Emerging systemic treatments for head and neck cancers, 2018

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OF OTOLARYNGOLOGY - HEAD AND NECK SURGERY AT THE STANFORD UNIVERSITY MEDICAL CENTER

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Head and Neck Cancer: State of the Art

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Grant/research support: AstraZeneca, Innate Pharma,
Bristol-Squibb Pharmaceuticals,
CellSight Technologies, Inc.,Tessa Therapeutics
Consultant: COTA, Inc., KeyQuest Health, LOXO Oncology, ATARA Biotherapeutics, Aduro Biotech, Inc.

The speaker will directly disclose the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

Prime 21st century SCCHN question: How to treat HPV positive SCC of the oropharynx

- Most important questions:

1. Drugs for rads or different systemic treatments? ECOG 1308, PMID 28029303
2. Do extranodal extension and number of nodes predict for worse outcome as in HPV- disease? PMID 29909888, 28939068.
3. What are acceptable surgical approaches? ECOG 3311 TORS closed 6/2017
4. Can postsurgical treatment be reduced? ECOG 3311 and PMID 28808988
5. Can definitive radiation be reduced? NRG HN002

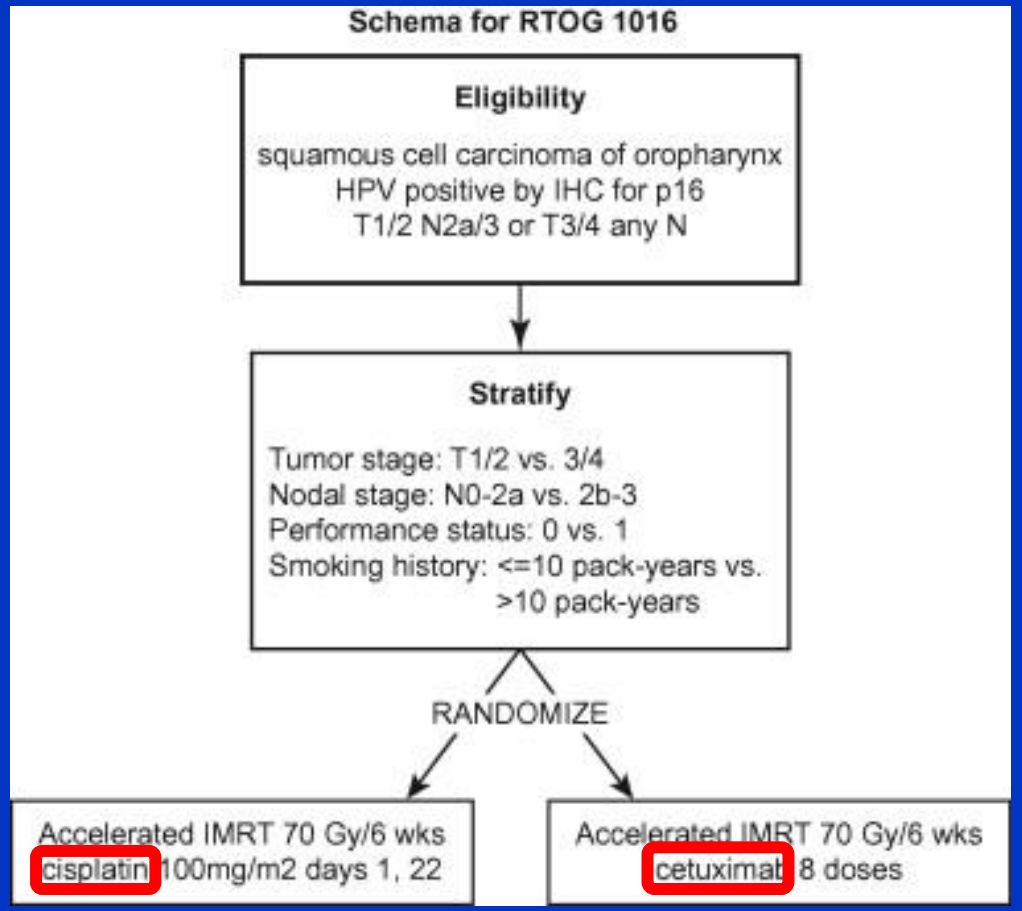
RTOG 1016: can cetuximab substitute for cisplatin with XRT in HPV+ SCCOP?

849 pts, 2011-2014

primary endpoint: OS equivalency

The answer is…

5 year est outcomes	cisplatin	cetuximab	
OS			
PFS			
LR failure			
Distant metastases			
AE gr 3-4/5			
Long term dysphagia			



If RTOG 1016 favors cisplatin in HPV+OPSCC…

- Do we assume cetuximab is no longer an acceptable standard with XRT in any cisplatin eligible patient?
- We still have not answered the question for taxanes with XRT
- Pharma is supporting a plethora of IO + chemo+XRT combinations: should they drop all cetuximab arms?
- Is there a role for cetuximab in any setting in SCCHN?

