Head and neck cancer updates, October 2021
California Cancer Consortium

A. Dimitrios Colevas MD

Stanford Cancer Institute

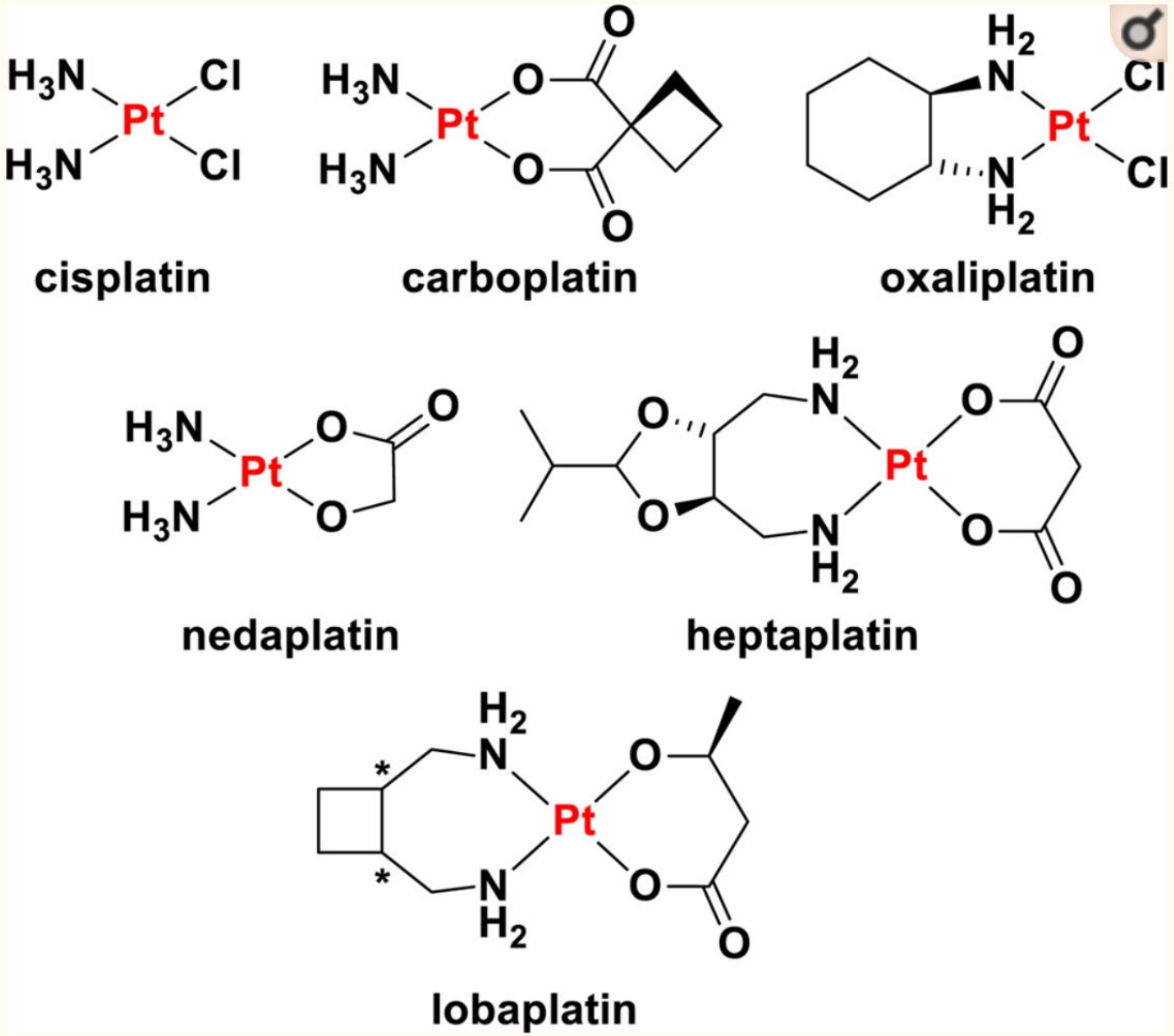
A good year for nasopharyngeal carcinoma (NPC) progress

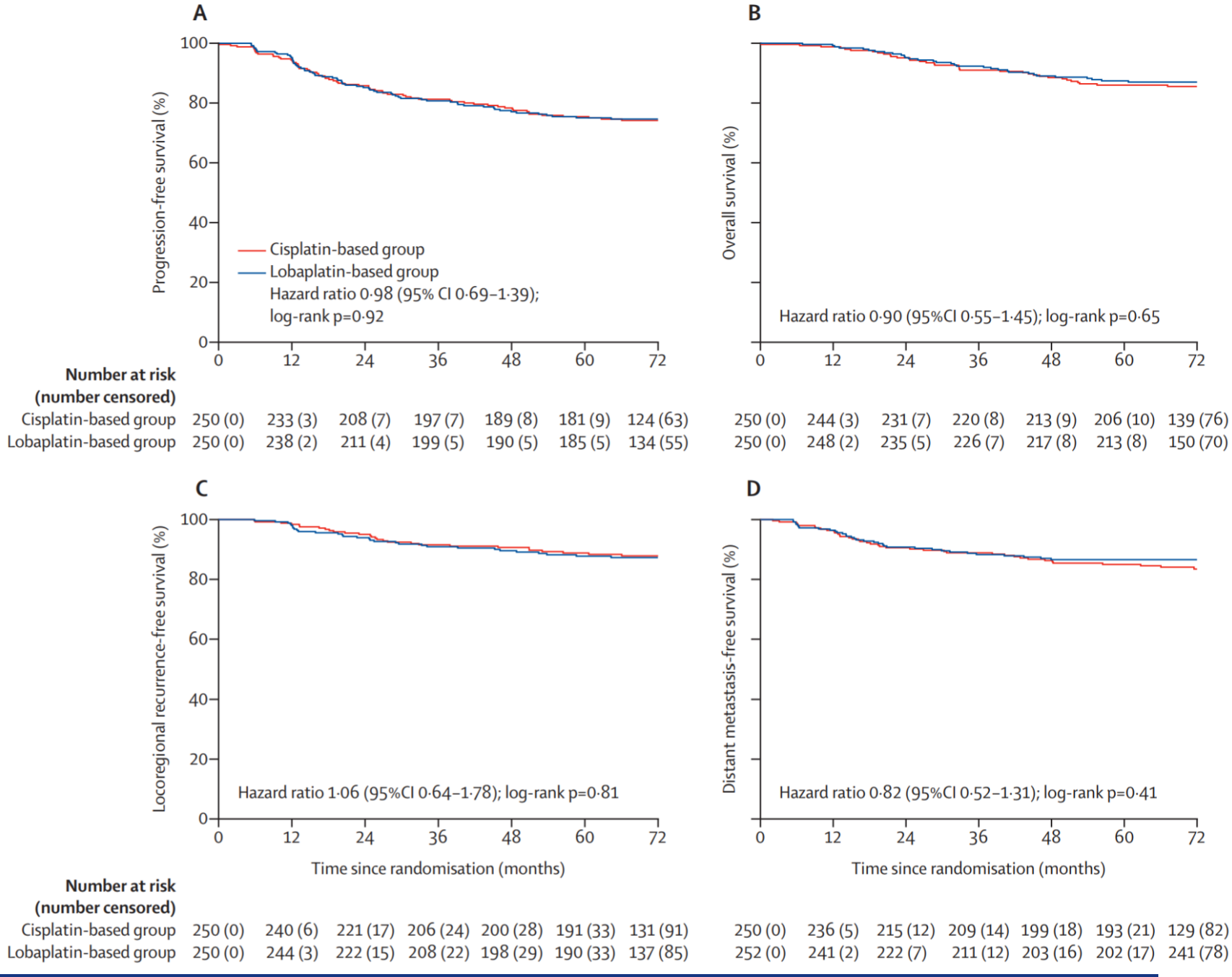
- Things to discuss:
- NPC issues of induction vs adjuvant
- NPC adjuvant capecitabine
- Radiation in metastatic NPC
- NPC ICI in R/M disease

