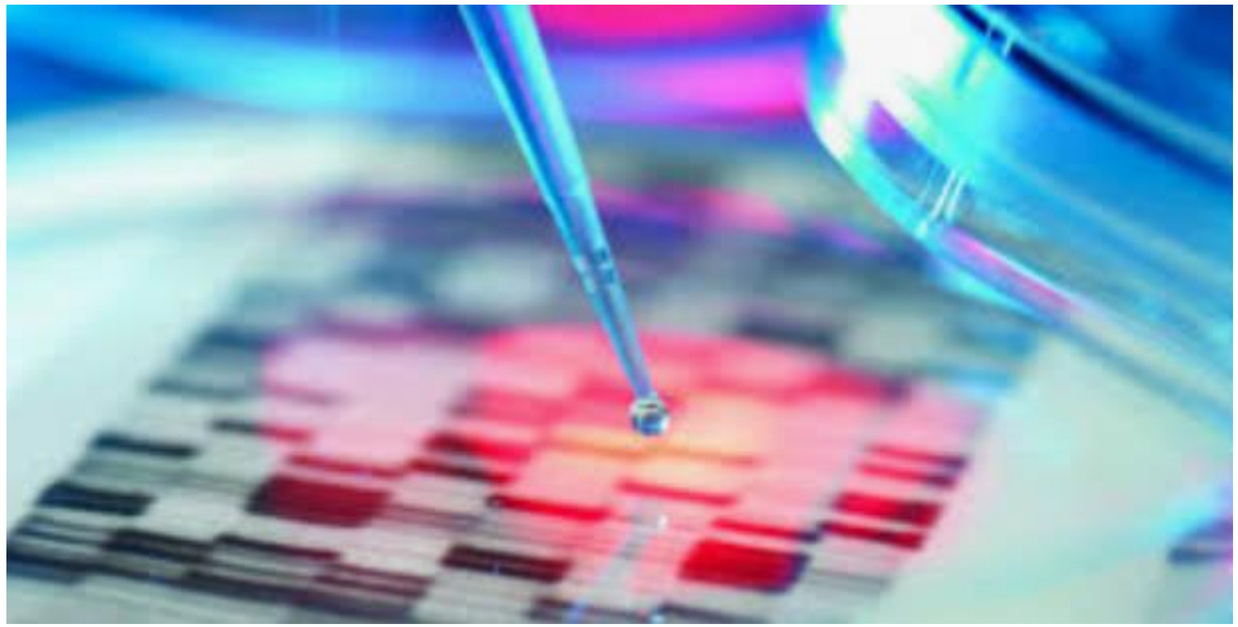
XVIIèmes Journées Liégeoises de Gynécologie-Obstétrique

Citadelle Gynécologie Obstétrique

CHU de Liège

LIÈGE université

Une organisation du Département de Gynécologie-Obstétrique de l'Université de Liège



CANCER ENDOMÉTRIAL : IMPLÉMENTATION CLINIQUE DU PROFIL GÉNÉTIQUE

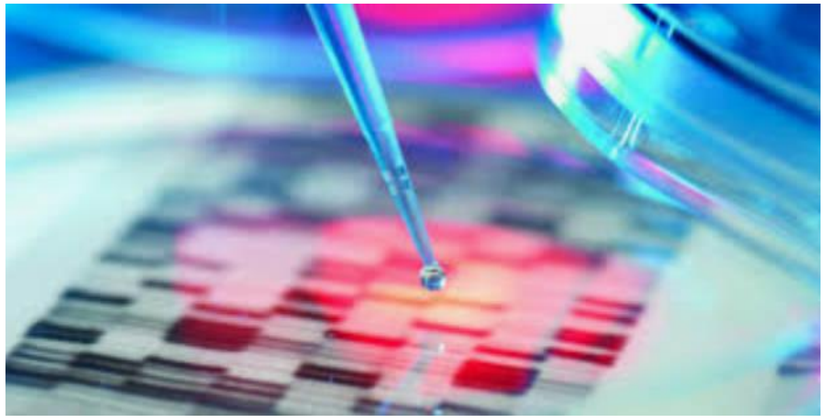
F KRIDELKA, F GOFFIN, A KAKKOS, CH GENNIGENS, E GONNE, CL PLEYERS, J HERMESSE, V BOURS, K SEGERS AND K DELBEQUE.

S BROUERS, V DUC, L KEMPENEER, MC LHOTE, M TYCHON AND C WILLEMS

ASS: A DHEUR, A SALMON

DEPARTMENT OF GYNECOLOGY AND OBSTETRICS - GYNE/ONCOLOGY UNIT - ULIÈGE

XVIIèmes Journées Liégeoises de Gynécologie-Obstétrique
Une organisation du Département de Gynécologie-Obstétrique de l'Université de Liège



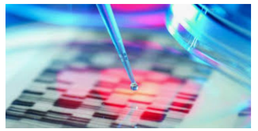
CANCER ENDOMÉTRIAL : IMPLÉMENTATION CLINIQUE DU PROFIL GÉNÉTIQUE

INTRODUCTION / RECOMMANDATIONS ACTUELLES

CRITÈRES PRONOSTICS HISTOPATHOLOGIQUES VS MOLÉCULAIRES

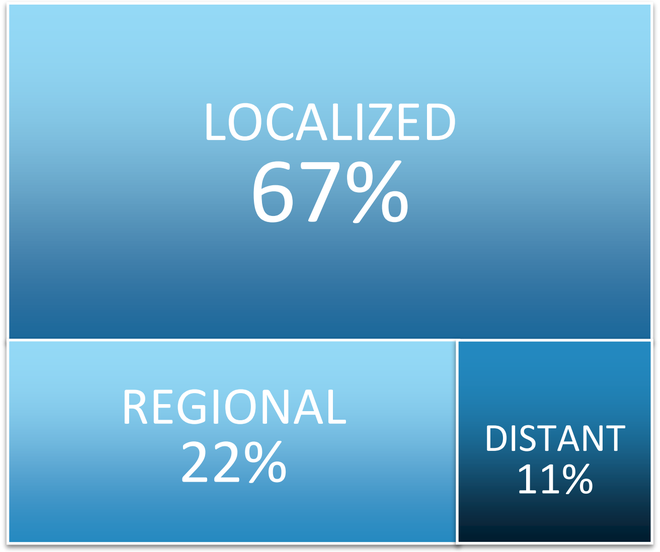
IMPLÉMENTATION CLINIQUE : PER-OP / POST-OP / RECHUTE

XVIIèmes Journées Liégeoises de Gynécologie-Obstétrique
Une organisation du Département de Gynécologie-Obstétrique de l'Université de Liège

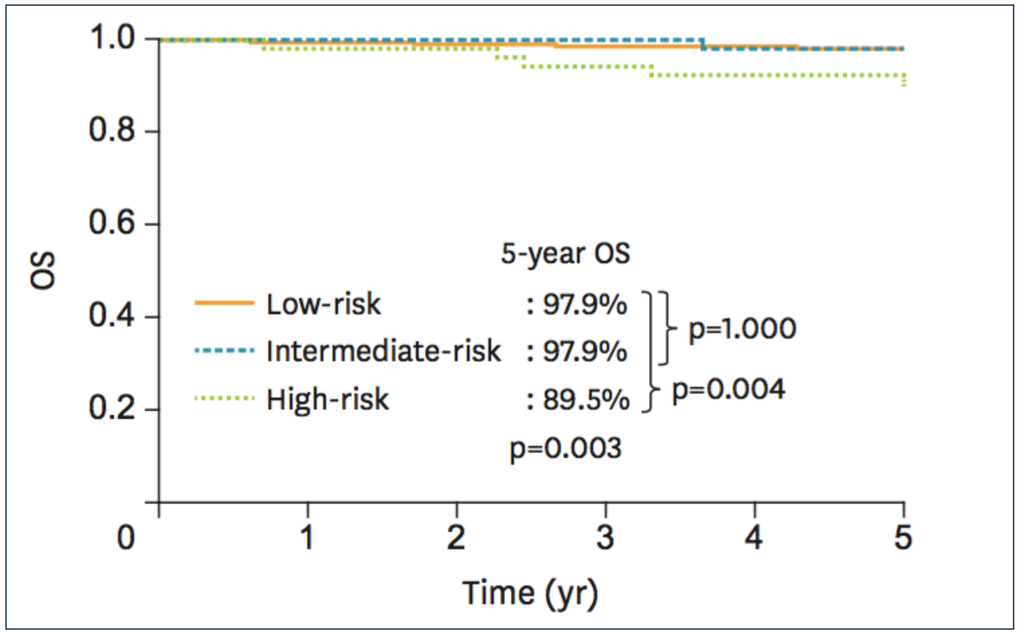


140000 PATIENTS

SEER Data - 2008/2014



OS AFTER HRT/NODES AND NO ADJUVANT TREATMENT



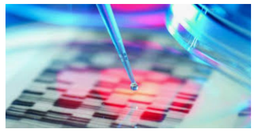
Sasada et al. J Gyn Onco 2018

CAUSE DE DÉCÈS APRÈS EC

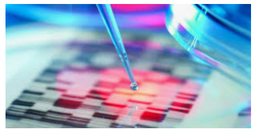
LOCALIZED LOW GRADE	LOCALIZED HIGH GRADE	ADVANCED LOW GRADE	ADVANCED HIGH GRADE
END CANCER : 7%	END CANCER : 26%	END CANCER : 33%	END CANCER : 57%
CV : 45%	CV : 35%	CV : 27%	CV : 15%
OTHER : 52%	OTHER : 39%	OTHER : 40%	OTHER : 28%

Ward et al. Gynecol Onco 2012

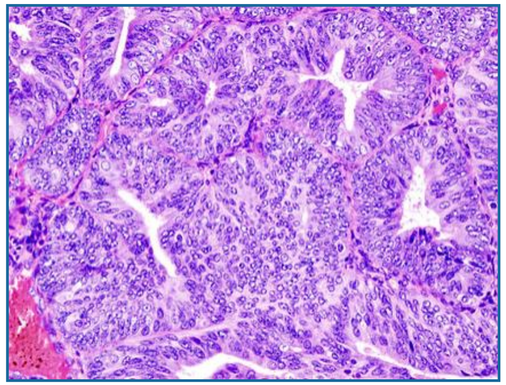
EC - INTRODUCTION / RECOMMANDATIONS ACTUELLES

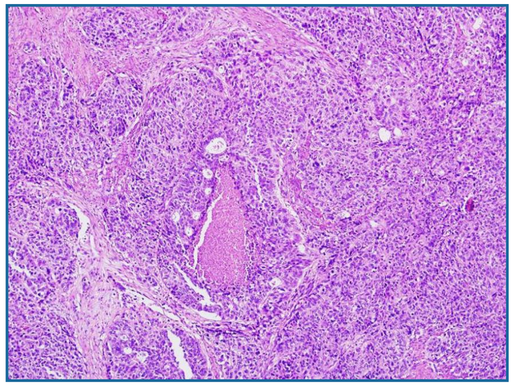


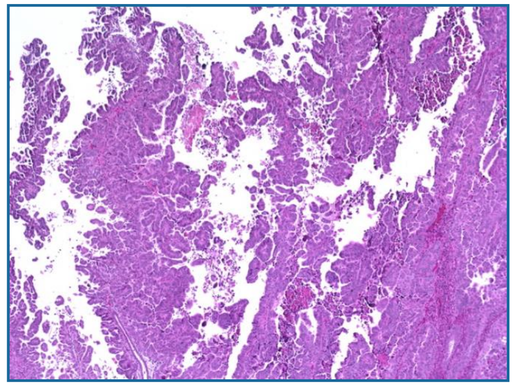
ST I - LR 32%	ST I - I/IHR 22%	ST I - HR 13%	HR REGIONAL 22%	DIS TANT 11%
OBSERVATION	IR OBSERVATION	ST I AND II XRT		SX RT/CT
	HIR VBT	ST III CCRT + CT WEIGH FFS BENEF / MORBIDITY		

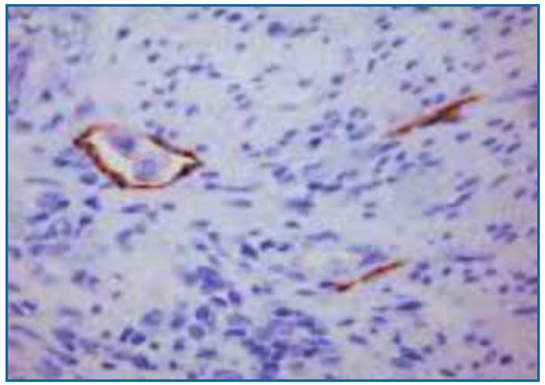


STRATIFICATION DIU RISQUE BASÉE SUR HISTOLOGIE



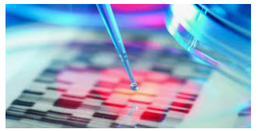






VARIABILITÉ INTEROBSERVATEUR ÉLEVÉE

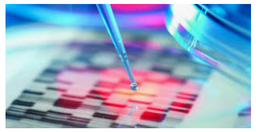
INÉLIGIBILITÉ : 24% (PORTEC 1), 14% (PORTEC 2) AND 8% (PORTEC 3)
QUANTIFICATION DES EMBOLES LYMPHOVASCULAIRES



ST I - LR	ST I - I/IHR	ST I - HR	HR REGIONAL	DIS TANT
32%	22%	13%	22%	11%

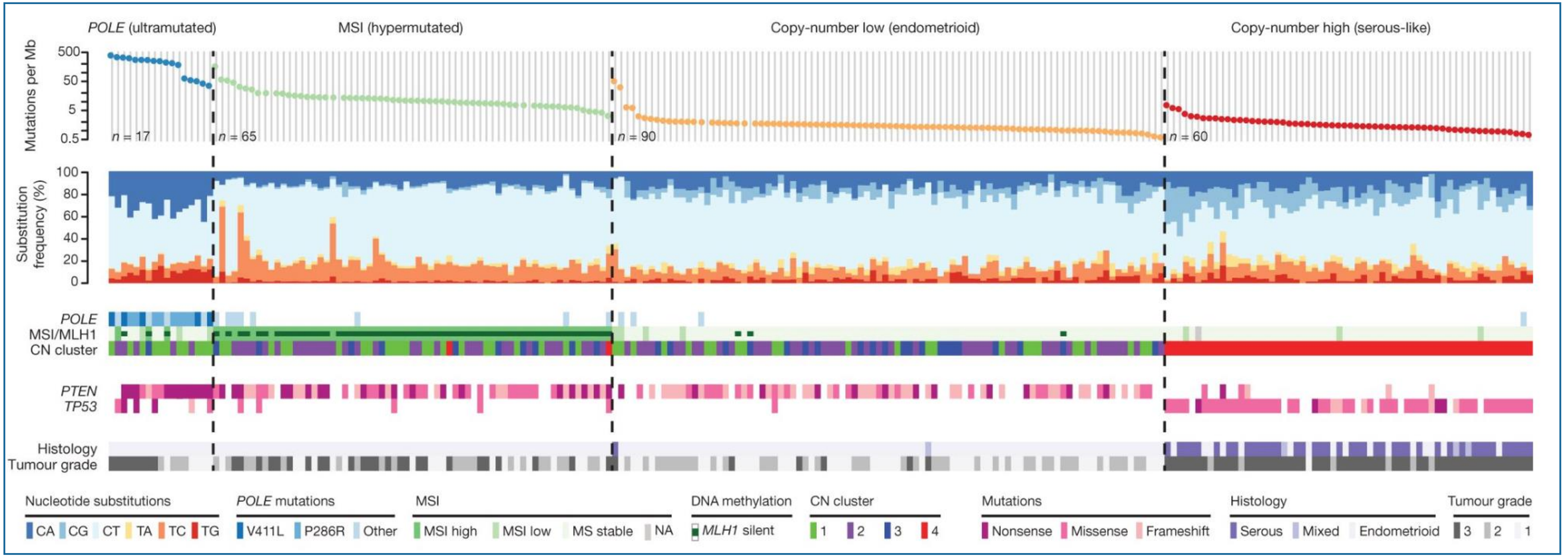
OBSERVATION	IR OBSERVATION	ST I AND II XRT	SX RT/CT
	HIR N0 : VBT	ST III CCRT + CT WEIGH FFS BENEF / MORBIDITY	

