Endometrial Cancer

Is Cinderella now a Princess ???

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Financial Disclosures

I have the following ongoing financial relationships with ACCME defined ineligible companies to report over the past 24 months:

- Employee: University of Milan-Bicocca and European Institute of Oncology IRCCS, Milan
- Consultant/Advisor: Roche; PharmaMar; AstraZeneca; Clovis Oncology; MSD; GlaxoSmithKline; Tesaro; Pfizer; BIOCAD; Immunogen; Mersana; Eisai; Oncxerna, Nuvation Bio
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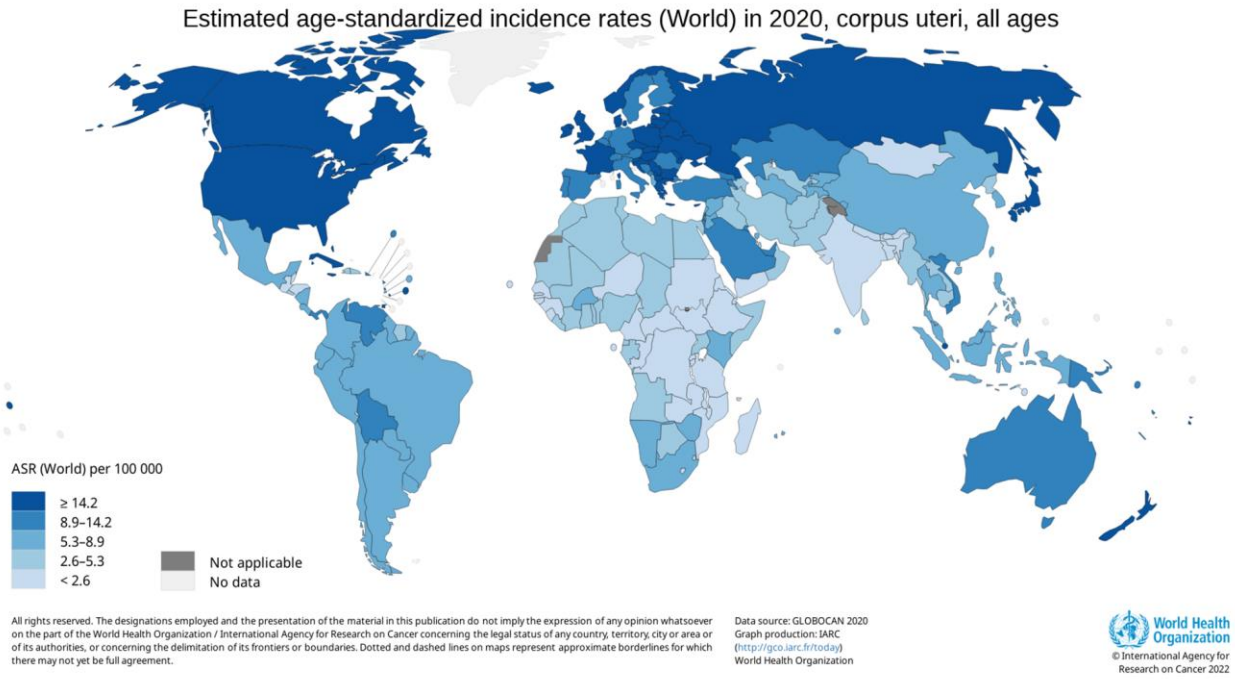
- Nonfinancial interests: Steering Committee Member for ESMO Clinical Guidelines, Chair Scientific Committee ACTO onlus

Cinderella was born to wealthy, unnamed parents who treated their daughter with great love. After the death of her mother, her father remarried, believing that she "needed a mother's care". He died shortly thereafter, upon which she was forced to work as a scullery maid for her wicked stepmother, Lady Tremaine and two stepsisters, Anastasia and Drizella.
Despite the cruelty of her jealous stepfamily, Cinderella remained kind, spirited, and internally beautiful.

ENDOMETRIAL CANCER…….. AS CINDERELLA

Despite being the most common gynecological cancer in the developed world and the only Gynecological Cancer with rising incidence and mortality

- 80% present with stage I disease with excellent prognosis
- Treated everywhere
- Very little interest for new agents and treatment modalities compared to the two stepsisters ovarian and cervical cancer



Cinderella was wearing very simple and poor dresses as any maid

Endometrial Cancer was thought to be a simple disease

1983 The Bokhman's dualistic model

	Type I	Type II
Precursor: estrogen related	Yes	No
Frequency	80%	20%
Histology	Endometrioid	CCC, serous, mucinous
Prognosis	Good	Bad

One Day

Invitation to the ball

The Fairy Godmother insists that Cinderella attends the ball and demonstrates her magical abilities..

……..as she transforms a pumpkin into a coach, mice into horses, Major into a coachman, and Bruno into a footman

…….before transforming Cinderella's ruined dress into a beautiful, sparkling ball gown, complete with glass slippers

Endometrial cancer classification: The fulfillment of a ProMisE

Bokhman : a dualistic model for endometrial tumorigenesis

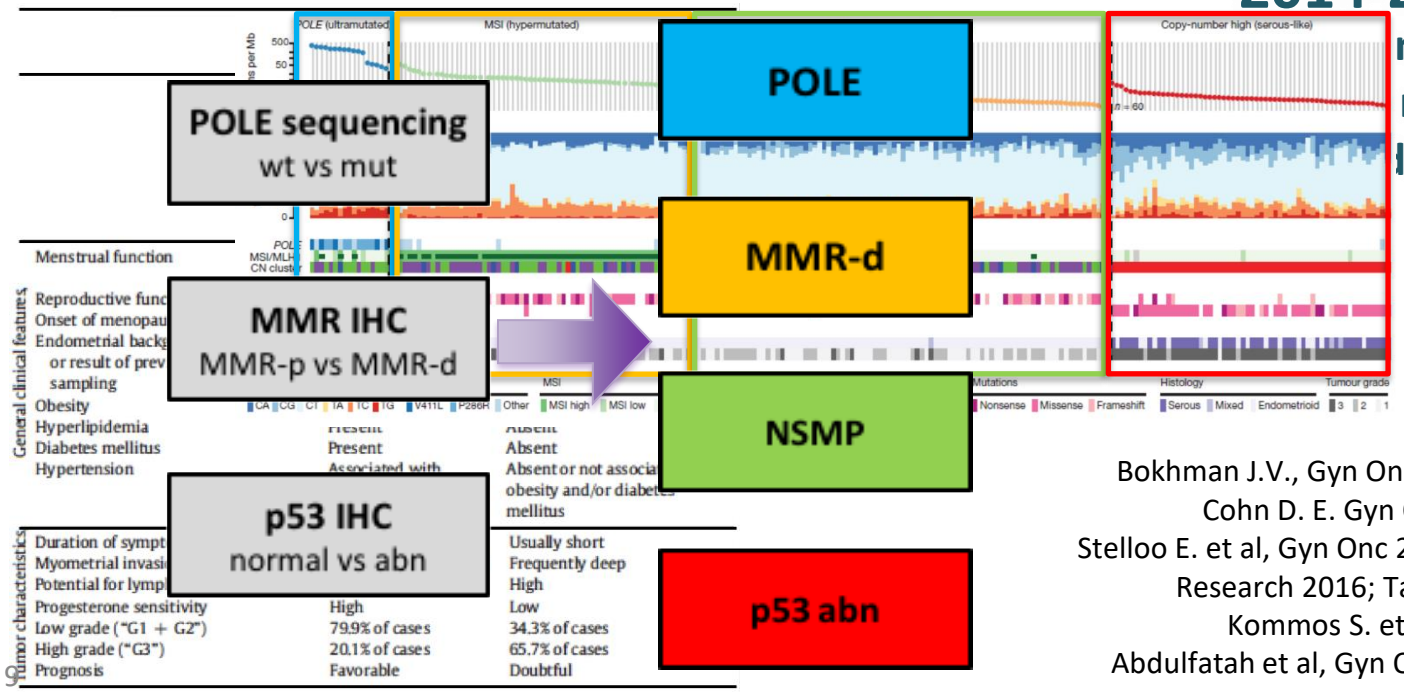
TCGA molecular model

1983

2013

2014-2018

nsPORTEC: molecular lel



Bokhman J.V., Gyn Onc 1983. Suarez A.A., Felix A.S., Cohn D. E. Gyn Onc 2017. TGCA, Nature 2013 Stelloo E. et al, Gyn Onc 2014; Stelloo et al, Clin Cancer Research 2016; Talhouk A. et al, Gyn Onc 2016; Kommos S. et al, Annals of Oncology, 2018: Abdulfatah et al, Gyn Onc 2019. Concin N. et al, IJGC 2021

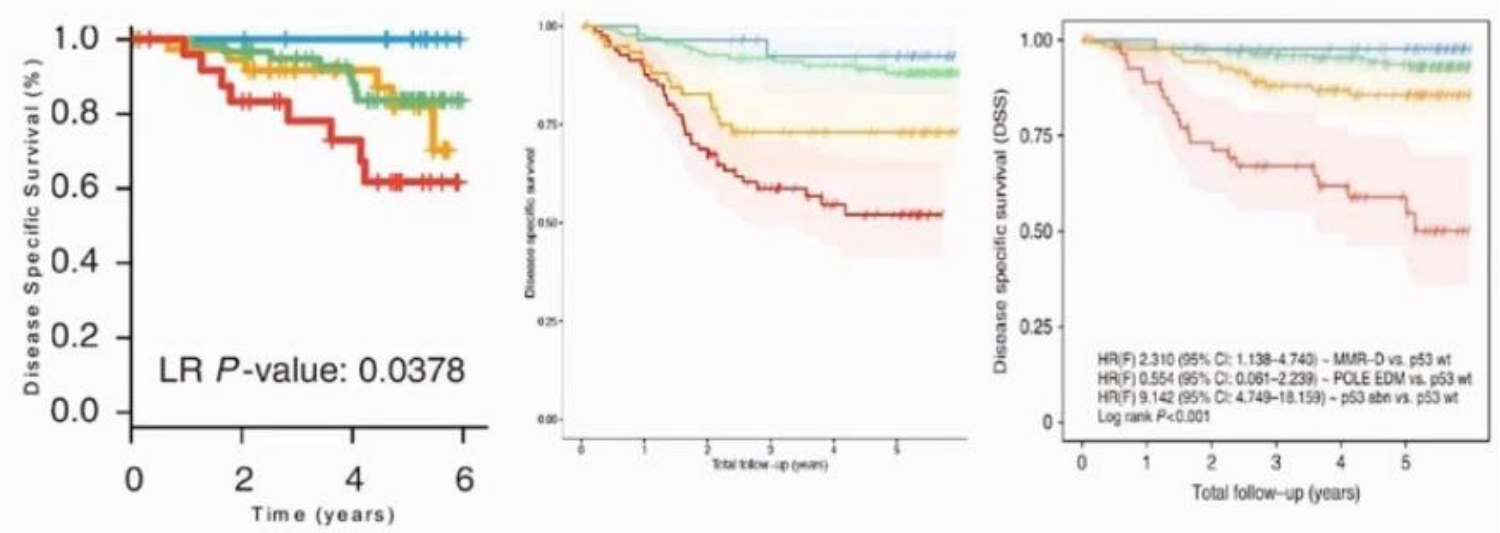
Clinical implications

Molecular classification's roles	
Prognostic factor	Estimate PFS and OS according to molecular class
Risk Assessment	More objective attribution to a specific risk class
Predictive factor	Identification of patients who may be more sensitive to different treatment options
Genetic screening	Identification of patients who may harbour genes' mutations (Lynch syndrome)

Prognostic role

Unselected cohorts

N=142 N=319 N=451



POLE

MMRd

NSMP

p53

Prognostic accuracy of surrogate markers is validated in several unselected ECs cohorts

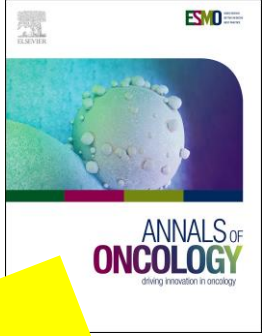
Talhouk at al, BJC 2015. Talhouk et al, Cancer 2017. Kommoss et al, Annals Onc 2018.

Classical risk factors

- Grade
- Myometrial invasion
- Histologic subtype
- LVSI
- Stage
- Age

ESGO-ESTRO-ESP (2020)

ESMO (2022)



FIGO Staging 2023

The ESGO-ESTRO-ESP guidelines (2020)

Risk Group	Molecular Classification Unknown	Molecular Classification Known[A],*
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 carcino… high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-… clear cell, undif… carcinosarcoma … invasion
High-intermediate	• Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade** … LVSI status • Stage II	
High	• St…	…al carcinoma with … no residual disease …P/MMRd serous, undifferentiated …, carcinosarcoma with myometrial …asion, with no residual disease
Advanced Metastatic		• Stage III-IVA with residual disease of any molecular type • Stage IVB of any molecular type

[A]For stage III-IVA *P*… …rial carcinoma, and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient … 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

Risk group	Description[a]
Low risk	Stage IA …) type and
	… focal
	…, undifferentiated … p53-abn cancers without … LVSI
	… endometrioid type (MMRd and NSMP) and no or
	Stage II G1 endometrioid cancer (MMRd and NSMP) and no or focal LVSI
intermediate risk	Stage I endometrioid (MMRd and NSMP) any grade and any depth of invasion with substantial LVSI
	Stage IB G3 with endometrioid type (MMRd and NSMP) regardless of LVSI
	Stage II G1 endometrioid cancer (MMRd and NSMP) with substantial LVSI
	Stage II G2-G3 endometrioid cancer (MMRd and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion
	All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion
	All Stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype[b]

EC, endometrial cancer; G1-G3, grade 1-3; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; MSI-H, microsatellite instability high/hypermutated; NSMP, no specific molecular profile.

