Nicole Concin

- Targeting p53wt

Targeting p53 wild-type

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DISCLOSURE INFORMATION

Nicole Concin

Consulting/Advisory: ImmunoGen, Seagen, Akesobio, Ensai, GSK, AstraZeneca, Mersana, Seattle Genetics, Kartos eTheRNA immunotherapies NV

Travel Expenses: Roche, Genmab, Amgen

Educational fees: Kartos, MSD, Medscape Oncology, TouchIME

Functions in societies:

President of ESGO

Chair of ENGOT Early Drug Development Network

p53 „Guardian of the Genome“

Sir David P. Lane
Nature 1992

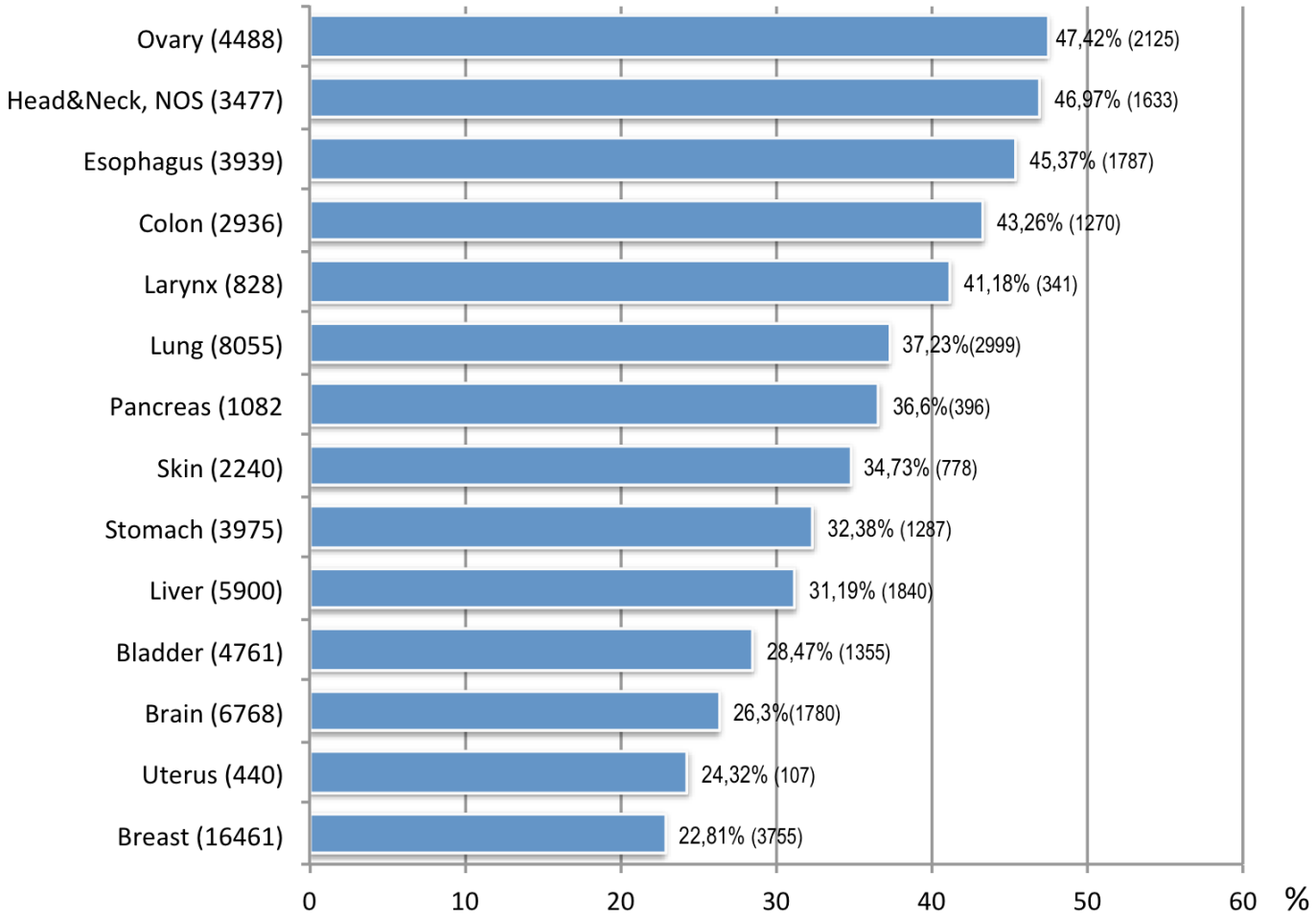
p53 protein = transcription factor

DNA damage
→ **accumulation of** normal **p53 protein**
→ **cell cyle arrest or apoptosis**

Levine, Cell 1997

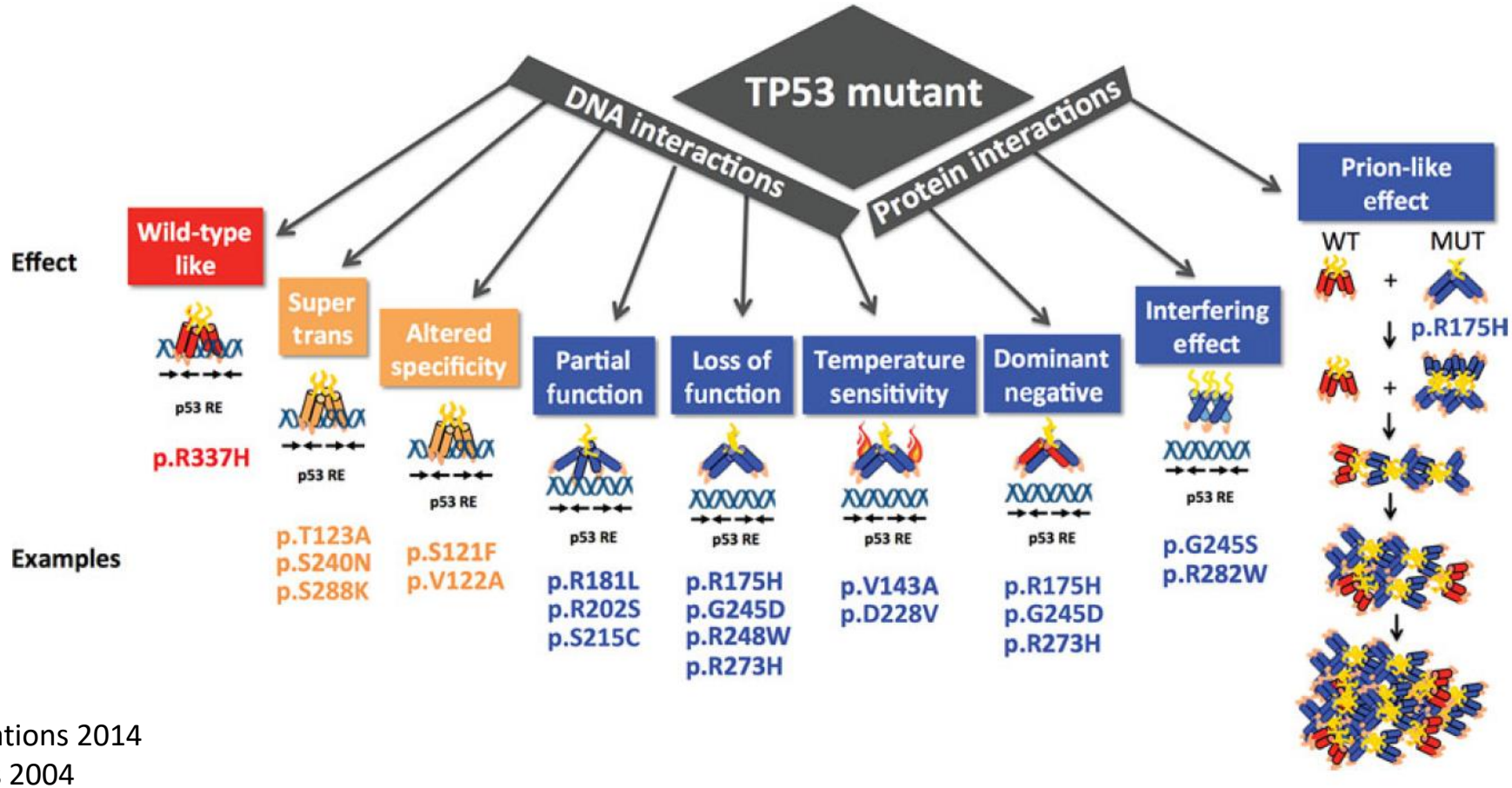
Protective function!

Prevalence of *TP53* mutations



IACR TP53 Database (http://p53.iarc.fr), November 2012
Petitjean et al, Hum Mutat. 28(6):622-9, 2007

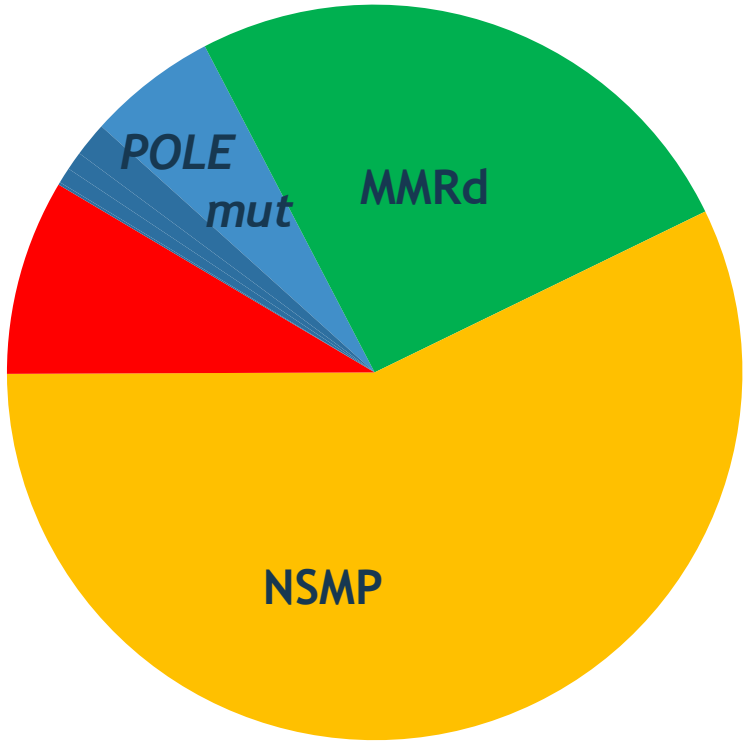
p53 Mutants in the Tower of Babel of Cancer Progression



Levine, Oncogene 2021
Bisio et al. Human Mutations 2014
Concin et al, Cancer Res 2004
Concin, Hofstetter et al Clinical Cancer Res, 2005
Concin et al, Brest Cancer Res Treat 2003

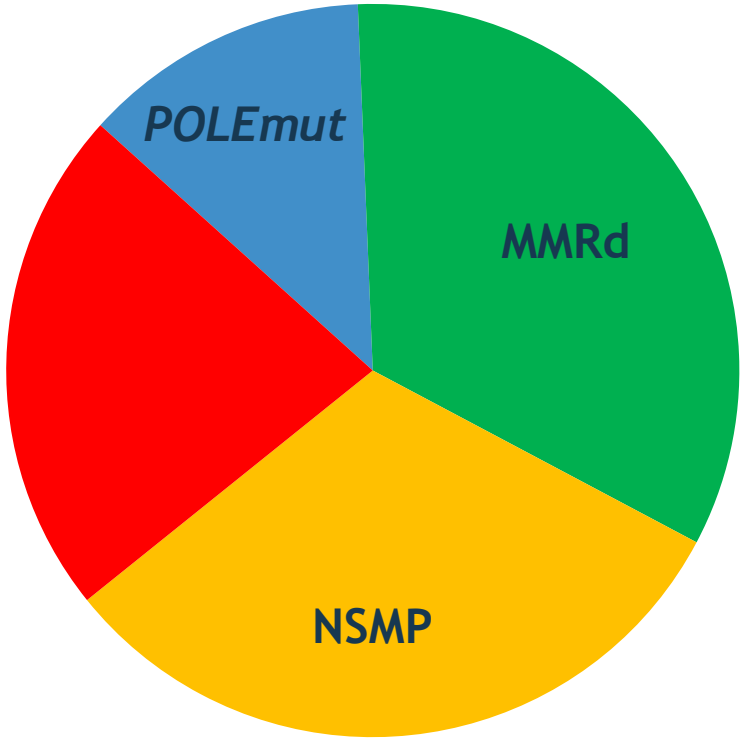
Prevalence of p53 alterations in Endometrial Carcinoma

PORTEC-1 and-2 cohorts
N=861



9% p53abn

PORTEC-3 high risk cohort
N=410



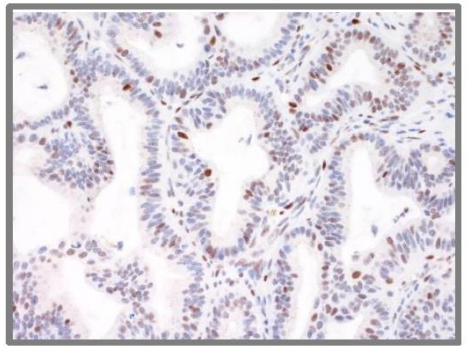
22% p53abn

Stelloo et al, Clinical Cancer Research 2016; Leon-Castillo et al, JCO 2020

p53 Immunohistochemistry (IHC) as surrogate marker for *TP53* mutational status

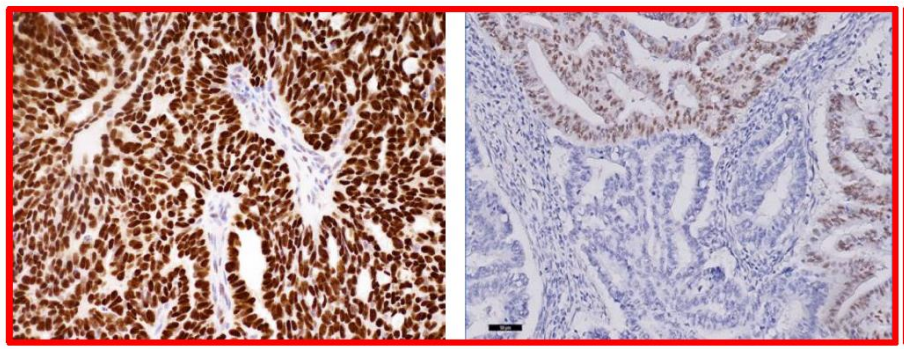
Normal p53-IHC

Scattered expression

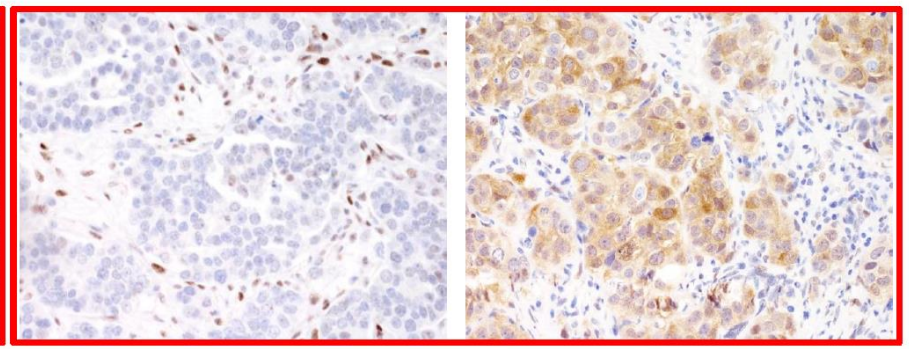


Abnormal p53-IHC (p53abn)