If RTOG 1016 favors cetuximab in HPV+OPSCC…

- What about HPV- disease? would cetuximab be OK there too?
- We still have not answered the question for taxanes with XRT
- Pharma is supporting a plethora of IO + chemo+XRT combinations: which CDDP arms would be irrelevant?
- What is role for cetuximab in a post- EXTREME for r/m disease era?

Isn’t cetuximab OK for the infirm , impaired, elderly…?
MEDICARE = 65 yo and above

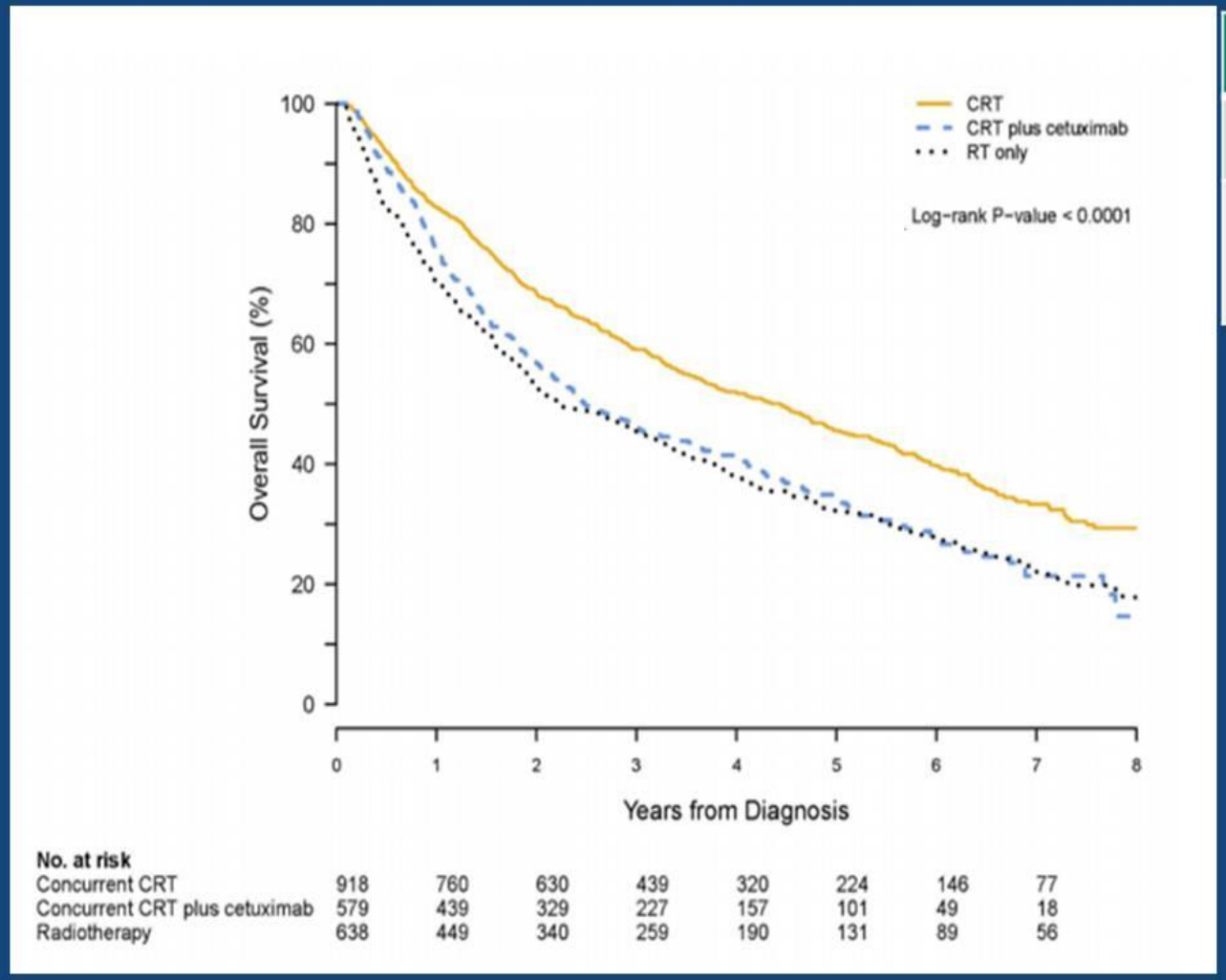
Definitive cetuximab-based (CRT-CX) vs. non-cetuximab based chemoradiation (CRT) in older patients with squamous cell carcinoma of the head and neck (HNSCC): Analysis of the SEER-Medicare linked database.

Dan P. Zandberg[1], Kevin J. Cullen[2], Vinod Varki[3], Ikumi Suzuki[4], Søren Bentzen[5], Olga G. Goloubeva[5]

[1]University of Pittsburgh Hillman Cancer Center, Pittsburgh, PA; [2]University of Maryland, Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; [3]Mercy Medical Center, Baltimore, MD; [4]Gettysburg Cancer Center, Gettysburg, PA; [5]University of Maryland School of Medicine, Department of Statistics, Baltimore, MD.