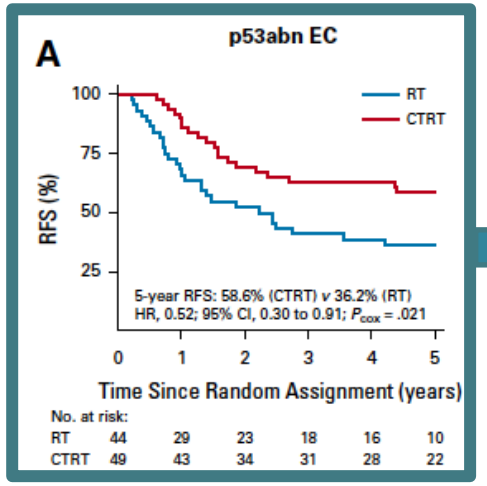
[a] Stage III-IVA if completely resected without residual disease; table does not apply to stage III-IVA with residual disease or for stage IV.

[b] MMRd and MSI-H: Both terms identify a similar EC population. Identification of a defective mismatch repair pathway by IHC (i.e. MMRd) or sequencing to determining microsatellite instability (i.e. MSI-H).

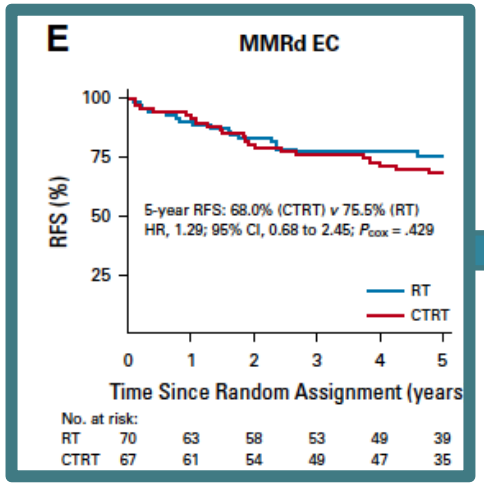
[c] *POLE*mut stage III might be considered as low risk. Nevertheless, currently there is no data regarding safety of omitting adjuvant therapy.

Predictive role

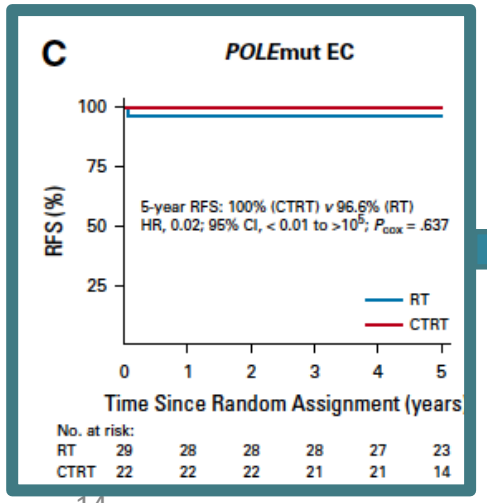
PORTEC-3



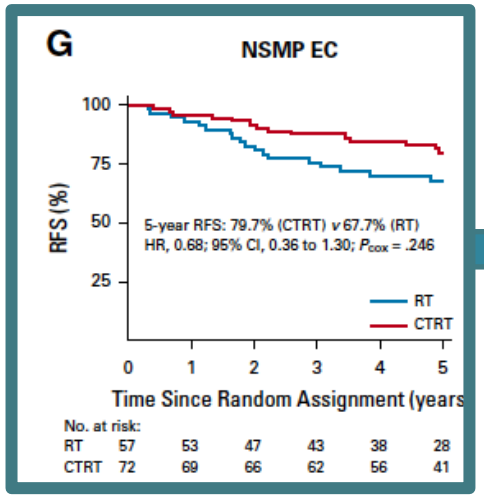
Great benefit from CT



No benefit from CT



No added benefit from CT

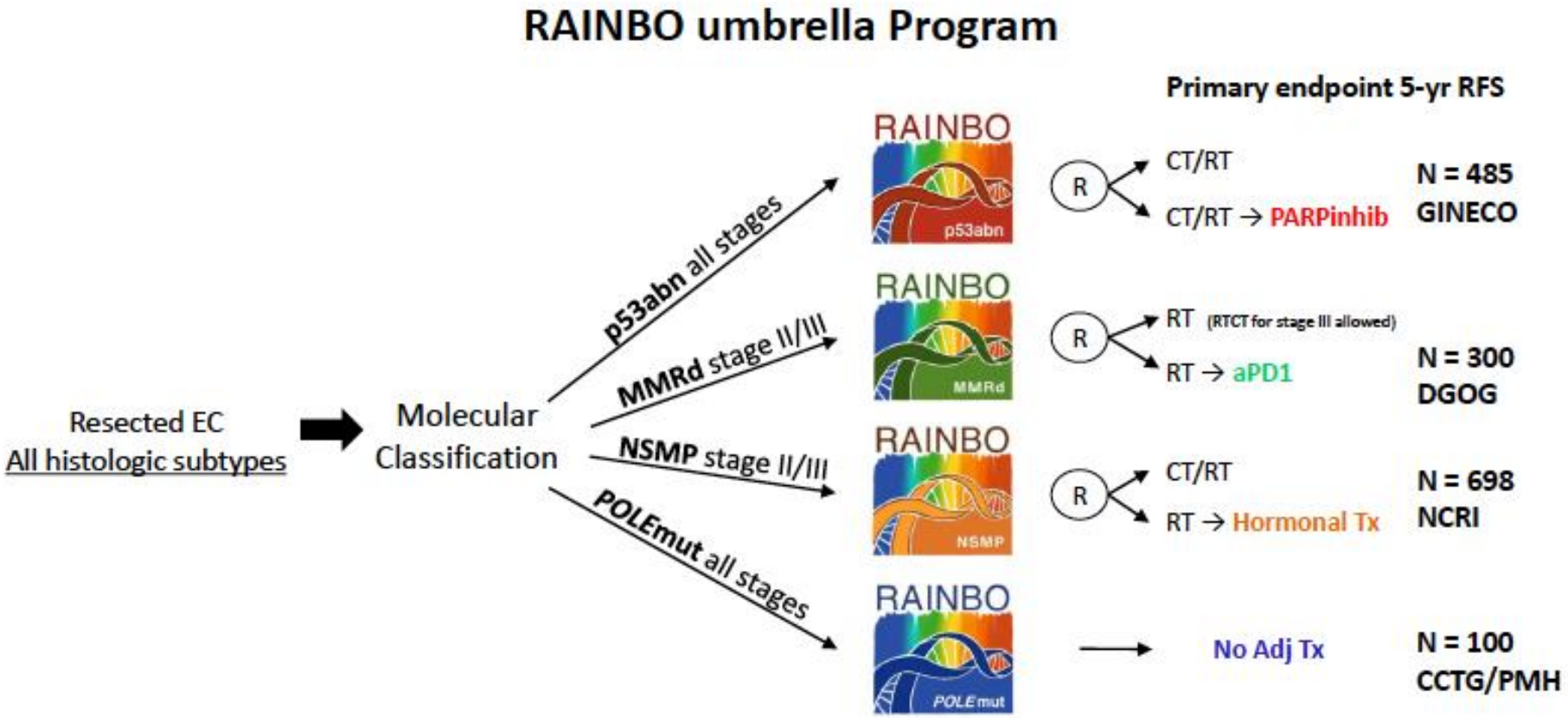


No statistically significant benefit from CT

Leon-Castillo et al, JCO 2020

14

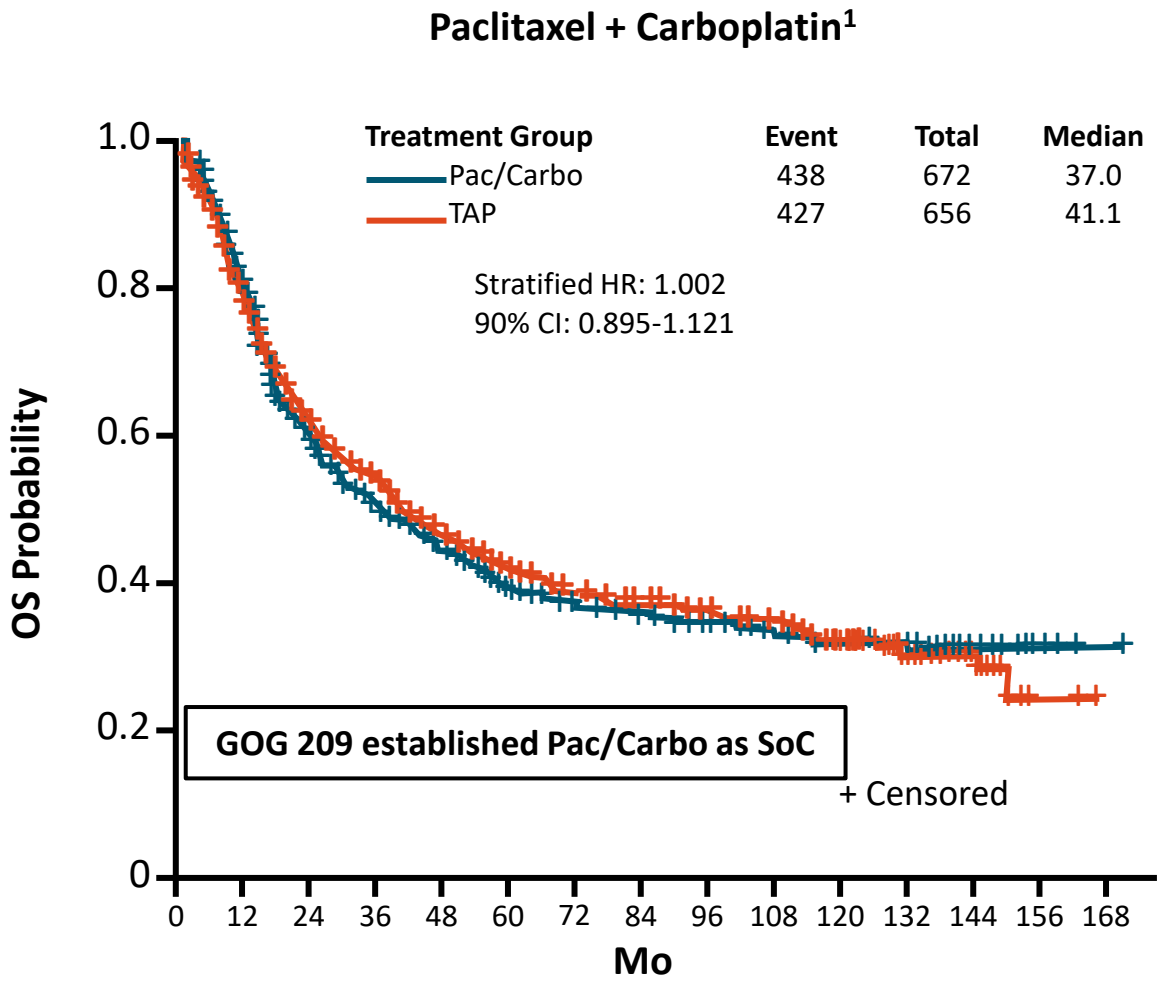
Future directions



RAINBO umbrella program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group

Sistemic treatment : one size does not fit all !!!!