(subclonal) overexpression



Loss of nuclear expression



		p53-IHC central					
		Normal	Overexpression	Absence	Cytopl	Subclonal	TOTAL
P53-IHC local	Normal	**68**	0	0	0	0	69
	Overexpression	1	**69**	0	1	0	72
	Absence	0	0	**14**	0	0	14
	Cytoplasmic	0	0	0	**1**	0	1
	Subclonal	1	0	0	0	**4**	5
	TOTAL	71	69	14	3	6	**164**

		TP53 mutation	
		Present	Absent
p53-IHC	Abnormal	**85**	4
	Normal	2	**32**
Sensitivity: 97.70% (95% CI 91.94% to 99.7%)			
Specificity: 88.89% (95% CI 73.94% to 96.89%)			
Accuracy: 95.12% (95% CI 89.68% to 98.19%)			

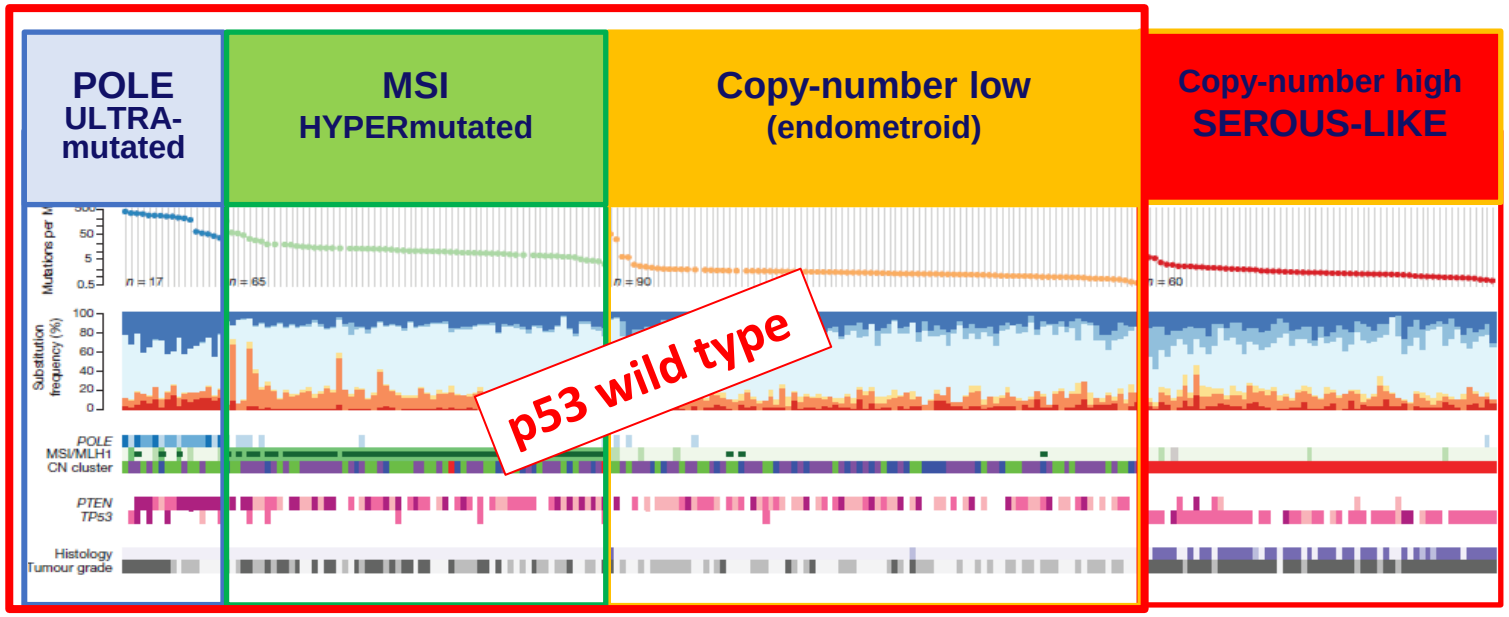
p53 IHC interpretation is reproducible, and an excellent surrogate marker for *TP53* mutations in EC with 95% accuracy

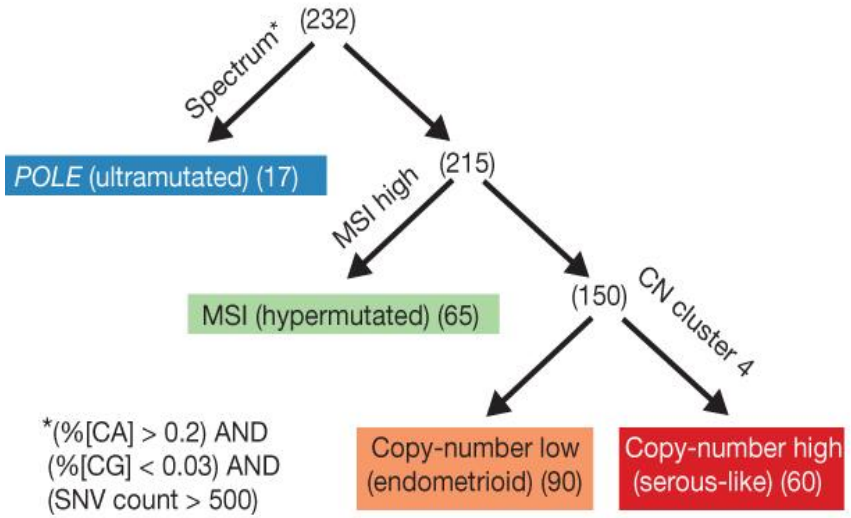
Singh et al, Journal of Pathology 2019

WHAT IS THE PATIENT-COHORT
- p53 wild-type?

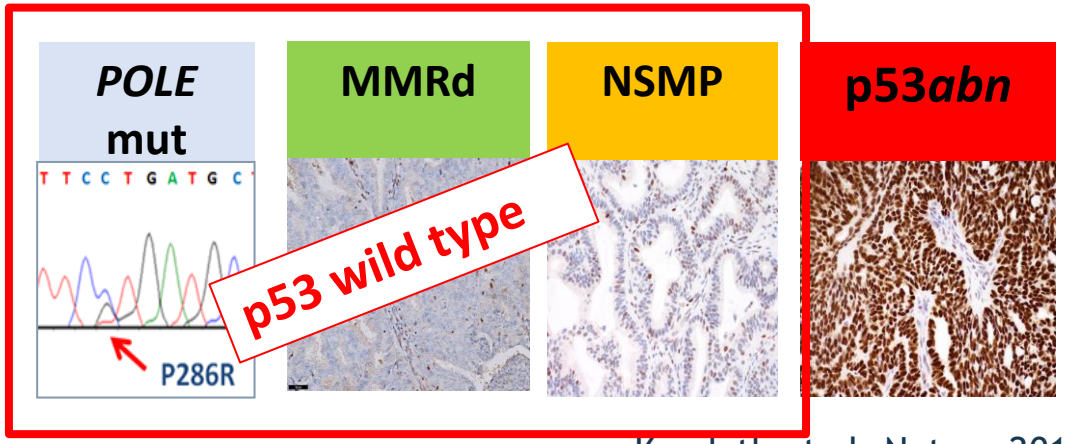
WHAT ARE THE DRUGS (experimental)
targeting p53 wild-type?

What The Cancer Genom Atlas (TCGA) has taught us?





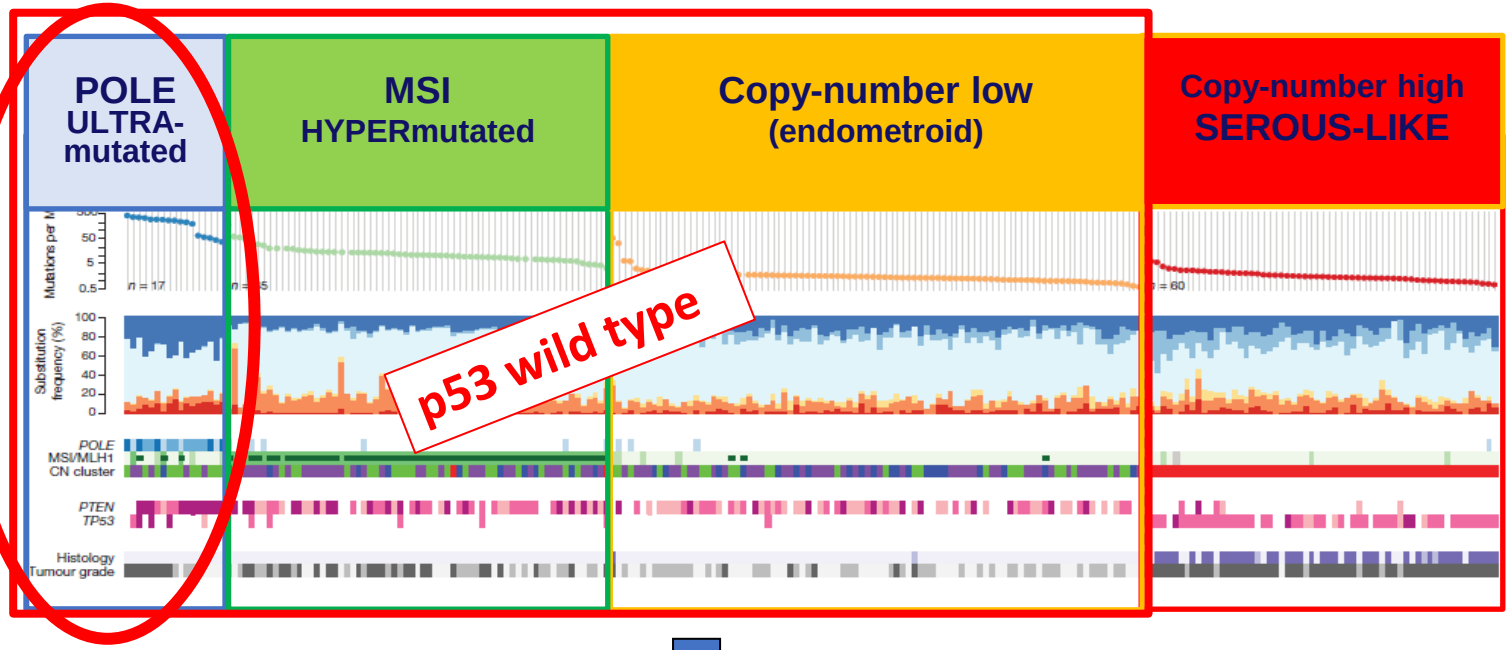
surrogate

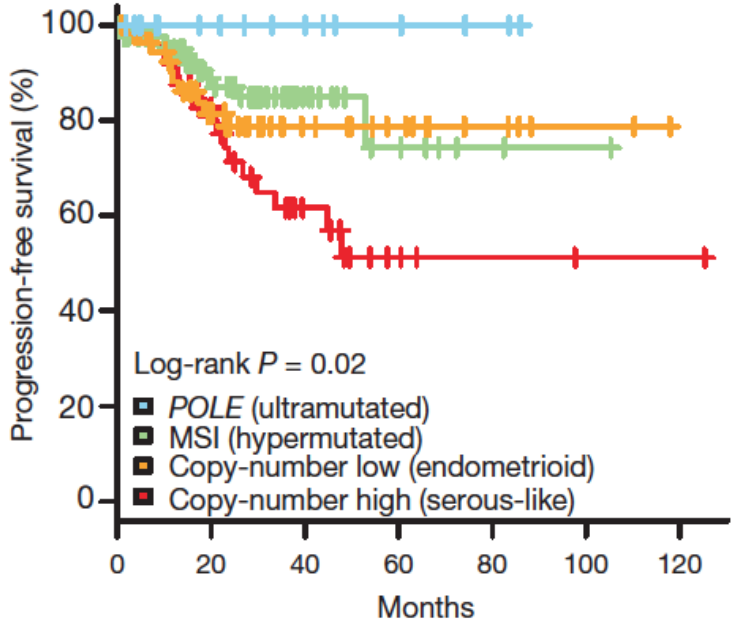


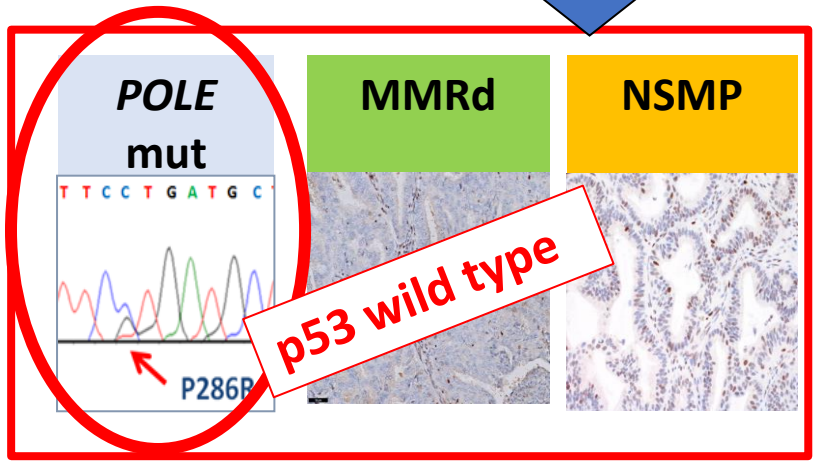
p53 wild-type carcinoma comprises of 3 molecular subtypes

Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

p53 wilde-type: *POLEmut*







***POLE* mutated EC:**

- Rare, 5-10% of ECs
- Excellent prognosis
- ULTRA-mutated

Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

p53 wild-type: *POLEmut*, early stage disease

ESGO-ESTRO-ESP Guidelines on Endometrial Cancer Management

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ,*]
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

For patients with endometrial carcinoma **stage I-II**, low-risk based on **pathogenic *POLE*-mutation**, **omission of adjuvant treatment should be considered** [**III, A**].

