“The role of immunotherapy in Gynecological Malignancy”

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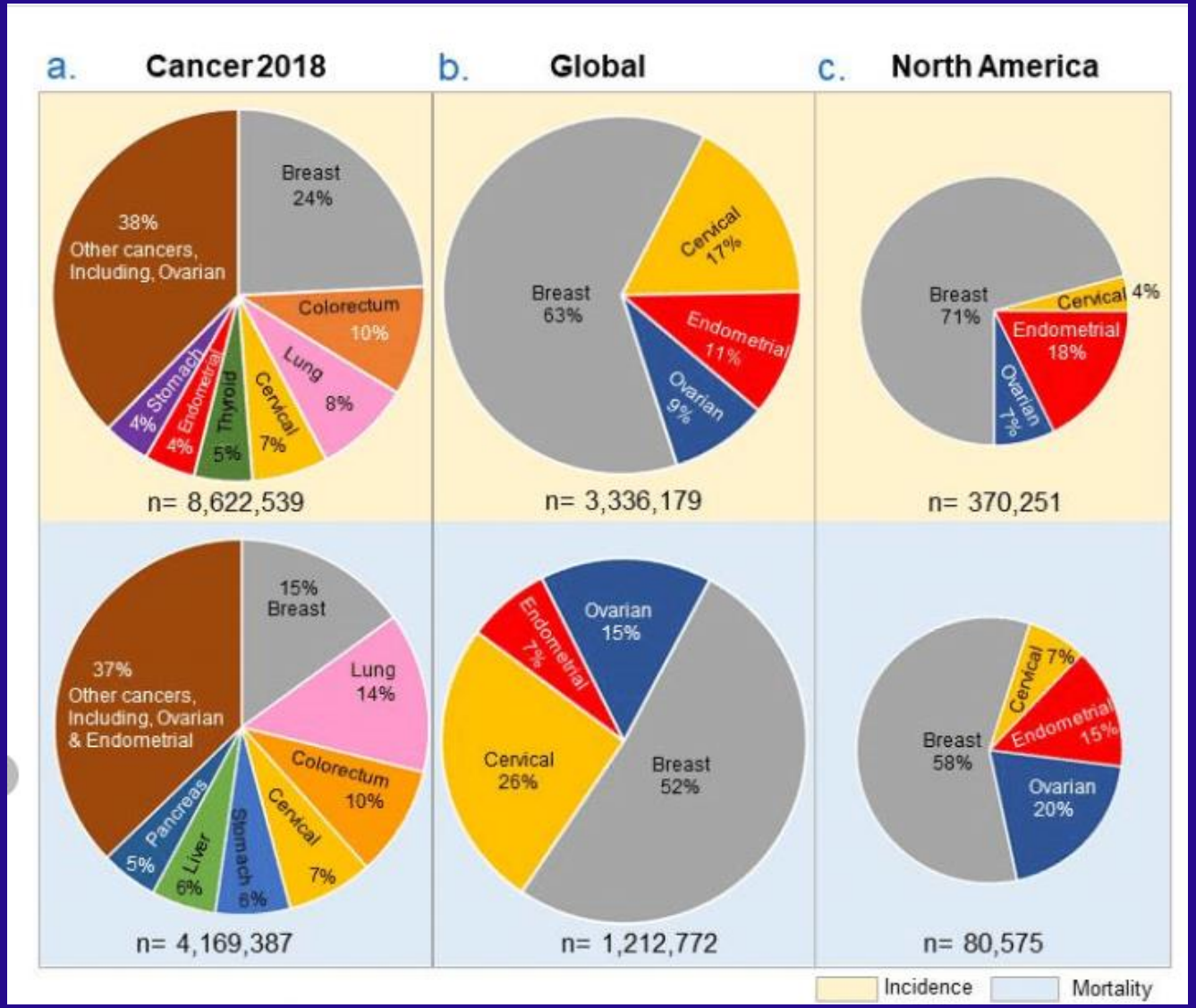
Outline

- Introduction
- Standard treatment of gynaecological malignancies
- Novel strategies
- Immunotherapy in gyneacological tumors
  - Cervical cancer
  - Endometrial cancer
  - Ovarian cancer
- Where are we going next?
- How to do a better assessment?

Incidence and mortality of women's cancer



Cancers 11(8):1193 · August 2019

Standard treatment of gynaecological malignancies

- Standard treatment of advanced gynaecological malignancies is based on cytoreductive surgery, followed by chemotherapy which remained the same over the past decades, and radiation therapy.

- However, the overall survival rate, in metastatic breast cancer, has not been improved…

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6141595/

https://www.cancerresearch.org/immunotherapy/cancer-types/ovarian-cancer

We definitely need Novel strategies

- To overcome chemoresistance and have better response:
  - Anti-angiogenic agents
  - PARP inhibitors
  - Immunotherapy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6141595/

https://www.cancerresearch.org/immunotherapy/cancer-types/ovarian-cancer

Immunotherapy in gyneacological tumors

- Where are we now?

Two FDA approvals

- In cervical Cancer (june 2018)
- Accelerated FDA approval since 17 September 2019 for endometrial cancer

Cervical cancer

Cervical cancer

- Fourth most common cancer in women worldwide with 99.7% of cases associated with HPV infection.

- Standard of care for recurrent/metastatic (R/M) disease without systemic therapy is cisplatin/paclitaxel + Bevacizumab (median OS <17 mo)

Cervical cancer

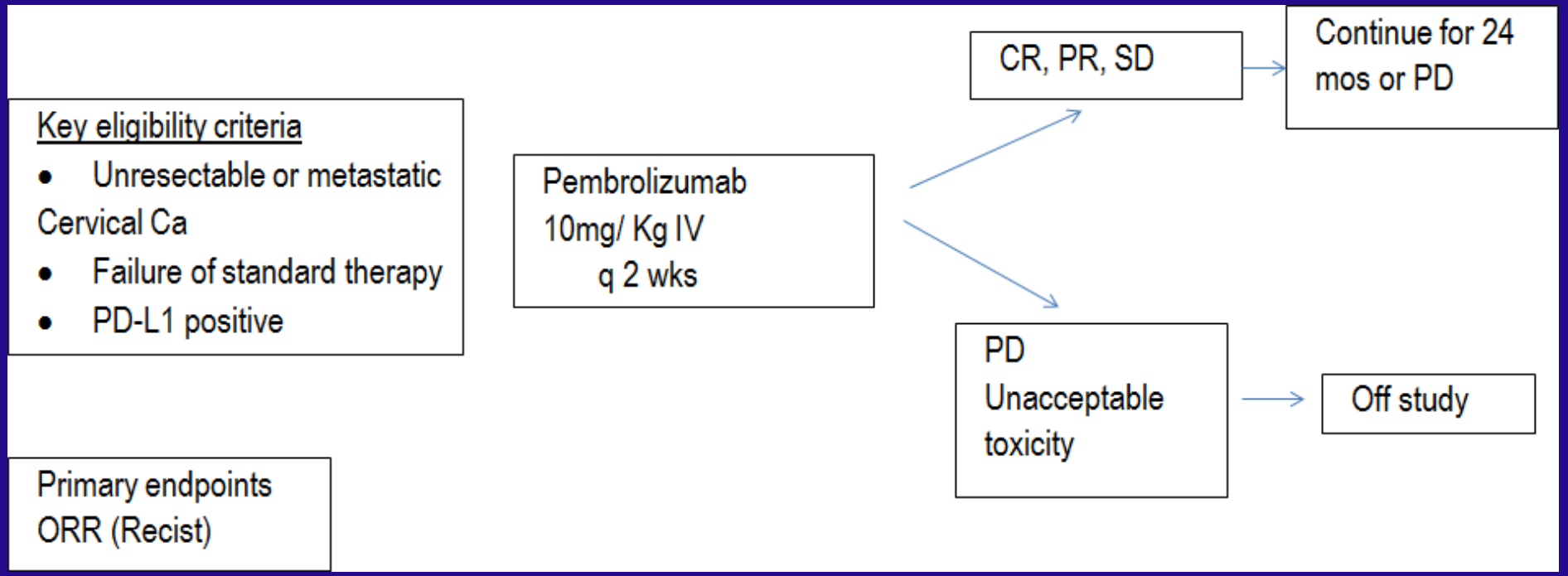
- Upregulation of PD-1 and PD-L1 expression has been reported in cervical cancer making this tumor type likely to respond to PD-1/PD-L1 based therapy