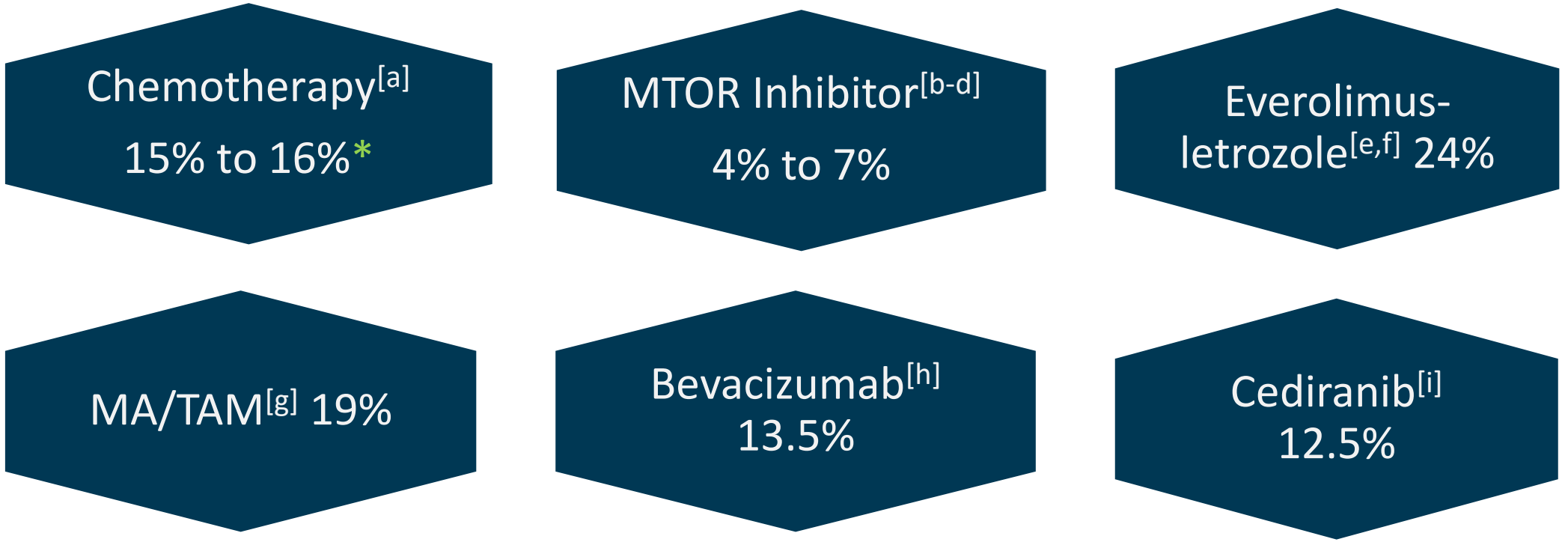
Standard of Care chemotherapy for Advanced/Recurrent Endometrial Cancer



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

Unmet Need in Second-Line Endometrial Cancer

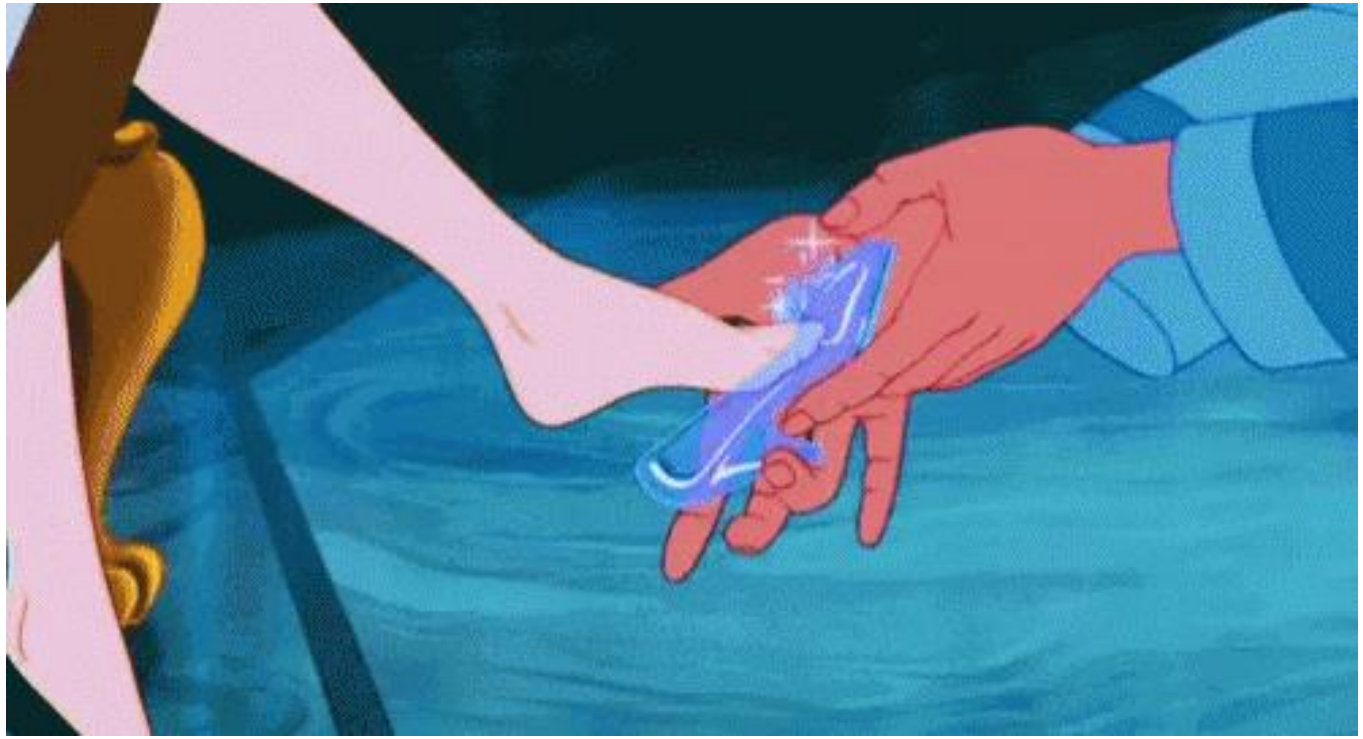
Objective Response Rates



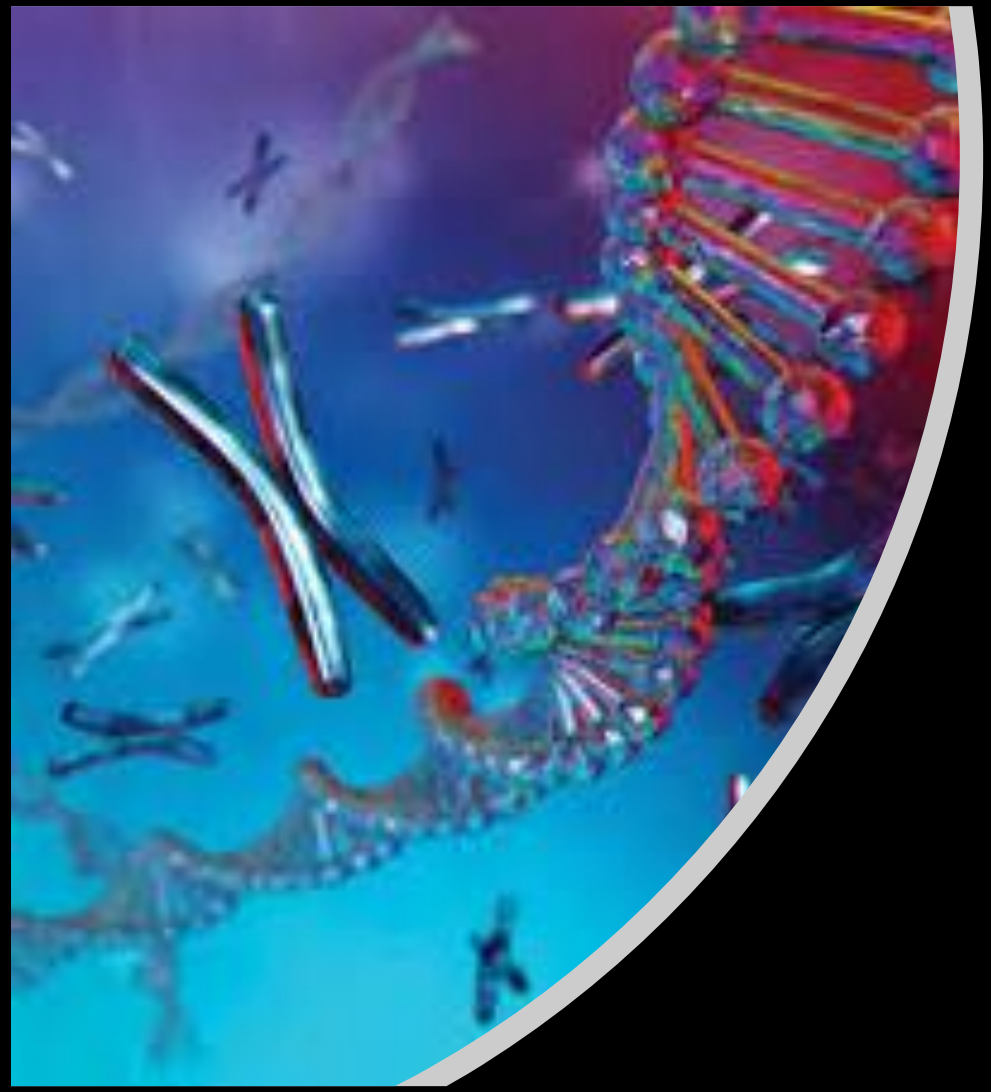
* Ixabepilone vs. doxorubicin vs paclitaxel (phase 3)

a. McMeekin S, et al. *Gynecol Oncol*. 2015;138:18-23; b. Oza AM, et al. *J Clin Oncol*. 2011;29:3278-3285; c. Colombo N, et al. *Br J Cancer*. 2013;108:1021-1026; d. Tsoref D, et al. *Gynecol Oncol*. 2014;135:184-189; e. Slomovitz BM, et al. C*ancer*. 2010;116:5415-5419; f. Slomovitz BM, et al. SGO 2018; g. Lee W-L, et al. *J Cin Med Assoc* 2014;77:221-226; h. Aghajanian C, et al. *J Clin Oncol* 2011;29:2259-2265; i. Bender D, et al. *Gynecol Oncol* 2015;138:507-512.

How to personalize sistemic treatment???????



The Duke slides the slipper onto Cinderella's foot, and it fits perfectly.



Can Molecular profiling improve the systemic treatment of endometrial cancer ?

Potential Therapeutic Impact of TGCA Classification of Endometrial Cancer

	POLE	MSI	Copy Number Low	Copy Number High
MSI/MLH methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Molecular profile	POLE (100%) PTEN (94%) PIK3CA (71%) FBXW7 (82%) ARID1A (76%) KRAS (53%) PD1/PD-L1 overexpression	PTEN (88%) RPL22 (37%) KRAS (35%) PIK3CA (54%) ARID1A (37%) PD-1/PD-L1 overexpression	PTEN (77%) CTNNB1 (52%) PIK3CA (53%) ARID1A (42%) FGFR2 (10.9%)	TP53 (92%) PPP2R1A (22%) FBXW7 (22%) PIK3CA (47%) PTEN (11%) FGFR (7%) HER2 (25%)
Potential drugs	PI3K/PTEN/AKT/ mTOR pathway Anti-PD-1/PD-L1 Hormones	PI3K/PTEN/AKT/mTOR pathway Anti-PD-1/PD-L1 Hormones	PI3K/PTEN/AKT/ mTOR pathway Hormones FGFR-I	HER2- I PI3K- I PARP-I Wee-1 I FGFR-I

Stelloo E, et al. *Clin Cancer Res.* 2016;22;4215-4224.

ENGOT-EN3/NSGO-PALEO

Endometrial Cancer

Primary stage 4 or relapsed disease

ER positive endometrioid adenocarcinoma

Randomization: 1:1
n = 78

Randomize

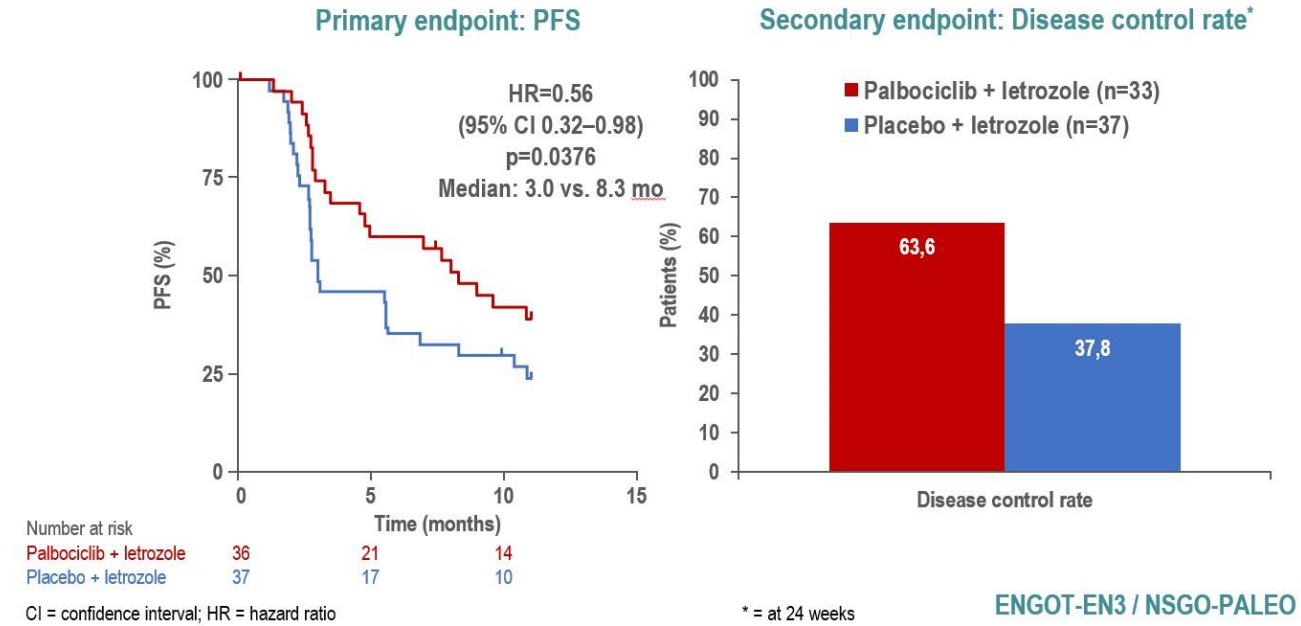
ARM A
Letrozole, 2.5mg d 1-28 every 28 days
Placebo 125mg d 1-21 every 28 days
Until progression