BESOIN DE CRITÈRES DE RISQUE DE RECHUTE ET D'INDICATIONS DE TRAITEMENTS ADJUVANTS PLUS ROBUSTES



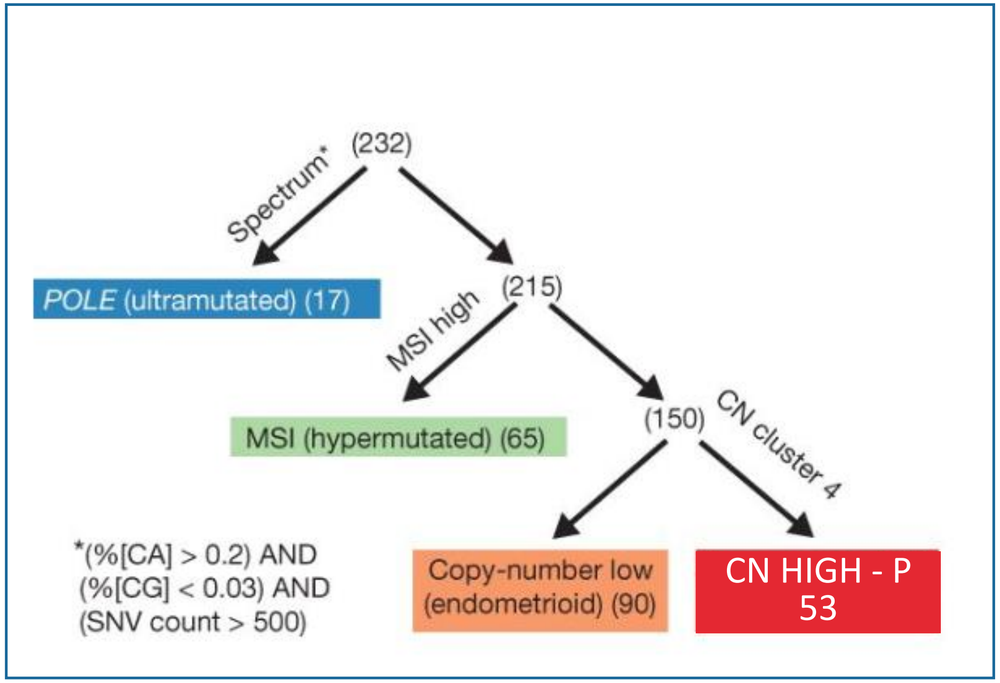
Integrated genomic characterization of endometrial carcinoma

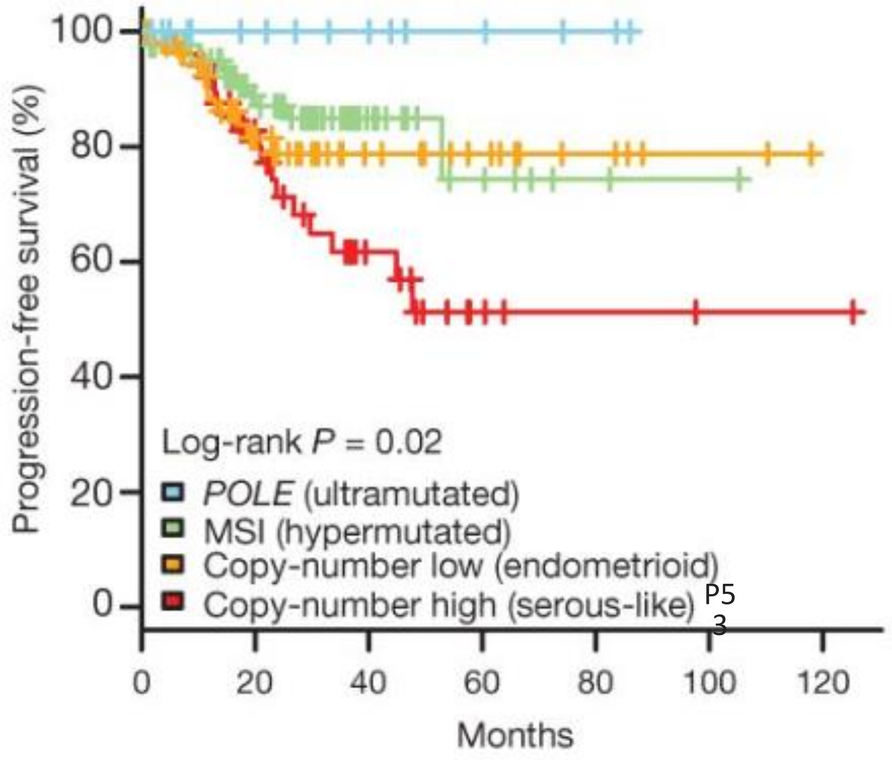
The Cancer Genome Atlas Research Network*



Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

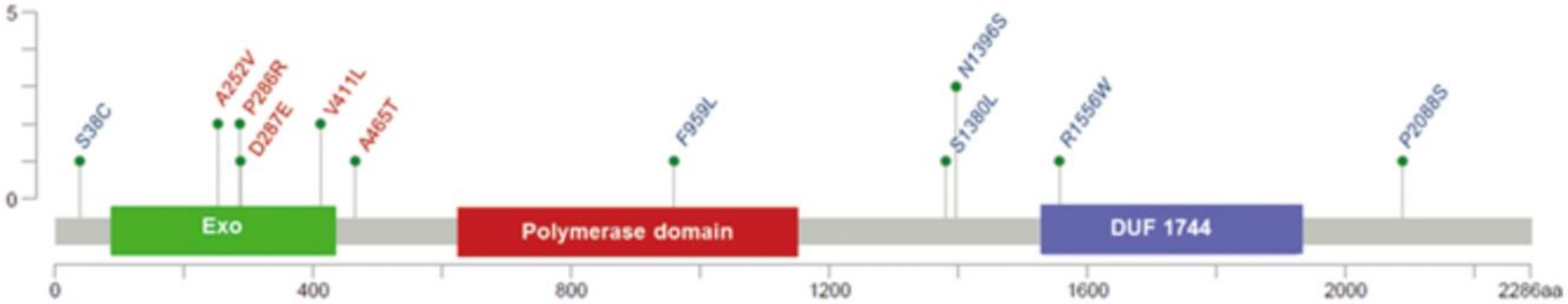




P53

POLE ULTRAMUTÉ

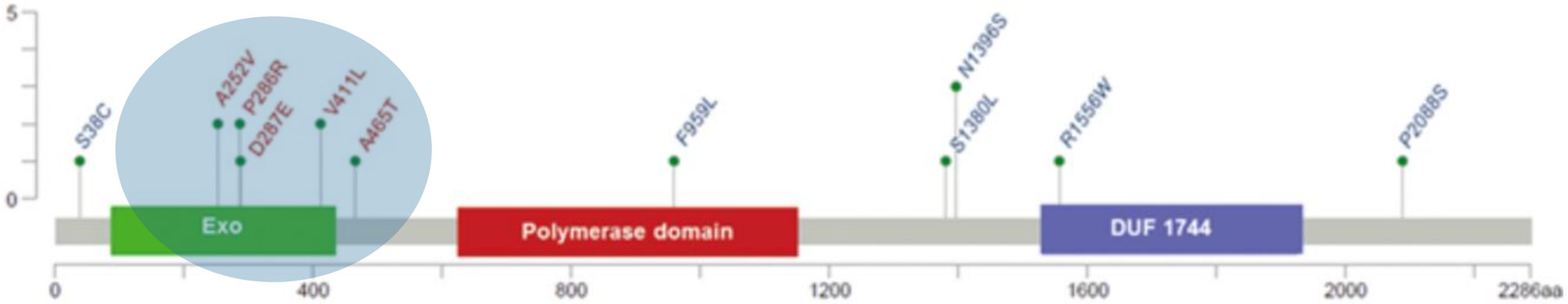
A UN RÔLE DS LA RÉPLICATION DU DNA + EXONUCLEASE VISANT À EXCISION/ RÉPARATION D'ERREURS « SINGLE BASE »
« CORRECTEUR ORTHOGRAPHIQUE »



POLE ULTRAMUTÉ

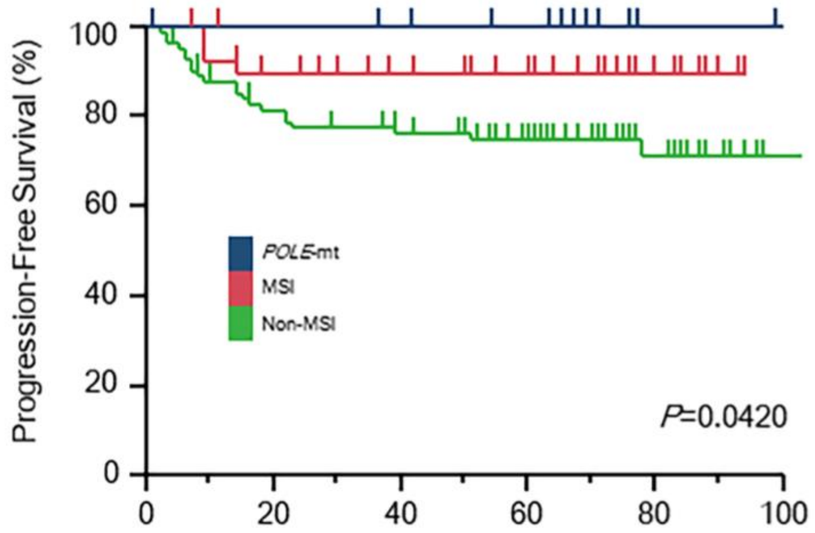
DIAGNOSTIC GÉNÉTIQUE CENTRÉ SUR 3 HOTSPOTS DANS LA RÉGION EXONUCLEASE (EDM)

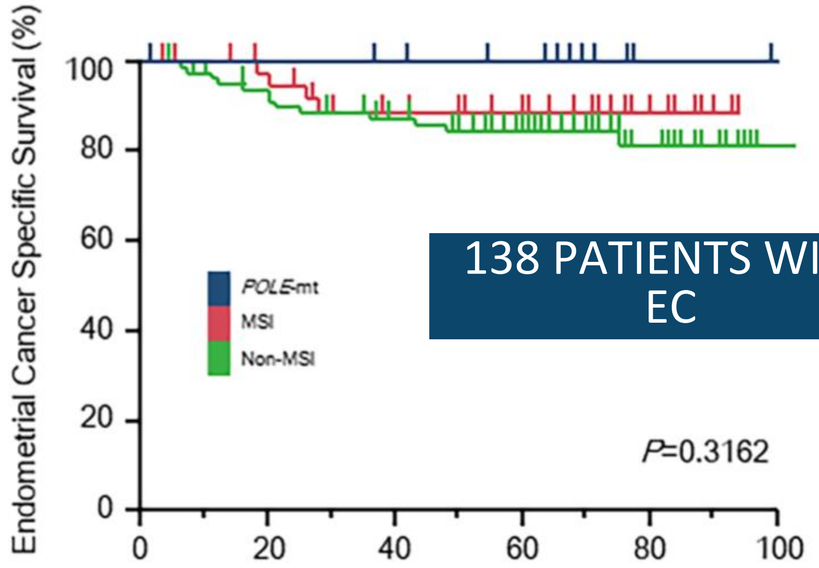
POLE MUTÉ INDUIT UN PHÉNOTYPE ULTRA MUTÉ : NEOANTIGÈNES MEMBRANAIRES ET TIL'S



POLE ULTRAMUTÉ - ENDOMETRIAL CANCER

6 TO 8% OF EC - 70% GR 3 / 35% DEEP MYO INV / 40% LVSI + ASSOCIATED WITH PARTICULARLY GOOD OUTCOME DUE TO ? ACCUMULATION OF NEOANTIGENS ?



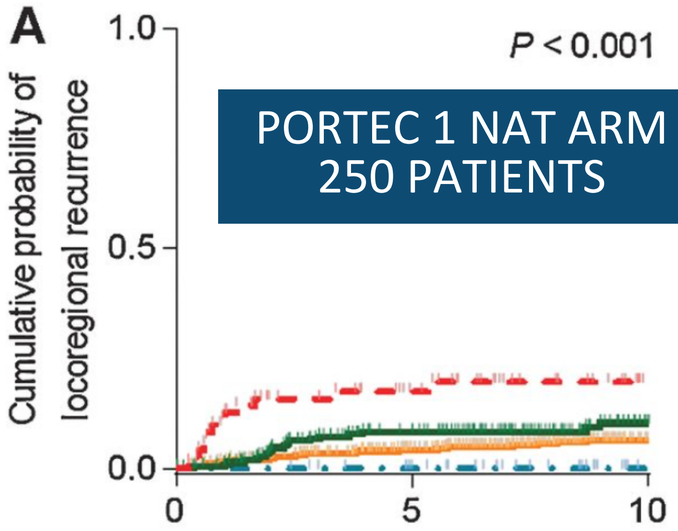


138 PATIENTS WITH EC

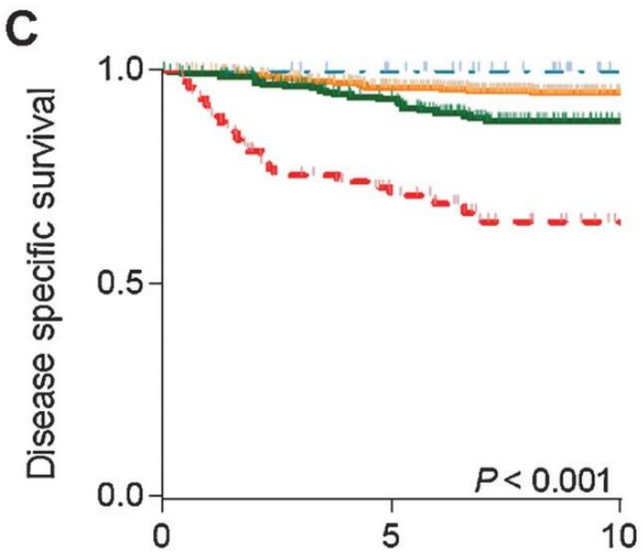
Haroma et al. Plos One - 2018

POLE ULTRAMUTÉ - ENDOMETRIAL CANCER

6 TO 8% OF EC - 70% GR 3 / 35% DEEP MYO INV / 40% LVSI + ASSOCIATED WITH PARTICULARLY GOOD OUTCOME DUE TO ? ACCUMULATION OF NEOANTIGENS ?

