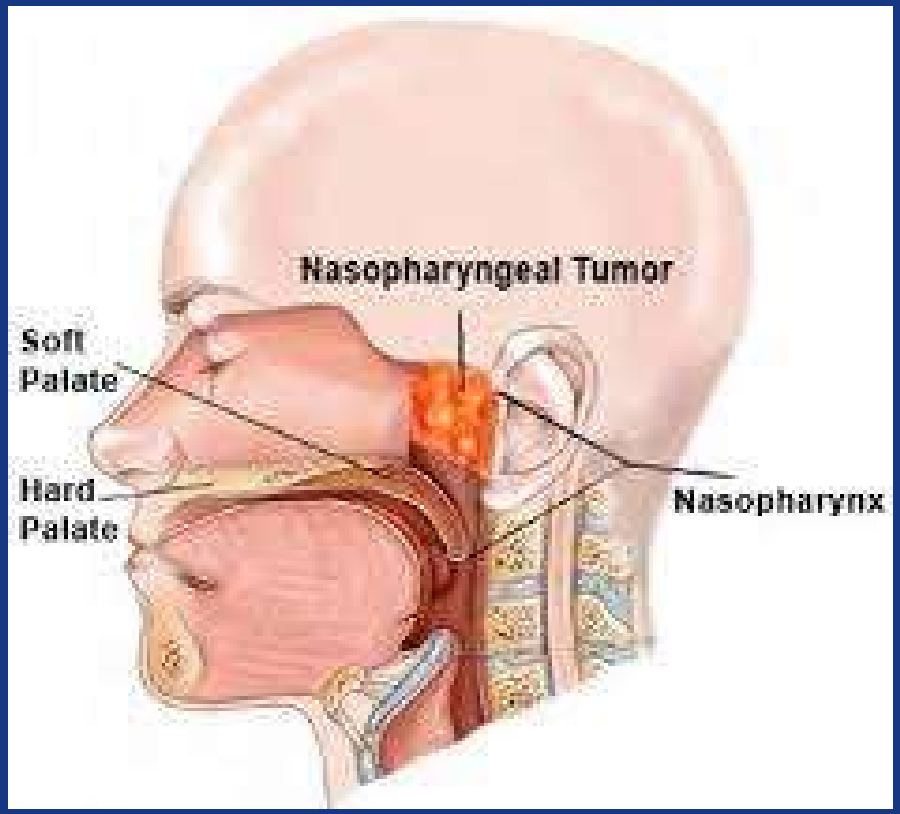
Nasopharyngeal carcinoma ("NPC") 2019

A. Dimitrios Colevas MD

Stanford Cancer Institute

Nasopharynx: the space behind your nasal passages and above your throat



A brief history of systemic treatment for NPC

1978

Otolaryngology. 1978 Sep-Oct;86(5):ORL-780-3.

Cis-platinum chemotherapy in head and neck cancers.

Jacobs C, Bertino JR, Goffinet DR, Fee WE, Goode RL.

" Cis- platinum… was effective in reducing tumor bulk in 75% of the patients [with head and neck cancers] "

1988

Am J Clin Oncol. 1988 Aug;11(4):427-30.

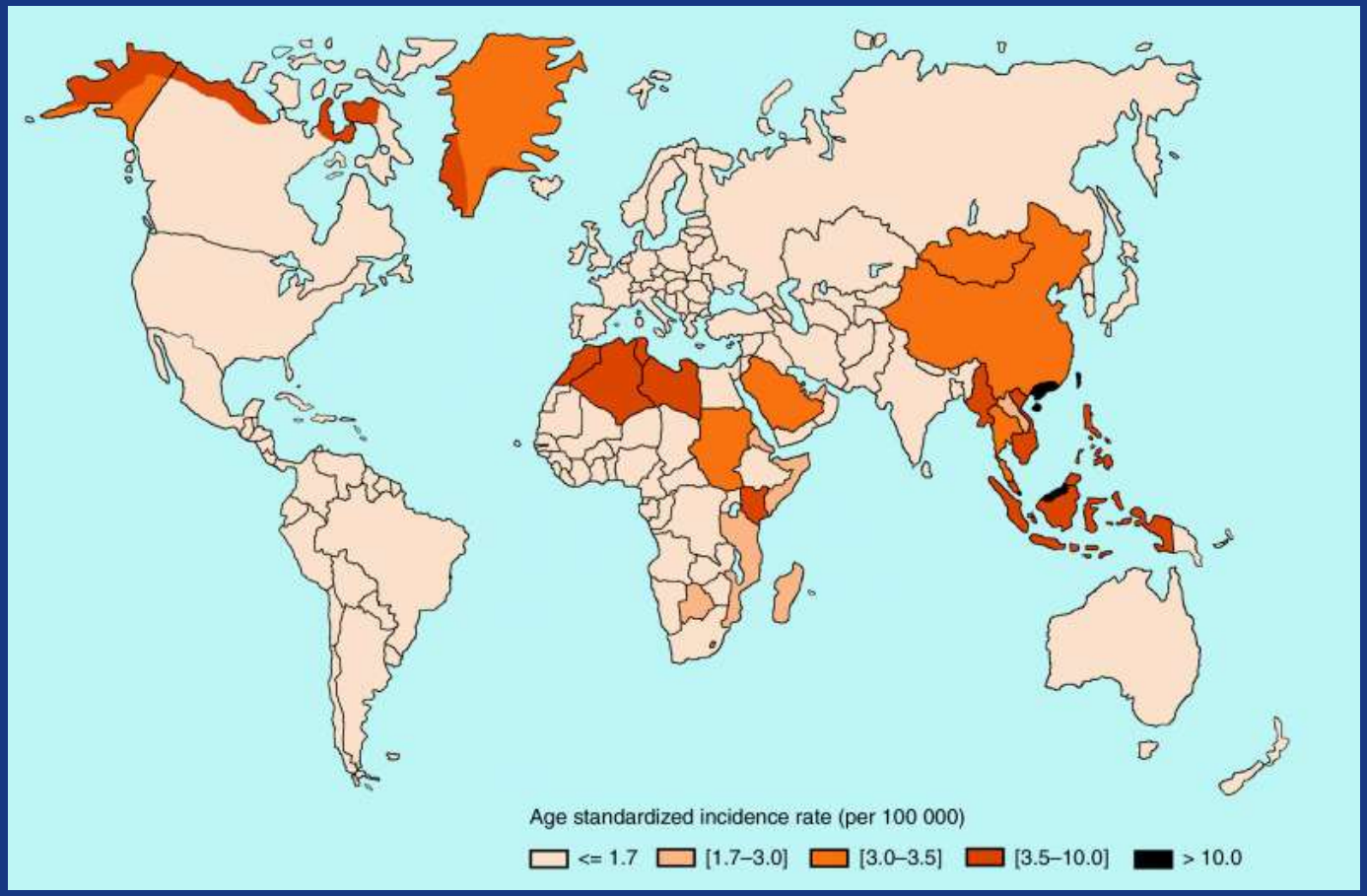
Excellent response to cis-platinum-based chemotherapy in patients with recurrent or previously untreated advanced nasopharyngeal carcinoma.

Al-Kourainy K[1], Crissman J, Ensley J, Kish J, Kelly J, Al-Sarraf M.

⊕ **Author information**

" An overall response of 75 % and a complete response of 50% were achieved by induction chemotherapy [mostly CDDP + 5FU]…Four patients were treated with concurrent cis- platinum and radiation therapy… response of 100%..."

Who gets NPC?


Age standardized incidence rate (per 100 000)
<= 1.7
[1.7–3.0]
[3.0–3.5]
[3.5–10.0]
> 10.0

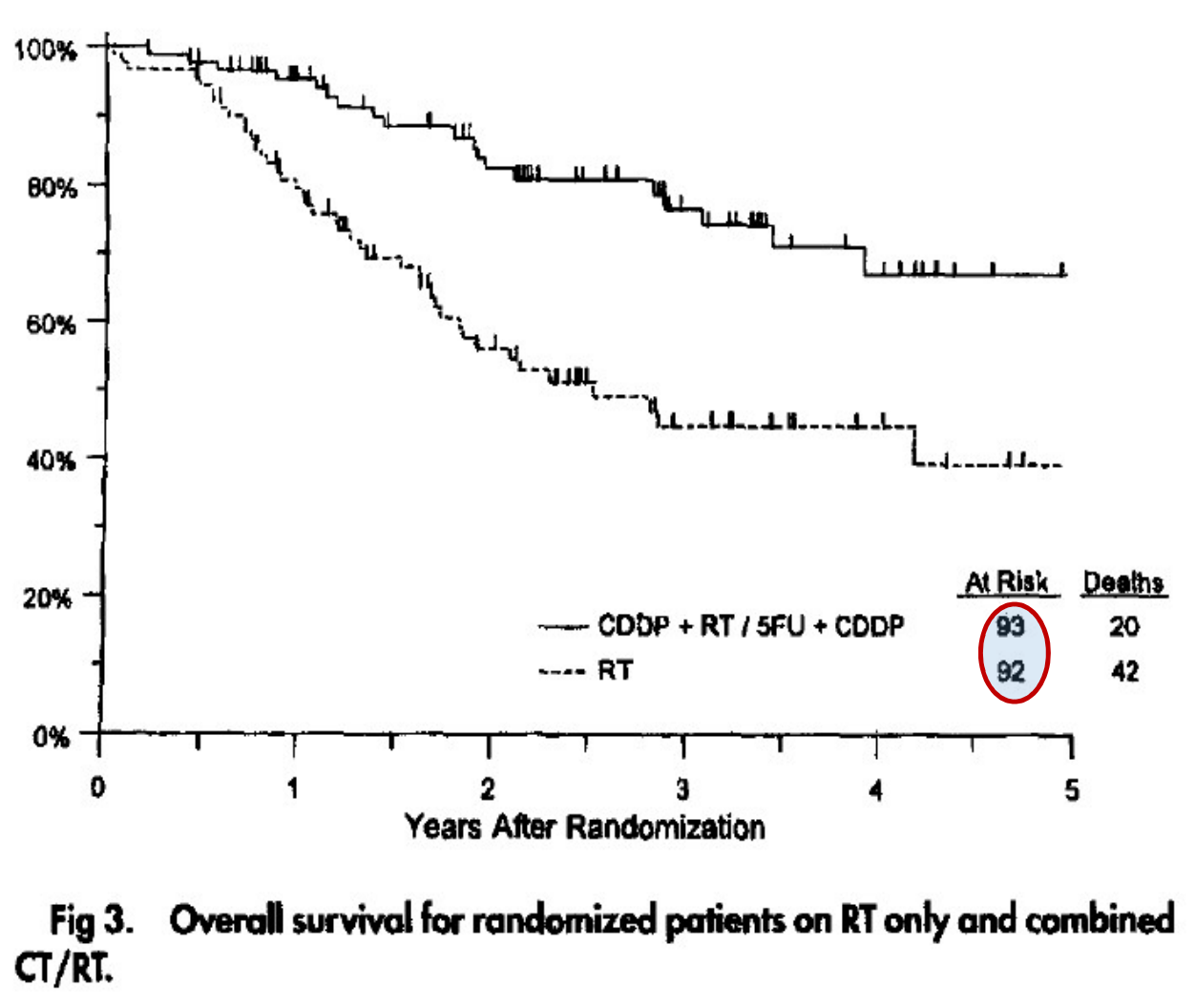


Fig 3. Overall survival for randomized patients on RT only and combined CT/RT.

