BSMO-Bordet 2022
Recent advances in nasopharyngeal cancer

Dr. Michael Saerens
Dept of Medical Oncology, Ghent University Hospital, Ghent, Belgium

Disclosures:

Speaker fee: Novartis, BMS and Pierre-Fabre. all institutional and non-personal
Advisory board: Novartis

UZ GENT

UNIVERSITEIT GENT

Chemo options in 1st line R/M NPC

R/M+ NPC
n=362

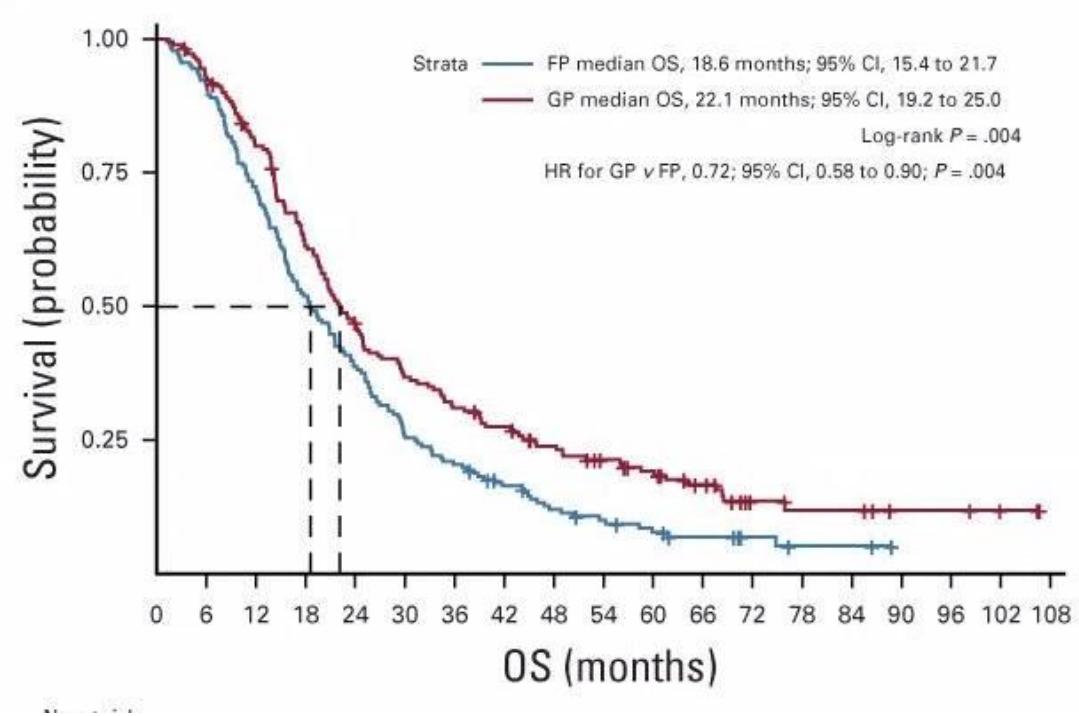
R
1:1

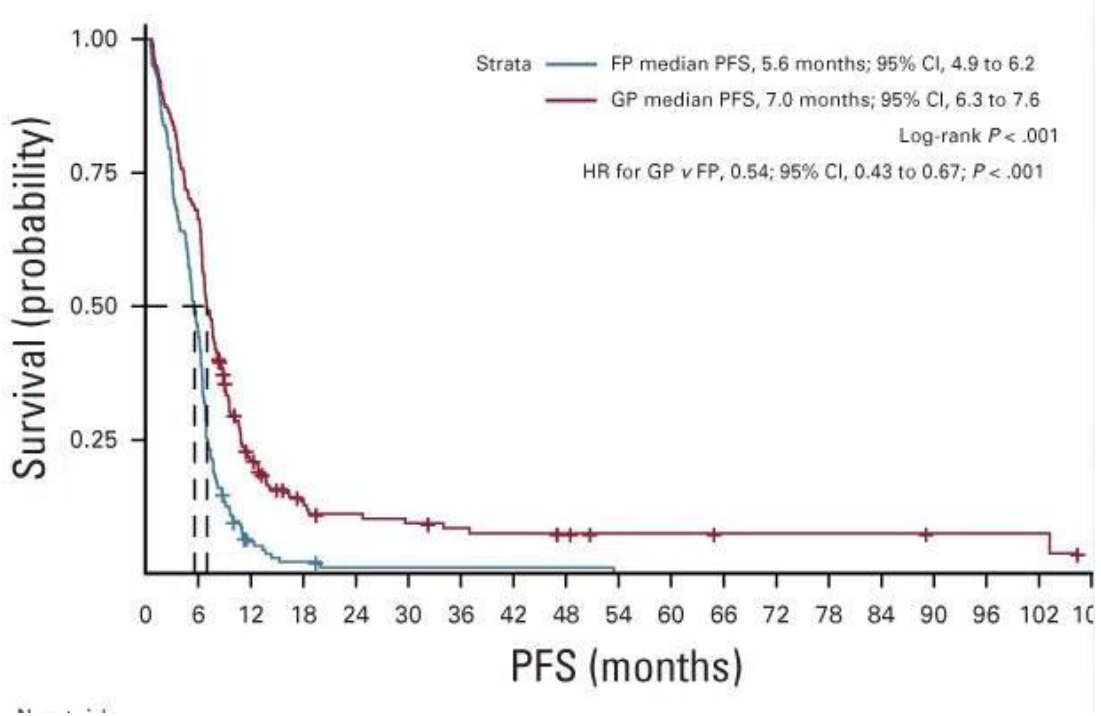
Cis 80mg/m² d1
+gem 1000mg/m²
d1d8 Q3w

Cis 80mg/m²
+ 5FU 4g/96h Q3w

PRIMARY outcome:
PFS superiority

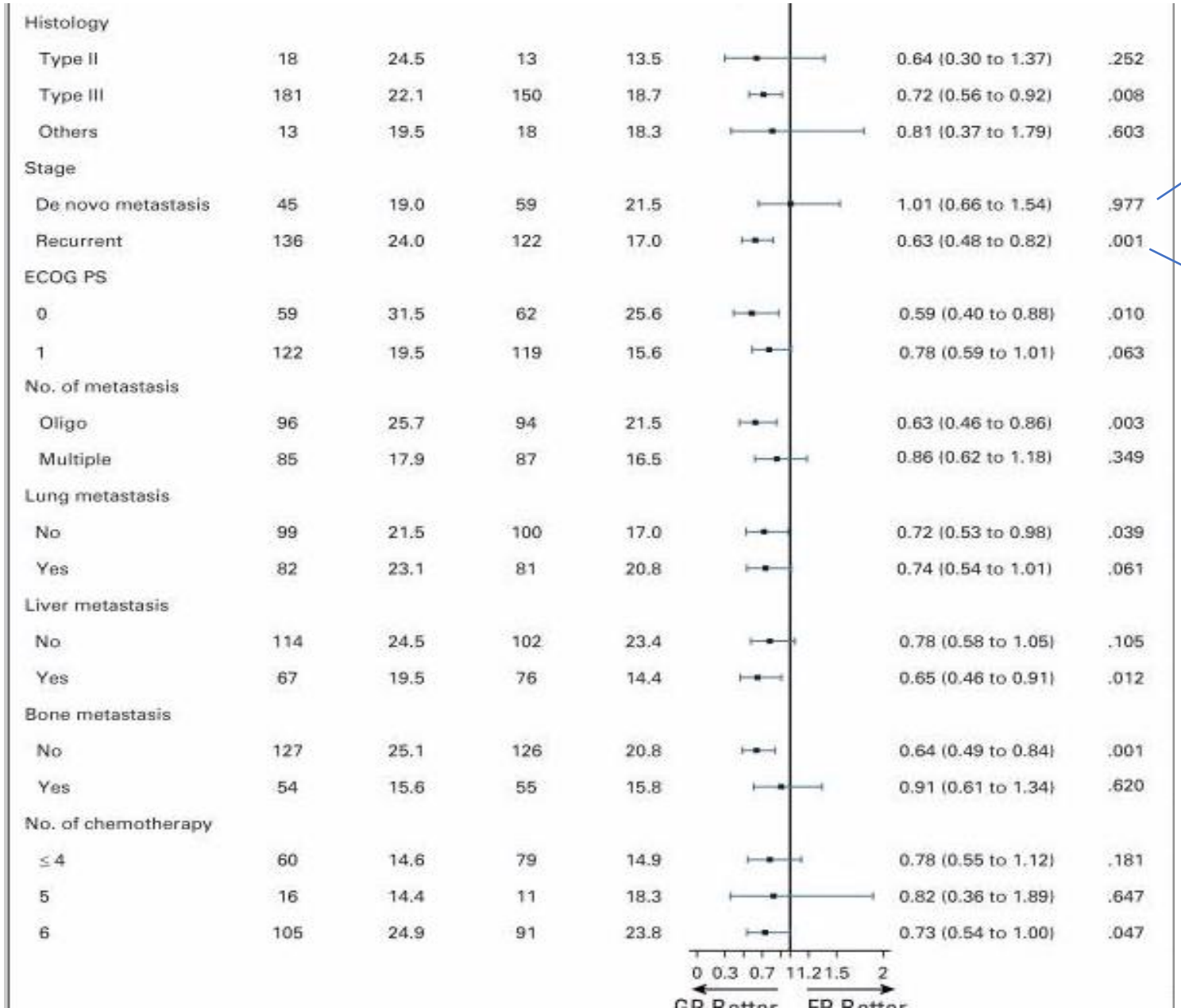
Secondary outcomes: OS, ORR, DoR





Hong, JCO 2021

Cis-Gem as first line regimen: for all?



Histology						
Type II	18	24.5	13	13.5	0.64 (0.30 to 1.37)	.252
Type III	181	22.1	150	18.7	0.72 (0.56 to 0.92)	.008
Others	13	19.5	18	18.3	0.81 (0.37 to 1.79)	.603
Stage						
De novo metastasis	45	19.0	59	21.5	1.01 (0.66 to 1.54)	.977
Recurrent	136	24.0	122	17.0	0.63 (0.48 to 0.82)	.001
ECOG PS						
0	59	31.5	62	25.6	0.59 (0.40 to 0.88)	.010
1	122	19.5	119	15.6	0.78 (0.59 to 1.01)	.063
No. of metastasis						
Oligo	96	25.7	94	21.5	0.63 (0.46 to 0.86)	.003
Multiple	85	17.9	87	16.5	0.86 (0.62 to 1.18)	.349
Lung metastasis						
No	99	21.5	100	17.0	0.72 (0.53 to 0.98)	.039
Yes	82	23.1	81	20.8	0.74 (0.54 to 1.01)	.061
Liver metastasis						
No	114	24.5	102	23.4	0.78 (0.58 to 1.05)	.105
Yes	67	19.5	76	14.4	0.65 (0.46 to 0.91)	.012
Bone metastasis						
No	127	25.1	126	20.8	0.64 (0.49 to 0.84)	.001
Yes	54	15.6	55	15.8	0.91 (0.61 to 1.34)	.620
No. of chemotherapy						
≤ 4	60	14.6	79	14.9	0.78 (0.55 to 1.12)	.181
5	16	14.4	11	18.3	0.82 (0.36 to 1.89)	.647
6	105	24.9	91	23.8	0.73 (0.54 to 1.00)	.047

Should we intensify treatment?