Induction chemotherapy with lobaplatin and fluorouracil versus cisplatin and fluorouracil followed by chemoradiotherapy in patients with stage III–IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised, controlled, phase 3 trial

Xing Lv, Xun Cao*, Wei-Xiong Xia*, Kui-Yuan Liu, Meng-Yun Qiang, Ling Guo, Chao-Nan Qian, Ka-Jia Cao, Hao-Yuan Mo, Xian-Ming Li, Zi-Huang Li, Fei Han, Yu-Xiang He, Yu-Meng Liu, Shao-Xiong Wu, Yong-Rui Bai, Liang-Ru Ke, Wen-Ze Qiu, Hu Liang, Guo-Ying Liu, Jing-Jing Miao, Wang-Zhong Li, Shu-Hui Lv, Xi Chen, Chong Zhao†, Yan-Qun Xiang†, Xiang Guo†*

Lancet Oncol 2021; 22: 716–26


cisplatin
carboplatin
oxaliplatin
nedaplatin
heptaplatin
lobaplatin



Number at risk (number censored)							
Cisplatin-based group	250 (0)	233 (3)	208 (7)	197 (7)	189 (8)	181 (9)	124 (63)
Lobaplatin-based group	250 (0)	238 (2)	211 (4)	199 (5)	190 (5)	185 (5)	134 (55)

Cisplatin-based group	250 (0)	244 (3)	231 (7)	220 (8)	213 (9)	206 (10)	139 (76)
Lobaplatin-based group	250 (0)	248 (2)	235 (5)	226 (7)	217 (8)	213 (8)	150 (70)

Number at risk (number censored)							
Cisplatin-based group	250 (0)	240 (6)	221 (17)	206 (24)	200 (28)	191 (33)	131 (91)
Lobaplatin-based group	250 (0)	244 (3)	222 (15)	208 (22)	198 (29)	190 (33)	137 (85)

Cisplatin-based group	250 (0)	236 (5)	215 (12)	209 (14)	199 (18)	193 (21)	129 (82)
Lobaplatin-based group	252 (0)	241 (2)	222 (7)	211 (12)	203 (16)	202 (17)	241 (78)

Lancet Oncol 2021; 22: 716–26

	Lobaplatin-based group (n=252)			Cisplatin-based group (n=249)			p value for events grades 1–2	p value for events grades 3–4	p value for events grade ≥1
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4			
Haematological									
Neutropenia	114 (45%)	21 (8%)	4 (2%)	97 (39%)	50 (20%)	9 (4%)	0·15	<0·0001	0·088
Leucopenia	129 (51%)	38 (15%)	1 (<1%)	114 (45%)	56 (22%)	0	0·23	0·045	0·70
Thrombocytopenia	69 (27%)	14 (6%)	4 (2%)	62 (25%)	8 (3%)	3 (1%)	0·53	0·19	0·21
Anaemia	168 (67%)	4 (2%)	0	151 (61%)	23 (9%)	4 (2%)	0·16	<0·0001	0·43
Non-haematological									
Dry mouth	169 (67%)	13 (5%)	0	149 (60%)	17 (7%)	0	0·093	0·43	0·18
Dermatitis	176 (70%)	6 (2%)	1 (<1%)	185 (74%)	10 (4%)	2 (1%)	0·27	0·23	0·089
Mucositis	143 (57%)	91 (36%)	11 (4%)	144 (58%)	89 (36%)	10 (4%)	0·81	0·87	0·80
Nausea	106 (42%)	1 (<1%)	1 (<1%)	187 (75%)	24 (10%)	0	<0·0001	<0·0001	<0·0001
Vomiting	54 (21%)	0	0	150 (60%)	16 (6%)	0	<0·0001	<0·0001	<0·0001
Diarrhoea	12 (5%)	4 (2%)	0	16 (6%)	2 (1%)	0	0·42	0·42	0·69
Nephrotoxicity	53 (21%)	0	4 (2%)	92 (37%)	0	2 (1%)	<0·0001	0·69*	<0·0001
Hepatoxicity	119 (47%)	5 (2%)	0	112 (45%)	6 (2%)	0	0·62	0·75	0·68
Neurotoxicity	1 (<1%)	0	0	0	0	0	1·000*	..	1·0*
Ototoxicity	0	0	0	1 (<1%)	0	0	0·49*	..	0·49*
Allergic reaction	8 (3%)	0	0	3 (1%)	0	0	0·13	..	0·13
Weight loss	80 (32%)	1 (<1%)	0	163 (66%)	5 (2%)	0	<0·0001	0·12*	<0·0001

Data are n (%). No grade 5 adverse events occurred during treatment. As prespecified by protocol, differences in adverse events were analysed using the χ^2 test; for adverse events that did not meet the requirement for χ^2 test, Fisher's exact test was used. *p values were calculated with Fisher's exact test.

Lancet Oncol 2021; 22: 716–26

Induction chemotherapy with lobaplatin and fluorouracil versus cisplatin and fluorouracil followed by chemoradiotherapy in patients with stage III–IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised, controlled, phase 3 trial

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- Challenges:
  - Lobaplatin approval limited to China
  - What about TPF and GC? Meta- analysis favors TPF but most use GC.
  - Why no QOL study? Do these AEs matter?
  - Would the results be the same with carboplatin? See Chitapanarux et al. PMID: 17467265, 32713518

2021 ASCO ANNUAL MEETING

CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD RECIPIENT

Philip Francis Mulvey, III, Endowed Merit Award

Supported by ***Therese Marie Mulvey, MD, FASCO***

Adjuvant Capecitabine in Locoregionally Advanced Nasopharyngeal Carcinoma: A Multicenter Randomized Controlled Phase III Trial

Capecitabine ,1000mg/m^2/BID, 14 days every 21-day cycle, 8 cycles

R 1:1

CCRT+AC arm

➢**CCRT**

IMRT: 68-72Gy/30-32f to PTVnx, 60-68Gy/30-32f to PTVnd, 60-64Gy/30-32f to $PTV_{high\text{-}risk}$, 54-58Gy/30-32f to $PTV_{low\text{-}risk}$