The most often cited trial in the US
Al- Sarraf et al. INT-0099

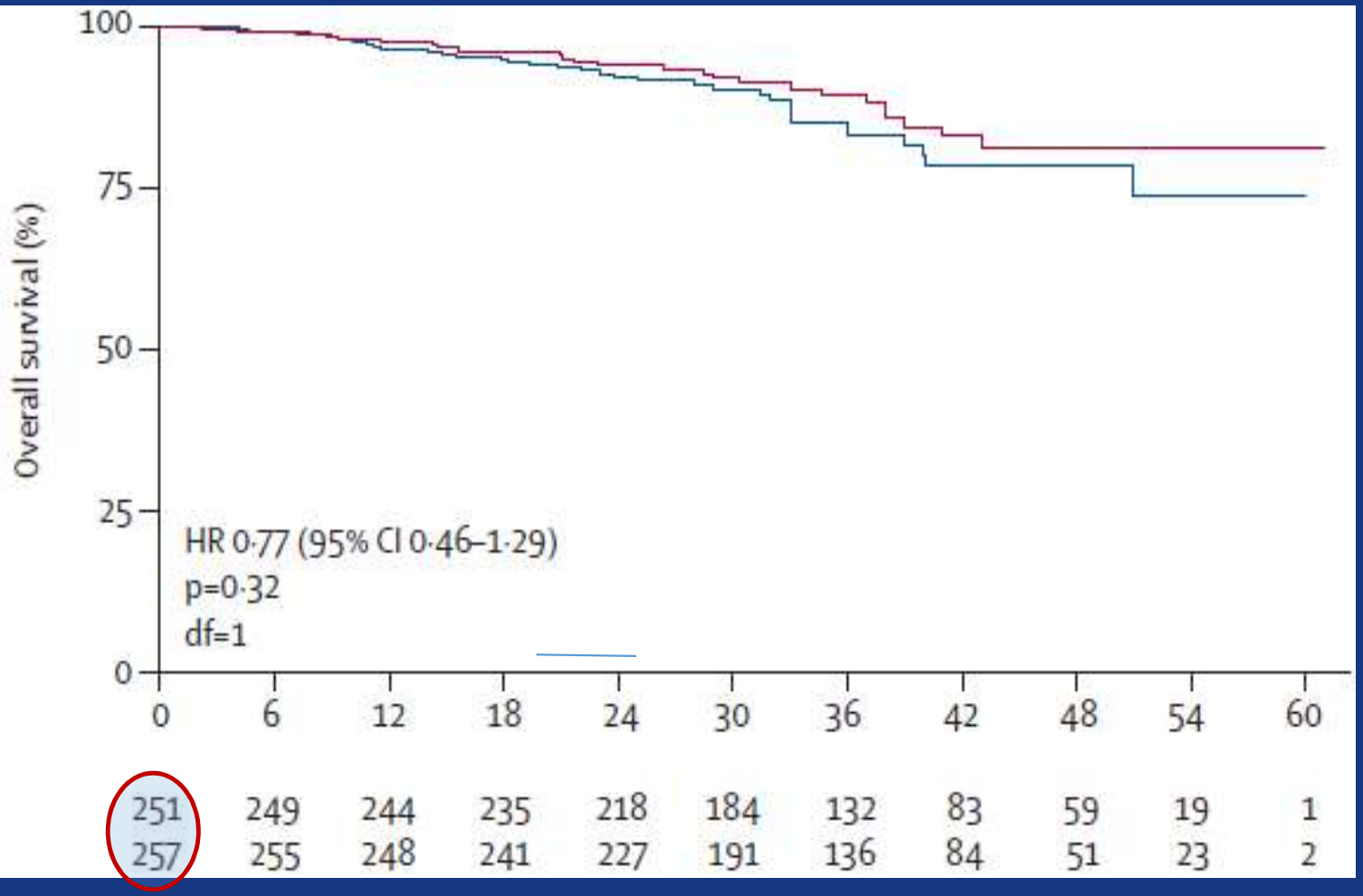
XRT

versus

CDDP (100 mg/m2x3) +XRT

=> PF x 3

Al-Sarraf et al. JCO1998;16:1310-7.



Overall survival .
Chen et al .
CDDP+XRT +/- PF

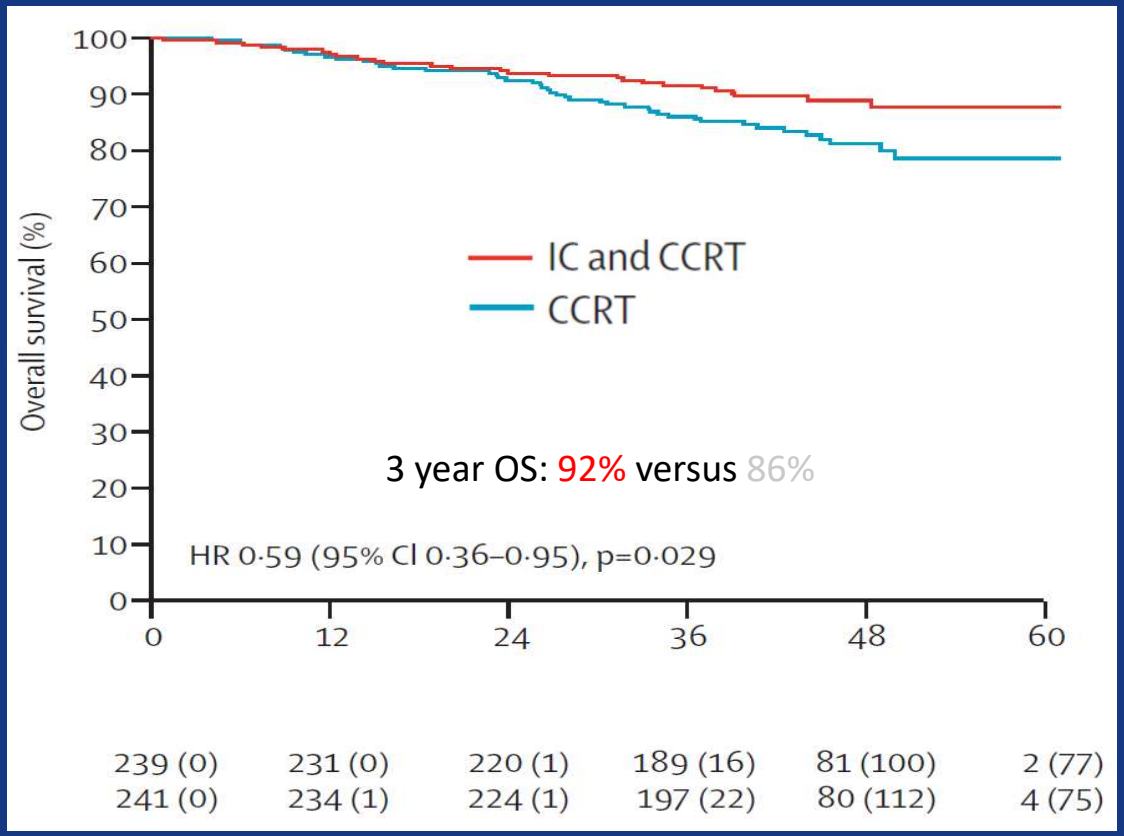
CDDP weekly + XRT

versus

CDDP weekly + XRT => PFx3

Chen et al. Lancet Oncol 2012;13:163-71.

Concurrent : CDDP 40mg/m2 weekly x 7. Adjuvant: CDDP 80 mg/m2 + 5-FU 4 g/m2 q 28d x 3



Induction chemotherapy plus concurrent CDDPXRT versus concurrent CDDPXRT alone in locoregionally advanced NPC: a phase 3 RCT.
TPF "lite"

TPF "lite"=
CDDP 60 mg/m2
docetaxel 60 mg/m2
5- FU 600 mg/m2/d d1-5 IVCI

CDDPXRT= CDDP 100 mg/m2 q 21 x 3

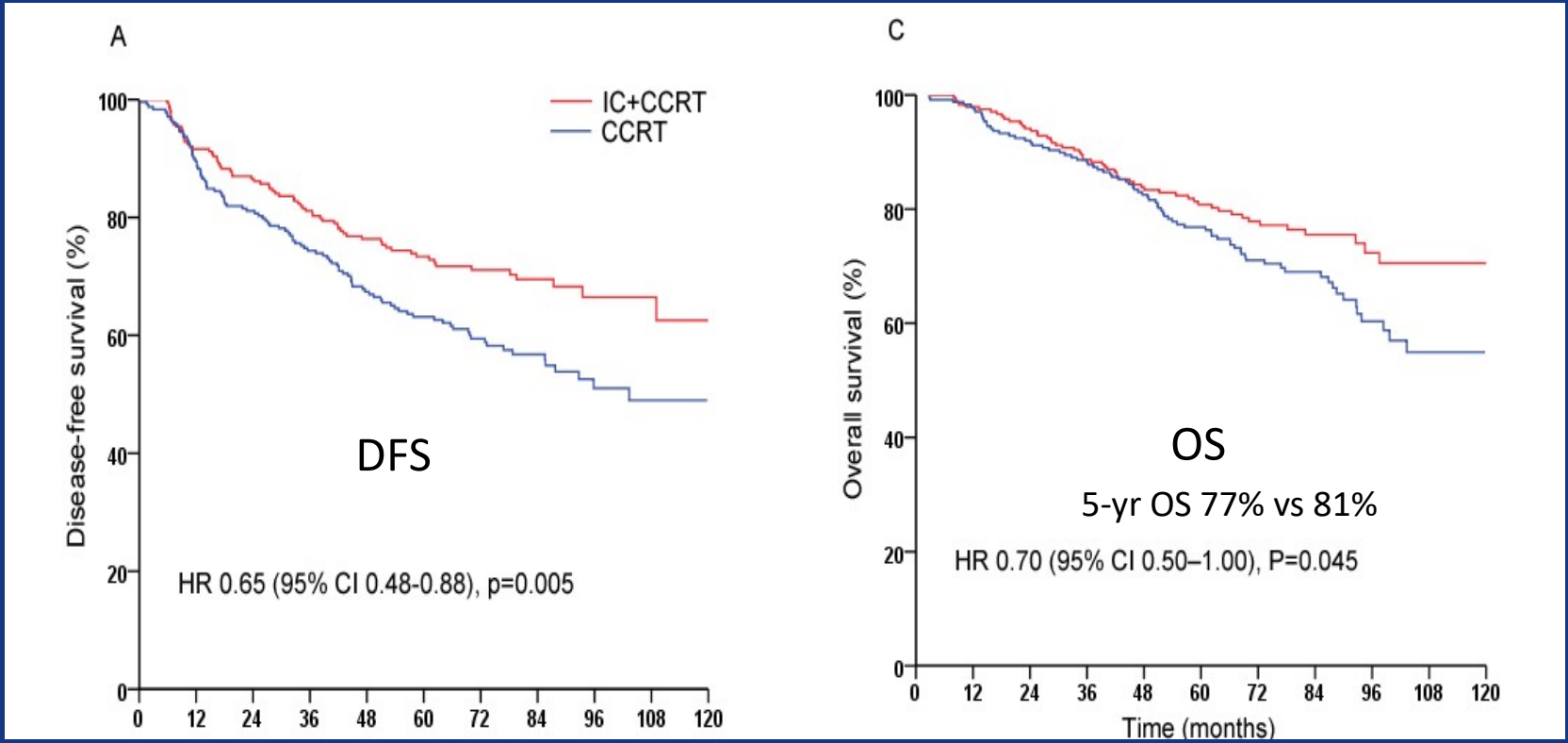
Sun et al. Lancet Oncol.
2016 Nov;17(11):1509-1520

So.. What is new in 2019 in NPC treatment?