Concin N et al, Int J Gynecol Cancer 2021; Radiother Oncol 2021; Virchows Arch 2021

New FIGO staging 2023 Endometrial Cancer

Molecular Finding in early endometrial cancer patients (Stages I & II after surgically staging+)
POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type

StageIAm$_{POLEmut}$

manuscirpt in press
Berek J…. Concin N, Int J Gynecol Obstet 2023

p53 wild-type: *POLE*mut, advanced stage/recurrent

→ Generate ULTRA-mutated EC

→ Predictive biomarker for benefit of PDL1/PD1 inhibition in endometrial carcinoma

Cancer Therapy: Clinical

Clinical Cancer Research

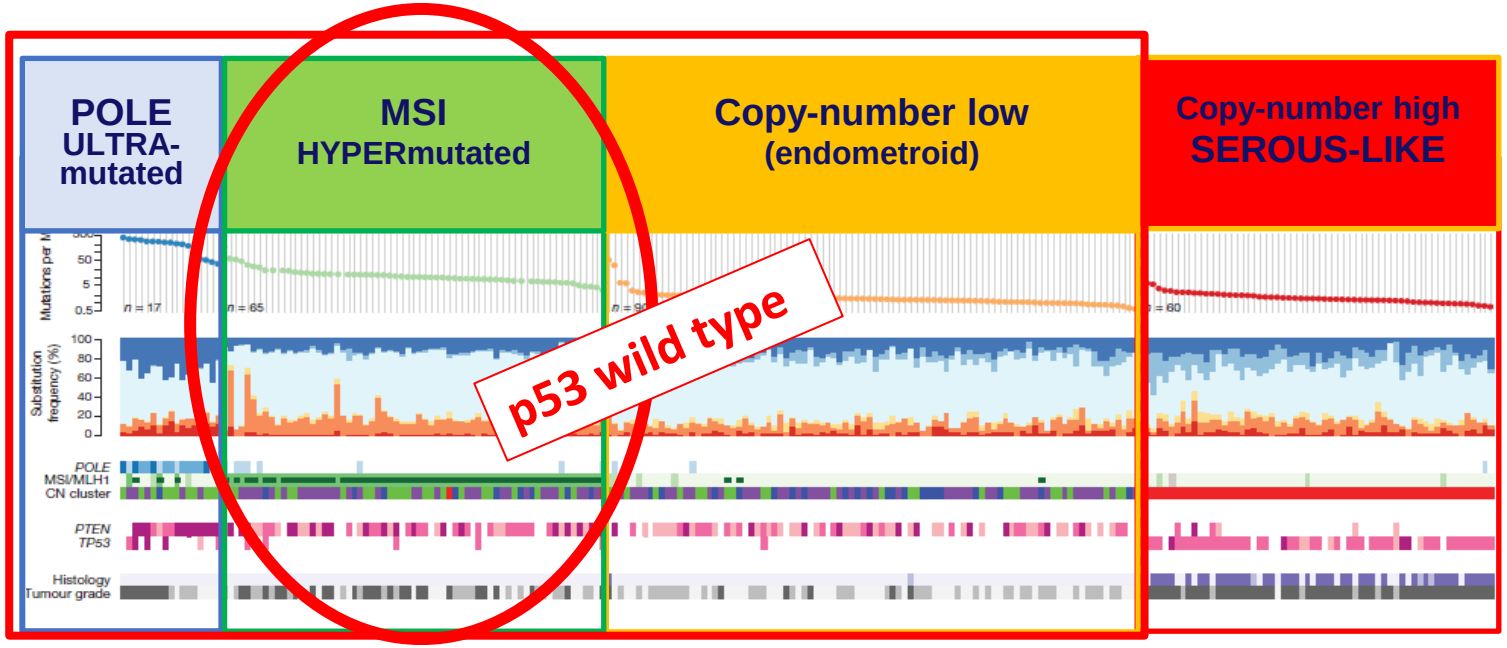
Regression of Chemotherapy-Resistant Polymerase ε (POLE) Ultra-Mutated and MSH6 Hyper-Mutated Endometrial Tumors with Nivolumab

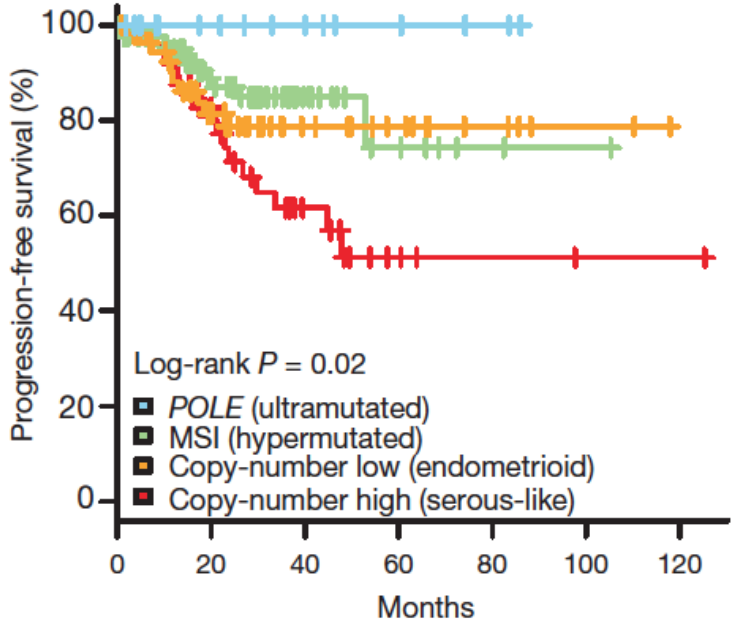
Alessandro D. Santin[1], Stefania Bellone[1], Natalia Buza[2], Jungmin Choi[3], Peter E. Schwartz[1], Joseph Schlessinger[4], and Richard P. Lifton[3]

JCI The Journal of Clinical Investigation

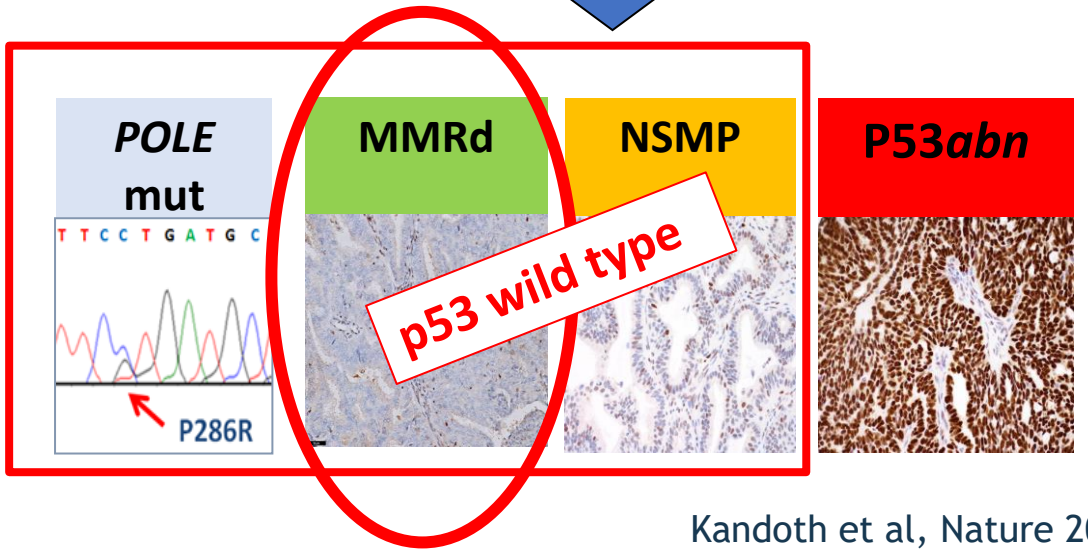
Immune activation and response to pembrolizumab in *POLE*-mutant endometrial cancer

p53 wild-type: MMRd





surrogate



MSI EC:

- more frequent: 20-30% of ECs
- poorer prognosis
- HYPER mutated

Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

p53 wild-type: MMRd

Evidence in ≥ second line endometrial cancer: Phase 1/2

MONO-therapy	Trial	N	dMMR/MSI-H ORR, % (95% CI)	pMMR/MSS ORR, % (95% CI)	Ref
Pembrolizumab	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH		57 (42 - 71)	11 (6 – 19)	(1)
Dostarlimab	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH		44 (34 – 53)	14 (9 – 21)	(2)
Avelumab		31	27 (8 – 55)	6 (0 – 30)	(3)
Durvalumab	PHAEDRA	71	47 (32 – 63)	3 (1 – 15)	(4)

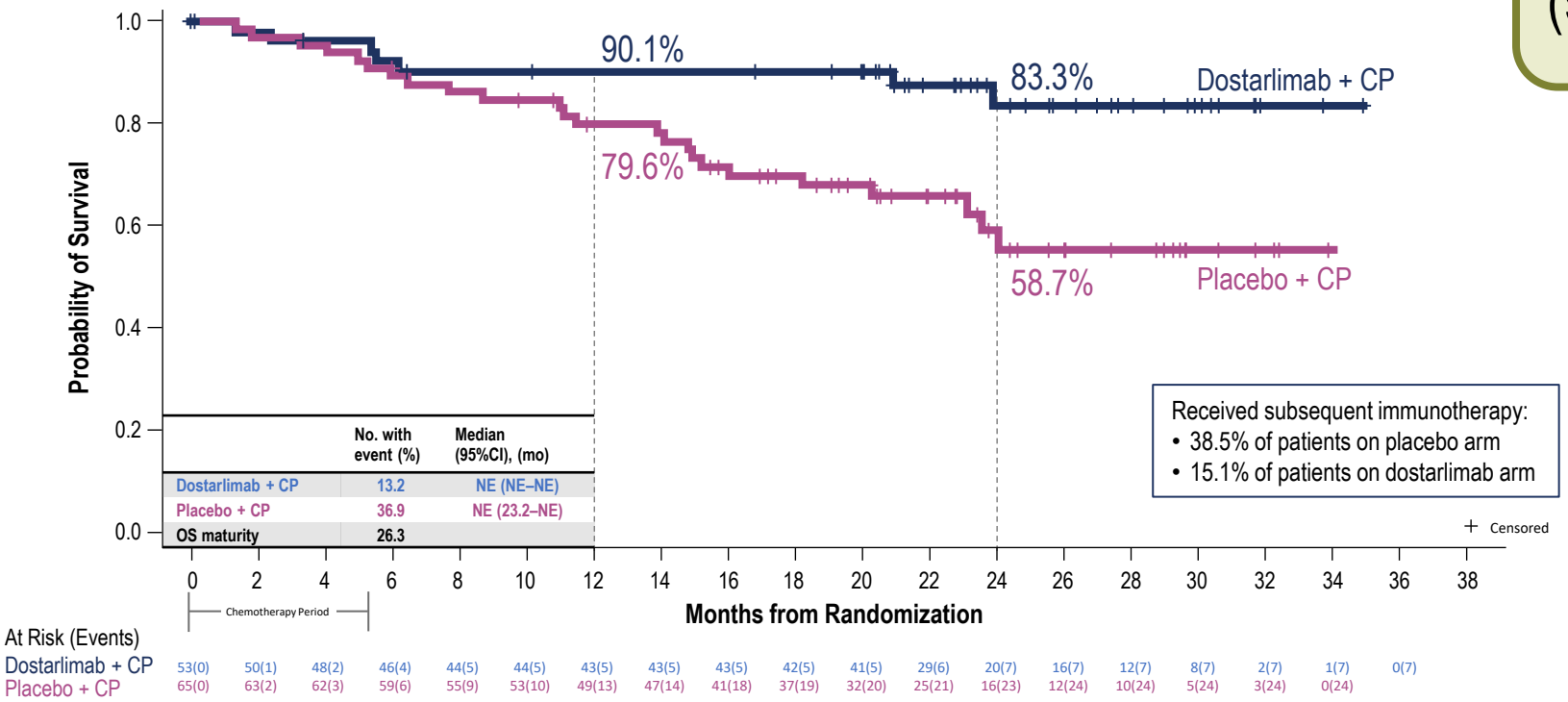
(1) O'Malley et al. ESMO 2019. Abstr 3394
(2) Oaknin A, et al. J Immunother Cancer. 2022 Jan;10(1):e003777
(3) Konstantinopoulos et al. JCO 37:2786-2794
(4) Antill et al. Journal for ImmunoTherapy of Cancer 2021;9:e002255

p53 wild-type: MMRd

First-line: RUBY/ENGOT-EN6/GOG-3031
OS per investigator assessment in dMMR/MSI-H

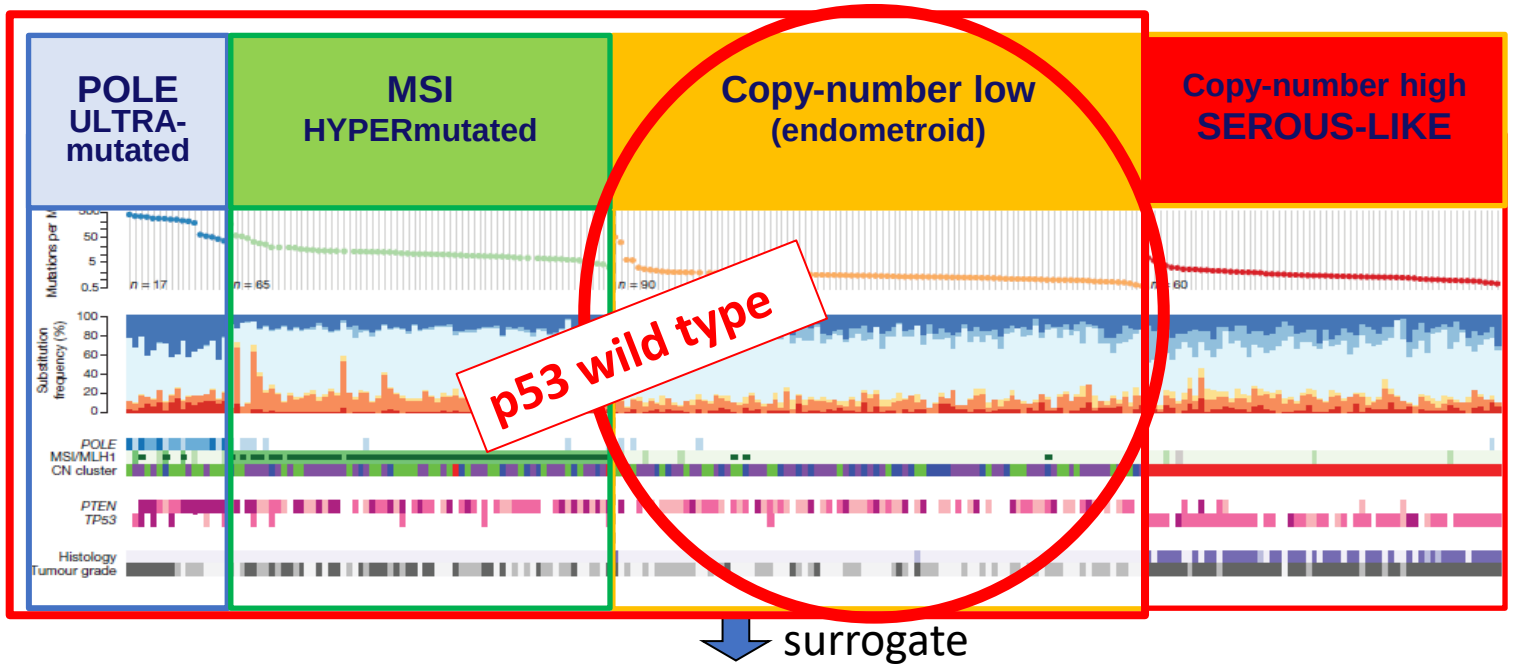
prespecified subgroup analysis

HR 0.30
(95% CI, 0.127–0.699)