CETUXIMAB XRT LOOKS NO BETTER THAN XRT ALONE] in the medicare population

Overall Survival by Treatment

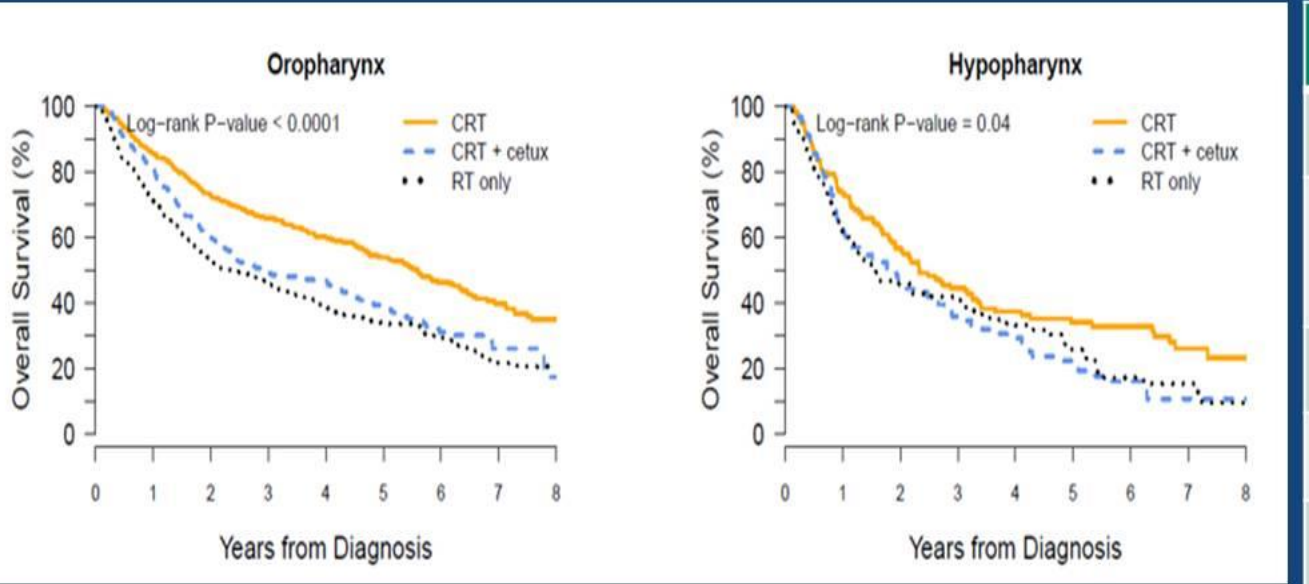


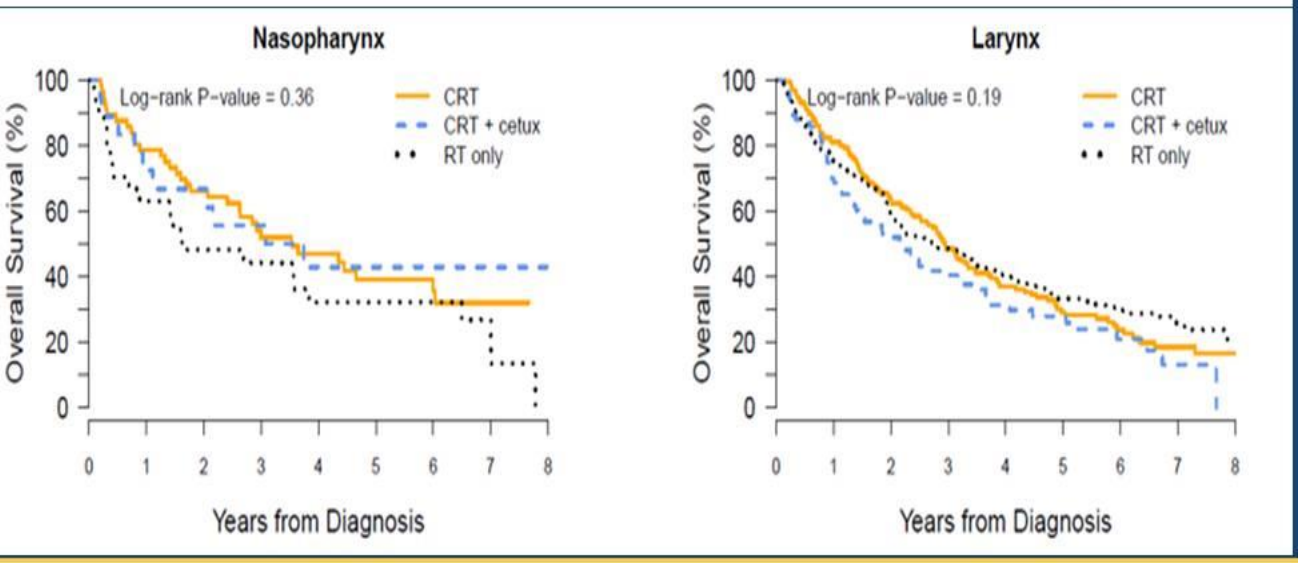
	CRT	CRT-CX	RT
5 Year OS	46%	35%	32%
Median OS(yr) (95% CI)	4.5 (3.8-4.9)	2.5 (2.2-3.0)	2.2 (2.0-3.0)

