子宮內膜癌的分子分型-異常p53表現

20230812

三軍總醫院

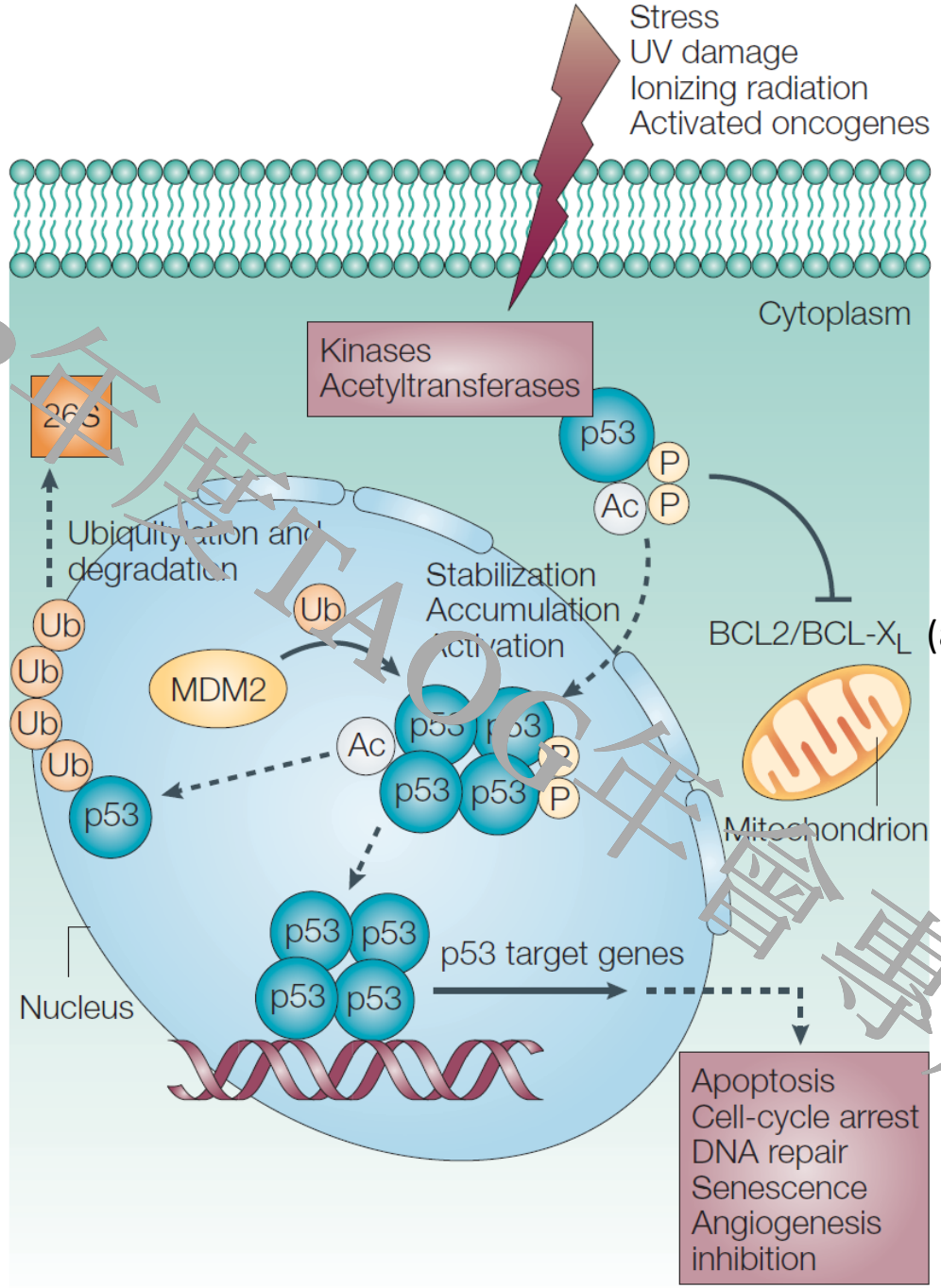
林宜欣

Content

- The role of p53 in carcinogenesis
- Diagnosis of abnormal p53 expression
- Significance of p53 mutation in endometrial cancer
  - Impact in prognosis
  - Selection of adjuvant therapy

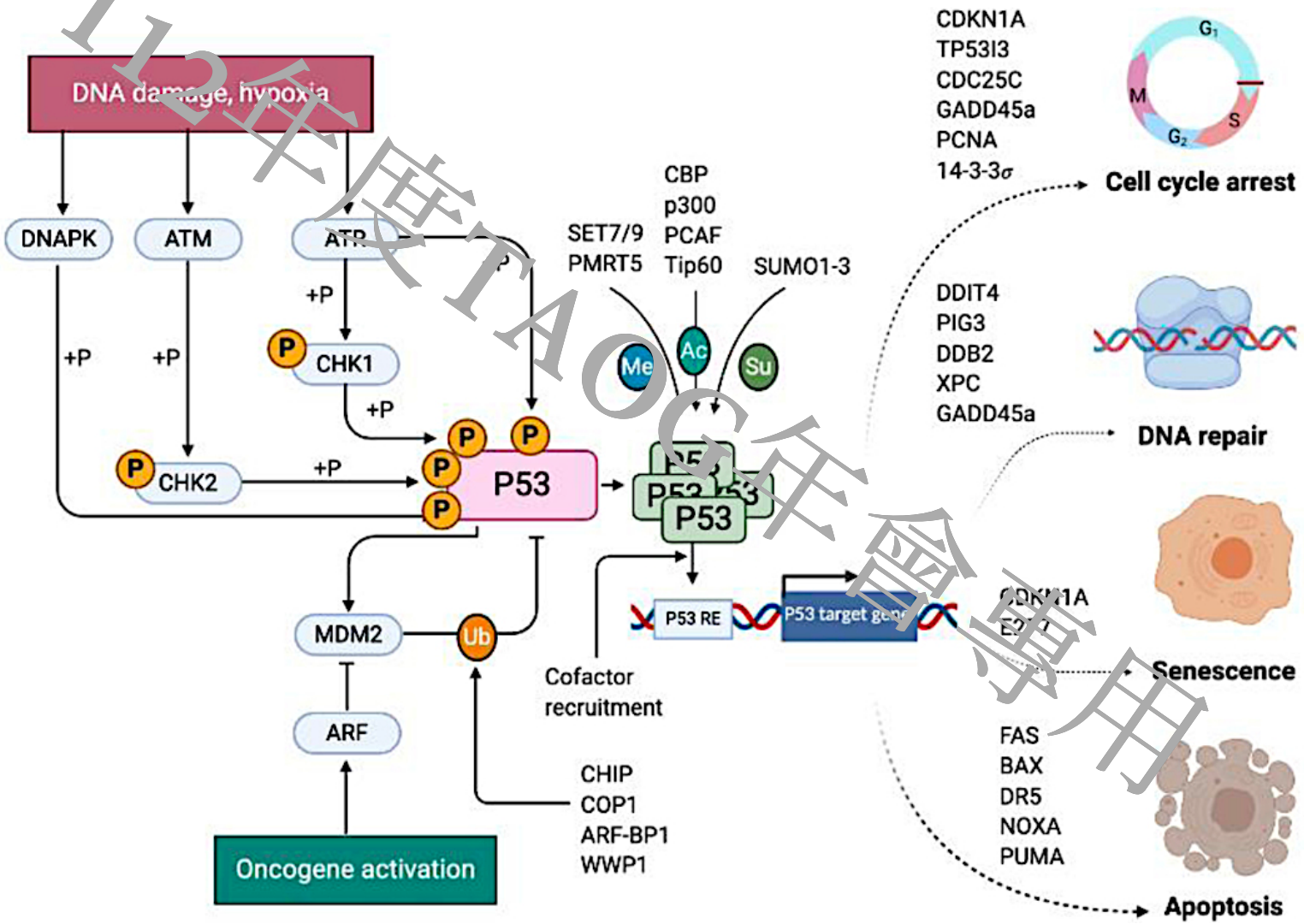
p53

- DNA: TP53 gene, tumor protein p53
- Protein: a DNA-binding transcription factor
- A tumor suppressor.



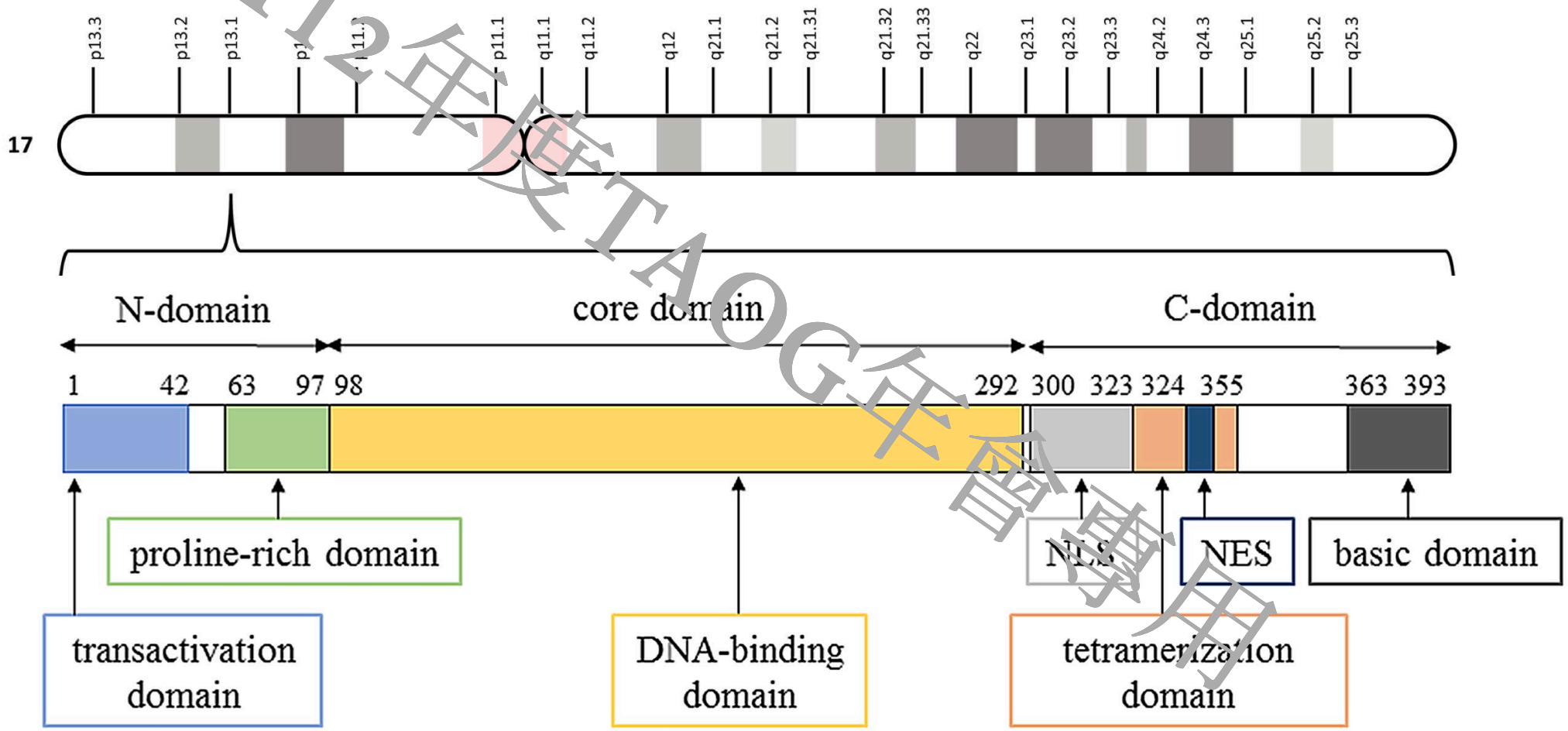
Nat Rev Cancer. 2004 Oct;4(10):793-805.

Overview of p53 activation, regulation, and transcriptional cellular response output.



Biochim Biophys Acta Rev Cancer. Aug 2021;1876(1):188556.

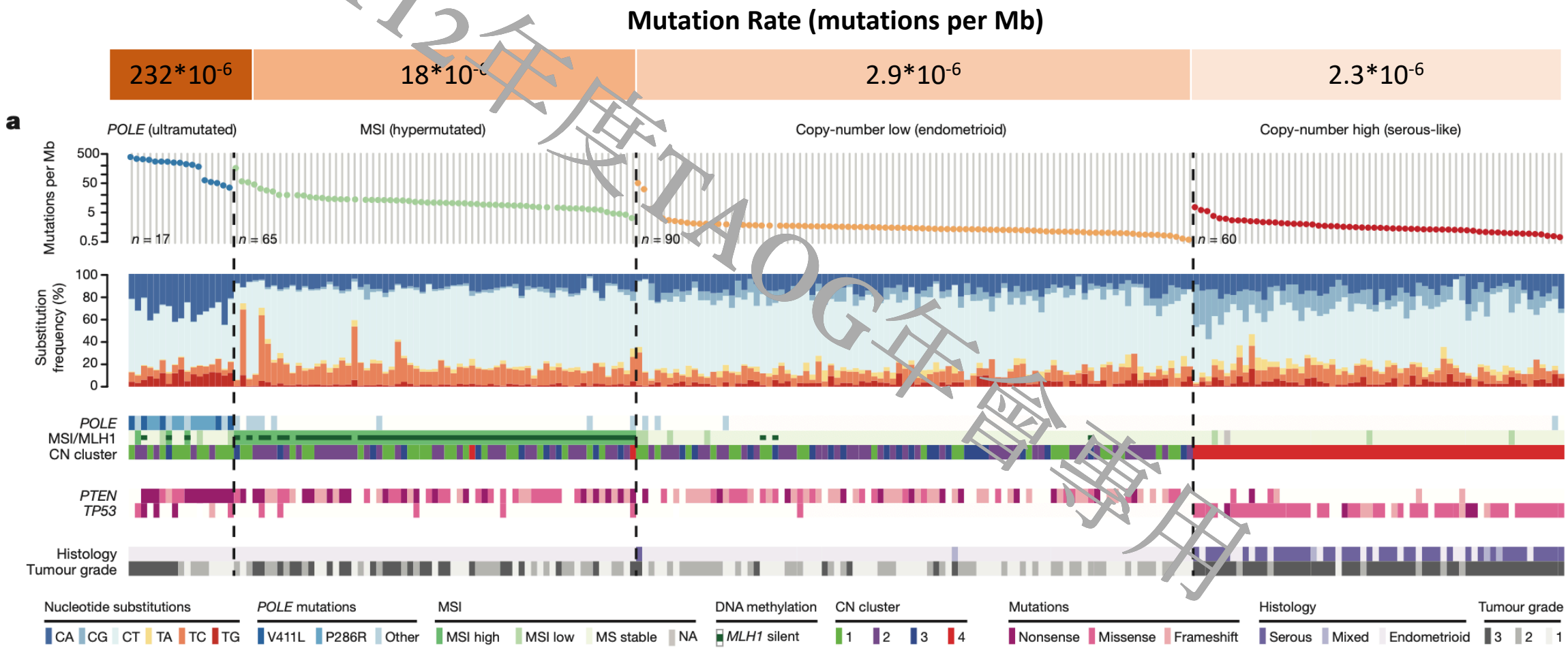
p53 structure



NLS: nuclear localization signal ; NES: nuclear export signal

Oncotarget. 2018 Mar 23; 9(22): 16234–16247.