Chen et al. , ASCO 2019 Abst 6004 :

PF > CDDPXRT versus CDDPXRT in LRA NPC, 476 pts. long term results

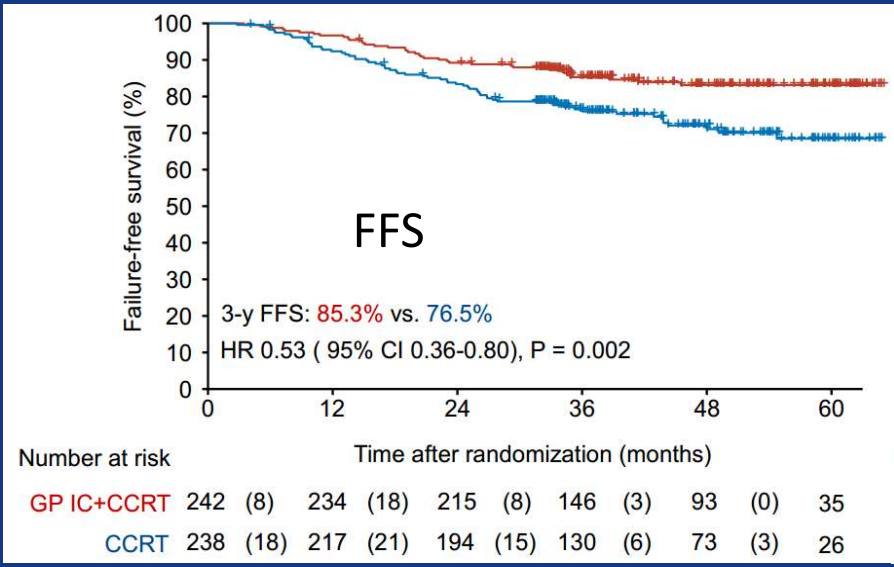
update:

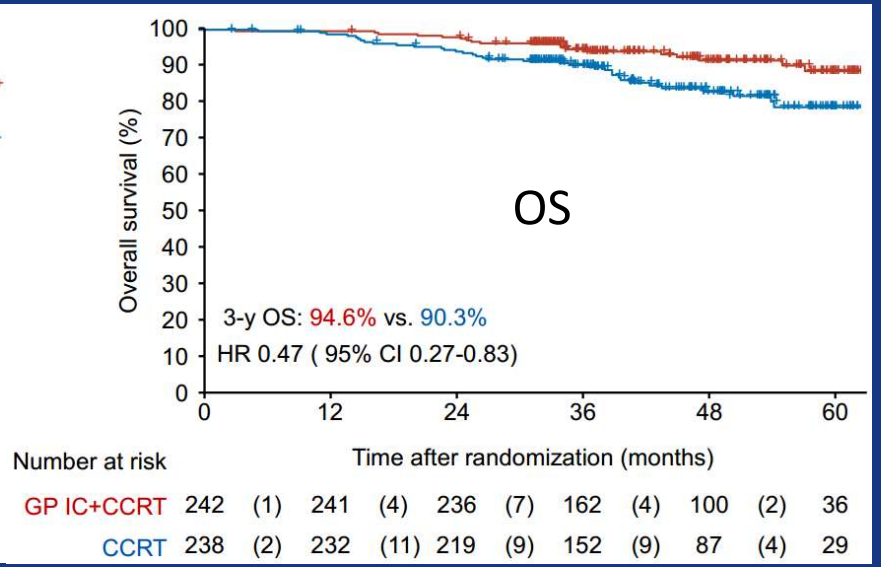


" PF" = CDDP 80 + 5FU 800x5, two cycles

"CDDPXRT" = CDDP 80 x 3 + XRT, 2DRT or IMRT

Ma et al. , ASCO 2019 Abst 6003:
GP > CDDPXRT versus CDDPXRT in NPC.
Primary endpoint FFS , secondary incl. OS



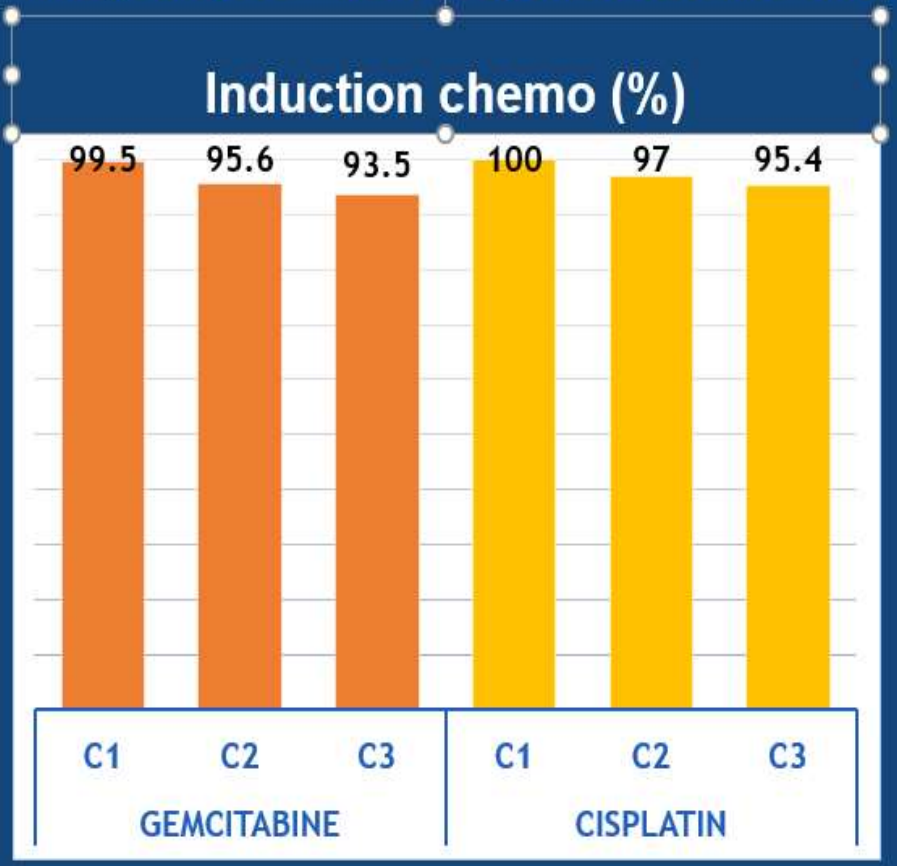


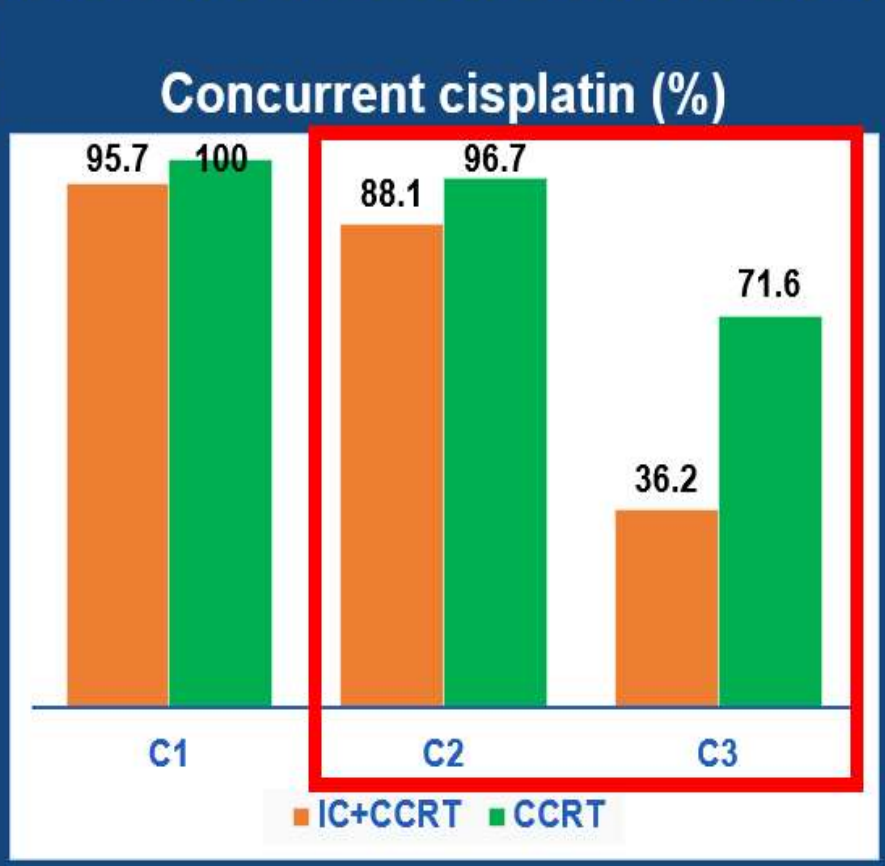
GP IC, q3w 3 cycles
- **Gemcitabine 1g/m^2, d1 & 8**
- **DDP 80mg/m^2 , d1**