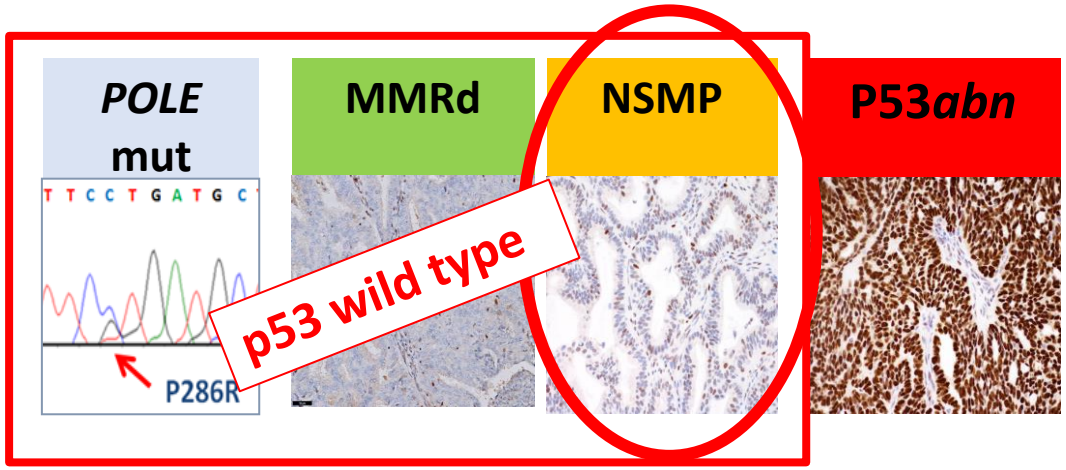


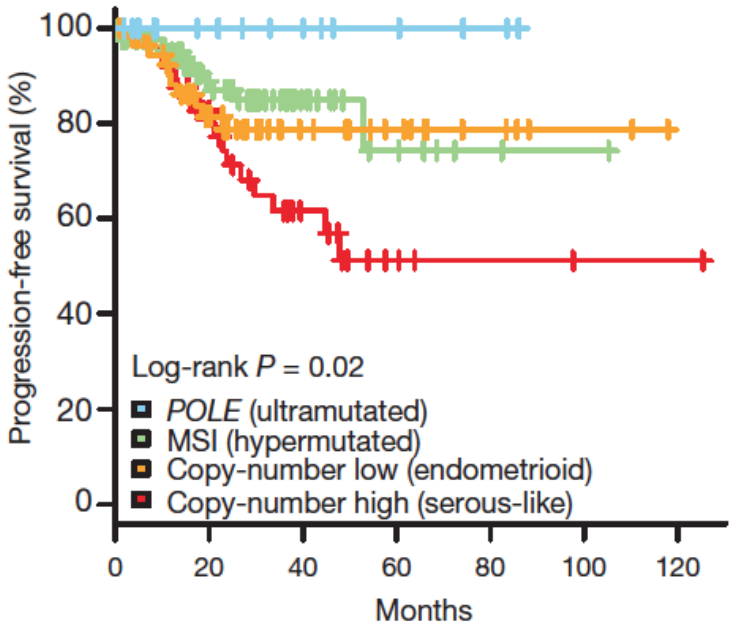
CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival.

p53 wild-type: NSMP



surrogate





- Overall EC: MAJORITY of ECs
  ca 35-50 %
- HETEROGENOUS group:
  histologically & molecularly & clinically

Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

Prognostic heterogeneity of NSMP

PROGNOSTIC RISK GROUPS integrating molecular markers

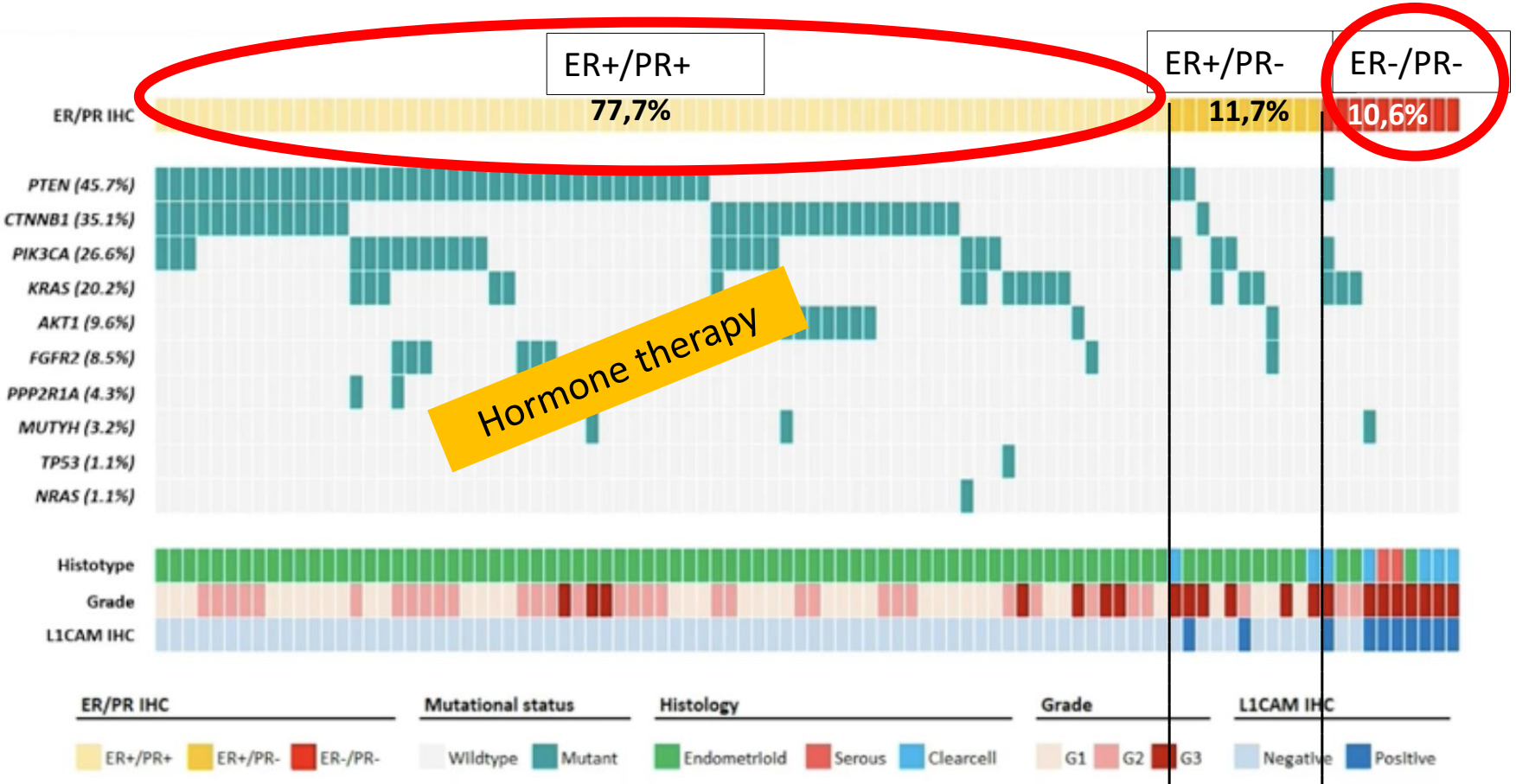
Risk group	Molecular classification unknown	Molecular classification known*†
Low	▶ Stage IA endometrioid + low-grade‡ + LVSI negative or focal	▶ Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ▶ Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	▶ 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

Concin et al. IJGC 2020: ESGO/ESTRO/ESP Guidelines for the management of patients with endometrial carcinoma 2020

Molecular landscape of NSMP high risk EC *(n=94)*

PORTEC-3 trial in high risk patients, n=122 NSMP cases with availabel FFPE material

Immunohistochemistry ER/PR & L1CAM , next Generation Sequencing



Lisa Vremij
ESGO congress Prague 2021

Frequent mut in PTEN, CTNNB1, KRAS
Favourable characteristics: - low grade
- endometroid
- L1CAM neg

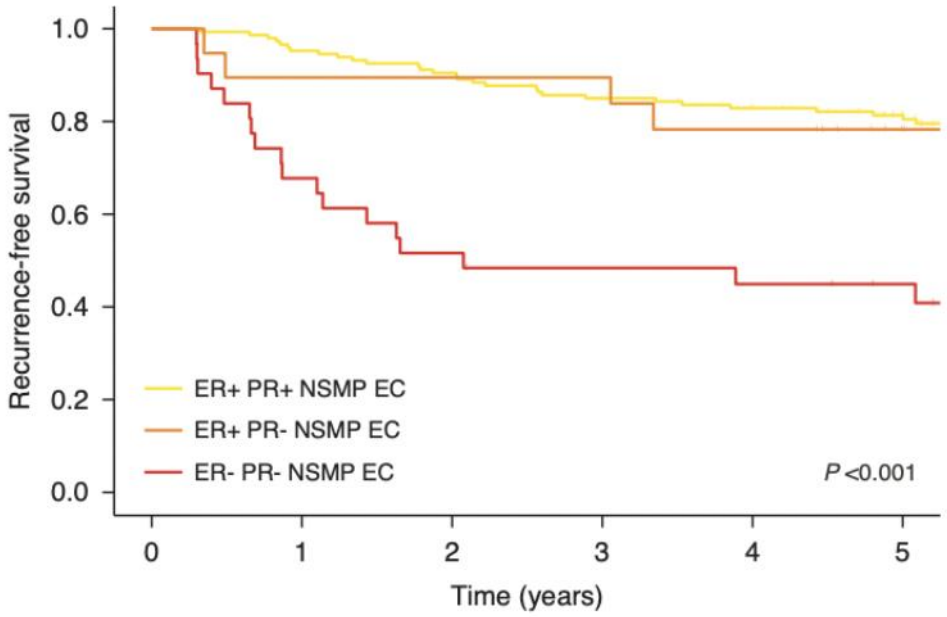
Mix of fav/ unfav charact.

Few somatic mutations
Unfavourable characteristics: - high grade
- none-endometroid
- L1CAM pos

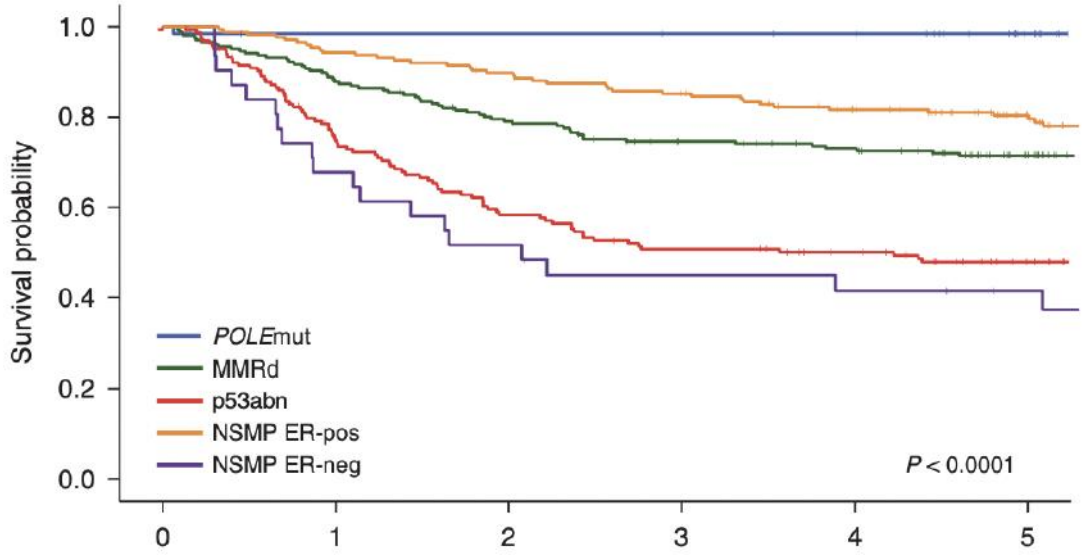
Impact of ER expression on outcome in NSMP high-risk endometrial cancers

n=648 high risk patients (Portec III & Dutch prospective clinical cohort)
thereof n=208 NSMP