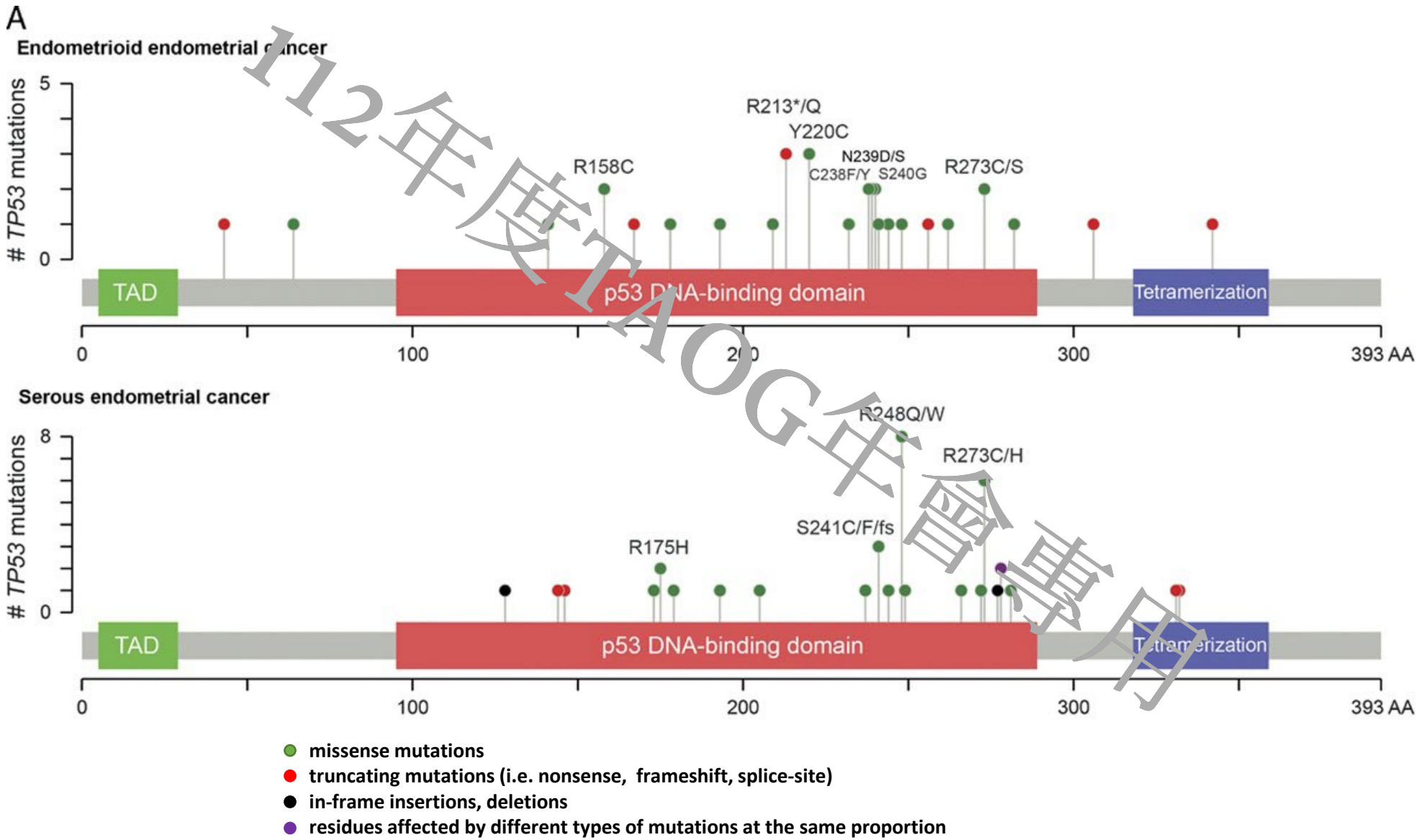
Exome sequence analysis



TMB-H was defined as 10 or more mutations per megabase.

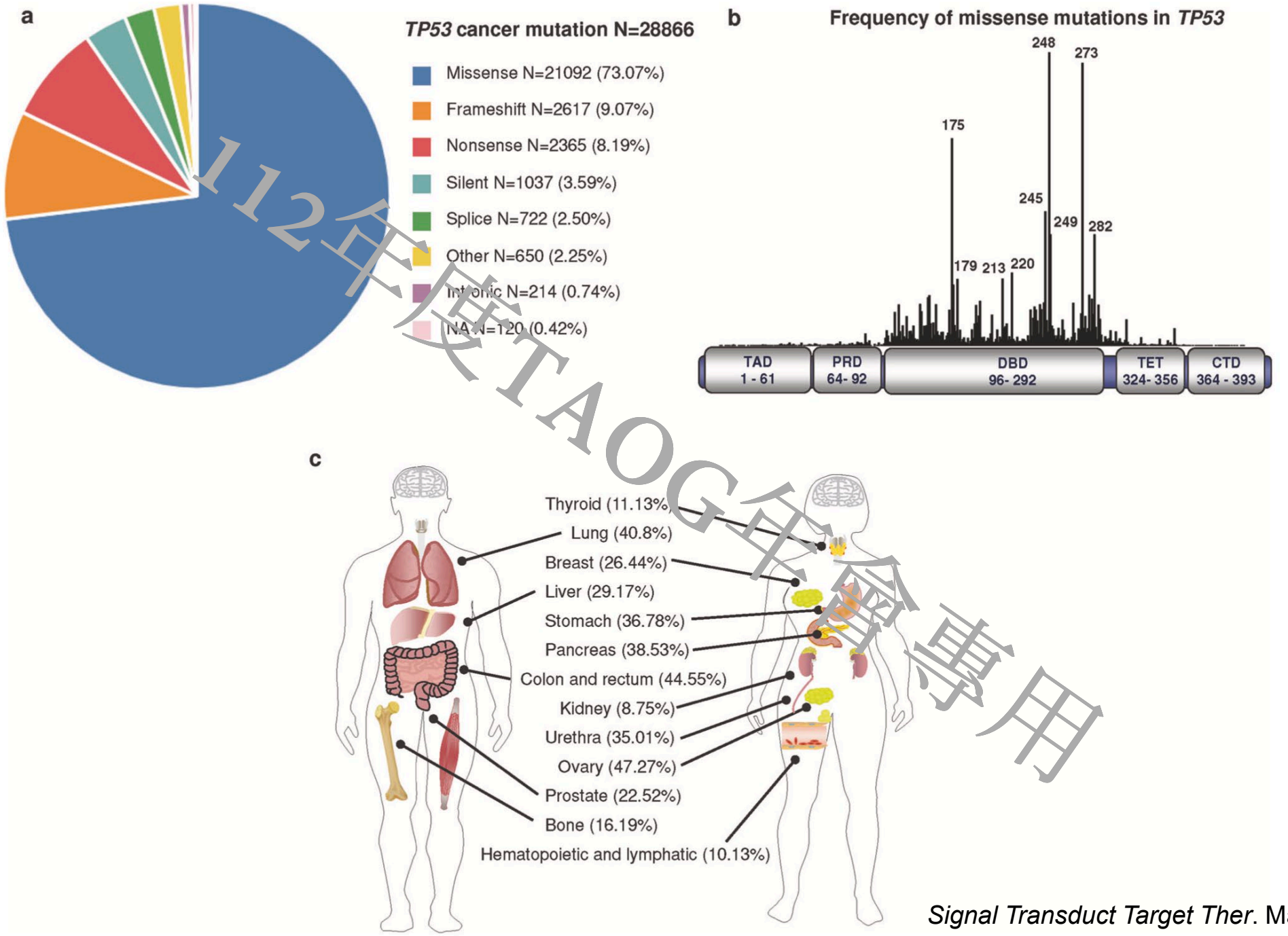
Nature volume 497, pages67–73(2013)

TP53 Mutational Spectrum in Endometrioid and Serous Endometrial Cancers



- missense mutations
- truncating mutations (i.e. nonsense, frameshift, splice-site)
- in-frame insertions, deletions
- residues affected by different types of mutations at the same proportion

Int J Gynecol Pathol. 2016 Jul;35(4):289-300



Signal Transduct Target Ther. Mar 1 2023;8(1):92.

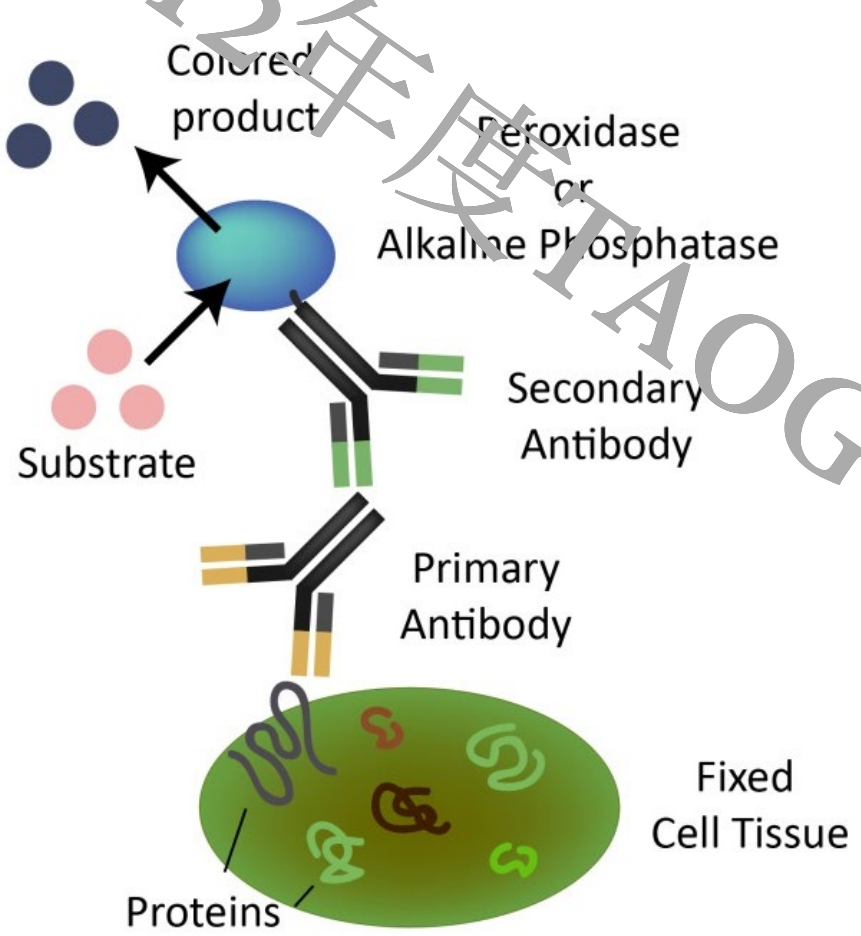
Content

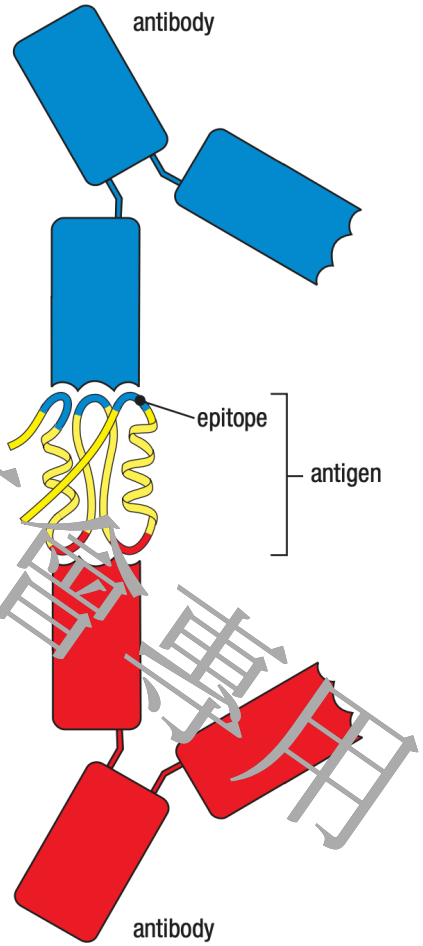
- The role of p53 in carcinogenesis
- Diagnosis of abnormal p53 expression
- Significance of p53 mutation in endometrial cancer
  - Impact in prognosis
  - Selection of adjuvant therapy

Diagnosis of abnormal p53 expression

- Immunohistochemistry staining: protein
- Next-generation sequencing: DNA

Immunohistochemistry (IHC) Staining





https://www.epigentek.com/catalog/immunohistochemistry-ihc-protocol-n-19.html

Janeways Immunolgy, 9th Ed.

VENTANA®

CONFIRM anti-p53 (DO-7) Primary Antibody

REF 800-2912

05278775001

IVD 50

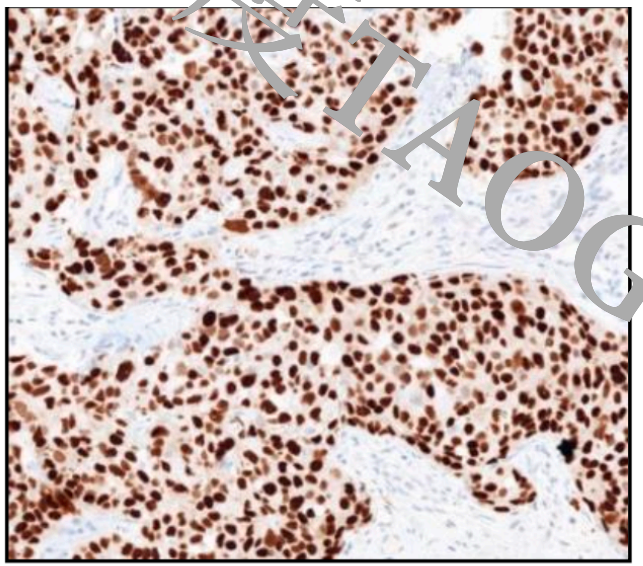


Figure 1. CONFIRM anti-p53 (DO-7) Primary Antibody exhibiting a nuclear staining pattern in colon adenocarcinoma tissue.

INTENDED USE

Ventana Medical Systems' (Ventana) CONFIRM anti-p53 (DO-7) Primary Antibody is a mouse monoclonal antibody (IgG1, kappa) directed against human p53. The antibody is intended for laboratory use to qualitatively identify by light microscopy wild type and mutant p53 in sections of formalin fixed, paraffin embedded tissue on a Ventana automated slide stainer.

The clinical interpretation of any staining, or the absence of staining, must be complemented by morphological studies and evaluation of proper controls. Evaluation must be

- Wild-type p53: short $T_{1/2}$ ➔ low concentrations
- Mutant p53: longer $T_{1/2}$ ➔ intra-nuclear accumulation ➔ overexpression

USCAP

www.nature.com/modpathol

ARTICLE OPEN

Check for updates

p53 immunohistochemistry in endometrial cancer: clinical and molecular correlates in the PORTEC-3 trial

Lisa Vermij[1], Alicia León-Castillo[1], Naveena Singh[2], Melanie E. Powell[3], Richard J. Edmondson[4], Catherine Genestie[5], Pearly Khaw[6], Jan Pyman[7], C. Meg McLachlin[8], Prafull Ghatage[9], Stephanie M. de Boer[10], Hans W. Nijman[11], Vincent T. H. B. M. Smit[1], Emma J. Crosbie[4,12], Alexandra Leary[13], Carien L. Creutzberg[10], Nanda Horeweg[10], Tjalling Bosse[1] ✉ and for the TransPORTEC consortium*

- Endometrioid, stage I, Gr. 3, deep MI or LVSI (or both),
- Endometrioid, stage II or III, or stage I to III with serous or clear cell histology

Standard molecular classification of endometrial cancers (EC) is now endorsed by the WHO and identifies p53-abnormal (p53abn) EC as the subgroup with the poorest prognosis and the most likely to benefit from adjuvant chemo(radio)therapy. P53abn EC are *POLE* wildtype, mismatch repair proficient and show abnormal immunohistochemical (IHC) staining for p53. Correct interpretation of routinely performed p53 IHC has therefore become of paramount importance. We aimed to comprehensively investigate abnormal p53 IHC patterns and their relation to clinicopathological and molecular features. Tumor material of 411 molecularly classified high-risk EC from consenting patients from the PORTEC-3 clinical trial were collected. p53 IHC was successful in 408 EC and was considered abnormal when the tumor showed a mutant expression pattern (including subclonal): overexpression, null or cytoplasmic. The presence of pathogenic mutations was determined by next generation sequencing (NGS). Abnormal p53 expression was observed in 131/408 (32%) tumors. The most common abnormal p53 IHC pattern was overexpression ($n = 89$, 68%), followed by null ($n = 12$, 9%) and cytoplasmic ($n = 3$, 2%). Subclonal abnormal p53 staining was observed in 27 cases (21%), which was frequently but not exclusively, associated with *POLE* mutations and/or MMRd ($n = 22/27$; $p < 0.001$). Agreement between p53 IHC and *TP53* NGS was observed in 90.7%, resulting in a sensitivity and specificity of 83.6% and 94.3%, respectively. Excluding *POLE*mut and MMRd EC, as per the WHO-endorsed algorithm, increased the accuracy to 94.5% with sensitivity and specificity of 95.0% and 94.1%, respectively. Our data shows that awareness of the abnormal p53 IHC patterns are prerequisites for correct EC molecular classification. Subclonal abnormal p53 expression is a strong indicator for *POLE*mut and/or MMRd EC. No significant differences in clinical outcomes were observed among the abnormal p53 IHC patterns. Our data support use of the WHO-endorsed algorithm and combining the different abnormal p53 IHC patterns into one diagnostic entity (p53abn EC).