CCRT
- **DDP 100mg/m^2 q3w 3 cycles**
- **IMRT 68-70Gy in 30-33fr over 6.5w**

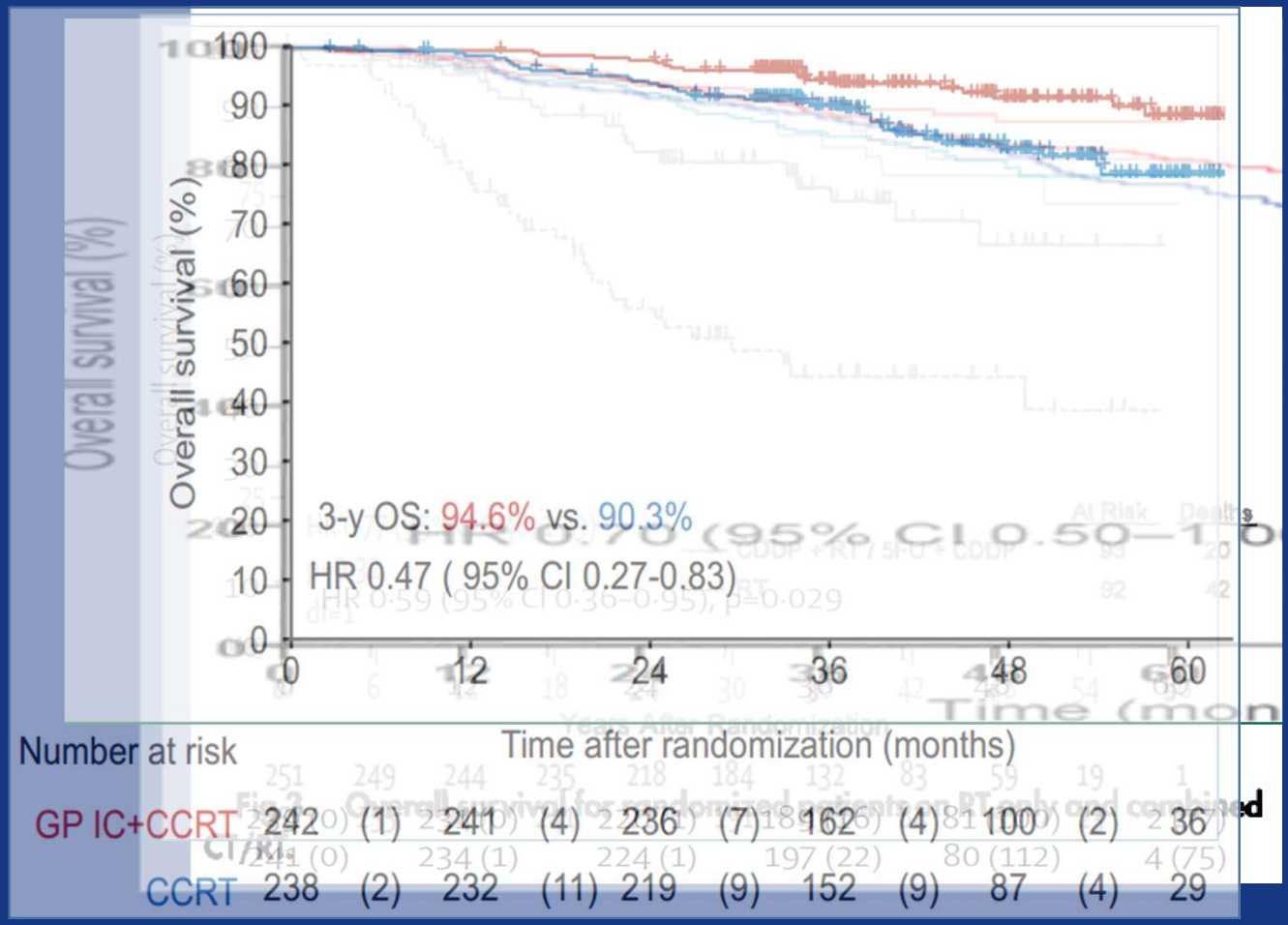
Compliance: mean relative dose intensity

Majority of the experimental arm received 2# of concurrent CDDP





Evolution



INT 0099

ADJ 2012

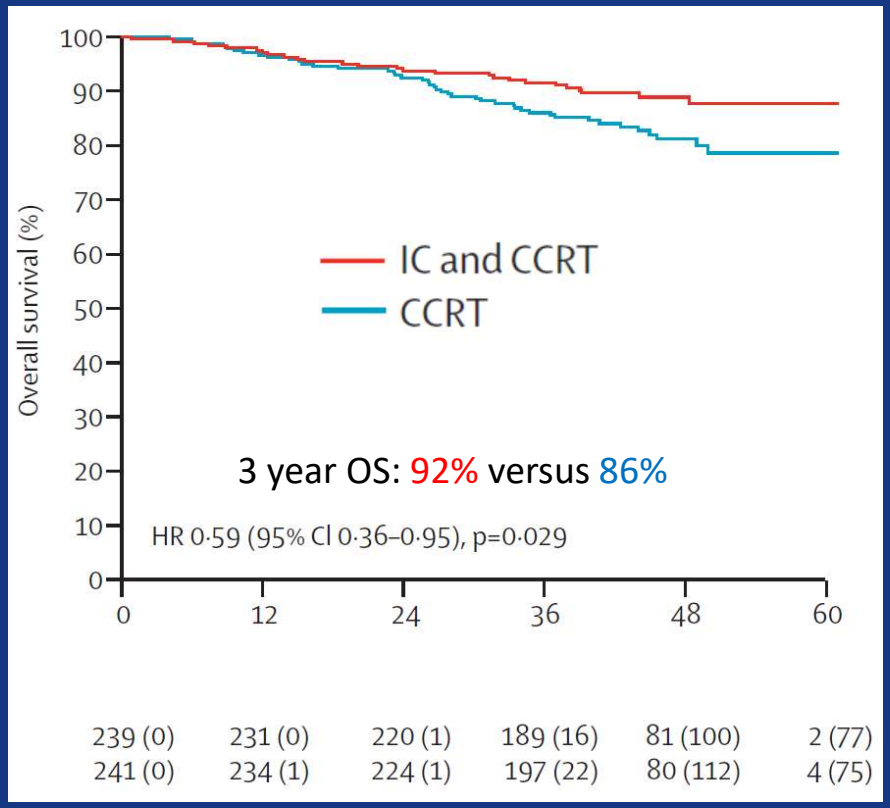
TPC 2016

PF 2018

GC 2019

What are we doing about NPC? LOTS!

Standard treatment cures many but not all patients.

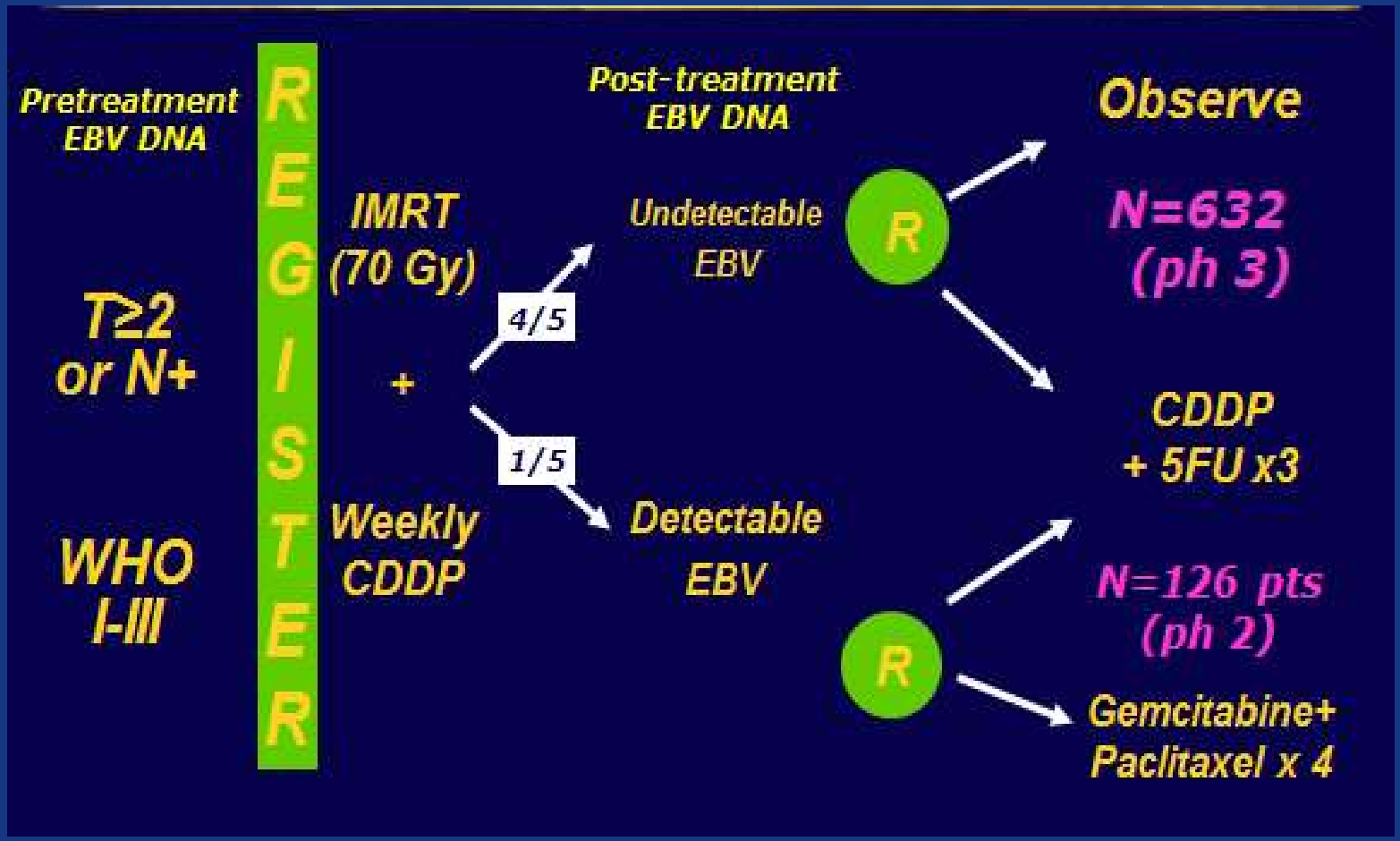


What we can expect with sequential chemoRT in 2019: TPF lite as an example. Sun et al. Lancet Oncol. 2016 Nov;17(11):1509-1520

NCCN National Comprehensive Cancer Network®

Clinical trials (preferred)
or
Concurrent systemic therapy/RT[f,g]
followed by adjuvant chemotherapy[f]
or
Induction chemotherapy[g,h] followed by chemo/RT[f,g]
or
Concurrent systemic therapy/RT[f,g] not followed by adjuvant chemotherapy

Patient- specific customized treatment : EBV DNA in blood as biomarker



NRG HN001 clinical trial

That's it?
In 2019 the best you have is conventional chemotherapy?

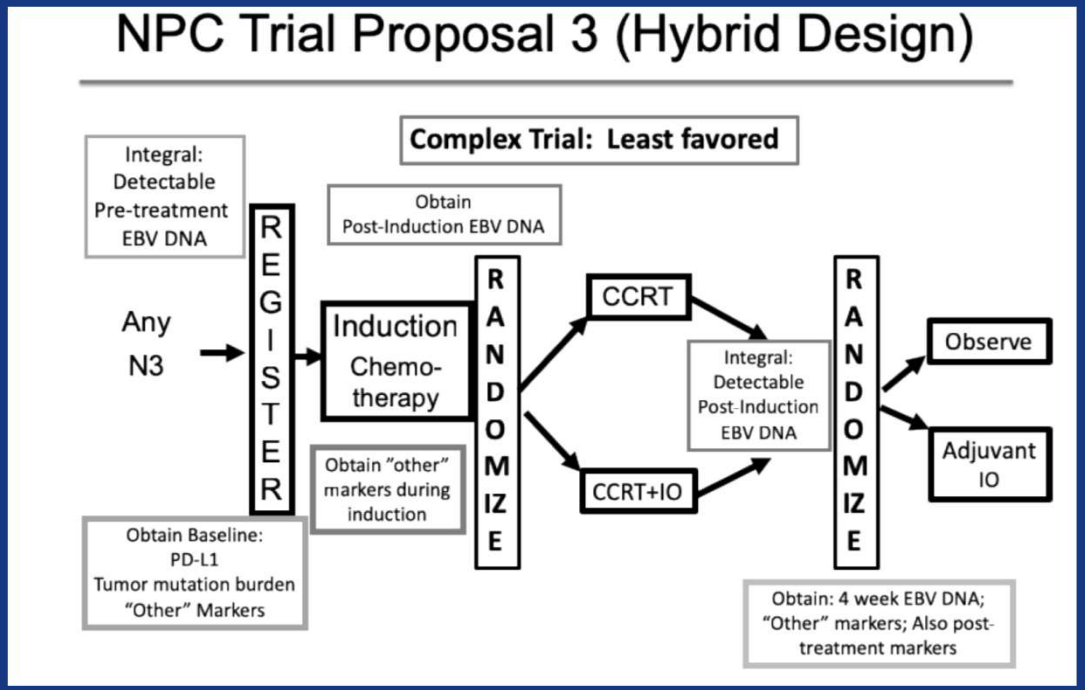
- When are we going to explore frontiers beyond cytotoxics?

