UCL CANCER INSTITUTE

UCL

Recent Changes in Practice: Endometrial and Cervical Cancers



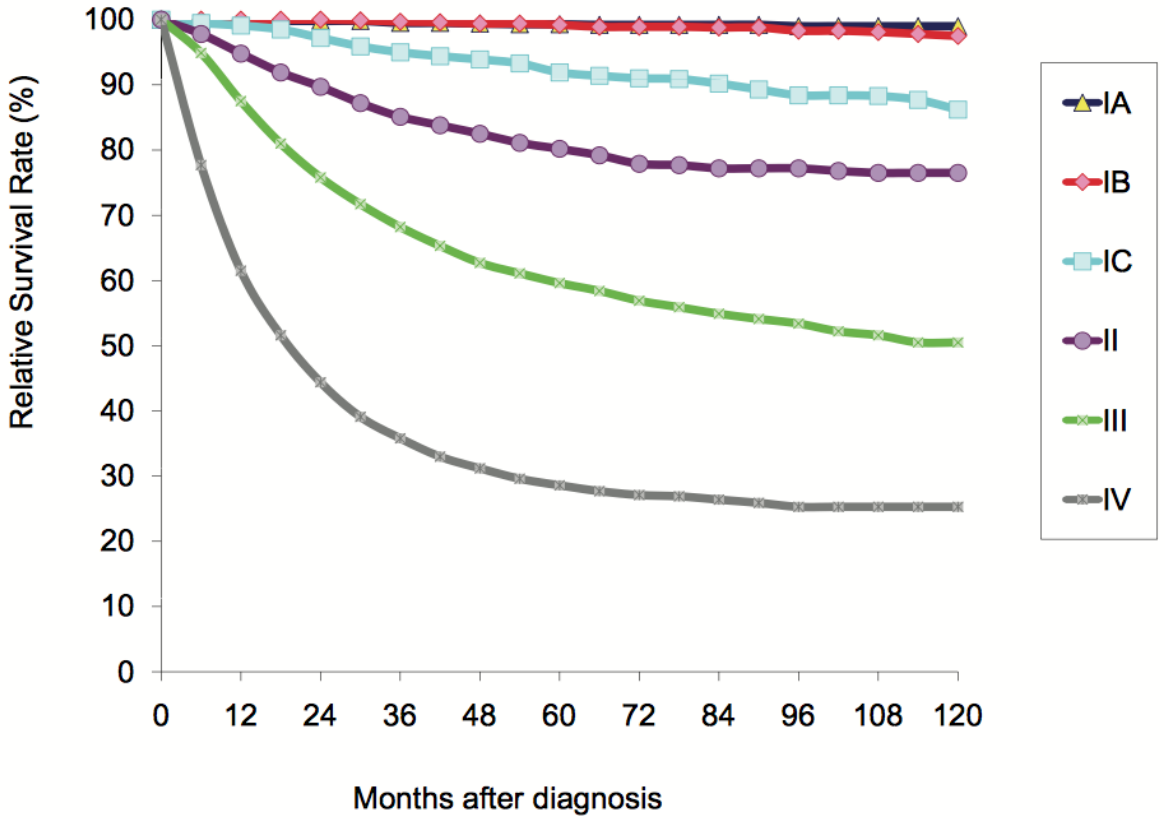
Jonathan Ledermann
UCL Cancer Institute,
University College London, UK

BAGP meeting, January 2021

CANCER RESEARCH UK | CITY OF LONDON CENTRE

UCL • King's • Barts • Crick

Treatment Strategies for Endometrial Cancers



SEER data: Relative survival 1988-2001

- Most patients present with early disease and are cured

  What is the contribution of adjuvant treatment?
  - Chemotherapy
  - Radiotherapy
  - Chemo-radiotherapy

- Advanced and recurrent disease is a major therapeutic challenge

  What is the affect of systemic therapies?
  - Hormonal treatment
  - Chemotherapy
  - Novel molecular therapies
  - Immunotherapy

Endometrial Cancer Classification

Pathology-based classification from 1980s to 2015

Pathological Classification after Bokhman 1983
Type 1 (~80%) Oestrogen-dependent endometrioid EC Associated hyperplasia; perimenopausal Often superficial invasion Low-grade endometrioid
Type 2 (~20%) Oestrogen-independent non-endometrioid EC Often atrophic endometrium and post menopausal Deep invasion common; poorer prognosis eg. serous, clear-cell, carcinosarcoma, mucinous, squamous….

Risk Group	Classification ESMO-ESGO-ESTRO 2015 FIGO (2009)
Low	Stage 1A Endometrioid + grade 1-2 $LVSI^{-}$
intermediate	Stage 1B Endometrioid + grade 1-2 $LVSI^{-}$ Stage IA Endometrioid + grade 3 $LVSI^{-}$
High-Intermediate	Stage 1 Endometrioid + Substantial $LVSI^{+}$ any grade/depth invasion Stage IB Endometrioid + grade 3- any $LVSI^{+ \text{ or } -}$ Stage II
High	Stage III with no residual disease Non endometrioid (serous/clear cell/ undifferentiated/ carcinosarcoma, mixed)
Advanced Metastatic	Stage III with residual disease/ Stage IVA Stage IVB

ESMO-ESGO-ESTRO consensus: risk groups

Risk Group	Description (FIGO 2009)
Low	• Stage IA Endometrioid + grade 1-2 + LVSI negative
Intermediate	• Stage IB Endometrioid + grade 1-2 + LVSI negative
High Intermediate	• Stage IA Endometrioid + grade 3, regardless of LVSI status • Stage I Endometrioid + grade 1-2 + LVSI unequivocally positive, regardless of depth of invasion
High 15%	• Stage IB Endometrioid + grade 3, regardless of LVSI status • Stage II & stage III with no residual disease • Non endometrioid (serous, clear cell, undifferentiated c carcinosarcoma, mixed >10%)
Advanced Metastatic	• Stage III with residual disease & IVA • Stage IVB

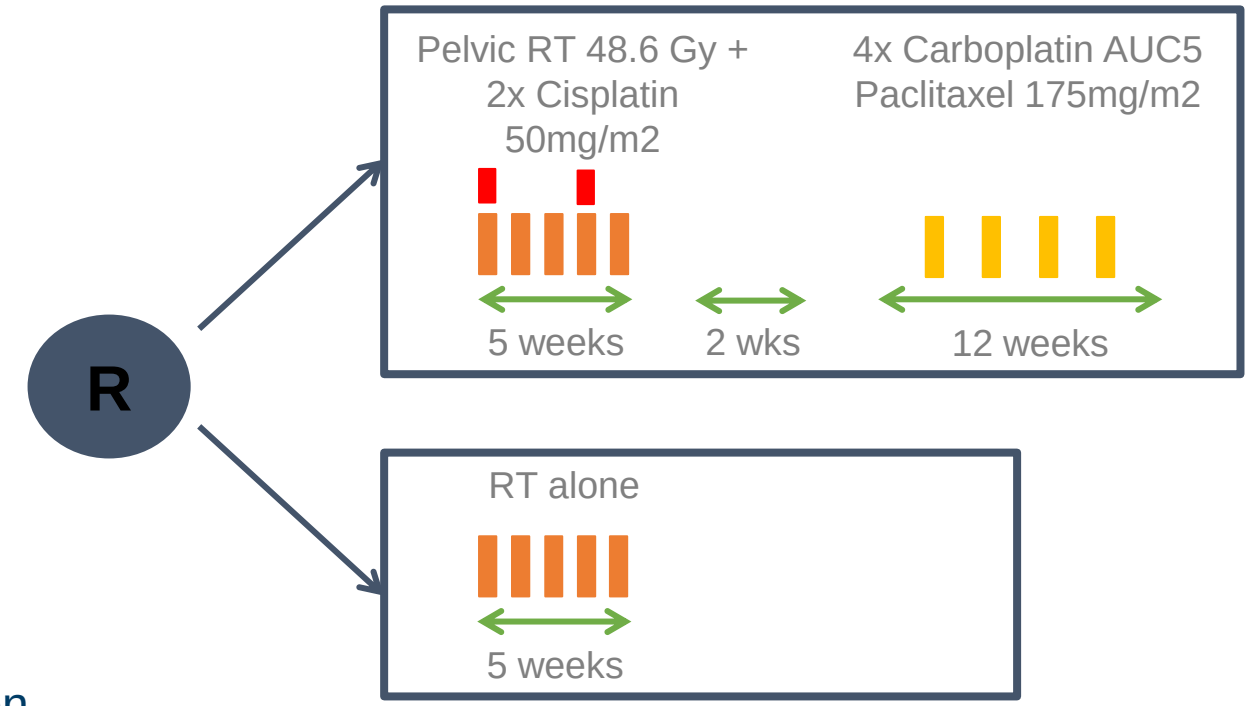
- Surgery alone
- Vaginal Brachytherapy
- Radiotherapy
- Radiotherapy?
- Chemotherapy ? Both?

ESMO ESGO ESTRO European Society for RADIOTHERAPY & ONCOLOGY

Colombo N. et al *Ann of Oncology* 2015

PORTEC-3 trial design

- High risk Endometrial carcinoma
  - stage I grade 3, with deep invasion or LVSI+
  - stage II – III EC
  - stage I-III serous or clear cell cancers (>25%)
- WHO PS 0-2
- No residual macroscopic tumor after surgery
- Pathology review before randomisation