Modern Pathology (2022) 35:1475–1483; https://doi.org/10.1038/s41379-022-01102-x

Mod Pathol. Oct 2022;35(10):1475-1483.

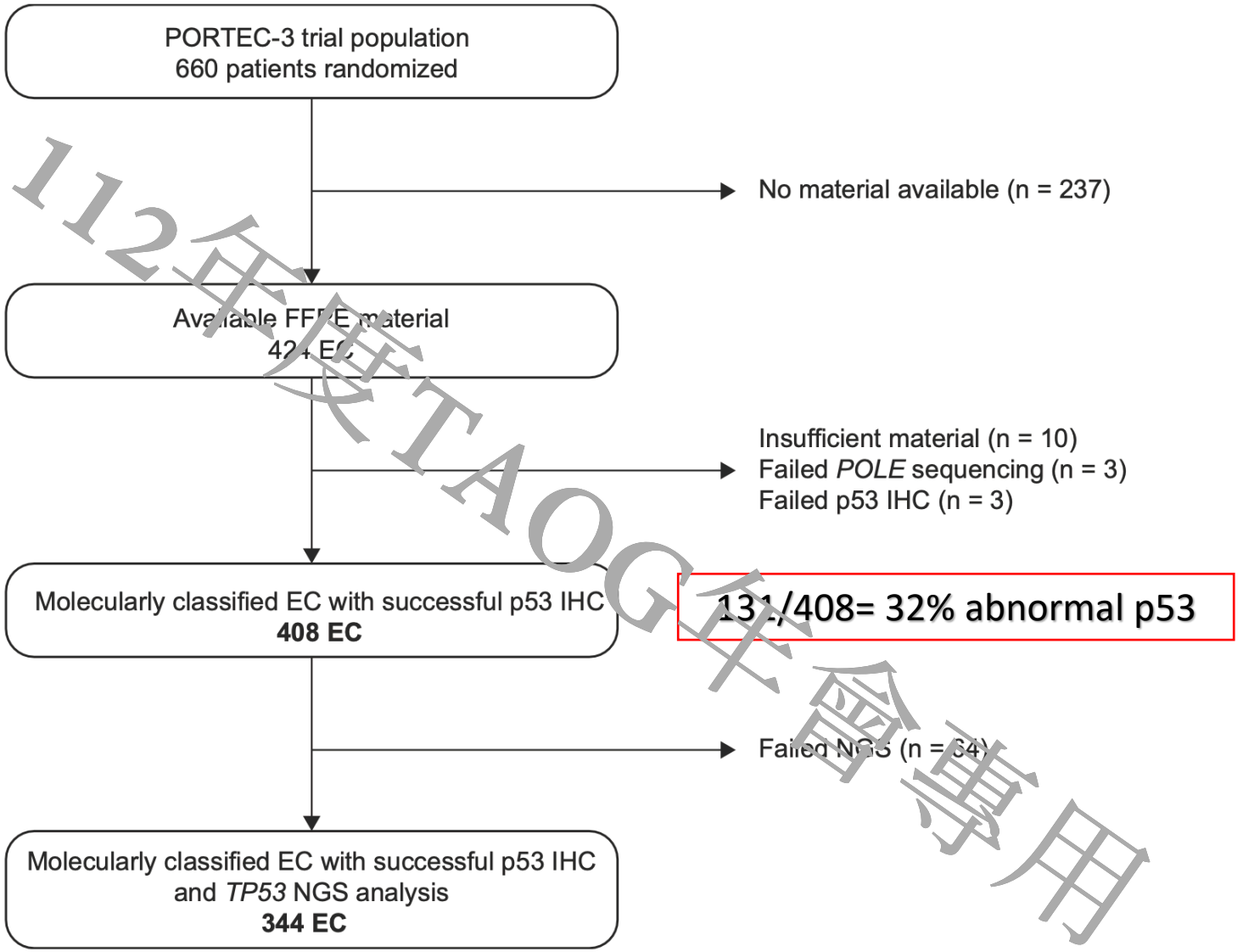
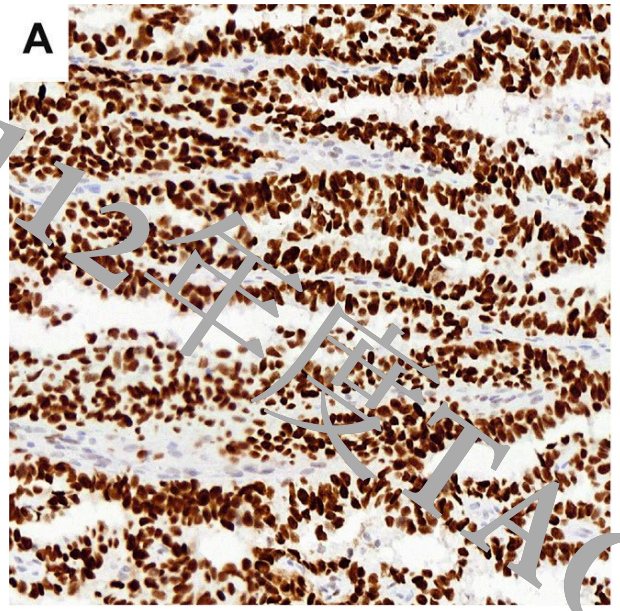


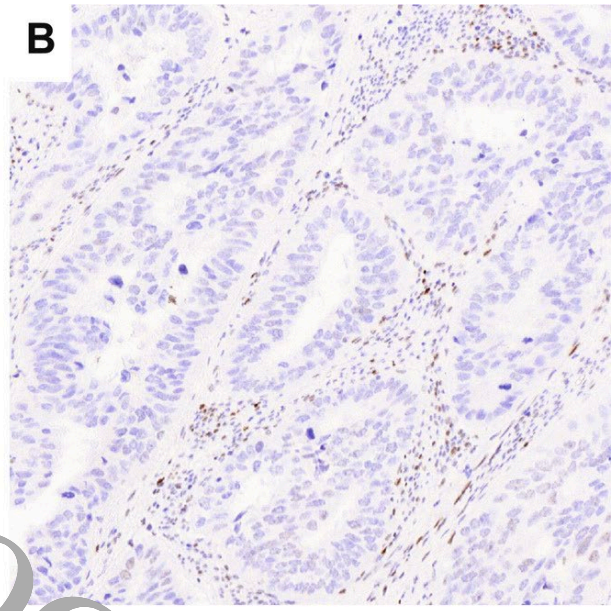
Fig. 2 Flowchart of cohort selection. FFPE, formalin-fixed, paraffin-embedded; EC, endometrial cancer; IHC, immunohistochemistry; NGS, next generation sequencing.

Mod Pathol. Oct 2022;35(10):1475-1483.

p53 (DO-7, 1:200; Agilent DAKO)

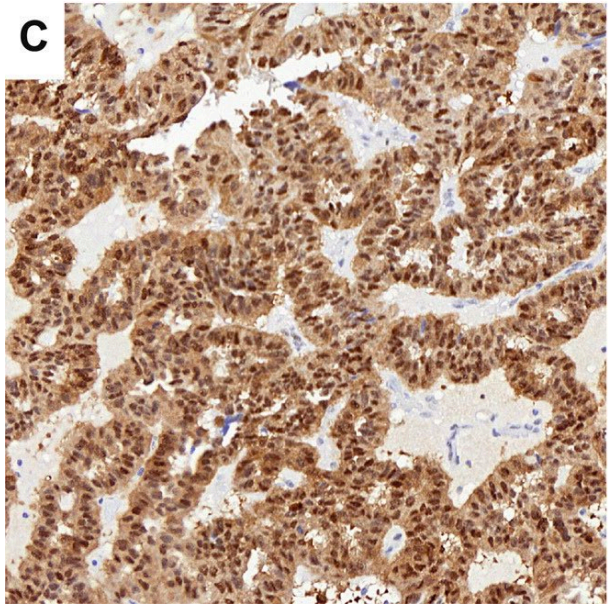
Mutant overexpression (nuclear)
n=89/131, 68%

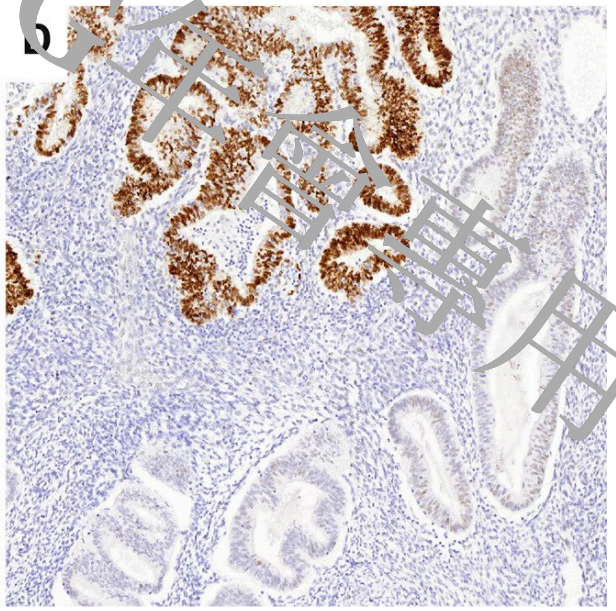




Null mutant
n=12/131, 9%

Cytoplalsmic
n=3/131, 2%





Subclonal abnormal p53 expression
n=27/131, 21%

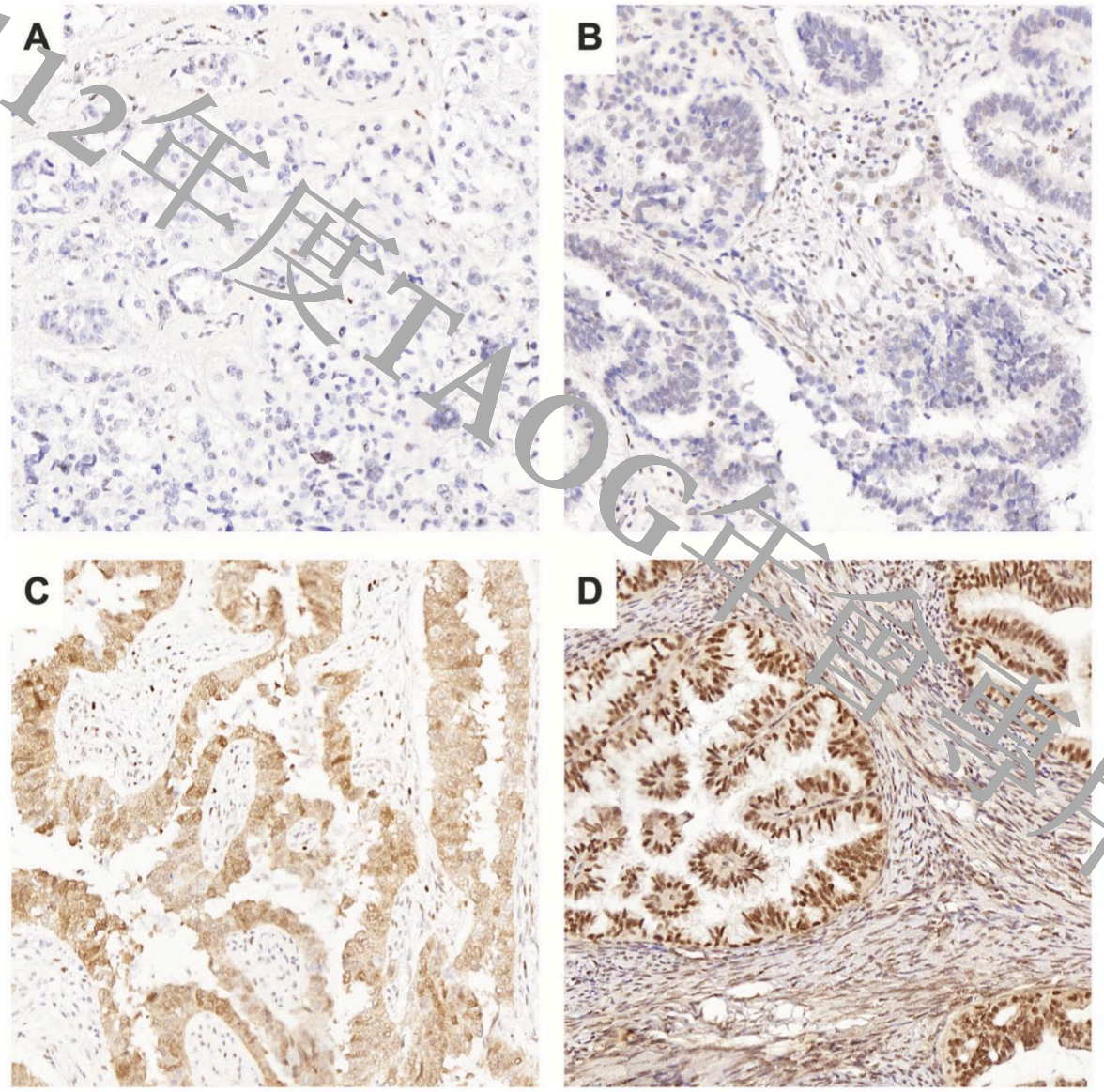
Mod Pathol. Oct 2022;35(10):1475-1483.

p53 IHC pattern

1. Wildtype p53 expression: nuclear staining of variable intensity in 1–80% of the tumor
2. Mutant overexpression:
   - Strong p53 (+) > 80% tumor nuclei
   - Missense mutations in the DNA binding domain
3. Null mutant
   - Complete p53 absence with positive internal control
   - frameshift / nonsense mutations
   - truncated p53 protein
4. Cytoplasmic
   - Cytoplasmic p53 (+) > 80% tumor
   - mutations in the tetramerization or C-terminal domain
5. Subclonal abnormal p53 expression
   - confined to a distinct geographic area, < 80% of the tumor volume
   - *TP53* is not always identified by sequencing method
6. Abnormal IHC indicates *TP53* mutation in EC biopsies: 94% specificity and 91% sensitivity.

Discordant results between p53 IHC and *TP53* NGS

IHC: p53-wt
NGS: frameshift *TP53*
Retrospect: null IHC



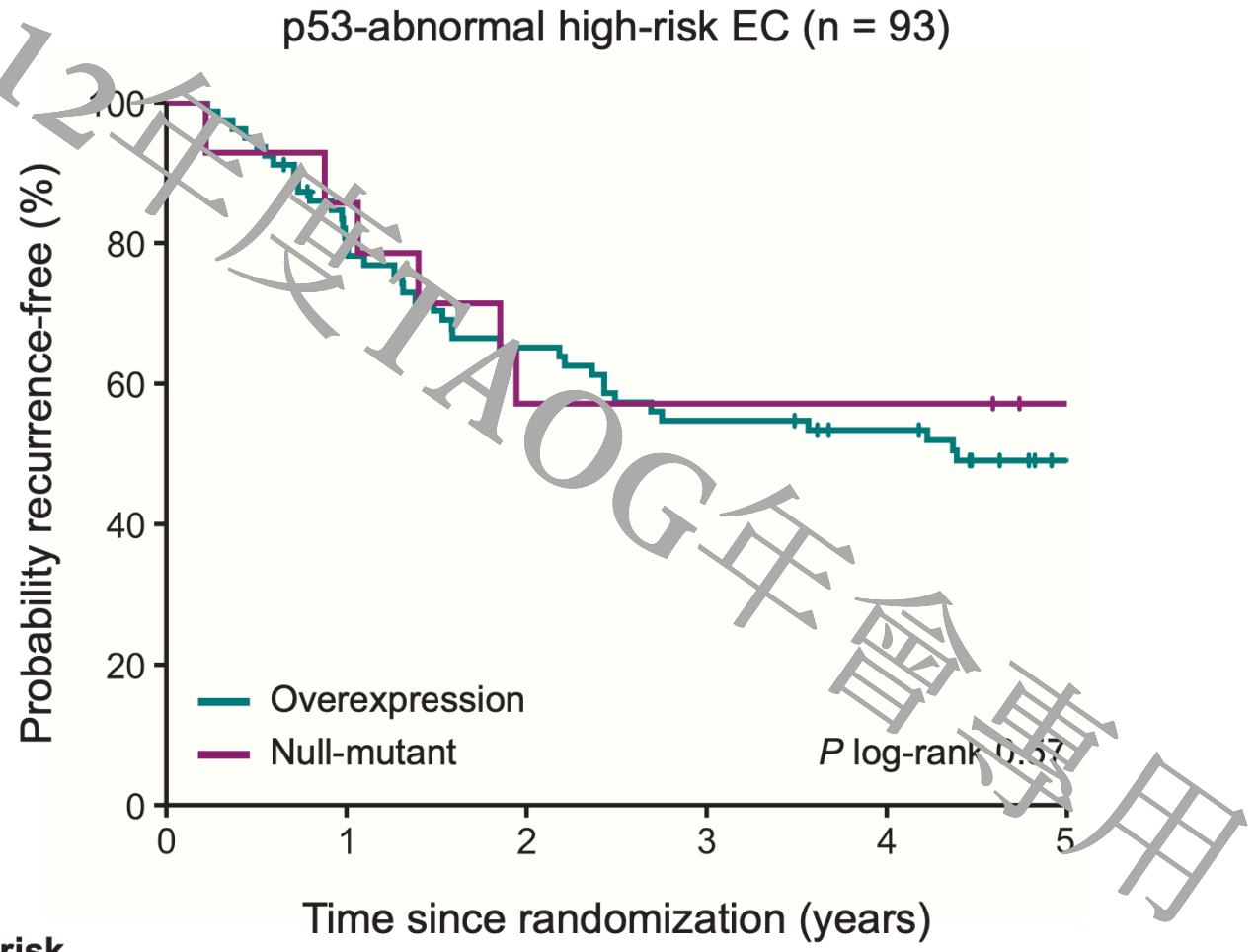
IHC: p53-wt
NGS: frameshift *TP53*
Retrospect: null IHC

IHC: p53-wt
NGS: nonsense *TP53*-mut
Retrospect: cytoplasmic

IHC: p53 overexpression
NGS: *TP53*-wt
Retrospect: overstained

Mod Pathol. Oct 2022;35(10):1475-1483.

p53 mutant overexpression and null-mutant: similar PFS



No. at risk						
Overexpression	79	61	50	42	38	28
Null-mutant	14	12	8	8	8	6

Mod Pathol. Oct 2022;35(10):1475-1483.