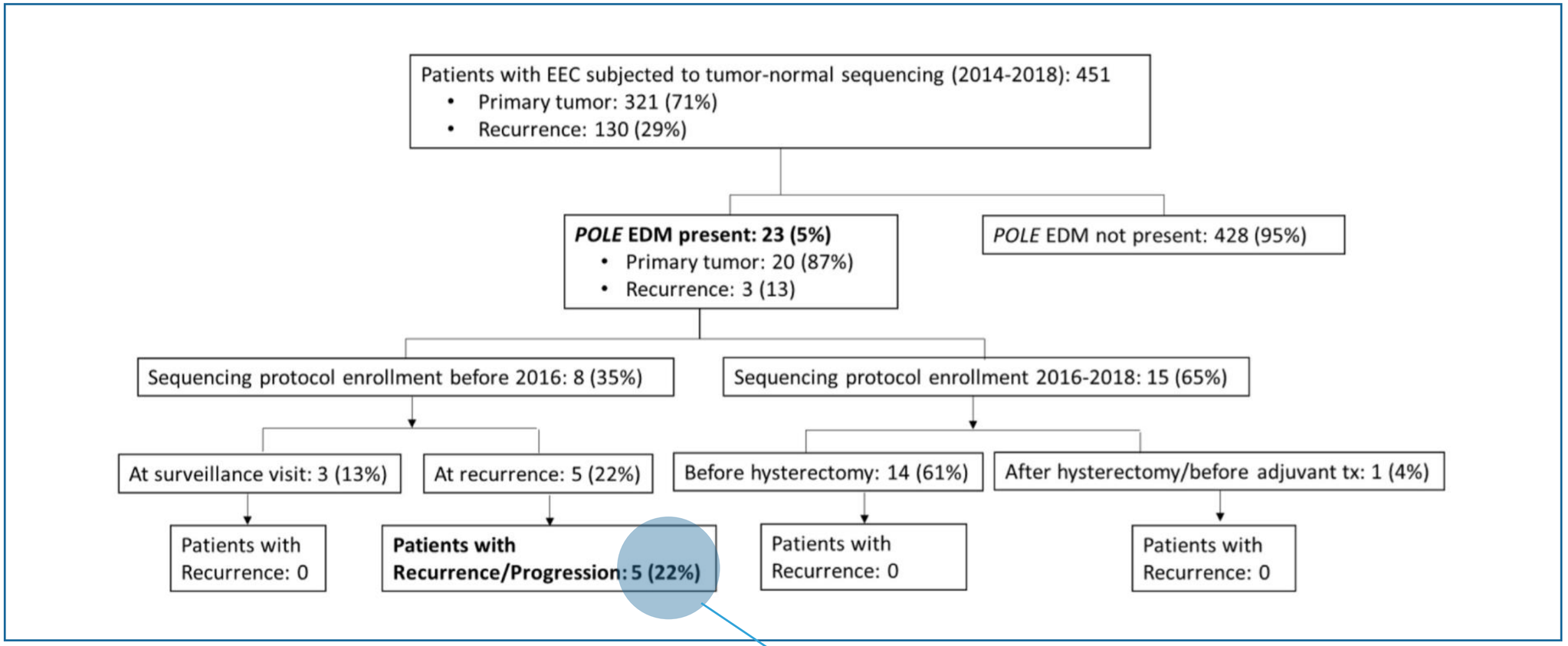


PORTEC 1 NAT ARM
250 PATIENTS



Stelloo et al. Clinical Cancer Research - 2016

POLE ULTRAMUTÉ - ENDOMETRIAL CANCER

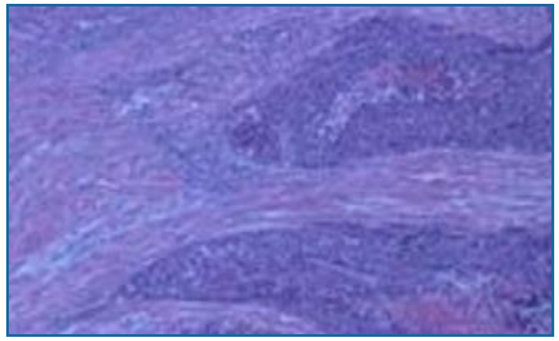


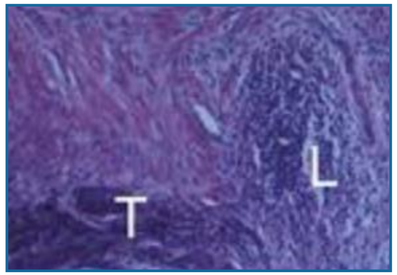
MAJORITY OF DISTANT METASTASES

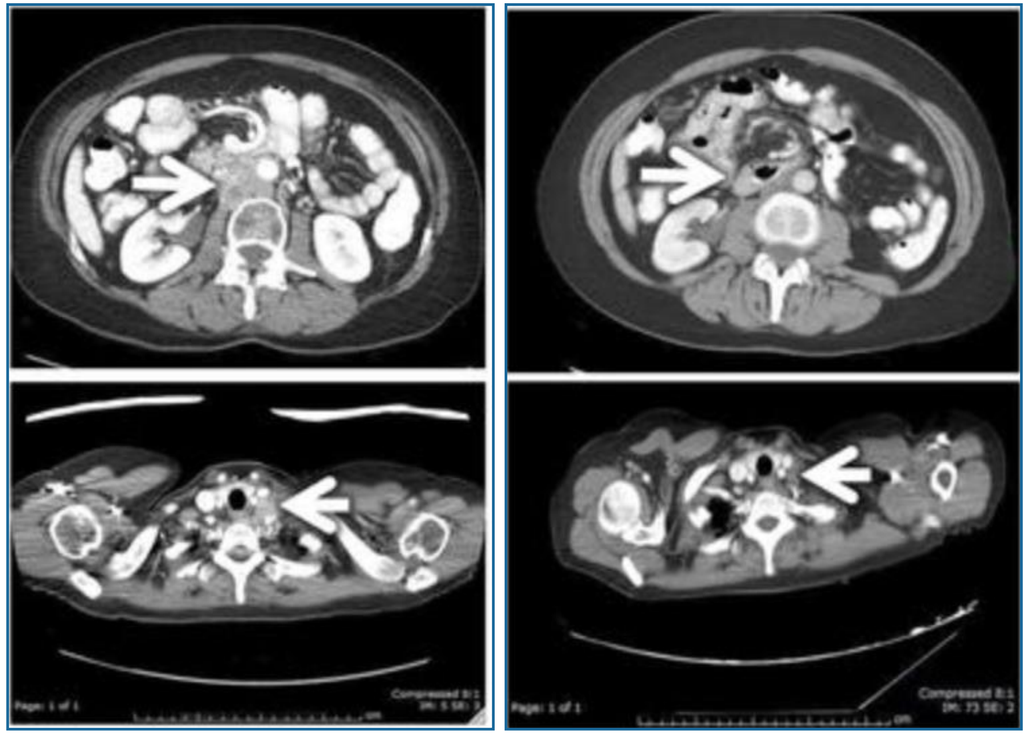
Stasenko et al. Gyneco Oncol 2020

POLE ULTRAMUTÉ - REC/MET ENDOMETRIAL CANCER

OPPORTUNITY FOR PD1/PDL1 INHIBITORS

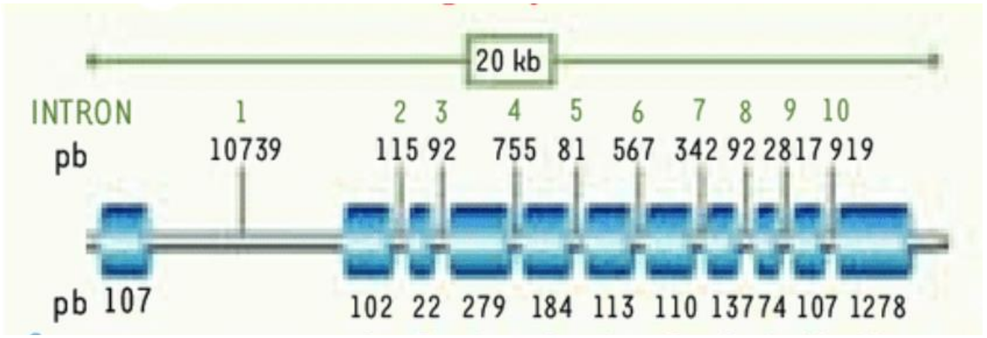


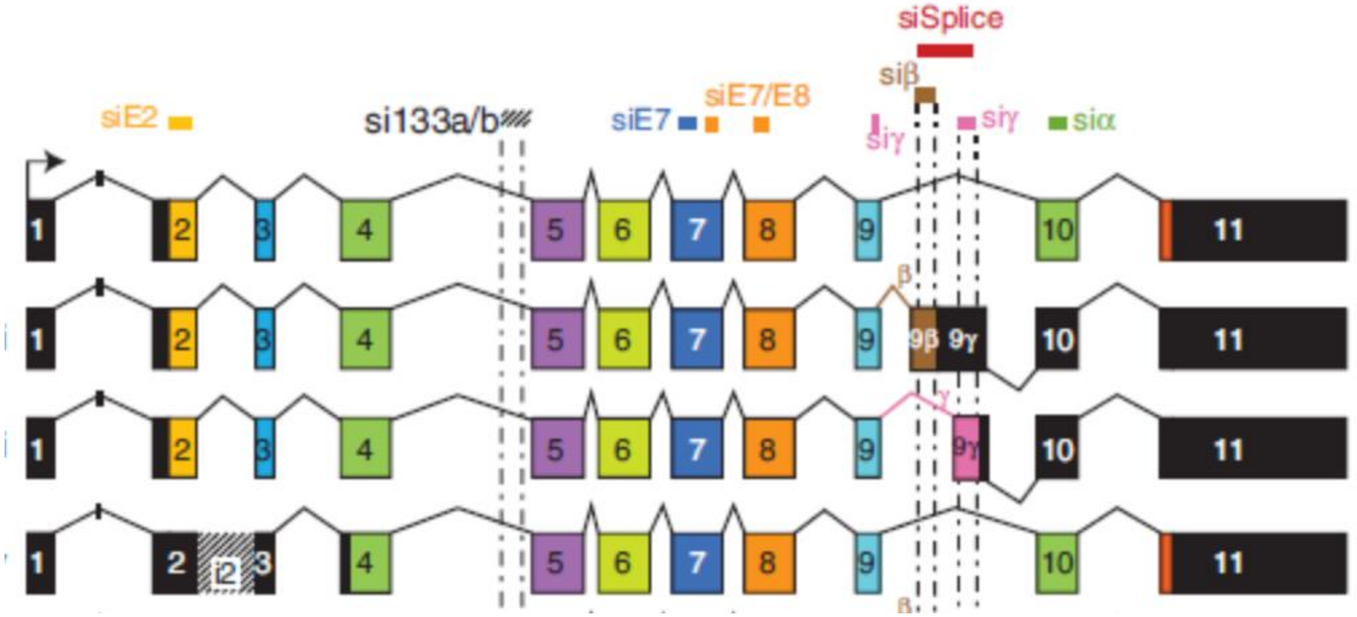




Menehrt et al. J Clin Invest 2018

P53 MUTATION





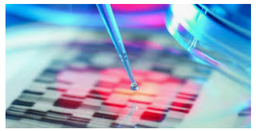
Encoded protein:

p53α or Δ40p53α or p53α and Δ40p53α

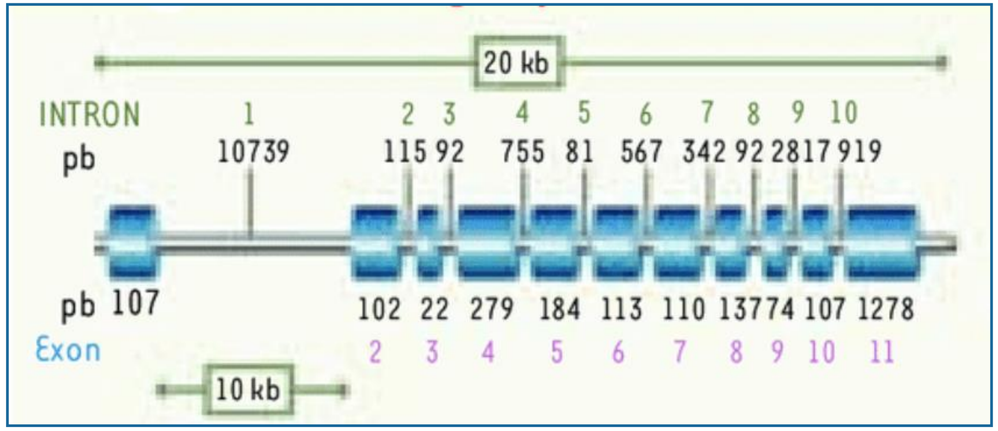
p53β or Δ40p53β or p53β and Δ40p53β

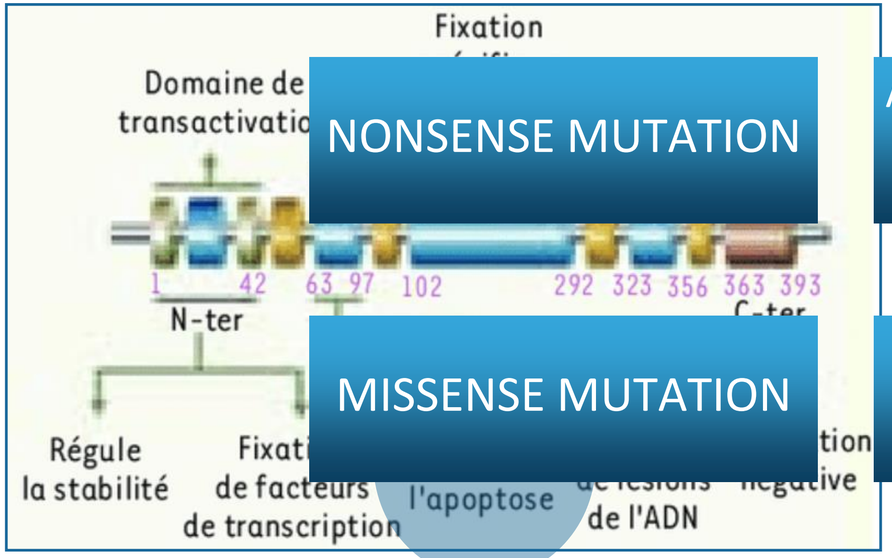
p53γ or Δ40p53γ or p53γ and Δ40p53γ

Δ40p53 only



P53 MUTATION

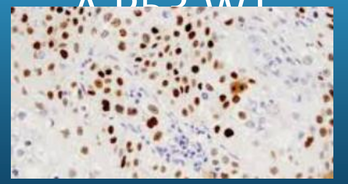




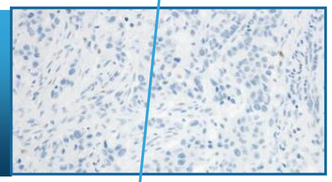
NONSENSE MUTATION

MISSENSE MUTATION

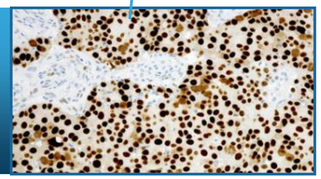
P53 MUTÉ
PAR OPPOSITION
À P53 WT



ABSENCE OF P53 PROTEIN
LOSS OF APOPTOTIC
FUNCTION



TRUNCATED PROTEINS
(NUCLEAR/CYTOPL
« NEGATIVE DOMINANT

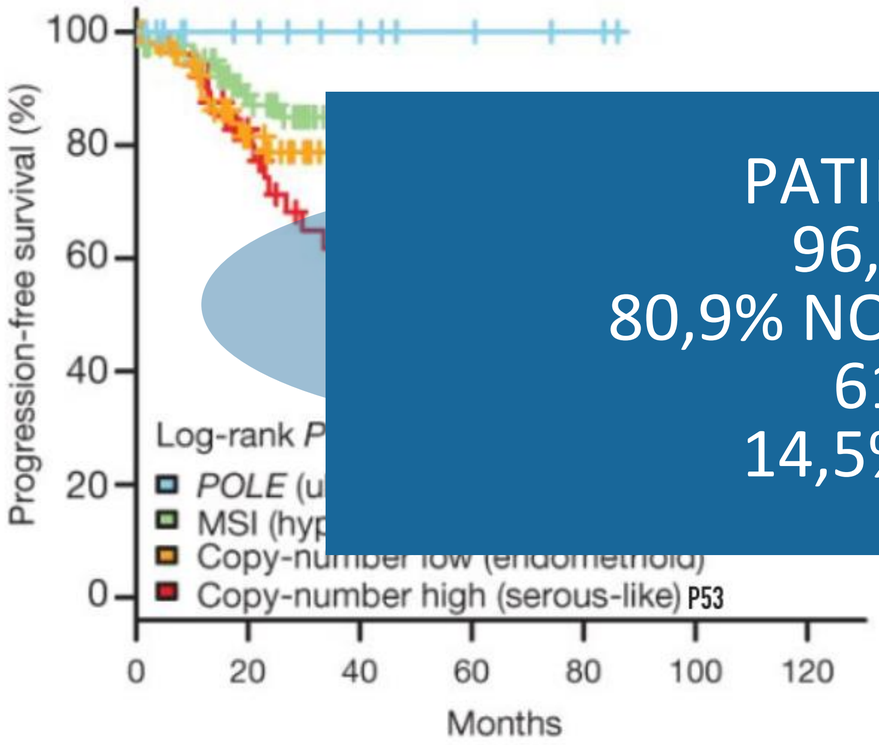


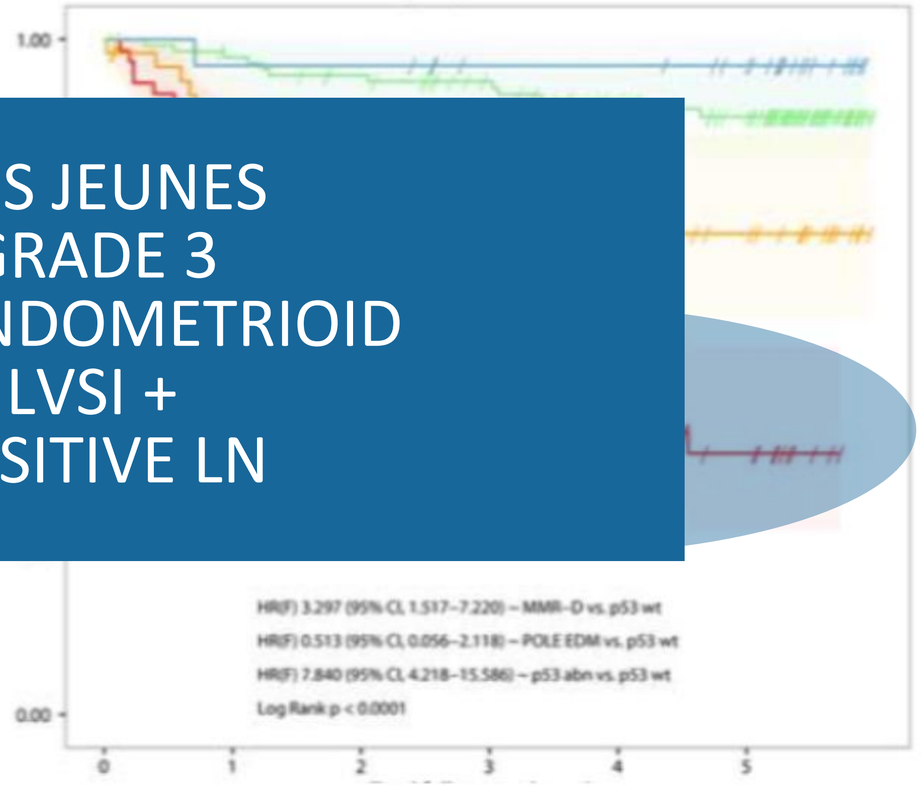
Singh et al. Journal of Pathology 2019

P53 MUTATION

NGS

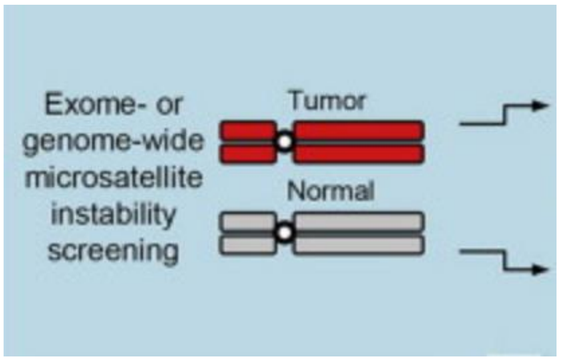
IHC

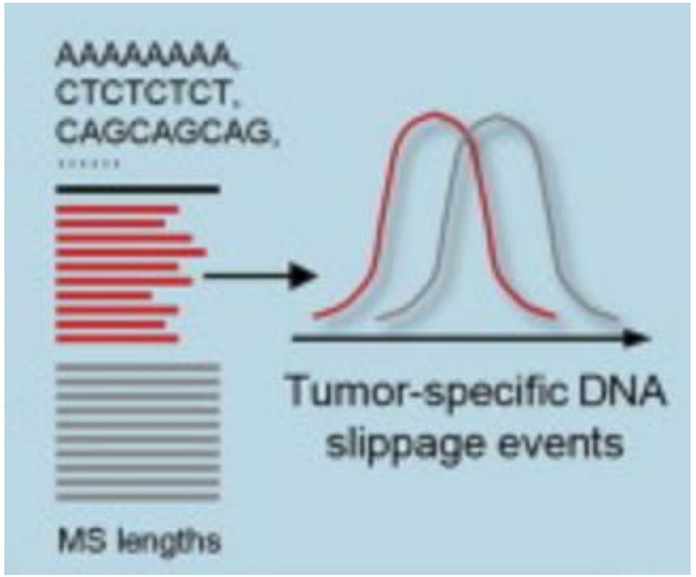


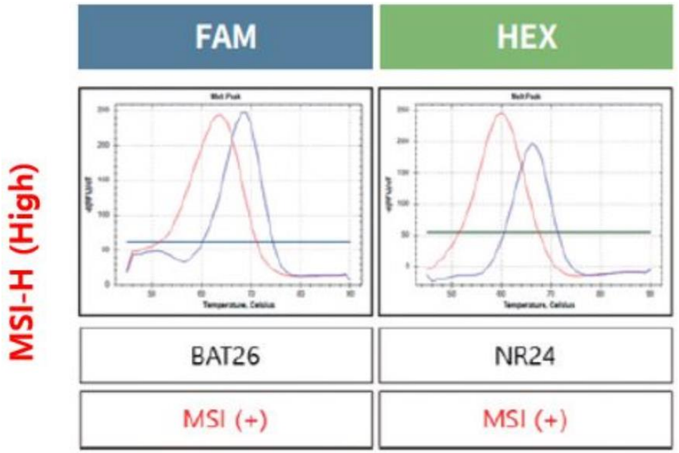


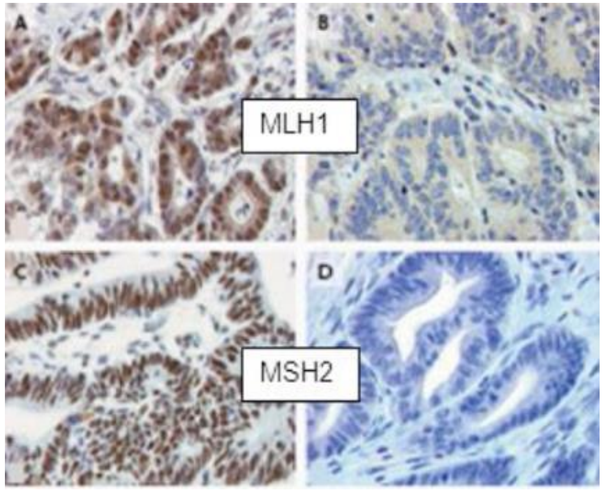
PATIENTES JEUNES
96,5% GRADE 3
80,9% NON ENDOMETRIOID
61,3% LVSI +
14,5% POSITIVE LN

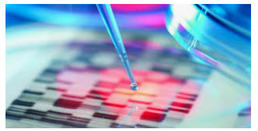
MSI - H


Exome- or
genome-wide
microsatellite
instability
screening
Tumor
Normal

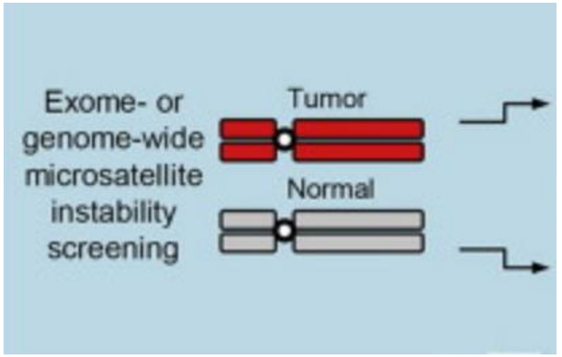

AAAAAAAA
CTCTCTCT
CAGCAGCAG
Tumor-specific DNA
slippage events
MS lengths

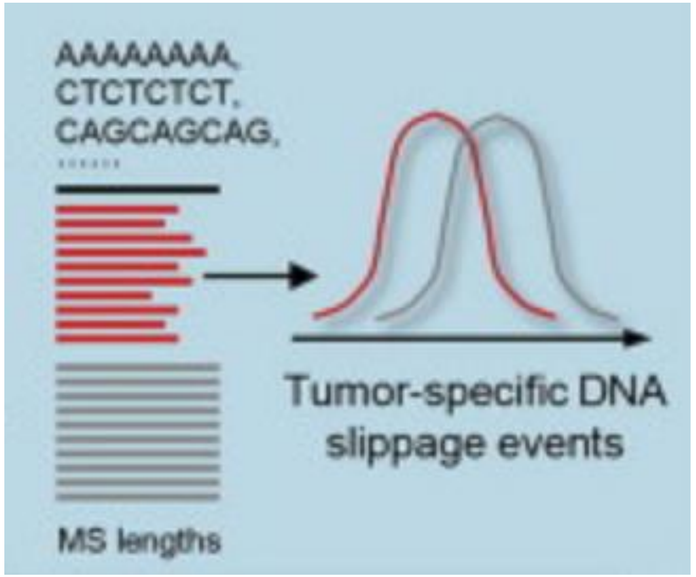

MSI-H (High)
FAM
HEX
BAT26
NR24
MSI (+)
MSI (+)

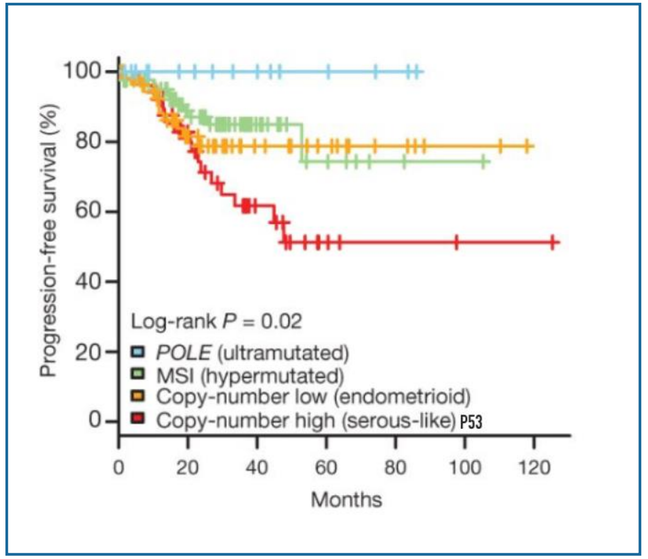

A
B
MLH1
C
D
MSH2

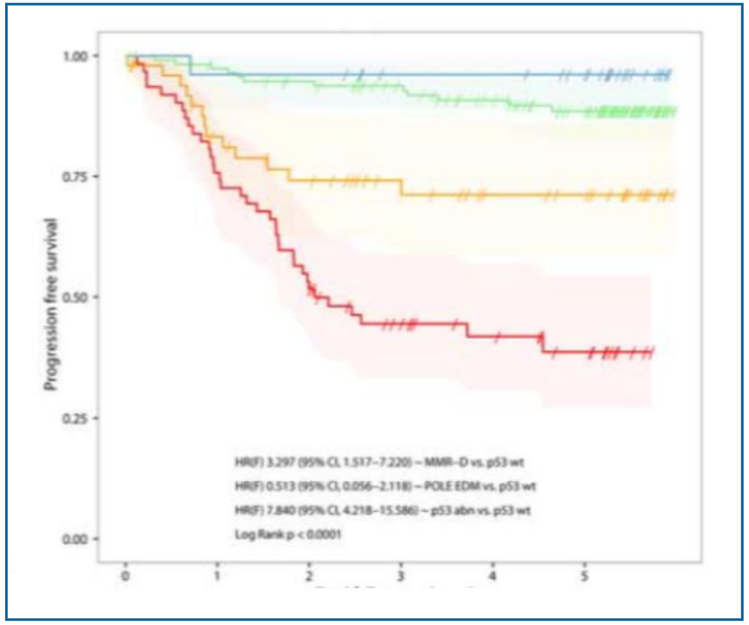


MSI - H

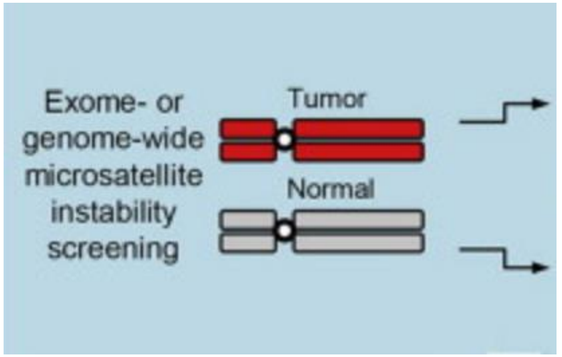

Exome- or
genome-wide
microsatellite
instability
screening
Tumor
Normal

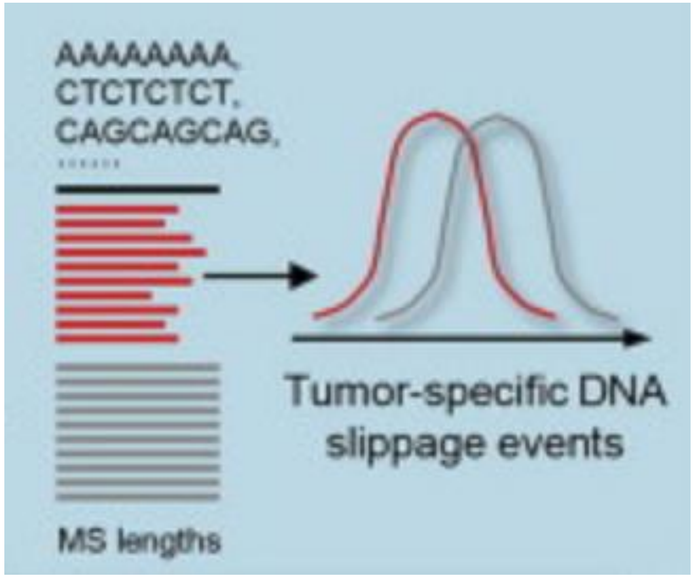

AAAAAAAA
CTCTCTCT
CAGCAGCAG
Tumor-specific DNA
slippage events
MS lengths


Progression-free survival (%)
100
80
60
40
20
0
Log-rank P = 0.02
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like) P53
0
20
40
60
80
100
120
Months