HR for risk of death for CRT-CX vs. CRT:

HR 1.41;95% CI: 1.24, 1.61; p<0.0001

Overall Survival by Treatment and Primary Site





		CRT	CRT-CX	RT
OP	5 Year OS	54%	39%	34%
	Median OS(yr) (95% CI)	5.59 (4.9-6.3)	2.95 (2.4-4.1)	2.24 (1.9-3.1)
HP	5 year OS	34%	22%	26%
	Median OS(yr) (95% CI)	2.33 (1.9-3.4)	1.78 (1.1-2.8)	1.6 (1.2-3.1)

HR for risk of death for CRT-CX vs. CRT:

OP: HR 1.52;95% CI: 1.28, 1.82; p<0.0001
HP: HR 1.45;95% CI: 1.05, 1.98; p 0.04

Is propensity adjustment the cure- all for retro eval?

Estimated HR for the risk of death: multivariable regression model *

	HR	95% CI	P-value
CRT-CX vs. CRT	**1.23**	**1.07, 1.42**	**0.005**
RT vs. CRT	1.36	1.17, 1.57	<0.001
Female vs. Male	1.04	0.91, 1.19	0.57
AA vs. CA	1.34	1.08, 1.65	0.008
Age at Diagnosis	1.05	1.04, 1.06	<0.001
Charlson CI: 1 vs. 0	1.36	1.18, 1.57	<0.001
Charlson CI: 2 vs. 0	1.81	1.57, 2.09	<0.001
Married vs. Not Married	0.79	0.70, 0.90	<0.001
Year of Dx	0.95	0.92, 0.99	0.006
Median Income	0.92	0.87, 0.97	0.002
Teaching Hospital vs. NT	0.92	0.82, 1.04	0.18

***Stratified for stage and primary site multivariable Cox regression model**

Update since CCC 2017 meeting:

What I told you last year about pembro…

Keynote -040: Pembrolizumab Versus Standard Treatment for Recurrent or Metastatic Head and Neck Cancer

Critical clinical trial design elements

- SCCHN, Failure of prior platinum therapy (NOS in CT.gov)
- Stratified by p16, PS, PD-L1
- Pembro 1:1 versus docetaxel or mtx or cetuximab
- primary endpoint OS
- 495 patients
- July 24, 2017: The trial did “not meet its pre-specified primary endpoint of overall survival (OS) (HR, 0.82 [95% CI, 0.67-1.01]; p = 0.03 [one-sided])”

2018: A good year for pembro.

Merck's Keynote -048:

pembro 200 mg versus EXTREME(CDDP100, 5FU IVCI 4000, cetuximab)

eligibility: SCCHN , PD-L1 CPS > 20, First line m/or r >6 mo post

dual primary endpoints: OS, PFS

PRESS RELEASE 7/25/18

"Based on an interim analysis conducted by the independent Data Monitoring Committee (DMC), treatment with KEYTRUDA monotherapy in these patients resulted in **significantly longer OS** compared to [EXTREME]..." (bold underline mine)

Reference:Merck Oncology Media Monitoring <aorban@w2ogroup.com>

Where can EXTREME hold on?

BMS' CheckMate 651:

nipi versus EXTREME

eligibility: SCCHN , **No PD-L1 required**, First line m/or r >6 mo post

dual primary endpoints: OS, PFS in PD-L1 Pos

secondary OS, PFS in all

Should this trial continue to enroll to the PD-L1 positive group?

Lots of other combos challenging EXTREME:

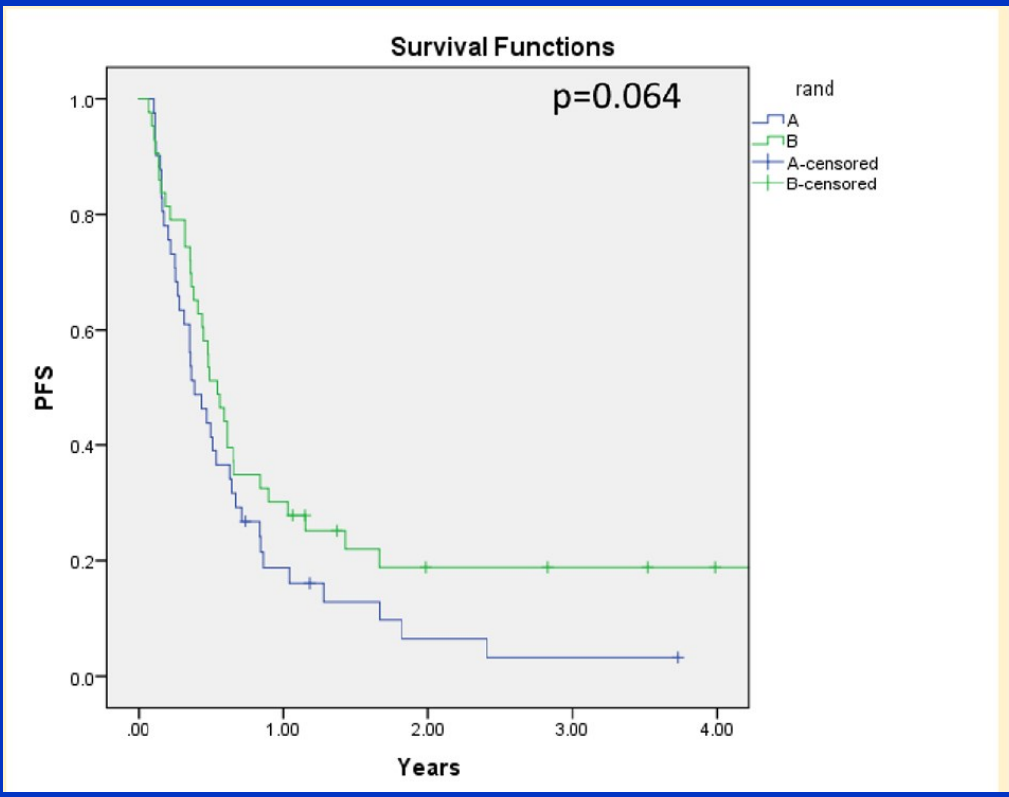
PD-1 plus IDOi: NCT 03358472, 03386838. remember 2017 data?

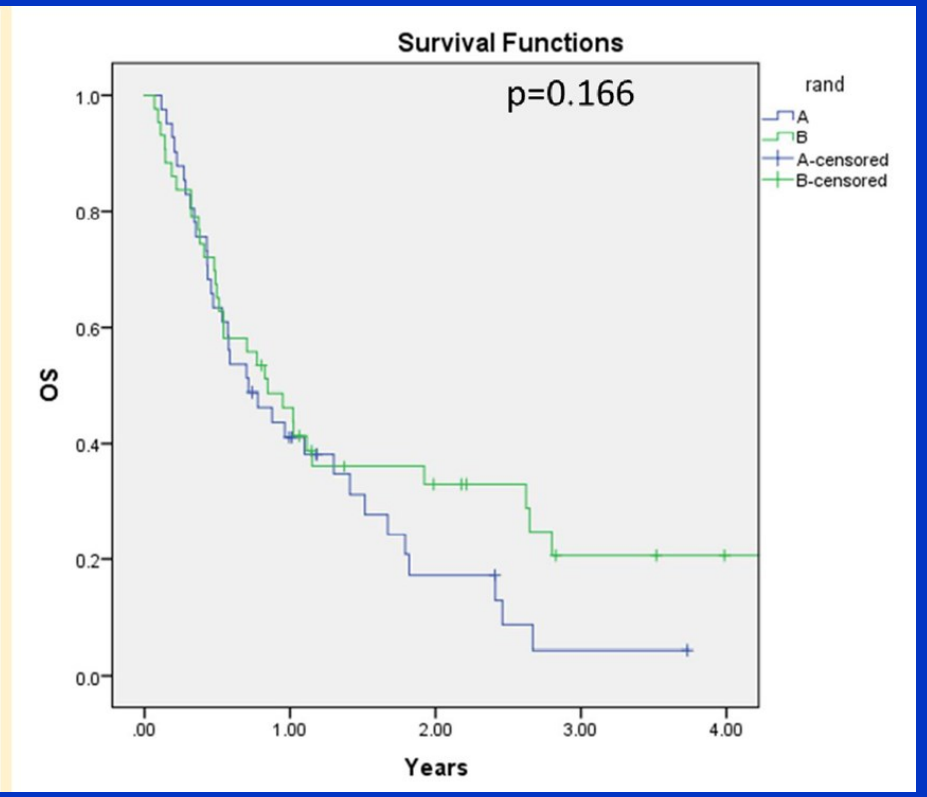
EXTREME being challenged from another direction. first randomized trial ever… and probably the last. Phase 2, 85 patients

Cisplatin/ 5-FU/cetuximab (“EXTREME”) = A

Versus

Paclitaxel/ carboplatin/cetuximab (“TPC”) = B





- Gr 3 AEs 60% v 40%
- ORR , PFS, OS, TTF, duration of response all better for TPC

Implications for SOC and backbone/ RCT Comparators in IO era

Friesland et al, ASCO 2018 abs 6032

Are all anti EGFR Moab alike?