Previous gem-cis for locoregional disease: N=1

Hong, JCO 2021

Addition of RT in de novo M+ NPC

New diagn
St IVc NPC
CR/PR after 3x cis+FU
n=126

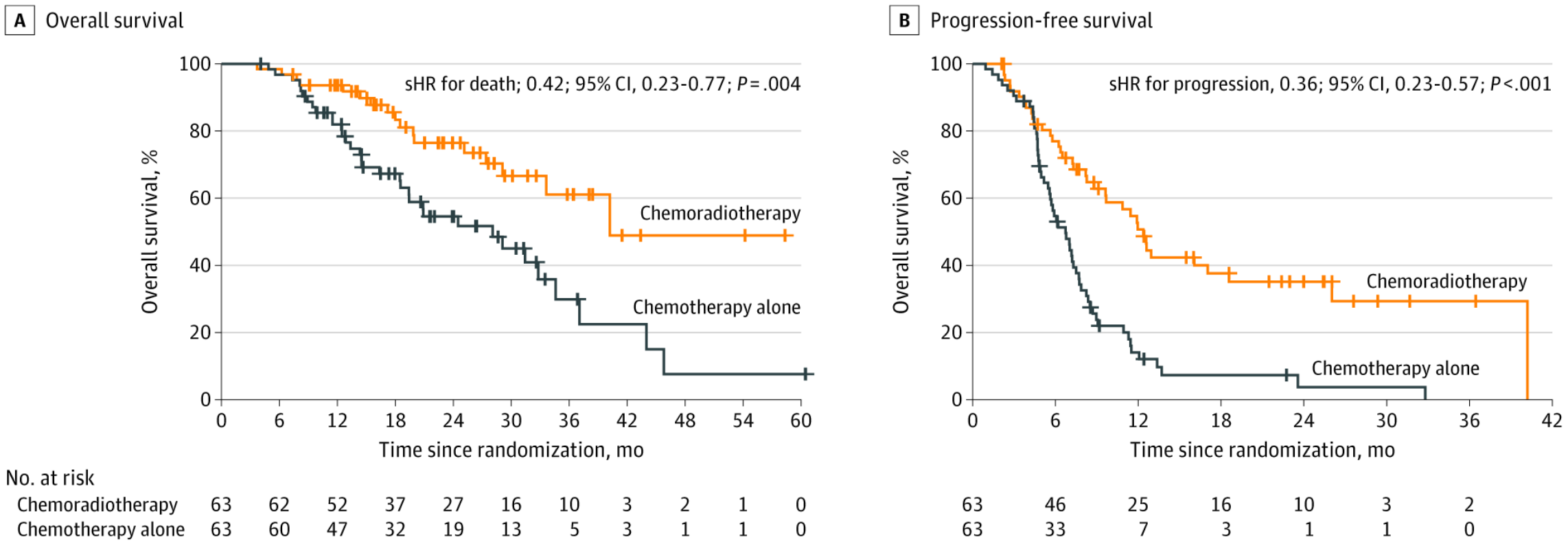
R
1:1

Cis 100mg/m² d1
+5FU 5g/m² d1-5 x3

Cis 100mg/m² d1
+ 5FU 5g/m² d1-5 x3

IMRT 70 Gy
on primary
+neck

PRIMARY outcome:
OS superiority
Secondary outcomes: OS, ORR, DoR



You, JAMA onc 2020

Maintenance capecitabine

New St IVc NPC

n=118

Cis 60mg/m² d1
+paclitaxl 150mg/m² d1
+ cap 1000mg/m² d1-14
x4-6

No PD
n=104

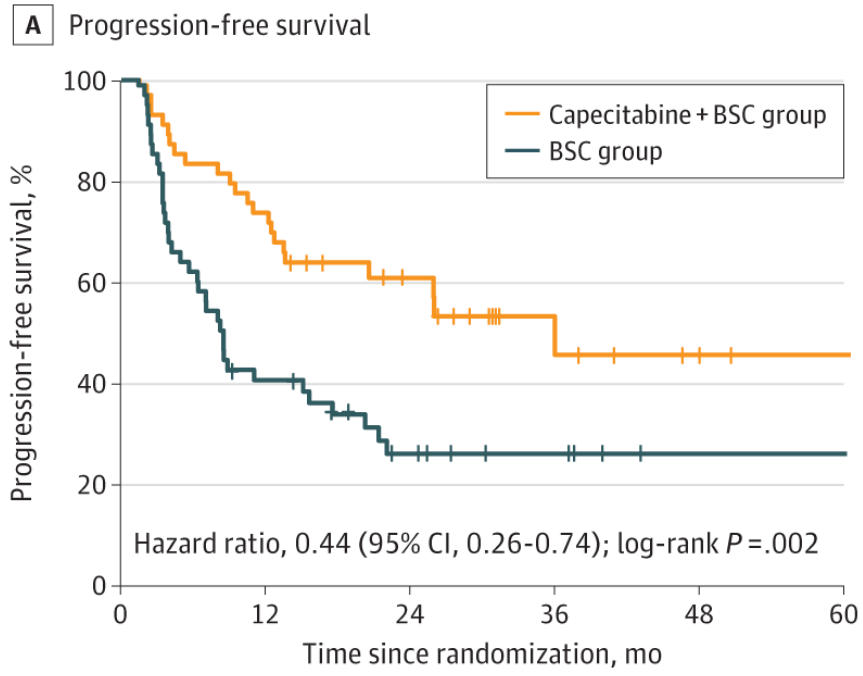
PD, refusal
n=14

R
1:1

Cap 1000mg/m² d1-14 maint

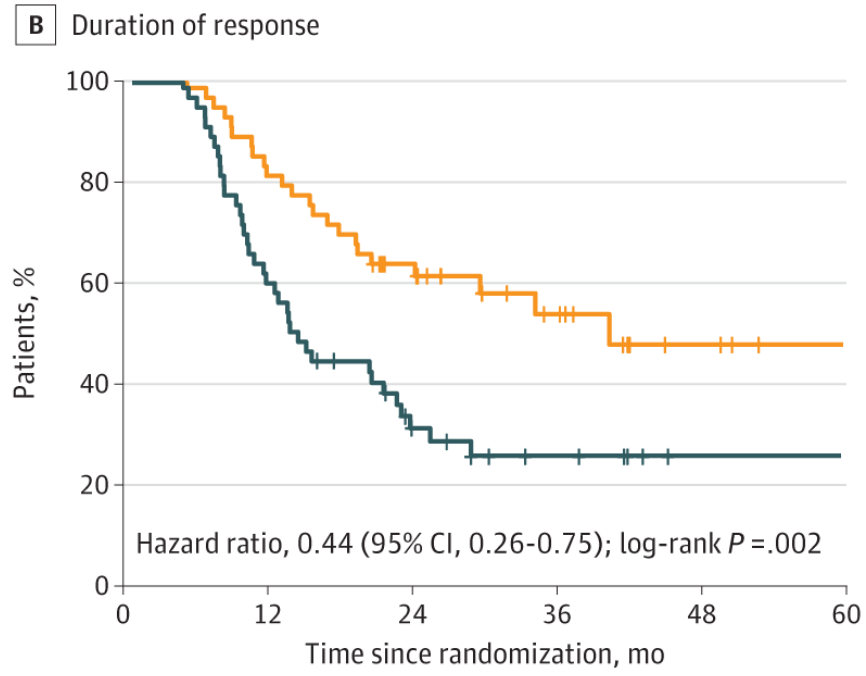
BSC

PRIMARY outcome:
PFS superiority
Secondary outcomes: OS, ORR, DoR



No. at risk

Maintenance group	52	38	19	6	4	1
BSC group	52	20	9	5	3	0

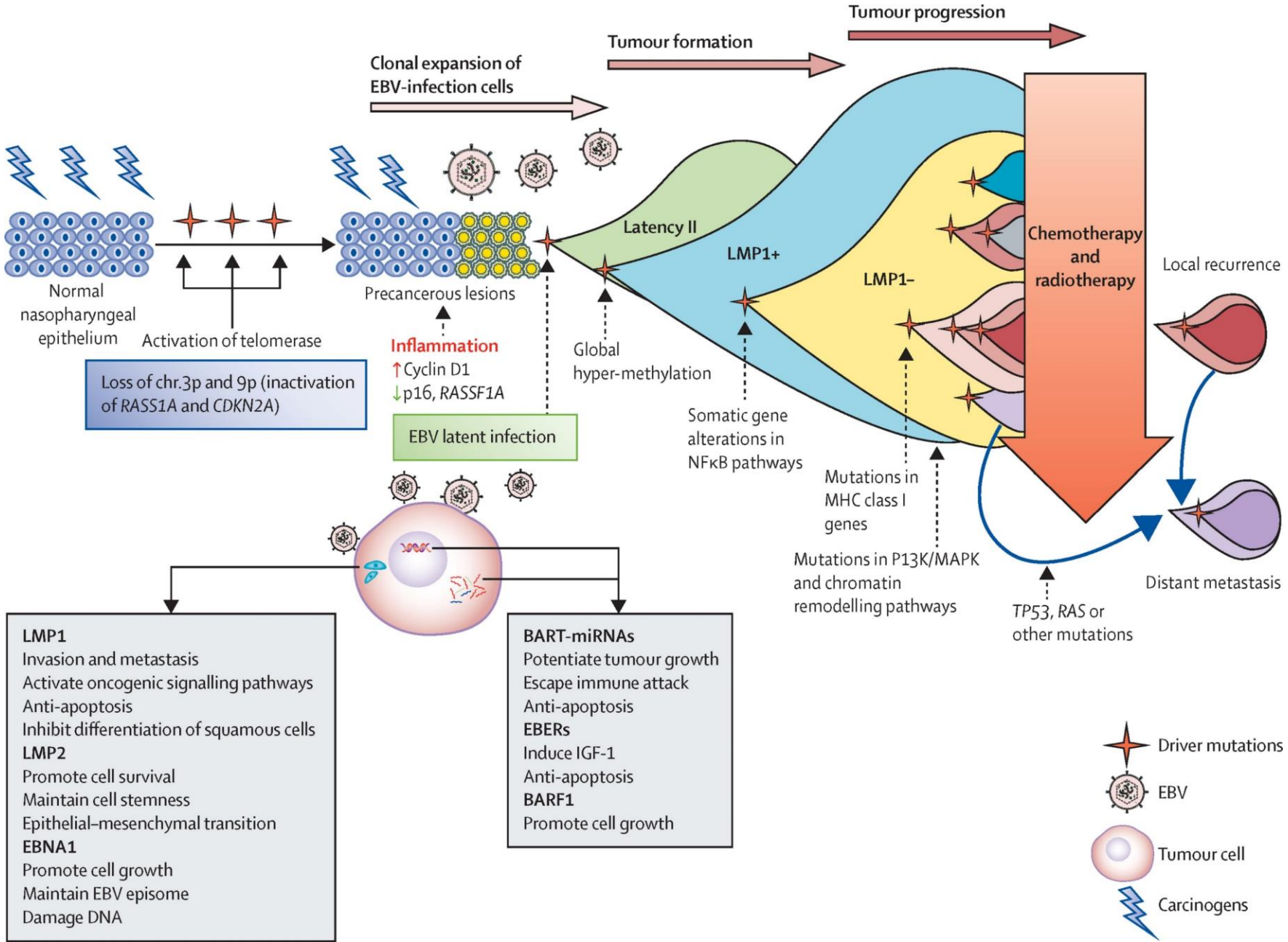


No. at risk

Maintenance group	52	48	28	15	6	1
BSC group	52	41	26	12	6	0

Liu, JAMA onc 2022

Rationale for ICI?



>80% harbour PD-L1 expression

LMP1 is the key oncoprotein:
Induction of genetic and epigenetic changes
MMP2 and MMP9 mediation
→ IL 6 upregulation
→ cellular mobility, invasion, cervical LN m+

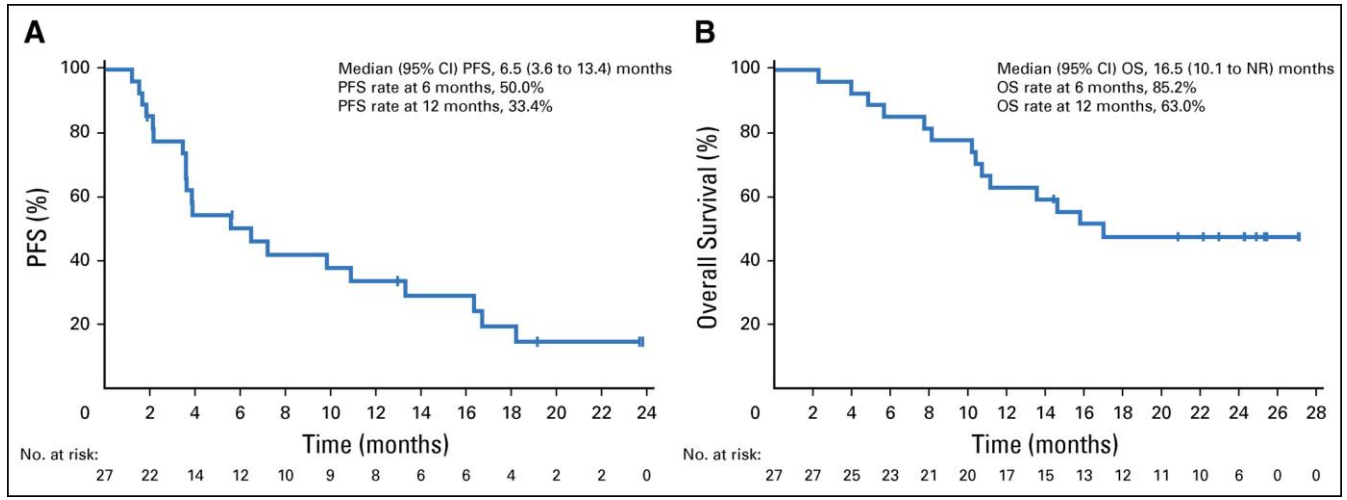
Chen et al. Lancet 2019

Keynote-028: NPC cohort

Phase 1b basket trial, N=27 pretreated NPC (PDL1+)