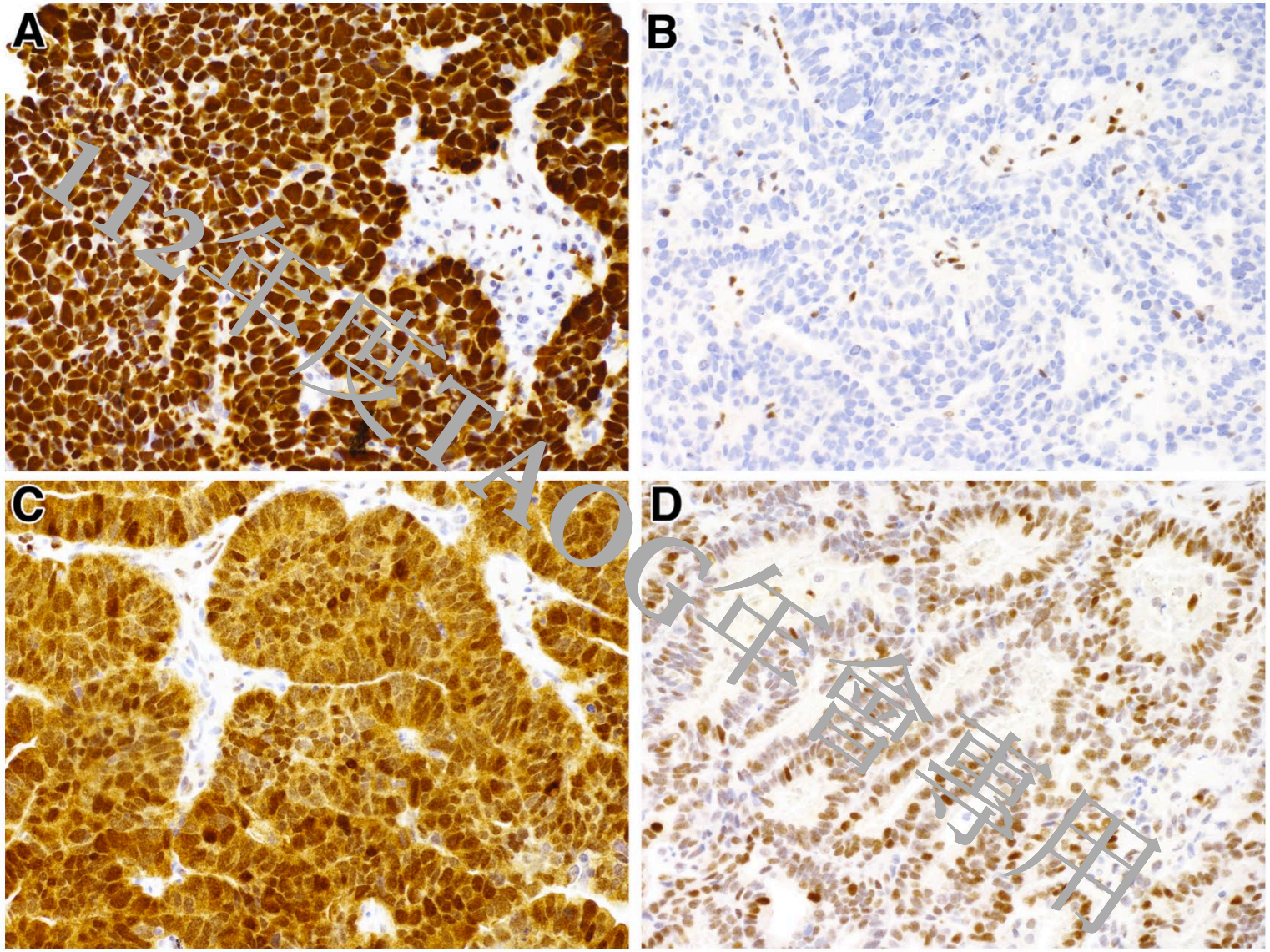


Figure 1. Expression patterns of p53 immunostaining. (A–C) Examples of p53abn overexpression, complete absence, and cytoplasmic patterns. (D) An example of normal (wild-type) expression.

J Pathol. Mar 2020;250(3):336-345.

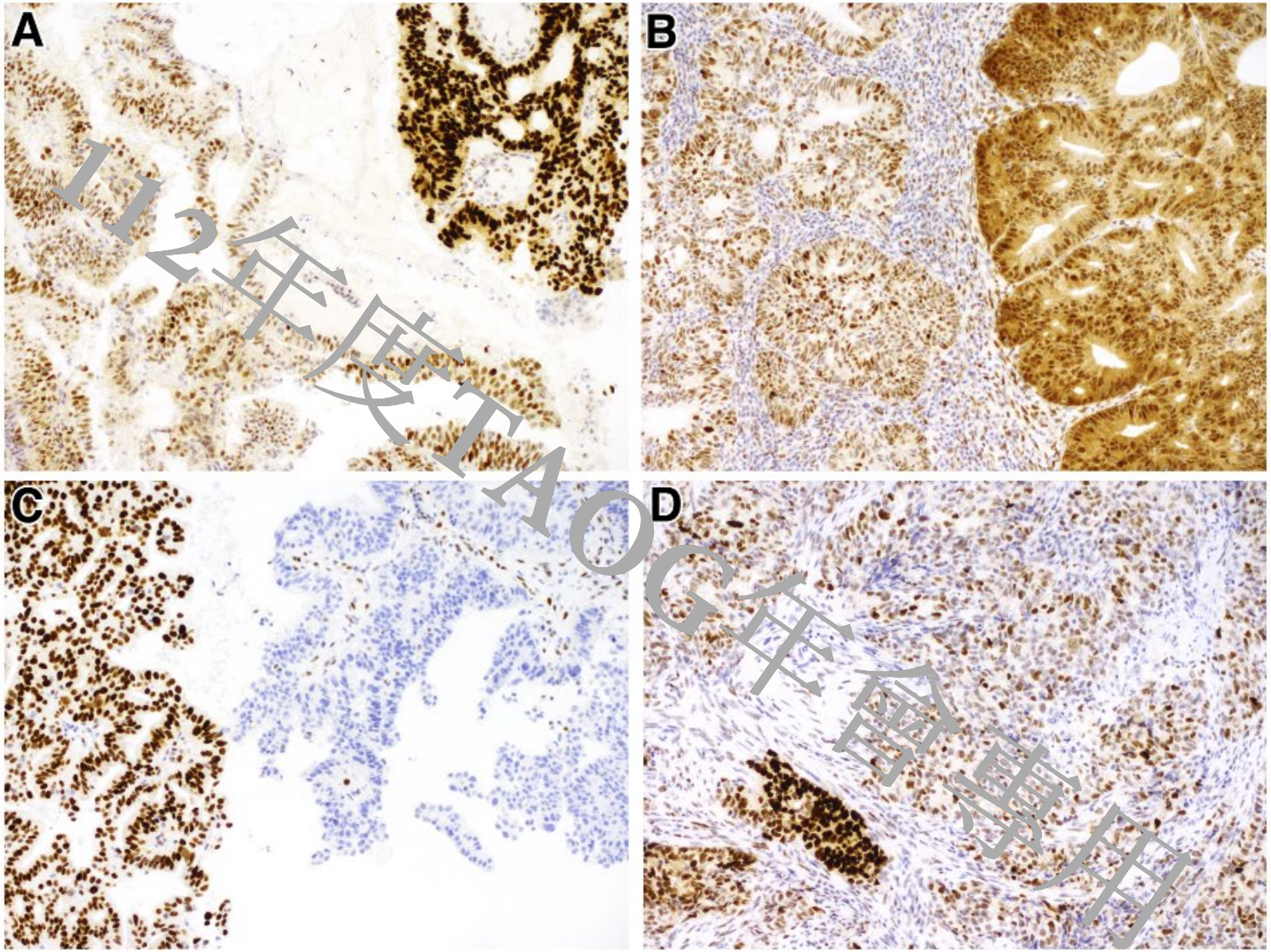


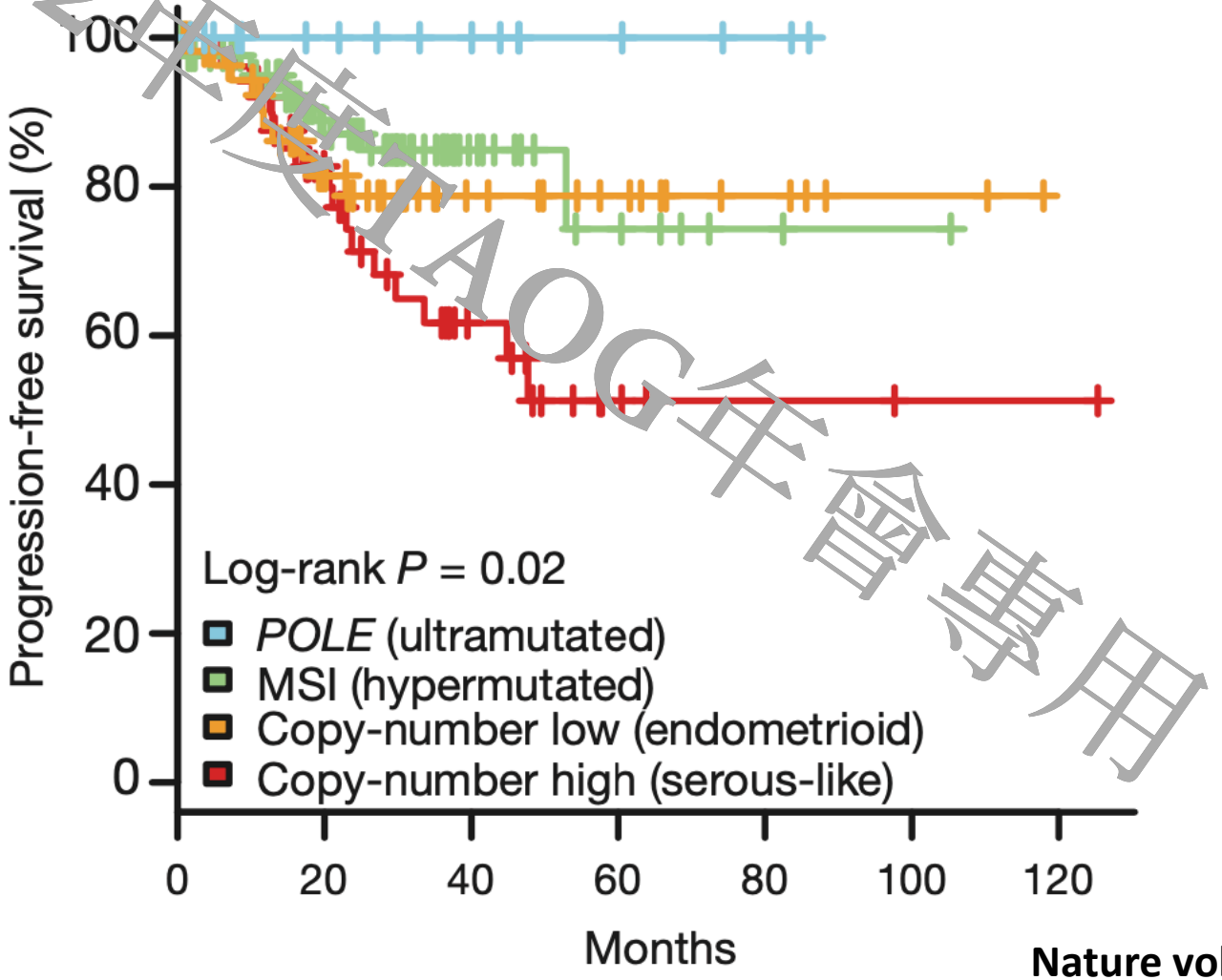
Figure 2. Subclonal p53 immunostaining. (A, B, D) Cases showing a combination of normal (wild-type) and p53abn expression (overexpression in A and D; cytoplasmic in B). (C) An example of two p53abn patterns, overexpression, and complete absence.

J Pathol. Mar 2020;250(3):336-345.

Content

- The role of p53 in carcinogenesis
- Diagnosis of abnormal p53 expression
- Significance of p53 mutation in endometrial cancer
  - Impact in prognosis
  - Selection of adjuvant therapy

Copy-number high tumors have the poorest outcome.



Nature volume 497, pages67–73(2013)

Clinical Cancer Research

Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer—Combined Analysis of the PORTEC Cohorts

Ellen Stelloo[1], Remi A. Nout[2], Elisabeth M. Osse[1], Ina J. Jürgenliemk-Schulz[3], Jan J. Jobsen[4], Ludy C. Lutgens[5], Elzbieta M. van der Steen-Banasik[6], Hans W. Nijman[7], Hein Putter[8], Tjalling Bosse[2], Carien L. Creutzberg[2], and Vincent T.H.B.M. Smit[1]

Abstract

Purpose: Recommendations for adjuvant treatment for women with early-stage endometrial carcinoma are based on clinicopathologic features. Comprehensive genomic characterization defined four subgroups: p53-mutant, microsatellite instability (MSI), *POLE*-mutant, and no specific molecular profile (NSMP). We aimed to confirm the prognostic capacity of these subgroups in large randomized trial populations, investigate potential other prognostic classifiers, and integrate these into an integrated molecular risk assessment guiding adjuvant therapy.

Experimental Design: Analysis of MSI, hotspot mutations in 14 genes including *POLE*, protein expression of p53, ARID1a, β-catenin, L1CAM, PTEN, ER, and PR was undertaken on 947 available early-stage endometrioid endometrial carcinomas from the PORTEC-1 and -2 trials, mostly high-intermediate risk (n = 614). Prognostic value was determined using univariable and multivariable Cox proportional hazard models. AUCs of different risk stratification models were compared.

Results: Molecular analyses were feasible in >96% of the patients and confirmed the four molecular subgroups: p53-mutant (9%), MSI (26%), *POLE*-mutant (6%), and NSMP (59%). Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Approximately 15% of high-intermediate risk patients had unfavorable features (substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM), 50% favorable features (*POLE*-mutant, NSMP being microsatellite stable, and *CTNNB1* wild-type), and 35% intermediate features (MSI or *CTNNB1*-mutant).

Conclusions: Integrating clinicopathologic and molecular factors improves the risk assessment of patients with early-stage endometrial carcinoma. Assessment of this integrated risk profile is feasible in daily practice, and holds promise to reduce both overtreatment and undertreatment. *Clin Cancer Res; 22(16); 4215–24.*

Clin Cancer Res. 2016 Aug 15;22(16):4215-24.

