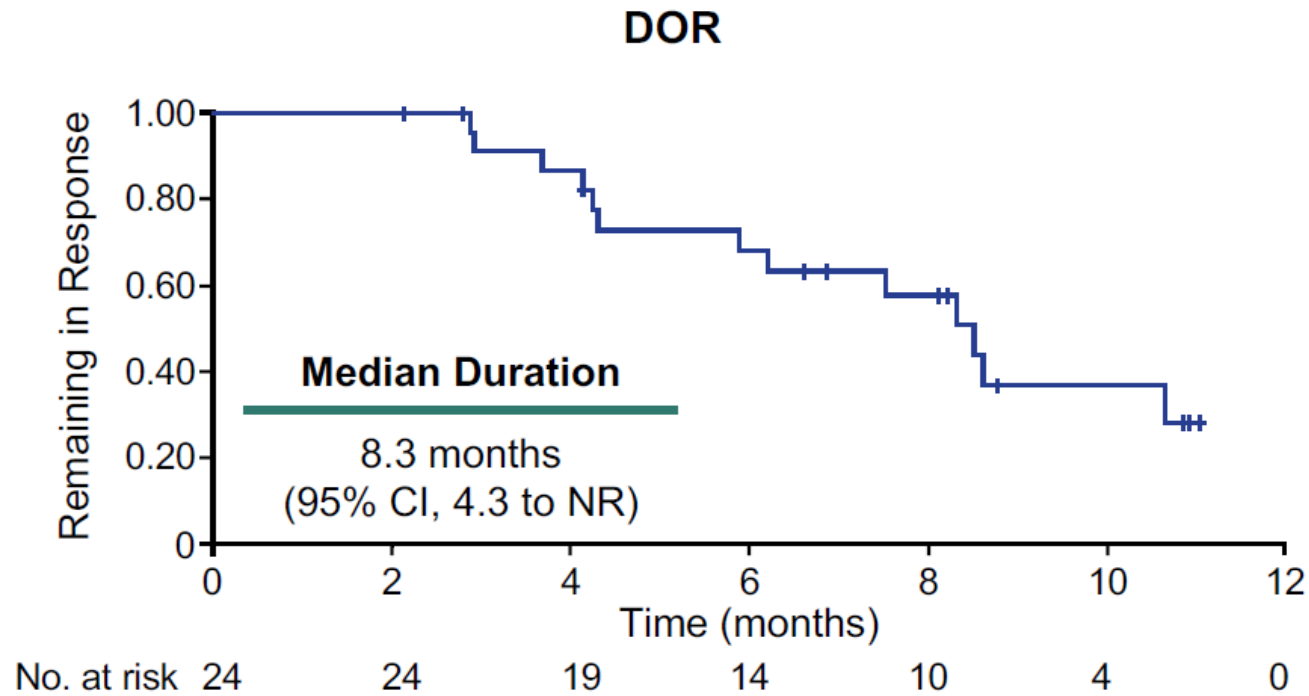
[a]Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b]Adjuvant or neoadjuvant chemotherapy or if administered with radiation therapy, was not counted as a prior systemic regimen. [c]June 2018 to April 2019. [d]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment. [e]Using one-sided exact binomial test at 0.025 significance level.

ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TTR, time to response.

Coleman RL, et al. Presented at ESMO Congress 2020, virtual. Abstract LBA24.

Antitumor Activity by IRC Assessment

	N=101
Confirmed ORR (95% CI),[a] %	**24 (15.9–33.3)**
CR, n (%)	7 (7)
PR, n (%)	17 (17)
SD, n (%)	49 (49)
PD, n (%)	24 (24)
Not evaluable, n (%)	4 (4)
Disease control rate (95% CI),[b] %	72 (62.5–80.7)



Clinically meaningful and durable responses were observed

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
[a]Based on the Clopper-Pearson method. [b]Patients with a confirmed response (CR or PR confirmed at least 4 weeks later) or SD (as measured at least 5 weeks after the first dose of tisotumab vedotin).
CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease.