IN: R/M+ NPC platinum pretreated → Pembro 10 mg/kg Q3w → Max 2yr or PD/tox/death

Primary outcome: ORR (>10%)



	Pembro (KN-027)
ORR	26%
DCR	37%
mPFS	6,5 months
mOS	16,5 months

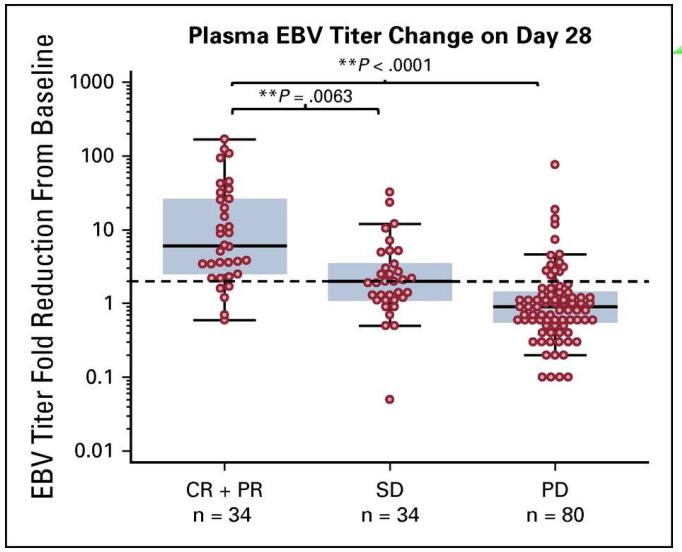
Hu et al. JCO 2017

ICI in pretreated NPC: single arm studies

	Pembro (KN-028) Hu, JCO 2017	Nivolumab (NCI9742) Ma, JCO 2018	Camrelizumab* (SHR-1210-101) Feng, Lancet Oncol 2018	Camrelizumab* (CAPTAIN) Zhang, ann onc 2020	Tislelizumab (CTR2016087219) Shen, JITC 2021	Toripalimab** (Polaris-02) Wang, JCO2021	Nivolumab + ipilimumab*** (NCT03097939) Kao, ESMOasia 2020
N	27	44	93	156	21	190	40
Phase	1b, pretreated	2, pretreated	1b, pretreated	2, ≥2 lines	1b/2, pretreated	2, 50% >2lines	2, ≥1L
primary outcome	ORR (>10%)	ORR (>20%)	safety and tolerability	ORR	ORR (>15%)	ORR (>24%)	ORR (>45%)
ORR	26%	20,5%	34%	28%	43%	20,5%	35%
DCR	37%	54,5%	59%	54,5%	86%	40%	52%
mDOR	16,5m	9m	NR	NR	8m	13m	5,9m
mPFS months (95%CI)	6,5m (95%CI	2,8m (1,8-7,4)	5,6 m (3,3–7,9)	3,7m (2.0 - 4.1)	10m (4,0-10,1)	1,9m (1,8-3,5)	5,3m (3,0-6,4m)
mOS Months (95%CI)	16,5m (10,1-NR)	17m (10,9-NR)	NA	17m (95% CI 15.1-NE)	NR	17,5m (11,7-22,9)	17,6m (13-30)
Trial result	Positive	Positive	Positive	Positive?	positive	Negative?	?

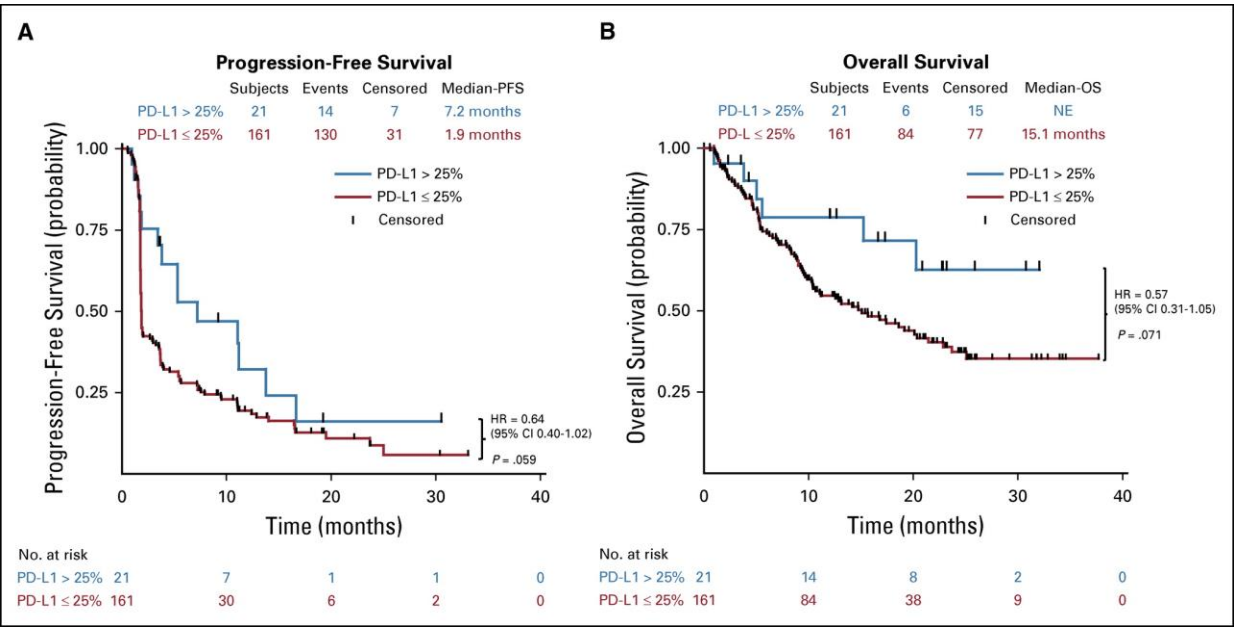
*Humanized antiPD1 MOAB escalating doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg Q2w, finally 200mg Q2w (phase 2 dose)
Humanized antiPD1 MOAB at 3mg/kg Q2w * nivolumab 3mg/kg + ipilimubab 1mg/kg Q6w

Biomarker of response? (Polaris-02)

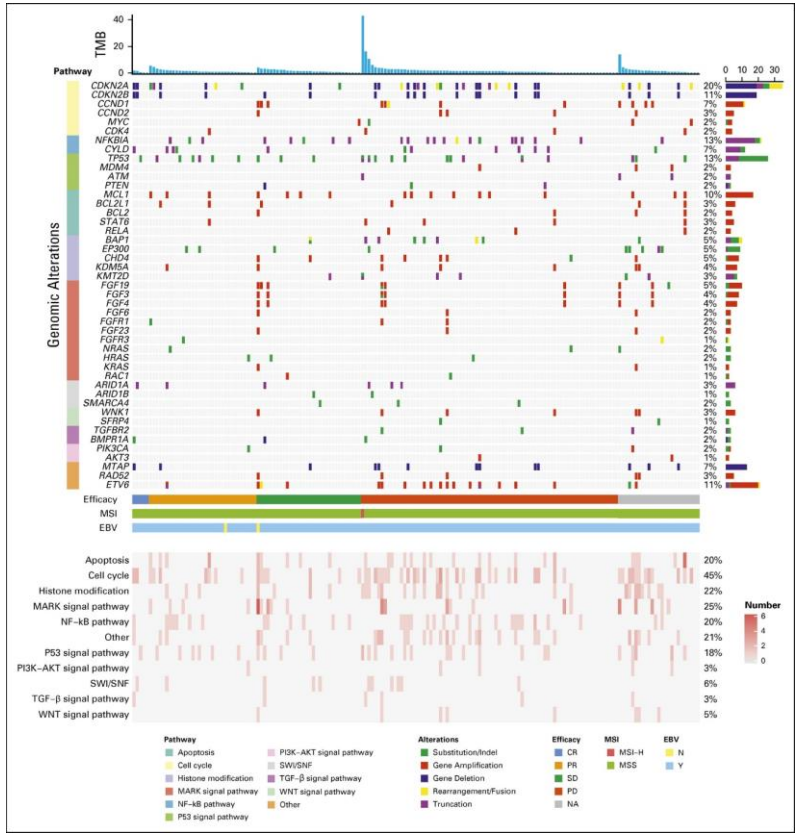


ORR EBV titer decline >50% (not baseline)

Trend for better survival in PD-L1 TPS>25 genomic signature: NS



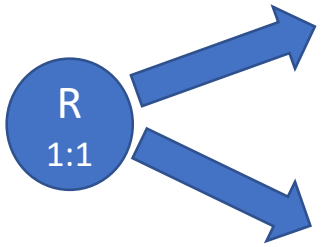
Wang, JCO 2021



IO in 2nd line NPC: RCT

Keynote122

R/M+ NPC platinum pretreated N=233



Pembrolizumab 200mg Q3w n=117

IC (gem, cap or doce) n=116

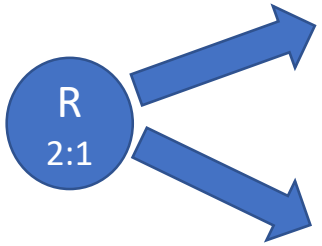
PRIMARY outcome:
Overall survival (HR 0,60)

Secondary outcomes: PFS, ORR, DoR

Chan, ESMO 2021 abstract 8580

NCT02505967

R/M+ NPC platinum pretreated N=122



Spartalizumab 400mg Q4w n=83

IC chemo n=39
Cap, gem, doce, vino, MTX, bleo, platinum, combinations

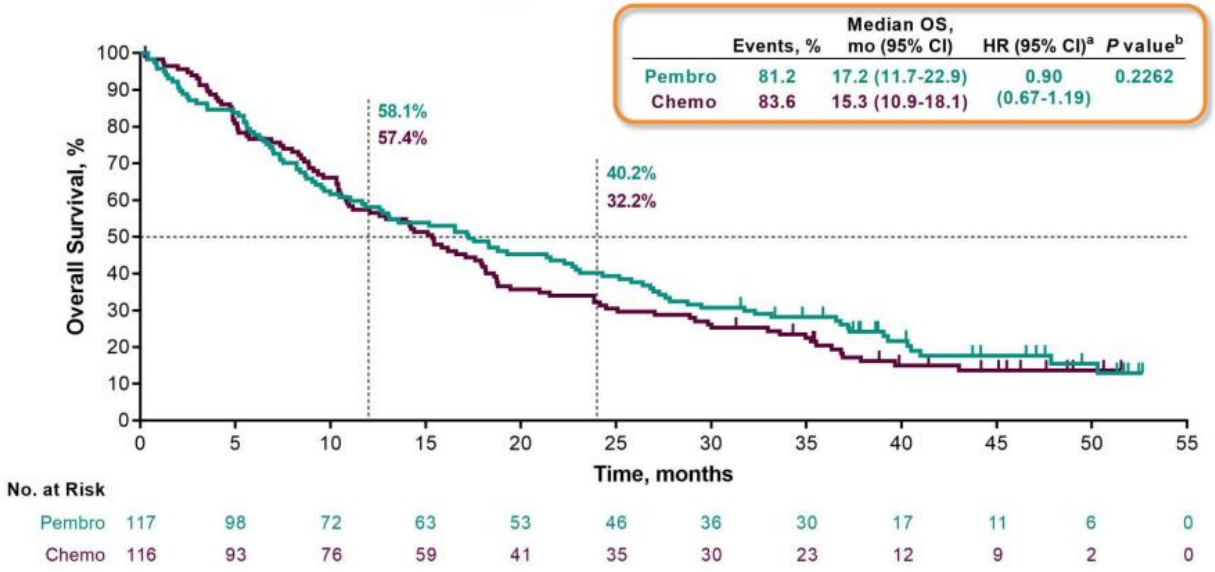
PRIMARY outcome:
Progression-free survival
HR 0.55; 1-β=85%; α=0,1