Cetuximab: chimeric, approved for CRC, SCCHN. IgG1

Panitumumab: fully human, approved for CRC. IgG2

Zalutumumab: fully human, Netherlands. IgG1

Matuzumab: humanized, Germany. Development stopped. IgG1

Nimotuzumab: chimeric, Cuba, approved in India, China, others. IgG1

Imgatuzumab(RO5083945): glycoengineered, investigational

A randomized phase III study of Nimotuzumab in combination with concurrent radiotherapy and Cisplatin versus radiotherapy and Cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck

Vijay M Patil

On behalf of Department of Medical Oncology

Head and Neck- Disease Management Group

Tata Memorial Centre, HBNI, Mumbai, India

3rd June 2018; 8:00 AM to 8:12 AM

Trial Design

ELIGIBILITY CRITERIA

- Age ≥ 18 years
- SCC of oral cavity/ oropharynx/ hypopharynx/ larynx
- Stage III / IV, no distant metastasis
- Definitive CRT
- Adequate organ function

Stratify

- T-group (T0,1,2 vs T3,4)
- N-group (N0,1 vs N2,3)
- Site (Oropharynx versus non oropharynx)
- Technique of radiation (conventional versus others)

Randomized 1:1 Open Label

n=268

Nimotuzumab (200mg) - weekly cisplatin 30mg/m^2 with of RT (NCRT)

RT: 70 Gy/35 #/-7 weeks

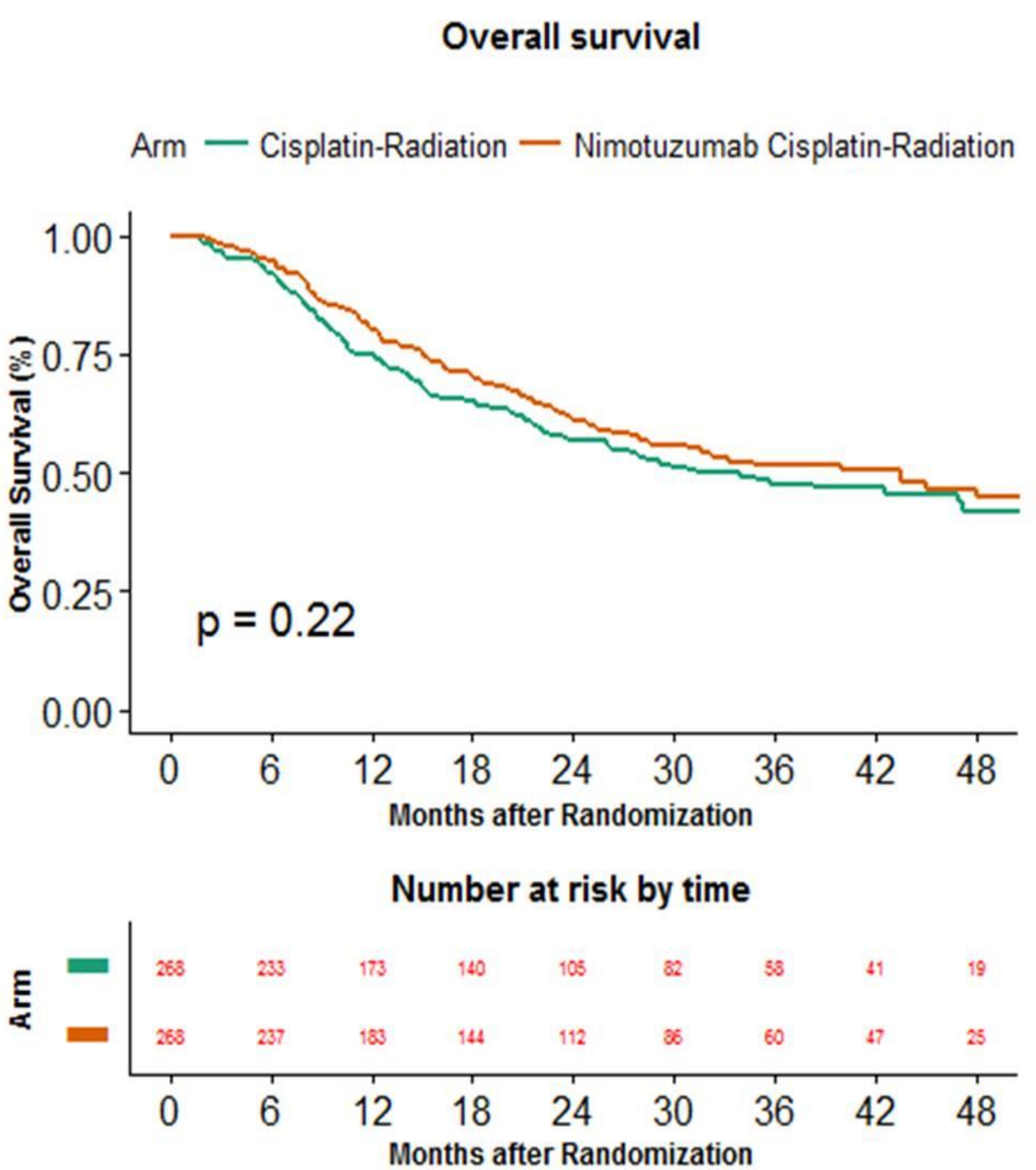
n=268

Weekly cisplatin 30mg/m^2 with RT (CRT)