ARM B
Letrozole, 2.5mg d 1-28 every 28 days
Palbociclib 125mg d 1-21 every 28 days
Until progression

Stratification:
- Number of prior lines (primary adv disease vs. 1st relapse vs. ≥2 relapses)
- Measurable vs. evaluable disease
- Prior use of MPA/Megace

ENGOT model: A
Sponsor: NSGO-CTU
Status: Trial closure
Last patient randomized: 21-12-2018
Total patient enrolled: 78 patients randomized
NSGO-CTU PM: Christel Johanneson Bertolt

- PFS and OS data presented by Mirza et al., oral presentation, ESMO 2020
- CSR and manuscript writing is ongoing



Mirza et al. ESMO 2020

ENGOT-en17/GINECO/EQ132-303/GOG-3075

- Grade 1 or Grade 2 Endometrioid
- No prior therapy for metastatic disease
- No prior endocrine therapy
- Stage IVB or Stage III/IV with measurable disease
- ECOG PS 0-1

n = 320

R

1:1

Double-Blinded

Letrozole 2.5 mg PO QD + Lerociclib 150 mg PO BID

Letrozole 2.5 mg PO QD + Placebo

Stratification variables:
- Tumor Stage (III vs. IV vs. recurrent)
- Tumor Grade (1 v. 2)
- Geographic Location

Primary endpoint: PFS by BICR
Secondary endpoints: PFS by IA, OS, ORR, DoR, QoL, AEs

- Hazard ratio for PFS: 0.63
- Significance level: 0.025 (1-sided)
- Randomization ratio: 1:1
- Median PFS in the control arm: 5 months
- Targeted PFS in the experimental arm: 7.94 months

Potential Therapeutic Impact of TGCA Classification of Endometrial Cancer

	POLE	MSI	Copy Number Low	Copy Number High
MSI/MLH methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
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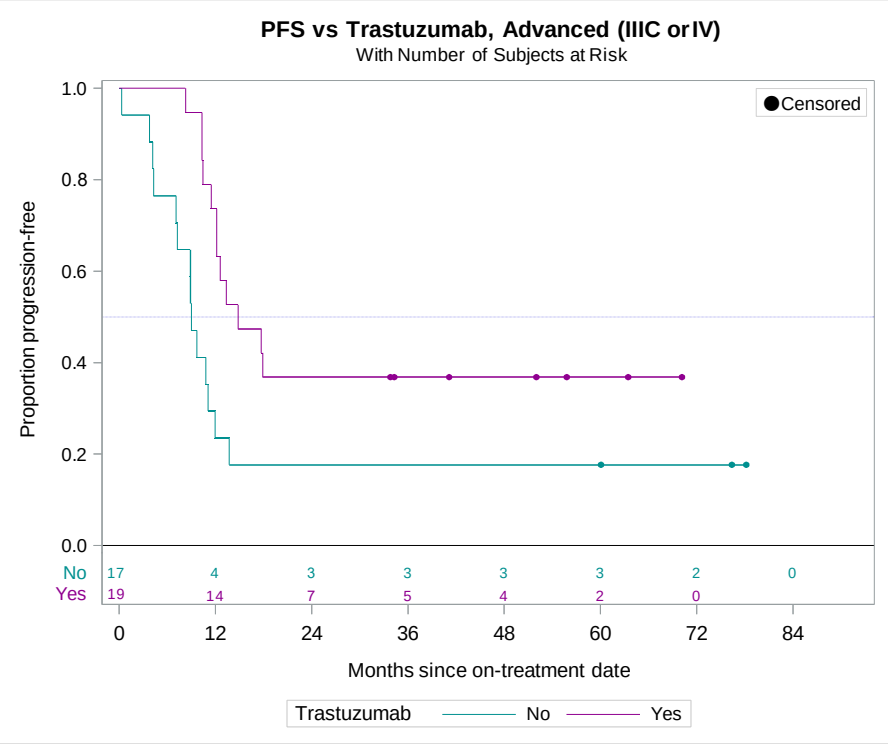
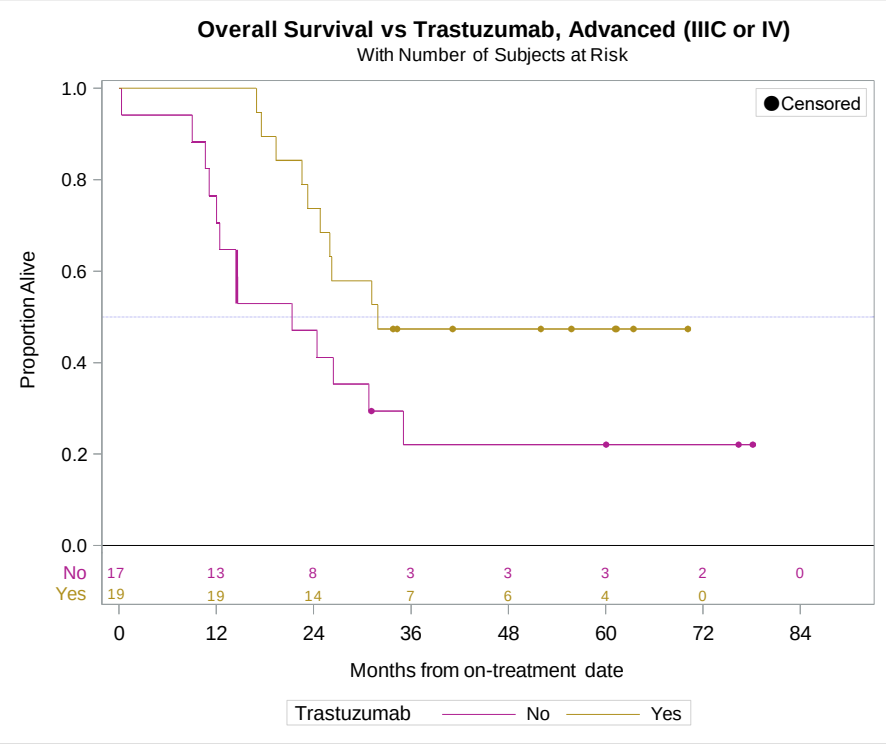
Potential drugs	PI3K/PTEN/AKT/ mTOR pathway Anti-PD-1/PD-L1 Hormones	PI3K/PTEN/AKT/mTOR pathway Anti-PD-1/PD-L1 Hormones	PI3K/PTEN/AKT/ mTOR pathway Hormones FGFR-I	HER2- I PI3K- I PARP-I Wee-1 I FGFR-I

Stelloo E, et al. *Clin Cancer Res.* 2016;22;4215-4224.

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

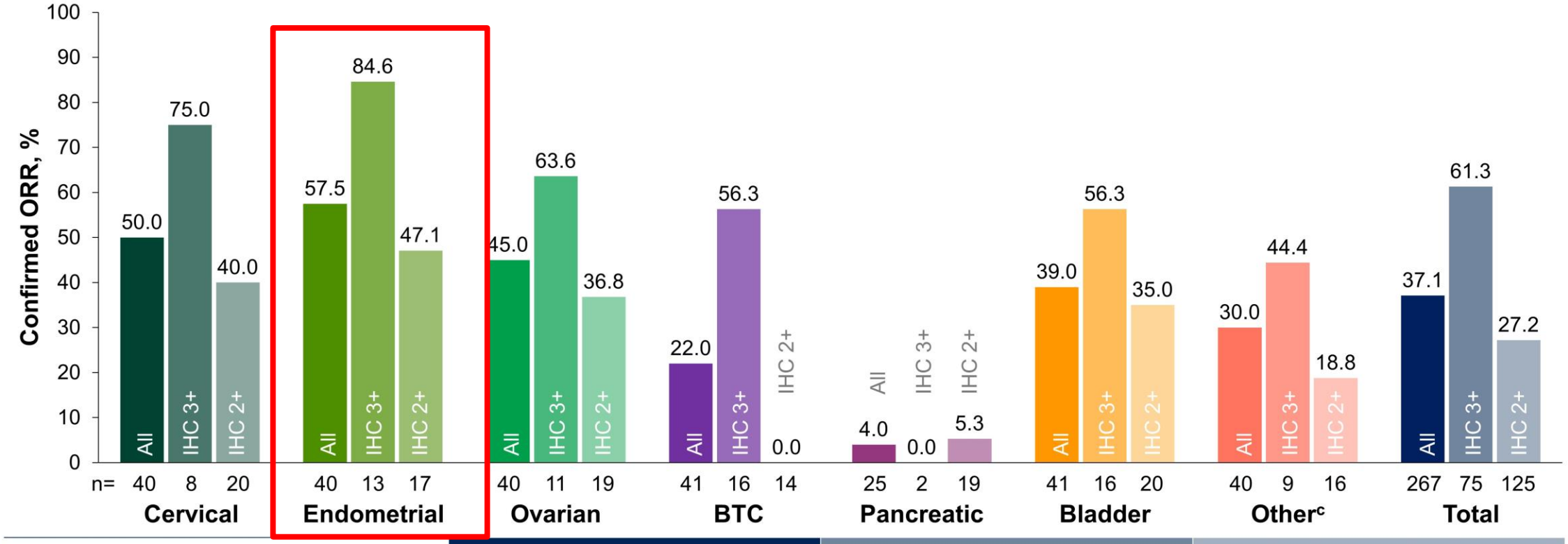




In a subset analysis of pts restricted to stage IIIC/IV disease, the addition of trastuzumab (n=17) continued to provide both (*left*) PFS benefit over control (n=19) and OS benefit over control (21.1 versus 31.9 months, HR 0.440 90% CI 0.219-0.882 p=0.0230).

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

Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

PRESENTED BY: Funda Meric-Bernstam, MD

Adavosertib (AZD1775) inhibits WEE1 and may be most active in p53-mutant background

Cell cycle checkpoints slow down the cell cycle

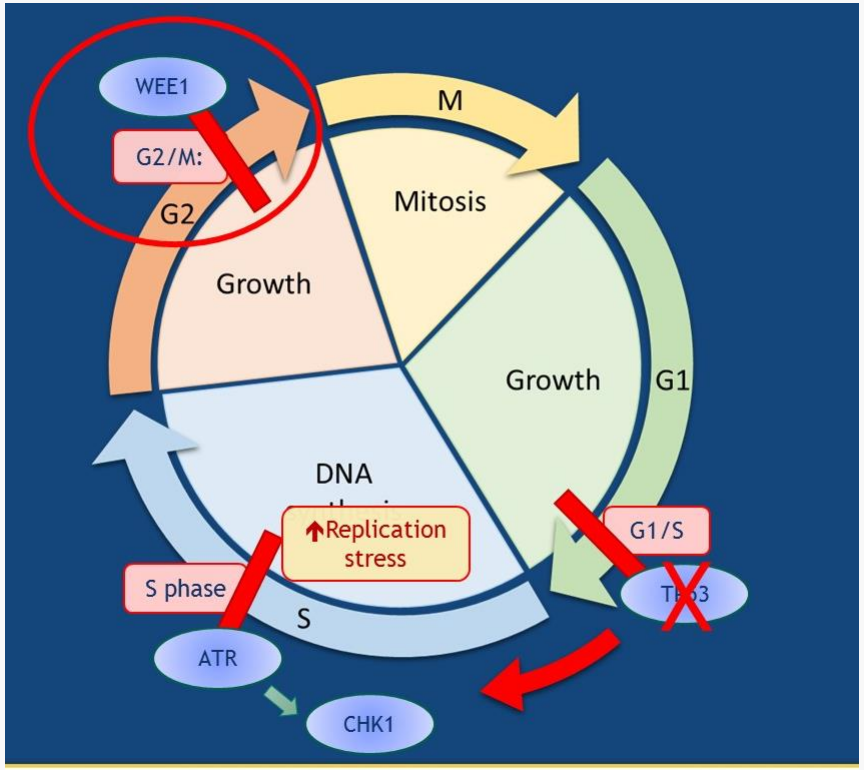
- Allow time for appropriate DNA replication
- Prevent progression to mitosis with DNA damage or underreplicated DNA

Cells with TP 53 mutation/loss lose their G1/S checkpoint

- Leads to early entry into S phase
- Increases replication stress
- Increases dependency on the G2/M checkpoint