NSMP stratified for ER

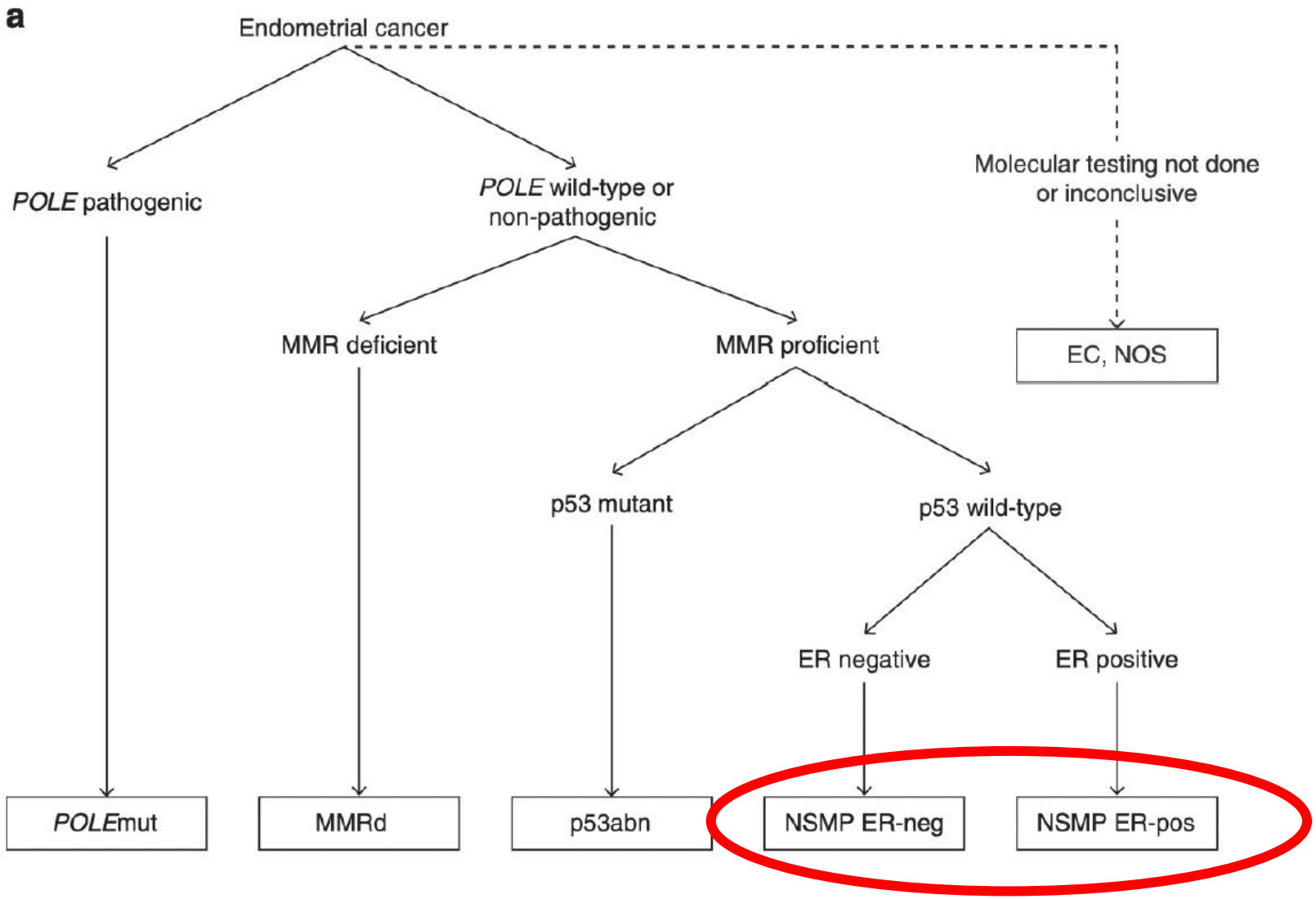


All groups including NSMP ER+/ER-



Vermij et al, British Journal of Cancer 2023

Integration of ER analysis into testing algorithm

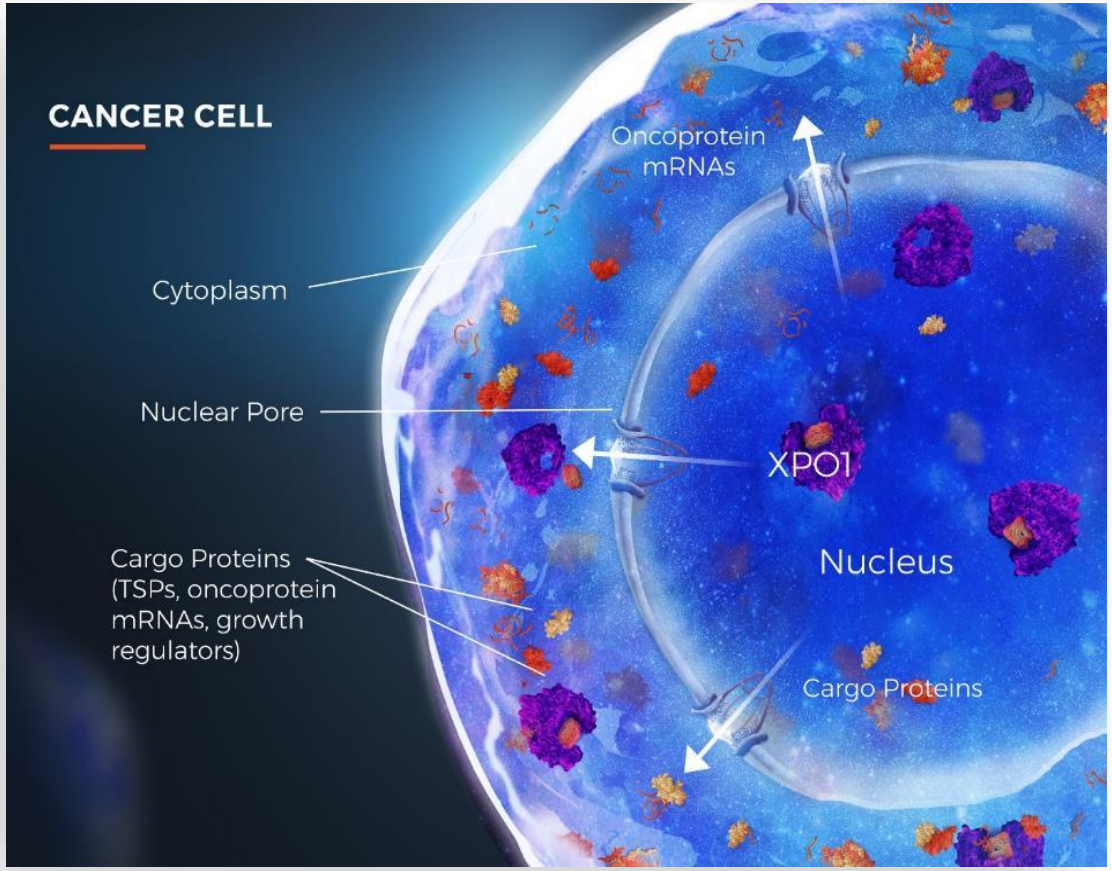


Vermij et al, British Journal of Cancer 2023

WHAT IS THE PATIENT-COHORT
- p53 wild-type?

WHAT ARE THE DRUGS (experimental)
- targeting p53 wild-type?

Selinexor: Oral XPO1 Inhibitor



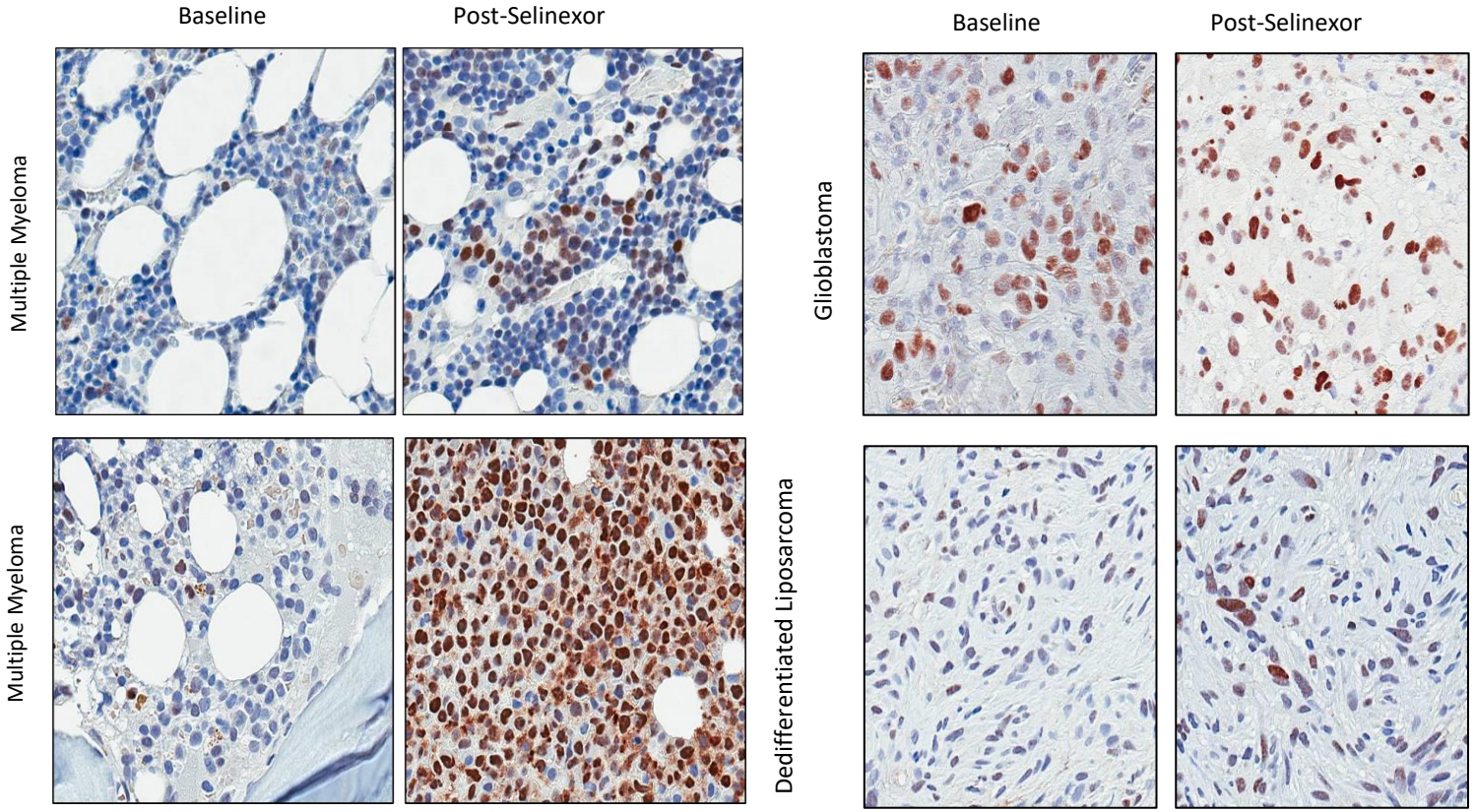
Selinexor is an oral selective inhibitor of XPO1-mediated nuclear export (SINE) compound

- XPO1 exports the major tumor suppressor proteins (TSPs) including p53 away from the nucleus, where TSPs carry out their function
- Tumor cells overexpress XPO1
- Tumor cells inactivate cytoplasmic *p53* through protein degradation
- Selinexor inhibits XPO1 nuclear export, leads to retention / reactivation of TSPs in the nucleus and stabilization of p53
- Retention of wild-type *p53* (p53wt) and other TSPs in the cell nucleus leads to selective killing of cancer cells, while largely sparing normal cells

Vicky Makker, ENGOT-EN5/GOG-3055/SIENDO, ASCO 2022
Ignace Vergote, SGO 2022

Selinexor (oral XPO1 inhibitor) induces nuclear accumulation of p53

p53 IHC in human patient samples

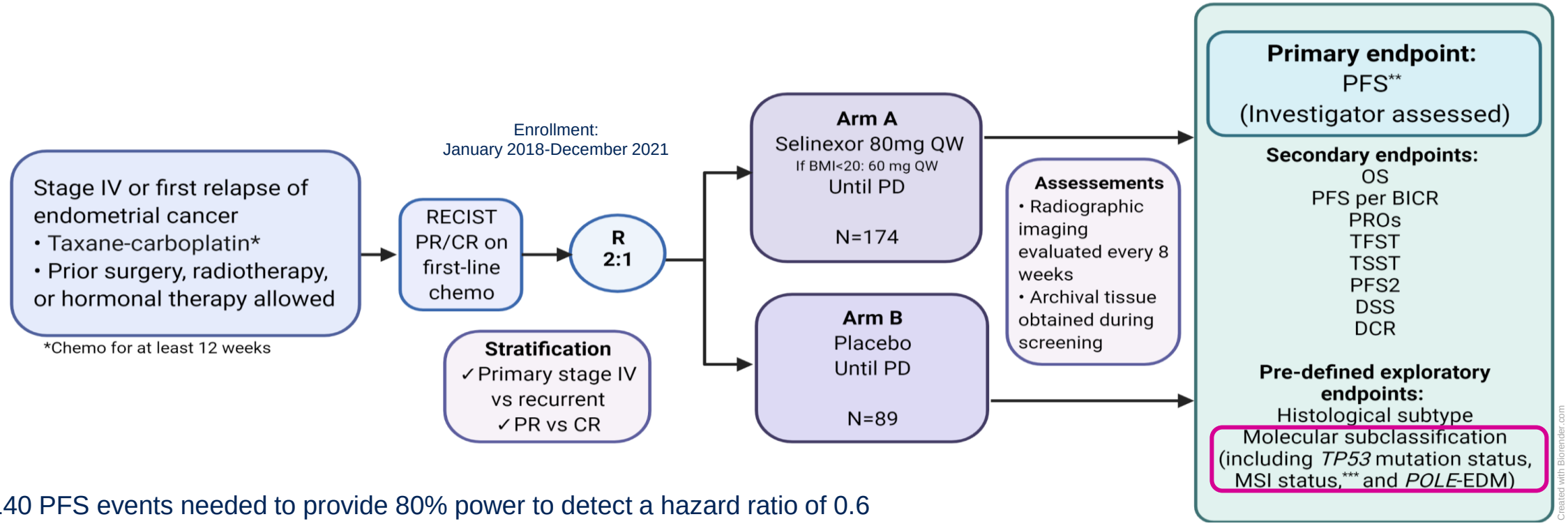


Inhibition of XPO1 leads to **nuclear accumulation of p53** across cancer types.

Vicky Makker, M.D., ENGOT-EN5/GOG-3055/SIENDO, ASCO 2022

Trial Design ENGOT-EN5/GOG-3055/SIENDO

Stage IV or first relapse of endometrial cancer
endometrioid, serous, undifferentiated, or carcinosarcoma



***Assessed by DNA sequencing and IHC

**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

Data cutoff: January 18, 2022

BICR; blinded independent central review; BMI, body mass index; CR, complete response; DCR, disease control rate; DSS, disease-specific survival; EDM, exonuclease domain mutation; IHC, immunohistochemistry; MSI, microsatellite instability; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes; QW, once weekly; R, randomized; RECIST, response evaluation criteria in solid tumors; TFST, time to first subsequent therapy; TSST, time to second subsequent treatment;

Previously presented at ESMO Virtual Plenary 2022 and SGO 2022

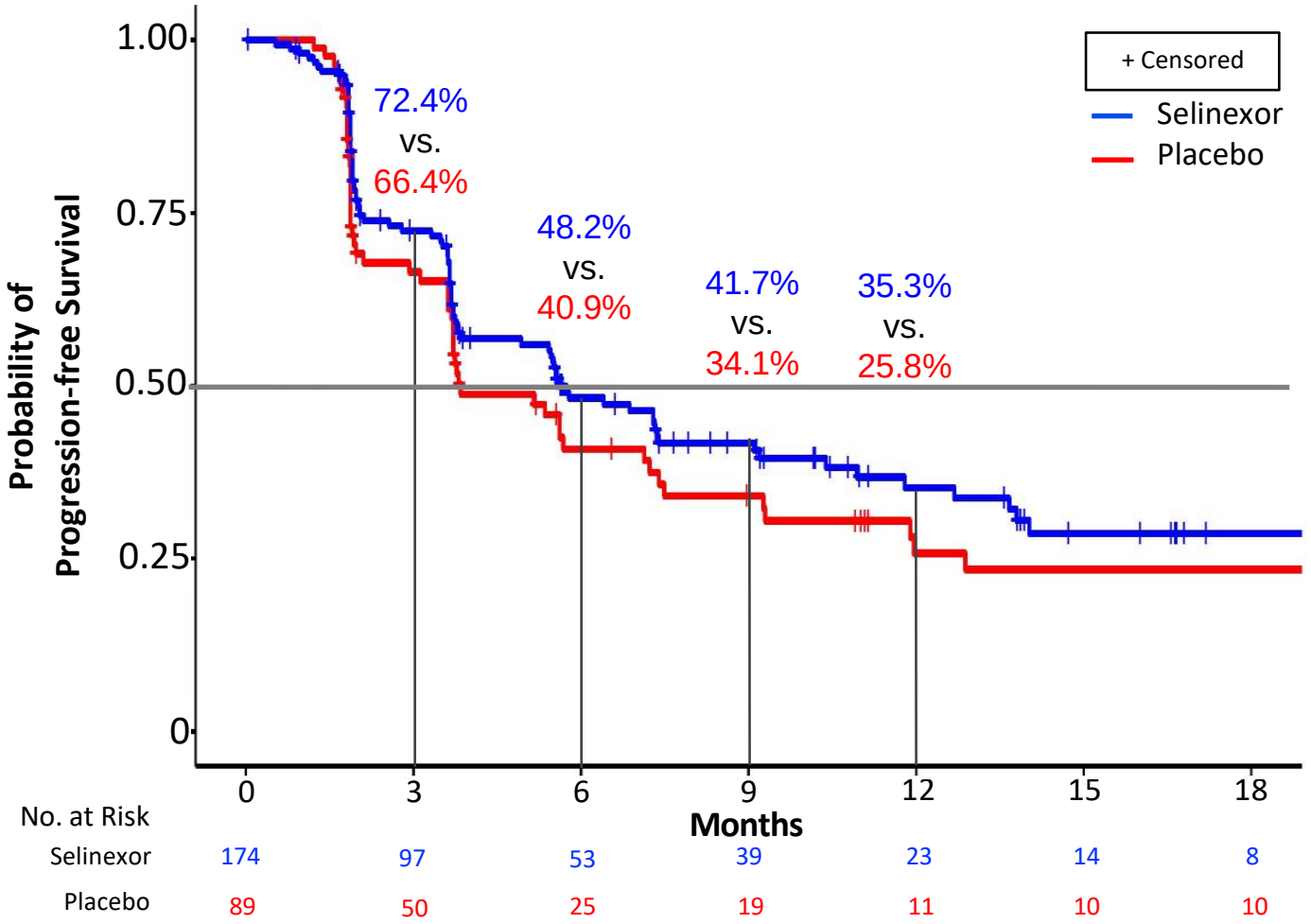
Patient Characteristics: ITT Population

CHARACTERISTICS	Selinexor N = 174	Placebo N = 89
Age, years median (range), n (%)	65.5 (40-81)	64.0 (33-81)
<70 years, n (%)	116 (66.7)	61 (68.5)
≥70 years, n (%)	58 (33.3)	28 (31.5)
ECOG performance status, n (%)		
0	99 (56.9)	54 (60.7)
1	71 (40.8)	35 (39.3)
2	1 (0.6)	0
Histology, n (%)		
Endometrioid	96 (55.2)	48 (53.9)
Serous	49 (28.2)	28 (31.5)
Undifferentiated	4 (2.3)	1 (1.1)
Carcinosarcoma	10 (5.7)	6 (6.7)
Endometrial Adenocarcinoma Not Otherwise Specified	15 (8.6)	6 (6.7)
Number of Prior Antineoplastic Regimens, n (%)		
1	172 (98.9)	85 (95.5)
2/3	2 (1.1)	3 (3.4)/1 (1.1)
Disease at Time of Taxane-Platinum Combination Therapy -audited, n (%)		
Primary Stage IV Disease	78 (44.8)	43 (48.3)
Recurrent Disease	96 (55.2)	46 (51.7)
Disease Status After the Most Recent Chemotherapy -audited, n (%)		
CR	70 (40.2)	40 (44.9)
PR	104 (59.8)	49 (55.1)

CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response

SIENDO / ENGOT-EN5: Maintenance With Selinexor/Placebo After Combination Chemotherapy in Participants With Endometrial Cancer

PFS in ITT Population



median follow-up: 10.2 months (95% CI 8.97, 13.57)

Median PFS

Selinexor (n=174): 5.7 mo (95% CI 3.81-9.20)

Placebo (n=89): 3.8 mo (95% CI 3.68-7.39)

Audited* (by electronic case report form)

HR = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

Unaudited* (by interactive response technology)

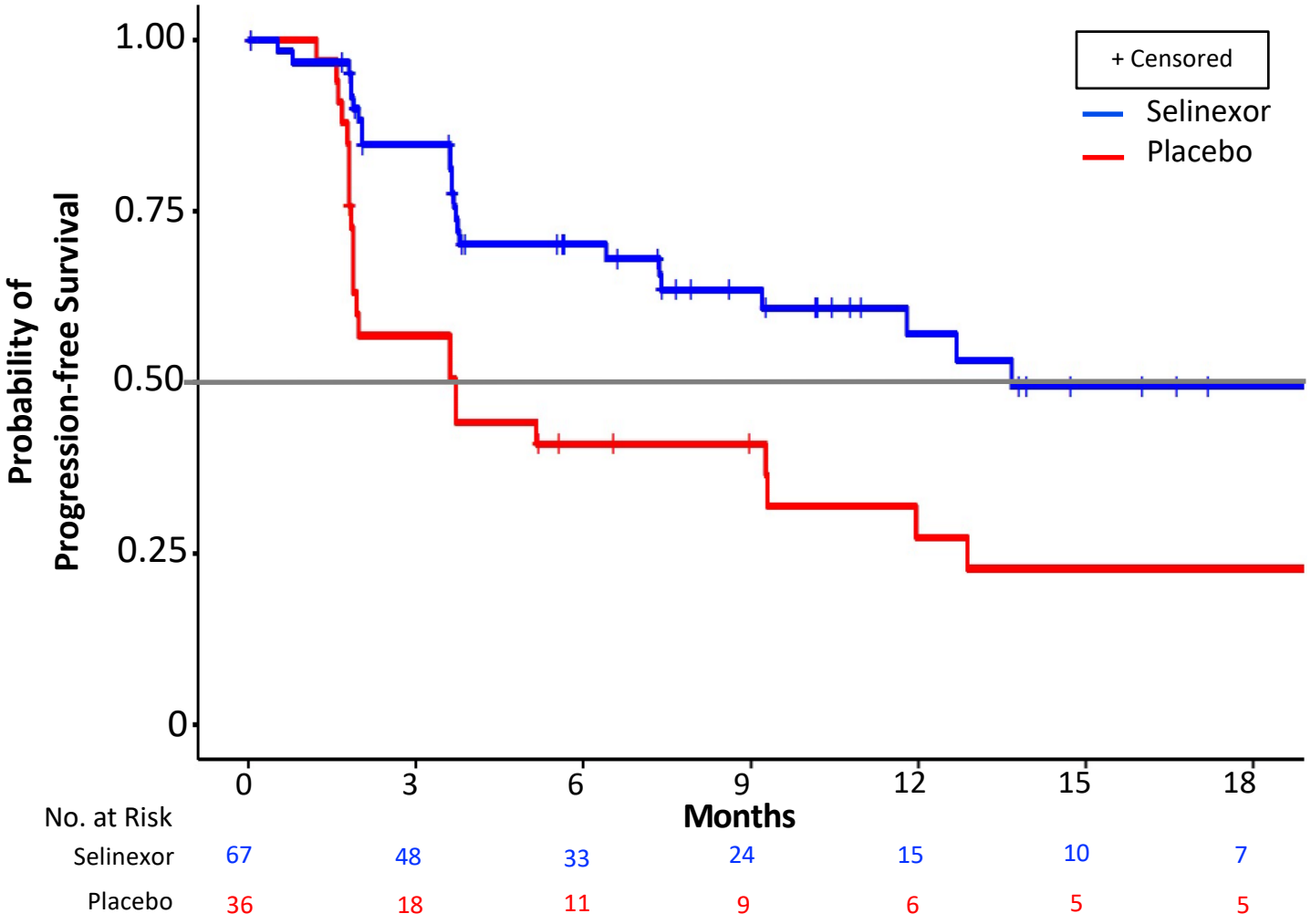
HR = 0.76 (95% CI 0.543-1.076)

One-sided P value = 0.063

*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with **p53 wild-type** EC



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)

Audited

HR = 0.375 (95% CI 0.210-0.670)

Nominal one-sided P value = 0.0003

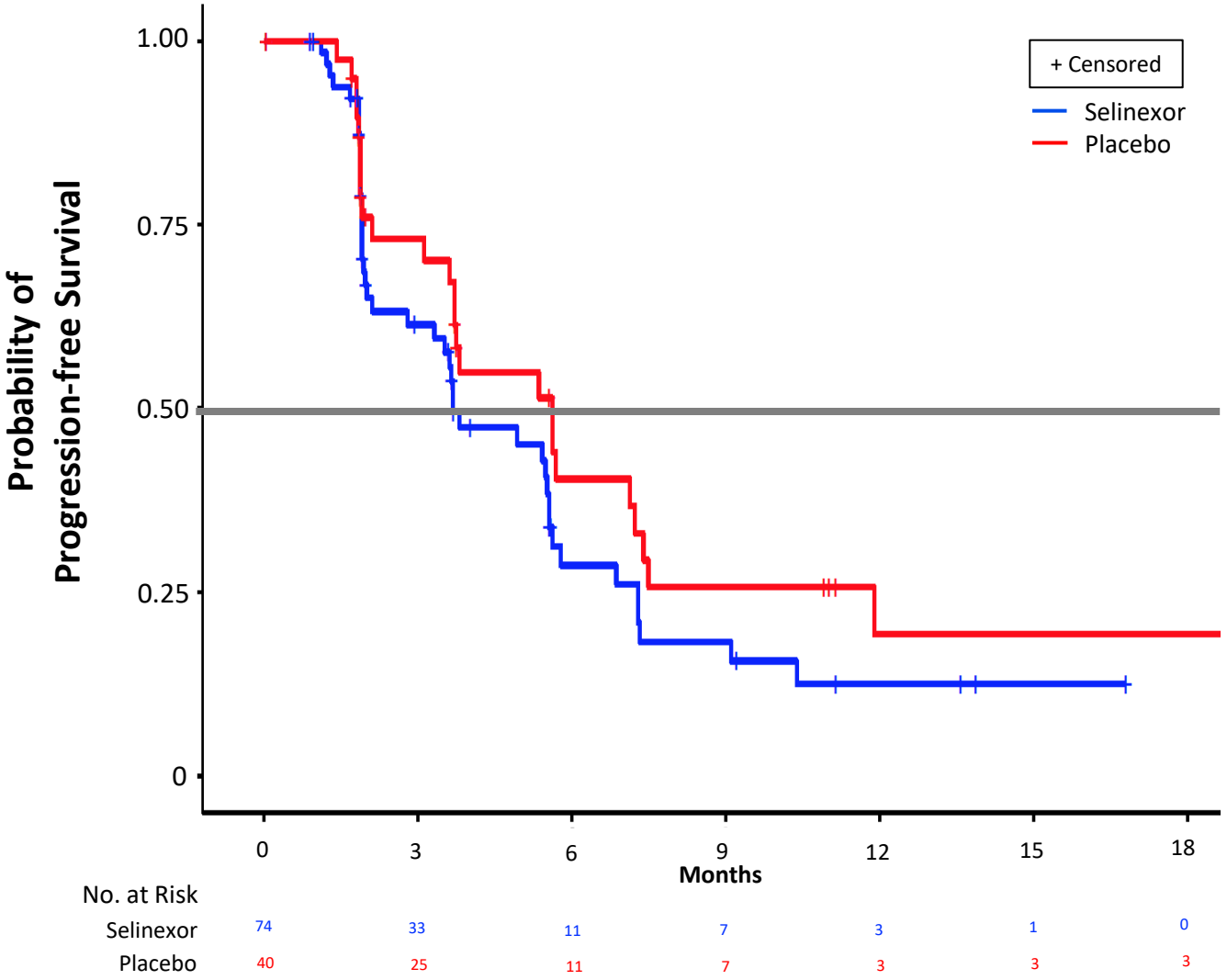
Unaudited

HR = 0.407 (95% CI 0.229-0.724)

Nominal one-sided P value = 0.0008

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 Mutant/Aberrant EC



Median PFS

Selinexor (n=74): 3.7 mo (95% CI 3.32-5.55)

Placebo (n=40): 5.6 mo (95% CI 3.71-7.49)

Audited

HR = 1.306 (95% CI 0.795-2.145)

Nominal one-sided P value = 0.8530

Unaudited

HR = 1.345 (95% CI 0.819-2.208)

Nominal one-sided P value = 0.8785

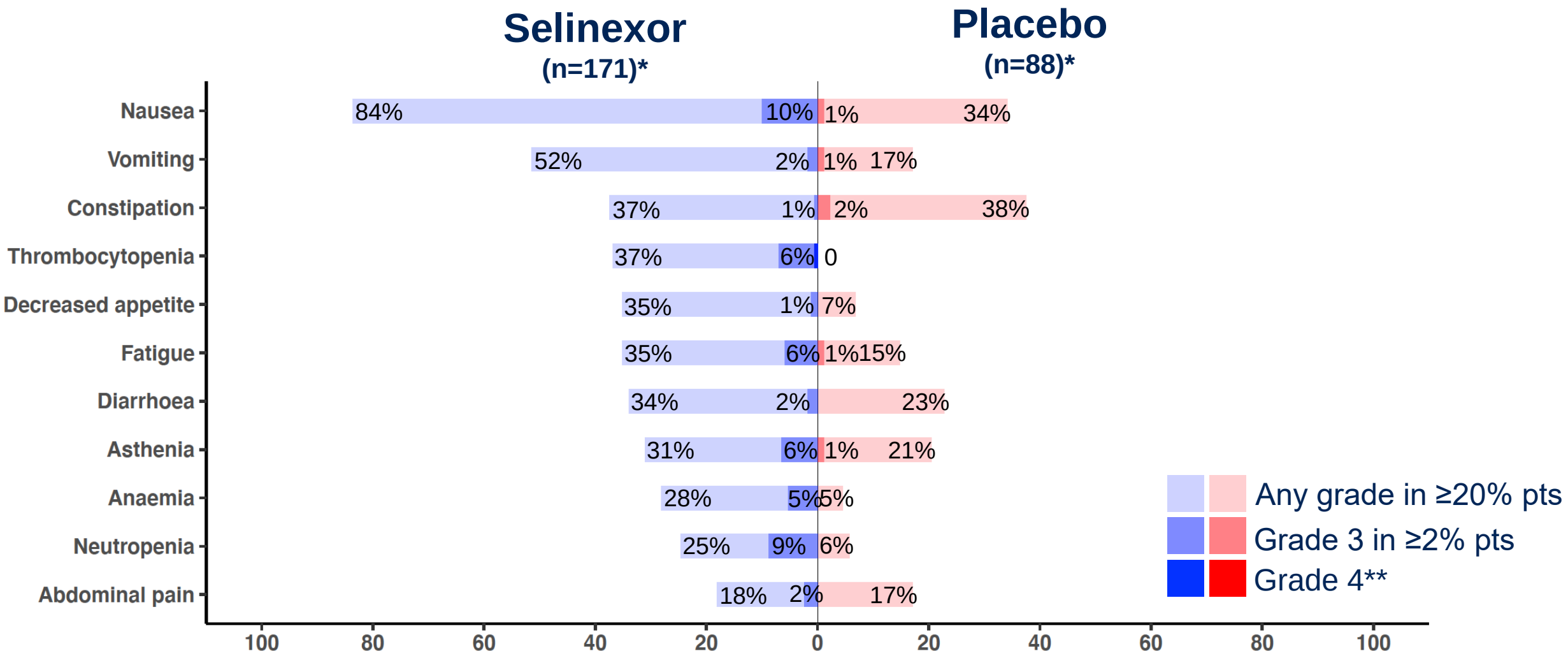
CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Preliminary Exploratory Analysis of Mutually-Exclusive TCGA Subgroups

	Selinexor	Placebo	*One-sided p-value* (nominal)	HR (95% CI)
	Progression-free survival — median, (months)			
POLE mutated (selinexor n=2, placebo n=4)				
Stratification-adjusted, audited	3.8	1.9	0.404	0.71 (0.04-11.79)
Stratification-adjusted, unaudited			0.404	0.71 (0.04-11.79)
MSI-H (selinexor n=18, placebo n=8)				
Stratification-adjusted, audited	6.4	NR	0.685	1.41 (0.35-5.67)
Stratification-adjusted, unaudited			0.685	1.41 (0.35-5.67)
Copy number low (selinexor n=37, placebo n=20)				
Stratification-adjusted, audited	NR	3.7	<0.0001	0.16 (0.06-0.44)
Stratification-adjusted, unaudited			0.0004	0.22 (0.09-0.58)
Copy number high (selinexor n=50, placebo n=33)				
Stratification-adjusted, audited	3.7	5.6	0.820	1.31 (0.74-2.31)
Stratification-adjusted, unaudited			0.860	1.37 (0.77-2.41)