CCT: DDP 100mg/m^2, 2-3 cycles

➢**AC**

Capecitabine ,1000mg/m^2/BID, 14 days every 21-day cycle, 8 cycles

CCRT alone arm

➢**CCRT**

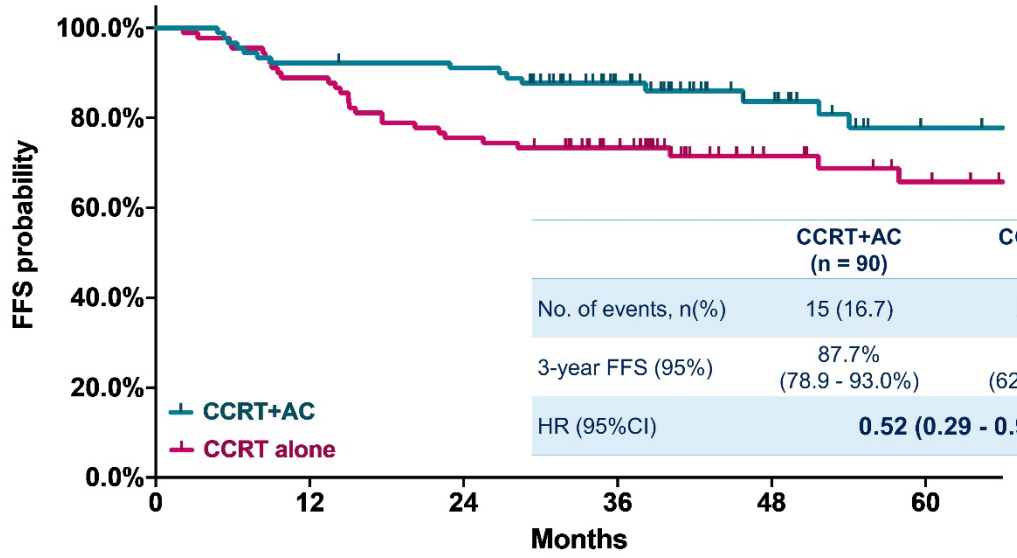
IMRT: 68-72Gy/30-32f to PTVnx, 60-68Gy/30-32f to PTVnd, 60-64Gy/30-32f to $PTV_{high\text{-}risk}$, 54-58Gy/30-32f to $PTV_{locw\text{-}risk}$

CCT: DDP 100mg/m^2, 2-3 cycles

Primary endpoint FFS

No induction chemotherapy

Primary Endpoint: FFS

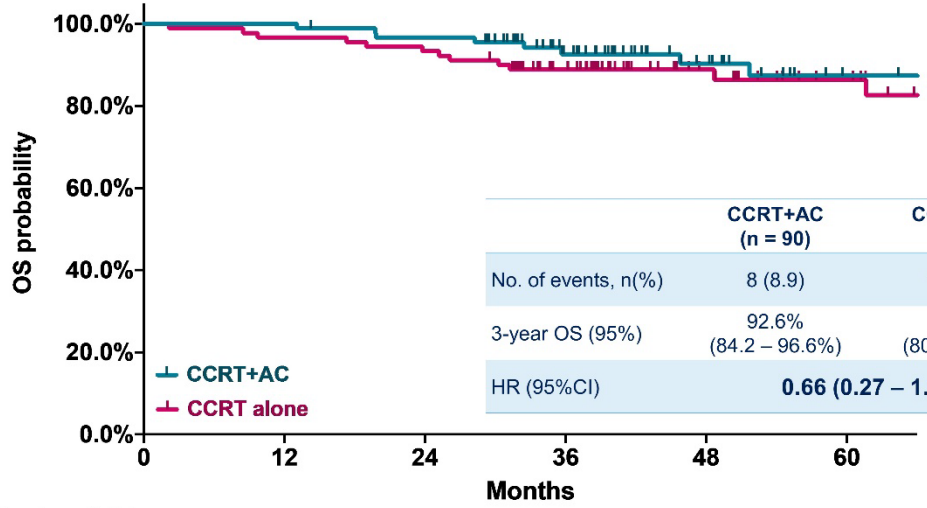


	CCRT+AC (n = 90)	CCRT alone (n = 90)	*P*
No. of events, n(%)	15 (16.7)	27 (30.0)	
3-year FFS (95%)	87.7% (78.9 - 93.0%)	73.3% (62.9 – 80.6%)	
HR (95%CI)	0.52 (0.29 - 0.97)		0.037

Number at risk:

CCRT+AC	90	84	82	55	36	23
CCRT alone	90	81	69	54	29	23

Secondary Endpoints: OS



	CCRT+AC (n = 90)	CCRT alone (n = 90)
No. of events, n(%)	8 (8.9)	12 (13.3)
3-year OS (95%)	92.6% (84.2 – 96.6%)	88.9% (80.3 – 93.8%)
HR (95%CI)	0.66 (0.27 – 1.61)	

Number at risk:

CCRT+AC	90	90	87	59	38	25
CCRT alone	90	88	85	65	37	27

THE LANCET

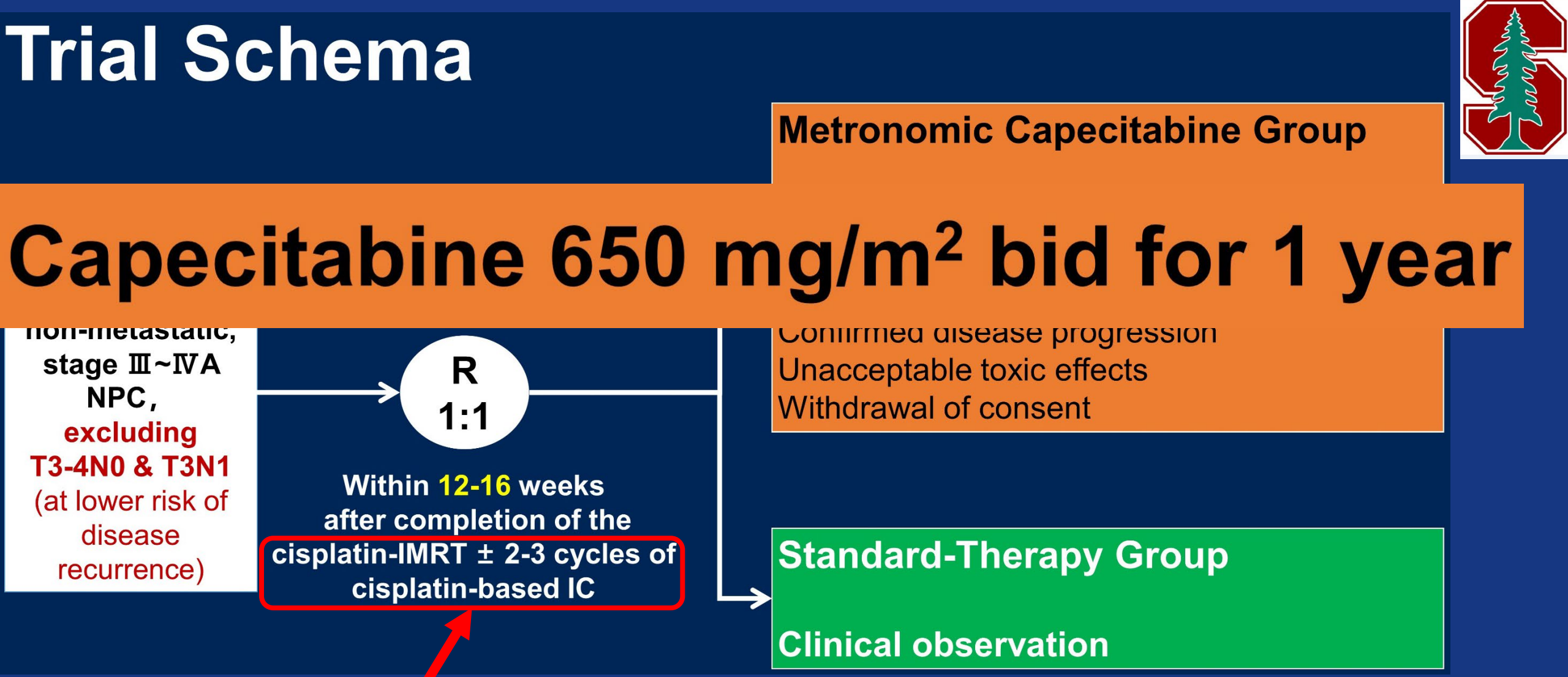
Articles

Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: a multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial

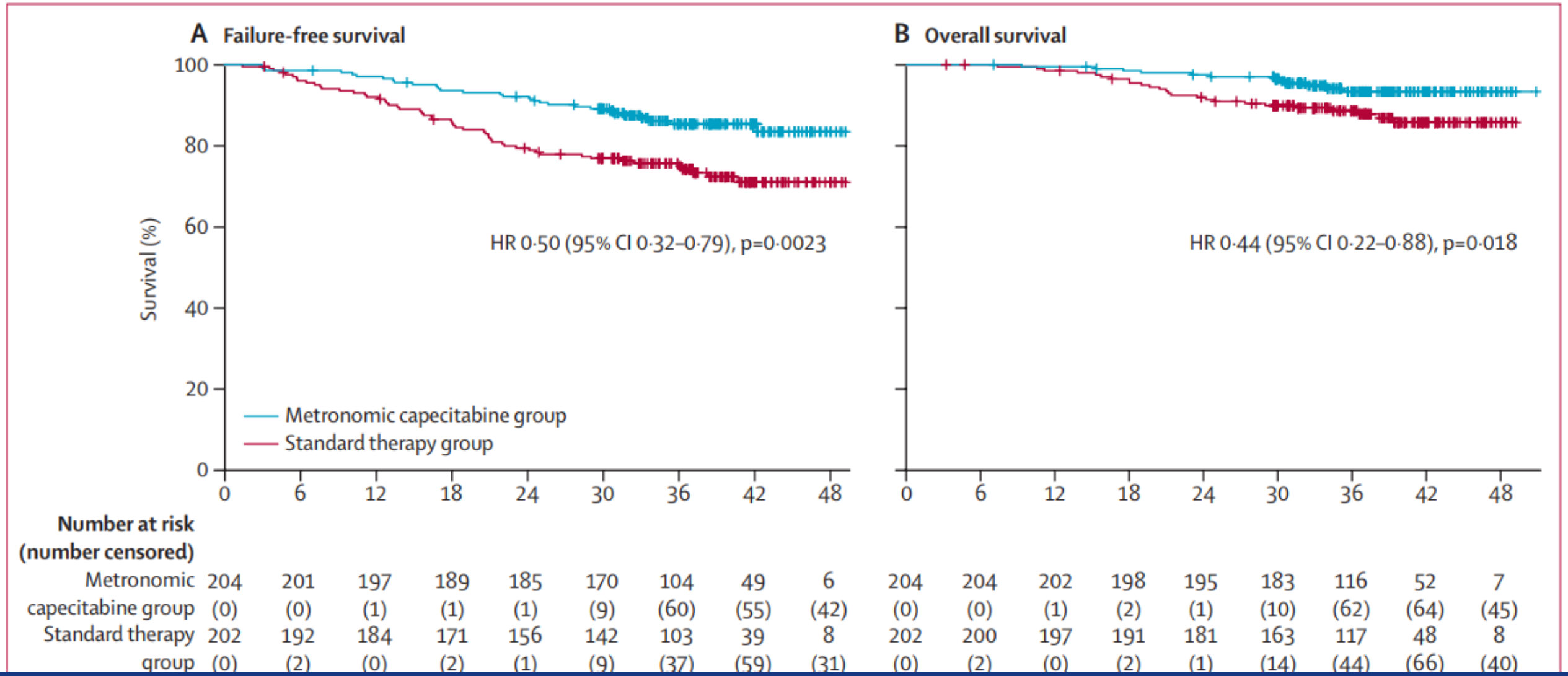
Yu-Pei Chen, Xu Liu*, Qin Zhou*, Kun-Yu Yang*, Feng Jin*, Xiao-Dong Zhu*, Mei Shi*, Guo-Qing Hu*, Wei-Han Hu*, Yan Sun, Hong-Fen Wu, Hui Wu, Qin Lin, Hui Wang, Ye Tian, Ning Zhang, Xi-Cheng Wang, Liang-Fang Shen, Zheng-Zheng Liu, Jing Huang, Xiu-Ling Luo, Ling Li, Jian Zang, Qi Mei, Bao-Min Zheng, Dan Yue, Jing Xu, San-Gang Wu, Yan-Xia Shi, Yan-Ping Mao, Lei Chen, Wen-Fei Li, Guan-Qun Zhou, Rui Sun, Rui Guo, Yuan Zhang, Cheng Xu, Jia-Wei Lv, Ying Guo, Hui-Xia Feng, Ling-Long Tang†, Fang-Yun Xie†, Ying Sun†, Jun Ma†*

Published Online June 7, 2021 https://doi.org/10.1016/ S0140-6736(21)01123-5

Trial Schema



primary endpoint : failure-free survival


A Failure-free survival
B Overall survival
Survival (%)
100
80
60
40
20
0
HR 0·50 (95% CI 0·32–0·79), p=0·0023
HR 0·44 (95% CI 0·22–0·88), p=0·018
Metronomic capecitabine group
Standard therapy group
0 6 12 18 24 30 36 42 48
Number at risk (number censored)
Metronomic capecitabine group 204 201 197 189 185 170 104 49 6
(0) (0) (1) (1) (1) (9) (60) (55) (42)
204 204 202 198 195 183 116 52 7
(0) (0) (1) (2) (1) (10) (62) (64) (45)
Standard therapy group 202 192 184 171 156 142 103 39 8
(0) (2) (0) (2) (1) (9) (37) (59) (31)
202 200 197 191 181 163 117 48 8
(0) (2) (0) (2) (1) (14) (44) (66) (40)

Important to note

- 77% of patients received both induction and concurrent chemoradiation
- Consistent benefit across T, N and stage grouping
- Time from completion of XRT to randomization approx. 14 weeks
- Median duration of capecitabine 12.1 months
  - 18% dose reduced
  - 26% interrupted
  - 74% completed 1 year
  - Dose intensity median 98%