  FDA approval dates:

5-Fluorouracil	**1962**
cisplatin	**1978**
paclitaxel	**1992**
gemcitabine	**1996**

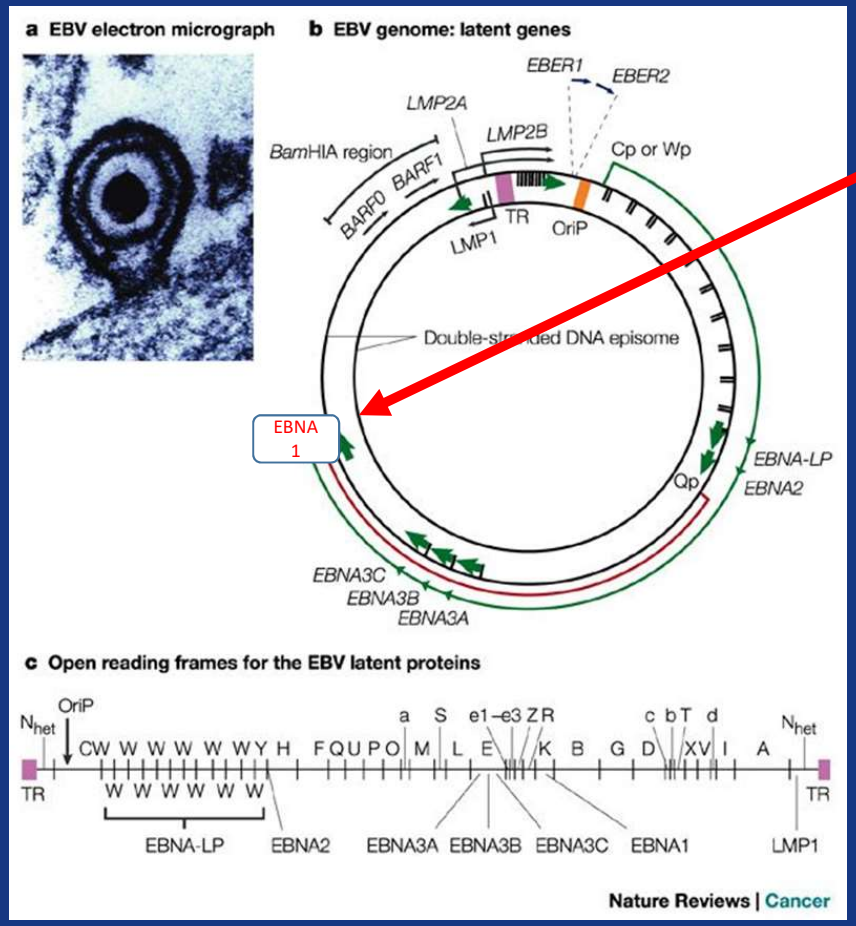
Immunotherapy for curable NPC: The present wave of trials:

- Open ChemoRT trials with PD-l1 or PD-1 directed MOABS
  - UCSF, SYSU, Taiwan
- NCI Clinical trials planning meeting in NPC:



J Natl Cancer Inst. 2019 Mar 26.
PMID: 30912808

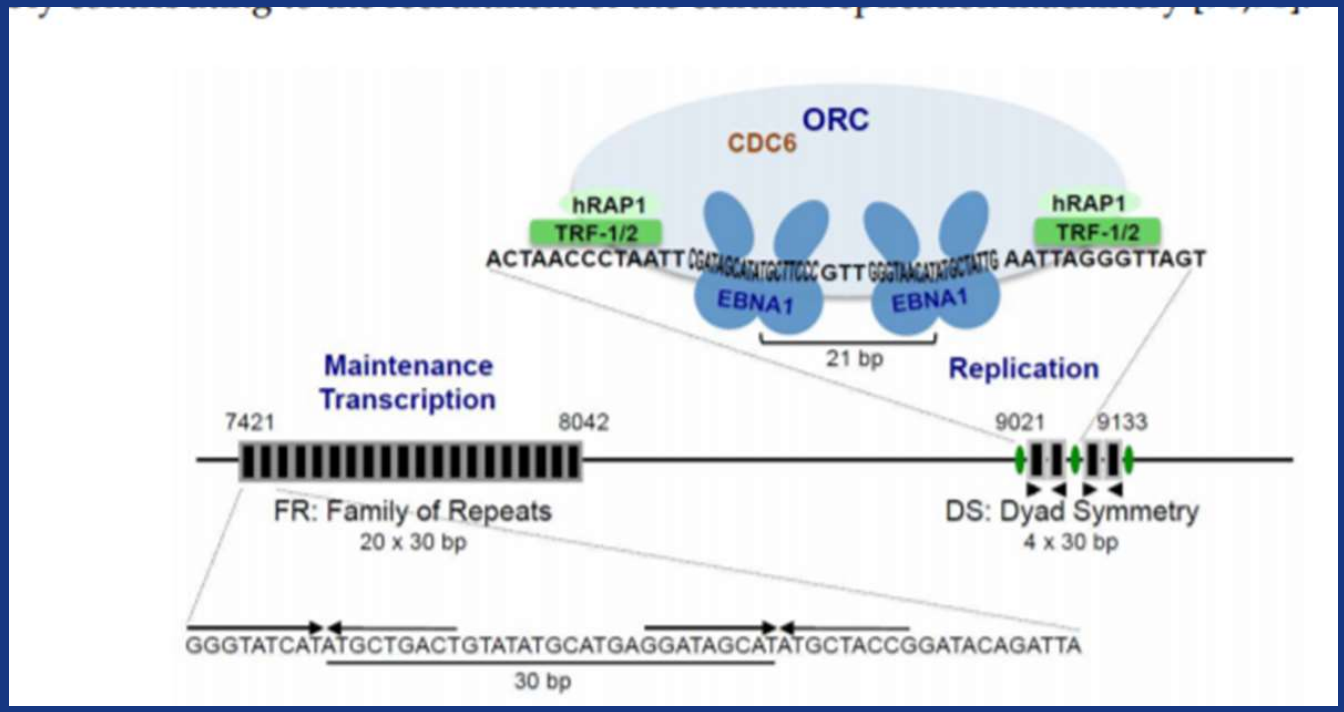
What causes NPC?
Epstein- Barr Virus (“EBV”)



EBNA1 functions relevant to cancer:

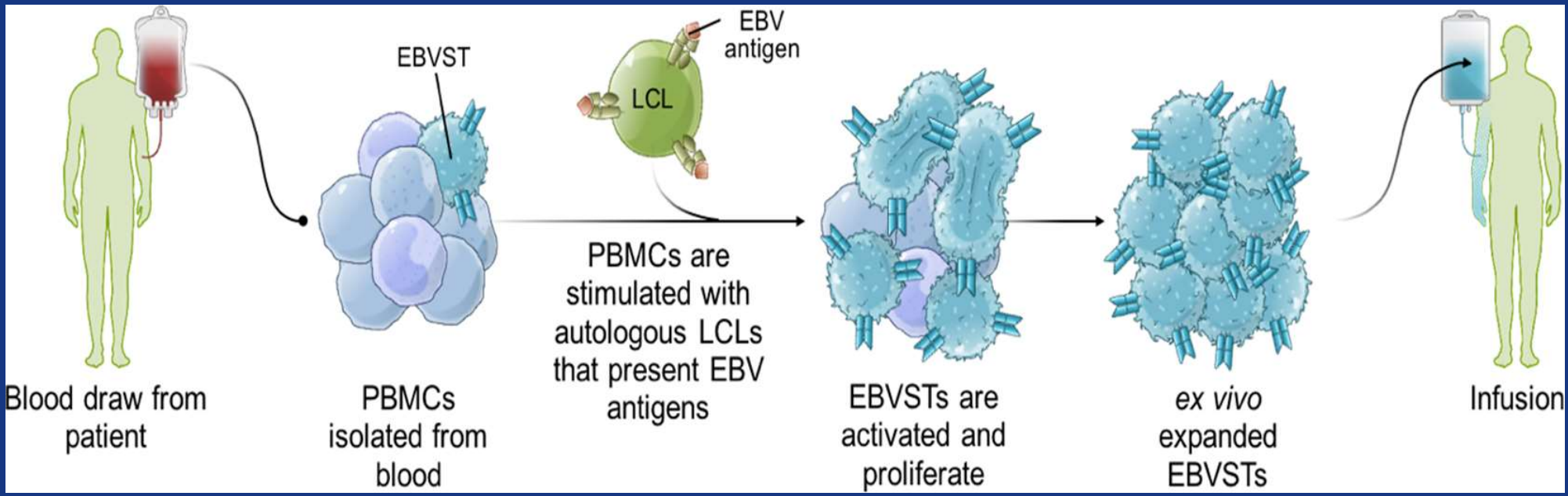
- Viral gene expression regulation
- Extrachromosomal replication
- Maintenance of EBV episomal genome
- CONSISTENTLY expressed in NPC

New options for NPC patients at Stanford: target the EBV virus machinery, “EBNA1”



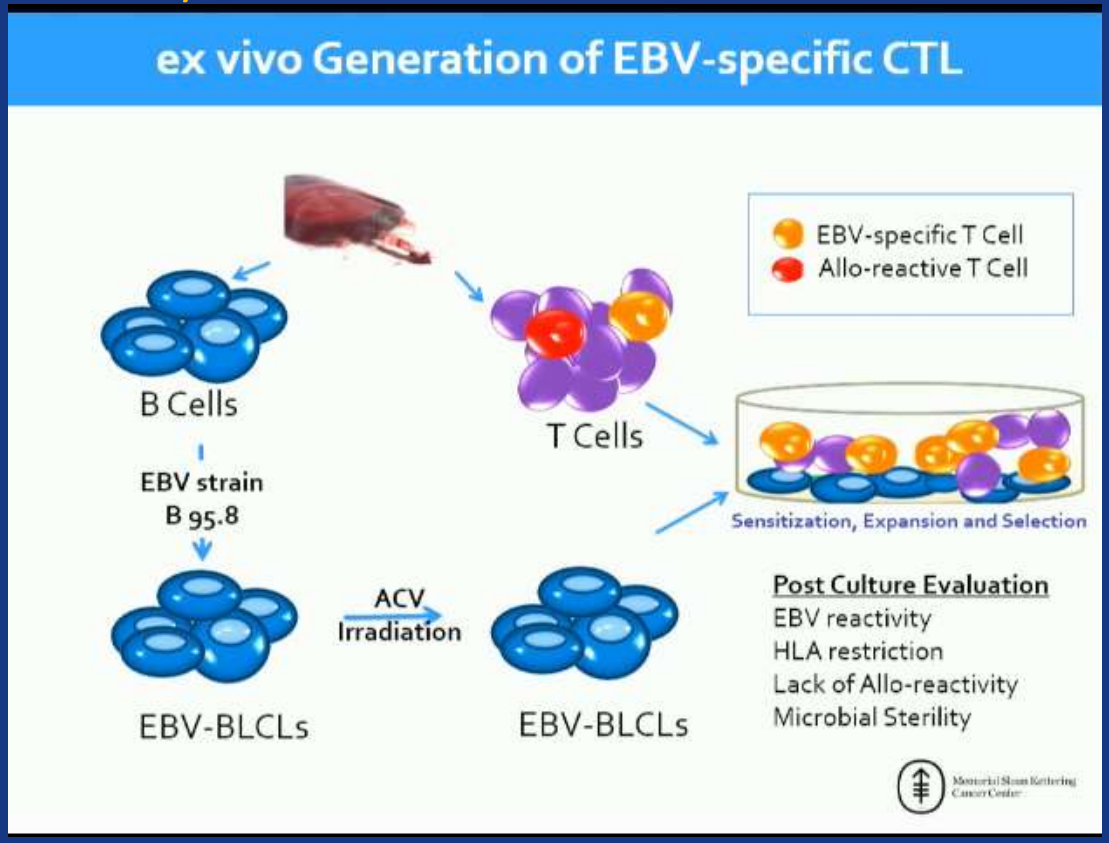
VK 2019, an EBNA1 specific inhibitor drug