- CTLA-4 is an inhibitory checkpoint that regulates adaptive immunity

Emerging strategies in recurrent cervical ca immune checkpoint inhibitors

Pembrolizumab in patients with advanced cervical Ca

Phase 1b Keynote-028 study



Frenel, JCO 2017

Pembrolizumab in advanced cervical cancer

KEY NOTE 028 results

Patients treated (%) (n=24)		Antitumor activity (%)		Grade 3 TRAE (%)	
Metastatic disease	100	ORR	17	Any	75
Prior RT	92	PR	17	Rash	21
Prior lines CT (≥3)	38	SD	13	Colitis	4
Prior Bev	42	PD	67	Guillain Barrè	4
Median response:		duration: 5.4 mo (4.1-7.5)			
Median OS:		duration: 11 mo (95% CI: 4-15)			

Median follow up: 11 mo (1.3-32.2)

Frenel, JCO 2017

Recent FDA approval

Pembrolizumab in advanced cervical cancer (FDA)

Phase II KEY NOTE 158 results

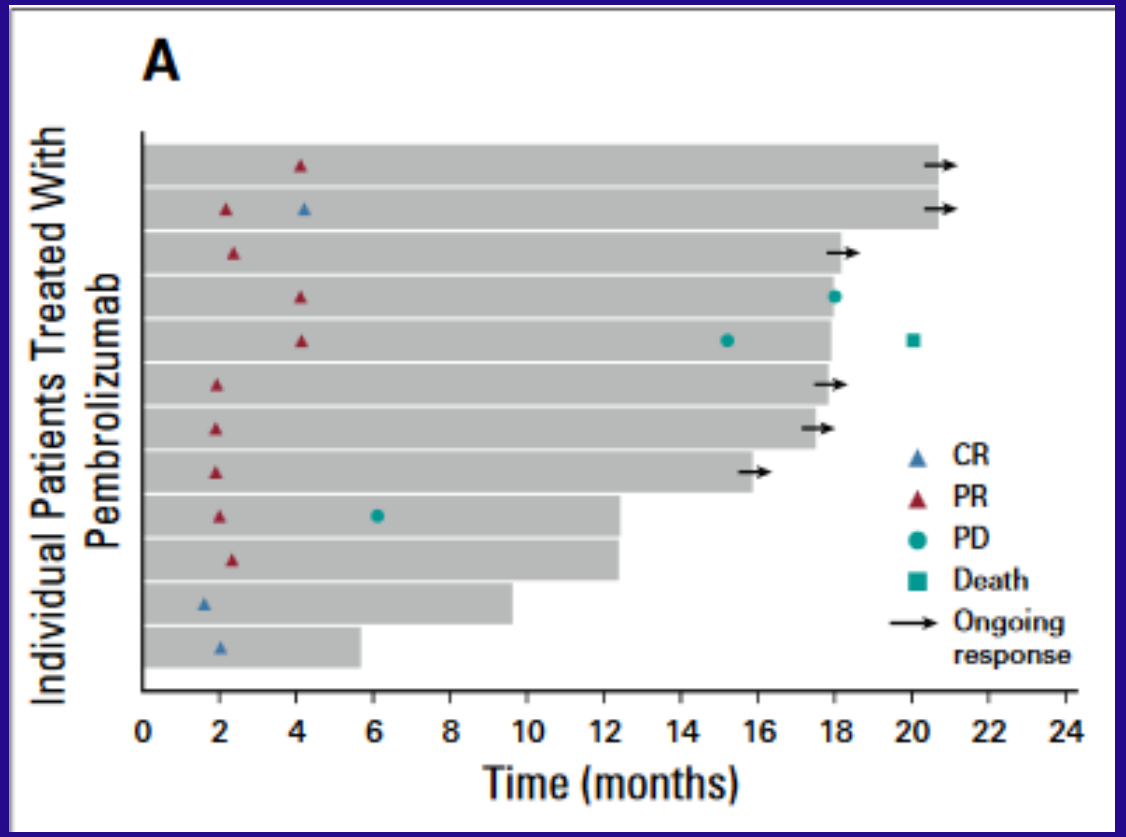
Patients treated (n=82)	Antitumor activity (pts number)	PD–L1+ (%)
OR	10	10
CR	3	3
PR	7	7
SD	17	14
PD	44	37

Pembrolizumab granted FDA approval for PD–L1+ Cervical Cancer 12 June 2018

ASCO, 2017

Pembrolizumab in advanced cervical cancer (FDA)