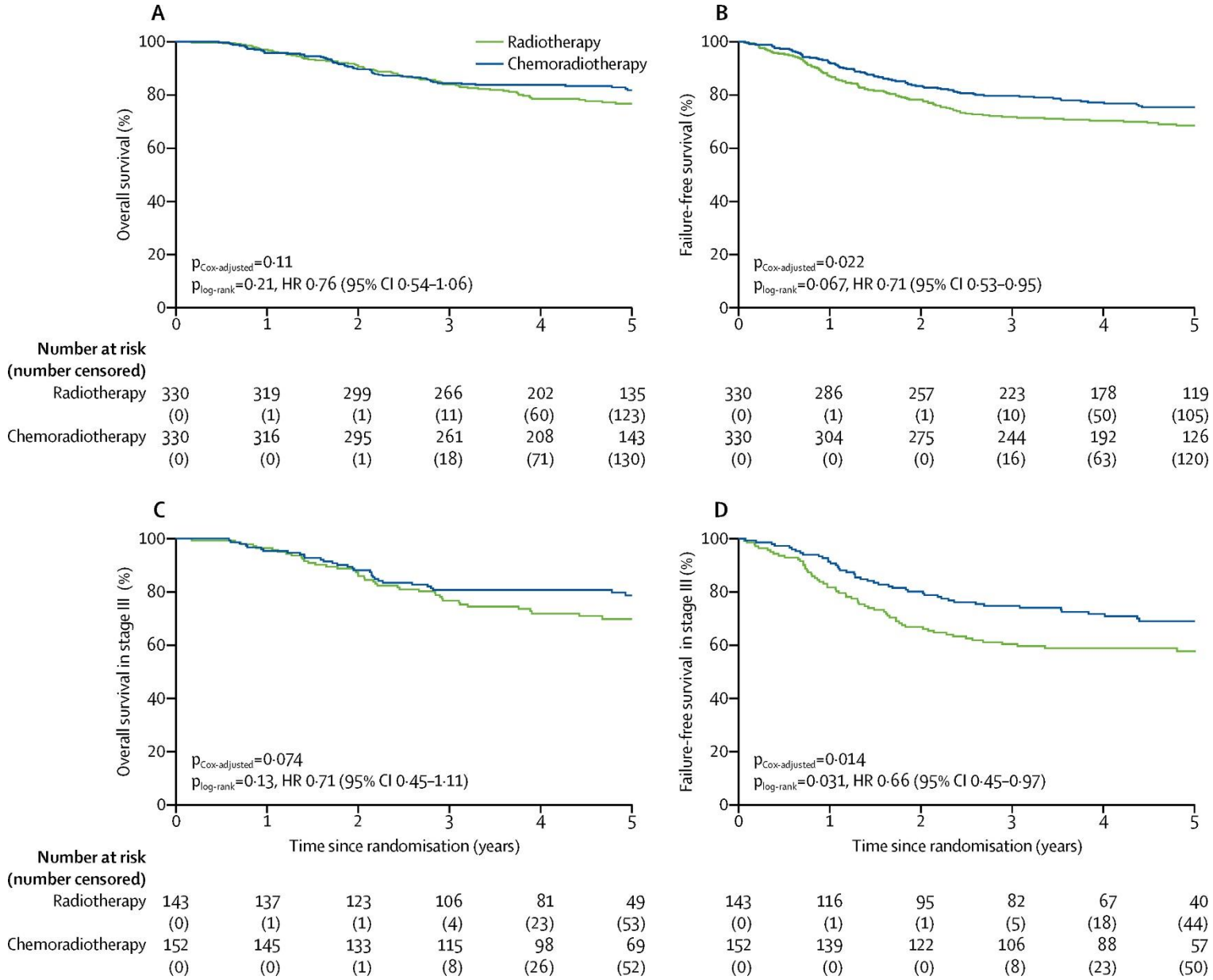


Stephanie de Boer: ASCO 2017
Lancet Oncology: Vol 19, N3, p295–309, March 2018

PORTEC 3 Trial

Overall population

Stage III



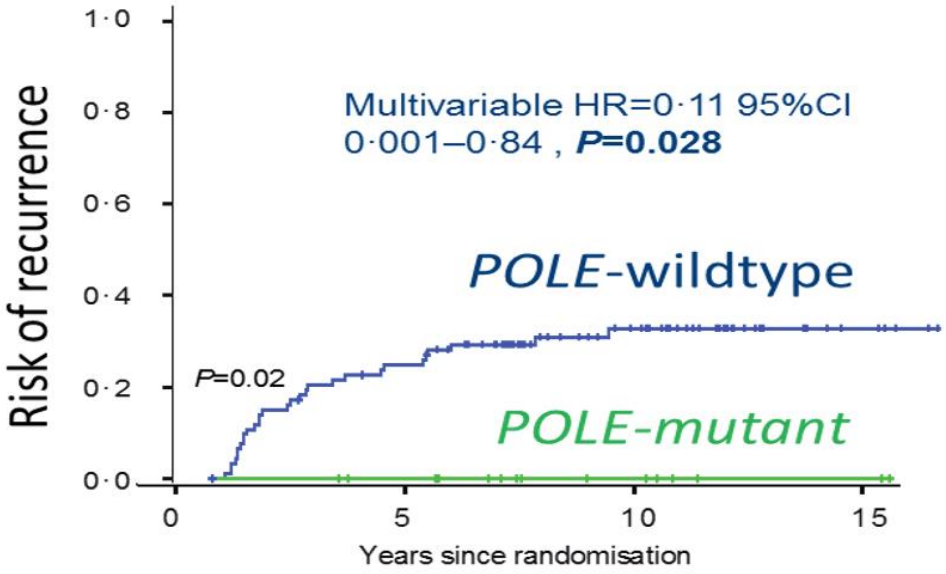
Stephanie de Boer: Lancet Oncology: Vol 19, N3, p295–309, March 2018

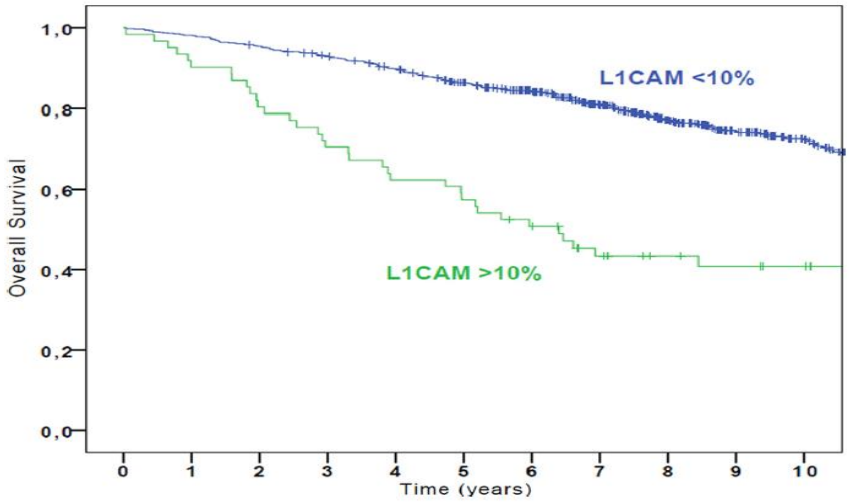
Molecular Classification of Endometrial Cancer

A

	POLE ultramutated	MSI hypermutated	Copy-number low, MSS	Copy-number high, serous-like
Mutation load				
Somatic copy number alterations load				
Histology	Endometrioid	Endometrioid	Endometrioid	Serous and endometrioid
Grade				
***PI3K* alterations**				
***KRAS* mutation**				
***TP53* mutation**	35%	5%	1%	>90%
Prognosis	Excellent	Intermediate	Intermediate	Poor

Morice et al Lancet 2016

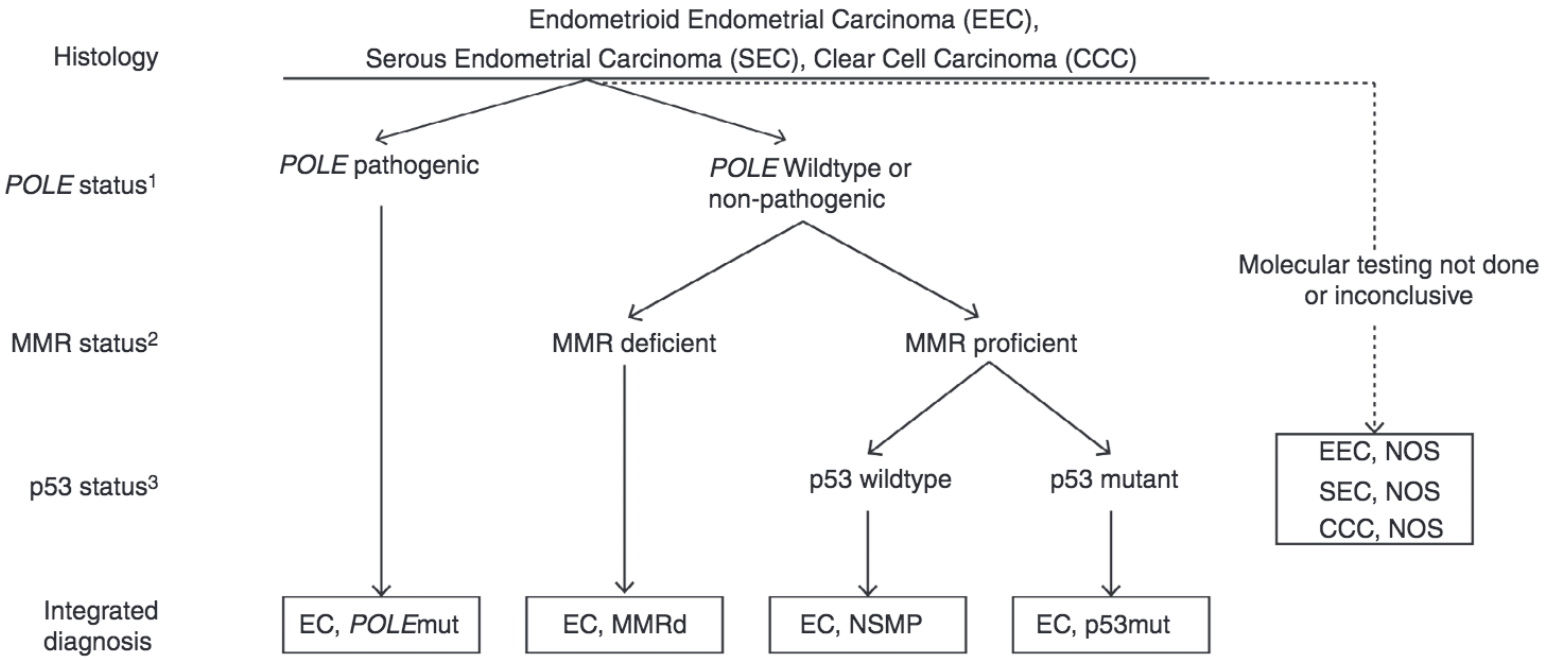




Church et al 2015 JNCI; Bosse et al 2014 EJC

Molecularly driven treatment of Endometrial Cancers

Moving away from chemotherapy

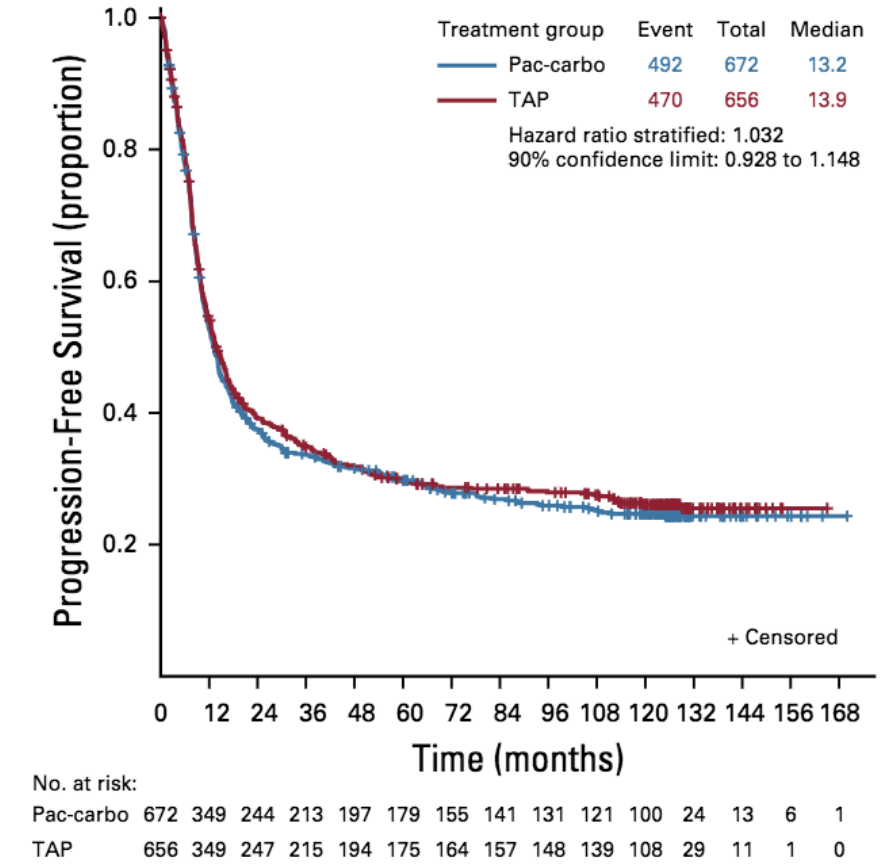


McAlpine et al J Pathol 2018

GOG- 0209

Stage III/IV endometrial cancer

Combination chemotherapy - PFS



Miller et al J Clin Oncol 2020

Joint statement



ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin ,[1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann ,[9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou ,[13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu ,[12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Concin N, *et al. Int J Gynecol Cancer* 2020;**0**:12–39. doi:10.1136/ijgc-2020-002230

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** 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

[Δ]For stage III-IVA ***POLE*mut** endometrial carcinoma, and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk-group in the molecular classification. Prospective registries are recommended