New options for NPC patients at Stanford:
Stimulate a patient's immune cells to attack EBV containing cancer cells. " Auto-"



Tessa clinical trial

New options for NPC patients at Stanford:
Treatment of EBV+ nasopharyngeal carcinoma with banked EBV-specific cytotoxic T cells "OFF THE SHELF "Allo-"



Atara clinical trial

Wrap up for NPC

- There are many CURATIVE options for patients with locoregionally advanced NPC
- Treatments are evolving and blood EBV DNA may be biomarker.
- Hope of replacing standard chemoRT approaches include:
  - Novel targeting of EBV machinery, such as EBNA1 inhibitors
  - " ALLO" T cell immunotherapy , EBV specific
  - " AUTO" T cell immunotherapy, EBV specific

How treatment options for recurrent / metastatic SCCHN have changed on 2019

- Results from immunotherapy and immunochemotherapy trials
- Alternatives to EXTREME
- Virally targeted strategies beyond NPC

SOC for R/M SCCHN at the dawn of 2019:

First line: EXT

(NEJM 2008;359:1116-27)

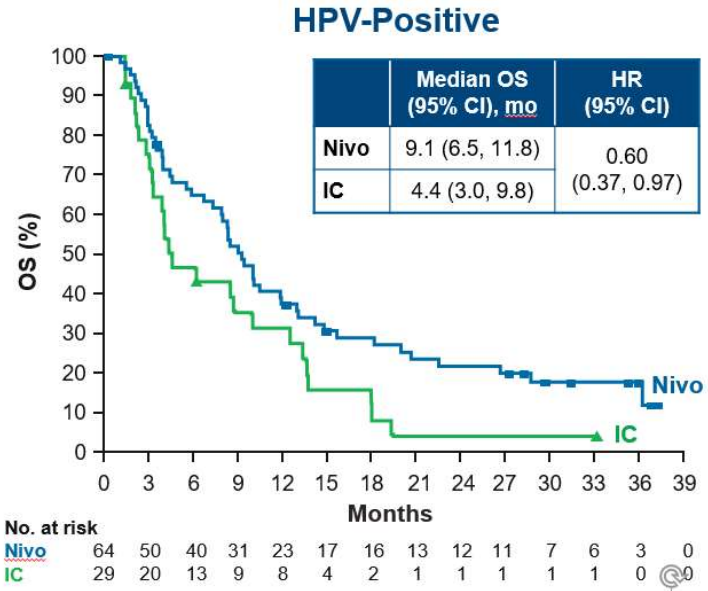
Second line:

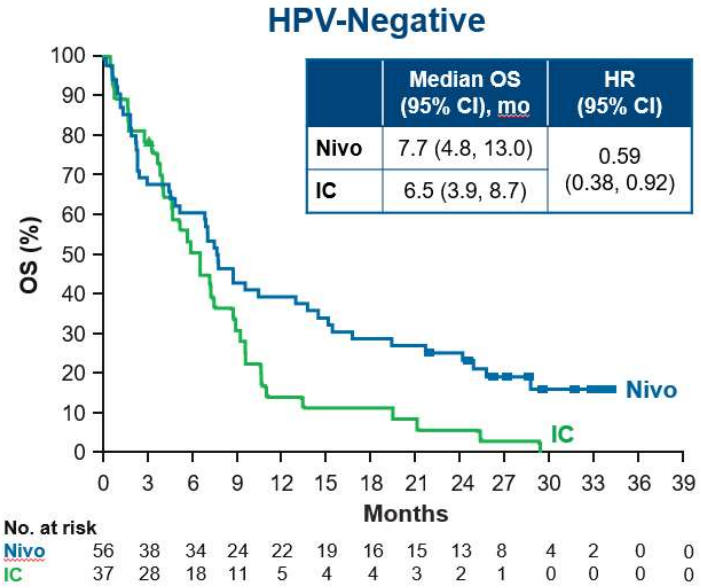
Nivolumab

(NEJM 2016;375:1856-1867)

OS by HPV Status[a]

- Nivolumab demonstrated survival benefit in patients with HPV-positive and HPV-negative tumors, with comparable HRs for risk of death vs IC

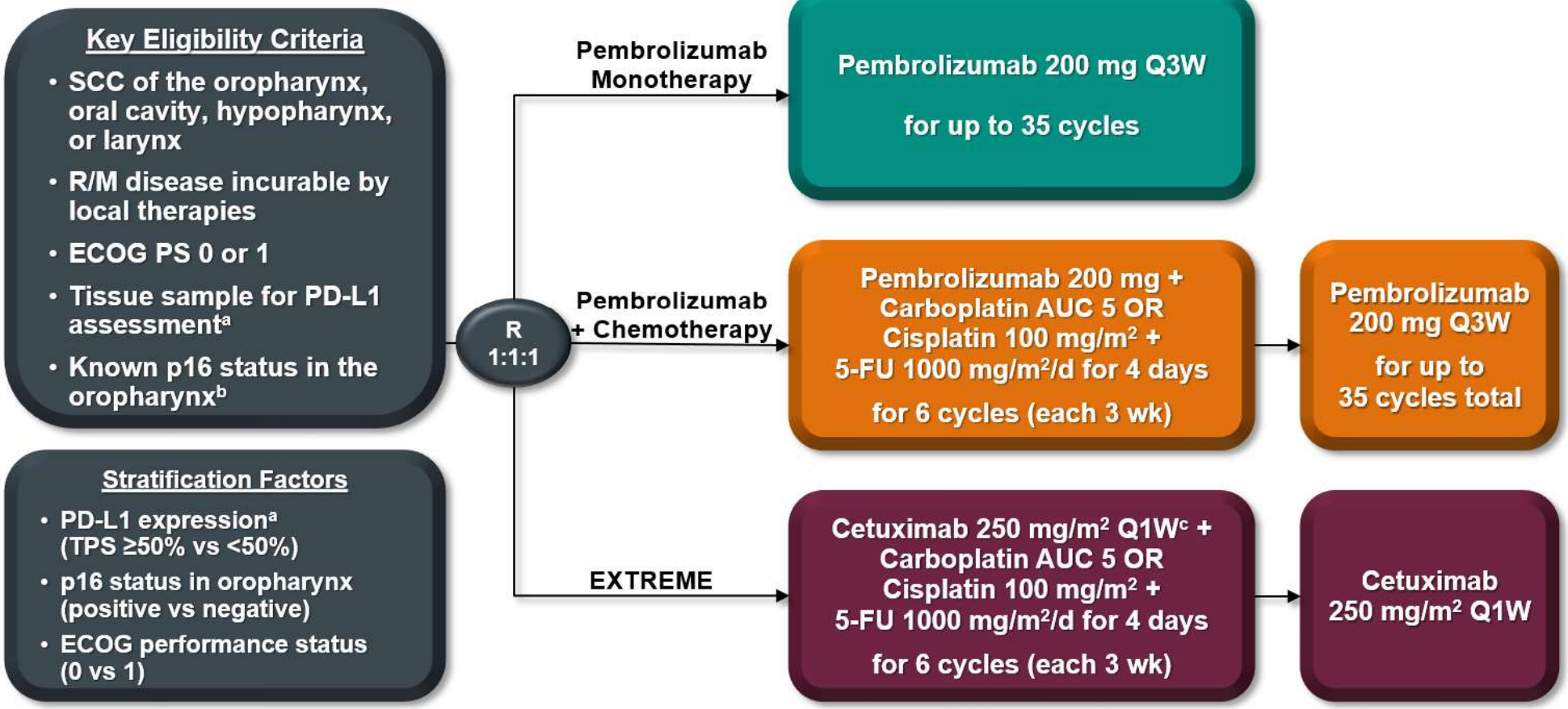




[a]HPV testing was required only for patients with OPC; symbols represent censored observations FROM: Ferris et al. AACR annual meeting 2018

Big Splash in R/M SCCHN, ASCO 2019:

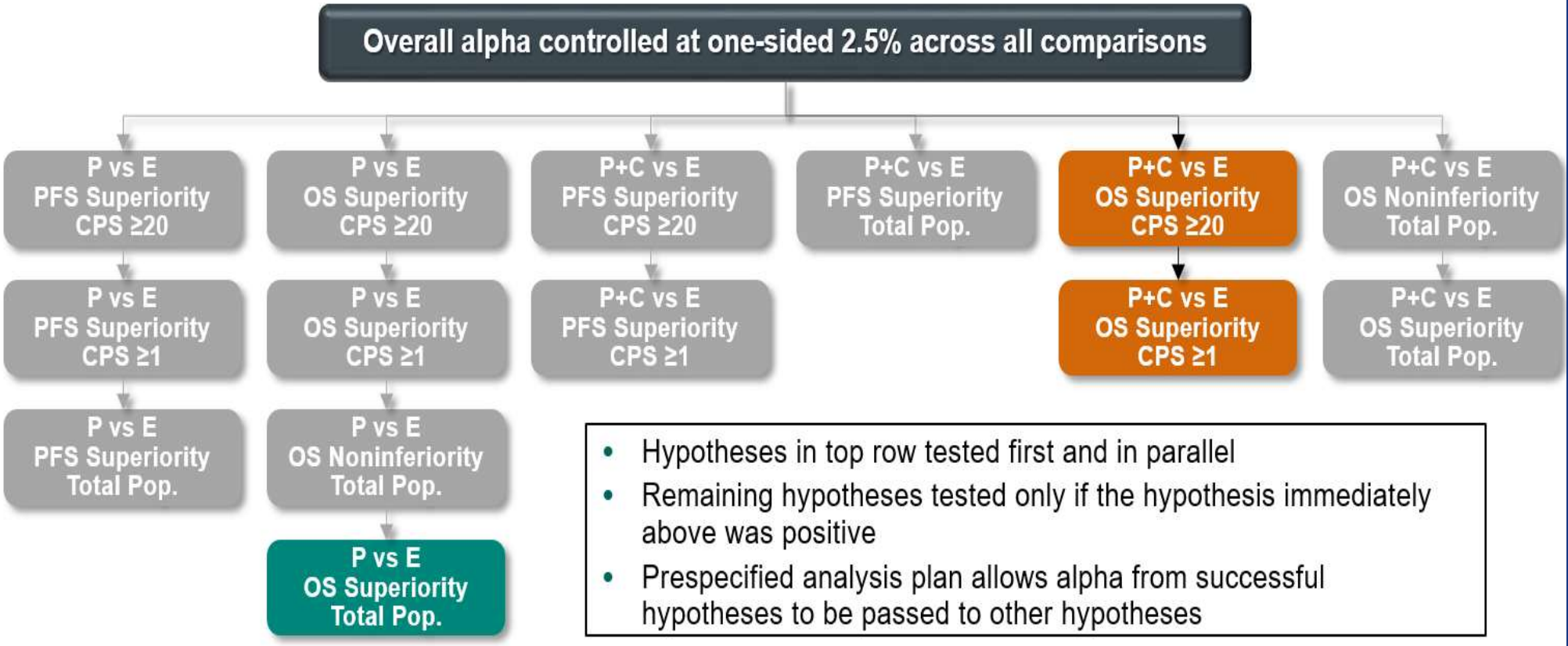
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.