Phase II KEY NOTE 158 results



90 % of responders
Still respond after 6 months

At 11 months of follow up:
median duration of response
Not Reached

No response for PDL1 -

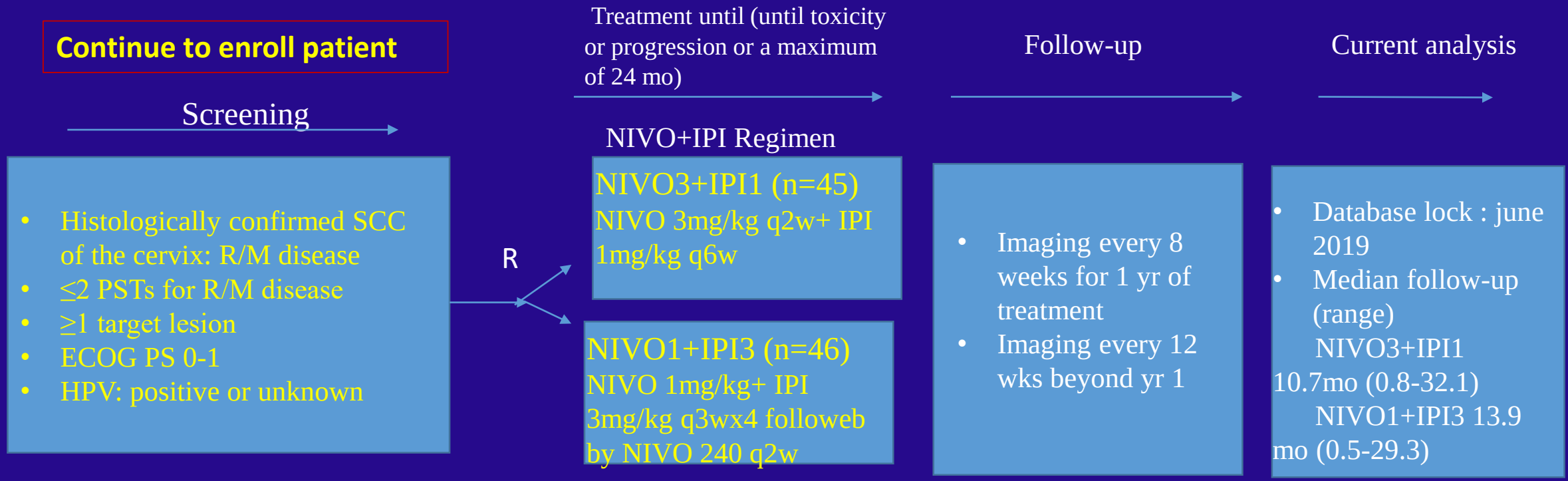
Pembrolizumab granted FDA approval for PD–L1+ Cervical Cancer 12 June 2018

ASCO, 2017

Ongoing Trial
Combination Immunotherapy

Nivo/Ipi

- Randomized cervical cancer cohorts of CheckMate 358 testing 2 combination regimens of nivolumab + ipilimumab for R/M disease



Study start date: October 2015
Estimated Completion date Decdember 2-10

Primary endpoint: investigator assessed ORR by RECIST 1.1
Secondary endopoints: OS, PFS, duration of response

Progression Free survival

- In the nivo1 + ipi3 arm → 8.5 months (95% CI, 3.7-not reached) in the patients with no prior systemic therapy for R/M disease and 5.8 months (95% CI, 3.5-17.2) in those who had received prior systemic therapy for R/M disease.

- The probability of PFS at 6 months was 60.9% in those with no prior systemic therapy for R/M disease and 47.6% in those with prior systemic therapy, and at 12 months, these percentages were 43.5% and 38.1%, respectively.

Median overall survival

- Median overall survival (OS) was not reached in the nivo3 + ipi1 group that had no prior systemic therapy for R/M disease and 10.3 months in those with prior systemic treatment for R/M disease.

- The corresponding median OS values in the nivo1 + ipi3 arm were not reached and 25.4 months, respectively

- Nivo1 + Ipi3 (ORR 45%)> Nivo3 + Ipi1(ORR 30%) with more toxicities

Checkmate 358 : Conclusion

- The combination of nivo + ipi suggests a clinical benefit in patients with R/M cervical cancer.
- Median duration of response was not reached.
- The treatment protocol had a Tolerable safety profile.
- We are still waiting for the long term follow up

Ongoing IO studies in Cervical Cancer

	Patient Population	Agent	Results
Single-Agent Immunotherapy			
Frenel et al (2017), KEYNOTE 028[53]	PD-L1+ recurrent diagnosis	Pembrolizumab	ORR, 17%; DOR, 6 months
Chung et al (2018), KEYNOTE 158[54]	PD-L1+ recurrent diagnosis	Pembrolizumab	ORR, 14.3%; DOR, not reached at 11.7 months
Lheureux et al (2018)[55]	Recurrent diagnosis	Ipilimumab	ORR, 2.9%
Hollebecque et al (2017), CheckMate 358[55]	Recurrent diagnosis	Nivolumab	ORR, 5%
Santin et al (2018), NRG-GY002[57]	Recurrent diagnosis	Nivolumab	ORR, 4%
GOG 3016, NCT03257267	Recurrent diagnosis	Cemiplimab (PD-1i)	Ongoing
Chemotherapy + Immunotherapy			
KEYNOTE 826, NCT03635567	First line	Chemotherapy + pembrolizumab	Ongoing
BEATcc, NCT03556839	First line	Chemotherapy + atezolizumab	Ongoing

Endometrial cancer

Endometrial Cancer

Epidemiology

- The most common gy cancer in Western countries
- Incidence 13/100'000 women/yr Europe
- Mortality 2-3/100'000 women/yr
- 80-90% post menopausal; 5% in <40 yrs old
- Median age 63 yrs
- 80% Stage I 5yr survival 95%
- 10 % stage IV 5 yr survival 17%

Risk factors	unopposed / excessive oestrogen exposure metabolic syndrome (obesity, hypertension): RR 1.89 nulliparity, early menarche/late menopause, diabetes treatment with tamoxifen in postmenopause
Genetic susceptibility	Lynch syndrome/ Hereditary Non-Polyposis Colorectal Cancer: 40-60% lifetime risk of both endometrial and CRC