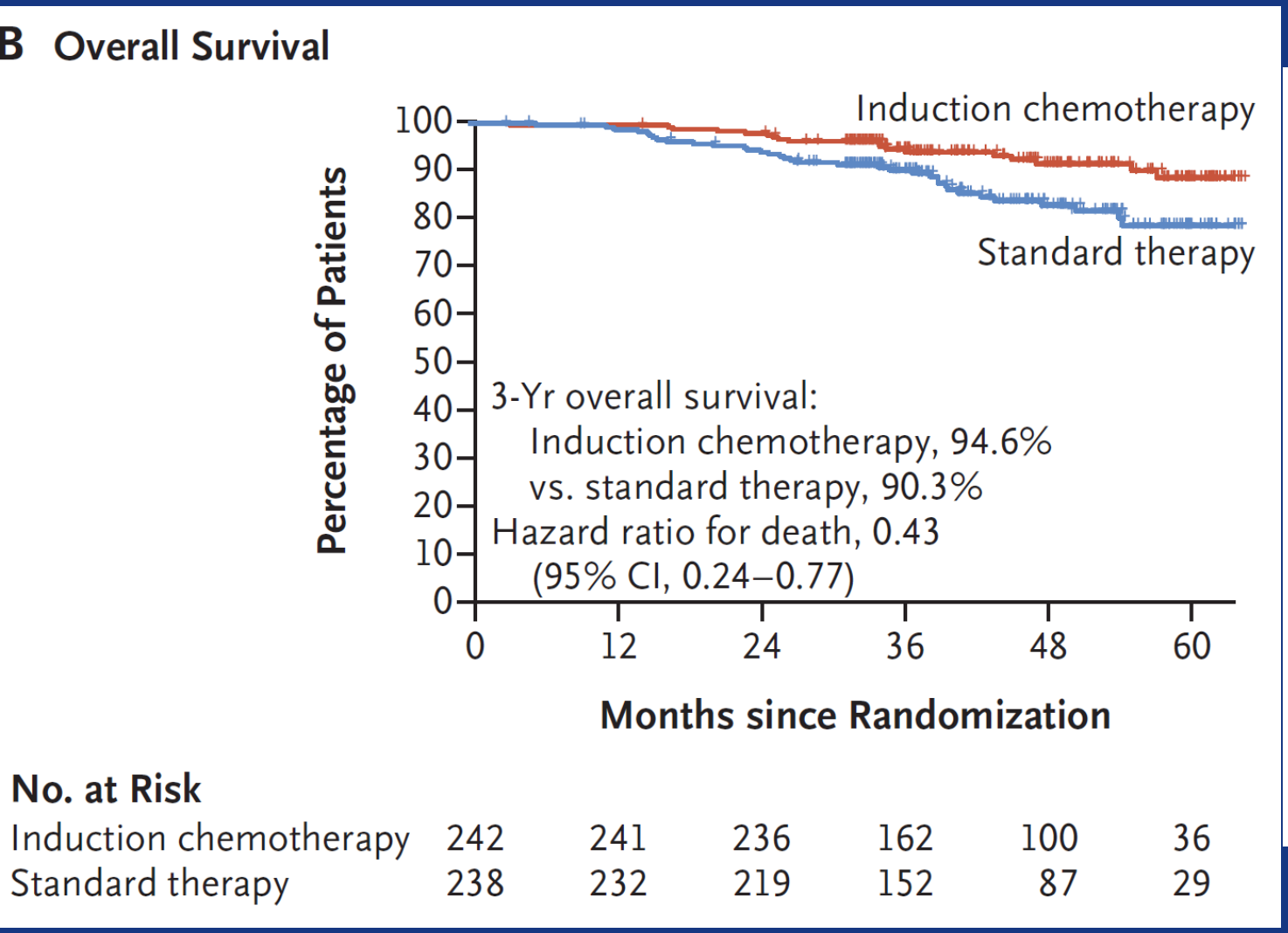
Should adjuvant capecitabine be SOC? For which patients?

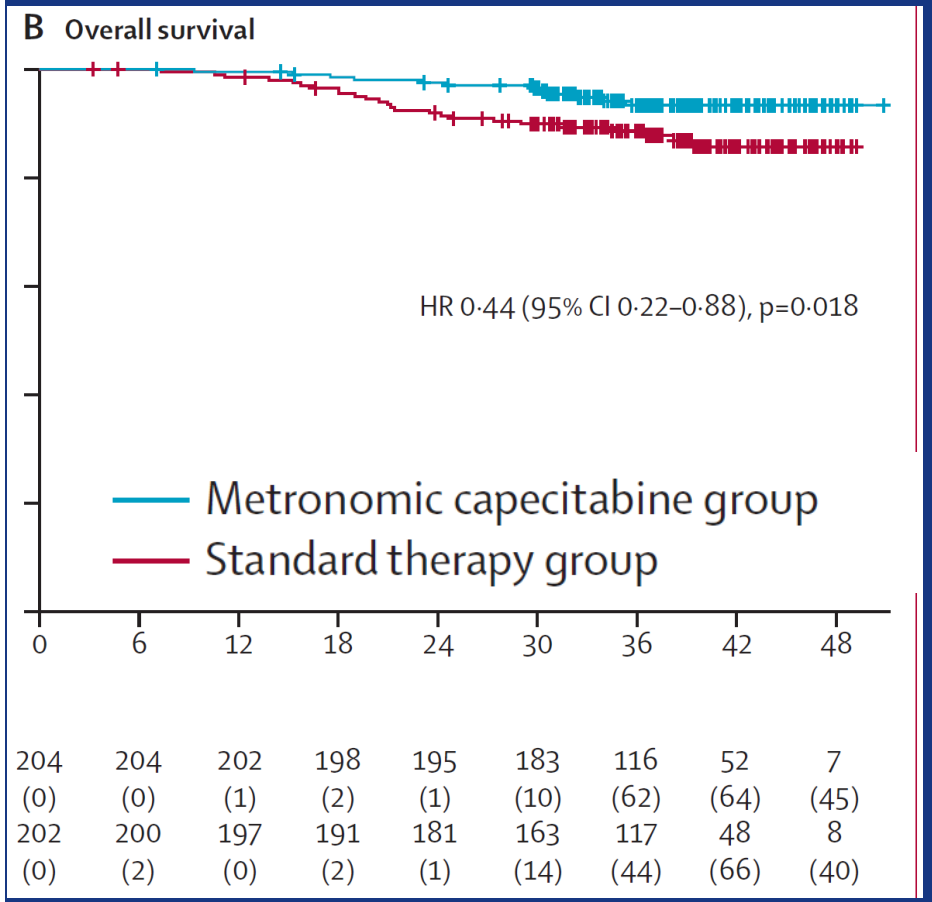
- ASCO discussant, Dr Herbert Loong, noncommittal

Next Steps …

- **Head to Head comparison** of IC – CRT – $AC_{capecitabine}$ vs. CRT – $AC_{capecitabine}$
- Head to Head comparison of **metronomic vs. standard dosing** of capecitabine
- Identification of **specific patient populations** and a more tailored approach

Let's look at relative SURVIVAL benefit, induction GC versus metronomic adjuvant capecitabine. Both sets of data from SYSU, Prof Jun Ma group