Why is this not yet published? My guess ITEM 1:

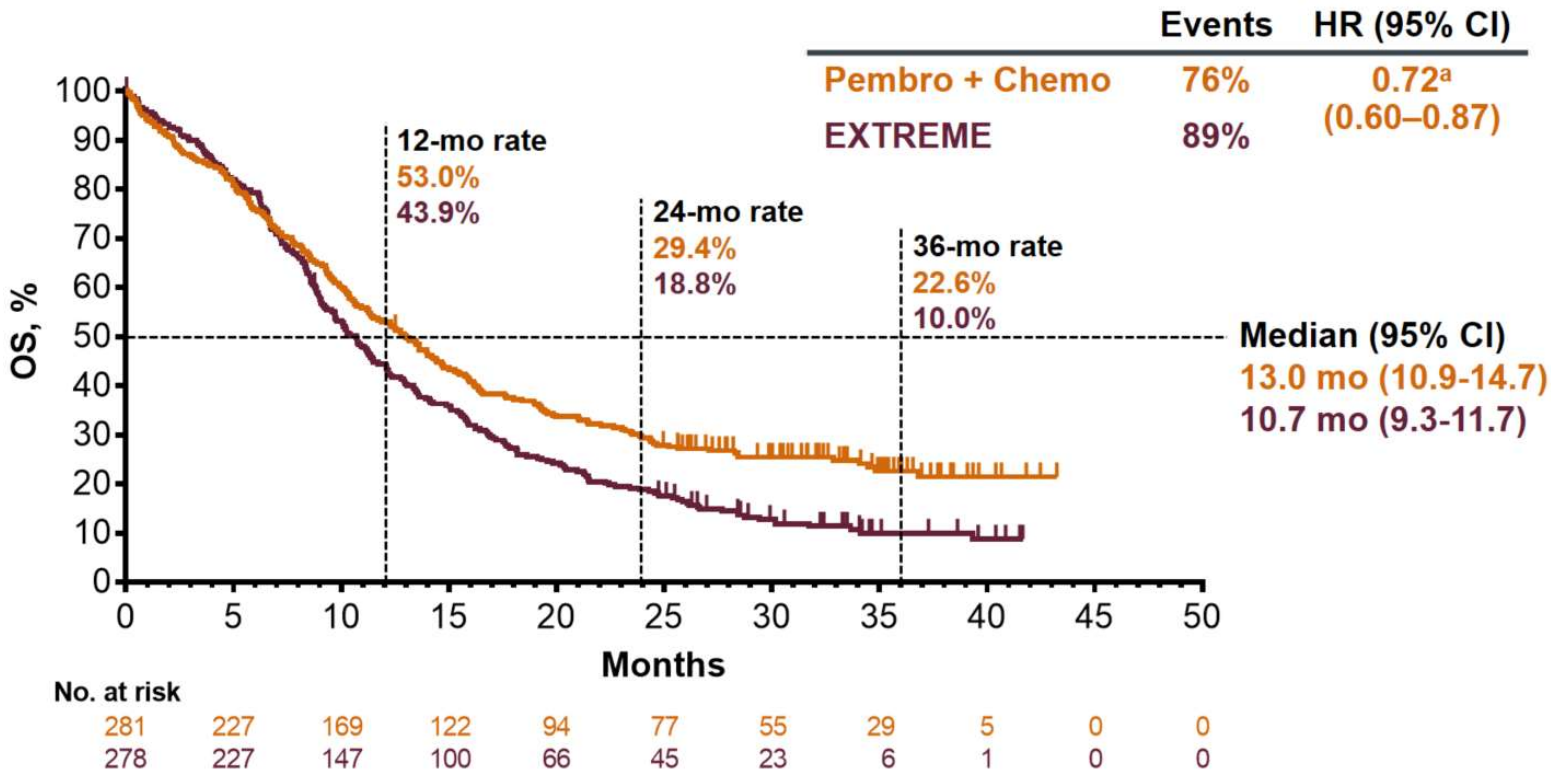
Statistical Considerations



- Hypotheses in top row tested first and in parallel
- Remaining hypotheses tested only if the hypothesis immediately above was positive
- Prespecified analysis plan allows alpha from successful hypotheses to be passed to other hypotheses

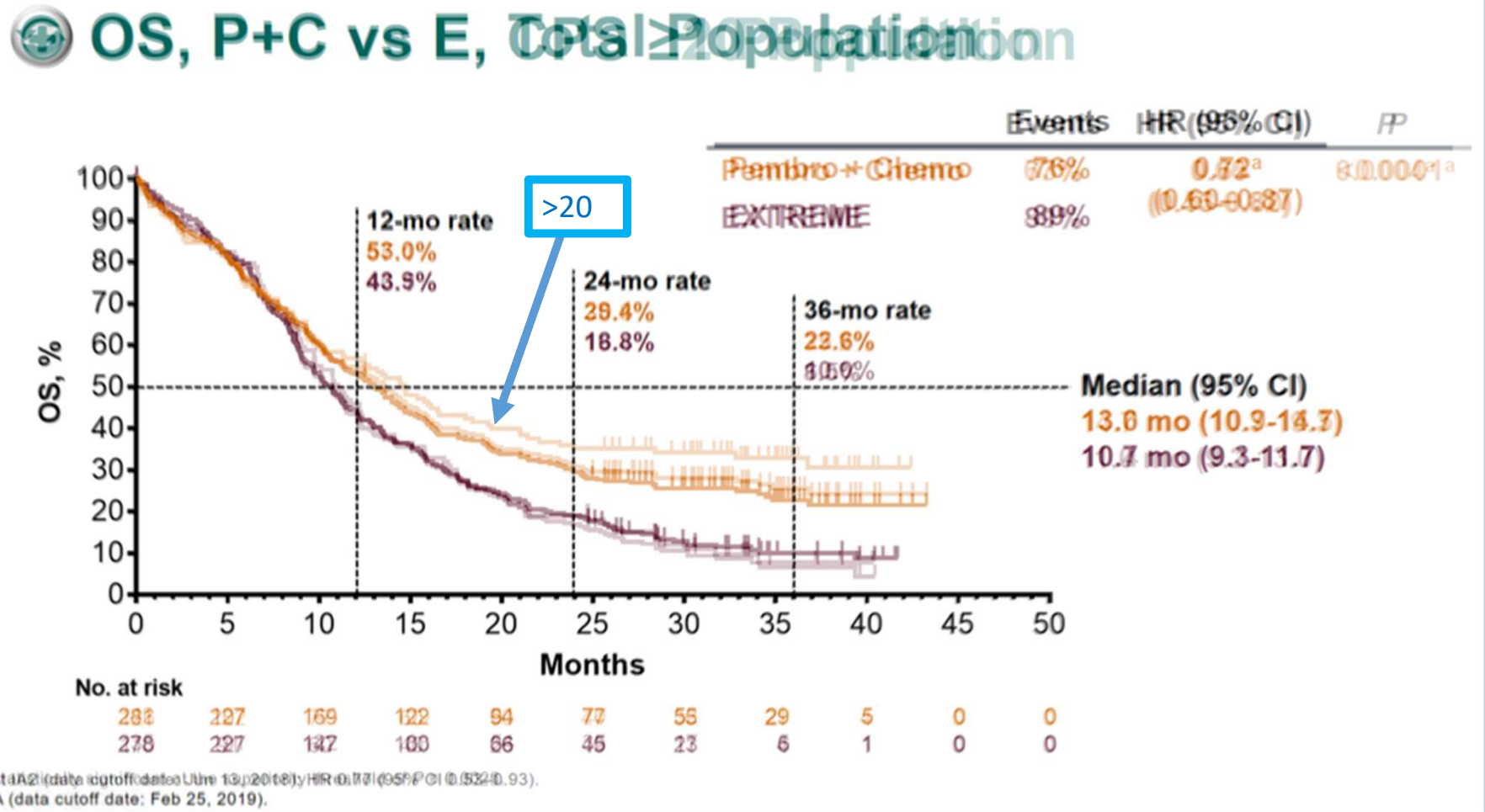
Pembro plus chemo vs EXTREME: OS

OS, P+C vs E, Total Population



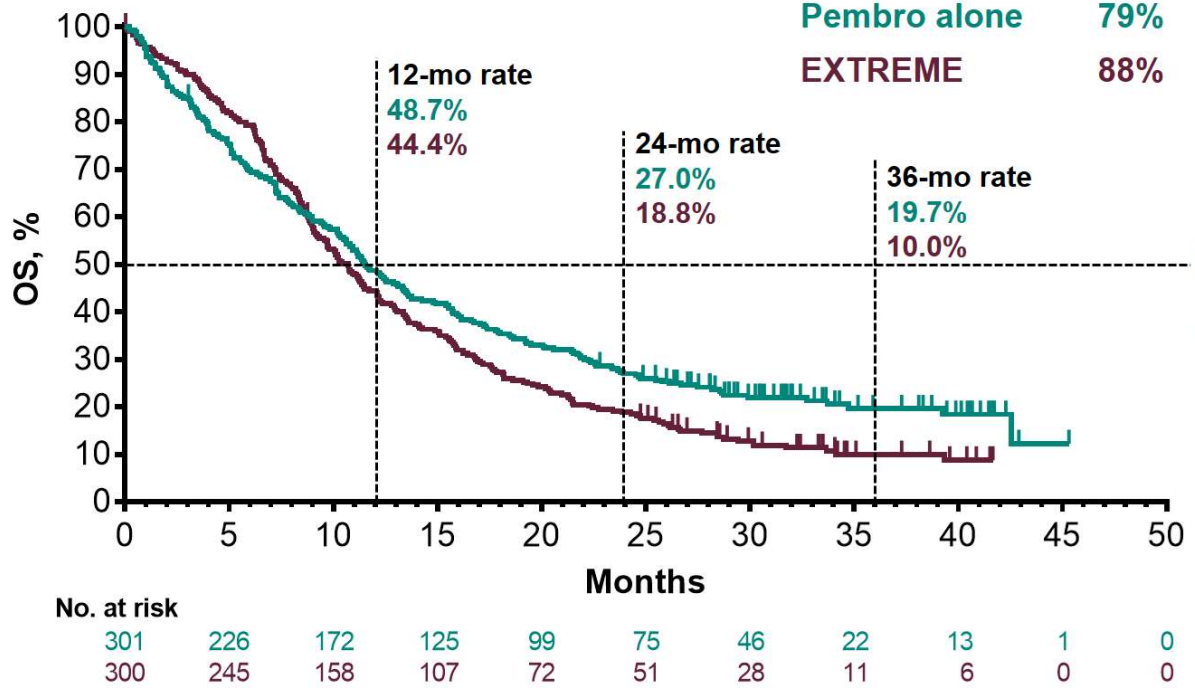
[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