Cancer Genome Atlas Research Network

Comprehensive genomic and transcriptomic analysis of endometrial cancer

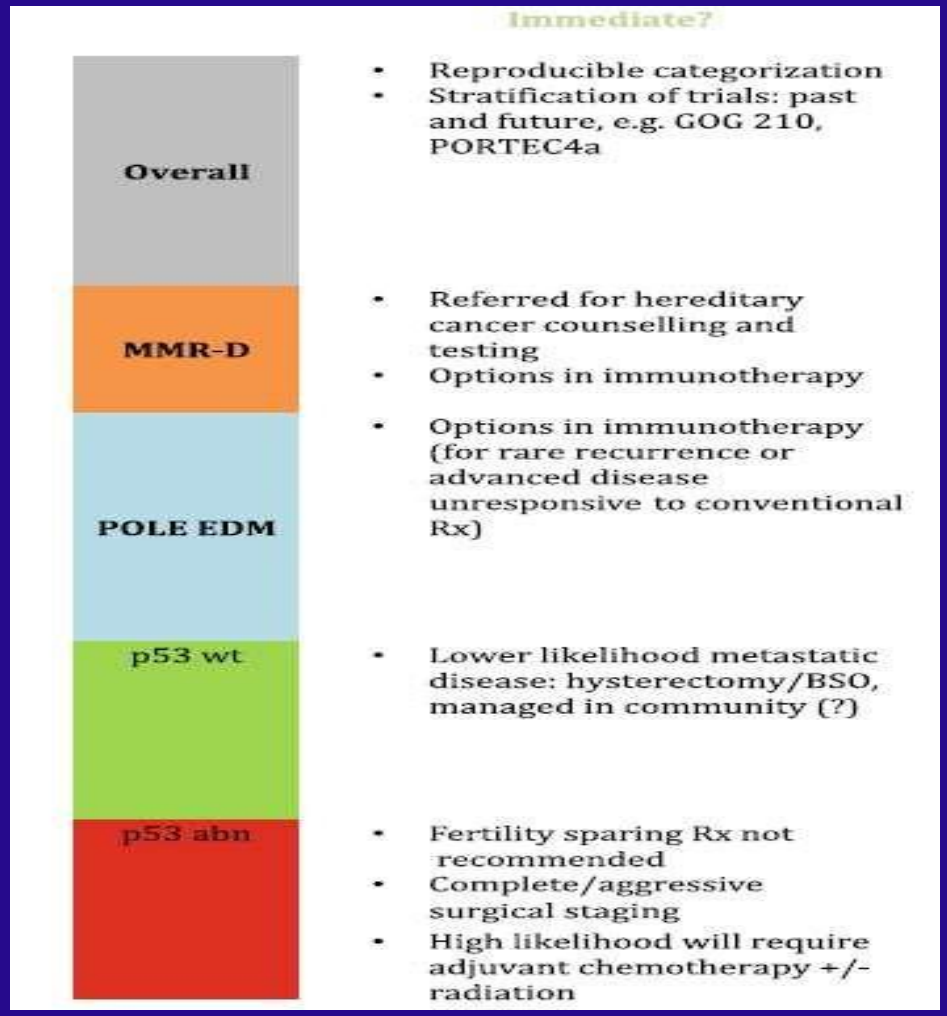
Four genomic classes

	POLE (ultramutated)	MSI (hypermutated)	Copy-number low (endometrioid)	Copy-number high (serous-like)
Copy-number aberrations	Low	Low	Low	High
MSI/*MLH1* methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Mutation rate	Very high (232×10^{-6} mutations/Mb)	High (18×10^{-6} mutations/Mb)	Low ($2{\cdot}9 \times 10^{-6}$ mutations/Mb)	Low ($2{\cdot}3 \times 10^{-6}$ mutations/Mb)
Genes commonly mutated (prevalence)	*POLE* (100%) *PTEN* (94%) *PIK3CA* (71%) *PIK3R1* (65%) *FBXW7* (82%) *ARID1A* (76%) *KRAS* (53%) *ARID5B* (47%)	*PTEN* (88%) *RPL22* (37%) *KRAS* (35%) *PIK3CA* (54%) *PIK3R1* (40%) *ARID1A* (37%)	*PTEN* (77%) *CTNNB1* (52%) *PIK3CA* (53%) *PIK3R1* (33%) *ARID1A* (42%)	*TP53* (92%) *PPP2R1A* (22%) *PIK3CA* (47%)
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid, and mixed serous and endometrioid
Tumour grade	Mixed (grades 1–3)	Mixed (grades 1–3)	Grades 1 and 2	Grade 3
Progression-free survival	Good	Intermediate	Intermediate	Poor
	7%	28%	39%	26%

Murali R, Lancet Oncol, 2014

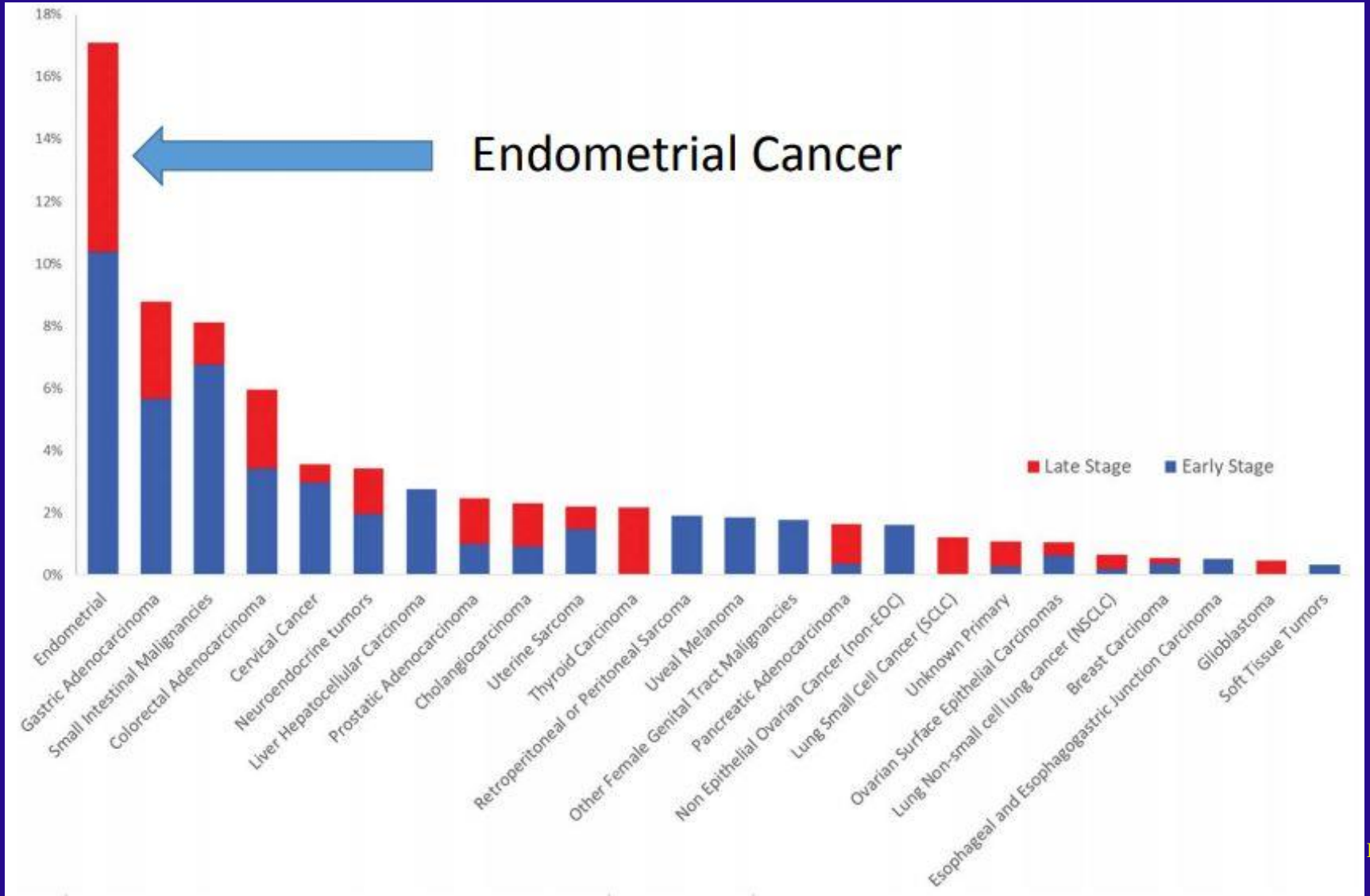
ENDOMETRIAL CANCER

Potential changes in practice through molecular categorization of EC



Gynecol. Oncol. Pract., 2016

Highest rate of MSI-H observed in endometrial cancer



Le D, et al. Science June 8, 2017

Endometrial cancer

- PD-1/PD-L1 inhibitors : active in metastatic MMRd cancers (Keynote-028: 13% PR, 13% SD)
- Pembrolizumab: Monotherapy for MSI-H endometrial cancer following prior treatment failure
- Lenvatinib : Oral multikinase inhibitor that targets VEGFR1-3, FGFR 1-4, PDGFRα, RET, and KIT
- KEYNOTE-146/Study 111: phase 1b/2 study: lenvatinib with pembrolizumab in patients with advanced EC regradless of MSI status.