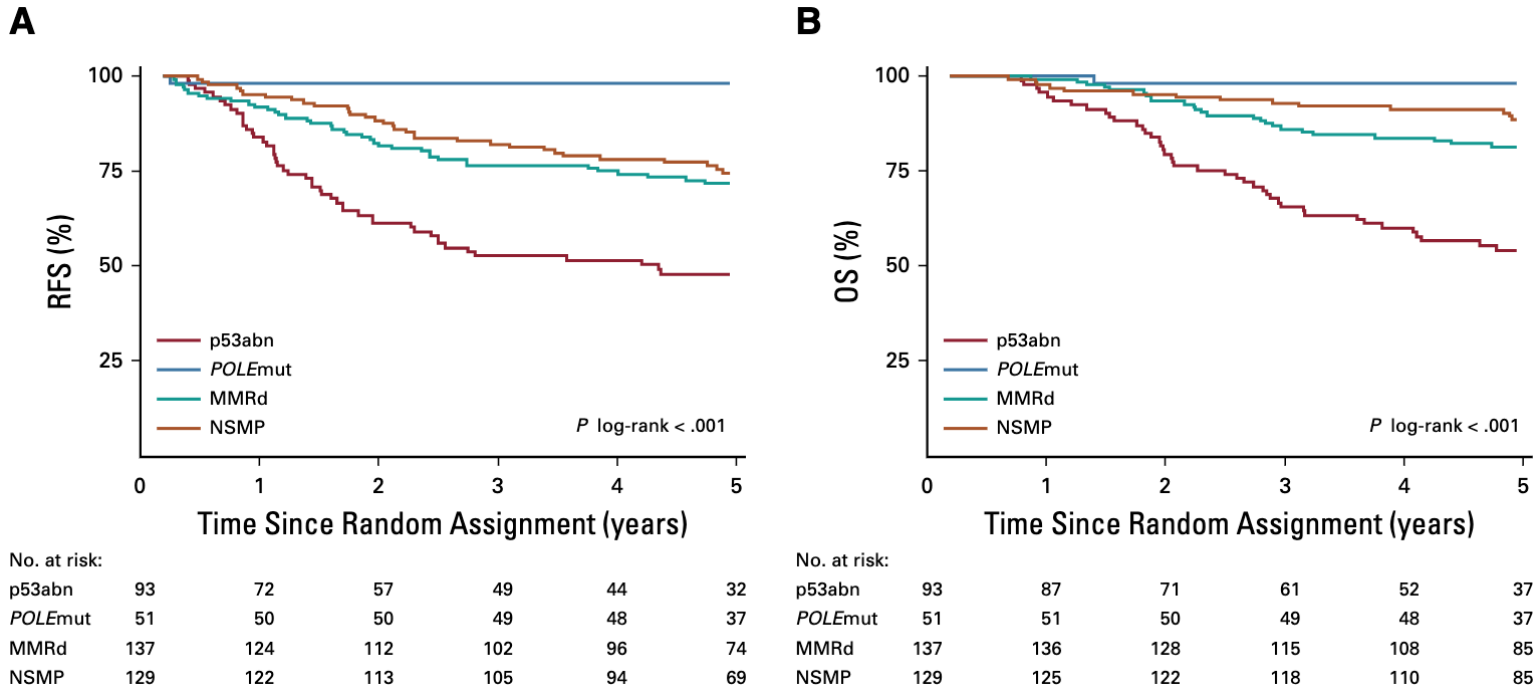
* see text on how to assign double classifiers (e.g. patients with both *POLE*mut and p53abn should be managed as *POLE*mut)

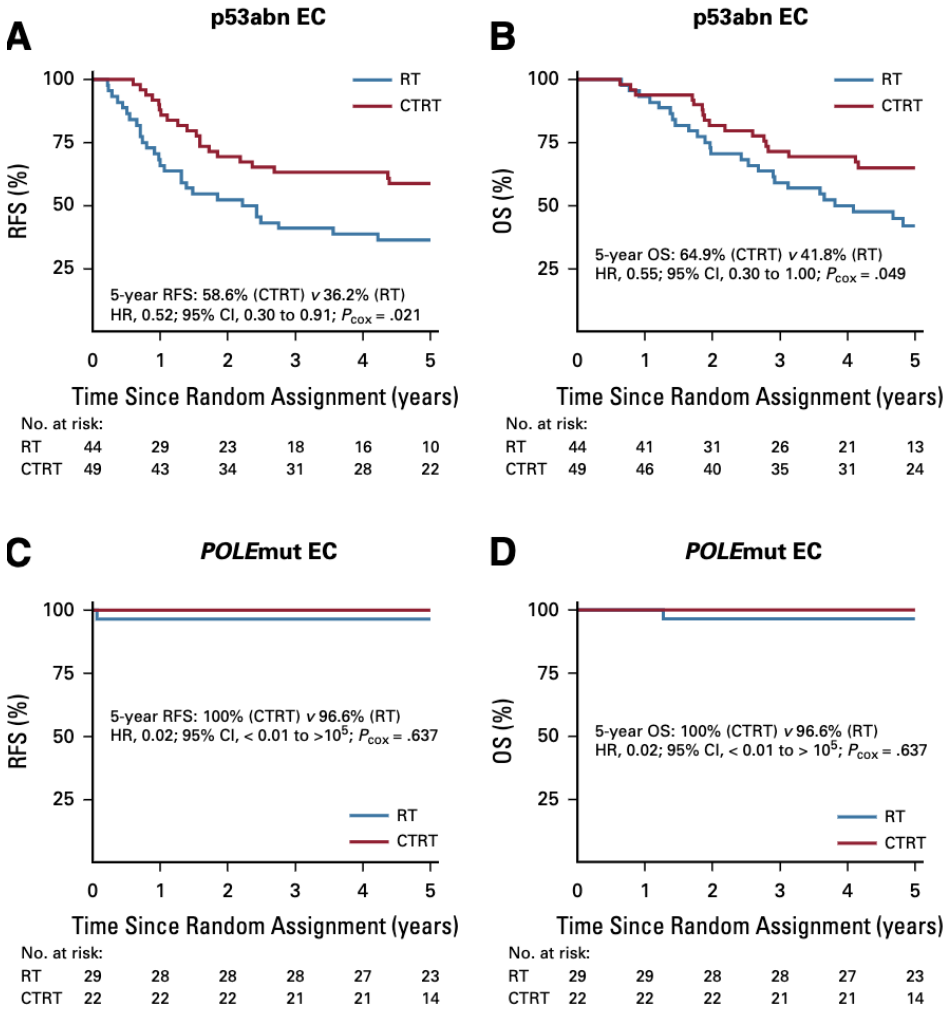
** according to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade, and grade 3 carcinomas are considered as high-grade.

p53abn: p53 abnormal, MMRd: Mismatch Repair Deficient, NSMP: nonspecific molecular profile, *POLE*mut: polymerase Ɛ mutated

Definition of prognostic risk groups

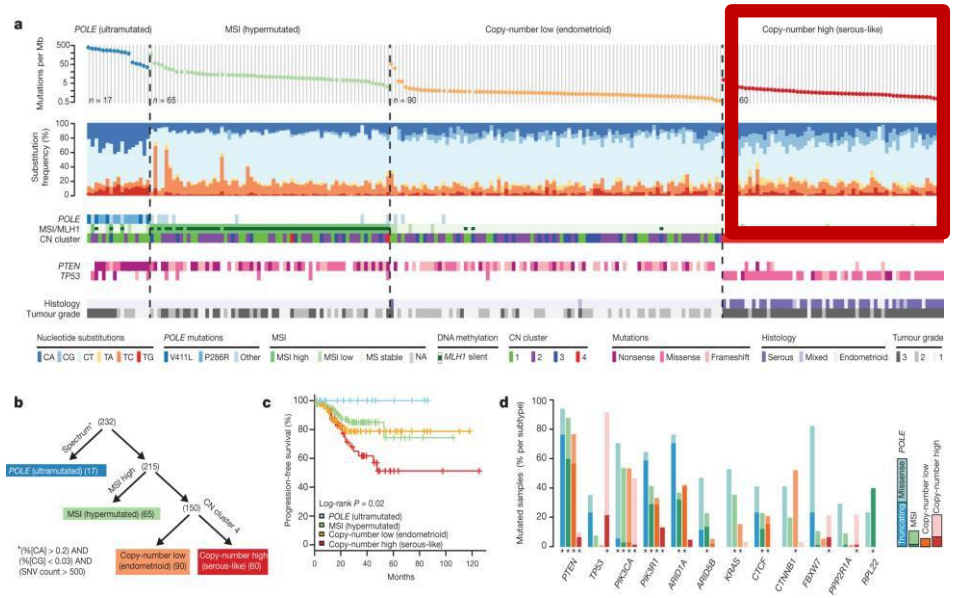
Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy





Leon-Castillo et al J Clin Oncol 2020

Differences between USC and Endometrioid Tumors

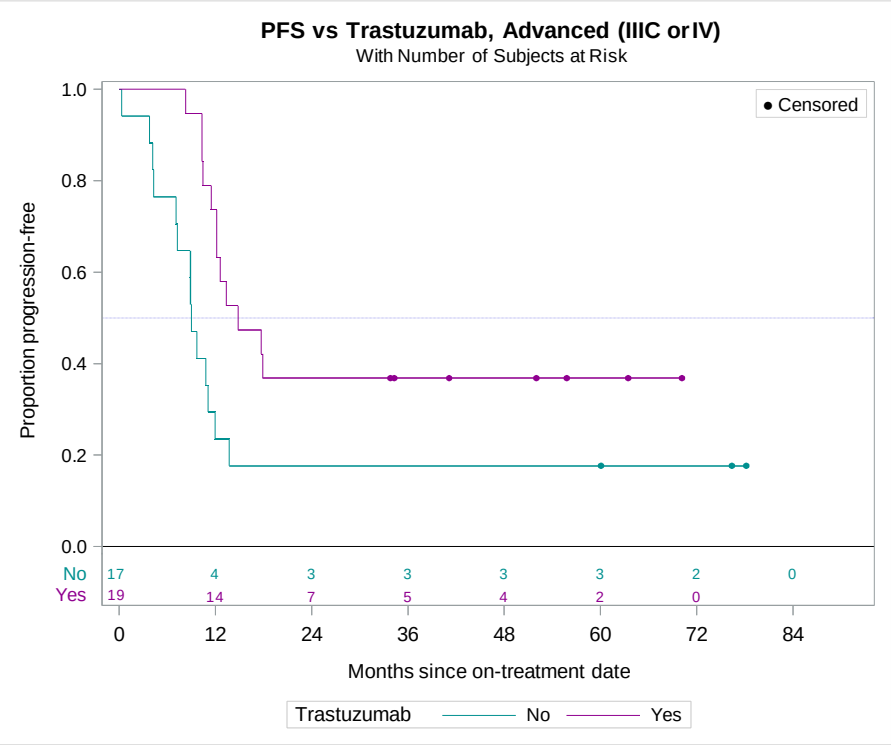


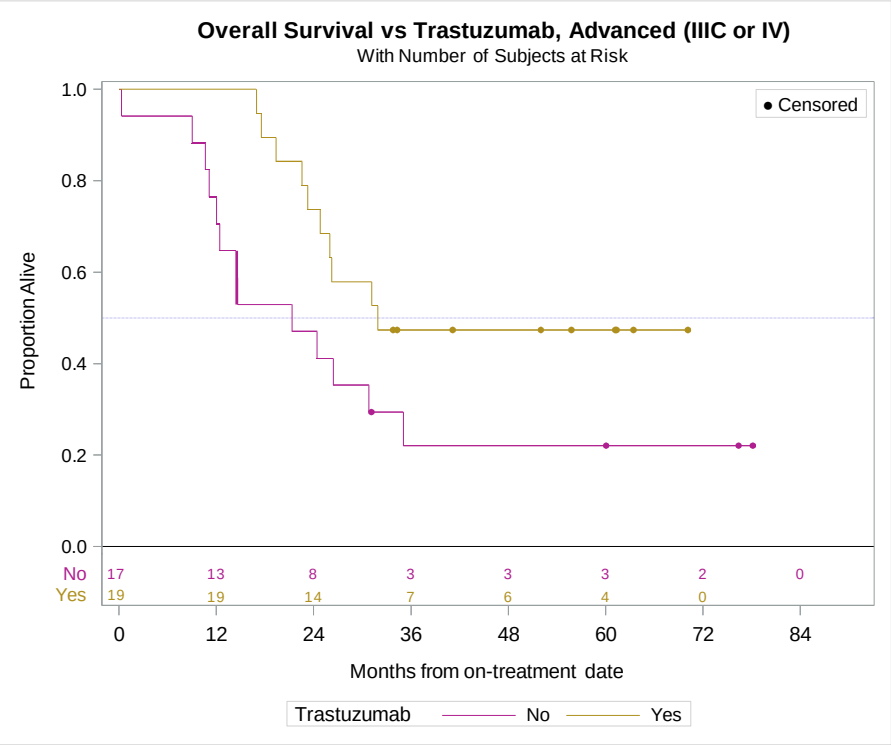
TCGA Data and USC

- High genomic instability
- Low tumor mutation burden
- *TP53* alterations in over 90% of cases

Molecular alterations	ECC	UPSC
ER/PR	ER/PR positive	ER/PR negative
p53	p53 mutation are rare	90% with p53 mutations
PTEN	80% PTEN mutations	PTEN mutations are rare
HER-2/neu	Over expressed in 10–30%	Over-expressed in 45–60%
Claudin 3/4	N/A	Over-expressed
Bcl-2	N/A	Over-expressed

Carboplatin/paclitaxel+/-Trastuzumab (NCT01367002) Updated Survival analysis stage III/IV