PORTEC-1 & -2

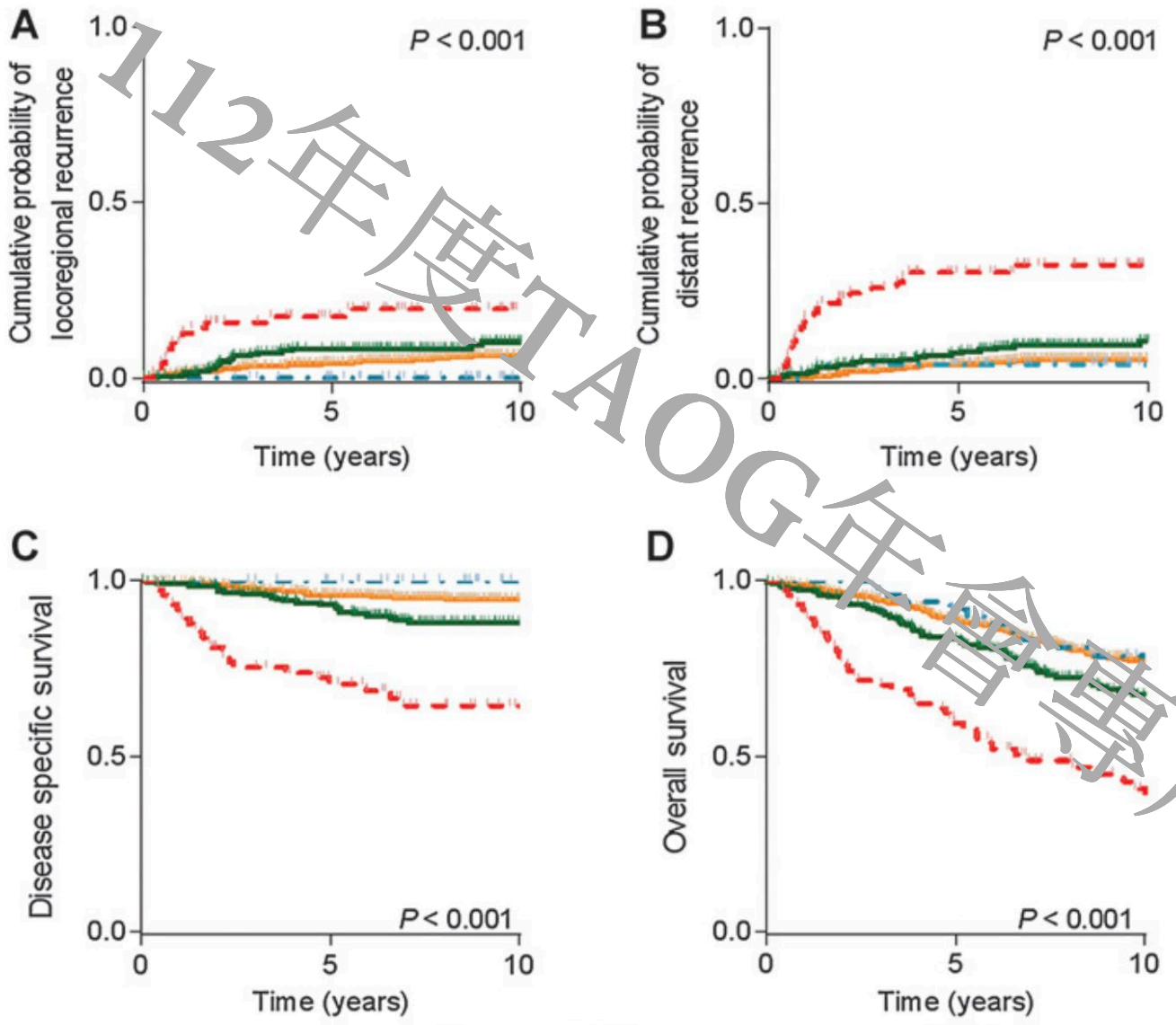


Figure 2.
Survival analyses of molecular subgroups in early-stage endometrial cancer (n = 834). Rate of locoregional recurrences (**A**), rate of distant recurrences (**B**), disease-specific survival (**C**), and overall survival (**D**).

p53 IHC:
clone DO-7, 1:2,000;
Ventana

NSMP: no specific molecular profile

Clin Cancer Res. 2016 Aug 15;22(16):4215-24.

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

Alicia León-Castillo, MD[1]; Stephanie M. de Boer, MD[2]; Melanie E. Powell, MD[3]; Linda R. Mileshkin, MBBS[4]; Helen J. Mackay, MD[5]; Alexandra Leary, MD, PhD[6]; Hans W. Nijman, MD, PhD[6,7]; Naveena Singh, MD, MBBS[8]; Pamela M. Pollock, PhD[9]; Paul Bessette, MD[10]; Anthony Fyles, MD[11]; Christine Haie-Meder, MD[12]; Vincent T. H. B. M. Smit, MD, PhD[1]; Richard J. Edmondson, MD[13]; Hein Putter, MD[14]; Henry C. Kitchener, MD[15]; Emma J. Crosbie, MD, PhD[13]; Marco de Bruyn, PhD[7]; Remi A. Nout, MD[2]; Nanda Horeweg, MD, PhD[2]; Carien L. Creutzberg, MD, PhD[2]; and Tjalling Bosse, MD, PhD[1] on behalf of the TransPORTEC consortium

PURPOSE The randomized Adjuvant Chemoradiotherapy Versus Radiotherapy Alone in Women With High-Risk Endometrial Cancer (PORTEC-3) trial investigated the benefit of combined adjuvant chemotherapy and radiotherapy (CTRT) versus radiotherapy alone (RT) for women with high-risk endometrial cancer (EC). Because The Cancer Genome Atlas defined an EC molecular classification with strong prognostic value, we investigated prognosis and impact of chemotherapy for each molecular subgroup using tissue samples from PORTEC-3 trial participants.

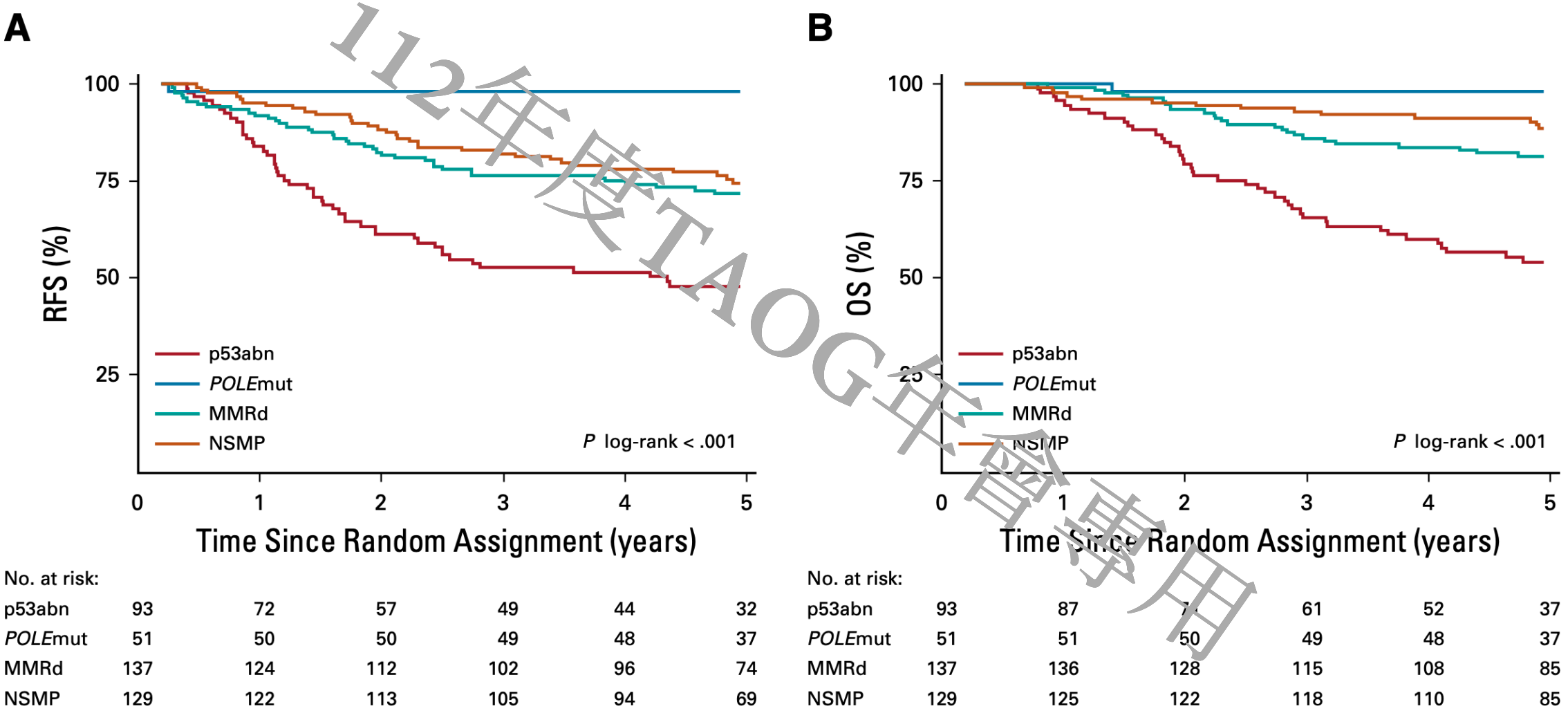
METHODS Paraffin-embedded tissues of 423 consenting patients were collected. Immunohistochemistry for p53 and mismatch repair (MMR) proteins, and DNA sequencing for *POLE* exonuclease domain were done to classify tumors as p53 abnormal (p53abn), *POLE*-ultramutated (*POLE*mut), MMR-deficient (MMRd), or no specific molecular profile (NSMP). The primary end point was recurrence-free survival (RFS). Kaplan-Meier method, log-rank test, and Cox model were used for analysis.

RESULTS Molecular analysis was successful in 410 high-risk EC (97%), identifying the 4 subgroups: p53abn EC (n = 93; 23%), *POLE*mut (n = 51; 12%), MMRd (n = 137; 33%), and NSMP (n = 129; 32%). Five-year RFS was 48% for patients with p53abn EC, 98% for *POLE*mut EC, 72% for MMRd EC, and 74% for NSMP EC ($P <$ .001). The 5-year RFS with CTRT versus RT for p53abn EC was 59% versus 36% (P = .019); 100% versus 97% for patients with *POLE*mut EC (P = .637); 68% versus 76% (P = .428) for MMRd EC; and 80% versus 68% (P = .243) for NSMP EC.

CONCLUSION Molecular classification has strong prognostic value in high-risk EC, with significantly improved RFS with adjuvant CTRT for p53abn tumors, regardless of histologic type. Patients with *POLE*mut EC had an excellent RFS in both trial arms. EC molecular classification should be incorporated in the risk stratification of these patients as well as in future trials to target specific subgroups of patients.

J Clin Oncol 38:3388-3397. © 2020 by American Society of Clinical Oncology

PORTEC-3



p53 IHC: clone DO-7, 1:2000, DAKO

J Clin Oncol. 2020 Oct 10;38(29):3388-3397.

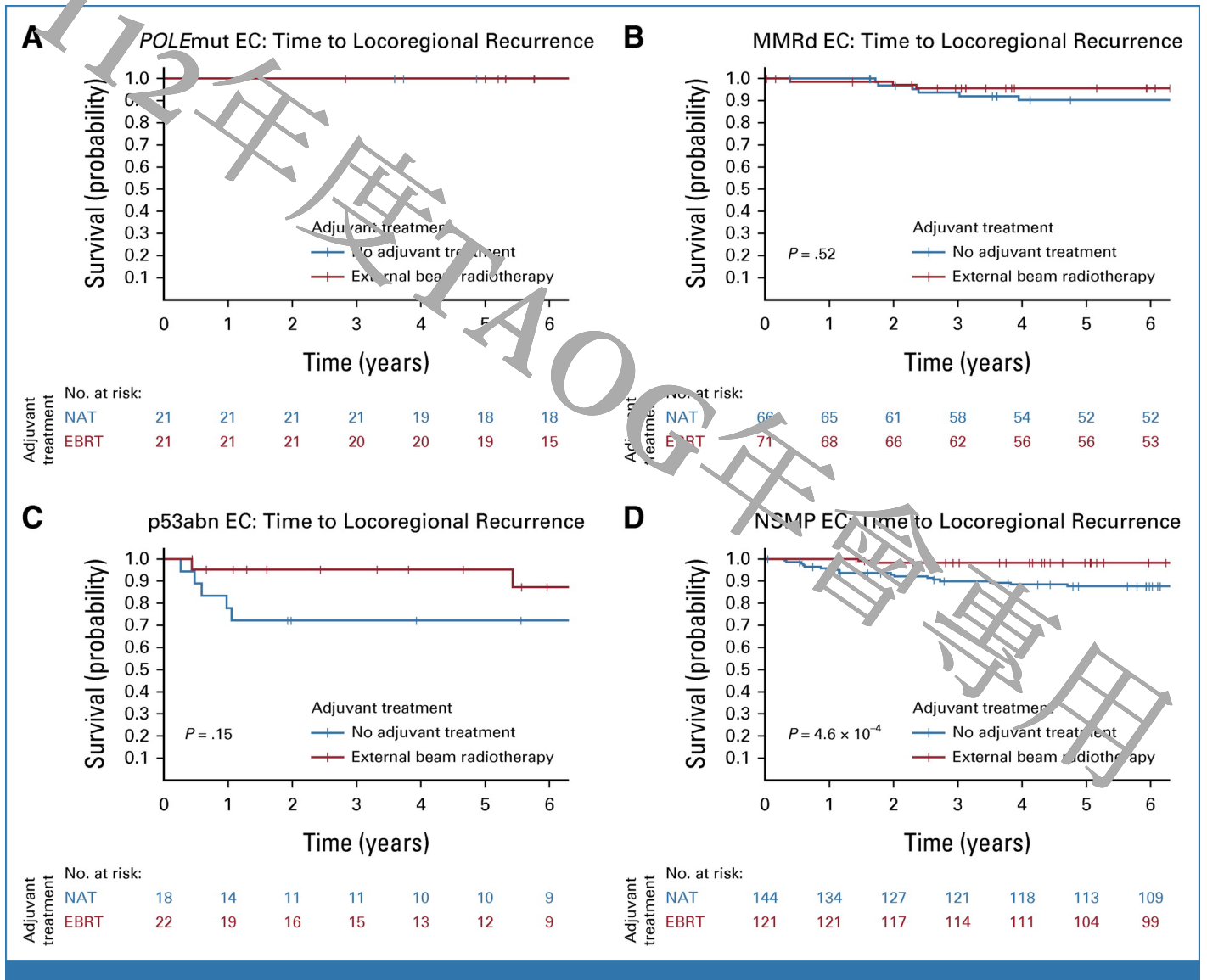
TP53 mutation in endometrial cancer

Significance in Prognosis

Choice of adjuvant therapy

Time to locoregional recurrence per molecular class in PORTEC-1

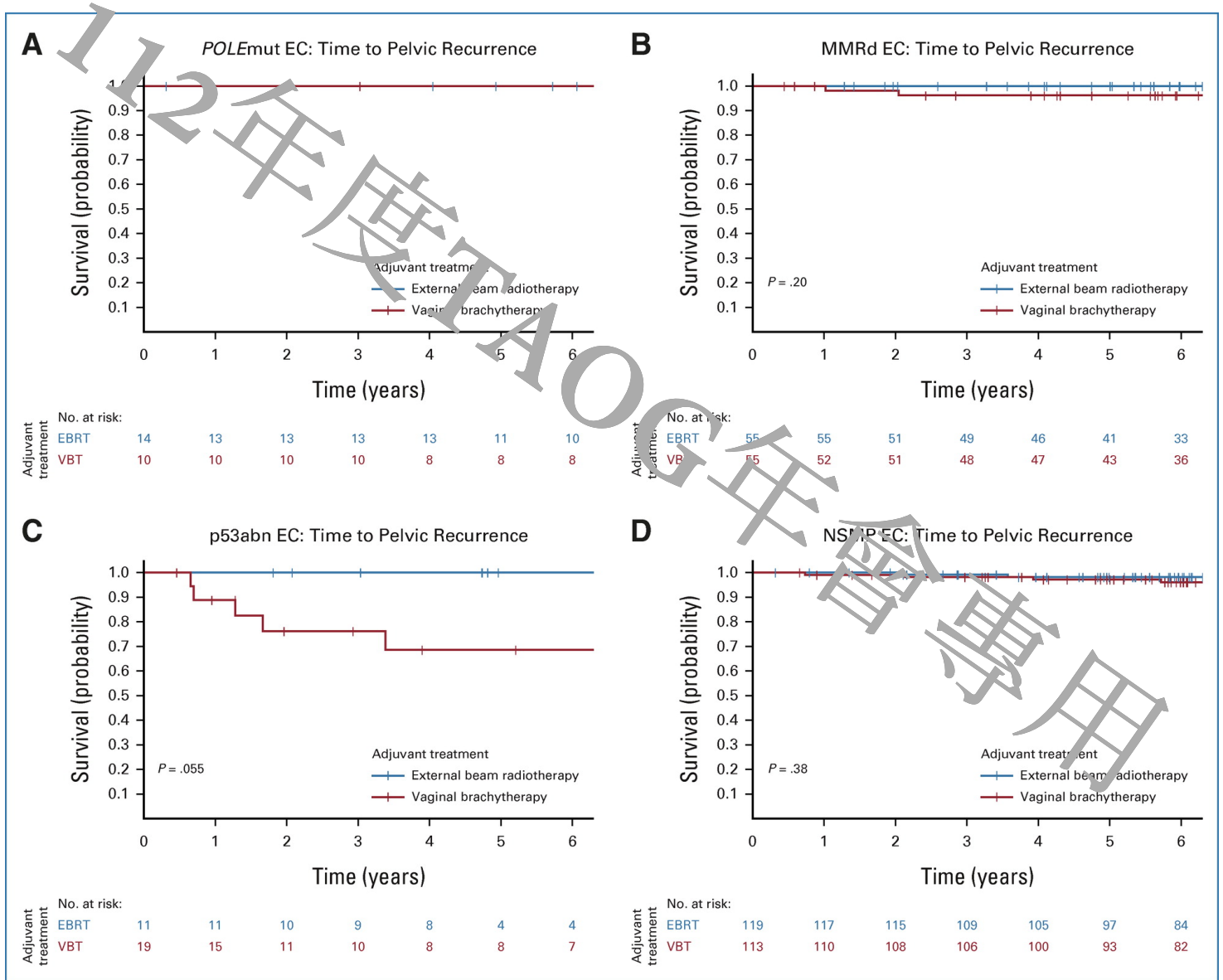
Stage IC, Gr. 1-2 or Stage IB Gr. 2-3 EC, EBRT vs NAT