Study Design

Key eligibility criteria

-Age≥ 18years

-Pathologically confirmed and metastatic endometrial carcinoma

-≤2 prior systemic therapies irRECIST

-ECOG performance status ≤1

-Life expectancy≥12 weeks

Lenvatinib 20mg/day(oral)

+

Pembrolizumab 200mg Q3W (IV)

Primary End Point

ORR at week 24

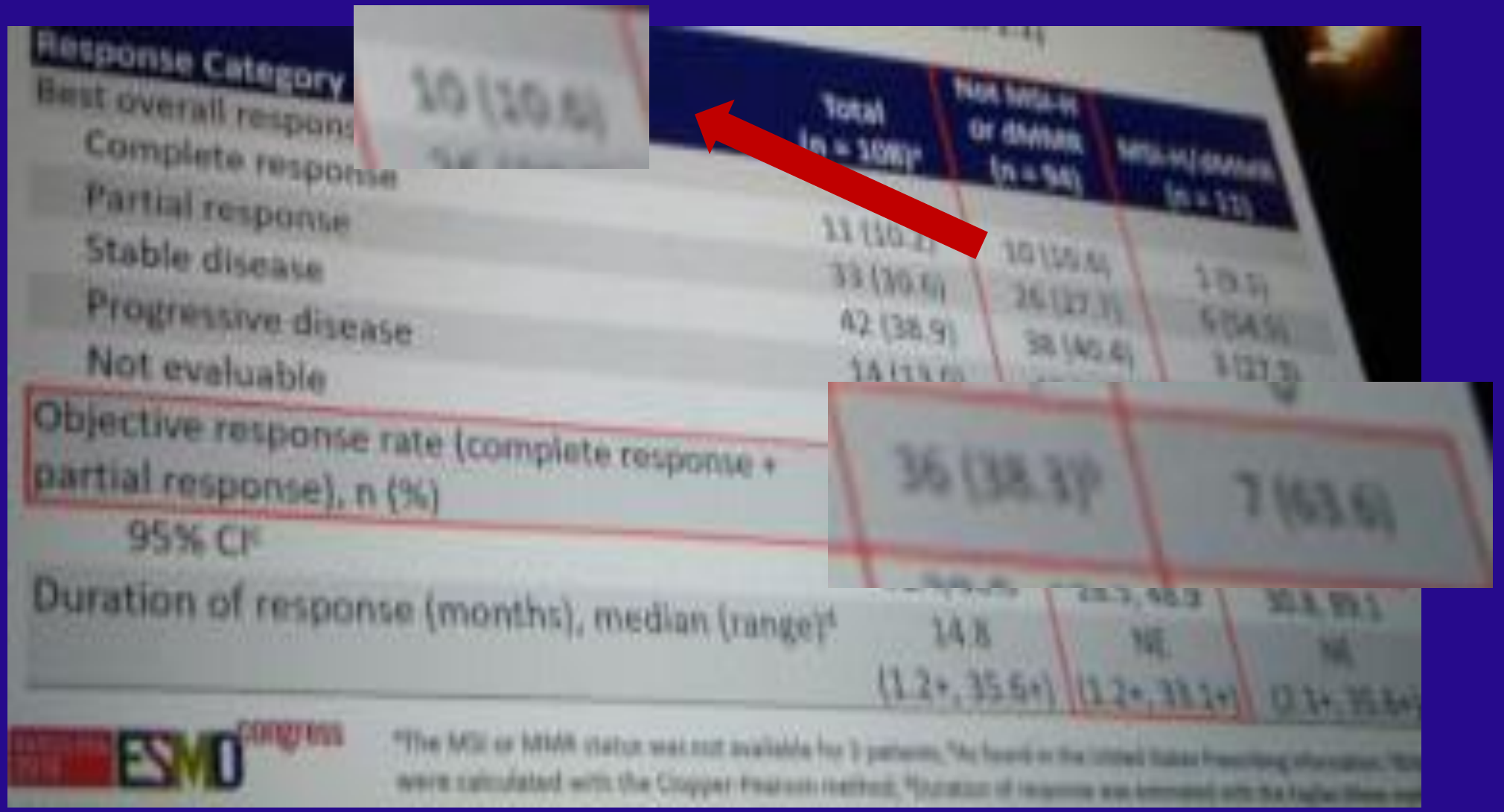
Key Secondary End Point

Overall ORR

DOR/PFS/OS/DCR/BR

Safety and tolerability

Tumor response



Accelerated approval

FDA Approves KEYTRUDA® (pembrolizumab) plus LENVIMA® (lenvatinib) Combination Treatment for Patients with Certain Types of Endometrial Carcinoma

SEPTEMBER 17, 2019

Combination Treatment Approved for Patients with Advanced Endometrial Carcinoma That Is Not Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR), Who Have Disease Progression Following Prior Systemic Therapy and Are Not Candidates for Curative Surgery or Radiation

Under New FDA-Initiated Program, Combination Treatment Is the First to Receive Simultaneous Review Decisions in the U.S., Australia and Canada

Simultaneous review decisions for pembrolizumab plus lenvatinib in Australia, Canada and US

PD-(L)1 trials in endometrial cancer (EC) Mono IO

Drug	Patients	Response
Pembrolizumab	Most MMRp/MSS EC, all PDL1	13% ORR (N=3 of 23)metastat
Avelumab	Recurrent/persistent EC	27% ORR in MSI-H/POLE (N=4 of 15) 6% ORR in MSS (N=1 of 16)
Durvalumab	Advanced EC	43% ORR in dMMR (N=15 of 35) 3% ORR in MMRp (N=1 of 35)
Atezolizumab	Recurrent EC	13% ORR overall (N=2 of 15)