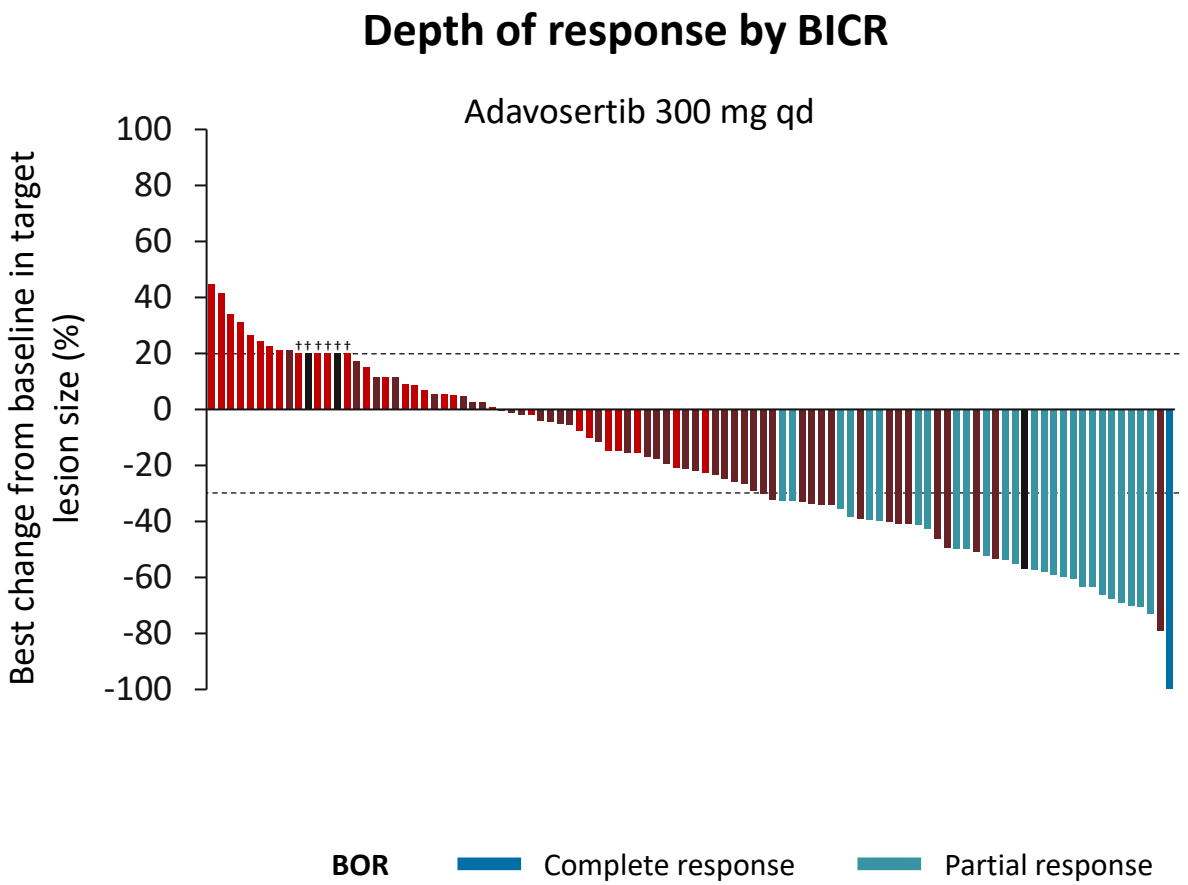
WEE1 is a Key regulator of G2/M checkpoint

- WEE1 inhibition leads to disregulation of the G2/M checkpoint and to mitotic catastrophy



Adavosertib | C27H32N8O2 - PubChem (nih.gov)

Deep and sustained responses were observed in some patients



ORR, n (%) [†] (95% CI)	**27 (26.0) (17.9–35.5)**
Disease control rate, n (%)[‡] (95% CI)	56 (51.4) (41.6–61.1)

[†]Indicates an imputed value; *Indicates progression due to non-target and/or new lesions
BICR, blinded independent central review; BOR, best overall response; qd, once daily

LIU et al, SGO 2023

The most common treatment-related serious adverse events were neutropenia and sepsis

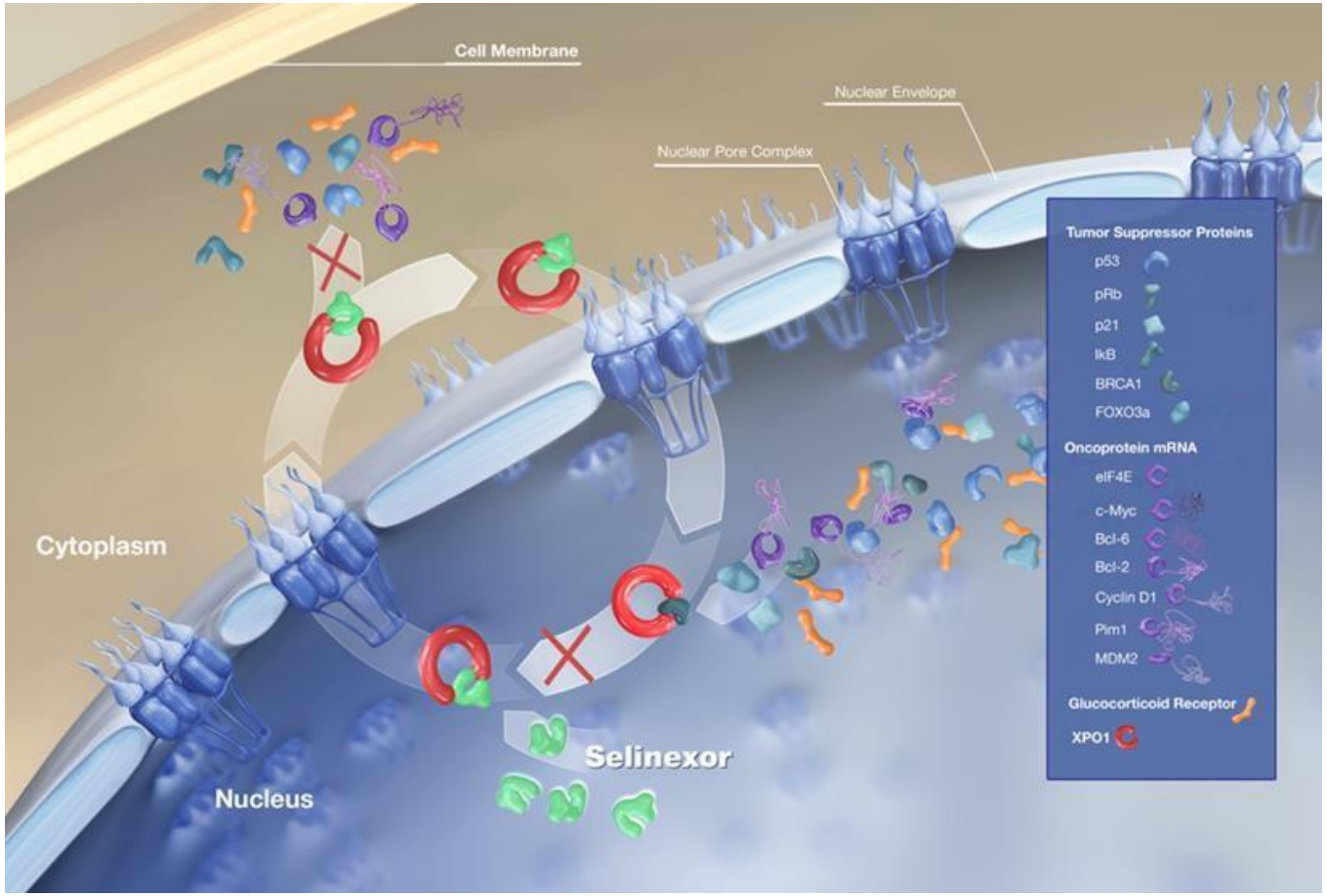
Total adavosertib 300 mg qd (N=109)	Number of patients (%)				
	Grade 2	Grade 3	Grade 4	Grade 5	All
Neutropenia	1 (0.9)	0	7 (6.4)	0	8 (7.3)
Sepsis	0	0	4 (3.7)*	1 (0.9)	5 (4.6)
Vomiting	1 (0.9)	3 (2.8)	0	0	4 (3.7)
Diarrhea	0	3 (2.8)	0	0	3 (2.8)

……while Wee1 inhibition results in antitumor activity and may remain a viable treatment target, the therapeutic window for adavosertib is narrow

Treatment-related serious adverse events recorded in ≥2% of patients are shown
*One patient had sepsis that was not associated with neutropenia/neutrophil count decrease
qd, once daily

P53: the other face of the coin

Selinexor: XPO1 inhibition



Exportin 1 (XPO1) is the major nuclear export protein for:[1]

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, PTEN, and FOXO1)

Inhibition of XPO1 results in:[1]

- The increase in nuclear levels and activation of TSPs
- Reduction of oncoprotein levels

Selinexor is an oral selective XPO1 inhibitor

Preclinical data for selinexor:[2]

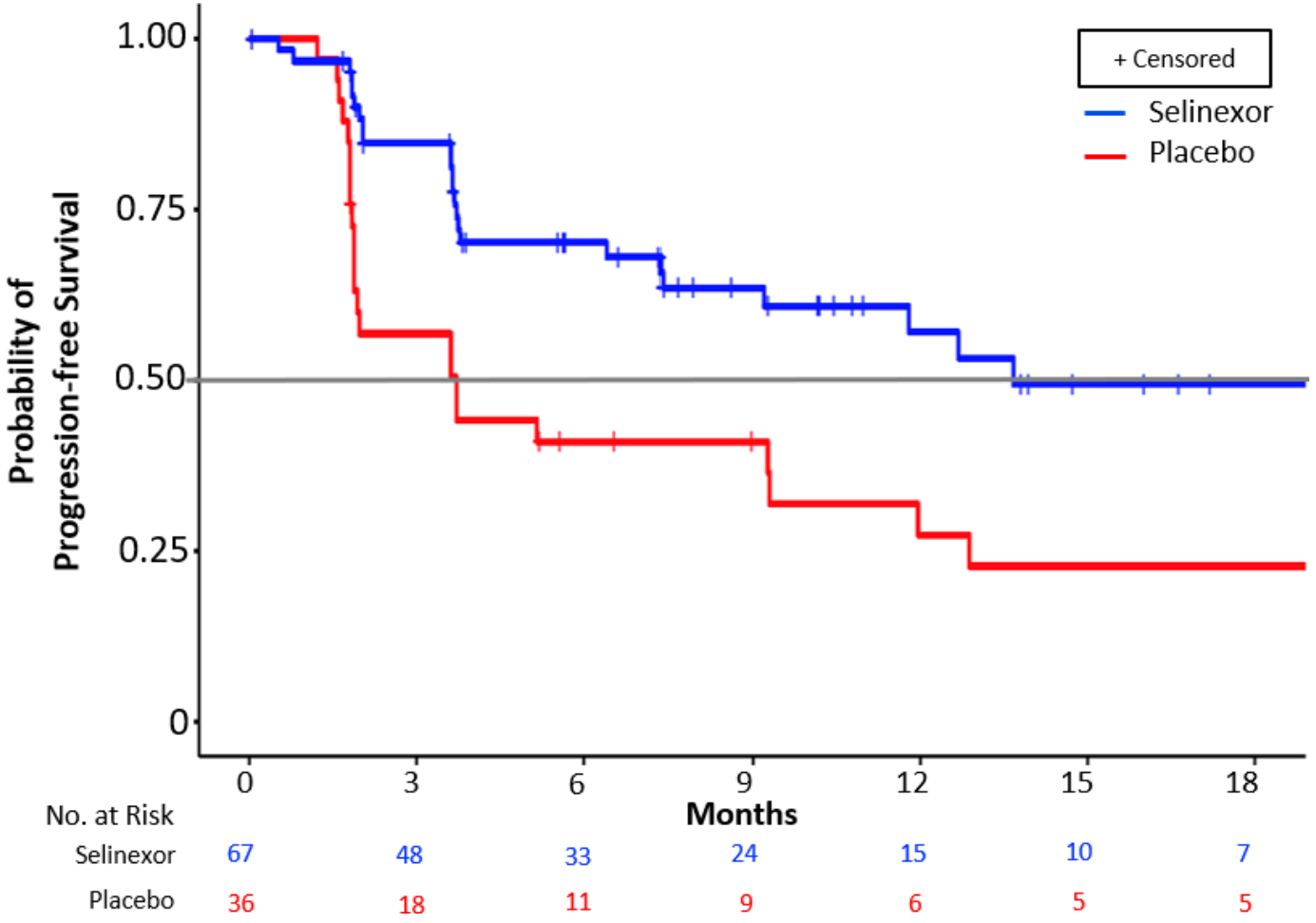
- Reactivates multiple TSPs, including p53 wild type, by preventing nuclear export

1. Fung HY, Chook YM. Atomic basis of CRM1-cargo recognition, release and inhibition. Semin Cancer Biol. 2014;27:52–61.
2. Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. Leukemia. 2014;28(1):155–165.