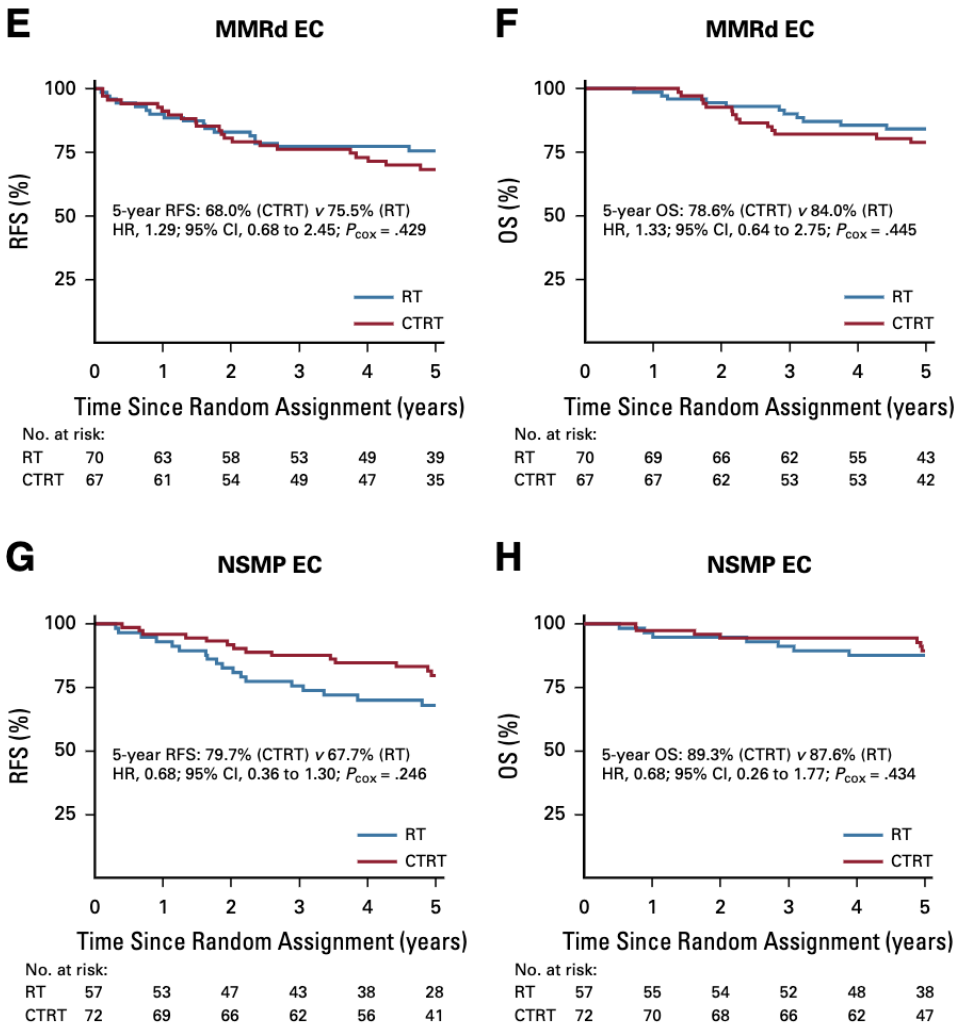




In a subset analysis of pts restricted to stage IIIC/IV disease, the addition of trastuzumab (n=17) continued to provide both (*left*) PFS benefit over control (n=19) and OS benefit over control (21.1 versus 31.9 months, HR 0.440 90% CI 0.219-0.882 p=0.0230).

Amanda N. Fader et al.,J Clin Oncol. 2018 Jul 10;36(20):2044-2051
Amanda N. Fader et al. , JCO 2020

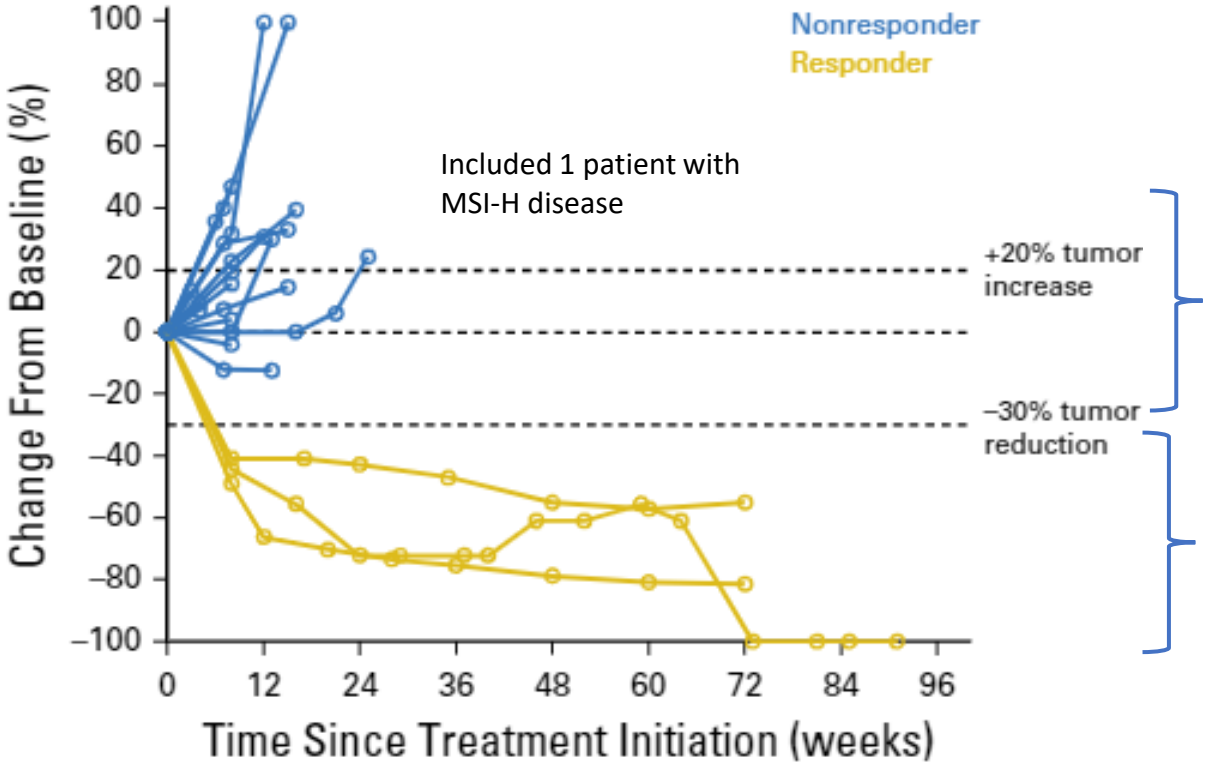
Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy



Leon-Castillo et al J Clin Oncol 2020

Identification of MMR deficiency as a predictive marker of response to Immune checkpoint inhibitors

Keynote-28



PDL-1+ tumours

PD-L1 expression is not a sufficient biomarker to identify patients who will respond to treatment

3 responses included:

- ***POLE* ultramutated: n = 1**
- **Non-MSI-H: n = 1**
- **MSI unknown: n = 1**

Investigator-assessed ORR in 3 patients (13.0%; 95% CI: 2.8, 33.6); all PR

Ott PA, et al. *J Clin Oncol 2017*.

Moving from MSI-High (MMRd) to MSS (Stable)

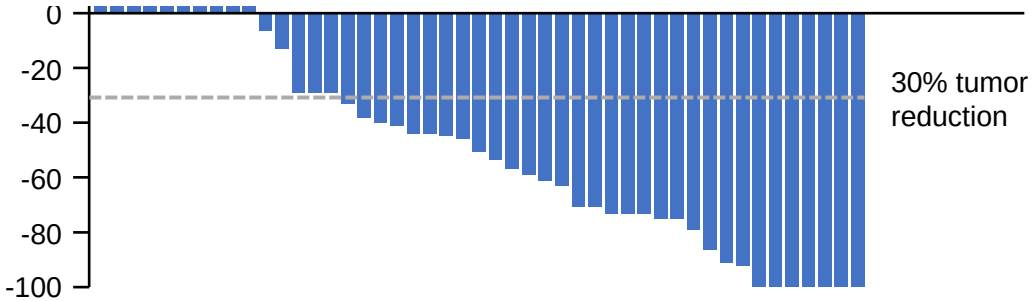
Pembrolizumab → Pembrolizumab + lenvatinib

Efficacy Outcome	Pembrolizumab-Treated [N = 49]
ORR, % (95% CI)	57.1 (42.2, 71.2)

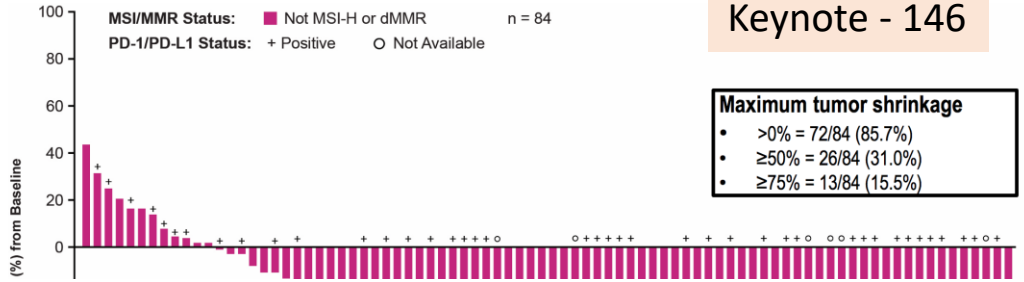
FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication May 2017

This is the FDA's first tissue/site-agnostic approval.

The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-center, single-arm clinical trials. Ninety patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types. Patients received either pembrolizumab, 200 mg every 3 weeks, or pembrolizumab, 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity, or disease



Marabelle A, et al. *J Clin Oncol*. 2020



Keynote - 146

On September 17, 2019, the Food and Drug Administration granted accelerated approval to the combination of pembrolizumab (KEYTRUDA, Merck) plus lenvatinib (LENVIMA, Eisai) for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. The FDA, the Australian Therapeutic Goods Administration, and Health Canada collaborated on this review, allowing for simultaneous decisions in all three countries.



Makker et al ESMO 2019

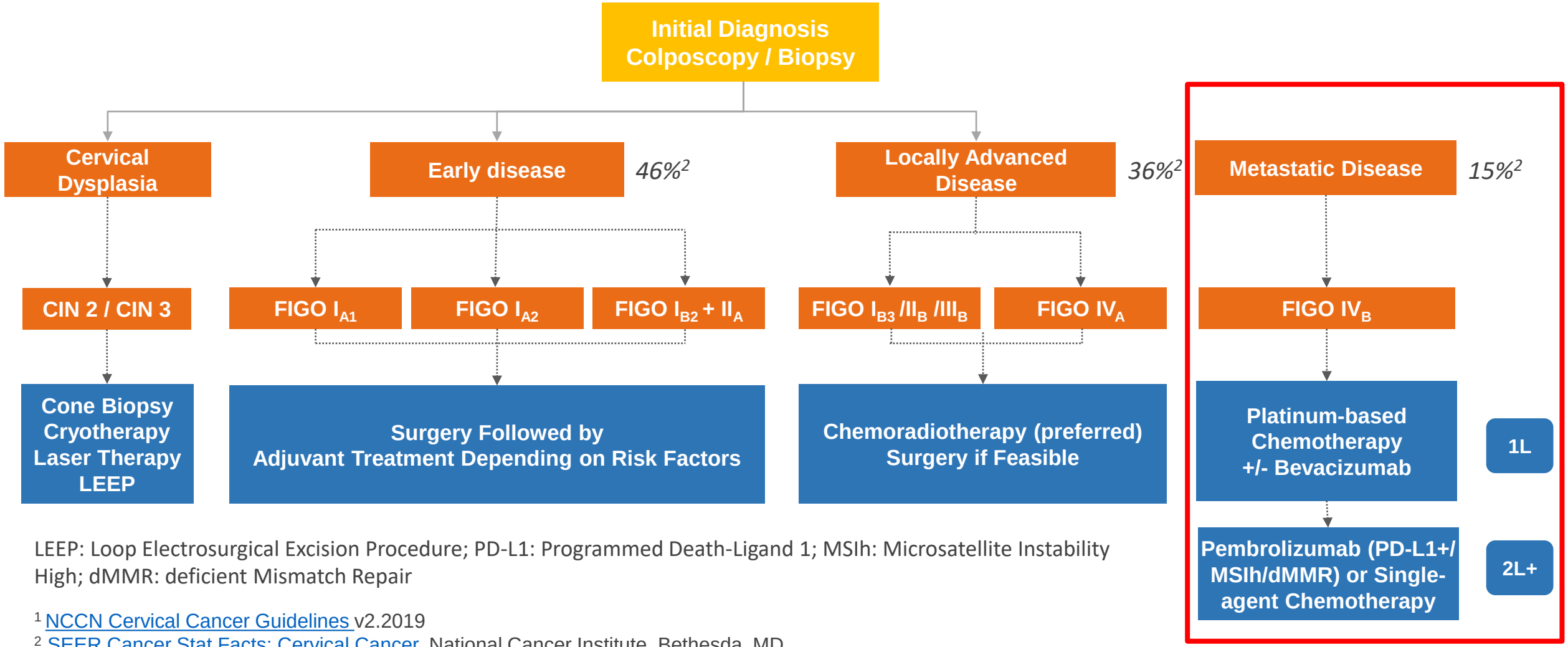
Summary

Pathway for development of new molecular therapies for endometrial cancer

- Similar activity seen with
  - Dostarlimab
  - Durvalumab
  - Avelumab
- Clear activity in MMRd
- Dostarlimab has some activity in MMRp