Ongoing studies in Endometrial Cancer
IO Combinations

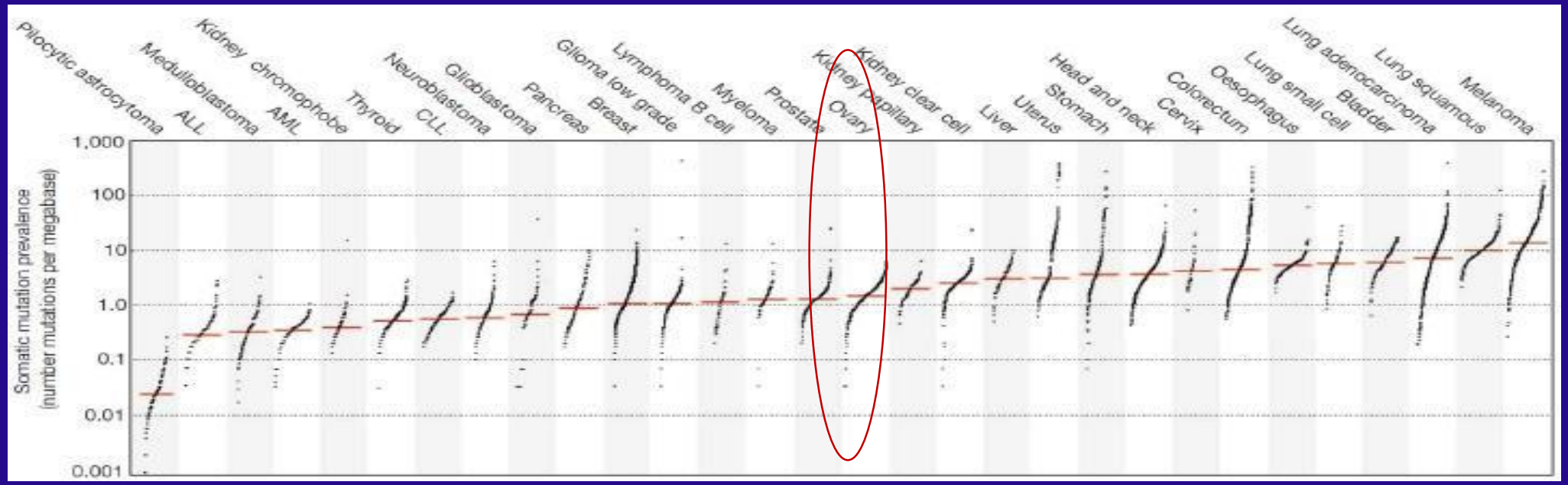
Antiangiogenesis + Immunotherapy			
Makker et al (2018), KEYNOTE 775[50]	Metastatic EC	Lenvatinib + pembrolizumab	ORR, 48%; DCR, 96%
NCT03526432	Recurrent EC	Bevacizumab + atezolizumab	Ongoing
NCT03367741	Recurrent EC	Nivolumab ± cabozantinib	Ongoing
Chemo + Immunotherapy			
NCT02549209	Advanced recurrent EC	Chemotherapy + pembrolizumab	Ongoing
NCT03276013	Recurrent EC	Doxorubicin + pembrolizumab	Ongoing
NCT03603184 (AtEND)	Advanced recurrent EC	Chemotherapy ± atezolizumab	Ongoing
NCT03503786 (MITO-END3)	Advanced recurrent EC	Chemotherapy ± avelumab	Ongoing

Ovarian cancer

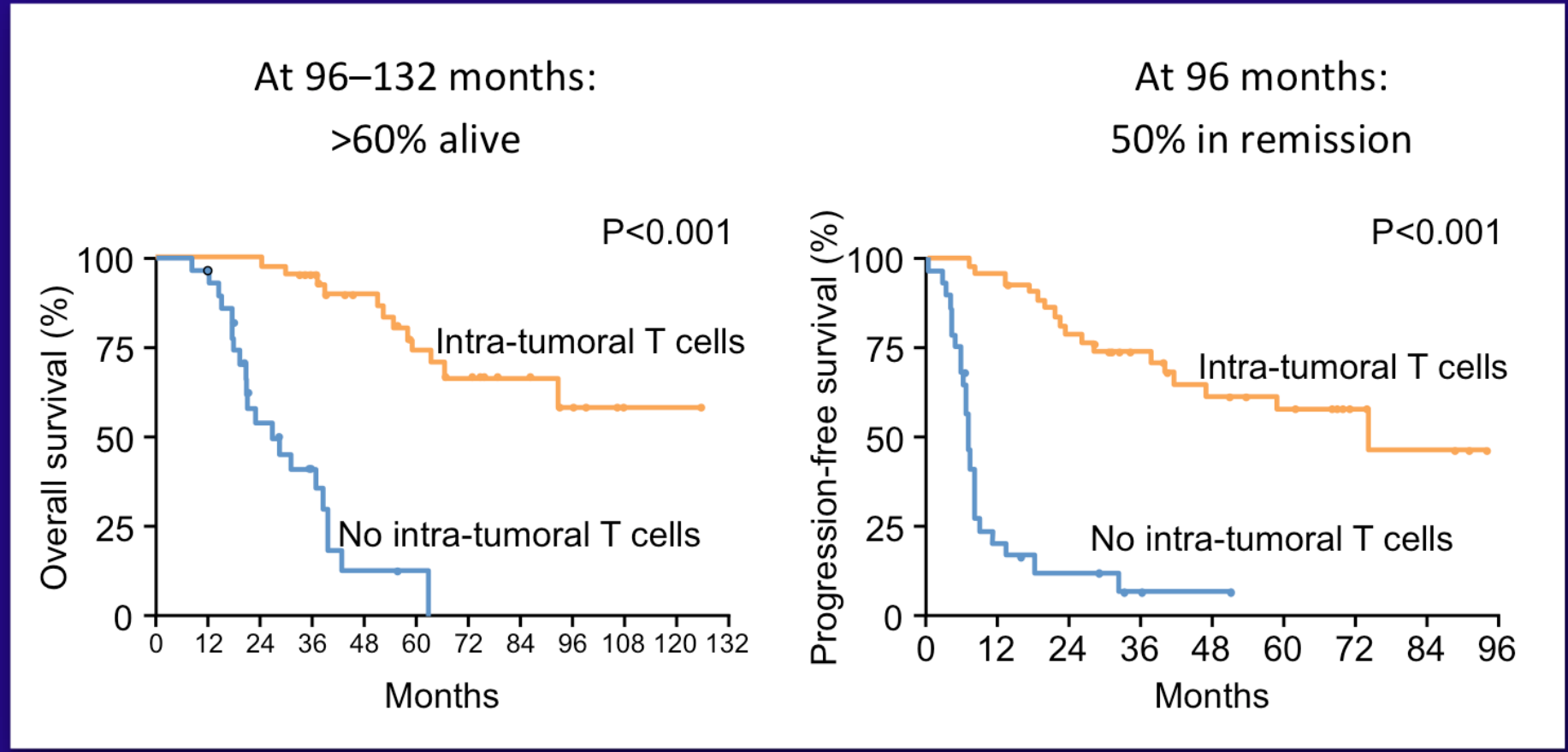
Ovarian Cancer: Immunogenicity

- The presence of intratumoral T cells is a prognostic factor in ovarian cancer
- PD-L1 is expressed in ovarian cancer although its role as prognostic factor contradictory

- Somatic Mutations Prevalence



TILs improve OS and PFS



After CR with chemotherapy, only patients with TILs survive or are in remission long-term

Zhang, et al. N Engl J Med 2003

IO Monotherapy in OC

Study/Author	Study Type	Agent	Patient Population	Overall Response Rate
Brahmer et al (2012)[6]	Phase I	PD-L1	Advanced diagnosis; multiple tumor types	6% (1/16)
Hamanashi et al (2015)[7]	Phase II	PD-1 nivolumab	Platinum resistant	15% (3/20)
JAVELIN, Disis et al (2019)[8]	Phase Ib	PD-L1 avelumab	Recurrent/refractory	10% (12/124)
Infante et al (2016)[9]	Phase Ia	PD-L1 atezolizumab	Recurrent/metastatic	22% (9/12)
KEYNOTE 28, Varga et al (2017)[10]	Phase Ib	Pembrolizumab	PD-L1^{+} tumors	11.5% (3/26)
KEYNOTE 100, Matulonis et al (2018)[11]	Phase II	Pembrolizumab	Recurrent diagnosis	9% (PD-L1+ CPS $\geq$ 1 [8/59]; PD-L1+ CPS $\geq$ 10 25% [5/20])