ENGOT-EN5/GOG-3055/SIENDO

SUBGROUP PFS: PATIENTS WITH WILD TYPE p53 EC

(BASED ON AUDITED STRATIFICATION FACTORS)



Median PFS

Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

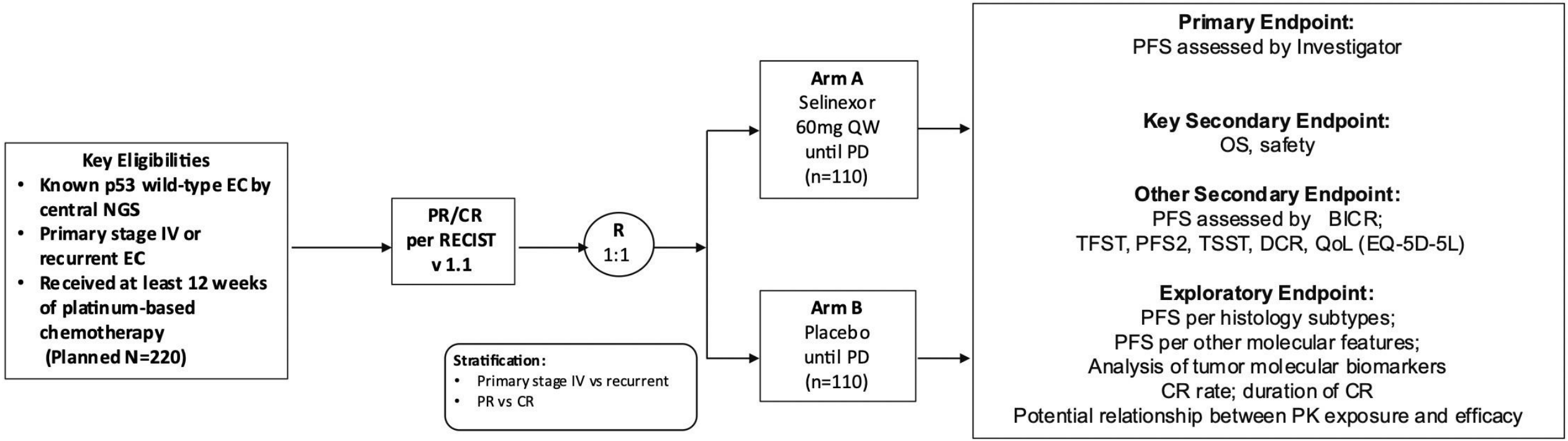
Placebo (n=36): 3.7 mo (95% CI 1.87-12.88)

HR (audited) = 0.375 (95% CI 0.210-0.670)

One-sided nominal P value = 0.0003

Vergote…..Mirza et al. SGO 2022

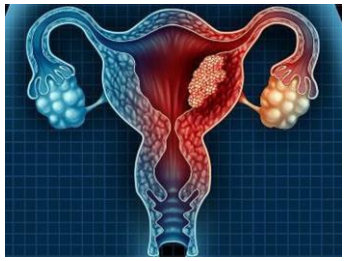
ENGOT-EN20 / XPORT



Vergote et al.

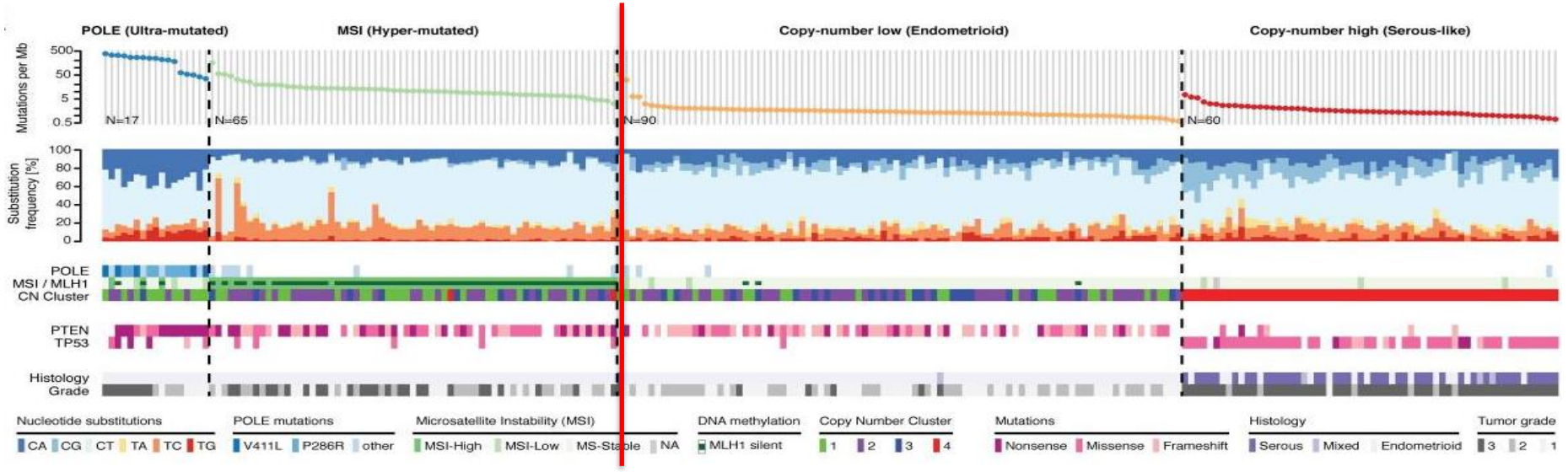
The perfect match : the prince

Endometrial carcinoma



Integrated Genomic Characterization of Endometrial Carcinoma

The Cancer Genome Atlas Research Network



Hot tumors

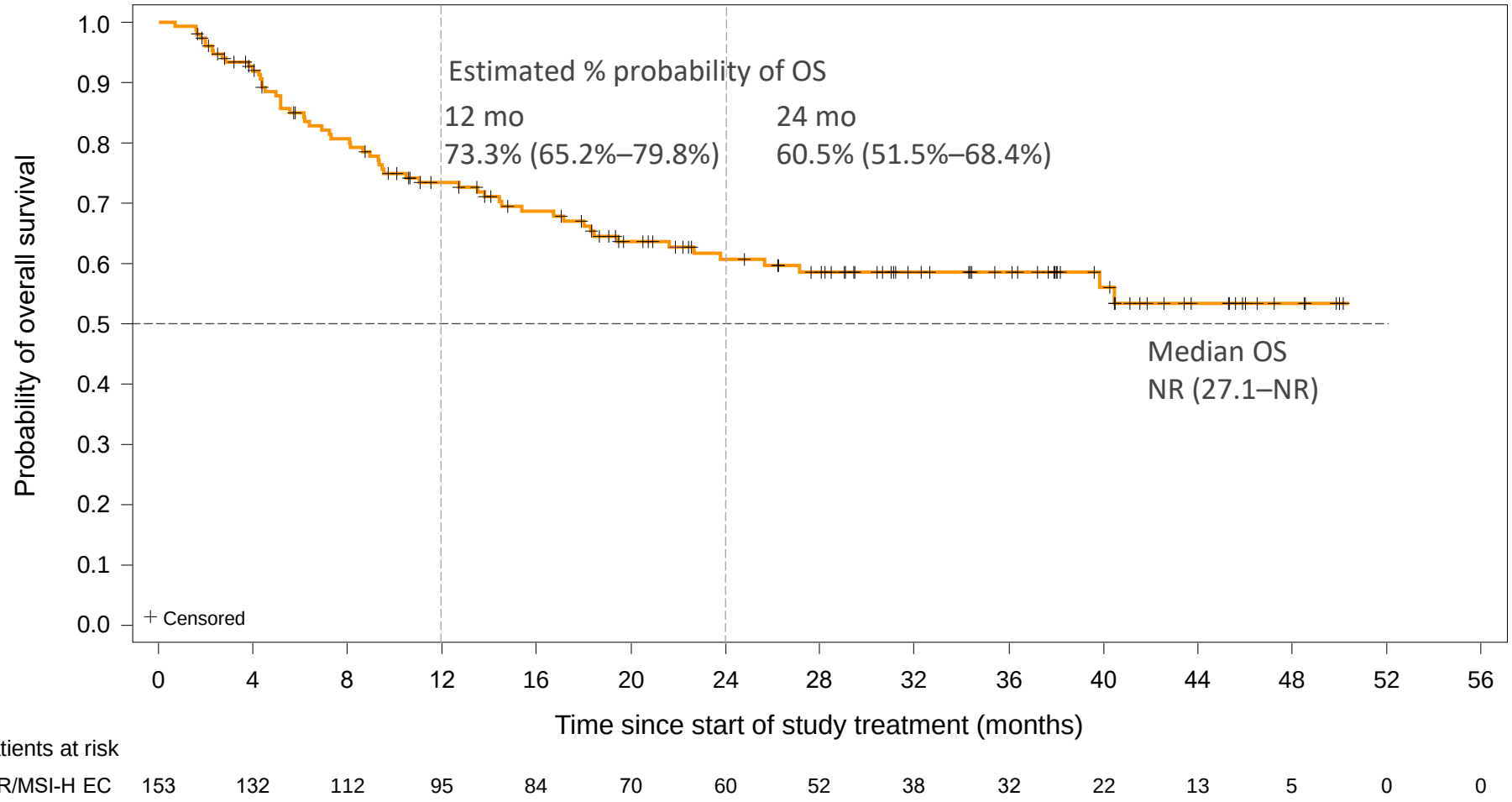
Good Response to Immunotherapy

Cold tumors

Poor Response to Immunotherapy

Nature. May 2,2013;497(7447): 67-73

Garnett study: ORR in dMMR: 45.5%
Probability of Survival: dMMR/MSI-H



Number of patients at risk

dMMR/MSI-H EC	153	132	112	95	84	70	60	52	38	32	22	13	5	0	0

dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability–high; NR, not reached; OS, overall survival.

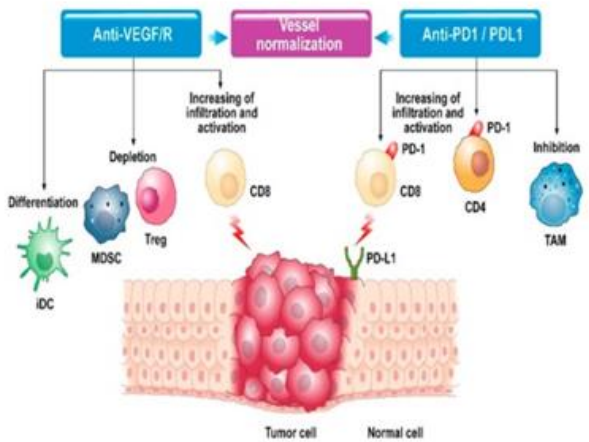
Ana Oaknin, ASCO 2022

Dancing with the prince will be enough to become princess ?

Combination Approaches: Leveraging ICI's Activity

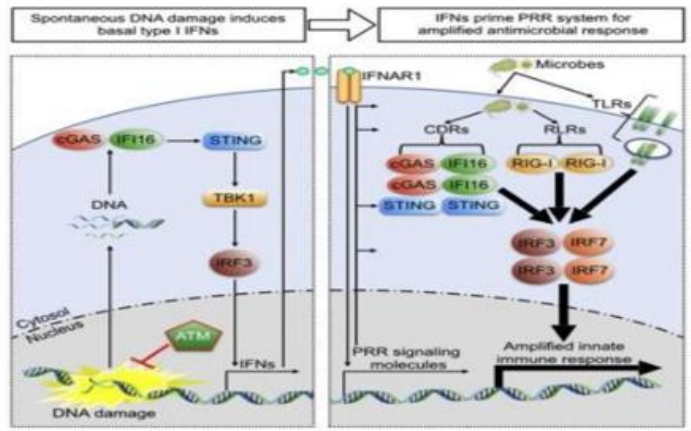
Antiangiogenic Agents

- Reduction in Treg activity
- Reversal of immunosuppressive effects of VEGF
- Improved T-cell trafficking and infiltration of CD8+ into the tumor bed



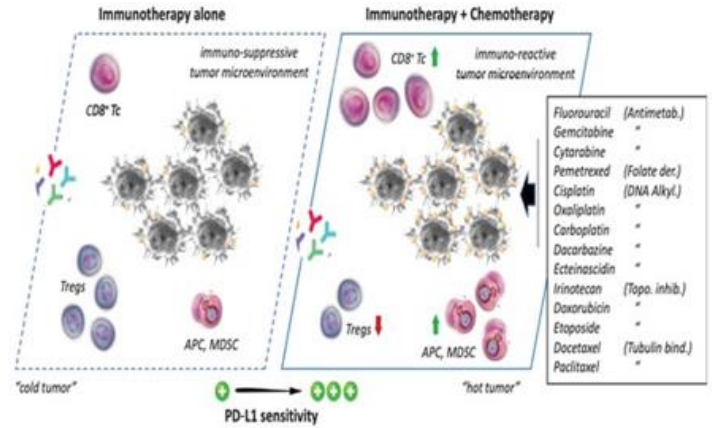
PARP inhibitors

- Enhanced DNA Damage with increased CD8+T Cells
- Potential Synergistic antitumor activity partly mediated by STING pathway



Chemotherapy

- Immunogenic cell death
- Enhanced presentation of tumor specific antigens
- Increased T-Cell activation by DC