Secondary outcomes: OS, ORR, DoR

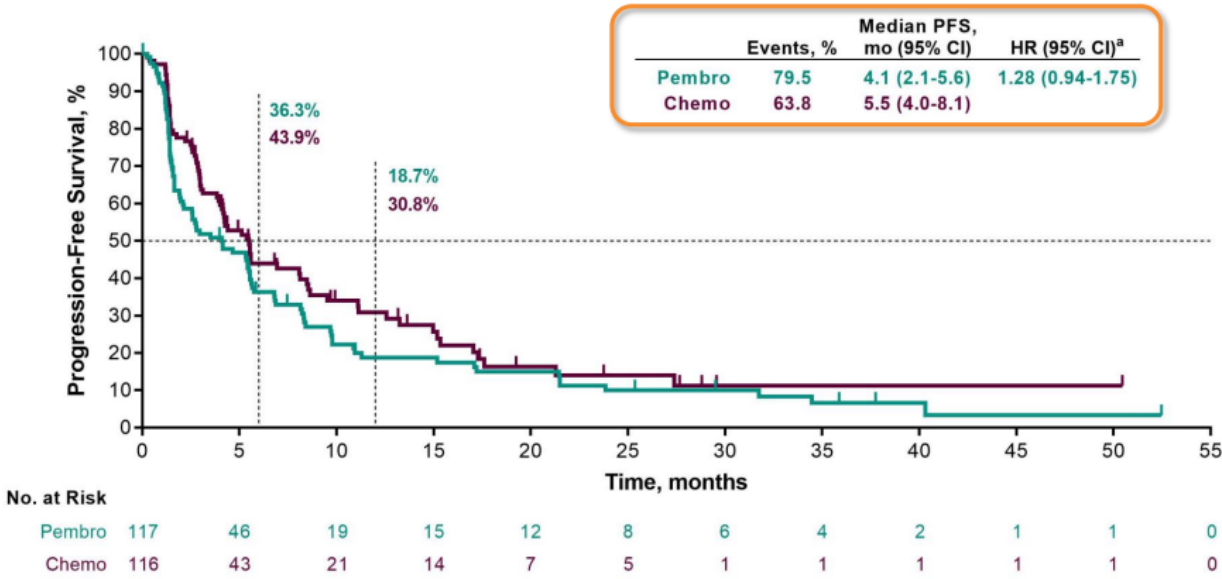
Even, clin can res 2021

Keynote-122: pembro vs IC

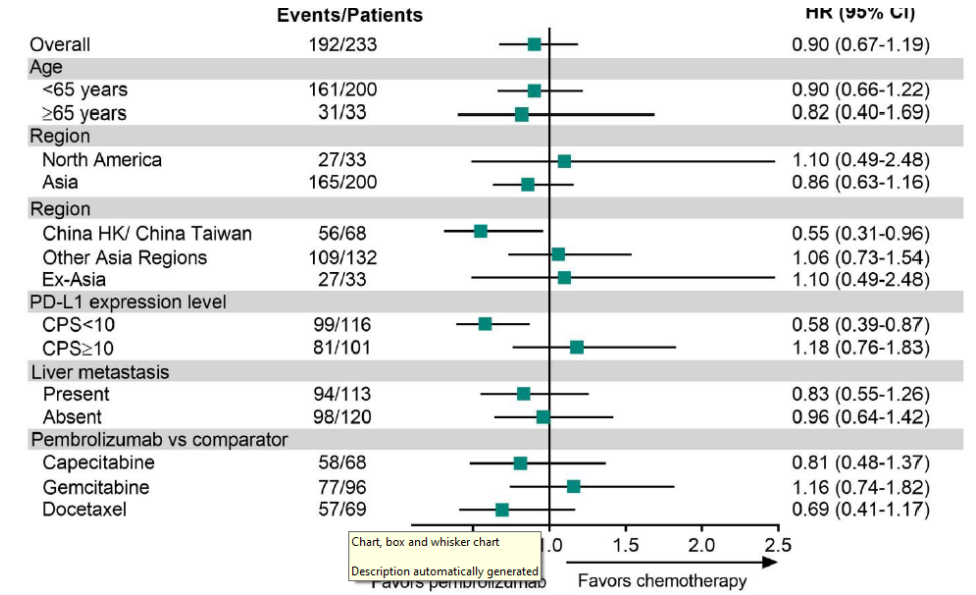
Overall Survival (ITT)



PFS per RECIST v1.1 by BICR (ITT)



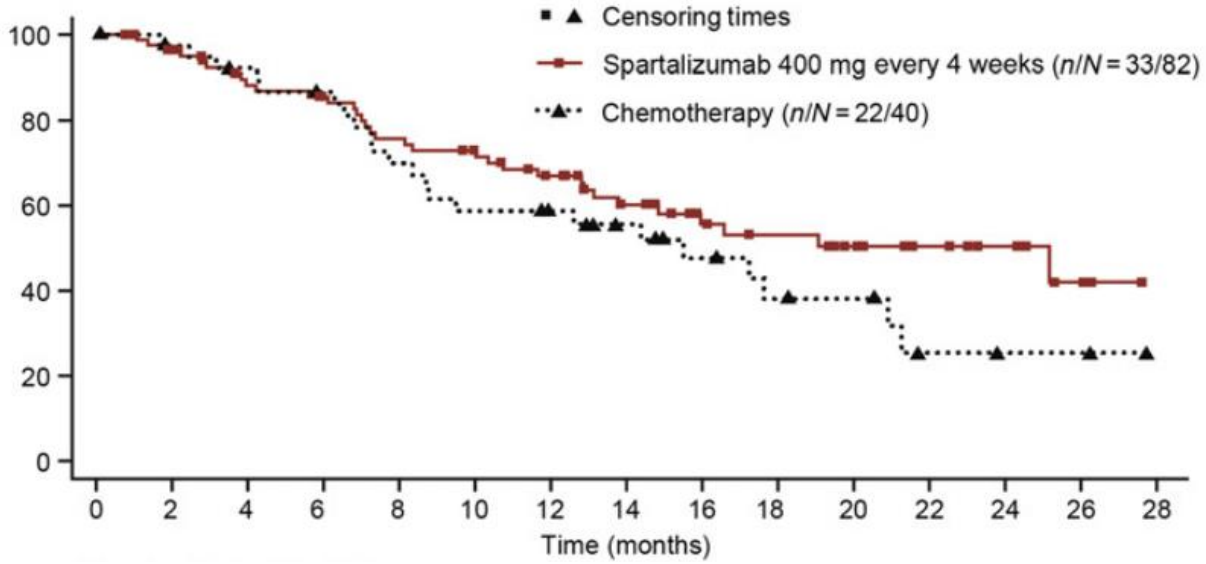
	Pembro (KN122)	IC (cap, gem or doce)
ORR	21%	23%
DCR	50%	64%
mPFS	4,1 months	5,5 months
mOS	17,2 months	15,3 months
	HR 0,90 (95%CI 0,67-1,19) → endpoint NOT MET	



Chan, ESMO 2021 abstract 8580

NCT02605967: spartalizumab vs IC

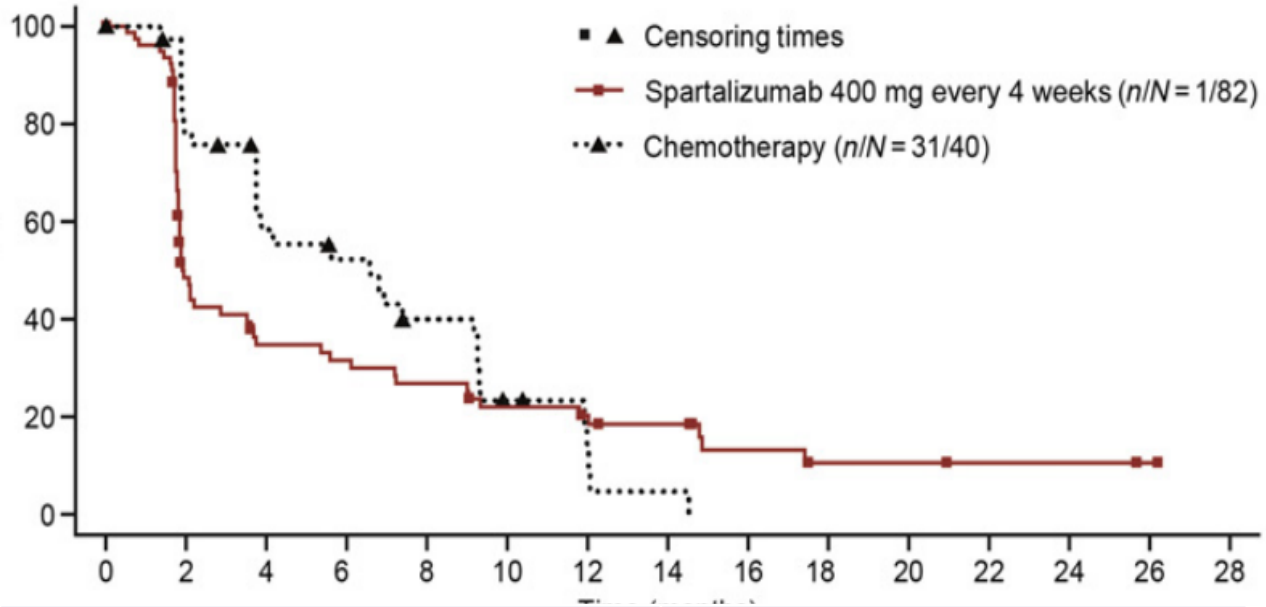
Overall survival (ITT)



	spartalizumab	IC
ORR	17%	35% (26% monotherapy – 58% for combo)
DCR	42%	70%
mOS	17,2 months	15,3 months
mPFS	1,9 months	6,6 months
	HR 1.36 (95% CI 0.87–2.12) ENDPOINT NOT MET	

Even, clin can res 2021

Progression-free survival

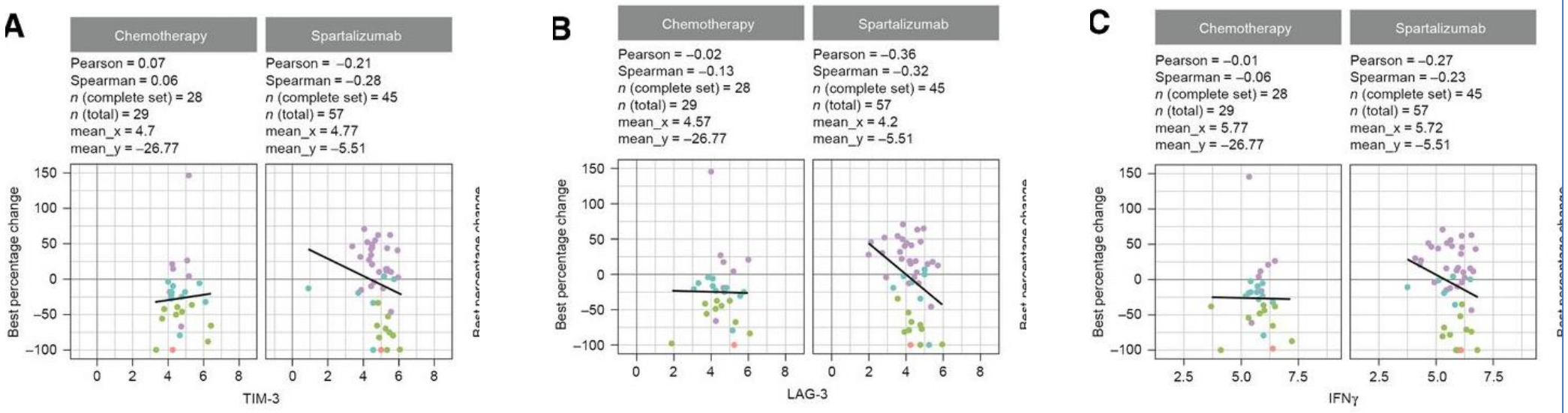


Chemotherapy regimen	N (%)
Monotherapy	**27 (69.2)**
Capecitabine	9 (23.1)
Docetaxel	7 (17.9)
Gemcitabine	6 (15.4)
Paclitaxel	4 (10.3)
Vinorelbine	1 (2.6)
Combination regimens	**12 (31.0)**
Bleomycin + methotrexate	1 (2.5)
Carboplatin + gemcitabine	1 (2.5)
Carboplatin + paclitaxel	1 (2.5)
Cisplatin + docetaxel	1 (2.5)
Cisplatin + gemcitabine	2 (5.1)
Cisplatin + paclitaxel	2 (5.1)
Gemcitabine + paclitaxel	1 (2.6)
Carboplatin + docetaxel; Capecitabine	1 (2.6)
Carboplatin + gemcitabine; Gemcitabine	1 (2.6)
Cisplatin + gemcitabine; Gemcitabine + vinorelbine	1 (2.6)

Biomarker analysis

Spartalizumab:

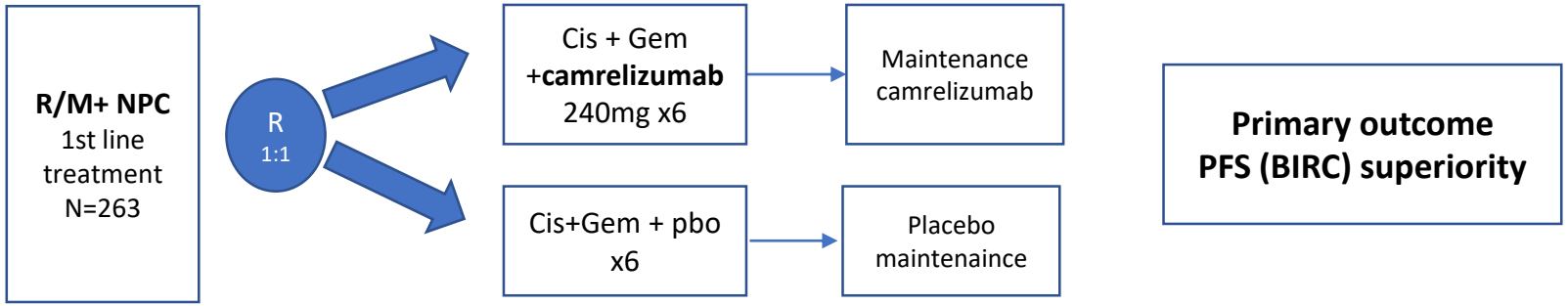
- Immune-inflamed subtype have better response rates
- EBV titer at baseline correlated with poorer prognosis, but not with response
- PD-L1 was not analysed as prognostic or predictive biomarker



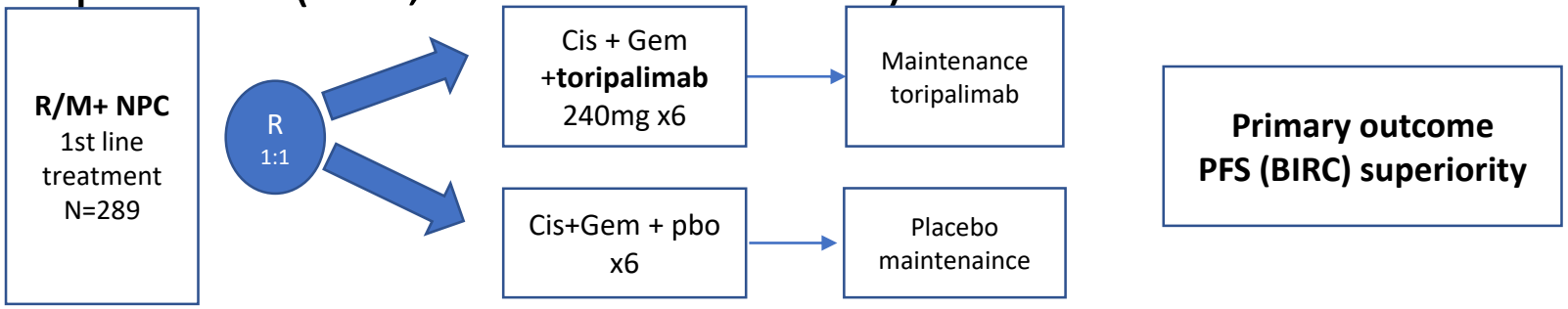
Even, clin can res 2021

ICI in 1st line: 3 RCTs

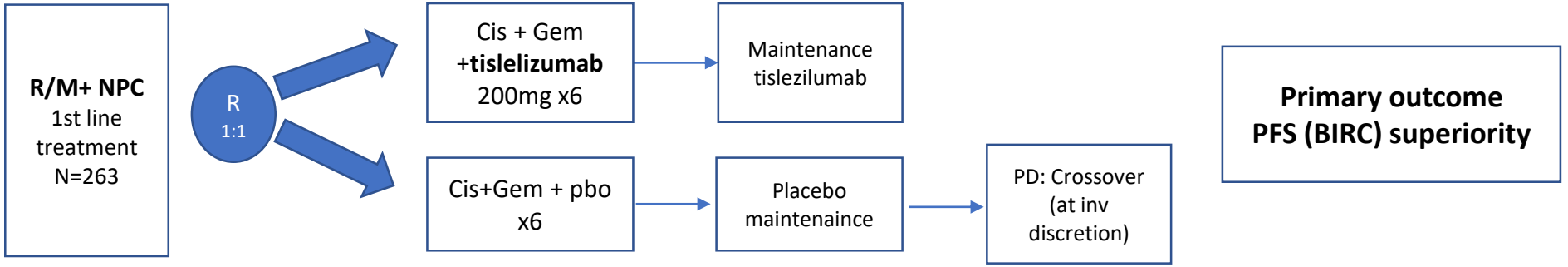
Camrelizumab: Captain-1st (Yang, Lancet Oncol 2021)



Toripalimab: Jupiter-02 (Mai, Nature Med 2021)



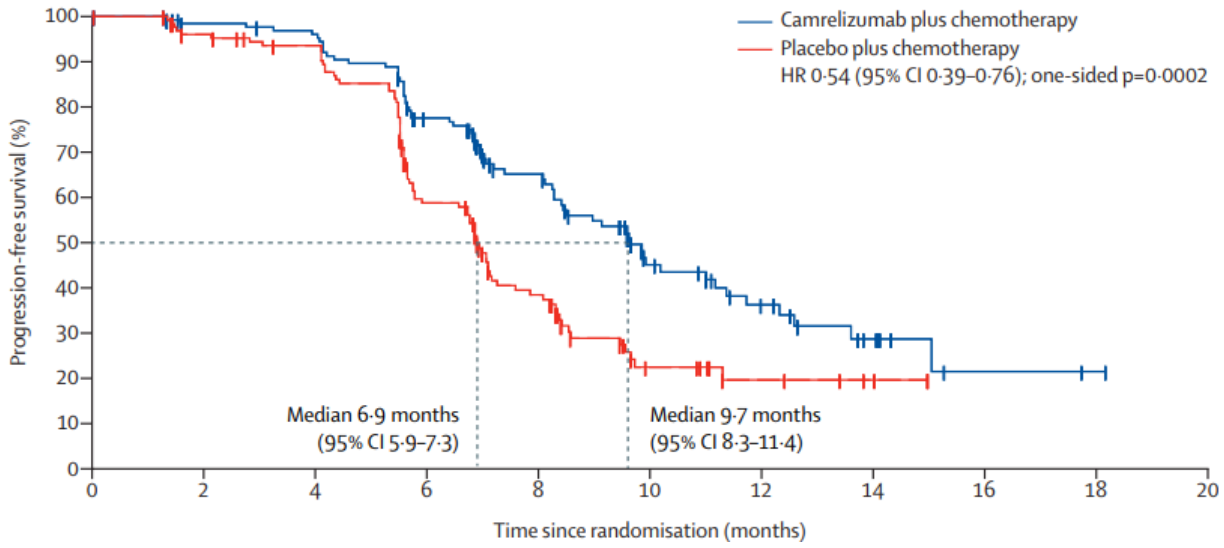
Tislelizumab RATIONALE-309 (Zhang, ASCO 2022)



ICI in 1st line NPC: patient characteristics

	CAPTAIN-1st (camrelizumab) Yang, Lancet Oncol 2021		Jupiter-02 (toripalimab) Mai, Nature med 2021		Rationale-09 (Tislelizumab) Zhang, ASCO virtual plenary 2022 ab384950	
	Cis + Gem + Camrelizumab	Cis + Gem	Cis + Gem + Toripalimab	Cis + gem	Cis + gem + tislelizumab	Cis+gem
N	134	129	146	143	131	132
Mean age (range)	52 (40-58)	49 (40-56)	46 (19-72)	51 (21-72)	50 (26-74)	50 (23-73)
Primary metastatic disease	35%	33%	42%	39%	96% (?)	94% (?)
Recurrent disease	65%	67%	58%	61%	4%	6%
Previous chemoradio	64%	64%	45%	48%	64%	63%
Liver mets	52%	51%			43%	43%
Plasma EBV DNA	Pos 71% Neg 29%	Pos 67% Neg 33%	<2000: 37% ≥2000: 63%	<2000: 38% ≥2000: 62%	<500: 20% ≥500: 80%	<500: 28% >500: 72%
PD-L1 ≥1	NA	NA	75%	76%	61% (CPS ≥10)	64% (CPS ≥10)

Captain 1st: results



	Camrelizumab+chemo	chemo
mOS	NE	NE
mPFS	9,7m	6,9m
	HR 0,54 (95%CI 0,39-0,76) (primary endpoint met)	

Table S6. Progression-free survival in patients with baseline positive and negative plasma EBV DNA level

	EBV DNA positive (n=181)	EBV DNA negative (n=82)†	HR (95% CI) *
Independent review committee-assessed			
Camrelizumab plus chemotherapy	9·9 (8·1–12·3)	15·1 (9·5–NR)	0·64 (0·37–1·11)
Placebo plus chemotherapy	6·8 (5·7–7·1)	9·5 (6·6–12·2)	0·51 (0·33–0·80)
Total	7·3 (6·9–8·4)	9·8 (8·3–15·1)	0·65 (0·46–0·91)

Table S7. Progression-free survival in patients with different plasma EBV DNA level change from baseline after 3 cycles of treatment *

	EBV DNA Positive to negative (n=122)	EBV DNA consistently positive (n=59)	HR (95% CI)†
Independent review committee-assessed			
Camrelizumab plus chemotherapy	12·3 (8·4–18·0)	6·7 (4·6–9·1)	0·37 (0·22–0·63)
Placebo plus chemotherapy	7·1 (6·7–8·3)	5·7 (5·5–5·9)	0·51 (0·30–0·84)
Total	8·4 (7·2–10·9)	5·7 (5·5–6·7)	0·43 (0·30–0·62)

(Yang, Lancet Oncol 2021)

Captain 1st: Toxicity

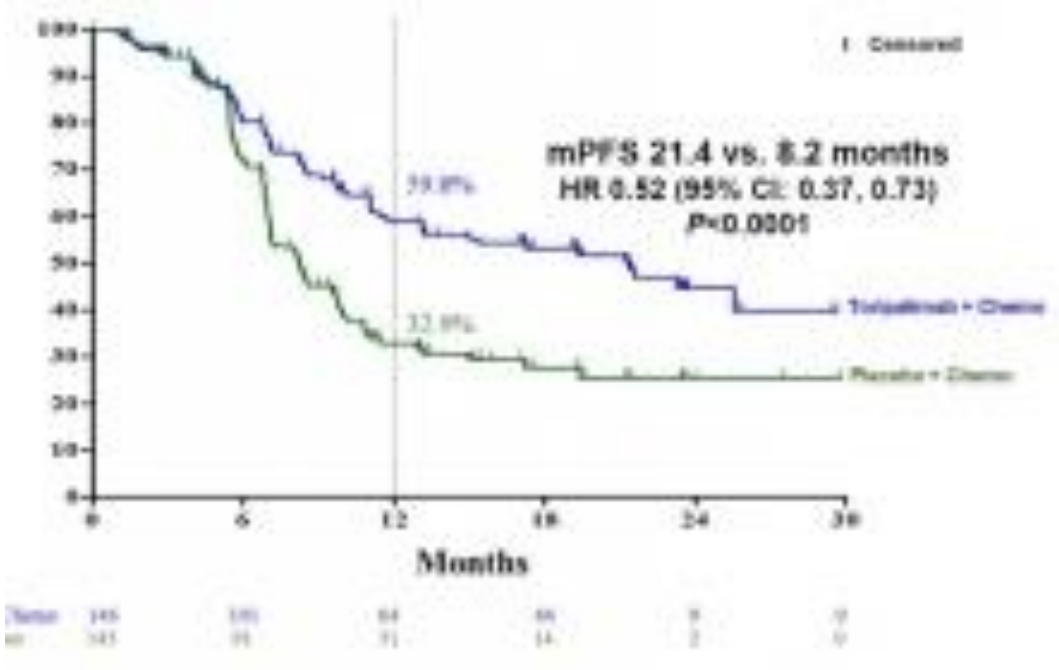
	Camrelizumab+chemo	chemo
Grade 3-4 TRAE	93% (mainly hemato)	90%
Grade 5 TRAE	10/134 (7%) MODS, fatal bleed, arrythmia, unkown	7/129 (5%)
SAE	44%	37%
Leading to discontinuation	13/134 (10%)	7/129 (5%)
Suspect irAE (any grade)	112/34 (84%)	65/129 (50%)
Gr 3-4 irAE	15%	1%
reactive capillary endothelial proliferation	58%	8 (6%)

Median time of onset: 4 weeks
Tends to resolve spontaneously after 4-6 months
May correlate with response