➔ **Response in unselected EOC only ≈ 10-15%**

Javelin study: Chemo-IO

Avelumab alone or in combination with pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase 3 JAVELIN Ovarian 200 trial

Table 1 Avelumab alone or in combination with pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase 3 JAVELIN Ovarian 200 trial

All patients	Ave (N=188)		Ave+PLD (N=188)		PLD (N=190)	
OS						
Median (95% CI), mo	11.8 (8.9; 14.1)		15.7 (12.7; 18.7)		13.1 (11.8; 15.5)	
Stratified hazard ratio vs PLD (repeated CI [RCI])	1.14 (0.948; 1.580)		0.89 (0.744; 1.241)		–	
P value vs PLD,1-sided log-rank test	0.8253(significance level, <0.0095)		0.2082(significance level, <0.0103)		–	
PFS						
Median (95% CI), mo	1.9 (1.8; 1.9)		3.7 (3.3; 5.1)		3.5 (2.1; 4.0)	
Stratified hazard ratio vs PLD (RCI)	1.68 (1.320; 2.601)		0.78 (0.587; 1.244)		–	
P value vs PLD,1-sided log-rank test	>0.999(significance level, <0.0003)		0.0301(significance level, <0.0002)		–	
PD-L1 evaluable	Ave		Ave+PLD		PLD	
	PD-L1+ (N=91)	PD-L1− (N=62)	PD-L1+ (N=92)	PD-L1− (N=58)	PD-L1+ (N=73)	PD-L1− (N=66)
OS						
Median (95% CI), mo	13.7(9.6; not estimable)	10.5(6.8; 15.3)	18.4(13.7; 22.0)	12.7(7.8; 18.7)	13.8(10.5; 17.7)	13.1(10.9; 15.7)
Hazard ratio vs PLD(95% CI)	0.797 (0.526; 1.207)	1.374 (0.879; 2.147)	0.719 (0.478; 1.079)	1.105 (0.685; 1.783)	–	–
P value vs PLD,2-sided log-rank test	0.2828	0.1617	0.1098	0.6822	–	–
PFS						
Median (95% CI), mo	1.9(1.8; 2.3)	1.8(1.8; 1.9)	3.7(2.2; 5.6)	3.9(1.9; 5.5)	1.9(1.9; 3.6)	3.7(3.2; 5.5)
Hazard ratio vs PLD(95% CI)	1.263 (0.881; 1.812)	1.776 (1.194; 2.641)	0.588 (0.406; 0.853)	0.924 (0.601; 1.421)	–	–
P value vs PLD,2-sided log-rank test	0.2026	0.0041	0.0048	0.7174	–	–

Promising Strategies in OC

PARPi + Immunotherapy			
Konstantinopoulos et al (2018), TOPACIO-KEYNOTE 162[29]	Platinum resistant	Niraparib + pembrolizumab	ORR, 25%; DOR, 9.3 months
Drew et al (2018), MEDIOLA[30]	Platinum sensitivity, $BRCA^+$	Olaparib + durvalumab	DCR, 81%
Lee et al (2018)[31]	86% platinum resistant	Olaparib + durvalumab	ORR, 14%; DCR, 37%
Javelin 100, PARP NCT03642132	First line	Chemotherapy + $PARP_m$ vs. chemotherapy/avelumab + PARP/ $avelumab_m$ vs. chemotherapy/ bevicizumab + $bevicizumab_m$	Ongoing
ENGOT-ov43, NCT03740165	First line	Chemotherapy vs. chemotherapy/ olaparib/pembrolizumab	Ongoing
ENGOT-ov44 (FIRST), NCT03602859	First line	Chemotherapy vs. chemotherapy/ niraparib/TSR-042	Ongoing
ATHENA (ENGOT-ov45), NCT03522246	First-line maintenance	PARPi/nivolumab vs. PARPi vs. nivolumab vs. placebo	Ongoing
ENGOT-ov41 (ANITA), NCT03598270	Platinum sensitive	Chemotherapy + $PARP_m$ vs. chemotherapy/atezolizumab + PARP/ $atezolizumab_m$	Ongoing
PARP + Antiangiogenesis + Immunotherapy			
ENGOT-ov46/DUO-O, NCT03737643	First line	Chemo/bevacizumab/durvalumab + bevacizumab/olaparib/$durvalumab_m$	Ongoing

Where are we going next?

Better patient selection and search for more efficient biomarkers!!!

Actual Biomarkers are they efficient???

Indicative of a T cell-inflamed tumor environment	**Related to tumor neoantigen burden**
PD-L1 protein expression on tumor and immune cells	Microsatellite instability (MSI)
Gene signatures of activated T cells (Le T cell-inflamed gene expression profile, GEP)	High tumor mutational burden (TMB)

Novel combination strategies are in development

- VEGFi + T cell modulators
- PARPi + I/O agents
  - PARP inhibition may increase immunogenicity
- I/O + chemotherapy
- I/O + I/O
- Triple Combos

….Waiting for the results!!!

Conclusion

- Immunotherapy is already a major player in gynaecological malignancies
- Two FDA approvals for cervical and endometrial cancer
- Many studies to come in ovarian, endometrial and cervical cancer
- Ovarian cancer: A little behind !!!