Eye Care

- Baseline eye exam
  - Visual acuity
  - Slit lamp exam
  - Schirmer's test

- Lubricating eye drops daily
- Steroid eye drops Cycle Day 1-4
- Vasoconstrictor eye drop prior to infusion

- Ice packs or cooling pads on eyes during infusion

Ochsner™ Health System

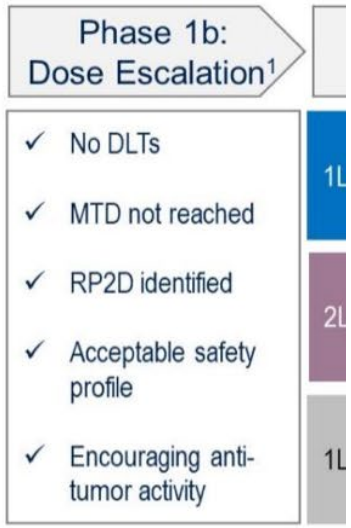
FDA Approval for Tisotumab Vedotin in Advanced Cervical Cancer

Roxanne Nelson, RN, BSN

DISCLOSURES | September 21, 2021

The US Food and Drug Administration (FDA) has granted accelerated approval to tisotumab vedotin-tftv (Tivdak, Seagen/Genmab) for the treatment of adult patients with recurrent or metastatic cervical cancer who have experienced disease progression on or after chemotherapy.

ENGOT-cx8/GOG 3024/innovaTV 205: Dose escalation phase



Meeting Abstract | 2022 ASCO Annual Meeting I

GYNECOLOGIC CANCER

Trial in progress update on ENGOT-cx8/GOG-3024/innovaTV 205: Addition of a new cohort with first-line (1L) tisotumab vedotin (TV) + pembrolizumab (pembro) + carboplatin (carbo) ± bevacizumab (bev) in recurrent/metastatic cervical cancer (r/mCC).

	ORR 40.6%
V +	**ORR 38.2%**
	ORR 54.5%

[a]Tumor response assessed every 6 weeks;
f/u, follow-up; r/mCC, recurrent or metastatic

1. Monk B, et al. International Gynecologic Cancer Society: 2021; 2. Vergote I, et al. European Society for Medical Oncology 2021. (initial disclosure of 1L TV + carbo and 2L/3L TV + pembro)

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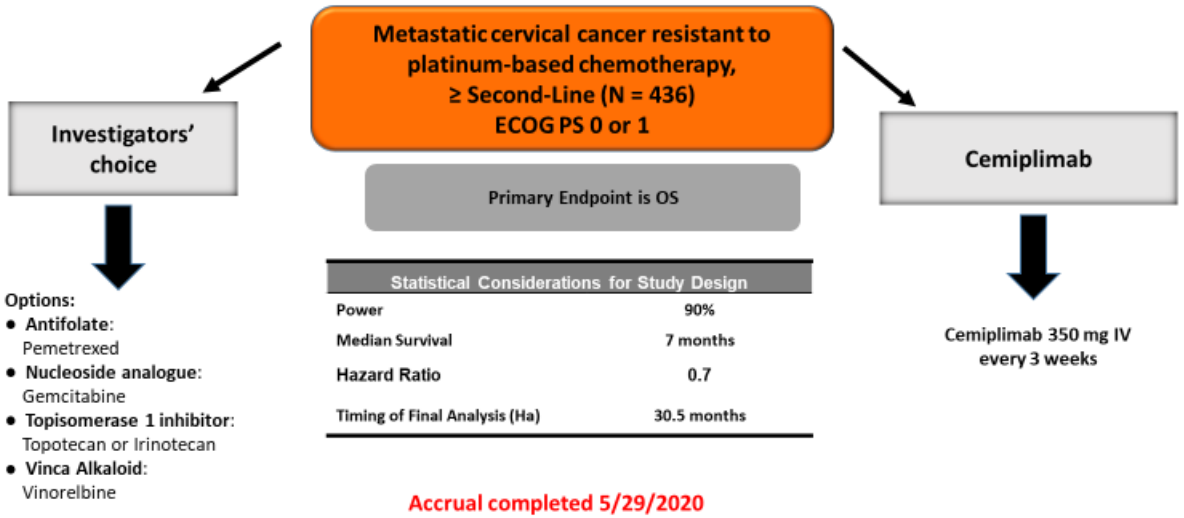
GOG 3016/ENGOT-cx9: Randomized Phase III Trial of Cemiplimab Versus Investigator's Choice Chemotherapy in Cervical Cancer: "EMPOWER- CERVICAL 1" NCT03257267



Accrual completed 5/29/2020

Population	Cemiplimab median OS months (n)	IC chemo median OS months (n)	Hazard ratio for death (95% confidence interval)	P value
SCC population	10.9 (n=239)	8.8 (n=238)	0.69 (0.56–0.85)	P=0.00023
Overall population	11.7 (n=304)	8.5 (n=304)	0.66 (0.55–0.79)	P<0.00001
AC population*	13.5 (n=65)	7.0 (n=66)	0.55 (0.37–0.81)	-
PD-L1 population (n=254)*				
PD-L1 ≥1%	13.9 (n=82)	9.3 (n=80)	0.70 (0.48–1.01)	-
PD-L1 <1%	8.2 (n=44)	6.7 (n=48)	0.85 (0.53–1.36)	-
PD-L1 population (n=371)*				
PD-L1 ≥1%	12.1 (n=116)	7.7 (n=121)	0.61 (0.45–0.83)	-
PD-L1 <1%	10.8 (n=66)	7.0 (n=68)	0.65 (0.43–0.98)	-

*Analysis of OS in the AC population and PD-L1 population subsets were exploratory with no adjustments for multiplicity.