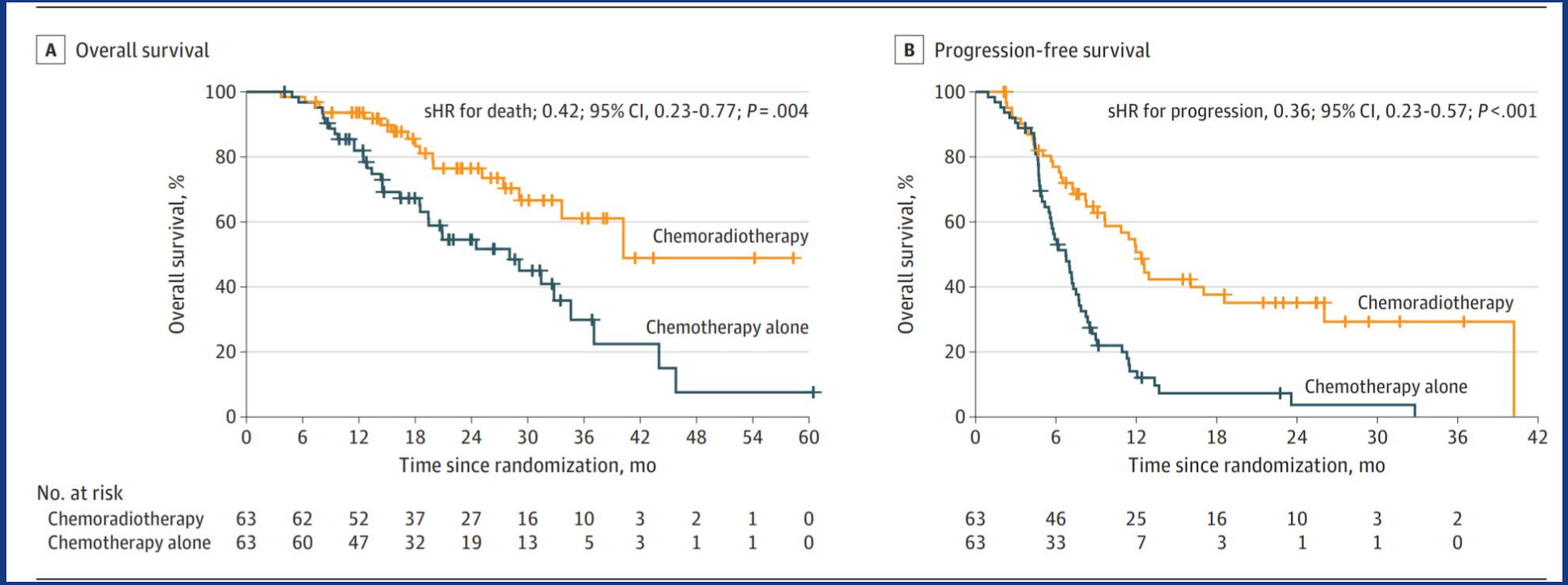
JAMA Oncology | Original Investigation

Efficacy and Safety of Locoregional Radiotherapy With Chemotherapy vs Chemotherapy Alone in De Novo Metastatic Nasopharyngeal Carcinoma
A Multicenter Phase 3 Randomized Clinical Trial

Rui You, MD, PhD; You-Ping Liu, MD; Pei-Yu Huang, MD, PhD; Xiong Zou, MD, PhD; Rui Sun, MD, PhD; Yu-Xiang He, MD, PhD; Yi-Shan Wu, MD; Guo-Ping Shen, MD, PhD; Hong-Dan Zhang, MD; Chong-Yang Duan, PhD; Sze Huey Tan, PhD; Jing-Yu Cao, MD; Ji-Bin Li, MD, PhD; Yu-Long Xie, MD; Yi-Nuan Zhang, MD; Zhi-Qiang Wang, MD; Qi Yang, MD, PhD; Mei Lin, MD; Rou Jiang, MD; Meng-Xia Zhang, MD; Yi-Jun Hua, MD, PhD; Lin-Quan Tang, MD, PhD; Ai-Hua Zhuang, MD; Qiu-Yan Chen, MD, PhD; Ling Guo, MD, PhD; Hao-Yuan Mo, MD; Yong Chen, MD; Hai-Qiang Mai, MD, PhD; Li Ling, PhD; Qing Liu, PhD; Melvin Lee Kiang Chua, MBBS, PhD; Ming-Yuan Chen, MD, PhD

JAMA Oncol. 2020;6(9):1345-1352

- MUST HAVE PR or CR to cisplatin and 5-FU to be eligible (173=>126 pts)



68% had at least 3 metastatic lesions

Systemic therapy alone or radiation for responders: issues

- PF is suboptimal. Will benefit hold up for regimens with higher activity? GC, GC plus ICI, TPFlite?
- What about PF nonresponders? Might they benefit more than PF responders?
- WHO ARE THESE PATIENTS? Highly selected oligometastatic or not?

Characteristic	No. (%)	
	Chemotherapy plus radiotherapy (n=63)	Chemotherapy alone (n=63)
Age, median (IQR), y	46.0 (37.0-52.0)	47.0 (39.0-52.0)
Liver metastases		
No	45 (71.4)	44 (69.8)
Yes	18 (28.6)	19 (30.2)
Lung metastases		
No	45 (71.4)	46 (73.0)
Yes	18 (28.6)	17 (27.0)
Treatment response[a]		
Complete	3 (4.8)	4 (6.3)
Partial	60 (90.4)	59 (93.7)
Metastatic lesions[a]		
1-2	19 (30.1)	20 (31.7)
≥3	44 (69.8)	43 (68.3)

nature medicine

ARTICLES

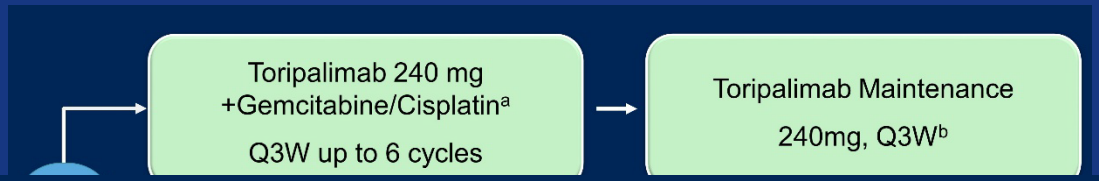
https://doi.org/10.1038/s41591-021-01444-0

Check for updates

Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial

2021 Aug 2. doi: 10.1038/s41591-021-01444-0. Online ahead of print. PMID 34341578.

Toripalimab: a recombinant, humanized IgG4 anti-PD-1 monoclonal antibody approved in China for melanoma, NPC

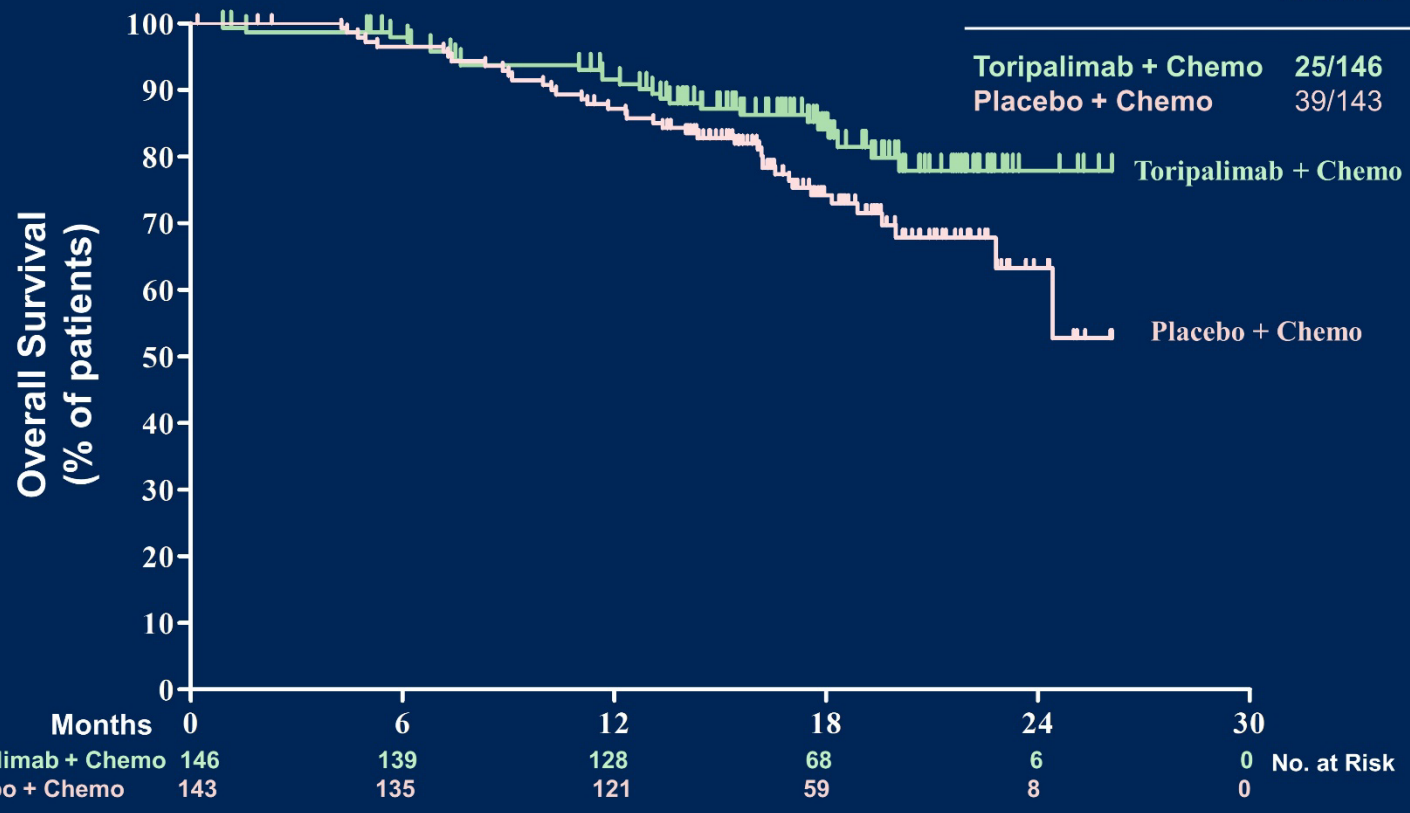


Primary endpoint:

Overall Survival Update

Nine-month OS update after PFS Interim Analysis on Feb 18, 2021

	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate % (95% CI)	2-Yr Overall Survival Rate % (95% CI)
Toripalimab + Chemo	25/146	NE (NE, NE)	91.6 (85.6, 95.1)	77.8 (68.0, 85.0)
Placebo + Chemo	39/143	NE (22.8, NE)	87.1 (80.4, 91.7)	63.3 (49.8, 74.1)



Stratified HR for death,

0.603 (95% CI 0.364-0.997); P=0.0462

2021 ASCO ANNUAL MEETING

CAPTAIN-1ST: CAMRELIZUMAB VERSUS PLACEBO IN COMBINATION WITH GEMCITABINE AND CISPLATIN AS FIRST-LINE TREATMENT FOR RECURRENT OR METASTATIC NASOPHARYNGEAL CARCINOMA: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

Li Zhang, MD

Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China.

June 7, 2021

Camrelizumab: a recombinant, humanized IgG4 anti-PD-1 monoclonal antibody approved in China for Hodgkin lymphoma.

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

Yunpeng Yang, Song Qu*, Jingao Li*, Chaosu Hu*, Mingjun Xu*, Weidong Li*, Ting Zhou*, Liangfang Shen, Hui Wu, Jinyi Lang, Guangyuan Hu, Zhanxiong Luo, Zhichao Fu, Shenhong Qu, Weineng Feng, Xiaozhong Chen, Shaojun Lin, Weimin Zhang, Xiaojiang Li, Yan Sun, Zhixiong Lin, Qin Lin, Feng Lei, Jianting Long, Jinsheng Hong, Xiaoming Huang, Lingzhi Zeng, Peiguo Wang, Xiaohui He, Ben Zhang, Qing Yang, Xiaojing Zhang, Jianjun Zou, Wenfeng Fang†, Li Zhang†*

www.thelancet.com/oncology Published online June 23, 2021

What is missing from this table?

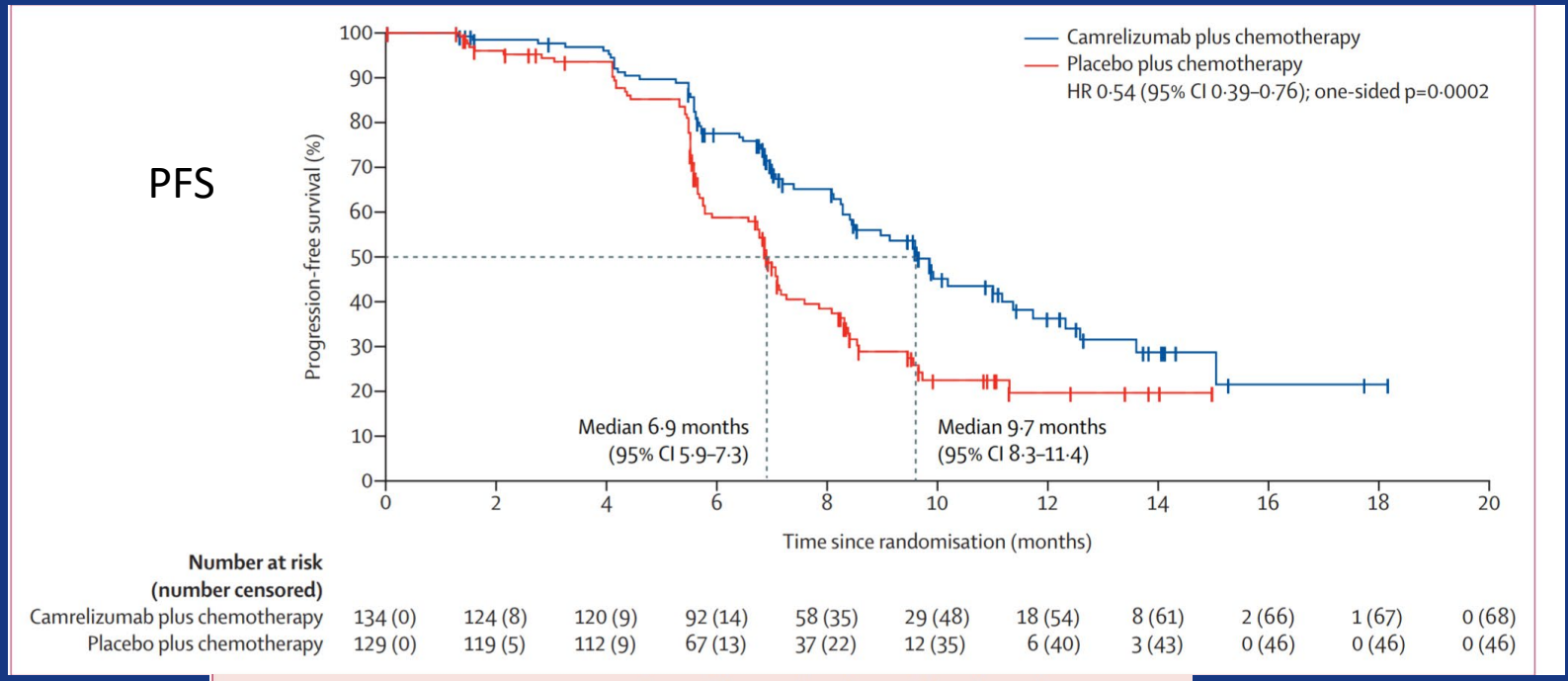
Third, we did not screen patients according to PD-L1 status at baseline, because the majority of patients from the endemic region had PD-L1-positive tumours and the predictive performance of PD-L1 expression in nasopharyngeal carcinoma patients undergoing immunotherapy is inconclusive.

	Camrelizumab plus gemcitabine and cisplatin (n=134)	Placebo plus gemcitabine and cisplatin (n=129)
Age, years		
Median	52 (40–58)	49 (40–56)
<50	59 (44%)	73 (57%)
≥50	75 (56%)	56 (43%)
Sex		
Male	113 (84%)	105 (81%)
Female	21 (16%)	24 (19%)
Ethnicity		
Asian	134 (100%)	129 (100%)
ECOG performance status		
0	47 (35%)	44 (34%)
1	87 (65%)	85 (66%)
Baseline plasma EBV DNA level		
Positive	95 (71%)	86 (67%)
Negative	39 (29%)	43 (33%)
WHO classification		
Keratinising	1 (<1%)	1 (<1%)
Non-keratinising differentiated	21 (16%)	21 (16%)
Non-keratinising undifferentiated	110 (82%)	106 (82%)
Others	2 (1%)	1 (<1%)
Lung metastases		
Yes	66 (49%)	61 (47%)
No	68 (51%)	68 (53%)
Liver metastases		
Yes	70 (52%)	66 (51%)
No	64 (48%)	63 (49%)
Concurrent chemoradiotherapy history		
Yes	86 (64%)	83 (64%)
No	48 (36%)	46 (36%)
Number of metastatic organs		
1	44 (33%)	48 (37%)
2	56 (42%)	42 (33%)
≥3	34 (25%)	39 (30%)
Stage		
Primary metastases	47 (35%)	42 (33%)
Recurrence with distant metastases	87 (65%)	87 (67%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. EBV=Epstein-Barr virus.