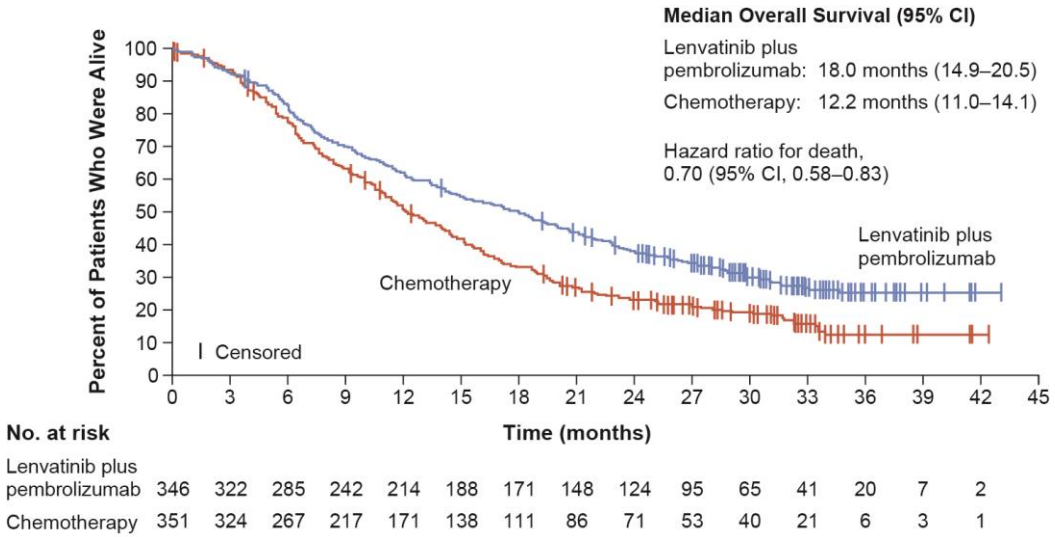


DC: Dendritic Cells
STING: Stimulator of Interferon Genes

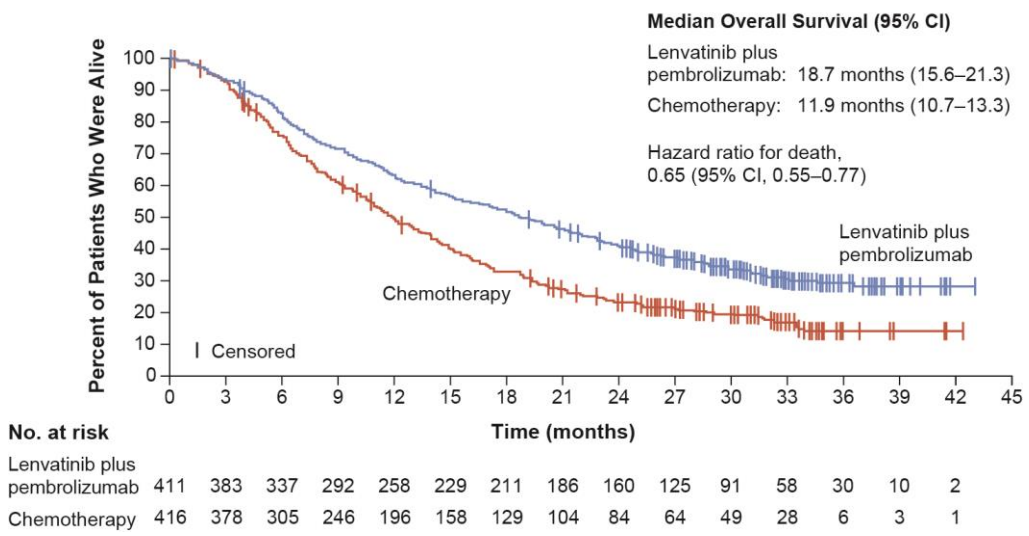
Ciciola P, et al. J Clin Med. 2020; Bailly C, et al. NAR Cancer. 2020;Huang J.,et al. *Biochem and Biophy Res Comm*. 2015; 463:551-6; Sen et al. Cancer Discov 2019

Continued OS benefit of lenvatinib plus pembrolizumab vs chemotherapy with follow-up extended by over 16 months

pMMR Population



All-Comer Population



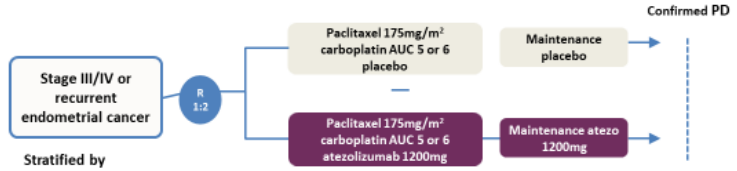
- OS favored lenvatinib plus pembrolizumab despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab.
- In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population received subsequent lenvatinib plus pembrolizumab.
- After excluding these pts, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71).

Vicky Makker, MD, ESMO 2022

Will Chemotherapy +ICIs replace chemotherapy alone in all comers?

A phase III double-blind randomised placebo-controlled trial of atezolizumab in combination with paclitaxel/carboplatin in women with advanced/ recurrent endometrial cancer: AtTEnd / ENGOT-en7/MaNGO

ENGOT-en7/MaNGO/AtTEnd



Recruiting

Stratified by
- Prior RT
- Recurrent disease
- MSI

Atezolizumab\Placebo will be administered:
- as I.V. infusion **every 21 days**
- until **progression confirmed at least 4 weeks after the first evidence of progression**

FPI: October 2018
LPI: Q4 2020

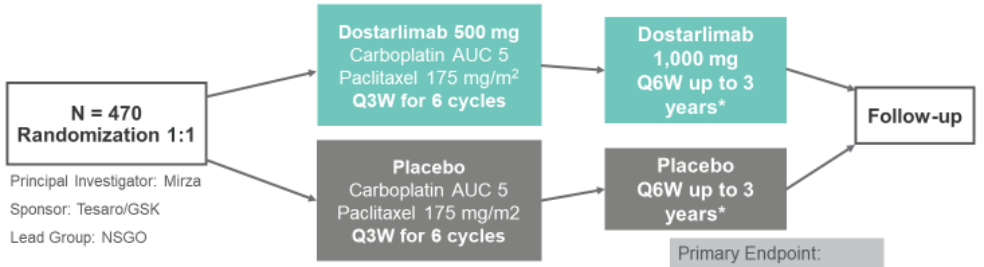
Primary Endpoint: OS and PFS
Secondary Endpoints: PFS in MSI, PFS2, RR, QoL, safety
Translational Endpoints: PD1, PDL1, TILs, blood based biomarkers
Study Duration: accrual 2 years; **Follow-up**: 2 years

ClinicalTrials.gov : NCT03603184
Global ENGOT PI on behalf of MaNGO: Nicoletta Colombo MD

ENGOT-EN6/NSGO-RUBY

Eligible Subjects
Recurrent or primary advanced (stage III or IV) endometrial cancer or first recurrent endometrial cancer with a low potential for cure by radiotherapy or surgery alone or in combination

Stratification:
- Microsatellite instability (MSI) status – MSI-high (MSI-H) or microsatellite stable [MSS]),
- Prior external pelvic radiotherapy (yes or no), and
- Disease status (recurrent, primary stage III, or primary stage IV).



Principal Investigator: Mirza
Sponsor: Tesaro/GSK
Lead Group: NSGO

*Treatment ends after 3 years, progression of disease, toxicity, withdrawal of consent, Investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the sponsor and the investigator.

Primary Endpoint:
- PFS (RECIST 1.1)

ClinicalTrials.gov: NCT03981796 (RUBY)

NRG-GY018: Randomized, phase 2/3 study of carboplatin + paclitaxel vs. carboplatin + paclitaxel + pembrolizumab in patients with advanced stage or recurrent endometrial cancer

- Stage 3/4 or recurrent endometrial cancer (stage 3 or 4A: measurable disease; stage 4B or recurrent whether there is measurable disease or not)
- Patients may have received prior radiation therapy or hormonal therapy
- Patients in whom both radiation and chemotherapy are planned must receive radiation prior to entry on study

R

Carboplatin/Paclitaxel + **placebo**

N=590 MMRp patients
N=185 dMMR patients

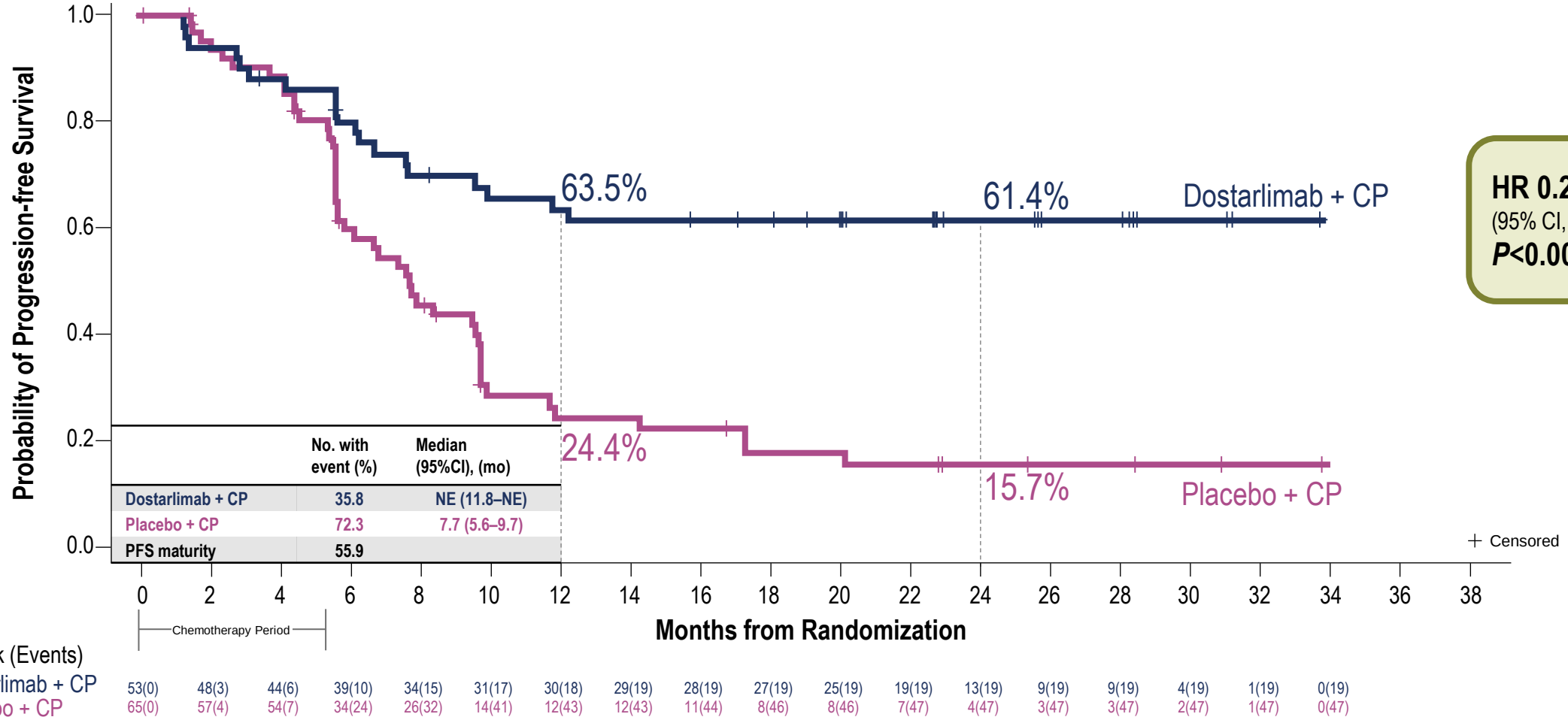
Carboplatin/Paclitaxel + pembrolizumab + maintenance pembrolizumab x 12 months

Stratified by: MMR-proficient (MMRp) vs. deficient MMR (dMMR), performance status, measurable disease

Primary Endpoint:
- PFS

dMMR, deficient mismatch repair, MMRp, mismatch repair proficient. ClinicalTrials.gov: NCT03914612 (NRG-GY018)

RUBY PRIMARY ENDPOINT: PFS IN dMMR/MSI-H POPULATION



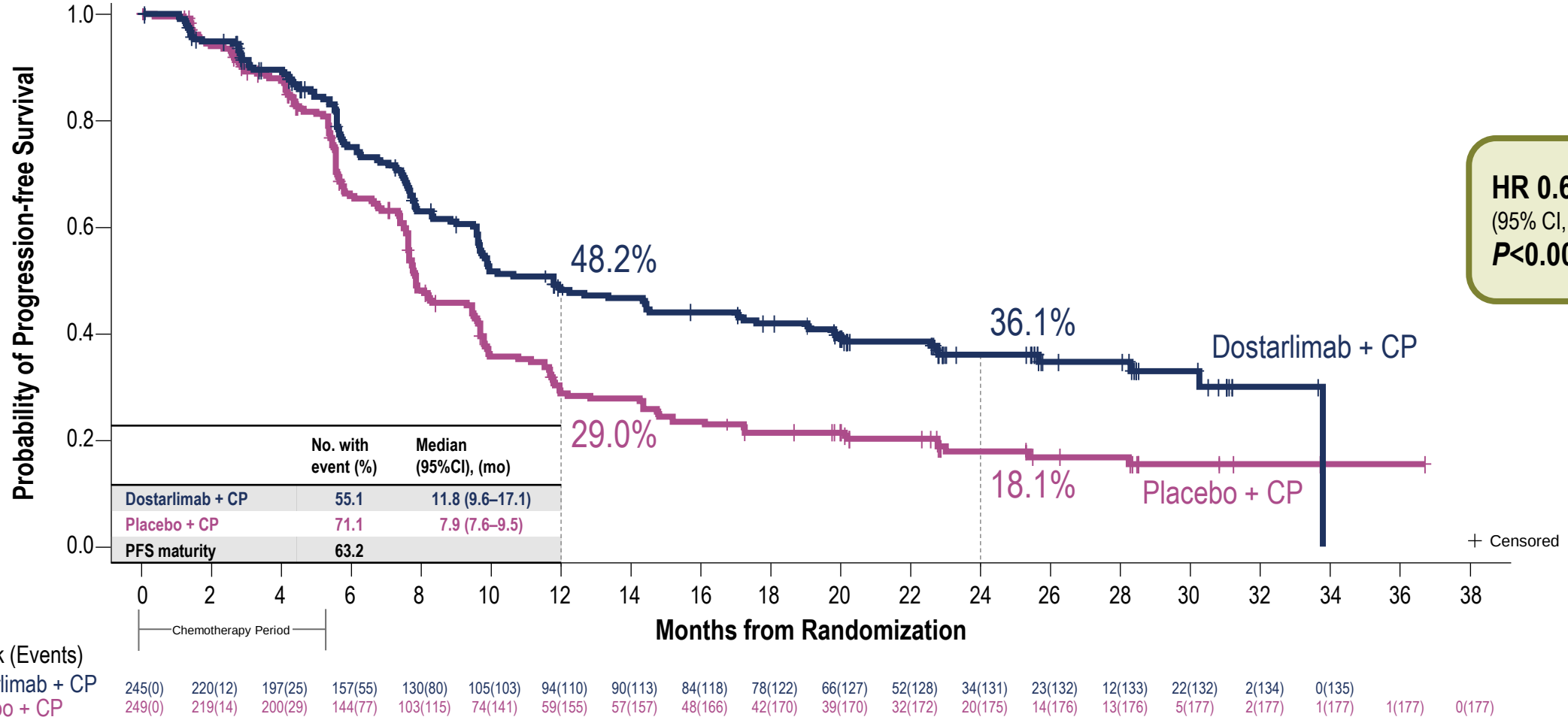
HR 0.28
(95% CI, 0.162–0.495)
***P*<0.0001**

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival.