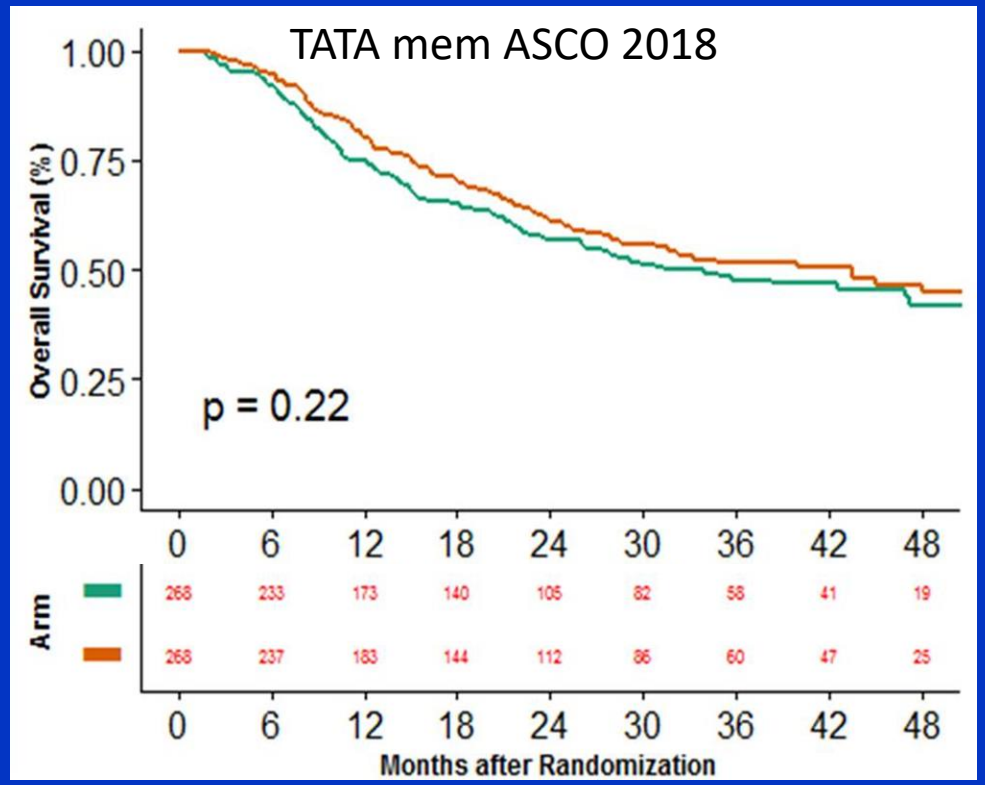
Follow-up: Weekly during CRT, then Q3 months x 2 years, then Q6 monthly

OS

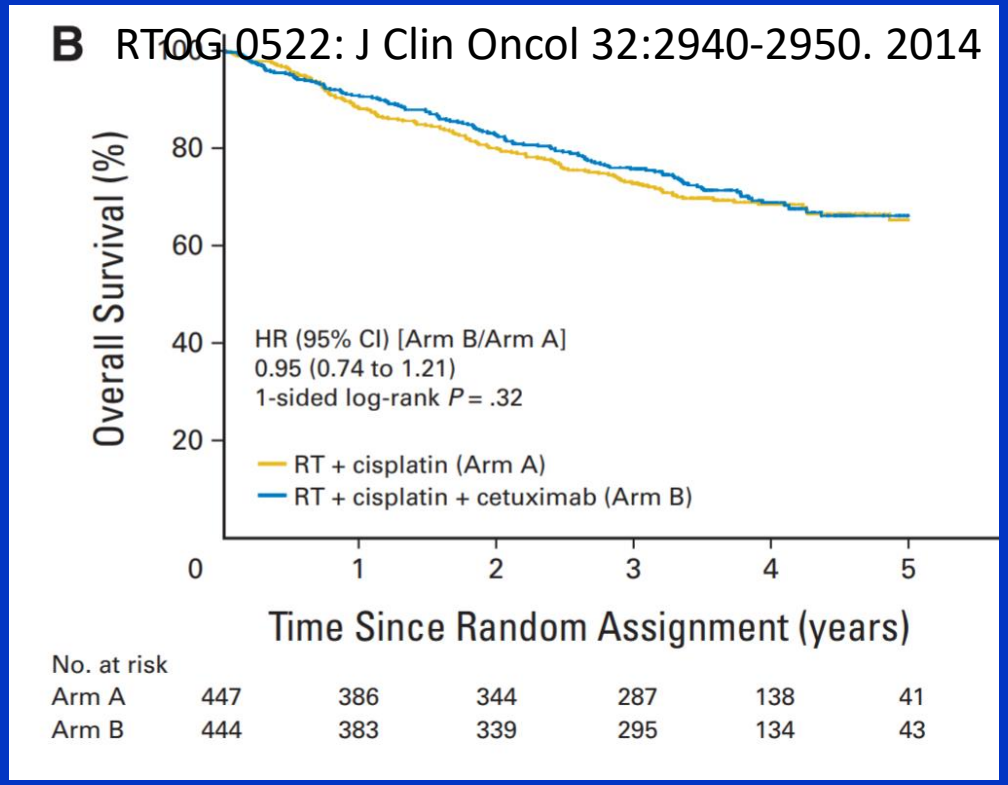
- The median overall survival was 31.3 months (95%CI 23.6-53.5) in the CRT arm while it was 43.4 months (95%CI 28.5 -NA) in the NCRT arm (P =0.220).
- The hazard ratio in favor of NCRT arm was 0.851, suggesting a 15% reduction in the risk of death (95% CI 0.65-1.10) but was not statistically significant.