PMID: 37487144

Time to locoregional recurrence per molecular class in PORTEC-2

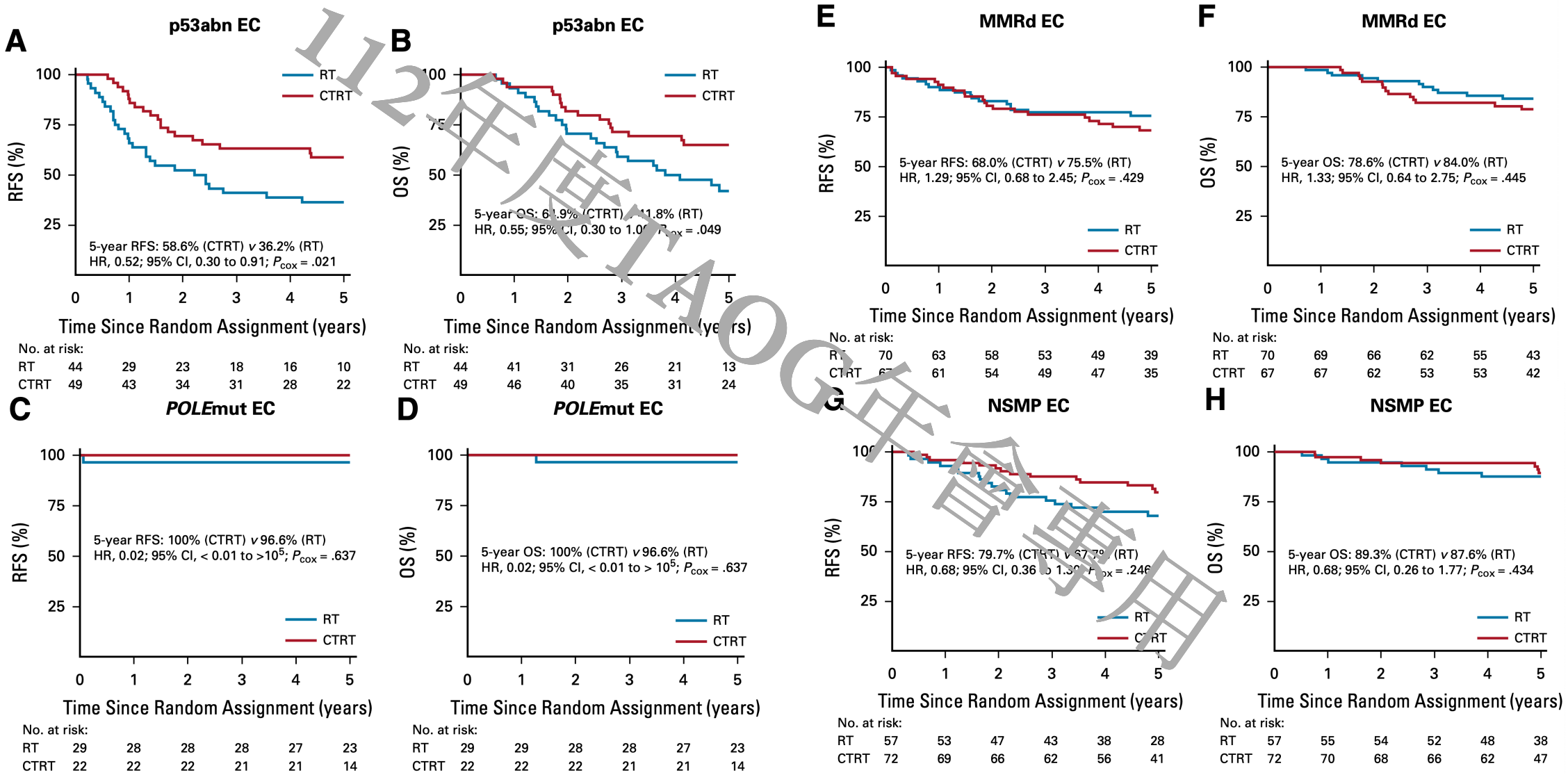
Stage I or stage IIA with HIR, EBRT vs VBT



PMID: 37487144

Impact of molecule characterictics in adjuvant therapy_ PORTEC-3

High-risk EC, RT+CT vs RT alone



p53 IHC: clone DO-7, 1:2000, DAKO

J Clin Oncol. 2020 Oct 10;38(29):3388-3397.

Gynecologic Oncology 161 (2021) 113–121

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: An NRG Oncology study

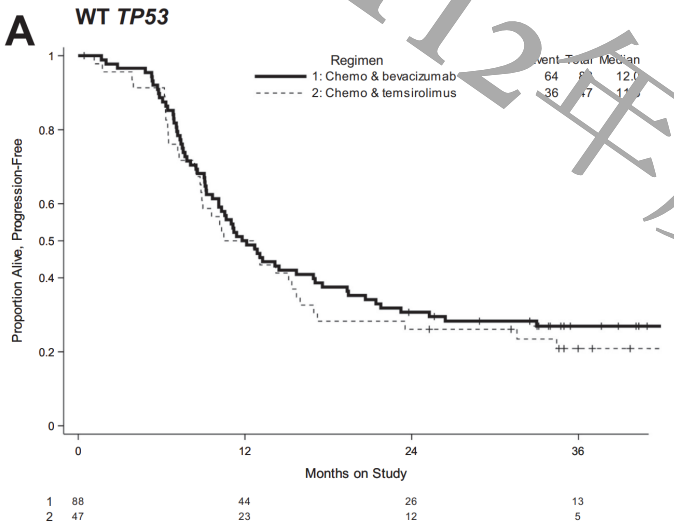
Kimberly K. Leslie [a,b,*,1], Virginia L. Filiaci [c], Adrianne R. Mallen [a,2], Kristina W. Thiel [a], Eric J. Devor [a,b,1], Katherine Moxley [d], Debra Richardson [d], David Mutch [e], Angeles Alvarez Secord [f], Krishnansu S. Tewari [g], Megan E. McDonald [a], Cara Mathews [h], Casey Cosgrove [i], Summer Dewdney [j], Yovanni Casablanca [k], Amanda Jackson [l], Peter G. Rose [m], XunClare Zhou [n], Michael McHale [o], Heather Lankes [p], Douglas A. Levine [q,3], Carol Aghajanian [r,3]

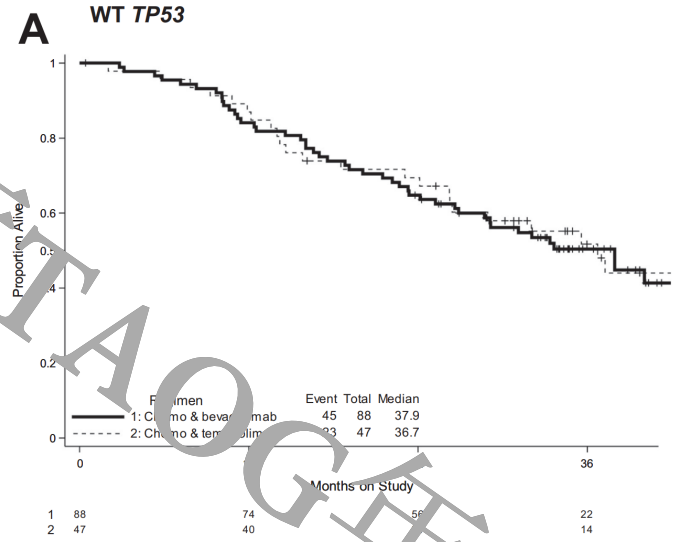
[a] Department of Obstetrics and Gynecology, University of Iowa, Iowa City, IA 52242, USA
[b] Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA
[c] NRG Oncology, Clinical Trial Development Division, Biostatistics & Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA
[d] Stephenson Cancer Center Gynecologic Cancers Clinic, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73117, USA
[e] Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO 63108, USA
[f] Duke University Institute, Duke University Health System, Durham, NC 27710, USA
[g] University of California Irvine Medical Center, Irvine, CA 92868, USA
[h] Women and Infants Hospital in Rhode Island/The Warren Alpert Medical School of Brown University, Providence, RI 02905, USA
[i] James Cancer Hospital and Solove Research Institute, Obstetrics and Gynecology, Ohio State University Medical Center, Columbus, OH 43210, USA
[j] Gynecology, Rush University Medical Center, Chicago, IL 60612, USA
[k] Gynecology, Walter Reed National Military Medical Center, Bethesda, MD 20814, USA
[l] Gynecologic Oncology Center, University of Cincinnati Cancer Institute, Cincinnati, OH 45219, USA
[m] Cleveland Clinic Foundation and Case Western Reserve University, Cleveland, OH 44195, USA
[n] Department of Gynecology, Hospital of Central Connecticut, New Britain, CT 06451, USA
[o] Department of Gynecology, University of California San Diego, La Jolla, CA 92037, USA
[p] Biopathology Center, The Research Institute at Nationwide Children's Hospital, Columbus, OH 43205, USA
[q] Gynecologic Oncology, NYU Langone Health, 240 E 38th St 19th Floor, New York, NY 10016, USA
[r] Memorial Sloan Kettering Cancer and Weill Cornell Medical Center, 1275 York Ave, New York, NY 10065, USA

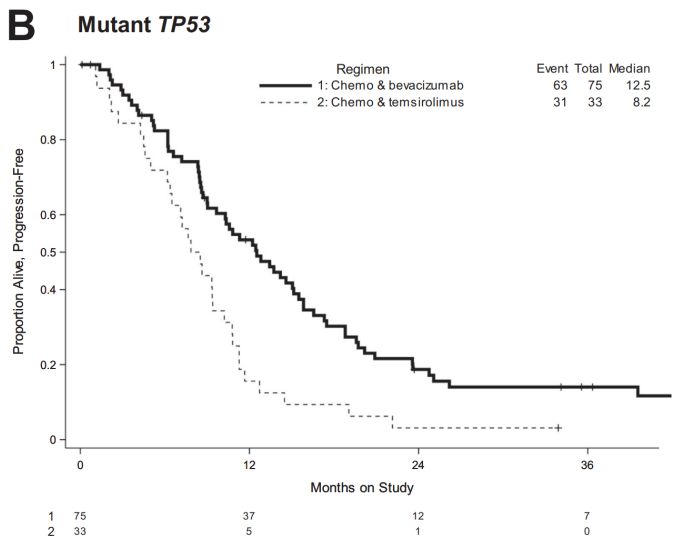
HIGHLIGHTS

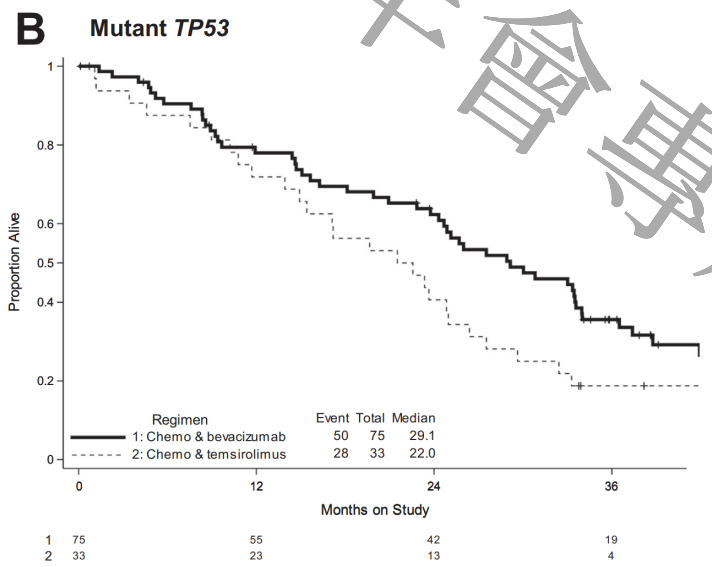
- In previous analyses of GOG-86P, the addition of upfront bevacizumab to chemotherapy did not improve outcomes overall.
- We now report that cases with mutations in the tumor suppressor *TP53* experienced longer PFS and OS with bevacizumab.
- OS with bevacizumab versus temsirolimus + chemotherapy doubled for cases with mutated *TP53* (30 versus 14.4 months).
- A mutation in *TP53* is a potential biomarker for sensitivity to bevacizumab when added to chemotherapy upfront.

TP53 mutation is associated with improved PFS/OS on bevacizumab-containing arm. GOG-86P









- Phase II trial,
- stage III/IVA, stage IVB or recurrent
- Arm 1: PC + bevacizumab
- Arm 2: PC + temsirolimus
- Arm 3: ixabepilone / carboplatin (IC) + bevacizumab

TP53 analysis: parallel sequencing using a custom Roche Noblemen SeqCap EZ system to enrich for targeted regions.

Gynecol Oncol. 2021 Apr;161(1):113-121.

Table 3. Ongoing trials for endometrial cancer (EC) treatment based on molecular classification.

Trial Name	Start Date	Estimated Completion Date	Country	Phase	Trial Type	Included EC Patients	Mutation	Treatment	Primary Outcome
PORTEC-4a NCT03469674	June 2016	Dec. 2025	EU	III	Randomized 2:1	HIR *	POLE CTNNB1 MMR TP53 L1CAM	(1) Vaginal brachytherapy (2) Experimental group: observation, brachytherapy, or EBRT	5-year vaginal recurrence
RAINBO	-	-	EU, USA, Canada, NZ, Australia	III	Non-randomized		POLE MMRd P53 NSMP	(1) P53: chemoradiation +/− PARPi (2) MMRd: radiation +/− checkpoint inhibitor (3) NSMP: Chemoradiation vs radiation + hormonal treatment (4) POLE: no adjuvant	5-year RFS
TAPER NCT04705649	July 2020	Dec. 2023	Canada	II, III	Single arm	Early stage EC	POLE NSMP	Observation	3-year pelvic recurrences (including vaginal)
CAN-STAMP NCT04159155	Nov. 2020	Sep. 2025	Canada	II, III	Randomized	Early & late stage	P53 serous	Early stage: (1): Chemotherapy + chemoradiation (2) Chemotherapy Late stage: (1): Chemotherapy (2): Chemotherapy + Niraparib	3-year RFS
NRG-GY018 NCT03914612 Pembrolizumab	July 2019	June 2023	Canada USA	III	Randomized	Stage III-IV, recurrent	MMRd	(1) Chemotherapy + placebo (2) Chemotherapy + Pembrolizumab	5-year PFS
NRG-GY020 NCT04214067 Pembrolizumab	Feb. 2020	Feb. 2024	USA Puerto Rico	III	Randomized Open label Two group	Stage I-II, HIR **	MMRd	(1) Radiation + placebo (2) Radiation + Pembrolizumab	5-year RFS

EU European Union; HIR high-intermediate risk; CTNNB1 catenin beta 1; L1CAM L1 cell adhesion molecule; MMRd mismatch repair deficient; EBRT external beam radiation therapy; NZ New Zealand p53wt p53 wild type; NSMP no specific molecular profile; RFS recurrent free survival; PFS progression free survival; * Stage IA, grade 3; stage IB, grade $\frac{1}{2}$ and age >60; stage IB grade $\frac{1}{2}$ and LVSI; stage IB grade 3 without LVSI; stage II microscopic, grade 1; ** GOG criteria for HIR: age > = 70 and one risk factor; 50–69 and two risk factors; <=50 and three risk factors; risk factors: LVSI, grade 3, >50% myometrial involvement.