My Deep Request for the MEMAGO

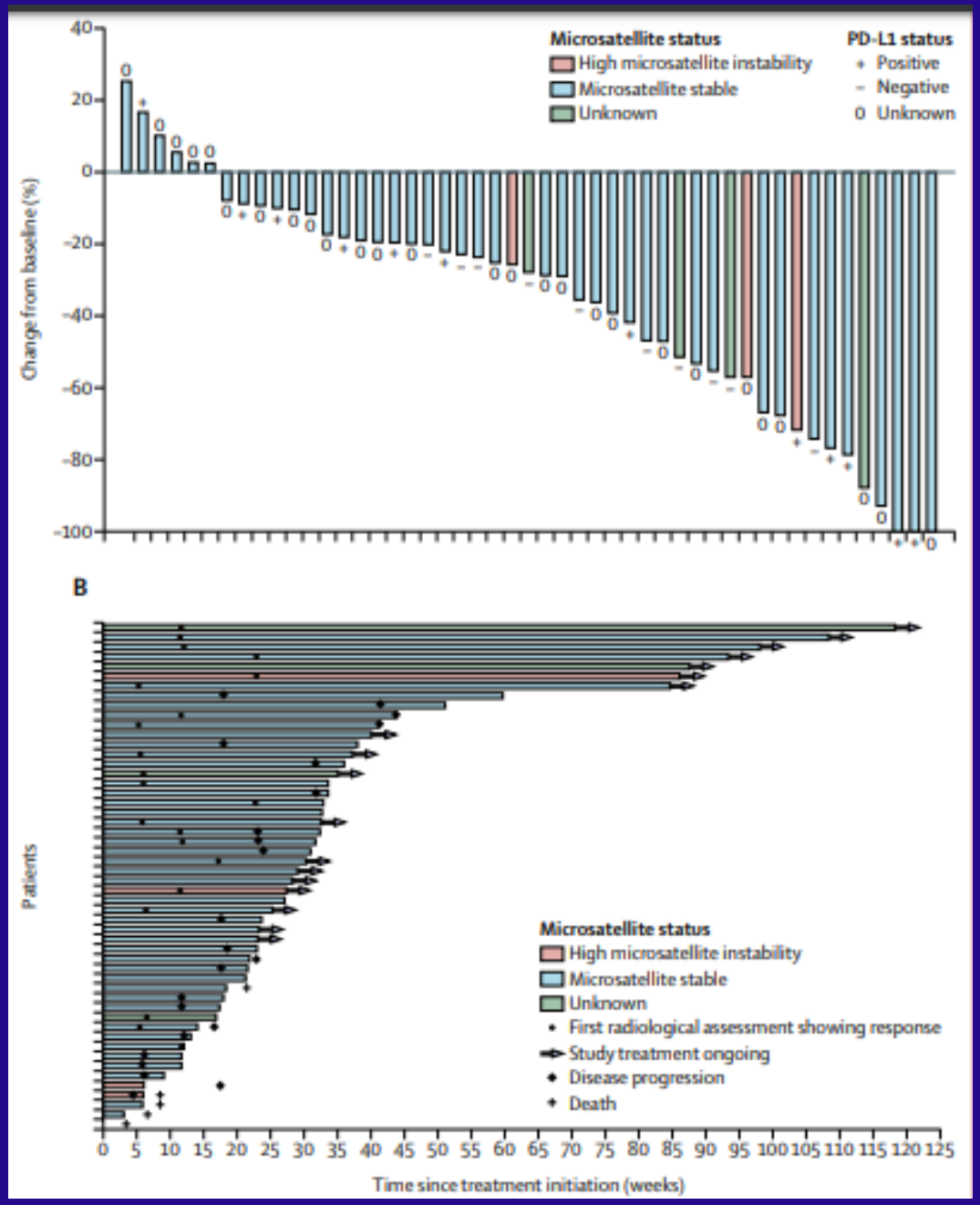
Let us do together our own research and trials!!!

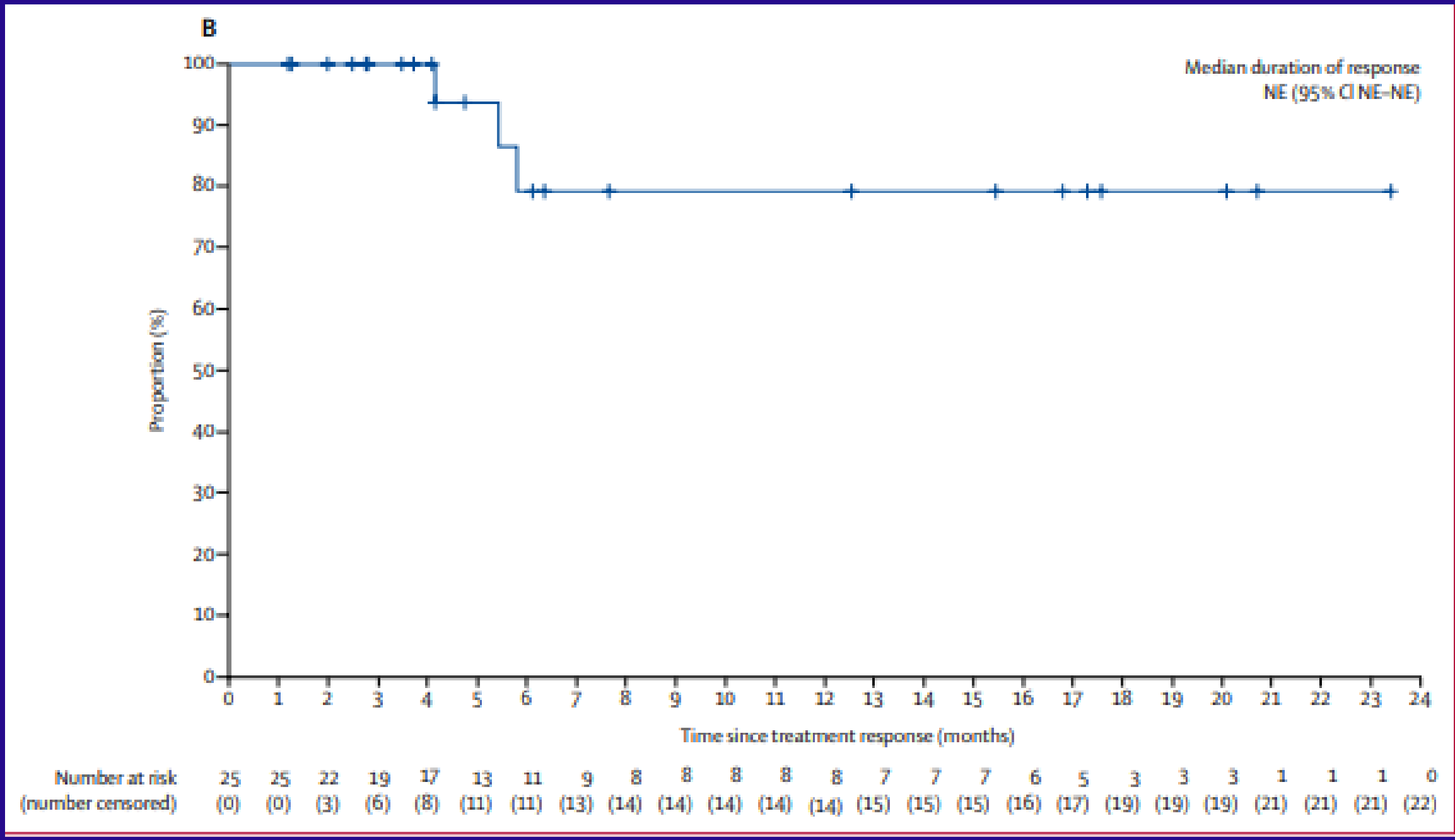
Vive le 4eme MEMAGO

A la Santé Du 5eme!!!

Thank you for your attention!!

- Backup


Microsatellite status
High microsatellite instability
Microsatellite stable
Unknown
PD-L1 status
+ Positive
– Negative
0 Unknown
Change from baseline (%)
40
20
0
-20
-40
-60
-80
-100
B
Patients
Microsatellite status
High microsatellite instability
Microsatellite stable
Unknown
First radiological assessment showing response
Study treatment ongoing
Disease progression
Death
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125
Time since treatment initiation (weeks)


B
Median duration of response
NE (95% CI NE–NE)
Proportion (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Time since treatment response (months)
Number at risk 25 25 22 19 17 13 11 9 8 8 8 8 8 7 7 7 6 5 3 3 3 1 1 1 0
(number censored) (0) (0) (3) (6) (8) (11) (11) (13) (14) (14) (14) (14) (14) (15) (15) (15) (16) (17) (19) (19) (19) (21) (21) (21) (22)