Progression free survival
1.00
0.75
0.50
0.25
0.00
HR(F) 3.297 (95% CI 1.517–7.220) – MMR-D vs. p53 wt
HR(F) 0.513 (95% CI 0.056–2.118) – POLE EDM vs. p53 wt
HR(F) 7.840 (95% CI 4.218–15.586) – p53 abn vs. p53 wt
Log Rank p < 0.0001
0
1
2
3
4
5

MSI - H





CONCENTRATION ELEVEE
DE PROTÉINES TRONQUÉES

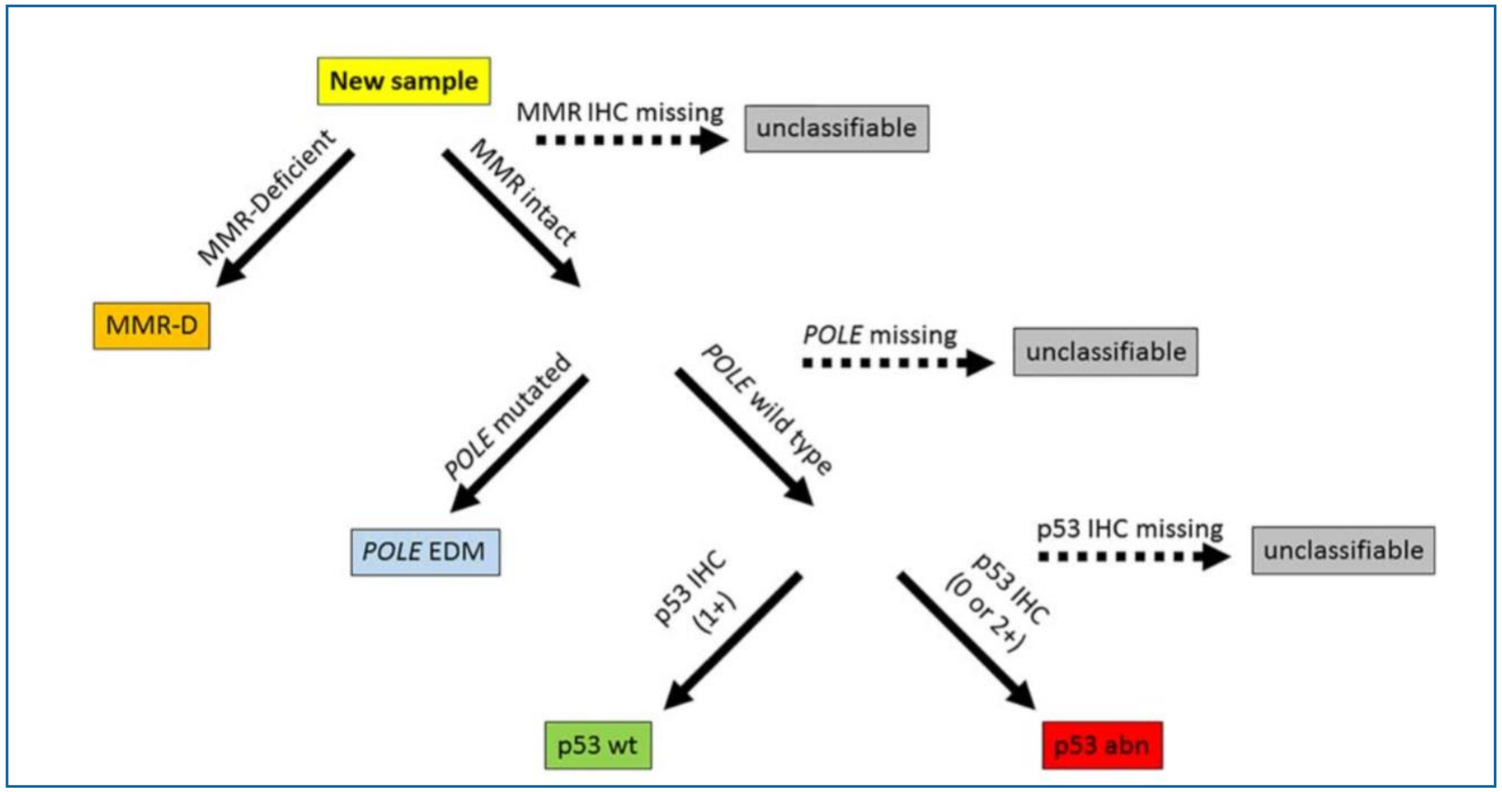
NEOANTIGENS
MEMBRANAIRES/TIL'S

OPPORTUNITY FOR LYNCH
(MSH2 AND 6) VS SOMATIC
(MLH1 AND PMS2) MMR-D
IDENTIFICATION

APPROCHE « PROMISE »

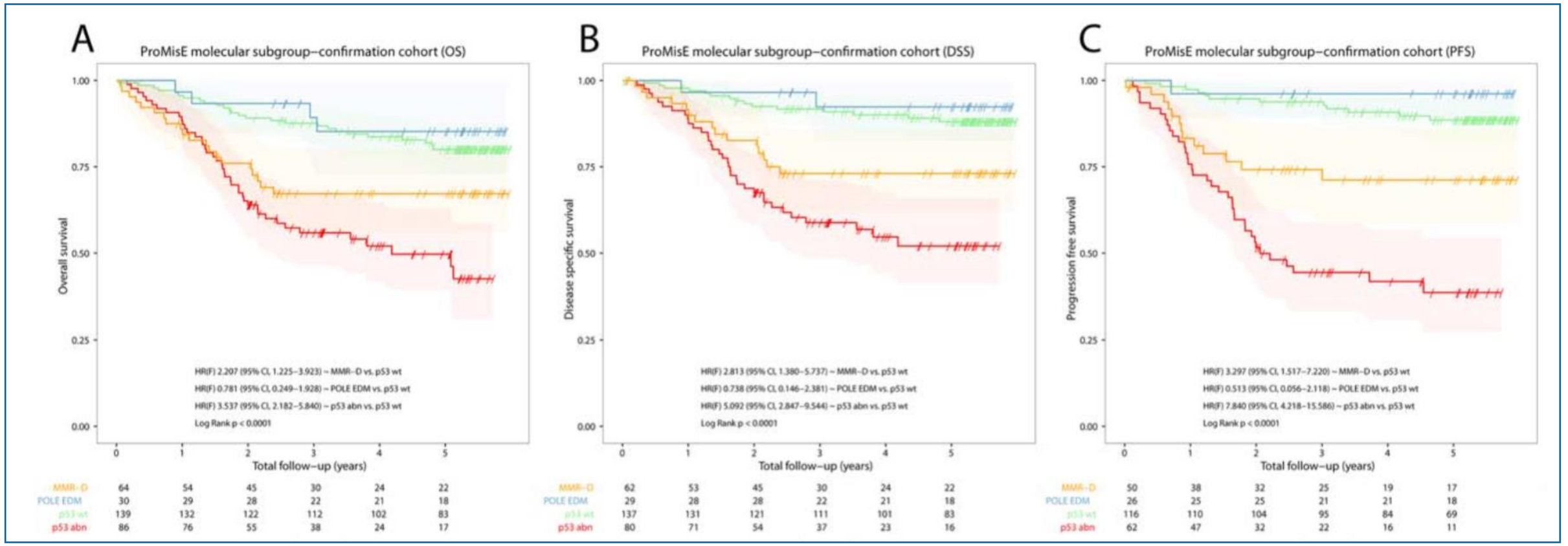
COHORTE
319 PATIENTS

ESMO LR: 30%
ESMO IR: 15,4%
ESMO HR: 54,6%



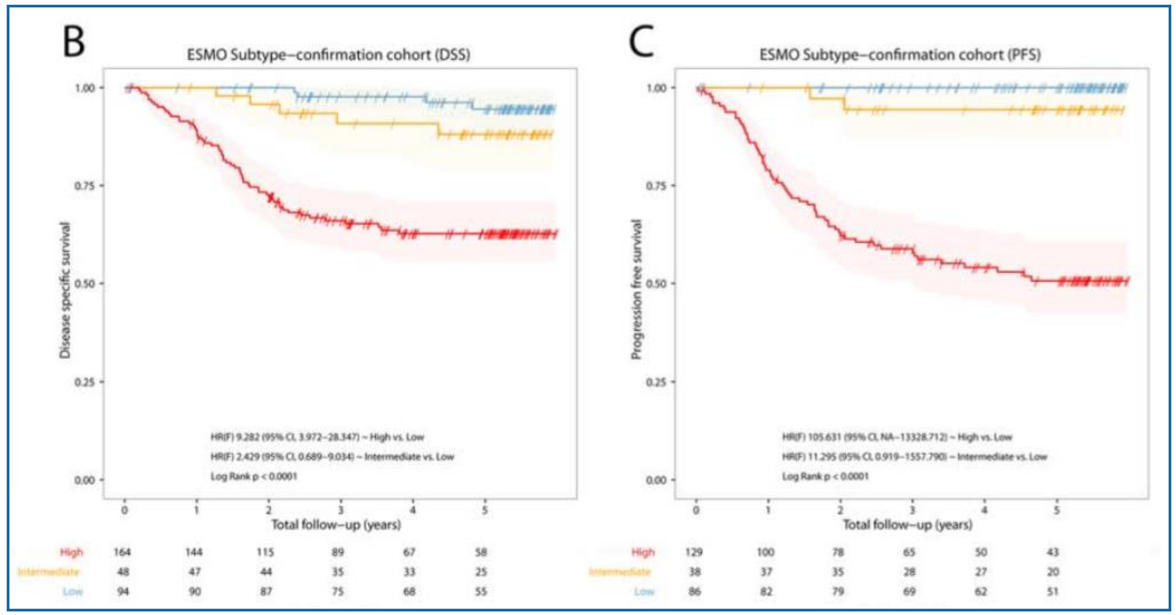
Tarouk et al. Cancer 2017

APPROCHE « PROMISE »

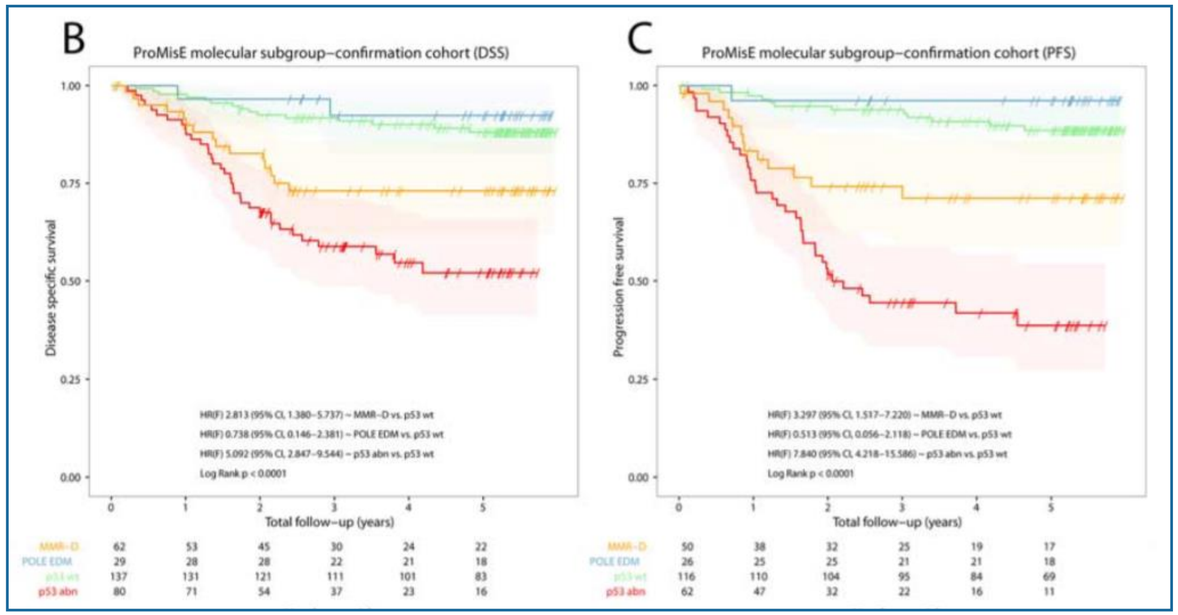


Tarouk et al. Cancer 2017

APPROCHE « PROMISE »



ESMO RISK GROUPS (3)



PROMISE RISK GROUPS (4)

Tarouk et al. Cancer 2017

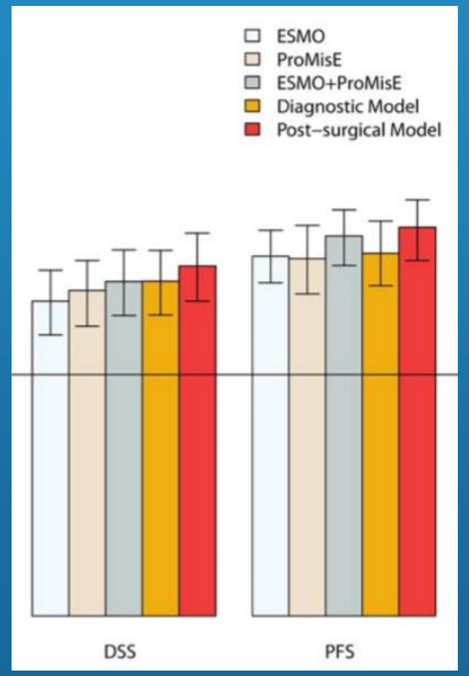
APPROCHE « PROMISE »

Parameter [Ref]	DSS, 54 of 261 Events		PFS, 55 of 219 Events	
	HR (95% CI)[a]	LRT *P*	HR (95% CI)[a]	LRT *P*
ProMisE molecular subgroup [p53 wt]				
MMR-D	1.32 (0.51-3.35)[F]	.0156[b]	0.64 (0.25-1.60)[F]	.0011[b]
POLE EDM	0.42 (0.04-1.88)[F]		0.19 (0.02-0.81)[F]	
p53 abn	2.28 (1.02-5.58)[F]		1.75 (0.84-3.96)[F]	