CI, confidence interval; HR, hazard ratio; mo, months; NR, not reached; PFS, progression-free survival

Treatment-Emergent Adverse Events in ITT Population



*Four patients did not receive treatment (n=3 selinexor; n=1 placebo)

**n=1 Grade 4 thrombocytopenia; No cases of severe bleeding in patients with thrombocytopenia; No cases of febrile neutropenia

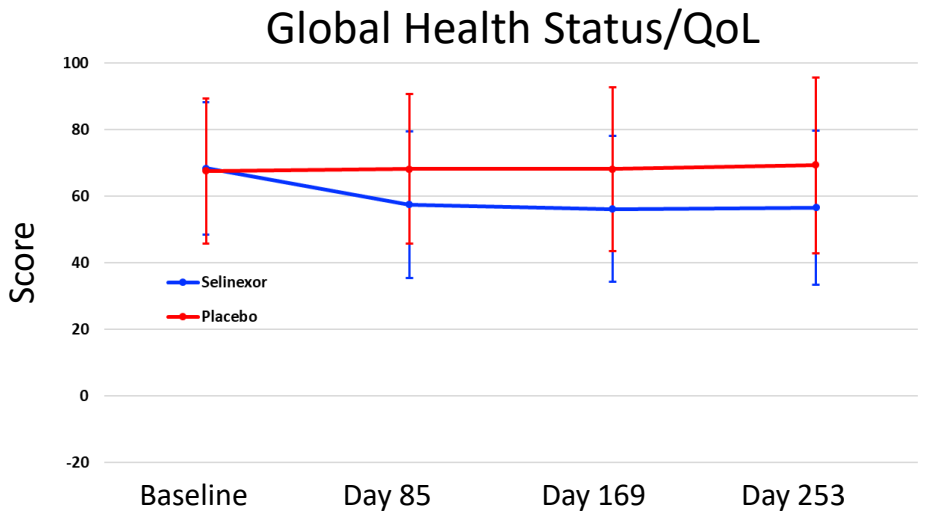
Safety

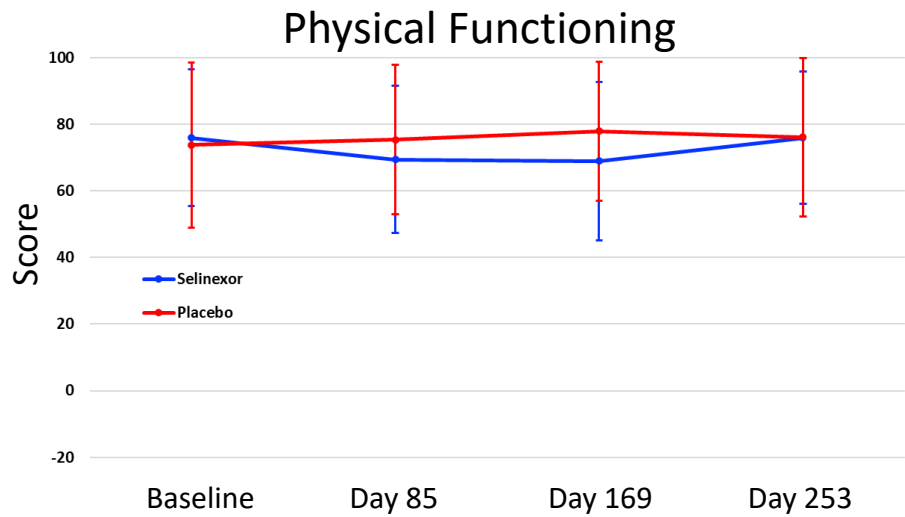
Event	Selinexor n=171* n (%) (per patient)	Placebo n=88* n (%) (per patient)
TEAE leading to:		
Dose reduction	85 (49.7)	3 (3.4)
Dose interruption	88 (51.5)	16 (18.2)
Discontinuation	18 (10.5)	1 (1.1)
Death	0	0

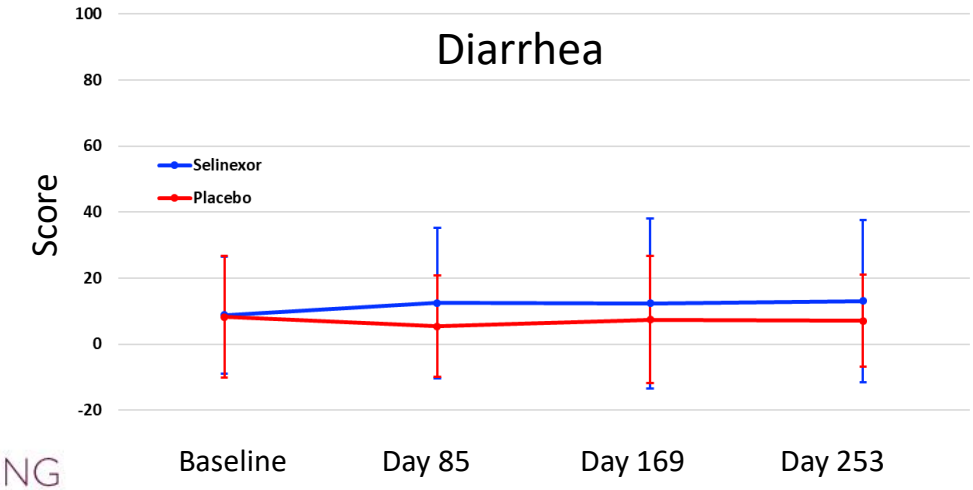
*Four patients did not receive treatment (n=3 selinexor; n=1 placebo)

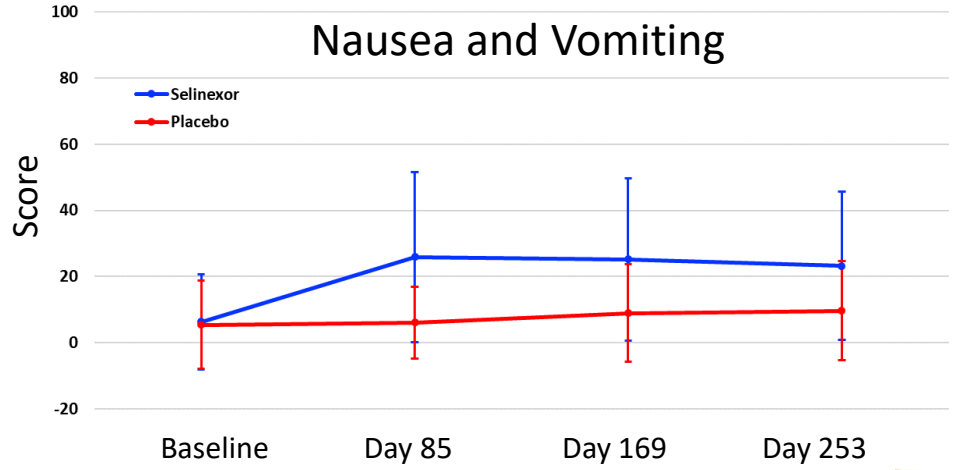
ENGOT-EN5/GOG-3055/SIENDO

QoL -Patient-Reported Outcomes (EORTC QLQ-C30)
No significant differences in global health, physical functioning or symptoms









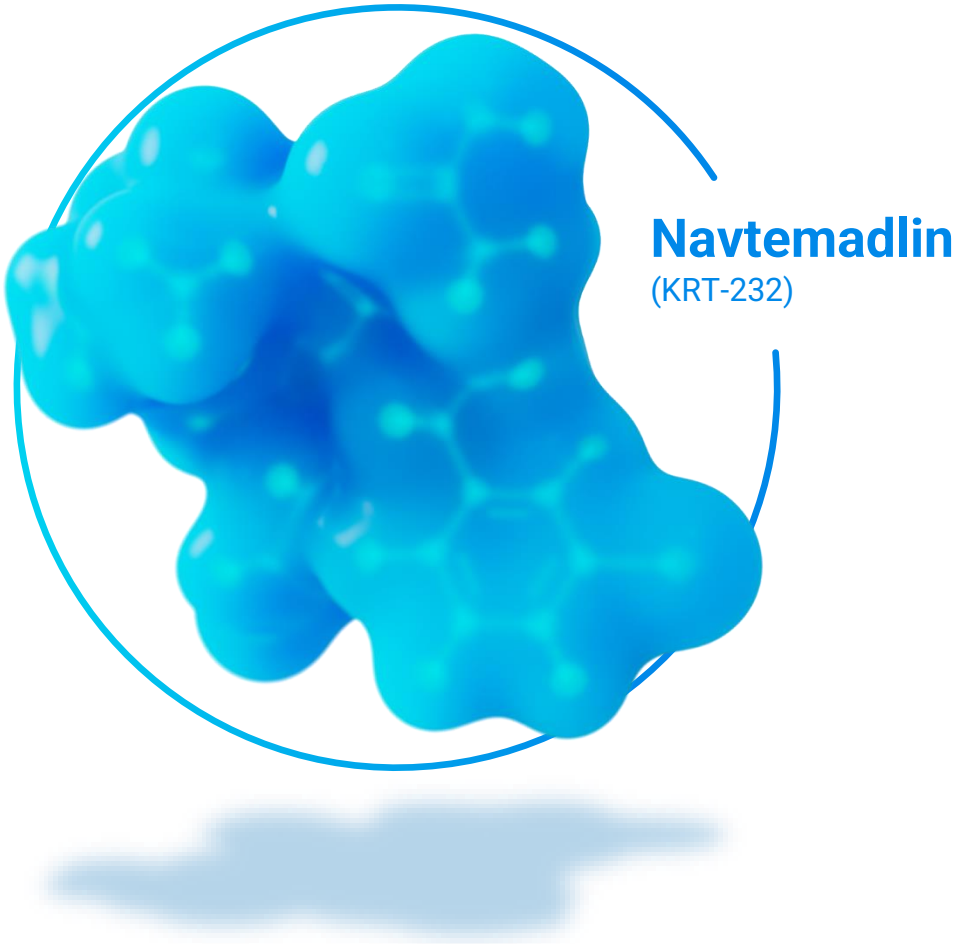
Ignace Vergote

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module

Novel p53 Potentiating Anticancer Agent

Navtemadlin is a potent, selective, orally available inhibitor of MDM2 that mediates p53-driven apoptosis[1,2]:

- Binding affinity[2] = 0.045 nM
- IC_{50}[2] = 9.1 nM
- Constant oral clearance across doses[3]
- Rapid absorption (1-3 hour T_{max})[3]
- $T_{1/2}$[3] = ~17 hours



Navtemadlin restores p53 function resulting in tumor cell apoptosis through MDM2 inhibition

Sources: [1]Canon et al. Mol Cancer Ther. 2015;14:649-658; [2]Sun et al. J Med Chem. 2014;57:1454-1472; [3]Ma et al. Blood. 2019;134 (Supplement_1):5766.
Abbreviations: IC_{50}, half maximal inhibitory concentration; MDM2, murine double minute 2; nM, nano molar; p53, tumor suppressor protein 53; $T_{1/2}$, half-life; T_{max}, time to maximum concentration.

MDM2 is a Key Negative Regulator of p53

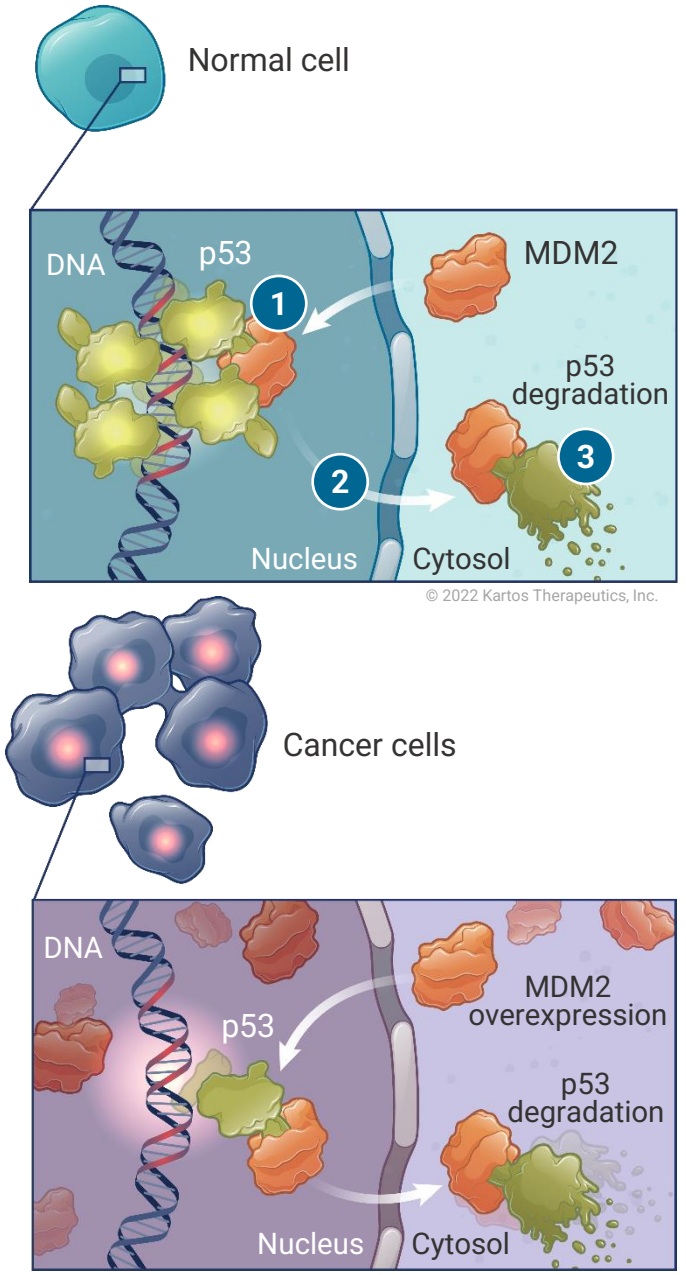
MDM2 modulates p53 activity by

1. Directly inhibiting p53 transcriptional activity
2. Transporting p53 out of the nucleus
3. Ubiquitinating and tagging p53 for proteasomal degradation

MDM2 upregulation or overexpression within malignant cells can drive cancer-cell proliferation

MDM2 inhibitors (Navtemadlin) can restore normal p53 tumor-suppressor function leading to cell death (apoptosis)

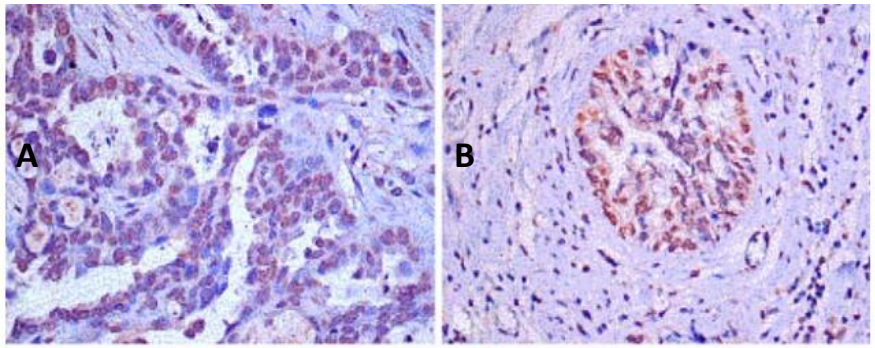
MDM2 is a promising target for anti-cancer drug development