Median duration of follow-up 24.79 months.

ENGOT-EN6-NSGO/GOG-3031/RUBY presented by Mansoor R Mirza at SGO 2023
NEJM 2023

RUBY PRIMARY ENDPOINT: PFS IN OVERALL POPULATION



HR 0.64
(95% CI, 0.507–0.800)
***P*<0.0001**

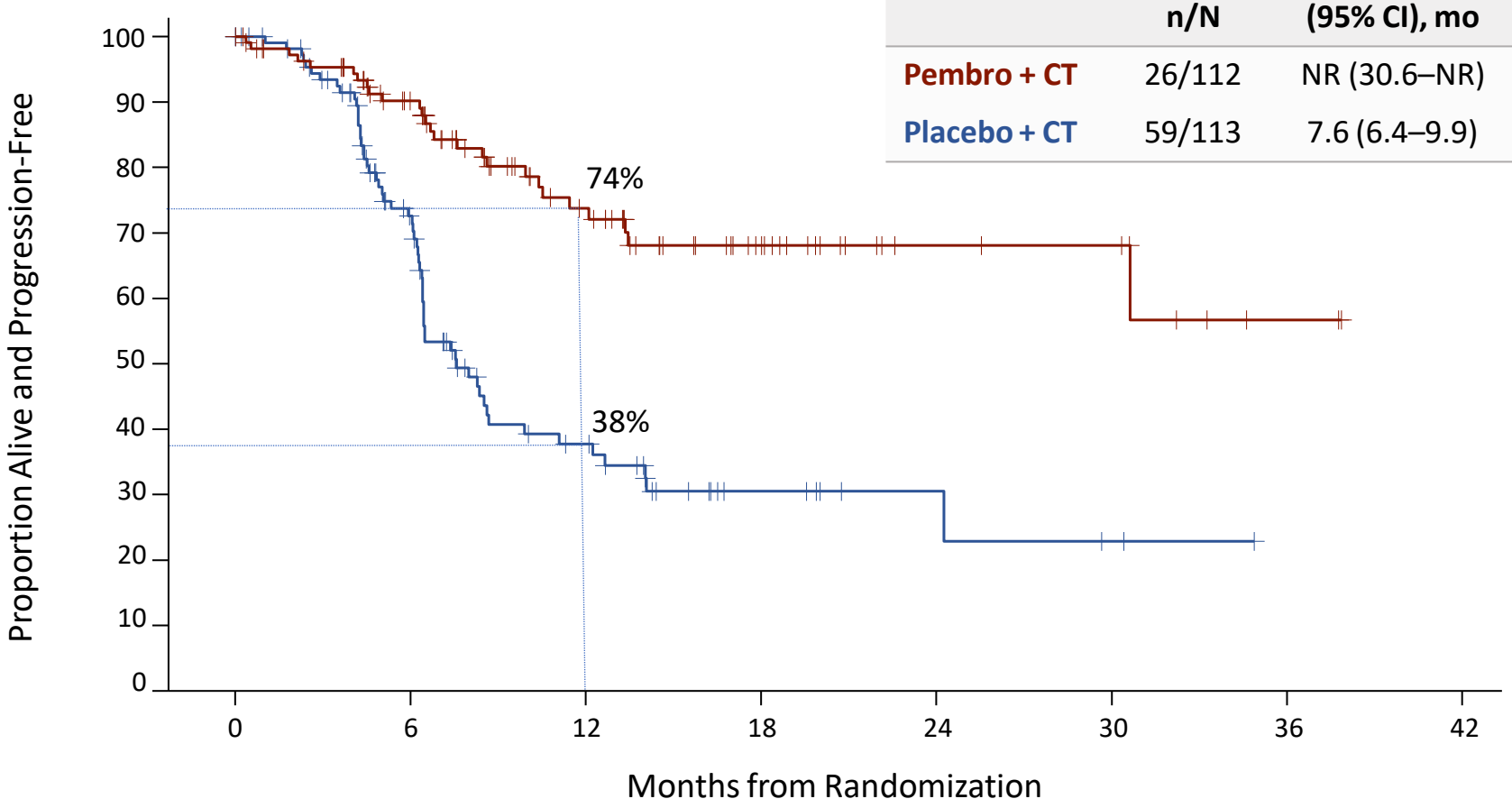
CP, carboplatin/paclitaxel; HR, hazard ratio; PFS, progression-free survival.

Median duration of follow-up 25.38 months.

ENGOT-EN6-NSGO/GOG-3031/RUBY presented by Mansoor R Mirza at SGO 2023
NEJM 2023

NRG-GY018 (NCT03914612)
PFS per RECIST v1.1: dMMR Population

	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	26/112	NR (30.6–NR)	**0.30 (0.19–0.48)**
Placebo + CT	59/113	7.6 (6.4–9.9)	***P* = <0.00001**



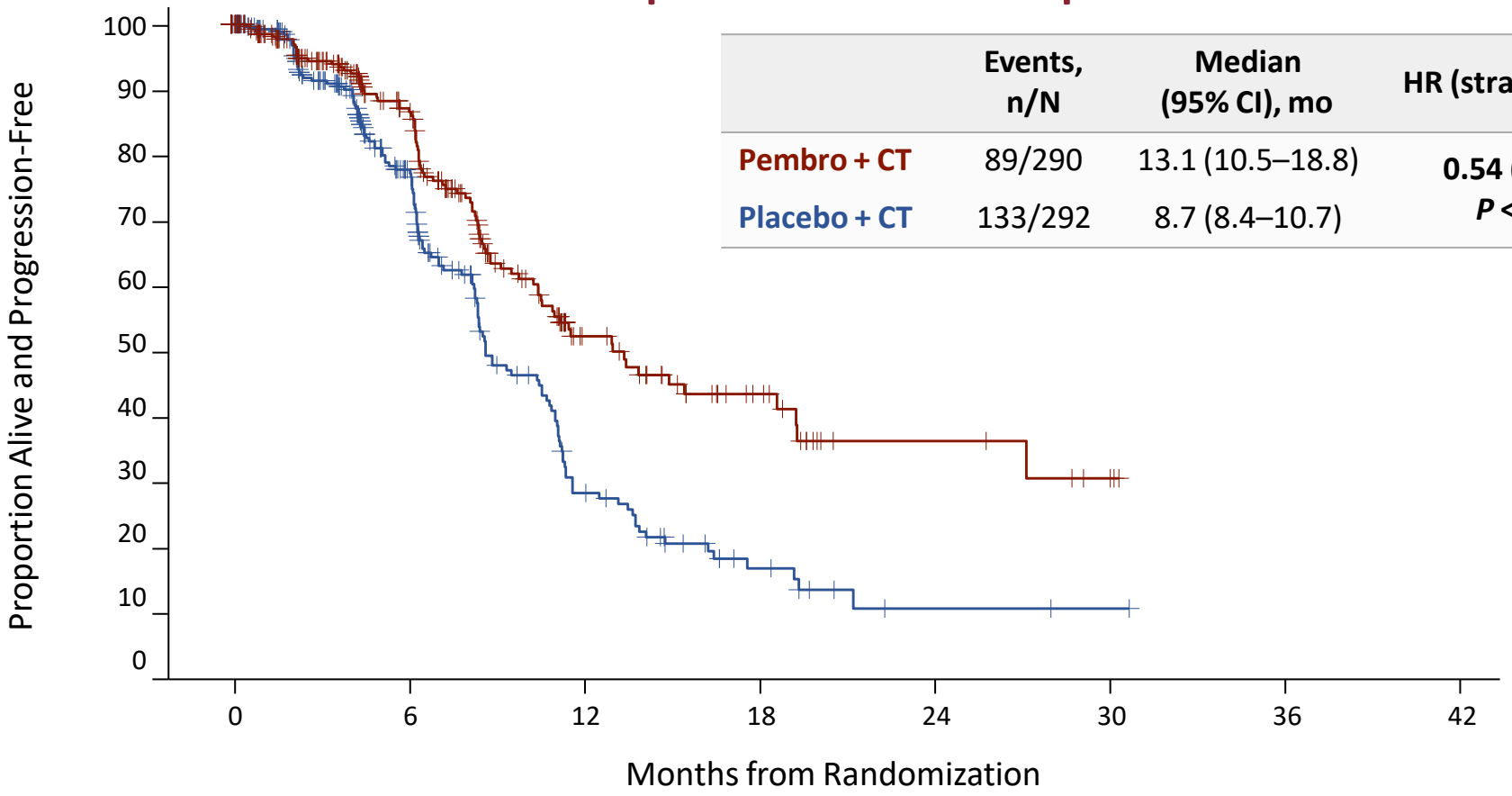
Number at Risk (Cumulative number censored)

Placebo + CT	113 (2)	62 (24)	24 (35)	8 (47)	4 (51)	2 (52)	0 (54)	
Pembro + CT	112 (1)	80 (22)	44 (46)	22 (65)	9 (78)	8 (79)	2 (84)	0 (86)

Eskander, SGO 2023; NEJM 2023

Data cutoff date: December 16, 2022.

NRG-GY018 (NCT03914612)
PFS per RECIST v1.1: pMMR Population



	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	89/290	13.1 (10.5–18.8)	**0.54 (0.41–0.71)**
Placebo + CT	133/292	8.7 (8.4–10.7)	***P* < 0.00001**

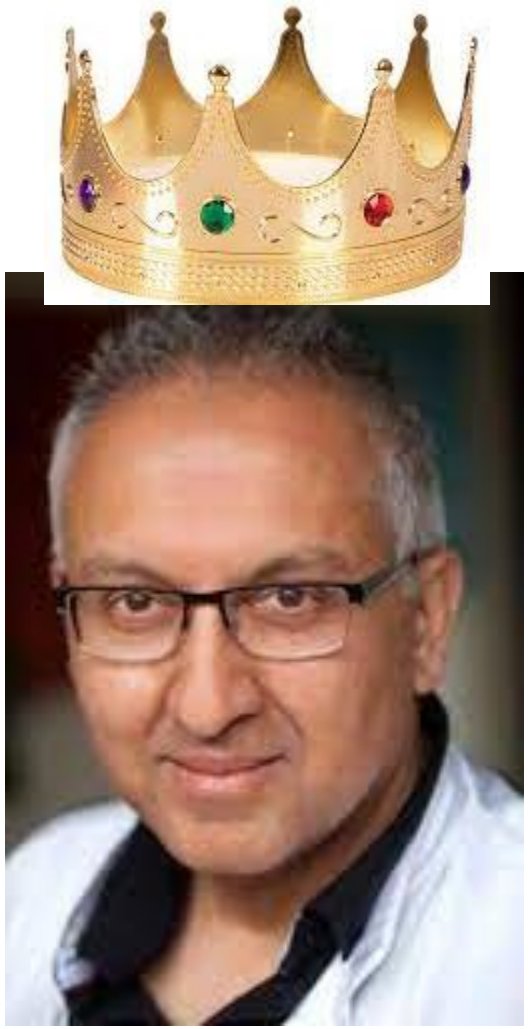
Number at Risk (Cumulative number censored)

Placebo + CT	292 (14)	129 (115)	33 (141)	10 (152)	2 (157)	1 (158)	0 (159)
Pembro + CT	290 (15)	150 (112)	45 (167)	20 (185)	7 (195)	3 (198)	0 (201)

Eskander, SGO 2023; NEJM 2023

Yes, Cinderella has become a princess !!!!

Endometrial cancer has become a princess because encountered not one but two princes



Will Cinderella(endometrial cancer) become a queen?

Endometrial Cancer: when will it become queen?

1. Role of immunotherapy in the early setting (neoadjuvant/ adjuvant setting)?
2. WILL ICIs replace chemotherapy in the front line setting of dMMR EC ?
3. Will Chemotherapy +ICIs replace chemotherapy alone in p-MMR?
4. Will pembrolizumab-Lenvatinib replace chemotherapy in front line? (For all, only for MSS?)
5. Will the addition of PARP-inhibitors improve outcome?
6. How to identify the bad d-MMR and the good pMMR ?
7. New drugs/ combinations for pMMR?
8. How to treat after ICI failure?

By the way….

Cinderella became a queen in her live-action remake.
This is due to the fact that it was evidently shown that the throne was passed to Charming after his father died, and Cinderella married him as King.