- Are Immune checkpoint inhibitors suitable for all?
- Is chemotherapy needed in addition to immune checkpoint inhibitors ?
- Should first-line treatment in high-risk patients with MMRd include immune checkpoint inhibitors?
  - Alone or in combination with chemotherapy
- Move towards validating a molecularly defined approach to assigning therapies for high risk or advanced/recurrent endometrial cancer
  - MMRd/p
  - P53 Mut
  - POL*E*

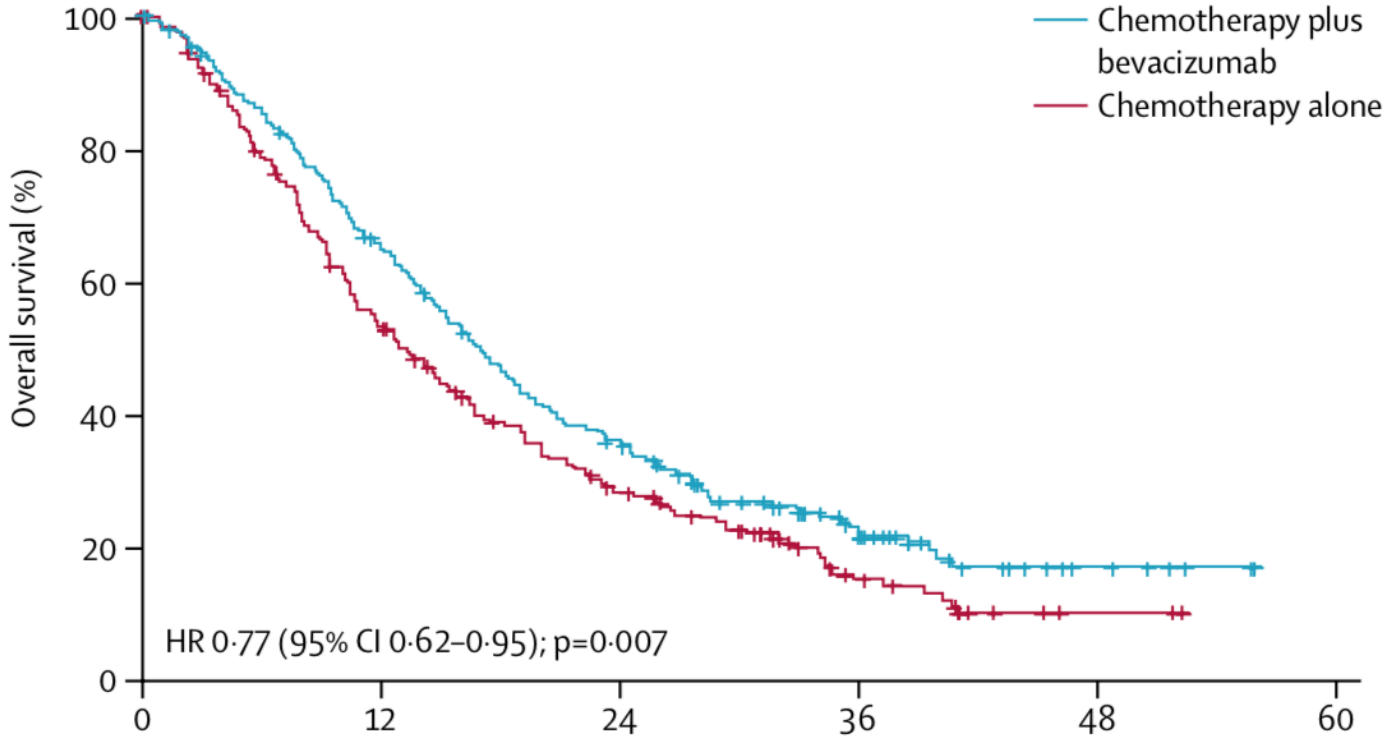
Cervical Cancer: Summary of Treatment



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

[1] NCCN Cervical Cancer Guidelines v2.2019
[2] SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD

Final Survival Analysis for GOG 240 chemotherapy + bevacizumab in recurrent cervical cancer



Number at risk (number censored)						
Chemotherapy plus bevacizumab	227 (0)	142 (9)	75 (12)	30 (31)	6 (51)	0 (57)
Chemotherapy alone	225 (0)	114 (9)	54 (18)	17 (35)	2 (45)	0 (47)

Chemotherapy + Bevacizumab *versus* chemotherapy	OS Hazard Ratio
All Chemotherapy	**HR 0·77** (95% CI 0·62–0·95); p=0·007
Cisplatin/paclitaxel	**HR 0·73** (95% CI 0·54–0·99); p=0·04
Topotecan/paclitaxel	**HR 0·80** (95% CI 0·59–1·08); p=0·15

Tewari et al, Abstract LBA26. *Annals of Oncology* 2014; 25 (5): 1-41.ESMO 2014; Tewari et al. The Lancet (2017)

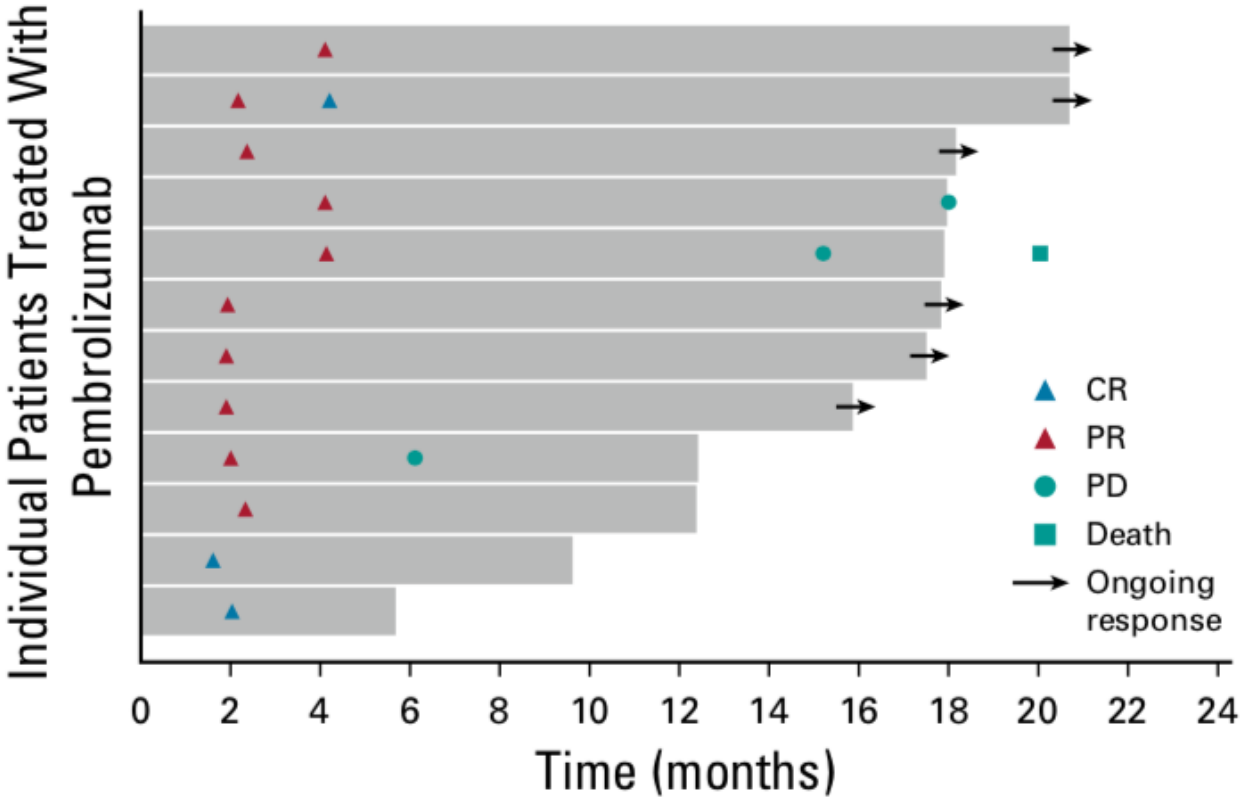
Keynote 158: Pembrolizumab in recurrent cervical cancer