OPEN ACCESS

PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer

Anne Sophie V M van den Heerik ,[1] Nanda Horeweg ,[1] Remi A Nout,[2] Ludy C H W Lutgens,[3] Elzbieta M van der Steen-Banasik,[4] G Henrike Westerveld,[5] Hetty A van den Berg,[6] Annerie Slot,[7] Friederike L A Kroppe,[8] Stefan Kommoss,[9] Jan Willem M Mens,[2] Marlies E Nowee,[10] Stefan Bijmolt,[11] David Cibula,[12] Tanja C Stam,[13] Ina M Jurgenliemk-Schulz,[14] An Snyers,[15] Moritz Hamann,[16] Aleida G Zwanenburg,[17] Veronique L M A Coen,[18] Katrien Vandecasteele,[19] Charles Gillham,[20] Cyrus Chargari,[21] Karen W Verhoeven-Adema,[22] Hein Putter,[23] Wilbert B van den Hout,[24] Bastiaan G Wortman,[1] Hans W Nijman,[25] Tialling Bosse,[26] Carien L Creutzberg[1]

For numbered affiliations see end of article.

Correspondence to
Anne Sophie V M van den Heerik, Radiotherapy, Leiden Universitair Medisch Centrum, 2333 ZA Leiden, Zuid-Holland, Netherlands; a.v.m.van_den_heerik@lumc.nl

Accepted 17 August 2020
Published Online First 12 October 2020

HIGHLIGHTS

- PORTEC-4a is the first trial to introduce molecular factors in the adjuvant treatment of endometrial cancer.
- Randomization between standard or individualized treatment based on the molecular risk profile.
- PORTEC-4a will show if omitting treatment in cases of favorable molecular profiles is safe and cost-effective.

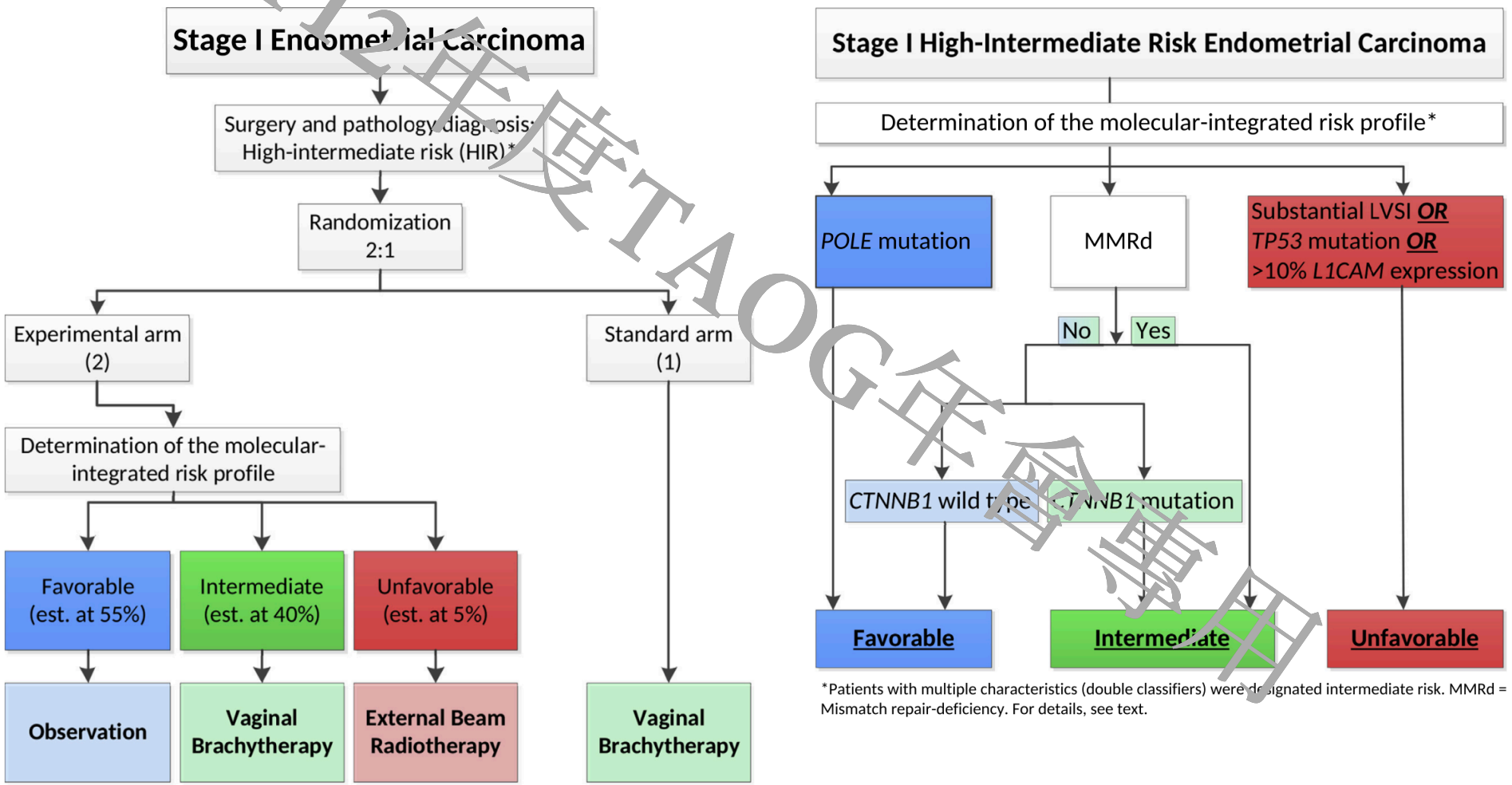
ABSTRACT

Background Vaginal brachytherapy is currently recommended as adjuvant treatment in patients with high-intermediate risk endometrial cancer to maximize local control and has only mild side effects and no or limited impact on quality of life. However, there is still considerable overtreatment and also some undertreatment, which may be reduced by tailoring adjuvant treatment to the patients' risk of recurrence based on molecular tumor invasion; (iii) stage IB grade 3 without lymph-vascular space invasion; or (iv) stage I (microscopic and grade 1).

Endpoints The primary endpoint is vaginal recurrence. Secondary endpoints are recurrence-free and overall survival; pelvic and distant recurrence; 5-year vaginal control (including treatment for relapse); adverse events and patient-reported symptoms and quality of life; and endometrial cancer-related healthcare costs.

Sample size 500 eligible and evaluable patients.

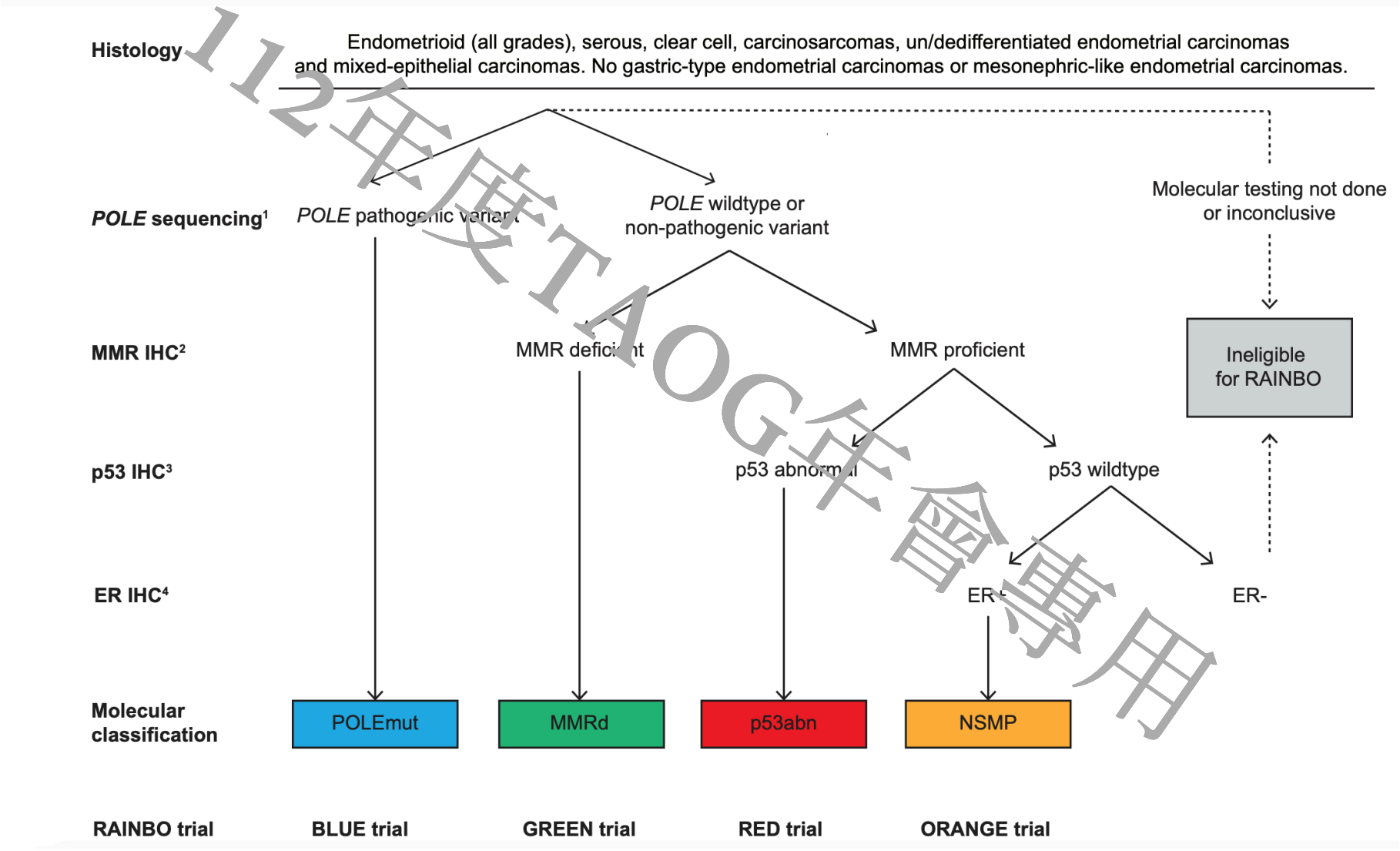
Study design of the **PORTEC-4a** trial



**High-intermediate risk (HIR) endometrial cancer:* stage IA (with invasion) and grade 3; stage IB, grade 1 or 2; with either age ≥ 60 or substantial lymph-vascular space invasion (LVSI); stage IB, grade 3 without LVSI; or stage II (microscopic) with grade 1. Est = estimated.

Gynecol Oncol. 2018 Oct;151(1):69-75.

The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) Algorithm



Int J Gynecol Cancer. Dec 20 2022;33(1):109-17.

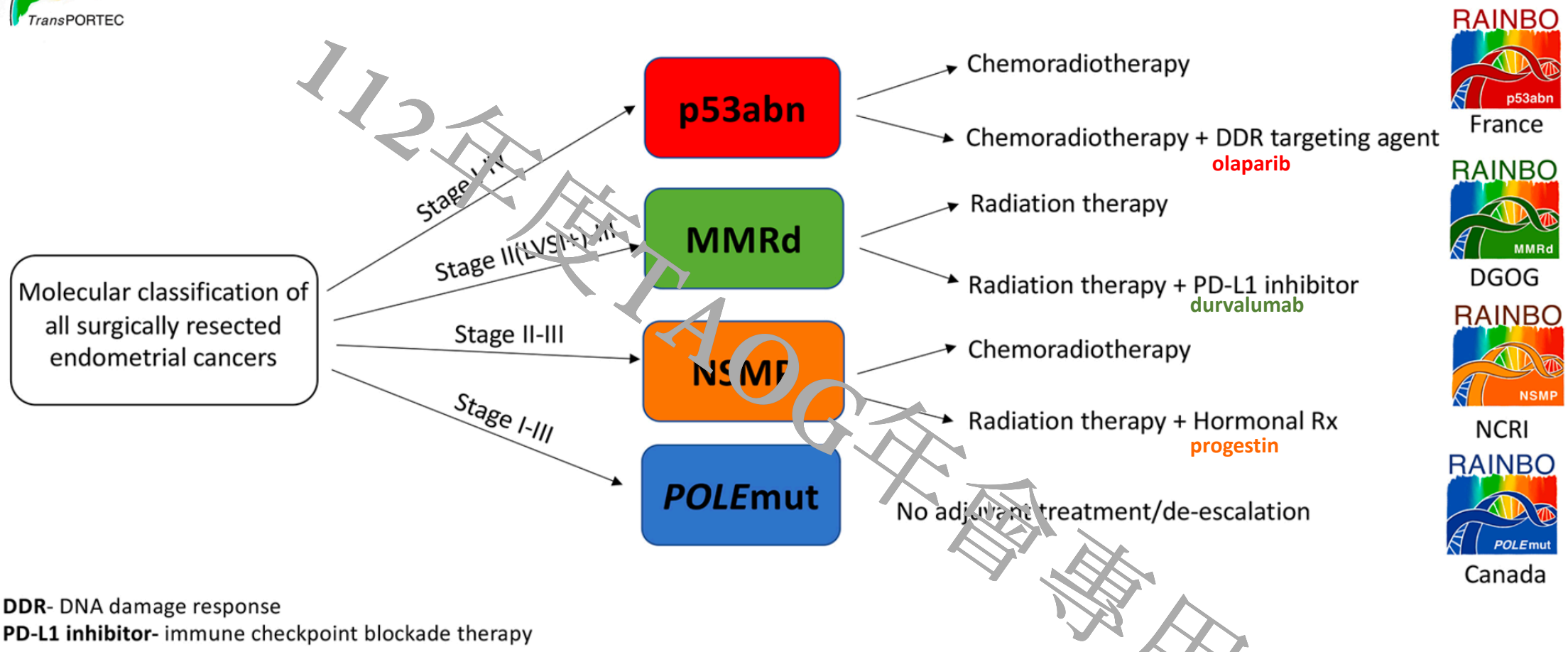
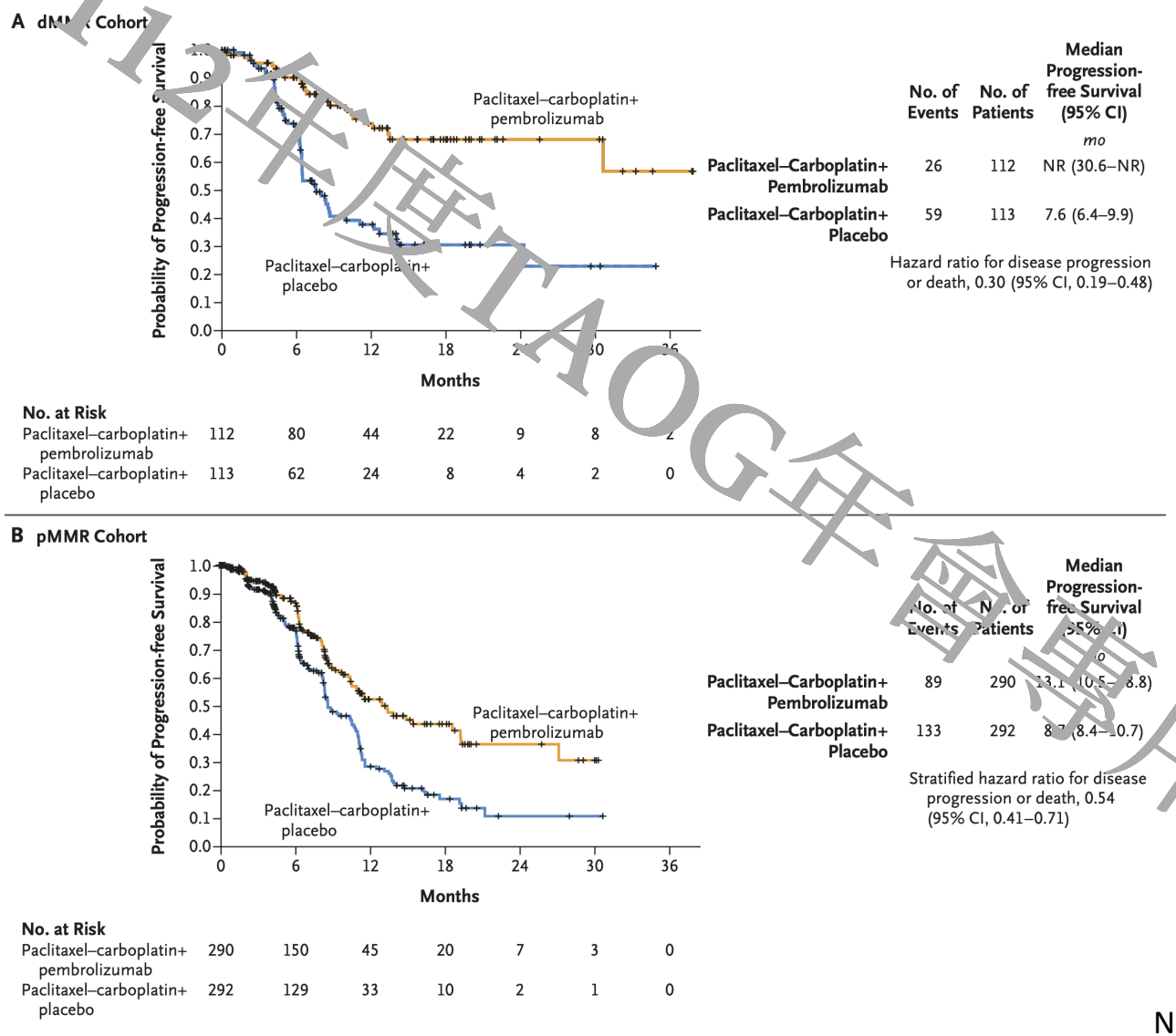