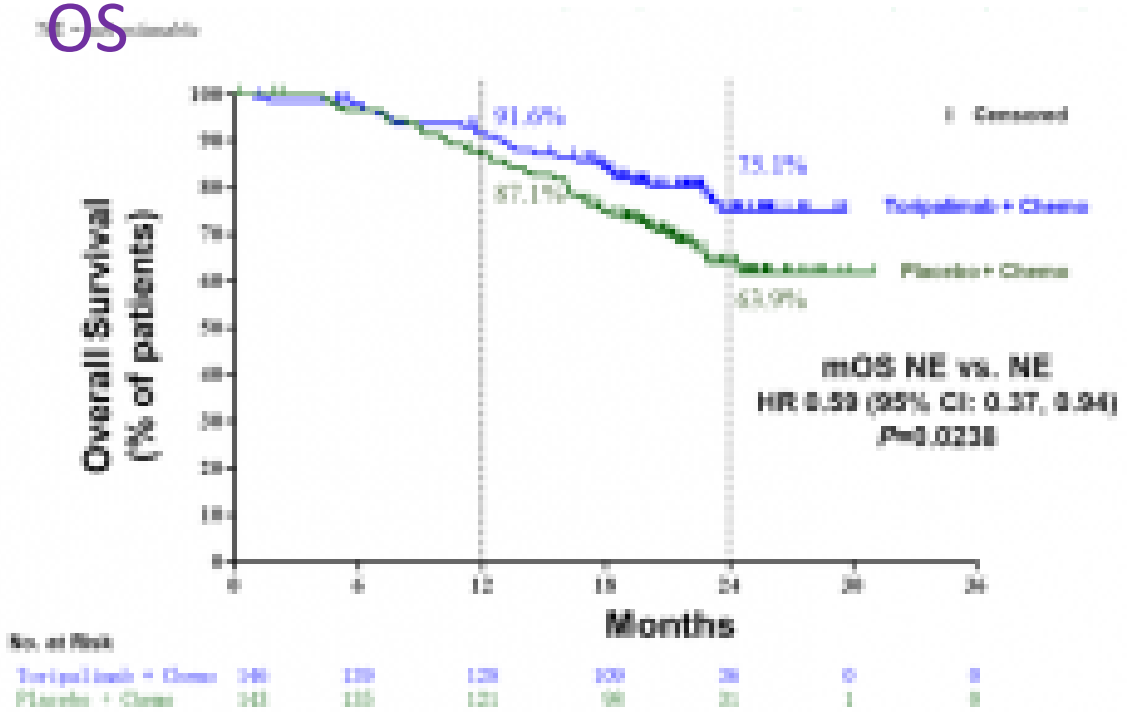
Wang, J Hematol Oncol 2020

Jupiter-02: results (2022 update)

PFS



OS



	Toripalimab+chemo	chemo
mOS	NE	NE
mPFS	21,4m	8,2m
	HR 0,52 (95%CI 0,37-0,73) (primary endpoint met)	

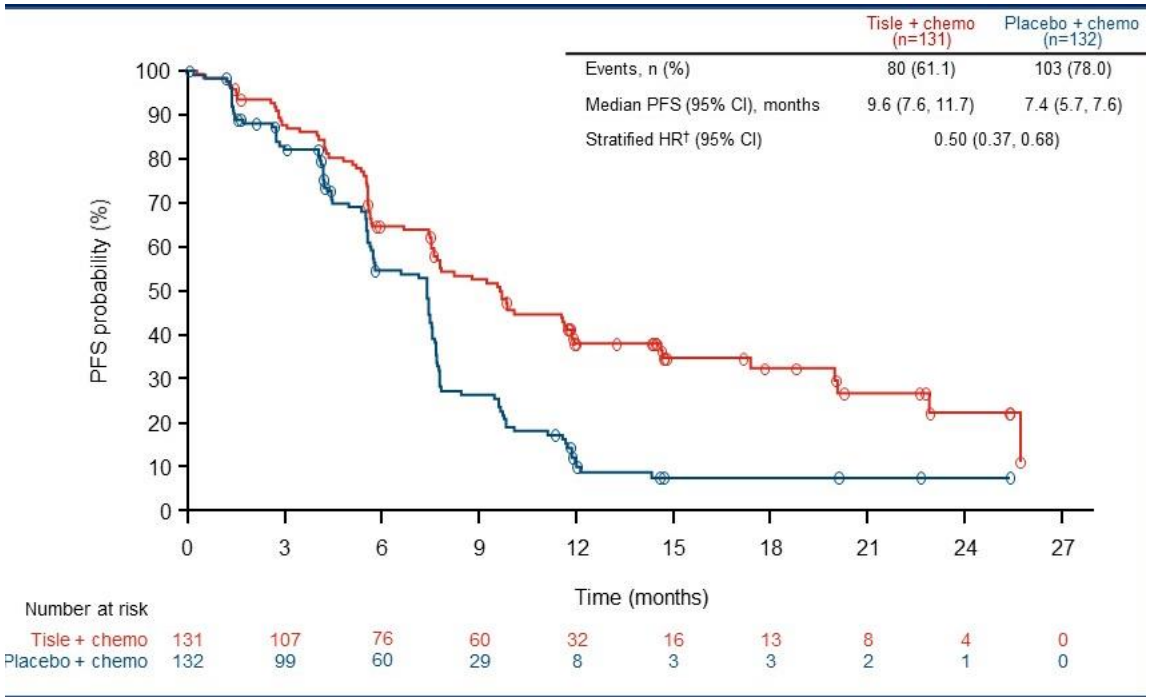
Mai, nature med 2021
AACR congres 2022

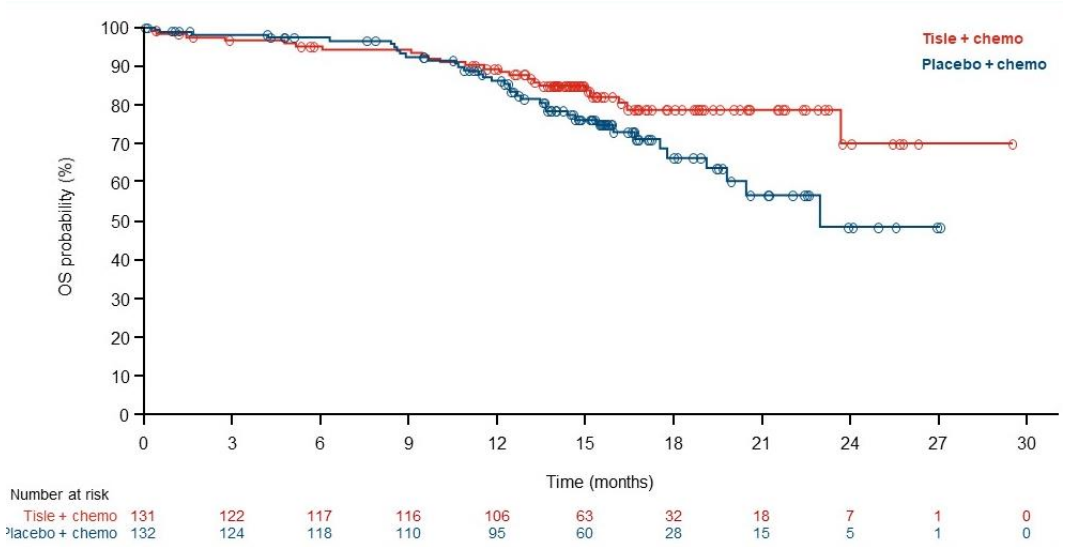
Jupiter-02:Toxicity

	Toripalimab+chemo	chemo
Grade 3-4 TRAE	89% (mainly hemato)	89,5%
Grade 5 TRAE	2,7%	2,8%
SAE	41%	43%
Leading to discontinuation	7,5%	4,9%
Suspect irAE (any grade)	40%	19%
Gr 3-4 irAE	7,5%	<1%

Mai, nature med 2021

Rationale-309: results



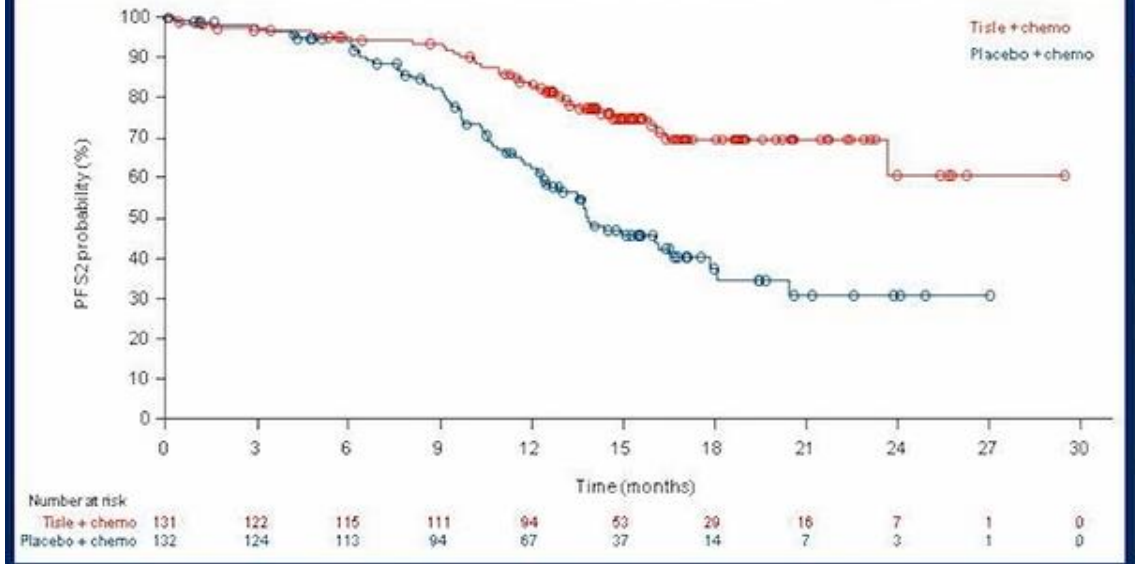


	Tislelizumab+chemo	chemo
mOS	NE	23,0m
mPFS	9,6m	7,4m
	HR 0,50 (95%CI 0,37-0,68) (primary endpoint met)	

ASCO 2022 virtual plenary abstract 384950

Rationale-309: PFS2 data

Median follow-up: 15.5 months*

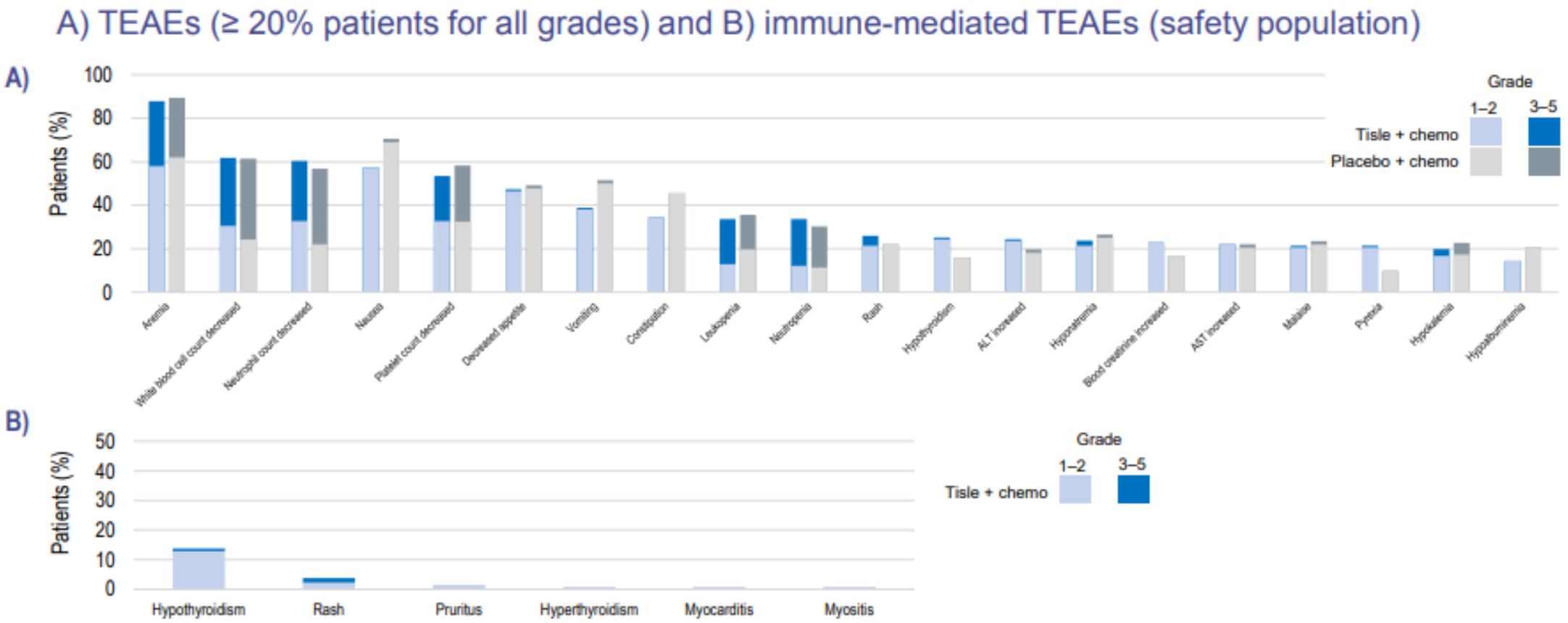


	Tisle + chemo (n=131)	Placebo + chemo (n=132)
PFS2 events, n (%)	32 (24.4)	65 (49.2)
Median PFS2 (95% CI), months	NR (23.7, NR)	13.9 (12.5, 17.9)
Unstratified HR (95% CI)	0.38 (0.25, 0.58)	
PFS2 rate, % (95% CI)		
6 months	95.3 (89.8, 97.9)	94.4 (88.6, 97.3)
9 months	93.6 (87.7, 96.8)	82.4 (74.3, 88.2)
12 months	83.4 (75.4, 88.9)	62.6 (53.1, 70.8)
Crossover to tislelizumab monotherapy, n (%)	–	65 (49.2)