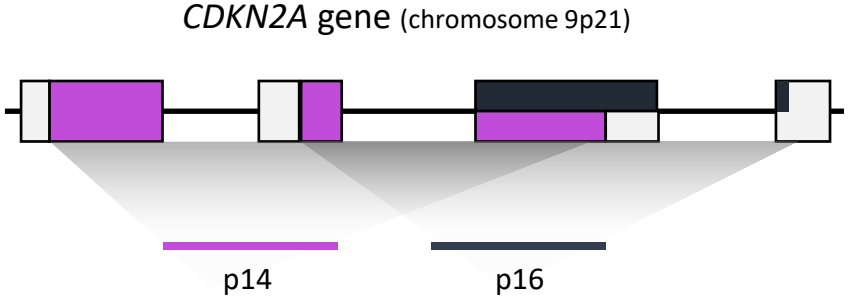
Abbreviations: MDM2, murine double minute 2; **p53**, tumor suppressor protein 53.

p14^{ARF}, MDM2 and p53 in Endometrial Cancer

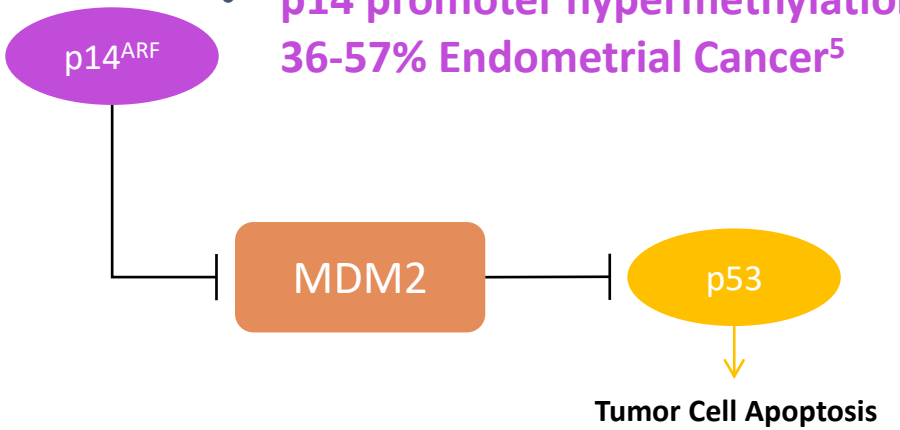
- In *TP53*^{WT} Endometrial Cancer, p53 may be alternatively inactivated by MDM2 overexpression or upregulation:
  - **40-50% of Endometrial Cancers overexpress MDM2[2]**
- **MDM2 overexpression** may be driven by
  - **MDM2 SNP309 promoter polymorphism[3]**
  - **p14^{ARF} inactivation (*CDKN2A* hypermethylation)[4]**



MDM2 protein overexpression in primary endometrial cancer (**A**) and metastatic lymph node (**B**)[2]



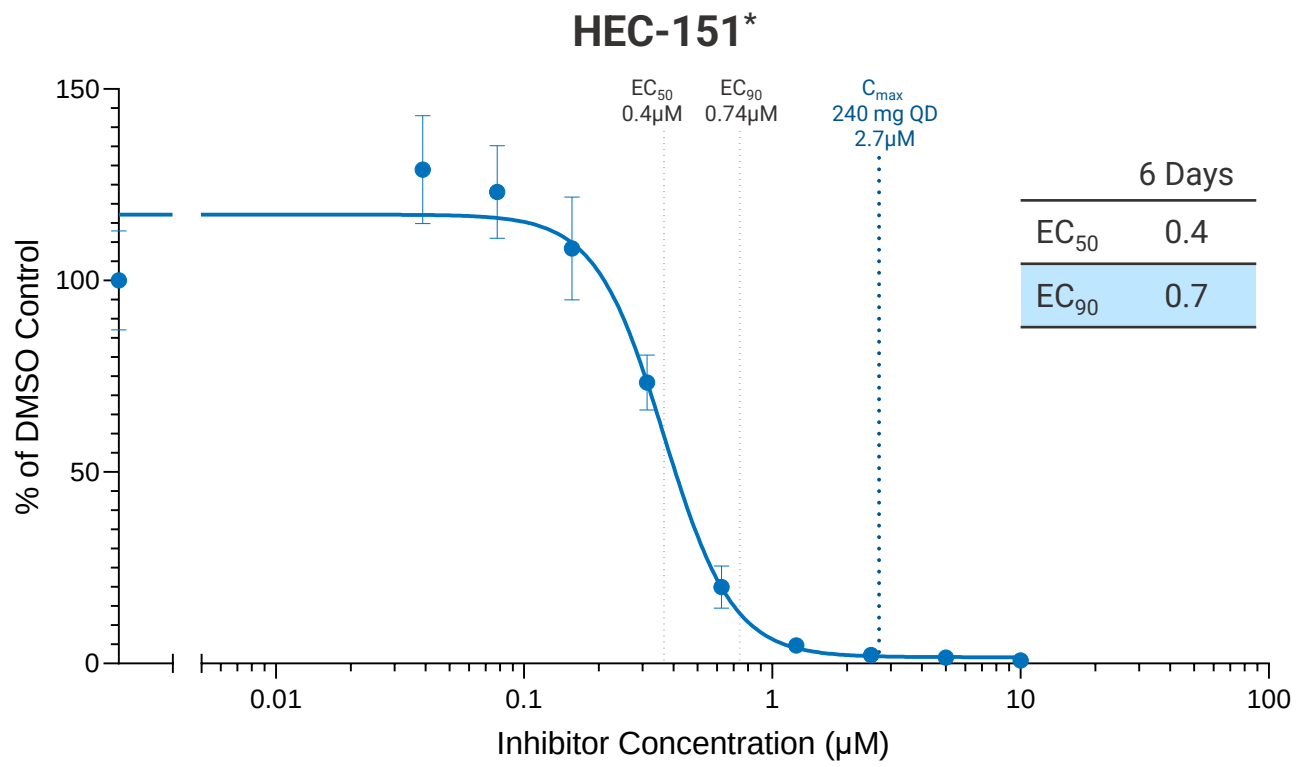
- **p14 promoter hypermethylation in 36-57% Endometrial Cancer[5]**



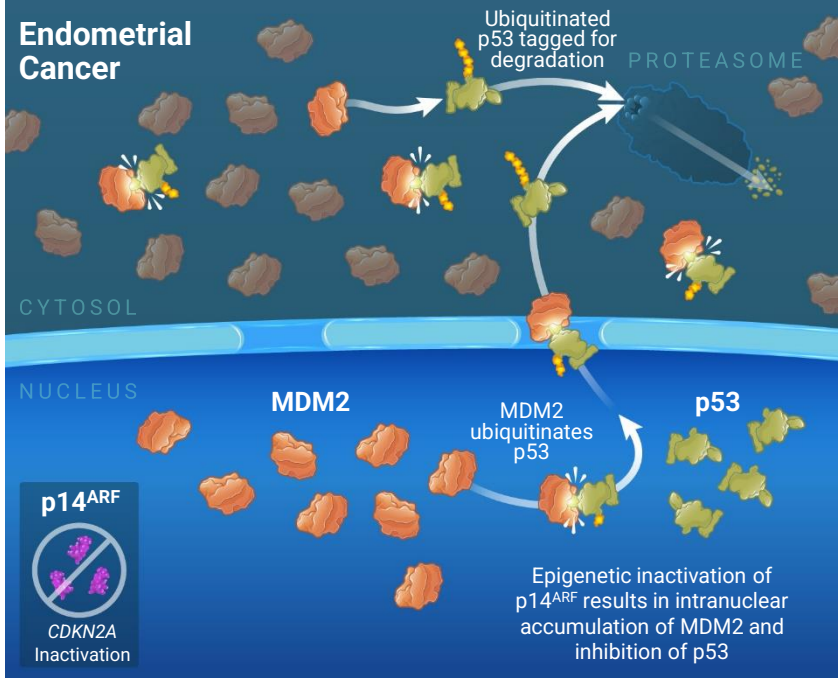
- **Sources:** [1]Miller et al. *JCO* 2020; [2]Jeczen et al. *Clin Exp Metastasis* 2007; [3]Yoneda et al. Oncol Rep 2013; [4]Kung & Weber Frontiers 2022; [5]Azizi & Tehrani 2017
- **Abbreviations: CKDN2A**, cyclin-dependent kinase inhibitor 2A; **p14^{ARF}**, p14 alternate reading frame; **MDM2**, murine double minute 2; **ORR**, objective response rate; **p53**, tumor suppressor protein 53; **SNP309**, single nucleotide polymorphism 309; **WT**, wild-type.

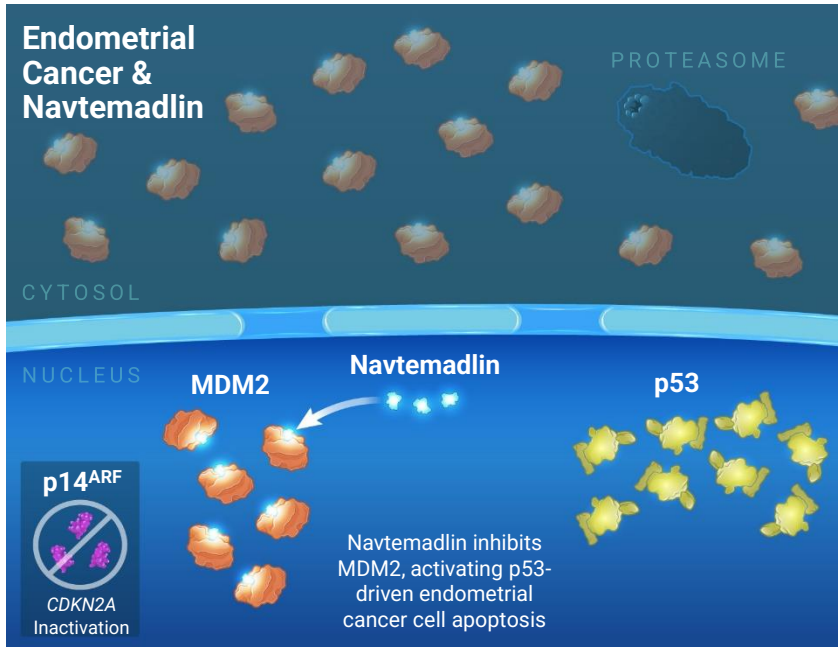
Endometrial Cancer, Navtemadlin and p53-Driven Apoptosis

Growth Inhibition in *TP53*^{WT} Endometrial Cancer Cell Line at clinical relevant dose exposures



	6 Days
EC_{50}	0.4
EC_{90}	0.7





Kartos Internal Data; *Results replicated in alternative *TP53*^{WT} endometrial cancer cell lines (HEC-265).
Abbreviations: C_{max}, maximum serum concentration; DMSO, dimethyl sulfoxide; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; μM, micromolar; *TP53*, tumor suppressor protein 53; WT, wild-type.

ENGOT (ENGOTen-21) - GOG - Kooperation

p53-based Approach in Advanced or Recurrent Endometrial Cancer

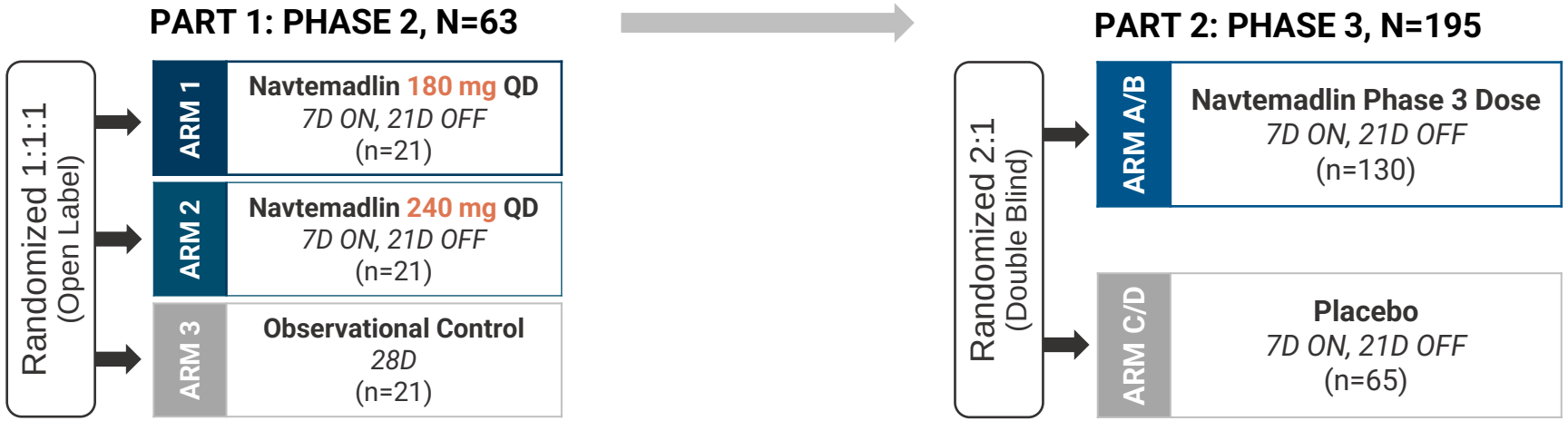
A Two-part, Randomized Phase 2/3 Study of Navtemadlin in Subjects with *TP53*^{WT} Advanced or Recurrent Endometrial Cancer Who Responded after Chemotherapy

Study KRT-232-118, Registration Directed Phase 2 Design

A Two-Part, Randomized Phase 2/3 Maintenance Study of Navtemadlin in Subjects With *TP53*^{WT} in Advanced or Recurrent Endometrial Cancer Who Responded After Chemotherapy

ENROLLMENT

Women with ***TP53***^{WT} **advanced or recurrent** endometrial cancer who have a **PR/CR after** completion of up to 6 cycles of **platinum-based chemotherapy**



	PRIMARY ENDPOINTS	KEY SECONDARY ENDPOINTS	EXPLORATORY OBJECTIVES
Part 1:	To determine the navtemadlin Phase 3 Dose	• To evaluate the ORR, DCR, PFS and OS • To determine the PK profile of navtemadlin	**Part 1 and Part 2:** • To evaluate efficacy and safety of navtemadlin relative to select PD markers • To monitor the PK of navtemadlin (Part 2 only)
Part 2:	To compare PFS (BIRC) between navtemadlin and placebo	• To compare the ORR, DCR, PFS, TFST and OS between navtemadlin and placebo	

1 Cycle: 28 days
Abbreviations: BIRC, blinded independent radiographical committee; CR, complete remission; D, day; DCR, disease control rate (CR + PR + stable disease); Inv, investigator assessed; NGS, next-generation sequencing; ORR, objective response rate (per RECIST v1.1); OS, overall survival; PFS, progression free survival; PK, pharmacokinetics; PR, partial response; TFST, time to first subsequent treatment.


Thank you!

Thank you