Tarouk et al. Cancer 2017

IMPLEMENTATION PRACTIQUE - POLE MUTATION

PROMISE



COHORTE 319 PATIENTS - 70% ESMO IR/HR

POLE MUTATION 30 PTS - LN STATUS POSITIVE: 0%

SN OU ABSTENTION DE STADIFICATION

Chang et al. Cancer 2019

Tarouk et al. Cancer 2017

IMPLÉMENTATION PRATIQUE - POLE MUTATION

PORTEC 1 - HIR

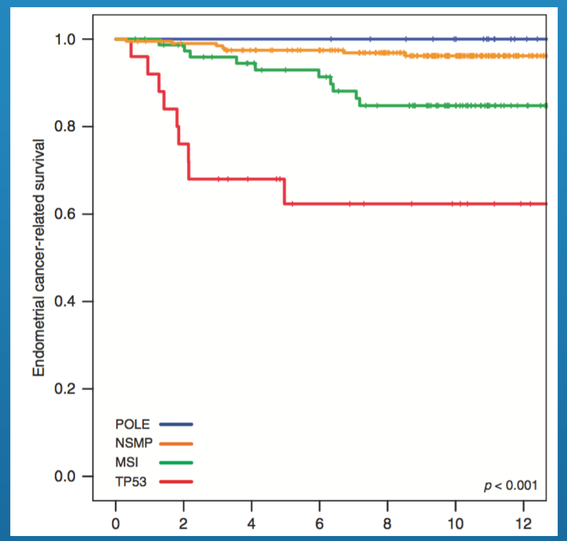
NAT ARM - 10Y RFS

POLE MUTATED : 100%
POLE NON MUTATED : 80,1%
HR: 0,143 - P = 0,049

NO ADJ TREATMENT

Wortman et al. Cancer 2018

PORTEC 2 - HIR



NO ADJ TREATMENT

Wortman et al. Cancer 2018

PORTEC 3 - HR

RT VS CTRT
5Y DFS

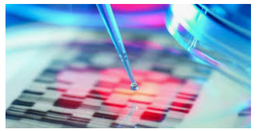
POLEmut EC		
RT	1	96,6
CTRT	0	100
NSMP EC		
RT	19	68,9
CTRT	17	81,2

NO INCREMENTAL CHEMOTHERAPY

Creutzberg et al. ESMO 2019

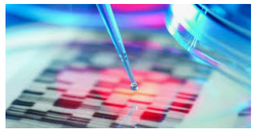
CO-MUTATION POLE/P53 IS A RARE EVENT - POLE EFFECT IS DOMINANT

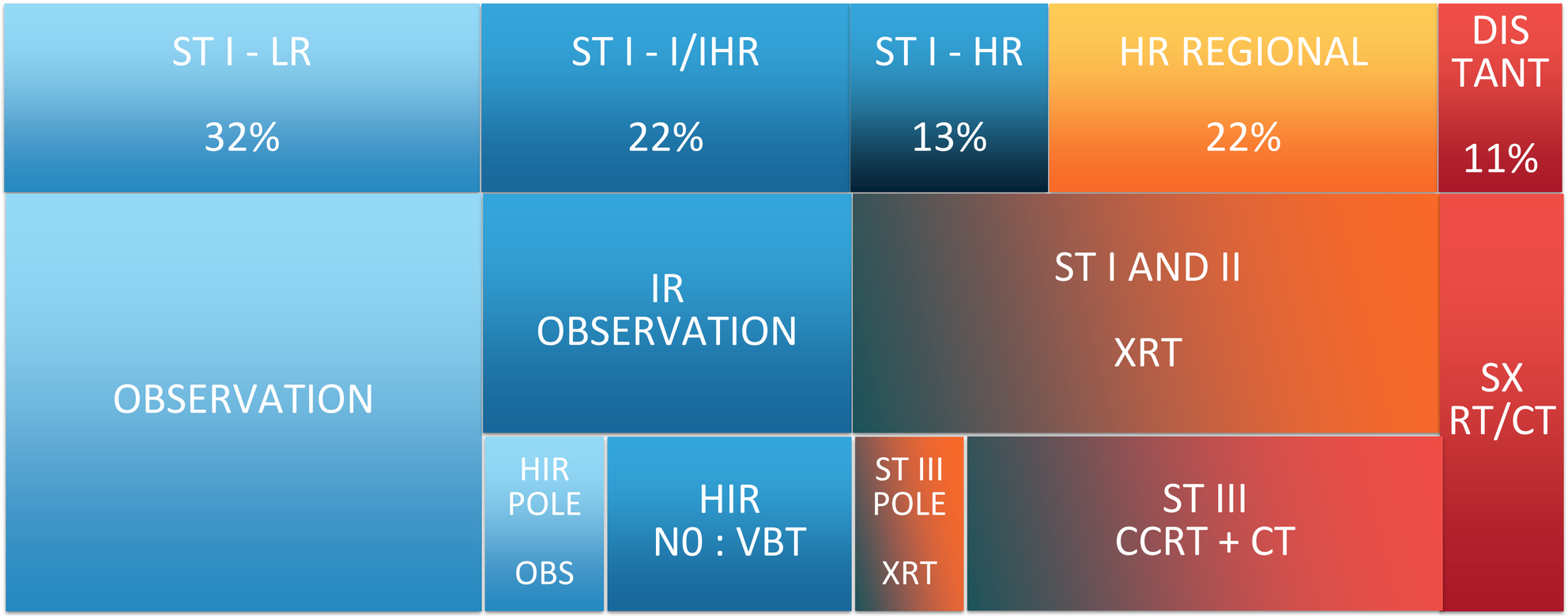
EC - VARIABLES MOLÉCULAIRES - POLE EXONUCLÉASE



ST I - LR 32%	ST I - I/IHR 22%	ST I - HR 13%	HR REGIONAL 22%	DISTANT 11%
OBSERVATION	IR OBSERVATION	ST I AND II XRT		SX RT/CT
	HIR N0 : VBT	ST III CCRT + CT WEIGH FFS BENEF / MORBIDITY		

EC - VARIABLES MOLÉCULAIRES - POLE EXONUCLÉASE





IMPLÉMENTATION PRATIQUE - P 53 MUTATION

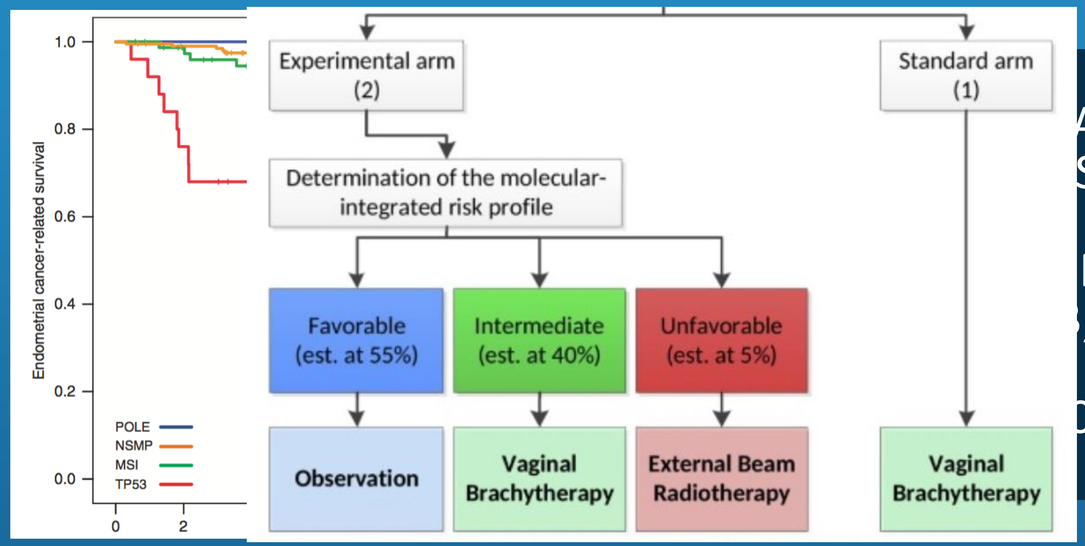
LOW RISK EC

RARE EVENT

2 TO 5% OF LOW RISK ARE P53 MUTATED

INCONCLUSIVE

PORTEC 4A HIR



ALYSIS
S WT

P 0,065)
,35 (P

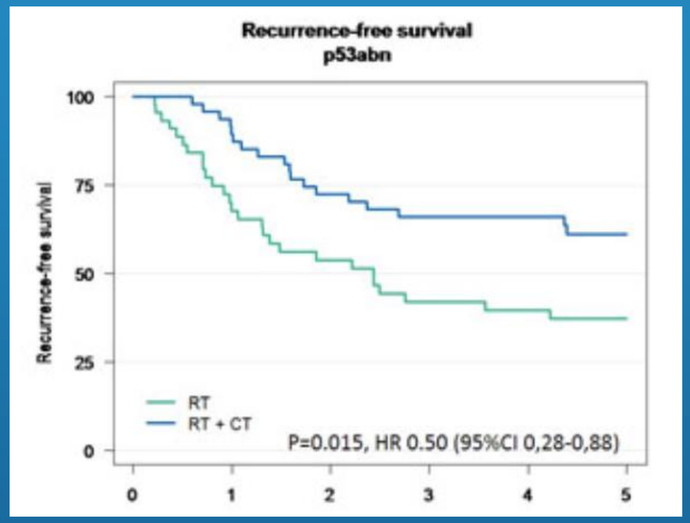
015)

SURROGATE FOR HR - VBT ⟶ XRT (+ CT ?)

Wortman et al. Cancer 2018

IMPLÉMENTATION PRATIQUE - P 53 MUTATION

PORTEC 3 HR



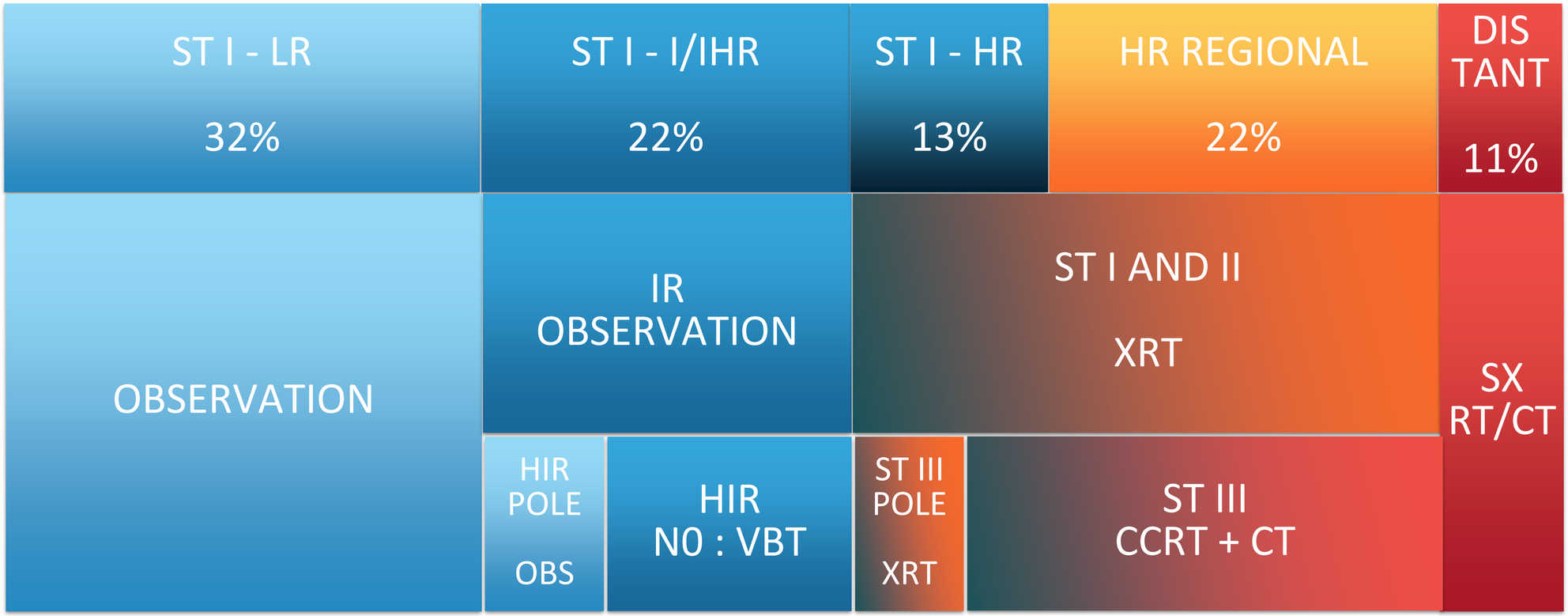
RFS CTRT VS XRT

HR: 0,5 (P 0,015)

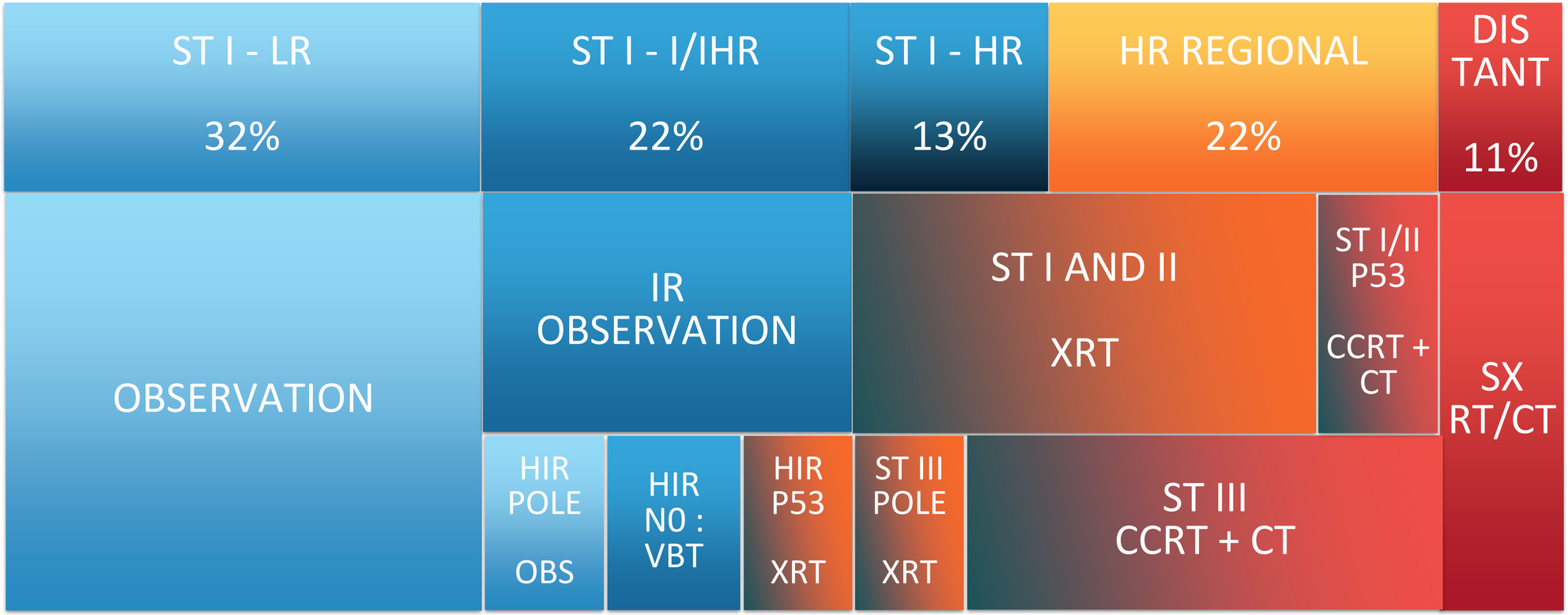
CONFIRMS NEED FOR ESCALATION WITH CT AMONGST HR EC