As cross-over was allowed, these data also advocate that antiPD1 should be used in first line, and not after PD on chemo

ASCO 2022 virtual plenary abstract 384950

Rationale-309: toxicity



Esmo immuno oncology 2021 – abstract 1210

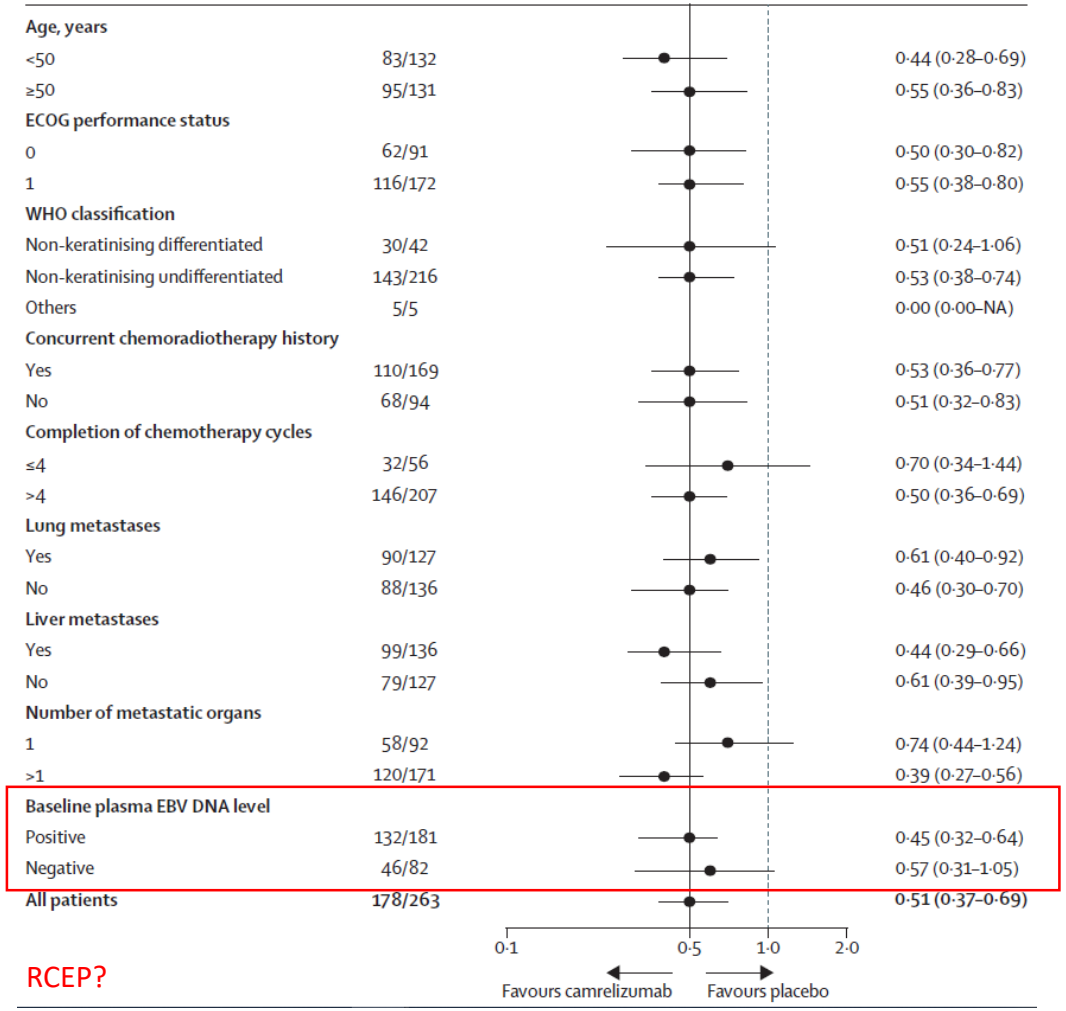
ICI in 1st line NPC:

	SHR-1210-101 Feng, Lancet Oncol 2018	CAPTAIN-1st(camrelizumab) Yang, Lancet Oncol 2021		Jupiter-02 (toripalimab) Mai, Nature med 2021		Rationale-309 (Tislelizumab) Zhang, ASCO virtual plenary 2022 ab384950	
design	1b	ph3 randomized double blind		ph3 randomized double blind		Ph3 randomized double blind	
Primary outcome	Safety	PFS superiority BIRC (HR<0,63)		PFS superiority (HR<0,67)		PFS superiority (HR<0,65)	
Regimen	Cis + Gem +Camrelizumab	Cis + Gem + Camrelizumab	Cis + Gem	Cis + Gem + Toripalimab	Cis + gem	Cis + gem + tislelizumab	Cis+gem
N	23	134	129	146	143	131	132
ORR	91%	87%	81%	77,4%	66,4%	69%	55%
DCR	100%	96,3%	94,6%	87,7%	79,7%	89%	84%
mDOR	NA	8,5m	5,6m	18,0m	6,0m	8,5m	6,5m
mPFS months (95%CI)	NA	10,8m	6,9m	21,2m (11,0-NE)*	8,2m (7,0-9,5)*	9,6m	7,4m
mOS Months (95%CI)	NA	NR	22,6	NR	NR	NR	23,0m
Trial result	**Positive**	**PFS: HR 0,50 (0,37-0,68)**		**PFS: HR 0.52 (95% CI: 0.37–0.73)**		**PFS: HR, 0.50 (95% CI, 0.37-0.68)**	

*AACR 2022 abstract CT226

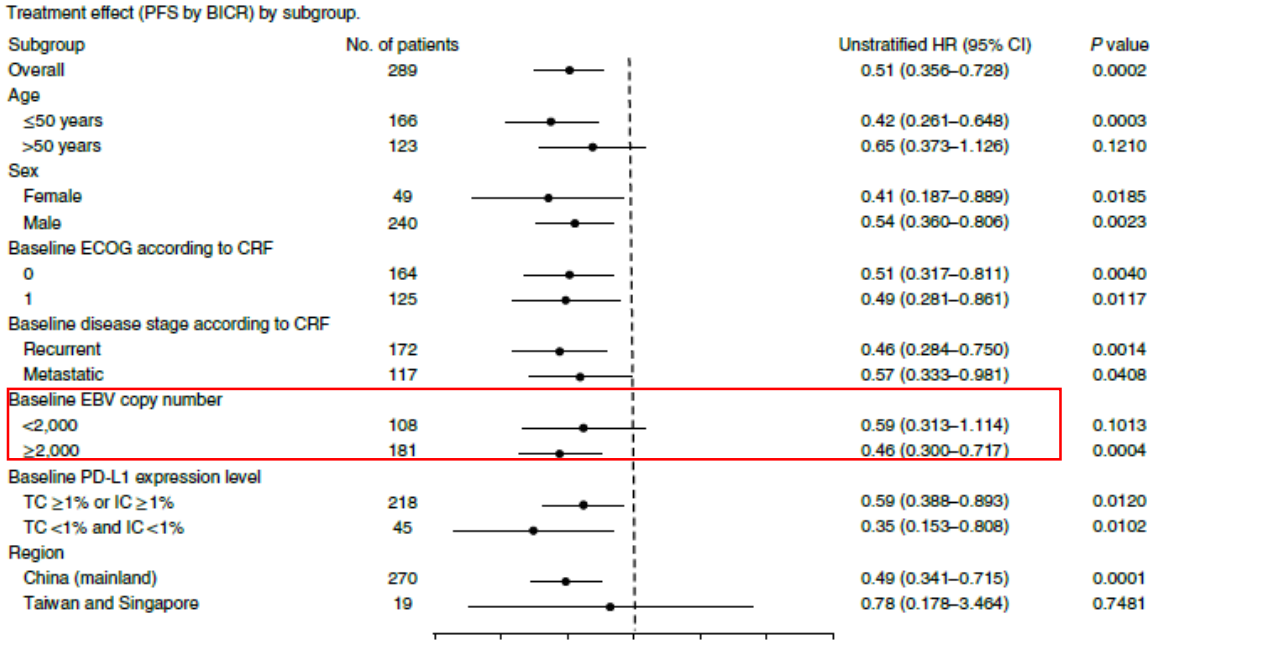
Markers of response?

CAPTAIN-1st

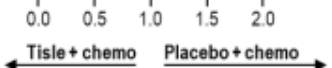


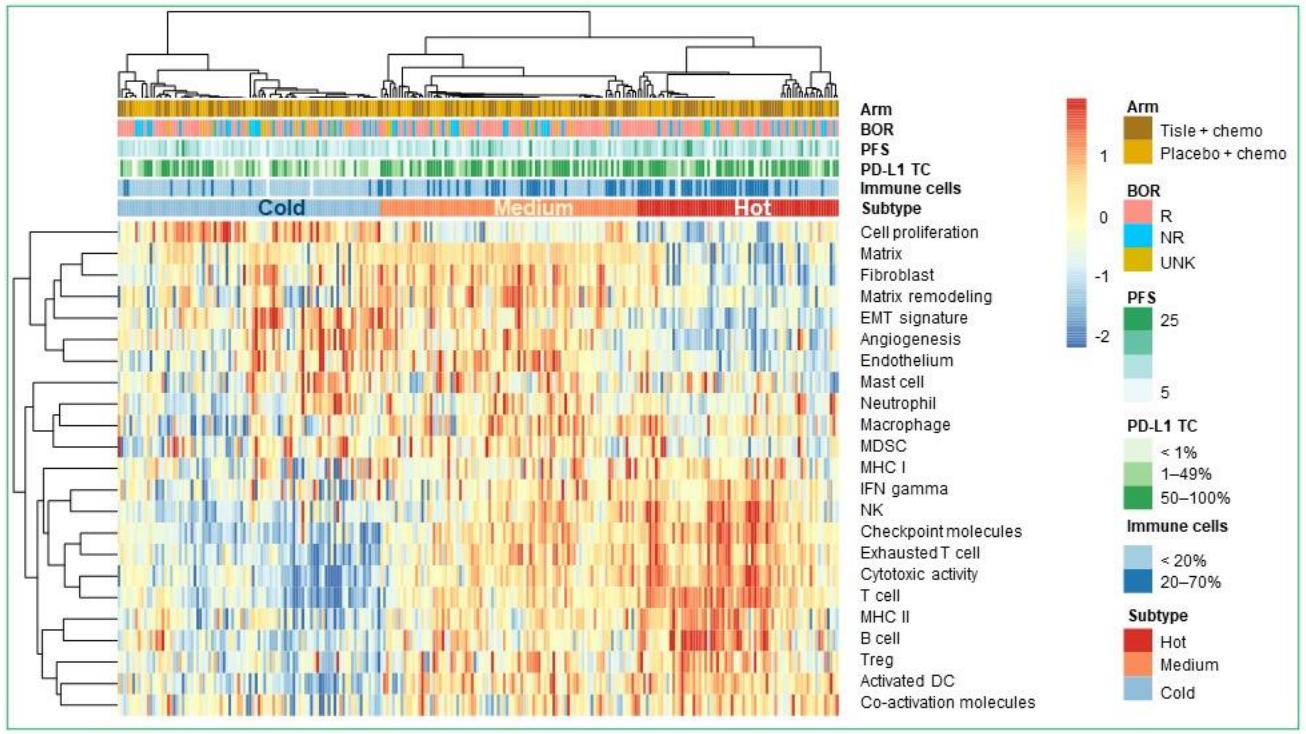
RCEP?