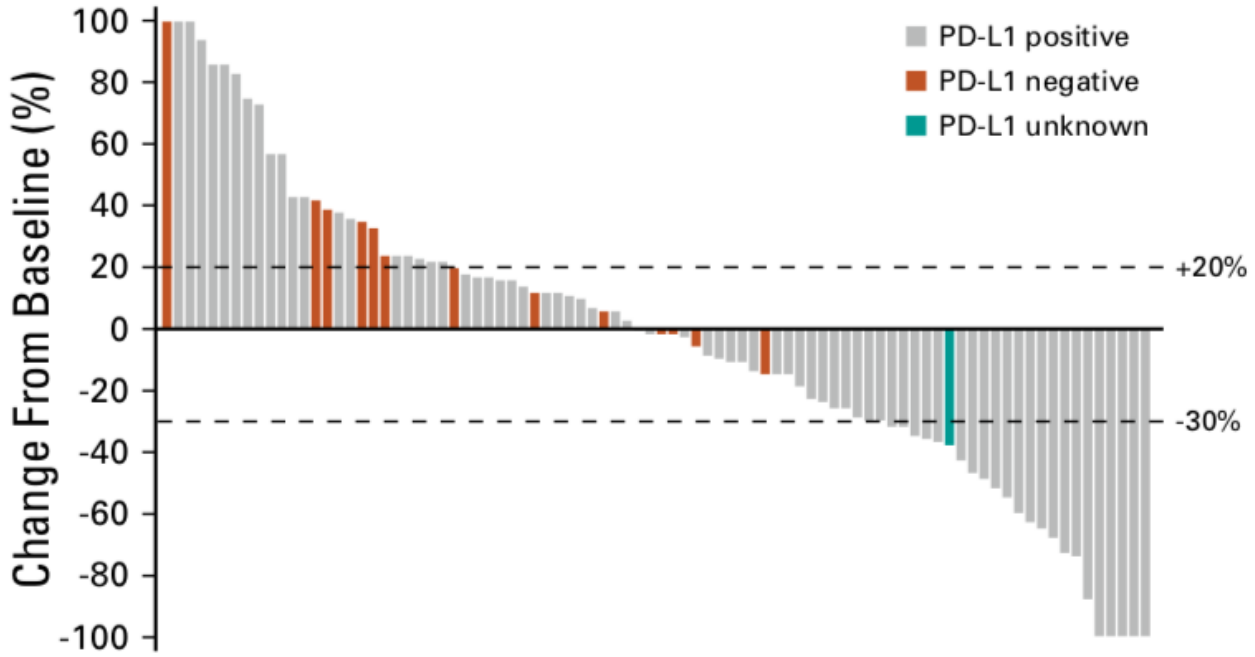
98 patients

ORR 12.2 %

All responses in PDL-1 +ve tumours

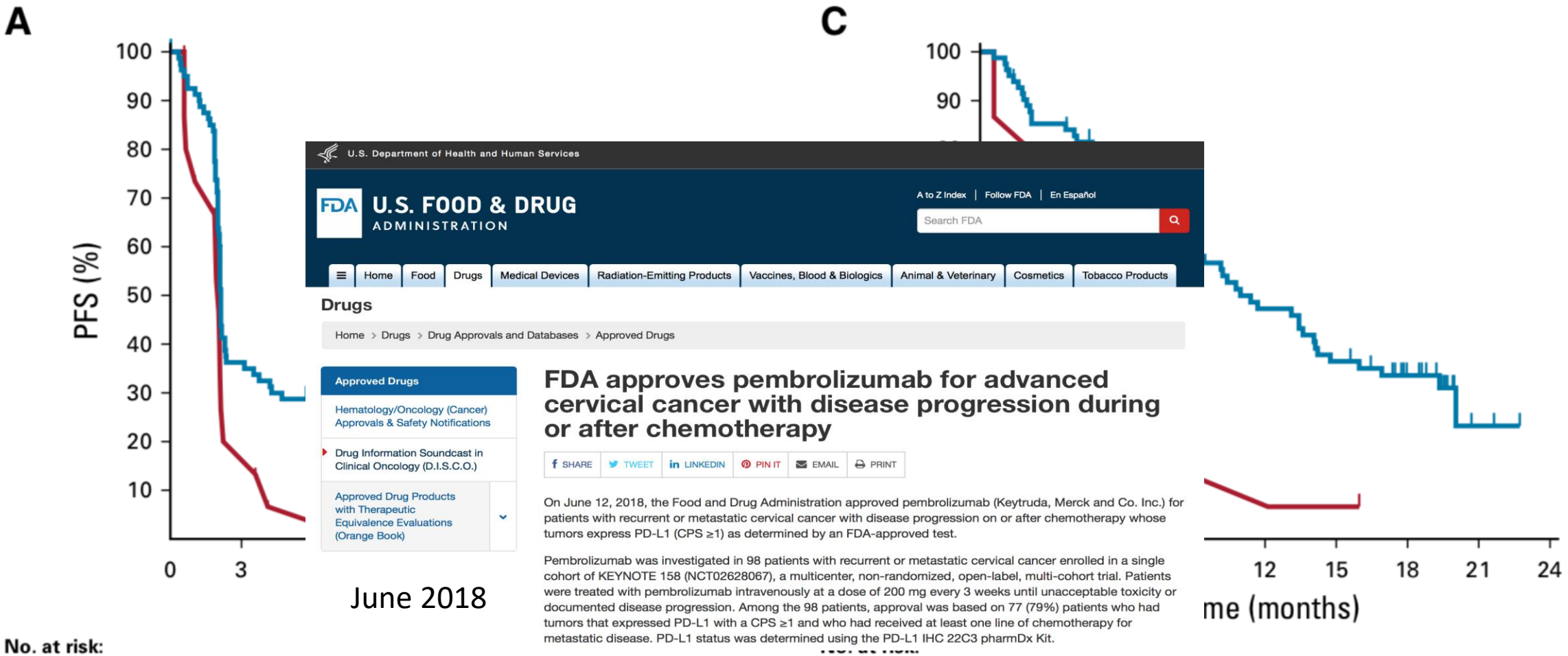
Median duration of response not reached





Chung et al J Clin Oncol 2019

Keynote 158: Pembrolizumab in recurrent cervical cancer- PDL1 +ve and PDL1 -ve



June 2018

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

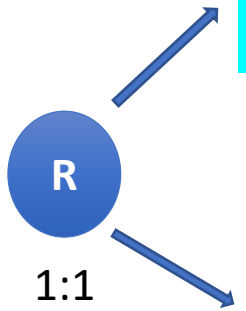
On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort of KEYNOTE 158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. Patients were treated with pembrolizumab intravenously at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression. Among the 98 patients, approval was based on 77 (79%) patients who had tumors that expressed PD-L1 with a CPS ≥1 and who had received at least one line of chemotherapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit.

Chung et al J Clin Oncol 2019

KEYNOTE-826: A phase III study of chemotherapy with or without pembrolizumab for first-line treatment of persistent, recurrent, or metastatic cervical cancer

- Metastatic, persistent or recurrent **squamous cell carcinoma, adenosquamous carcinoma or cervical adenocarcinoma**
- Not previously treated with chemotherapy
- Not amenable to curative treatment
- Measurable disease per RECIST v1.1
- ECOG-PS 0–1



Every-3-week pembrolizumab 200 mg PLUS investigator choice of chemotherapy*

Every-3-week placebo PLUS investigator choice of chemotherapy*

N = 600
149 Sites

All treatments are administered until disease progression or toxicity, for up to 35 cycles (up to approximately 2 years)

*paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2
WITH or WITHOUT bevacizumab 15 mg/kg
OR
paclitaxel 175 mg/m^2 PLUS carboplatin AUC 5
WITH or WITHOUT bevacizumab 15 mg/kg

Stratification:
- Metastatic at diagnosis (yes vs no)
- Bevacizumab use (yes vs no)
- PD-L1 status (CPS<1 vs CPS 1 to <10 vs CPS ≥10)

Primary endpoints: (1) Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as assessed by blinded independent central review (BICR); or (2) overall survival (OS)
Secondary endpoints: ORR, DOR, PFS, AEs, PROs

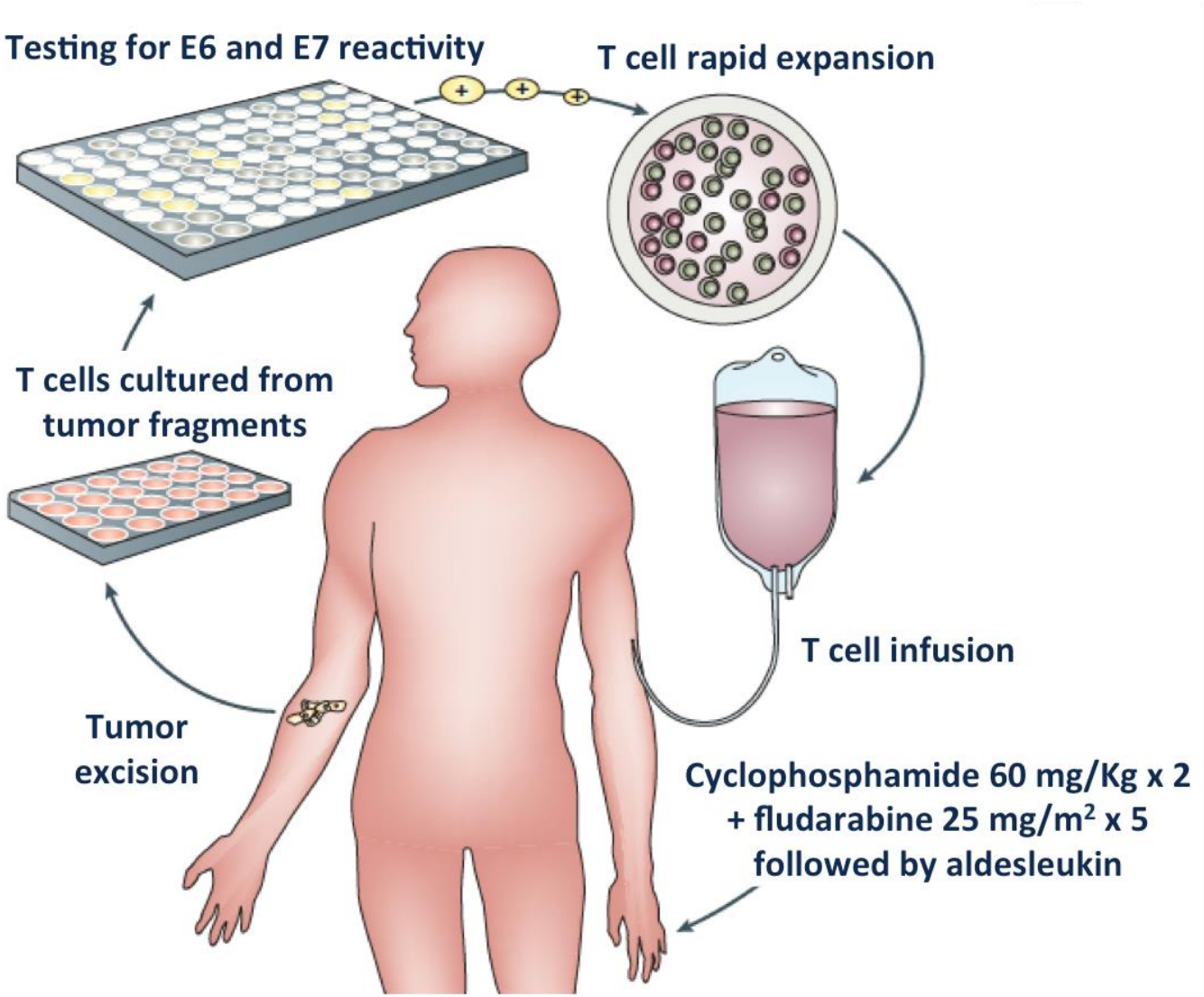
https://clinicaltrials.gov/ct2/show/NCT03635567. Accessed April 11, 2020 "Active not recruiting"

DOI: 10.1200/JCO.2019.37.15_suppl.TPS5595 Journal of Clinical Oncology 37, no. 15_suppl
Published online May 26, 2019.

Ongoing randomised immune checkpoint inhibitor trials in cervical cancer

NAME	CRITERIA	AGENTS	HISTOLOGY/STRATIFICATION
BEATcc ENGOT-Cx10 /GOG#3030/JGOG1084	Recurrent/persistent	Platinum, paclitaxel, Bevacizumab ± Atezolizumab/placebo	Squamous vs Adeno (including adenosquamous)
EMPOWER- CERVICAL 1" (GOG 3016)/ ENGOT	Recurrent second line	Non-platinum chemo ± Cemiplimab	Squamous (closed adeno entry)
FERMATA/ ENGOT Cx13	Recurrent/persistent	Platinum/paclitaxel (Bevacizumab) ± BCD-100/placebo	
MITO-ENGOT CX11	Maintenance post C-RT	Pembrolizumab/placebo	PD-L1 status (CPS<10 versus CPS via CPS 10 ≥10)
ATOMIC	Maintenance post C-RT	Dostarlimab/observation	squamous vs adenocarcinoma/adenosquamous
CALLA	Primary C-RT	Durvalumab/placebo	Any
CheckMate 358	1-2 prior chemo	Nivolumab ± ipilumumab (CTLA4)	Squamous Strat: HPV +/ -
SKYSCRAPER- 04	Recurrence post chemo	Atezolizumab ± Tiragolumab (TIGIT)	PDL-1 positive

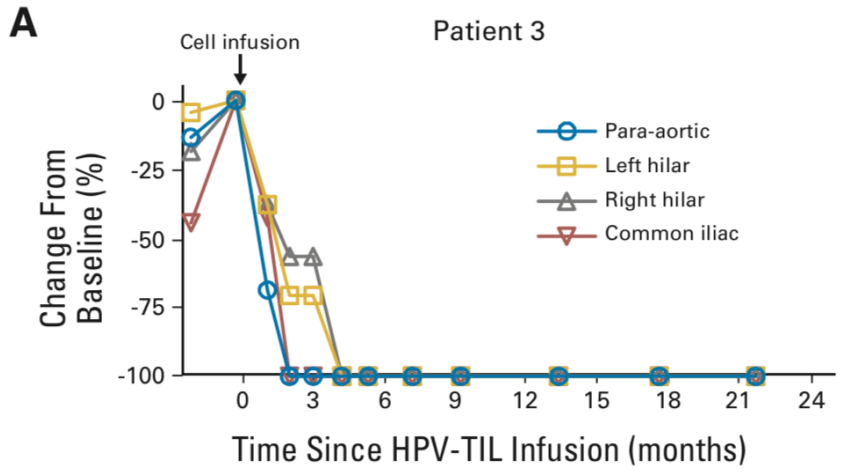
Treatment Schema for HPV-Targeted Tumor-Infiltrating Lymphocytes (HPV-TIL)