Table 1: **Baseline demographics and disease characteristics (full analysis set)**

PFS



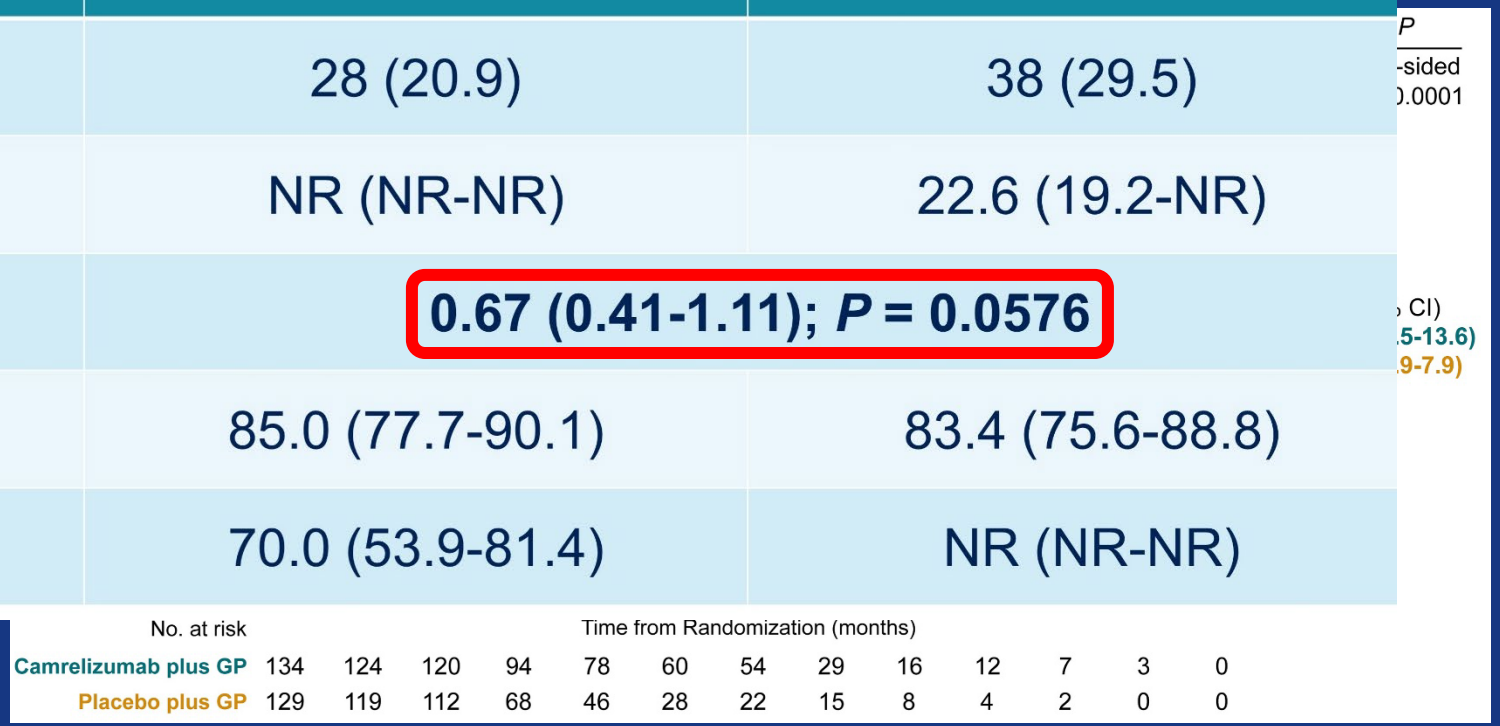
	Camrelizumab plus gemcitabine and cisplatin (n=134)	Placebo plus gemcitabine and cisplatin (n=129)
Best overall response		
Complete response	7 (5%)	4 (3%)
Partial response	110 (82%)	100 (78%)
Stable disease	12 (9%)	18 (14%)
Progressive disease	2 (1%)	4 (3%)
Not assessable	3 (2%)	3 (2%)
Objective response	87·3% (80·5–92·4)	80·6% (72·7–87·1)
Disease control rate	96·3% (91·5–98·8)	94·6% (89·1–97·8)
Duration of response, months	8·5 (6·9–11·1)	5·6 (5·2–6·9)

Camrelizumab (200 mg on day 1)
+ gemcitabine (1000 mg/m² on days 1 and 8)
+ cisplatin (80 mg/m² on day 1)

Camrelizumab (200 mg on day 1)
Q3W until disease progression, unacceptable

Overall Survival

	Camrelizumab plus GP (N = 134)	Placebo plus GP (N = 129)
Events, n (%)	28 (20.9)	38 (29.5)
Median (95% CI), months	NR (NR-NR)	22.6 (19.2-NR)
Hazard ratio (95% CI)	**0.67 (0.41-1.11); *P* = 0.0576**	
12-month rate, % (95% CI)	85.0 (77.7-90.1)	83.4 (75.6-88.8)
24-month rate, % (95% CI)	70.0 (53.9-81.4)	NR (NR-NR)



SCIENCE VIA PRESS RELEASE

Press Releases

BeiGene Announces Positive Topline Results from Phase 3 Trial of Tislelizumab in Combination with Chemotherapy as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Cancer

May 21, 2021 at 7:00 AM EDT

Tislelizumab combined with chemotherapy demonstrated a statistically significant improvement in progression-free survival at the interim analysis

Safety findings of tislelizumab were consistent with known risks

Tislelizumab: a recombinant, humanized IgG4variant anti-PD-1 monoclonal antibody approved in China for Hodgkin lymphoma, NSCLC, Bladder Ca .

"The company intends to share the latest data with health authorities".

primary endpoint:
PFS as assessed by IRC

- RATIONALE 309 is a randomized, double-blind, placebo-controlled Phase 3 clinical trial (NCT03924986) designed to evaluate the efficacy and safety of tislelizumab combined with gemcitabine and cisplatin versus placebo combined with gemcitabine and cisplatin as a first-line treatment for patients with recurrent or metastatic NPC. The trial's primary endpoint is PFS as assessed by IRC in the ITT population. A total of 263 Asian patients were enrolled …
- Several emails to Beigene to learn more, no response yet. ben.yong@beigene.com

Should anti- PD-1 moabs with GC be the SOC now in NPC?

- ASCO discussant , Anthony Chan, says no.
- None if these drugs are available in the US.
- Are pembrolizumab or nivolumab or other ICIs an appropriate substitution?
- NRG HN007 ceased enrollment to its NPC trial of GC+/- nivolumab
- What will I do with the next NPC patient with R/M disease?

Are the USA and EU relegated to the back seat in new treatments for NPC? Where are new SOC being defined?

- Lobaplatin as substitute for cisplatin
- New adjuvant approaches following chemoradiation
- Immune checkpoint therapy for R/M NPC

17th Annual California Cancer Consortium Conference August 20-22, 2021

END