Creutzberg et al. ESMO 2019

EC - VARIABLES MOLÉCULAIRES - P53



EC - VARIABLES MOLÉCULAIRES - P53



IMPLEMENTATION PRATIQUE - MMR/D

LOW / IR / HIR EC

MULTIVARIATE ANALYSIS
MMR/D VS NSMP

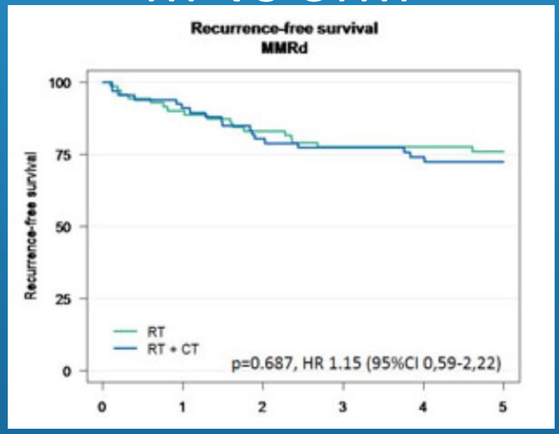
OS, PFS, DSS : HR NOT SIGNIFICANT

INCONCLUSIVE

Tarouk et al. Cancer 2017

PORTEC 3 - HR

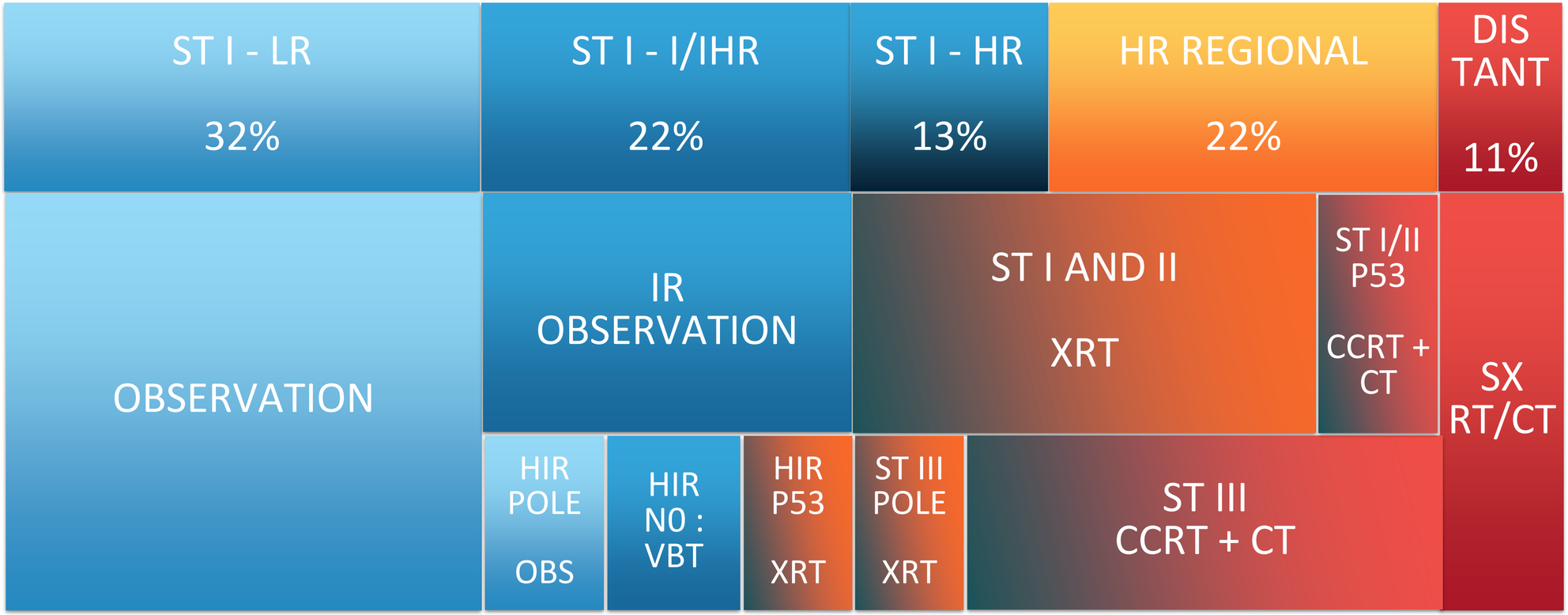
RT VS CTRT



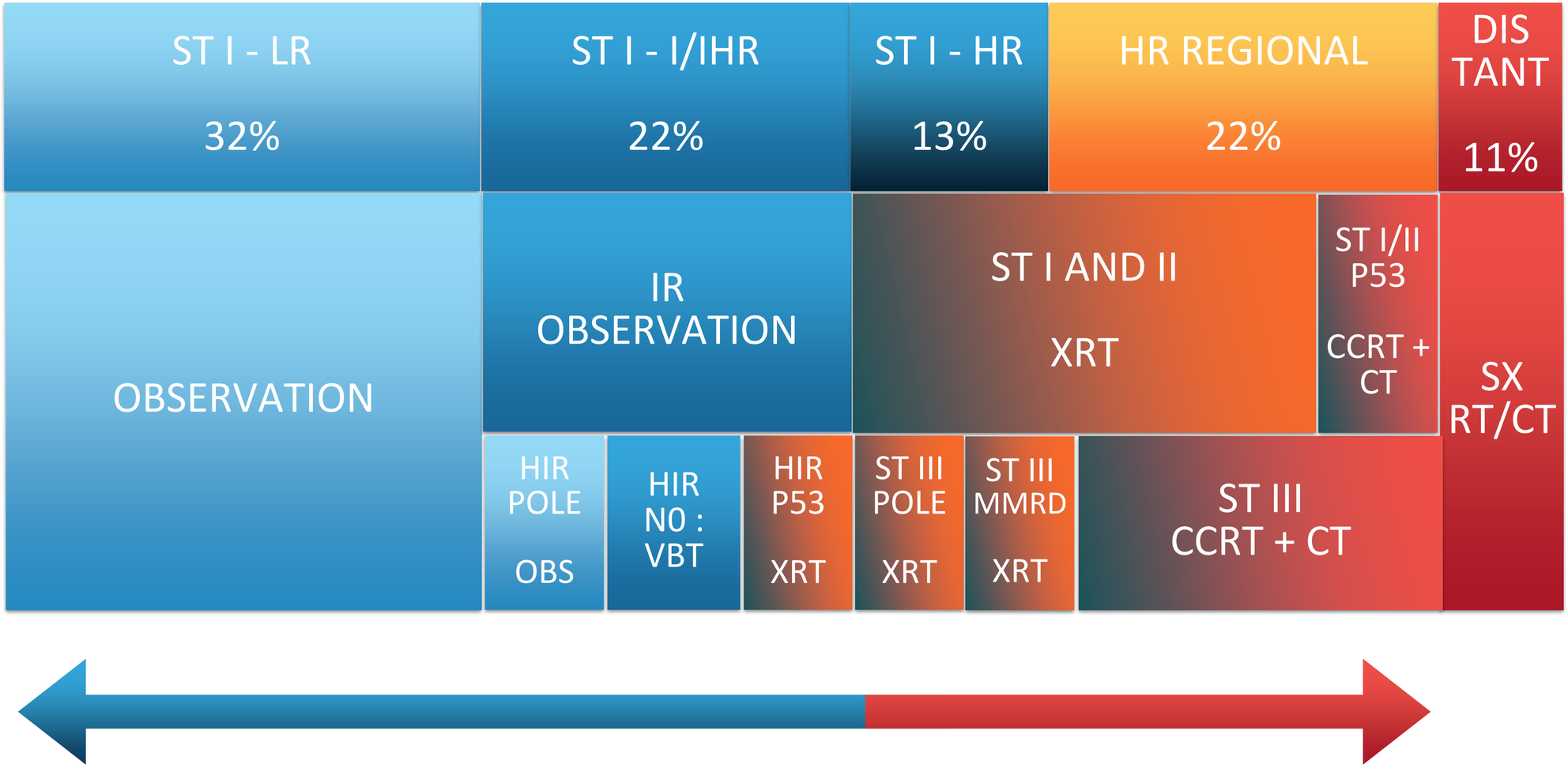
NO INCREMENTAL CHEMOTHERAPY

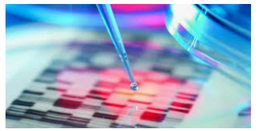
Creutzberg et al. ESMO 2019

EC - VARIABLES MOLÉCULAIRES -MMR/D



EC - VARIABLES MOLÉCULAIRES -MMR/D





TransPORTEC RAINBO Umbrella Trial

RAINBO

TransPORTEC

Molecular classification of all surgically resected endometrial cancers

- Stage I-IV → **p53abn**
  - → Chemoradiotherapy
  - → Chemoradiotherapy + DDR targeting agent
- Stage II(LVSI+)-III → **MMRd**
  - → Radiation therapy
  - → Radiation therapy + PD-L1 inhibitor
- Stage II-III → **NSMP**
  - → Chemoradiotherapy
  - → Radiation therapy + Hormonal Rx
- Stage I-III → ***POLE*mut**
  - → No adjuvant treatment/de-escalation

RAINBO p53abn — France

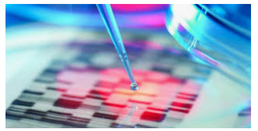
RAINBO MMRd — DGOG

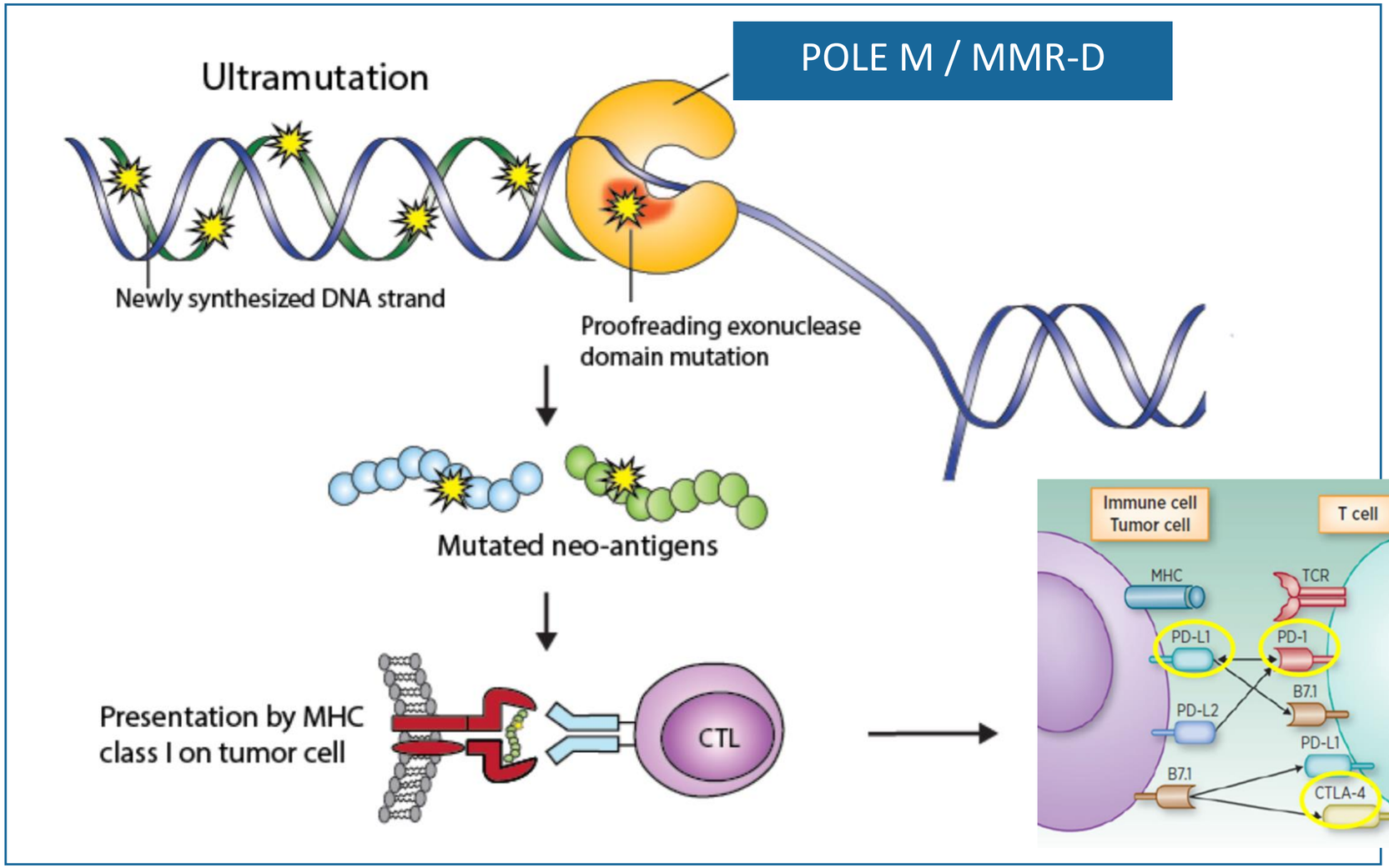
RAINBO NSMP — NCRI

RAINBO *POLE*mut — Canada

DDR- DNA damage response

PD-L1 inhibitor- immune checkpoint blockade therapy





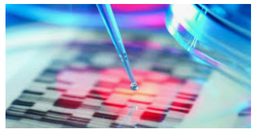
Van Gool et al. Oncoimmunology 2015

Le et al. Science 2017

EC - VARIABLES MOLÉCULAIRES - MALADIE EN RECHUTE

ST I - LR 32%	ST I - I/IHR 22%	ST I - HR 13%	HR REGIONAL 22%	DISTANT 11%
OBSERVATION	IR OBSERVATION	ST I AND II XRT	ST I/II P53 CCRT + CT	SX RT/CT
	HIR POLE OBS	HIR N0 : VBT	HIR P53 XRT	ST III POLE XRT	ST III CCRT + CT
RECURRENT DISEASE				
MMR-D AND POLE : POTENTIAL ROLE FOR IMMUNOTHERAPY ONGOING PHASE I/III STUDIES WITH PD1/PDL1 CHECKPOINT BLOCKERS PHASE I - PODIUM 101 (INCMGA00012) / PHASE III - EN6 (CT +/- DOSTARLIMAB)				

EC - VARIABLES MOLÉCULAIRES - MALADIE EN RECHUTE



	Keynote-158[1]	NCT02912572[2]	GARNET[3]	PHAEDRA[4]
Treatment	Pembrolizumab	Avelumab	Dostarlimab	Durvalumab
Phase	1/2	2	1/2	**2**
Population	Previously treated dMMR-recurrent or persistent EC	dMMR recurrent EC	Previously treated recurrent/advanced dMMR EC	Advanced dMMR EC, 0-3 prior therapies
Patients, n	49	15	125	35
ORR, %	57%	27%	45%	**47%**
DCR, %	73%	—	—	50% at 24 weeks
mPFS	26 mo	4.4 mo	—	8.3 mo
mOS	12-mo OS= 73%	—	—	NR

NR: not reached 1. O'Malley, et al. Presented at ESMO 2019; 2. Konstantinopoulos et al. *J Clin Oncol. 2019;*37:2786-2794; 3. Oaknin A, et al. Presented at ESMO, 2020, 4. Antill Y et al. *J Immunother Cancer.* 2021 Jun;9(6):e002255.