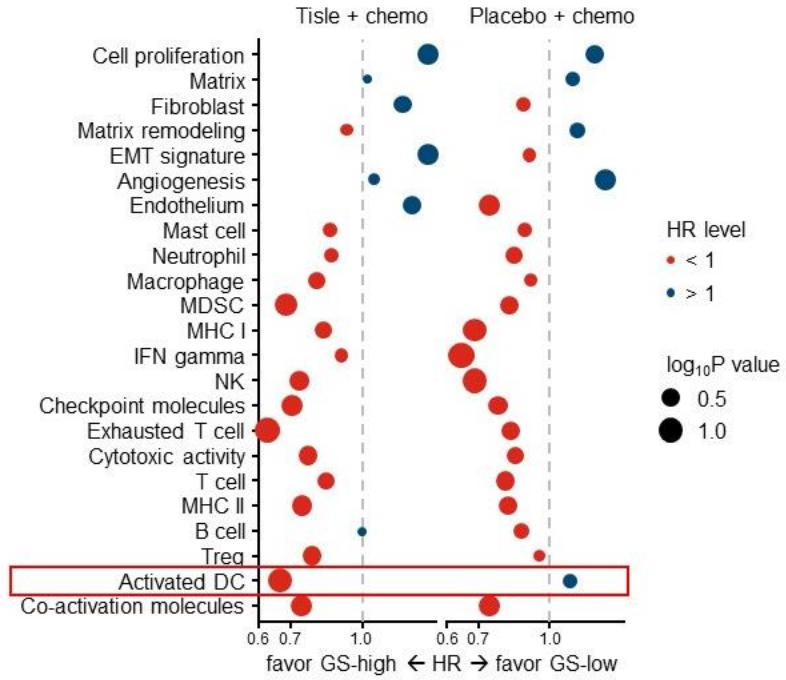
Jupiter02

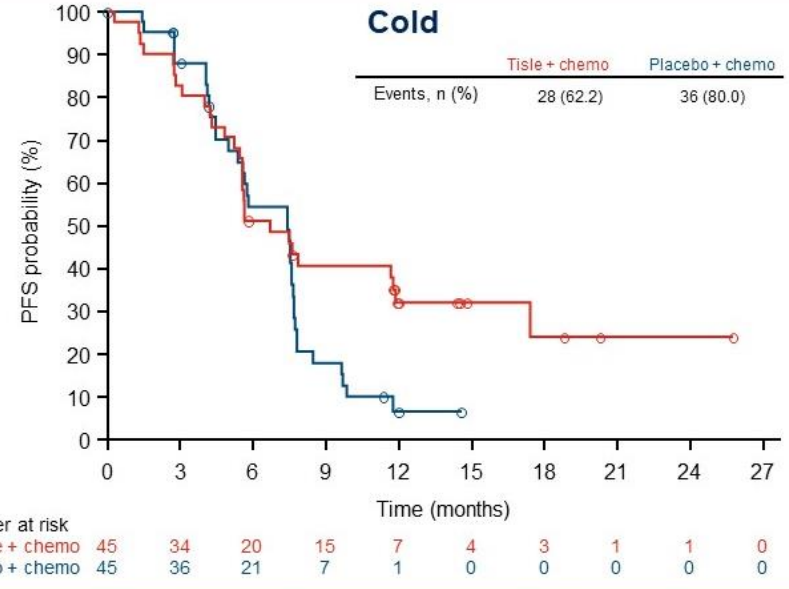


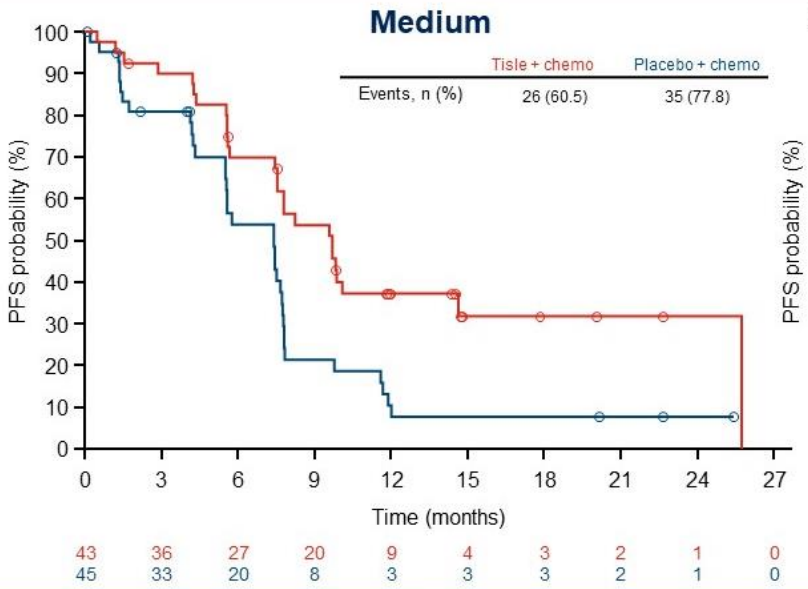
Subgroup		Events/patients Tisle + chemo	Events/patients Placebo + chemo	HR for PD or death (95% CI)
Overall		65/131	87/132	0.51 (0.37, 0.71)
Age group	< 65 years	57/121	80/120	0.46 (0.32, 0.64)
	≥ 65 years	8/10	7/12	1.93 (0.69, 5.38)*
Sex	Male	50/103	68/103	0.53 (0.37, 0.77)
	Female	15/28	19/29	0.44 (0.22, 0.89)
ECOG PS	0	27/51	35/46	0.42 (0.25, 0.70)
	1	38/80	52/86	0.58 (0.38, 0.88)
Smoking status	Never	38/74	45/66	0.40 (0.26, 0.63)
	Current	4/7	4/6	0.97 (0.22, 4.35)*
	Former	23/50	38/60	0.63 (0.37, 1.05)
Disease status	Primary Metastatic	64/126	83/124	0.53 (0.38, 0.74)
	Recurrent	1/5	4/8	NE (NE, NE)
Liver metastases at baseline	Yes	33/56	46/57	0.48 (0.31, 0.77)
	No	32/75	41/75	0.55 (0.34, 0.87)
EBV DNA level	< 500 IU/mL	11/26	20/37	0.45 (0.21, 0.94)
	≥ 500 IU/mL	54/105	67/95	0.52 (0.36, 0.75)
PD-L1 expression on tumor cell	PD-L1 ≥ 10%	42/80	57/84	0.53 (0.35, 0.79)
	PD-L1 < 10%	20/42	23/33	0.38 (0.20, 0.72)
	NE	3/9	7/15	0.87 (0.22, 3.49)*

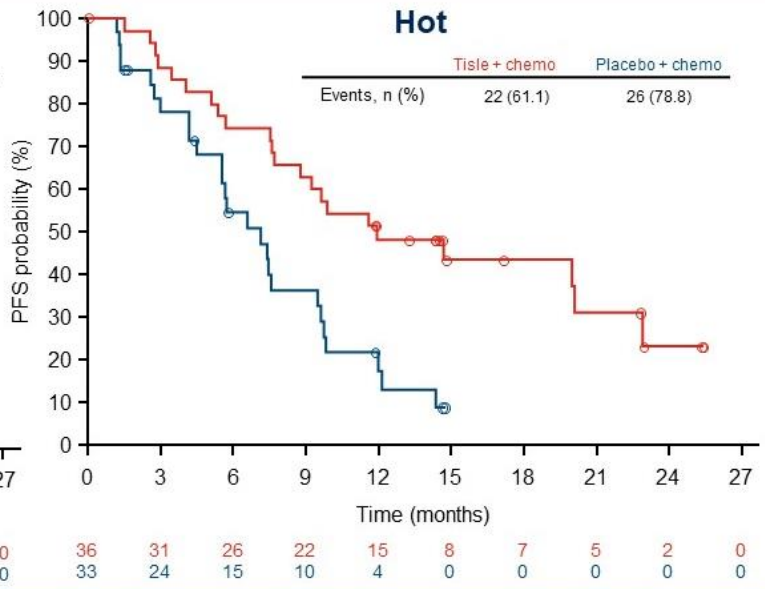












Highest expression of tumor proliferation and endothelium; lowest expression of immune profiles

Higher expression of IFNγ, macrophages, and fibroblast gene signatures

Highest expression of T, NK and dendritic cells, and MHC and IFNγ signatures

Future directions

Type	NCT	Phase	Regimen	outcome	Location	Est completion
Neoadjuv	NCT04458909	3	cis+gem+nivolumab vs cis+gem	OS	China, Canada, US	2028
	NCT04974398	3	cis+gem+penpulimab vs cis+gem	PFS	China	2023
IO+RT	NCT03734809	2	Cis+gem+pembro x3 → cis+pembro+RT → pembro	PFS	Hong Kong, singapore	2024
	NCT03984357	2	Cis+Gem+nivo x3 → cis+nivo+RT	FFS	China	2026
	NCT03925090	2	Toripalimab → cis+toripalimab+RT vs pbo+cis+RT	PFS	China	2023
	NCT03427827	3	Cis+RT → camrelizumab vs cis+RT → observation	DFS	China	2026
	NCT03700476	3	Cis+gem+sintilimab → cis+sin+RT → sin vs cis+gem → cis+RT	FFS	China	2025
	NCT04447612	2	Cis+gem+durvalumab → cis+dur+RT → durv vs cis+gem → cis+RT	PFS	Hong Kong	2025
IO+VEGF	NCT05063552	3	atezo+beva vs atezo beva carbo doce	PFS, OS	USA	2027
	NCT04562441	2	avelumab+axitinib	ORR	Hong Kong	2026
	NCT04548271	2	camrelizumab + apatinib	ORR	China	2023
	NCT03813394	1 /2	pembrolizumab + bevacizumab	ORR	Singapore	2023
	NCT05020925	1 /2	SHR-1701 + famitinib	ORR	China	2022
	NCT04872582	2	sintilimab + bevacizumab	ORR	China	2022
	NCT04996758	2	toripalimab + anlotinib	ORR	China	2023
IO+PARP	NCT04978012	2	Camrelizumab + fluzoparib	ORR	China	2024
	NCT04825990	2	Pembrolizumab + olaparib	ORR	Italy	2024
	NCT05162872	2	Sintinlimab + niraparib	ORR	China	2023
Other	NCT05222035	2	Camrelizumab + G-CSF vs camrelizumab	ORR	China	2023
	NCT05166577	1 /2	Pembrolizumab + nanatinostat + valganciclovir	Safety	US, Aus, Can, asia	2024
	NCT04945421	1 /2	Sintilimab + IBI310	ORR	China	2022

Conclusions

Cis-Gem as preferred 1st line regimen in R/M HNSCC (ESMO MCBS I, GRADE A)
if used as induction regimen=?

Add RT to primary if de novo M+ and response (ESMO MCBS II, GRADE A),
Role of maintenance capecitabine=?

Chemo+IO combo provide PFS benefit in 1st line R/M NPC, OS data immature

Toripalimab: EMA submission filed
questions: Concommitant vs maintenance? Biomarkers?

ICI in second line: promising ph 2, RCT's > NEGATIVE

Asian population, new drugs!

ICI in frontline management are under investigation

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Michael Saerens, MD

Dept of Medical Oncology
Ghent University Hospital

E michael.saerens@ugent.be
T +32 9 332 2692
msaerens01

References

Chen, Y. P., Chan, A. T., Le, Q. T., Blanchard, P., Sun, Y., & Ma, J. (2019). Nasopharyngeal carcinoma. The Lancet, 394(10192), 64-80.

Chan A. T., et al. 858O Results of KEYNOTE-122: A phase III study of pembrolizumab (pembro) monotherapy vs chemotherapy (chemo) for platinum-pretreated, recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC). Annals of Oncology, 2021, 32: S786.

Even C., et al. Phase II, Randomized Study of Spartalizumab (PDR001), an Anti–PD-1 Antibody, versus Chemotherapy in Patients with Recurrent/Metastatic Nasopharyngeal Cancer. Clin Cancer Res 2021;27:6413–23

Mai H, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. Nature Medicine, 2021, 27.9: 1536-1543.

Yang et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial, Lancet Oncol 2021; 22: 1162–74

ICI in pretreated NPC: randomized trials

	Keynote 122 (Chan, ESMO2021)		NCT02605967 (Even, clin can res 2021)	
	Pembro	Chemo IC	Spartalizumab	Chemo IC
Phase	3, all pretreated		2, all pretreated	
Primary outcome	OS superiority		PFS superiority	
N	117	116	84	39
ORR	21%	23%	17%	35%
DCR	50%	64%	42%	70%
mPFS months(95%CI)	4,1 m	5,5 months	1,9 months	6,6 months
mOS months(95%CI)	17,2m	15,3 months	17,2 months	15,3 months
Trial result	HR 0,90 (95%CI 0,67-1,19) → NEG		HR 1,62 (95% CI 0.87–2.12) → NEG	

*Humanized antiPD1 MOAB escalating doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg Q2w, finally 200mg Q2w
**Humanized antiPD1 MOAB at 3mg/kg Q2w