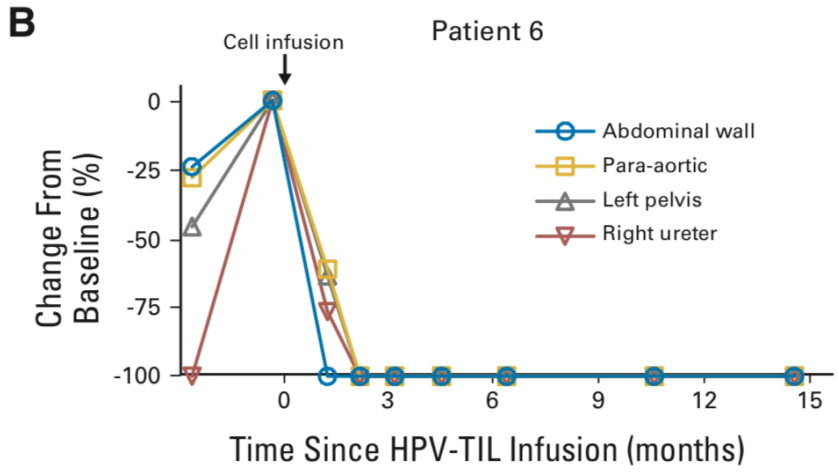


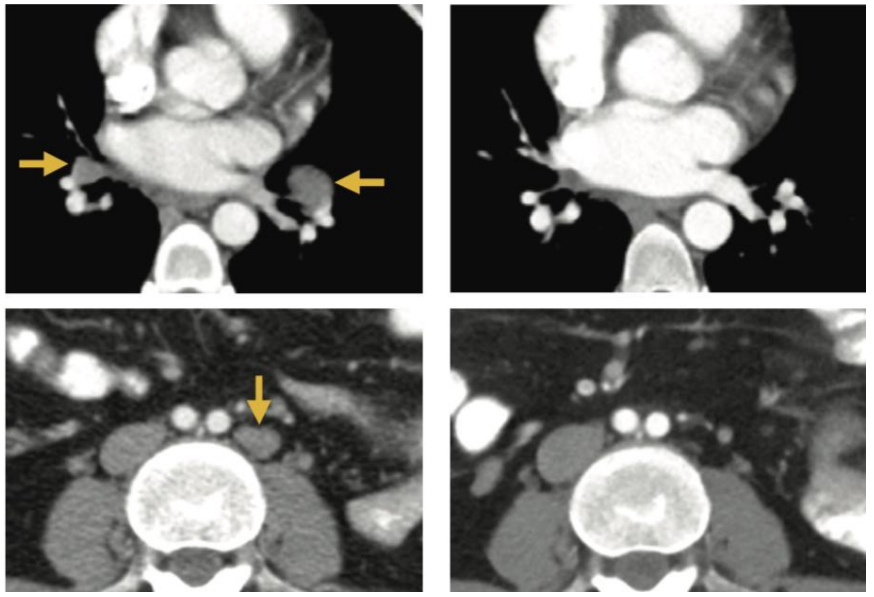
Hinrichs CS, et al. *J Clin Oncol*. 2014;32(5s): Abstract LBA3008.

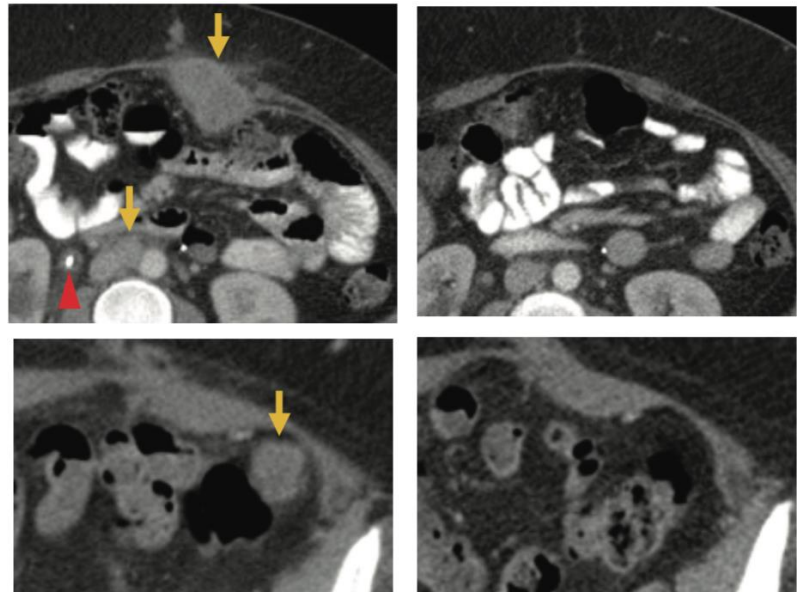
HPV-Targeted Tumour-Infiltrating Lymphocytes

- **Objective tumour responses in 3/9 patients**
  - 1 PR (3 months), 2 CR (22+ months and 15+ months)
- **HPV-reactive infused T cells in 6/8 patients**
  - 3/6 patients with reactivity had responses
  - 0/2 patients without reactivity had responses
- **Repopulation of peripheral blood with HPV reactive T cells in 2/4 patients**
  - 2/2 with repopulation had tumour responses
  - 0/2 without repopulation had tumour responses





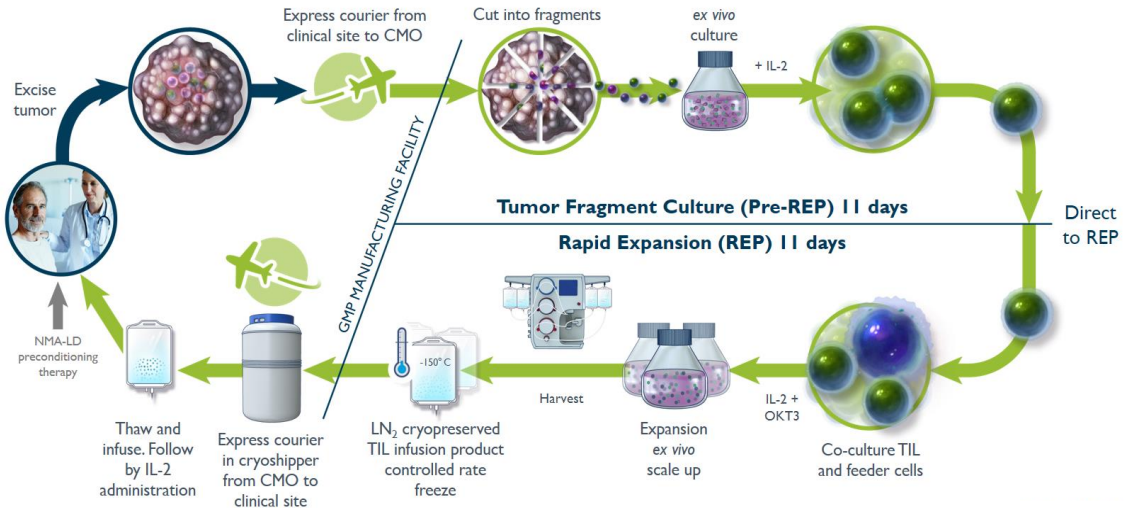




Stevanovic S, et al. *J Clin Oncol.* 2015;33(14):1543-1550.

Protocol: C-145-04

A Phase II, Multicentre Study of Autologous Tumor Infiltrating Lymphocytes **(LN-145)** in Recurrent, Metastatic or Persistent Cervical Carcinoma



CHARACTERISTIC	N=27, (%)
Age	
Median	45
Min, Max	30, 68
Prior therapies, n (%)	
Mean # prior therapies	2.4
Platinum-Based	27 (100)
Taxane	26 (96)
Anti-VEGF	22 (82)
Radiotherapy	20 (74)
Anti-PD-1/PD-L-1	4 (15)
Cancer Status at Screening	
Metastatic	14 (52)
Recurrent	10 (37)
Persistent	3 (11)

CHARACTERISTIC		N=27, (%)
ECOG score, n (%)	Screening	Baseline
0	19 (70)	9 (33)
1	8 (30)	17 (63)
≥2	0	1 (4)
Histologic Cell Type, n (%)		
Squamous Cell Carcinoma		12 (44)
Adenocarcinoma		12 (44)
Adenosquamous Carcinoma		3 (11)
Target Lesion Sum of Diameters (mm)		
Mean (SD)		61 (38)
Min, Max		10, 165
Number of Target & Non-Target Lesions (at Baseline)		
>3		17 (63)
Mean (Min, Max)		4 (1,9)

Key Inclusion Criteria:

- Measurable metastatic disease and ≥1 resectable lesion for TIL generation.
- Previous Platinum therapy
- ≤ 2prior systemic therapies
- ECOG PS 0-1

Endpoints:

- Efficacy and safety

Clinicaltrials.gov: NCT03108495.

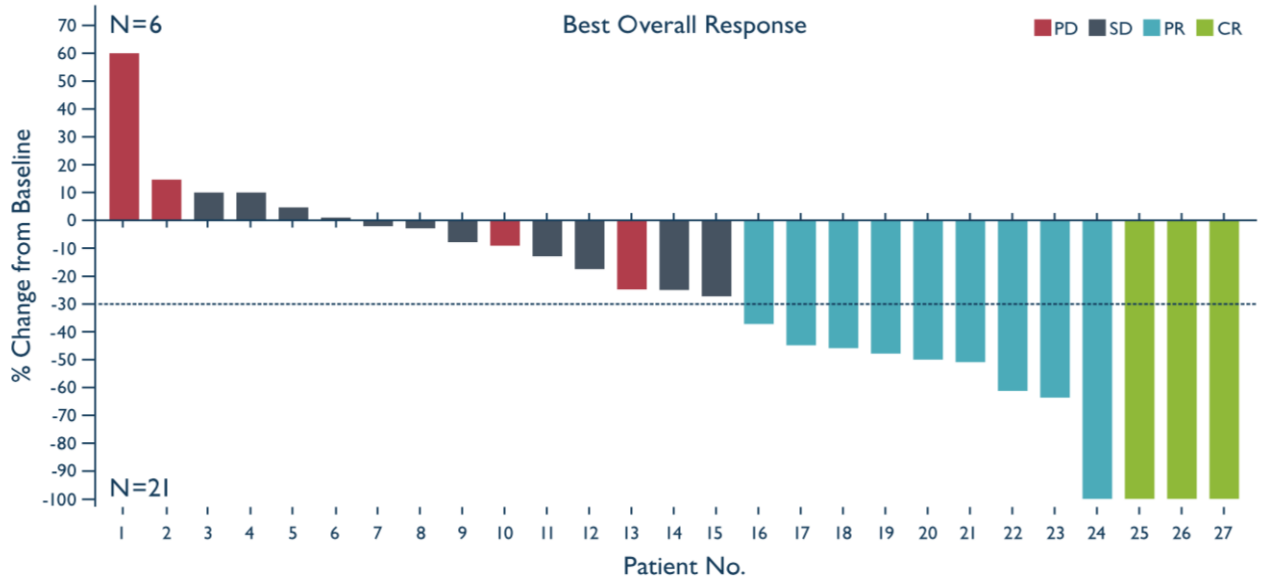
Safety & efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma

Preliminary Results

Table 3. Efficacy

RESPONSE (RECIST v1.1)	PATIENTS, N=27 n (%)
Objective Response Rate (ORR)	**12 (44.4%)**
Complete Response (CR)	3 (11.1%)
Partial Response (PR)	9 (33.3%)
Stable Disease (SD)	11 (40.7%)
Progressive Disease (PD)	4 (14.8%)
Non-Evaluable	0
Disease Control Rate (DCR)	23 (85.2%)
Median Duration of Response (DOR)	**Not Reached**
Min, Max (range)	2.6+ to 9.2+ months