Figure 1. The planned treatment arms for the TransPORTEC RAINBO program of clinical trials.
DDR, DNA damage response; PD-L1, programmed death-ligand 1; POLE, polymerase epsilon; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; RAINBO, refining adjuvant treatment in endometrial cancer based on molecular profile.

Ther Adv Med Oncol. 2021;13:17588359211035959.

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer_NRG-GY018



N Engl J Med. 2023 Jun 8;388(23):2159-2170.

Table 2. Treatment options in p53abn/copy number high endometrial cancer

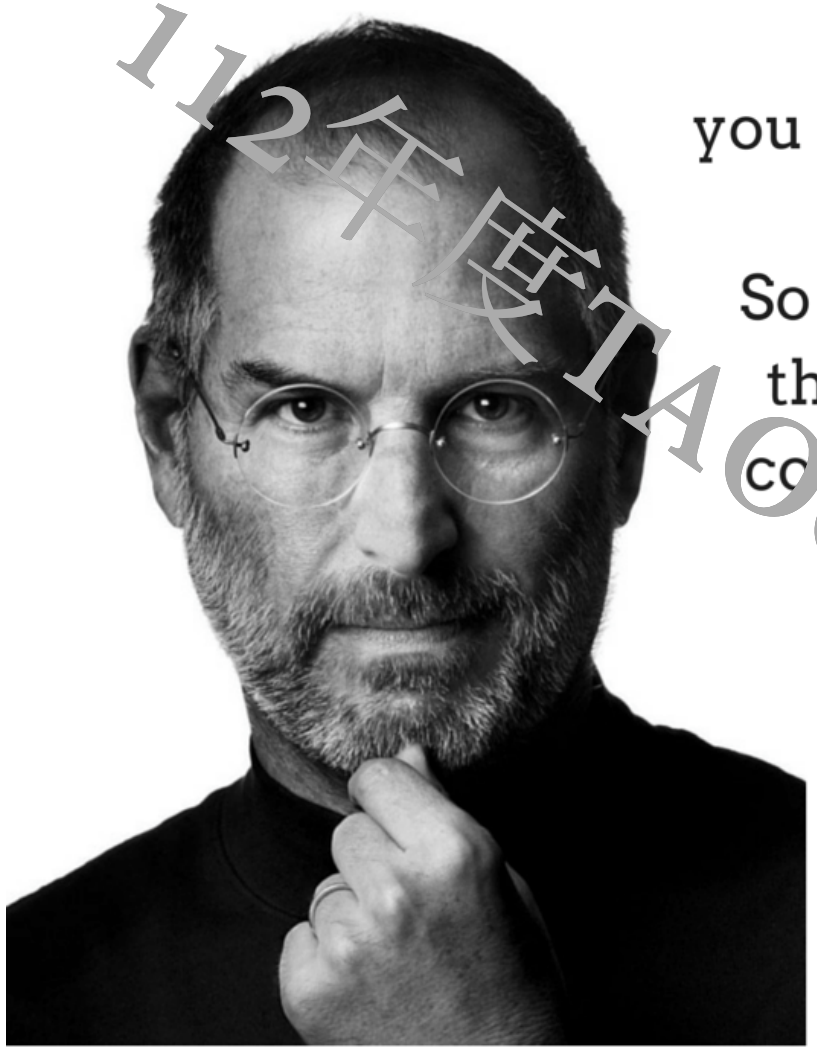
Status	Mechanism of action	Agents	Trial(s)
FDA-approved	Anti-PD-1 antibody + multikinase inhibitor	Pembrolizumab + Lenvatinib	KEYNOTE-775, KEYNOTE-146
Published	Anti-HER2 antibody + chemotherapy	Trastuzumab + Carboplatin/ Paclitaxel	NCT01367002
Under study	Anti-HER2 antibody + chemotherapy	Trastuzumab + pertuzumab + Carboplatin/Paclitaxel	NRG-GY026
	PARPi + chemotherapy	Niraparib + Carboplatin/ Paclitaxel	CAN-STAMP
	PARPi + chemoradiation	Olaparib + Chemoradiation	RAINBO
	Antibody drug conjugates	Trastuzumab-deruxtecan	STATICE,
		Trastuzumab-deruxtecan	DESTINY-Pan Tumor02 Agent- DB-1303, Trial- NCT05150691 Agent- STRO-002, Trial-NCT03748186
	Antibody drug conjugates + PARPi	Trastuzumab-deruxtecan + Olaparib	NCI-2020-07841
	WEE1 inhibitor	Adavosertib	18-316 agent- Zn-c-3, study- NCT04814108

Curr Opin Obstet Gynecol. 2023 Jun 1;35(3):270-278.

Transitioning from Histology to Genomics

- *TP53* mutation is associated with worst prognosis.
- It’s important to recognize abnormal p53 IHC staining correctly.
- Studies on the molecule-integrated risk profile are expected to provide a clinical decision-making tool for adjuvant treatment of patients with HIR and high-risk EC to increase RFS with less toxicity.

Thank you!



"You can't connect the dots
looking forward;
you can only connect them
looking backward.
So you have to trust that
the dots will somehow
connect in your future."

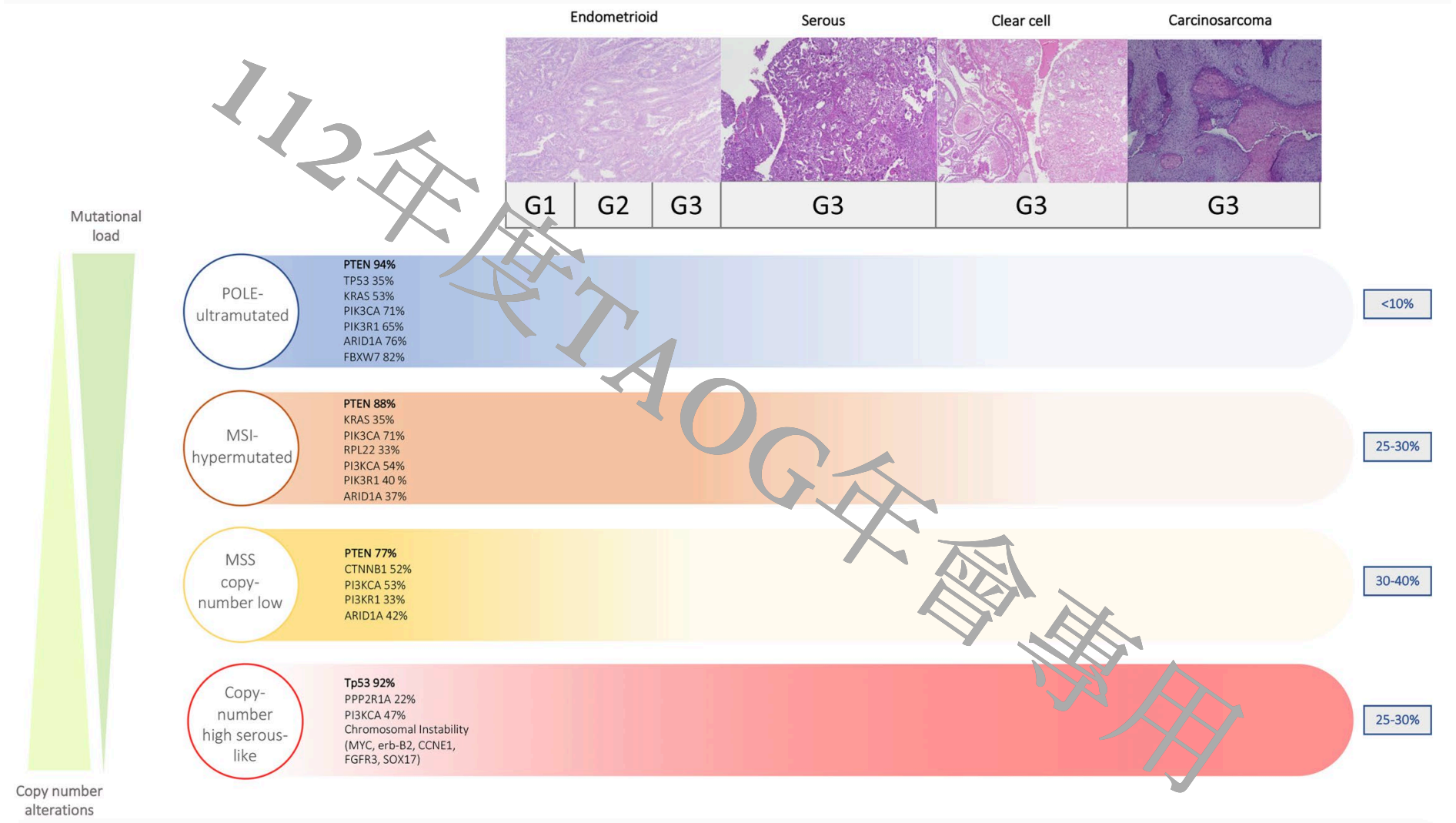
- Steve Jobs

READINGGRAPHICS
ACTIONABLE INSIGHTS IN ONE PAGE

Table 2
Clinicopathological and molecular features, and potential therapeutic agents in four molecular subtypes identified by TCGA.

Molecular classification	POLE ultra-mutated/ POLE mut	Microsatelite instability hypermutated/MMRd	Copy-number high/p53abn	Copy-number low/NSMP p53 wt
Frequency in all EC	6.4–12.4%	28.0–33.5%	12.2–25.9%	33.4–50.4%
Clinical morphology	Age: younger BMI: low Advanced case: few	Age: intermediate-older BMI: intermediate-high Advanced case: intermediate	Age: older BMI: intermediate Advanced case: many	Age: intermediate BMI: high Advanced case: intermediate Others: relation with diabetes
Prognosis (PORTEC-3 cohort)	5-year RFS: 98.0% 5-year OS: 98.0%	5-year RFS: 71.4% 5-year OS: 83.3%	5-year RFS: 48.0% 5-year OS: 54.0%	5-year RFS: 74.4% 5-year OS: 88.5%
Histological distribution (PORTEC-3 cohort)	Endometrioid (G1/2): 7.8 Endometrioid (G3): 56.9% Serous: 11.8% Others: 23.6%	Endometrioid (G1/2): 43.1% Endometrioid (G3): 34.3% Serous: 5.1% Others: 17.5%	Endometrioid (G1/2): 4.3% Endometrioid (G3): 22.6% Serous: 49.5% Others: 23.7%	Endometrioid (G1/2): 72.9% Endometrioid (G3): 12.4% Serous: 4.7% Others: 10.1%
Molecular feature	CNA: low TMB: very high (>100/Mb) Representative altered genes: POLE (100%), PTEN (94%)	CNA: low TMB: high (>10/Mb) Representative altered genes: PTEN (88%), PIK3CA (54%), PIK3R1 (40%), ARID1A (37%), KRAS (35%)	CNA: high TMB: low (<10/Mb) Representative altered genes: TP53 (92%), PIK3CA (47%), FBXW7 (22%), PPP2R1A (22%), PTEN (10%), ERBB2 (amplification, 25%),	CNA: low TMB: low (<10/Mb) Representative altered genes: PTEN (77%), PIK3CA (53%), CTNNB1 (52%), ARID1A (42%) ER/PR expression (approximately 50%)
Potential therapeutic target	High immunogenicity	Sensitivity for radiotherapy High immunogenicity	Sensitivity for chemotherapy Homologous recombination deficiency HER2/Neu	ER/PR overexpression PI3K/AKT/mTOR pathway
Current and potential treatment	Immune checkpoint inhibitors (alone or in combination)	Radiotherapy Immune checkpoint inhibitors	Chemotherapy PARP inhibitors Anti-HER2 antibodies	Aromatase inhibitors Metformin mTOR inhibitors

EC: endometrial cancer, BMI: body mass index, RFS: recurrrent free survival, OS: overall survival, G: grade, CNA: copy number alteration, TMB: tumor mutational burden, Mb; megabase, ER: estrogen recepto, PR: orogesterone receptor



Front Oncol. 2021; 11: 612450.

The Post Operative Radiation Therapy in Endometrial Carcinoma trial				
	PORTEC-1	PORTEC-2	PORTEC-3	PORTEC-4a
	1990–1997	2002-2006	2006-2013	
Case No.	714	427	660	
Purpose	Stage I EC, 手術後比較 EBRT vs observation	HIR EC 手術後比較 EBRT vs VBT	High-risk EC 手術後比較 RT+CT vs RT alone	針對HIR EC, 使用molecular-integrated risk profile比較 VBT vs observation對局部復發的效果
結論	EBRT should be avoided in patients with low- and intermediate-risk EC.	1. Local control EBRT較好但OS沒差別 2. VBT is standard for HIR EC	Adjuvant CT 對OS沒差,但增加 failure-free survival.	
	Stage IC Grade 1-2 or Stage IB Grade 2-3 EC		stage I, GR. 3 endometrioid, deep MI, LVSI (or both), endometrioid-type stage II or III, or stage I to III with serous or clear cell histology	Type 1 endometrioid Stage IA, Gr. 3 Stage IB, Gr. 1-2, age≥60, and or LVSI(+) Stage IB, Gr. 3, LVSI(-) Stage II , microscopic and Gr. 1
		PMID: 30356126	PMID: 29449189	PMID: 33046573

Post Operative Radiation Therapy in Endometrial Carcinoma
PORTEC-1

- PORTEC-1 trial: 1990-1997
- pelvic external bean radiotherapy versus no additional treatment (EBRT vs NAT)
- N=714
- HIR (≥ 2/3 risk factors): Gr.3, ≥ 60y/o, MI > ½
- Conclusion: EBRT should be avoided in patients with low- and intermediate-risk EC.

Post Operative Radiation Therapy in Endometrial Carcinoma
PORTEC-2

- Stage I or stage IIA with HIR
- HIR (≥ 2/3 risk factors): Gr.3, ≥ 60y/o, MI > ½
- N=427
- pelvic external bean radiotherapy versus vaginal brachytherapy (EBRT vs VBT)
- 20020527-20060925
- VBT is effective for vaginal control. Less toxicity => sufficient for HIR
- EBRT has better local control but similar OS.