Pembro plus chemo vs EXTREME: OS



Pembro vs EXTREME: OS

OS, P vs E, Total Population



	Events	HR (95% CI)	*P*
Pembro alone	79%	0.83 (0.70-0.99)	0.0199[a]
EXTREME	88%		

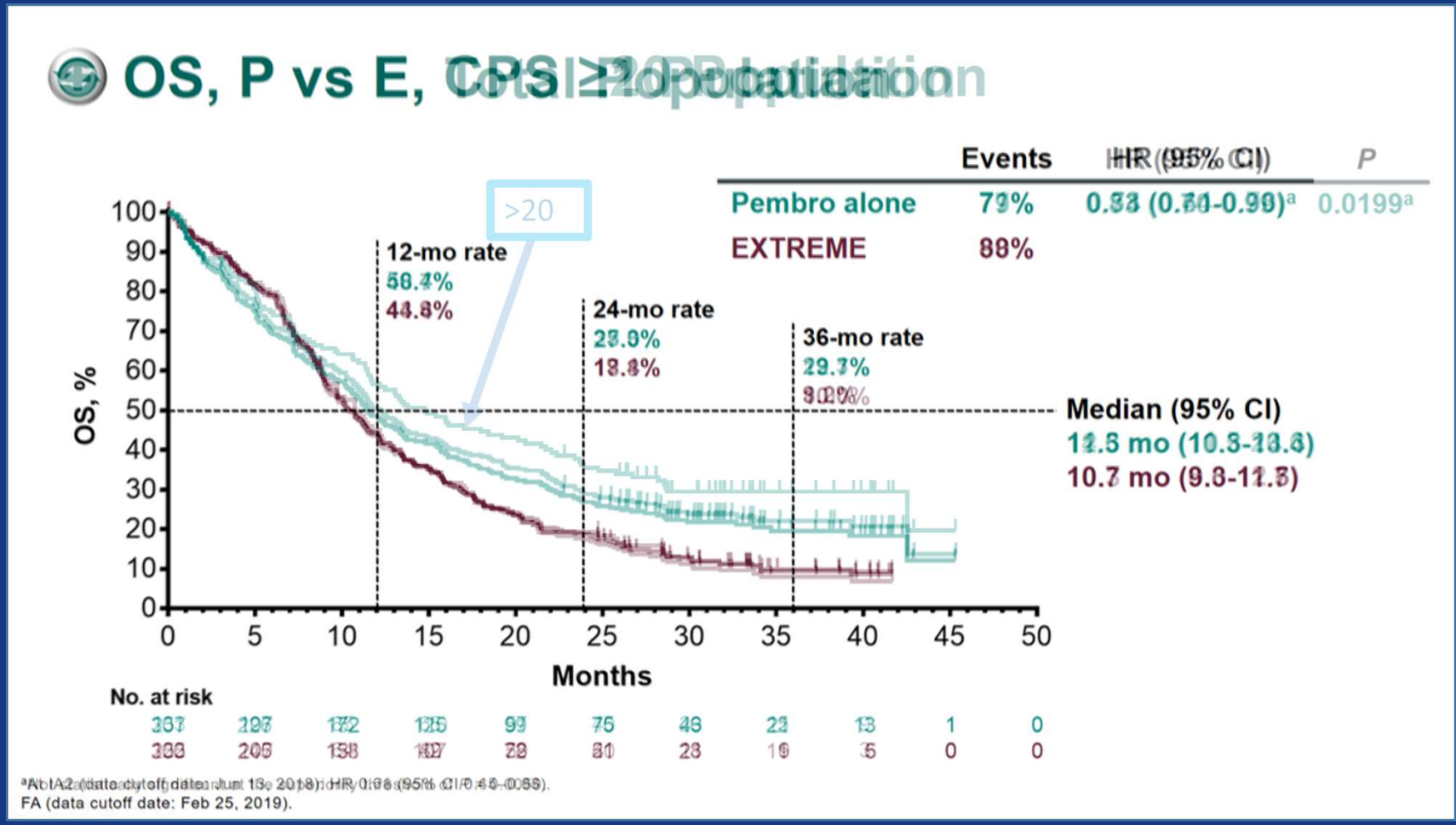
Median (95% CI)
11.5 mo (10.3-13.4)
10.7 mo (9.3-11.7)

No. at risk

301	226	172	125	99	75	46	22	13	1	0
300	245	158	107	72	51	28	11	6	0	0

[a]Not statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

Pembro vs EXTREME: OS



Why is this not yet published? My guess ITEM 2:

- Glaringly obviously omitted:
  - How much of OS benefit in total population within the CPS > 20% group? Look at 0-20% CPS group
  - Pembro versus Pembro plus chemo?
  - The data needed for the above analyses are known to Merck
  - Write to Merck and ask. Don't accept " these were not prespecified endpoints"

Cherry on top: " chemo versus EXTREME"
Can we stop using and EXTREMELY toxic regimen in R/M SCCHN?

TPExtreme study design (NCT 02268695)

KEY ELIGIBILITY CRITERIA

- → R/M HNSCC not suitable for locoregional treatment
- → Age 18-70 years
- → PS 0-1
- → Creatinine clearance >60 mL/min
- → Prior cisplatin ≤300 mg/m²
- → No Anti-EGFR for 1 year

MINIMIZATION FACTORS

- → PS
- → Metastatic status
- → Previous cetuximab
- → Country

R 1:1

N = 270

EXTREME
(Reference arm)

6 cycles Q3W CT

CISPLATIN → 100 mg/m² IV
5FU → 4000 mg/m² 96h continuous infusion
CETUXIMAB → 400 mg/m² (loading dose), then 250 mg/m² IV weekly

– Maintenance cetuximab 250 mg/m²
– WEEKLY
– until progression or unacceptable toxicity

N = 269

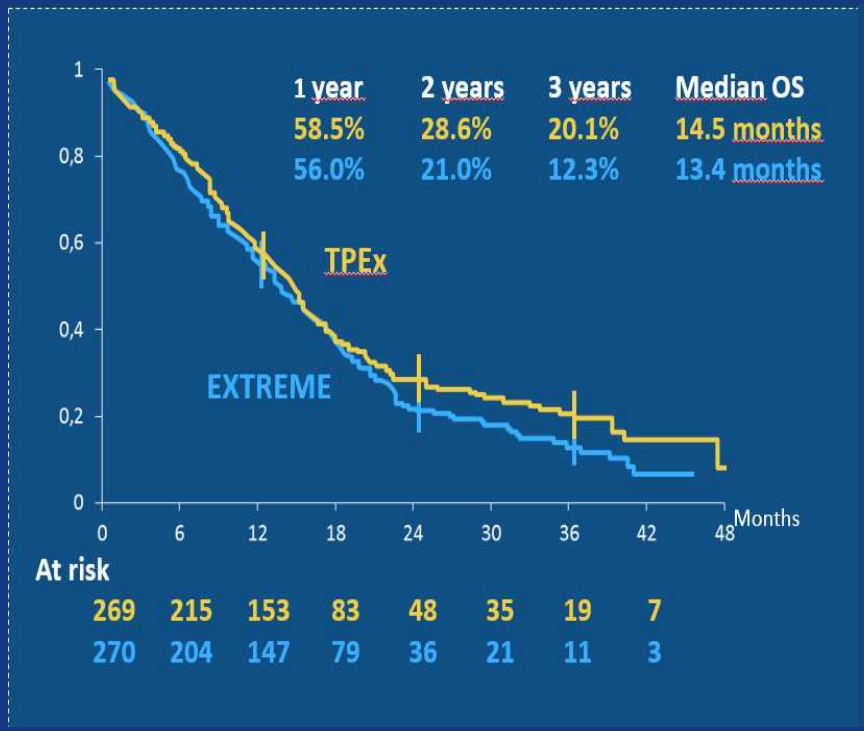
TPEx
(Experimental arm)

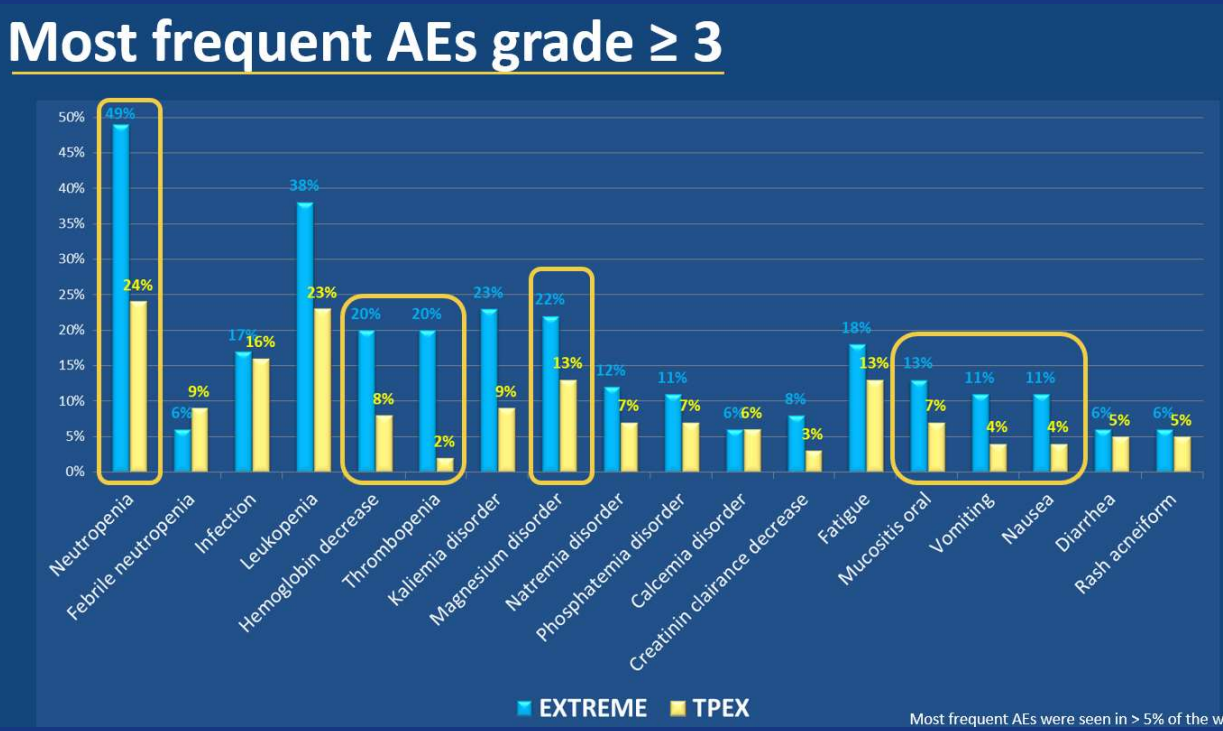
4 cycles Q3W CT

CISPLATIN → 75 mg/m² IV
DOCETAXEL → 75 mg/m² IV
CETUXIMAB → 400 mg/m² (loading dose), then 250 mg/m² IV weekly
+ G CSF after each cycle

– Maintenance cetuximab 500 mg/m²
– EVERY 2 WEEKS
– until progression or unacceptable toxicity

TPC versus EXTREME: OS and toxicity





Survival HR 0.87, p= 0.15

36% pts had grade ≥4 AEs during CT vs 51% in EXTREME (p<0.001)

A modest proposal:

There is an excellent data- supported rationale for treating R/M SCCHN patients with CPS $\geq$ 20 with :

Platinum

Taxane

Pembrolizumab

+/- Cetuximab

As a first line strategy.

It will cost a fortune.

END