1. A. Oakin Annals of Oncology (2022) 33 (suppl_7): S235-S282. 10.1016/annonc/annonc1054

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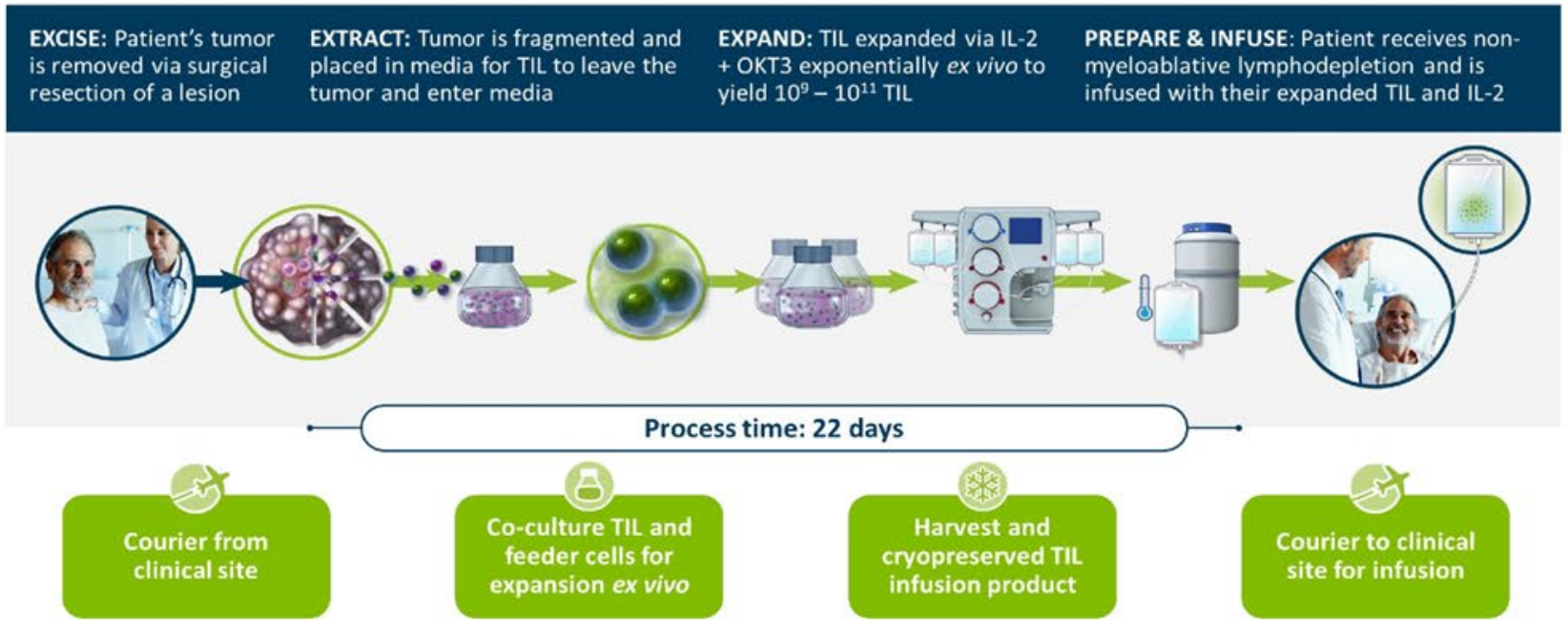
Iovance Technology

Cryopreserved Autologous TIL (LN-145)