EC - VARIABLES MOLÉCULAIRES - IMPLICATION SCIENTIFIQUE

P53 STATUS: A STRONG NEGATIVE PROGNOSTIC FACTOR IN ENDOMETRIAL CARCINOMA

Dheur A. (1), Salmon A. (2), Streel S. (2). Bours V. (3), Delbecque K. (4), Gonne E. (2), Pleyers C. (5), De Cuypere M. (1), Goffin F. (1), Lovinfosse P. (6), Kridelka F. (1), Kakkos A. (1), Gennigens C. (2)

(1) Department of Gynaecology and Obstetrics, CHU Liège, Belgium
(2) Department of Medical Oncology, CHU Liège, Belgium
(3) Department of Human Genetics, CHU Liège, Belgium
(4) Department of Pathology, CHU Liège, Belgium
(5) Department of Radiation Oncology, CHU Liège, Belgium
(6) Department of Nuclear Medicine and Oncological Imaging, CHU Liège, Belgium

INTRODUCTION

Endometrial carcinoma (EC) is the most common gynaecological cancer in developed countries. The recent implementation of molecular classification has changed the approach to risk stratification, distinguishing EC into 4 molecular subgroups: POLE ultramutated, mismatch repair deficient, p53-abnormal (p53abn), non-specific molecular profile. Patients presenting with p53abn have the worst prognosis. We aimed to compare the clinical profile, progression free survival (PFS) and overall survival (OS) according to p53 status.

METHODS

Between January 2019 and October 2022, we conducted a retrospective study of 158 patients with EC treated at the CHU of Liège. The p53 status was determined by immunohistochemistry as wild-type (p53wt) or abnormal (p53abn). Data were available for 154 patients. Factors studied were age, body mass index (BMI), histological subtypes, tumour grade, lymph node status and FIGO stage. Association between p53 status and these factors was assessed using Chi-square or Fisher's exact tests. PFS and OS were represented by the Kaplan-Meir method stratified by p53 status. Cox regression analyses investigated the impact of p53 status and other clinical and tumour characteristics on PFS and OS. Among these characteristics, only those that presented a p-value<0.10 in Chi-square tests, Fisher's exact tests or in univariate Cox regression analyses, were used in the multivariate stepwise Cox regression. Results were considered significant at the 5% confidence level.

Table 1. – Comparison between clinical and tumour characteristics according to p53 status

Characteristics	p53wt (n=114)	p53abn (n=40)	p-value
Age at diagnosis, mean ± SD (years)	70.1 ± 10.3	70.7 ± 11.9	0.73
BMI, median (P25-P50) (kg/m²)	28.5 (24.7-33.6)	28.3 (24.1-32.8)	0.71
Histological subtypes, n (%)			<0.0001
Endometrioid	102 (90.3)	20 (54.1)	
Not-endometrioid	11 (9.70)	17 (45.9)	
Tumour grade, n (%)			<0.0001
G1-G2	81 (72.3)	13 (34.2)	
G3	31 (27.7)	25 (65.8)	
Nodal staging, n (%)			0.24*
N0	90 (92.8)	22 (84.6)	
N1-N2	7 (7.20)	4 (15.4)	
FIGO stage, n (%)			0.087*
IA	40 (35.4)	19 (51.4)	
IB	53 (46.9)	10 (27.0)	
II-IVB	20 (17.7)	8 (21.6)	

*Fisher exact

RESULTS

Of the 154 patients, 114 were p53wt (74.0%) and 40 were p53abn (26.0%). The p53abn status was associated with worse pathological features. Non endometrioid tumours were found in 45.9% of p53abn compared with 9.70% of p53wt groups (p<0.0001). Grade 3 tumours were observed in 65.8% and 27.7% of p53abn/wt population, respectively (p<0.0001).
No association was established between p53 status and nodal stage (p=0.24) or FIGO stage (p=0.087) (Table 1). Regarding PFS, no statistical difference was noted between the two groups (p=0.062) (Table 2 - Fig. 1). This result is confirmed in multivariate analyses (p=0.44). In this model, PFS is associated with age and tumour grade. The risk of recurrence is increased by 8% per additional year (HR=1.08, p=0.029) and multiplicated by 11.8 in patients with grade 3 tumours compared to patients with grade 1 and 2 (HR=11.8, p=0.024). OS was significantly reduced in p53abn patients compared to p53wt patients (HR = 6.13, p=0.0032) (Table 2 - Fig. 1). In multivariate analyses, only p53 status is associated with OS. The risk of death is increased by 5.5 in patients with p53abn tumour compared to patients with a wild-type p53 status (HR=5.49, p=0.0067) (Table 2).

Table 2. Cox-regression analyses to identify clinical or tumour characteristics associated with PFS and OS

Variables	Progression Free Survival				Overall Survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis (years)	1.10 (1.03-1.17)	0.0007	1.08 (1.01-1.17)	0.029	1.06 (1.00-1.12)	0.071		
BMI (kg/m²)	0.95 (0.85-1.06)	0.33			0.99 (0.90-1.08)	0.75		
p53 IHC								
p53wt	1		1		1		1	
p53abn	3.27 (0.94-11.4)	0.062	1.67 (0.46-6.13)	0.44	6.13 (1.84-20.4)	0.0032	5.49 (1.60-18.8)	0.0067
Histological subtypes								
Endometrioid	1				1			
Not-endometrioid	8.34 (2.31-30.0)	0.0012			3.63 (1.14-11.5)	0.029		
Tumour grade								
G1-G2	1		1		1			
G3	12.9 (2.10-78.9)	0.0057	11.8 (1.38-102)	0.024	3.82 (1.14-12.8)	0.029		
Nodal staging								
N0	1				1			
N1-N2	0.70 (0.03-15.7)	0.82			1.26 (0.15-10.2)	0.83		
FIGO stage								
IA	1				1			
IB	3.84 (0.45-32.9)				0.77 (0.16-3.81)			
II-IVB	6.62 (0.74-59.3)	0.23			2.84 (0.68-11.9)	0.14		

HR: Hazard ratio

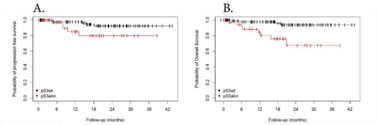


Fig 1. Survival curves showing the PFS (A) and OS (B) trends in p53wt vs. p53abn status

CONCLUSION

The presence of an abnormal p53 status in patients with EC is a strong negative prognostic factor associated with aggressive clinicopathological features and decreased OS. Therefore, p53 status should be routinely determined to define the patient's prognosis.

Agreement between immunohistochemistry and molecular techniques to assess microsatellite instability and p53 status in endometrial cancer

Salmon A.[1], Streel S.[1], Dheur A.[2], Bours V.[3], Delbecque K.[4], Gonne E.[1], Pleyers C.[5], De Cuypere M.[2], Goffin F.[2], Lovinfosse P.[6], Kakkos A.[2], Kridelka F.[2], Gennigens C.[1]

[1]Department of Medical Oncology, CHU Liège, Belgium - [2]Department of Gynaecology and Obstetrics, CHU Liège, Belgium - [3]Department of Human Genetics, CHU Liège, Belgium - [4]Department of Pathology, CHU Liège, Belgium - [5]Department of Radiation Oncology, CHU Liège, Belgium - [6]Department of Nuclear Medicine and Oncological Imaging, CHU Liège, Belgium

INTRODUCTION

Endometrial carcinoma (EC) is the most common gynaecological cancer in developed countries. The recent implementation of molecular classification has changed the approach to risk stratification. Microsatellite instability (MSI) and p53 status are major prognosis and predictive biomarkers to be determined for this classification. Immunohistochemistry (IHC) and molecular techniques are used to assess them. We aimed to compare the agreement between these two techniques for evaluating MSI and p53 status.

Table 1. Molecular profile of EC tumors (n=158)

Variables	No. of patients	Frequency, n (%)
POLE	136	
Wildtype		125 (91.9)
Ultra-mutated		11 (8.09)
MMR IHC	156	
MMRd		53 (34.4)
MMRp		101 (65.6)
MSI PCR	118	
MSS		75 (63.6)
MSI-high		43 (36.4)
p53 IHC	154	
Normal		114 (74.0)
Abnormal		40 (26.0)
TP53	129	
Normal		98 (76.0)
Mutated		31 (24.0)

POLE: POlymerase Epsilon, MMR: MisMatch Repair, MMRd: MisMatch Repair deficient, MMRp: MisMatch Repair proficient, MSS: MicroSatellite Stable

METHODS

Between January 2019 and October 2022, we conducted a retrospective study of 158 patients treated for EC (all stages) at the CHU of Liège. Among the 158 patients, 118 patients had both results carried out by IHC and polymerase chain reaction (PCR) analyses for MSI status. Concerning p53 status, 126 patients had both results established by IHC and next generation sequencing (NGS). McNemar's test and Cohen's Kappa coefficient were used to evaluate the agreement between IHC and molecular techniques (gold standard). Sensitivity, specificity and accuracy were also calculated.

RESULTS

The molecular profile of EC tumors is presented in Table 1. Regarding MSI status, the same proportion of MSI was detected by IHC (40.7%) and by PCR (36.4%) (p = 0.17). Sensitivity was 90.7% and specificity was 88.0%, yielding a global accuracy level of 89.0% (Table 2). Cohen's Kappa was 0.77 (95% CI: 0.65-0.89).

Table 2. Agreement between MMR IHC status and MSI PCR testing (n=118)

		MSI PCR	
		MSI High	MSS
MMR IHC status	MMRd	39	9
	MMRp	4	66
	Sensitivity	90.7% (95% CI: 77.9-97.4)	
	Specificity	88.0% (95% CI: 78.4-94.4)	
	Accuracy	89.0% (95% CI: 81.9-94.0)	
	Cohen's Kappa	0.77 (95% CI: 0.65-0.89)	

For p53 status, the proportion of p53-mutated type by IHC (23.0%) and by NGS (27.8%) was comparable (p=0.20). Specificity and sensitivity were 85.6% and 72.4% respectively, with an accuracy of 82.5% (Table 3). Cohen's Kappa was 0.54 (95% CI: 0.37-0.71).

Table 3. Agreement between p53 IHC and TP53 NGS analysis (n=126)

		TP53 mutation	
		Present	Absent
p53 IHC	Abnormal	21	14
	Normal	8	83
	Sensitivity	72.4% (95% CI: 52.8-87.3)	
	Specificity	85.6% (95% CI: 76.9-91.9)	
	Accuracy	82.5% (95% CI: 74.8-88.7)	
	Cohen's Kappa	0.54 (95% CI: 0.37-0.71)	

CONCLUSIONS

Concerning the determination of MSI status, IHC and PCR showed equivalent diagnostic performance. However, for the p53 status, the agreement between IHC and NGS methods was only moderate which would imply that they cannot be used interchangeably. Further studies are needed to explore the reasons underlying these observations.

Int J Mol Sci. 2023 Mar 2;24(5):4866. doi: 10.3390/ijms24054866.

Diagnostic Performance of Immunohistochemistry Compared to Molecular Techniques for Microsatellite Instability and p53 Mutation Detection in Endometrial Cancer

Sylvie Streel [1], Alixe Salmon [1], Adriane Dheur [2], Vincent Bours [3], Natacha Leroi [3], Lionel Habran [4], Katty Delbecque [4], Frédéric Goffin [2], Clémence Pleyers [5], Athanasios Kakkos [2], Elodie Gonne [1], Laurence Seidel [6], Frédéric Kridelka [2], Christine Gennigens [1]

Affiliations + expand

PMID: 36902292 PMCID: PMC10002995 DOI: 10.3390/ijms24054866

Free PMC article

Abstract

Molecular algorithms may estimate the risk of recurrence and death for patients with endometrial cancer (EC) and may impact treatment decisions. To detect microsatellite instabilities (MSI) and p53 mutations, immunohistochemistry (IHC) and molecular techniques are used. To select the most appropriate method, and to have an accurate interpretation of their results, knowledge of the performance characteristics of these respective methods is essential. The objective of this study was to assess the diagnostic performance of IHC versus molecular techniques (gold standard). One hundred and thirty-two unselected EC patients were enrolled in this study. Agreement between the two diagnostic methods was assessed using Cohen's kappa coefficient. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of the IHC were calculated. For MSI status, the sensitivity, specificity, PPV and NPV were 89.3%, 87.3%, 78.1% and 94.1%, respectively. Cohen's kappa coefficient was 0.74. For p53 status, the sensitivity, specificity, PPV, and NPV were 92.3%, 77.1%, 60.0% and 96.4%, respectively. Cohen's kappa coefficient was 0.59. For MSI status, IHC presented a substantial agreement with the polymerase chain reaction (PCR) approach. For the p53 status, the moderate agreement observed between IHC and next generation sequencing (NGS) methods implies that they cannot be used interchangeably.

LE CANCER ENDOMÉTRIAL A UN EXCELLENT PRONOSTIC

LES VARIABLES HISTO ONT UN HAUT DEGRÉ DE VARIABILITÉ INTEROBSERVATUER - DES VARIABLES PLUS ROBUSTES SONT NÉCESSAIRES

LA BIOMOL IDENTIFIE EFFICACEMENT DES SOUS-GROUPES DE RISQUES - LENT ET COÛTEUX - IHC EST UNE ALTERNATIVE À LA BIOMOL

EC AVEC MUTATIONS POLE M ET/OU MMR-D : DÉSESCALADE THÉRAPEUTIQUE PEUT ÊTRE DISCUTÉE/ADOPTÉE (OBS VS VBT, XRT VS CTRT)

P53 M EC ONT UN PRONOSTIC TRÈS DÉFAVORABLE - CONSOLIDE L'INDICATION DE CTRT(PORTEC3) CHEZ LES HR EC
PAS DE DATA PROSPECTIFS SUPPORTANT CTRT IN LR/IR/HIR EC

MMR-D/MSI-H ET POLE NEOANTIGENS/TIL'S/PDL-1 PROFIL SUPPORTE L'UTILISATION DE IT EN RECHUTE PRÉTRAITÉE (PD1/PDL1 CPI)

CANCER ENDOMÉTRIAL : IMPLÉMENTATION CLINIQUE DU PROFIL GÉNÉTIQUE

F KRIDELKA, F GOFFIN, A KAKKOS, CH GENNIGENS, E GONNE, CL PLEYERS, J HERMESSE, V BOURS, K SEGERS AND K DELBEQUE.

S BROUERS, V DUC, L KEMPENEER, MC LHOTE, M TYCHON AND C WILLEMS

ASS: A DHEUR, A SALMON

DEPARTMENT OF GYNECOLOGY AND OBSTETRICS - GYNE/ONCOLOGY UNIT - ULIÈGE

XVIIèmes Journées Liégeoises de Gynécologie-Obstétrique
Une organisation du Département de Gynécologie-Obstétrique de l'Université de Liège