Figure 4. Efficacy: Best Overall Response



- Mean time to first response 1.9 months
- Mean time to best response 2.4 months

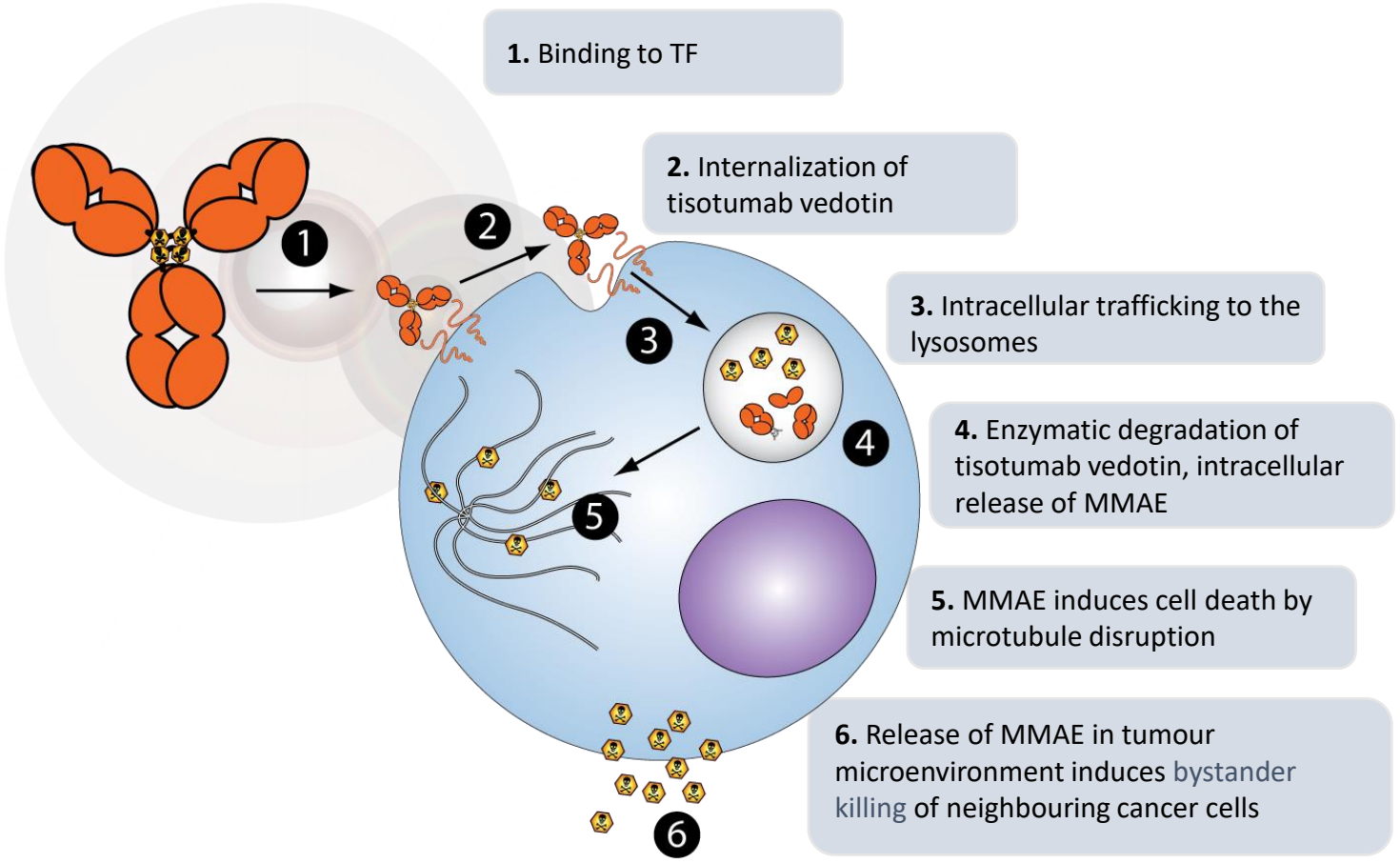
Amir A. Jazaeri et al; *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 2538-2538.

Clinicaltrials.gov: NCT03108495.

Tisotumab Vedotin Mechanism of Action

- **Tisotumab vedotin is an antibody-drug conjugate (ADC) composed of a human mAb specific for tissue factor (TF), a protease-cleavable linker, and the microtubule-disrupting agent MMAE[1,a]**
- **TF is a transmembrane protein that is the main physiological initiator of coagulation and is involved in angiogenesis, cell adhesion, motility, and cell survival[3]**
- **TF is aberrantly expressed in a broad range of solid tumours, including cervical cancer, and is associated with poor prognosis[4,5]**

Mechanism of action[1,2]

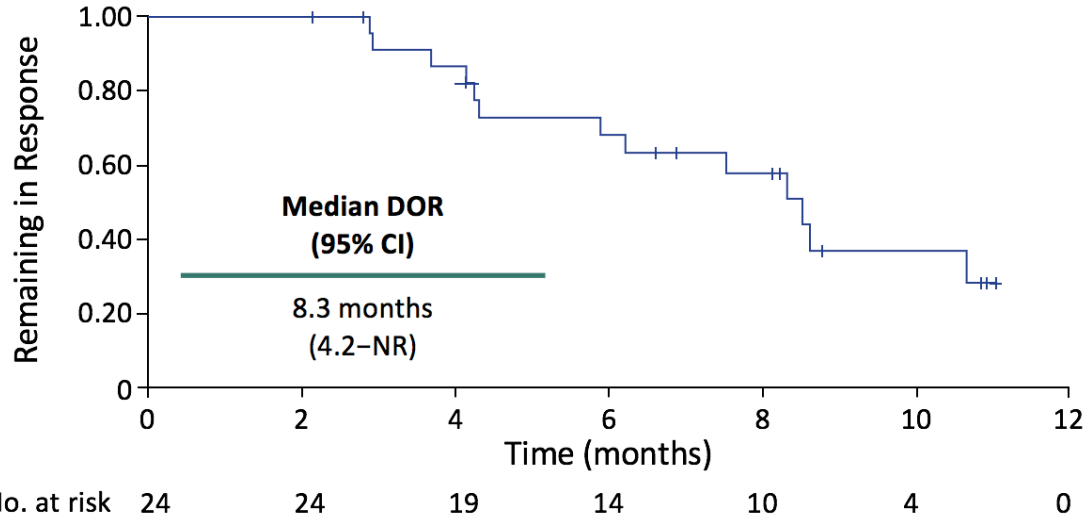


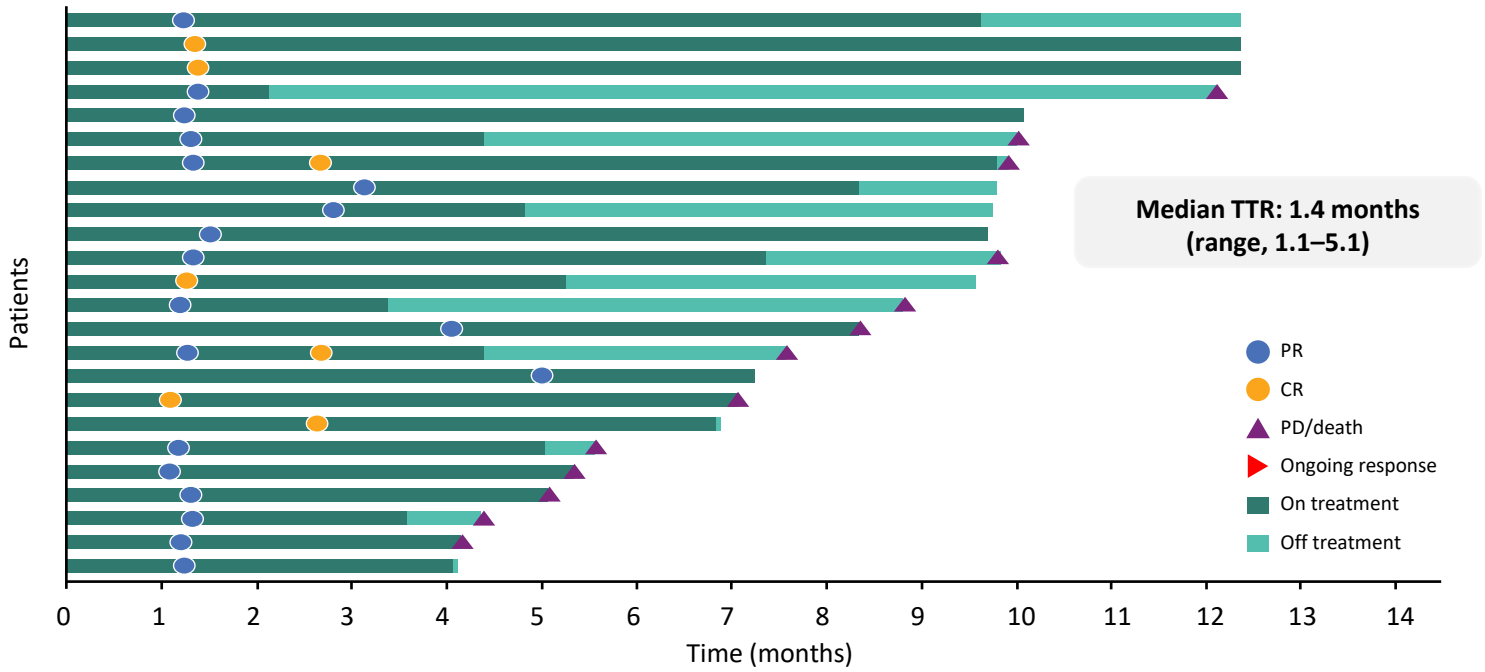
MMAE, monomethyl auristatin E
[a]Tissue factor is known as TF, CD142, and thromboplastin.

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. Chu AJ. *Int J Inflam*. 2011;2011:367284. 4. Förster Y et al. *Clin Chim Acta*. 2006;364(1-2):12-21. 5. Cocco E et al. *BMC Cancer*. 2011;11:263.

innovaTV 204/ GOG-3023/ENGOT-cx6

	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)

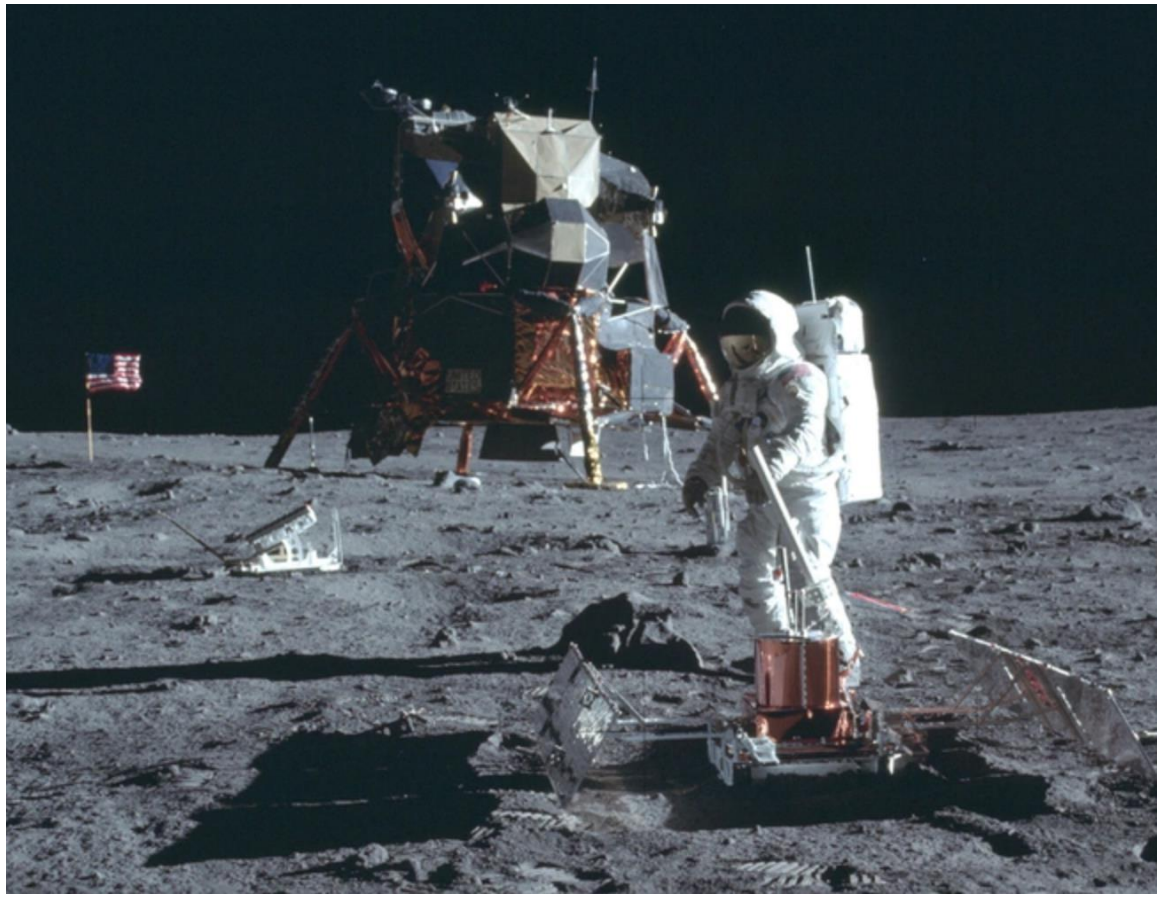




Coleman et al ESMO 2020

Molecular Therapy for Gynaecological Tumours

The frontier of targeted therapy has been crossed



Targeted therapies have already improved the treatment of women with gynaecological cancers
But still much to explore and understand……

The future lies in team working with biologists, pathologists and clinical trialists to continue the road to improvement