Manufacturing Process: 22-Days



https://www.iovance.com/

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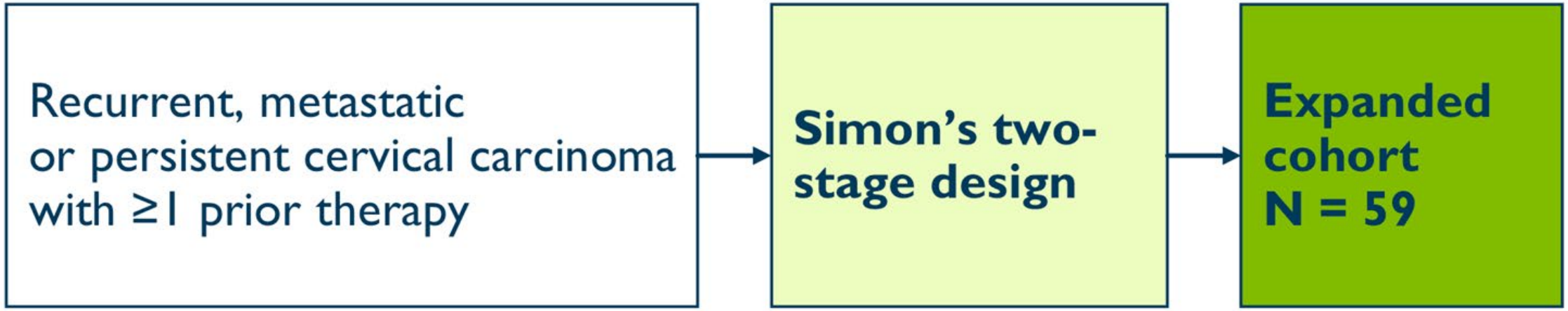
Safety & efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma



Endpoints

- Primary: Objective Response Rate (ORR) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
- Secondary: safety and efficacy **Key updates**
- Protocol amended to increase total to 59 patients, and ORR as determined by Blinded Independent Review Committee (BIRC)
- Fast Track and Breakthrough designations (May 21, 2019) received

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NCT03108495 Amir A. Jazaeri et al ASCO 2019

Cervical Cancer Updates Summary

- **Early stage**
  - **Minimally invasive is inferior to open radical surgery**
- **Locally advanced**
  - **Weekly cisplatin plus radiotherapy (CCRT) global standard in locally advanced primary disease**
  - **Ongoing Trials assessing addition of Triapine and IO**

CALLA:
Durvalumab Added to Standard of Care CCRT

- **Primary locally advanced carcinoma of the cervix (Ib2-IIB node positive or IIIA-IVA any nodal status)**
- **Measurable disease by RECIST v1.1**
- **ECOG-PS: 0-1**
- **N=714 pts**

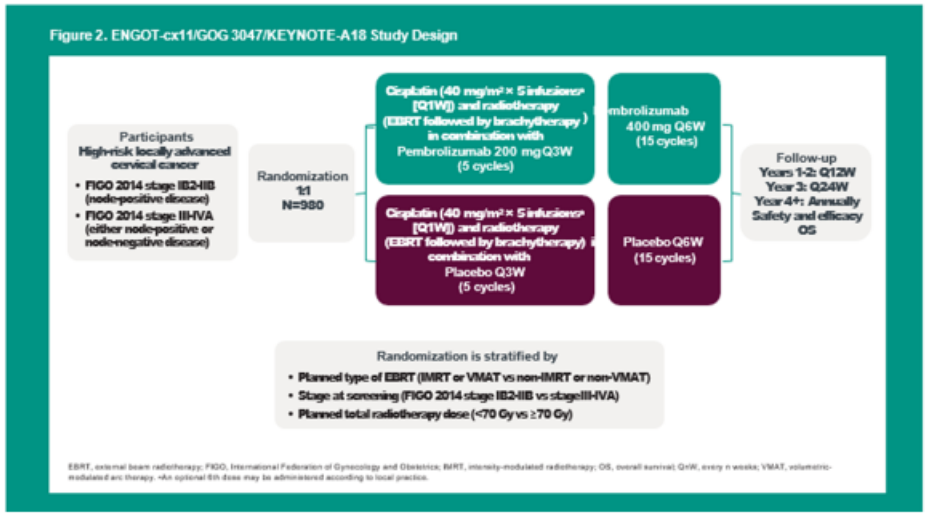
→ **R 1:1**

- **CCRT + durvalumab up to 24 months or until progression**
- **CRT + placebo up to 24 months or until progression**

Primary Endpoints:
Progression-free Survival (PFS)
Secondary Endpoints:
- OS
- ORR
- DOR
- Safety
- HR-QOL

NCT03830866
CCRT = Concurrent Chemotherapy and Radiotherapy

MK-3475-A18/KEYNOTE-A18-cx11/GOG-3047



Cervical Cancer Updates Summary

- **1st line metastatic disease**
  - **Platinum + paclitaxel +/- bevacizumab (+/- pembrolizumab PD-L1+ tumors)**
  - **Ongoing Trial evaluating Tisotumab Vedotin + Pembro + Chemo +/- Bev**

- **2nd line metastatic disease**
  - **Pembrolizumab PD-L1+ tumors**
  - **Tisotumab Vedotin**
  - **Cytotoxic chemotherapy (topotecan, pemetrexed)**

Thank you

Questions?

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