Remember RTOG 0522? Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma.

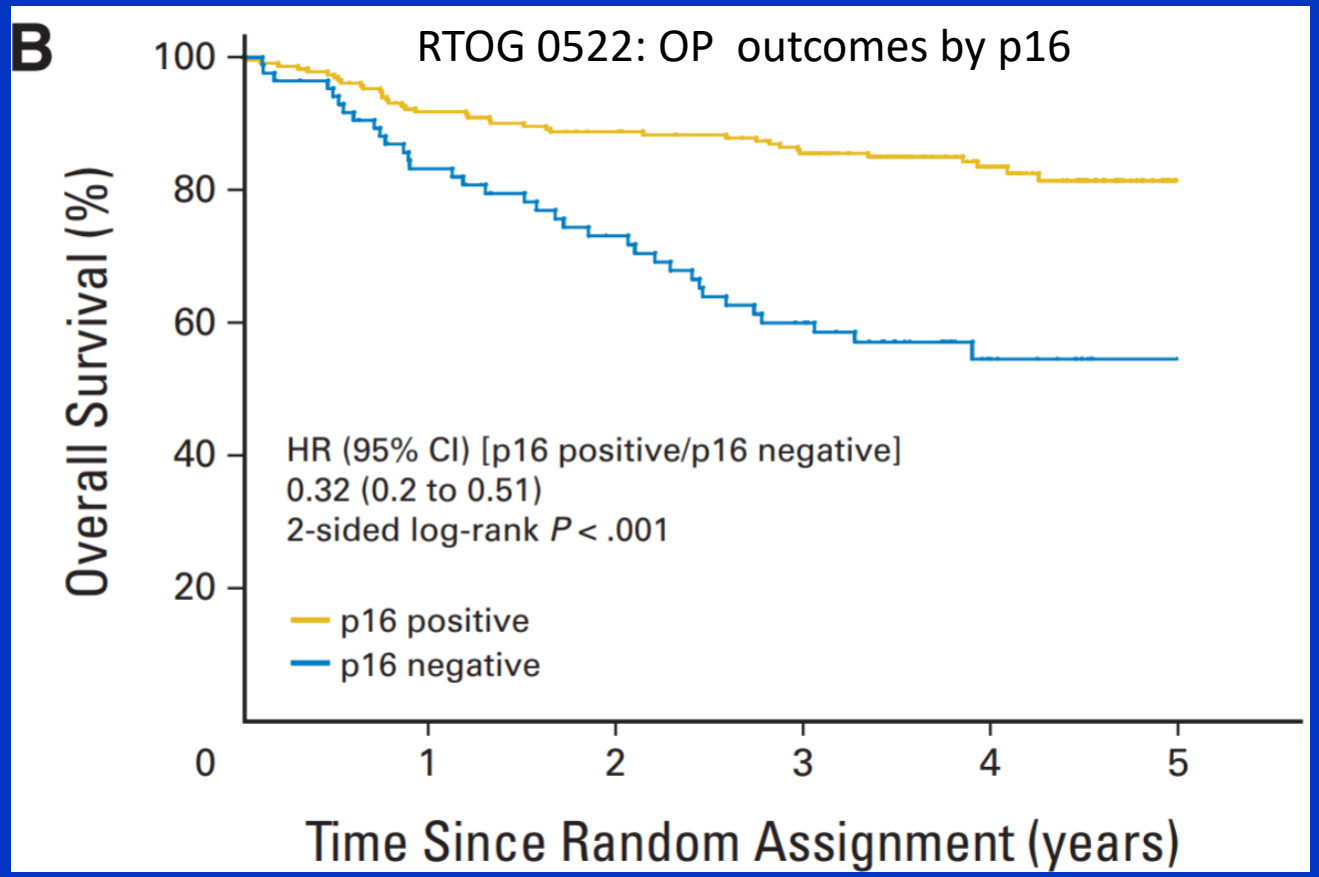


Nimotuzumab
CDDP 30 weekly
OP 50%
HPV < 6%
XRT 85% conventional



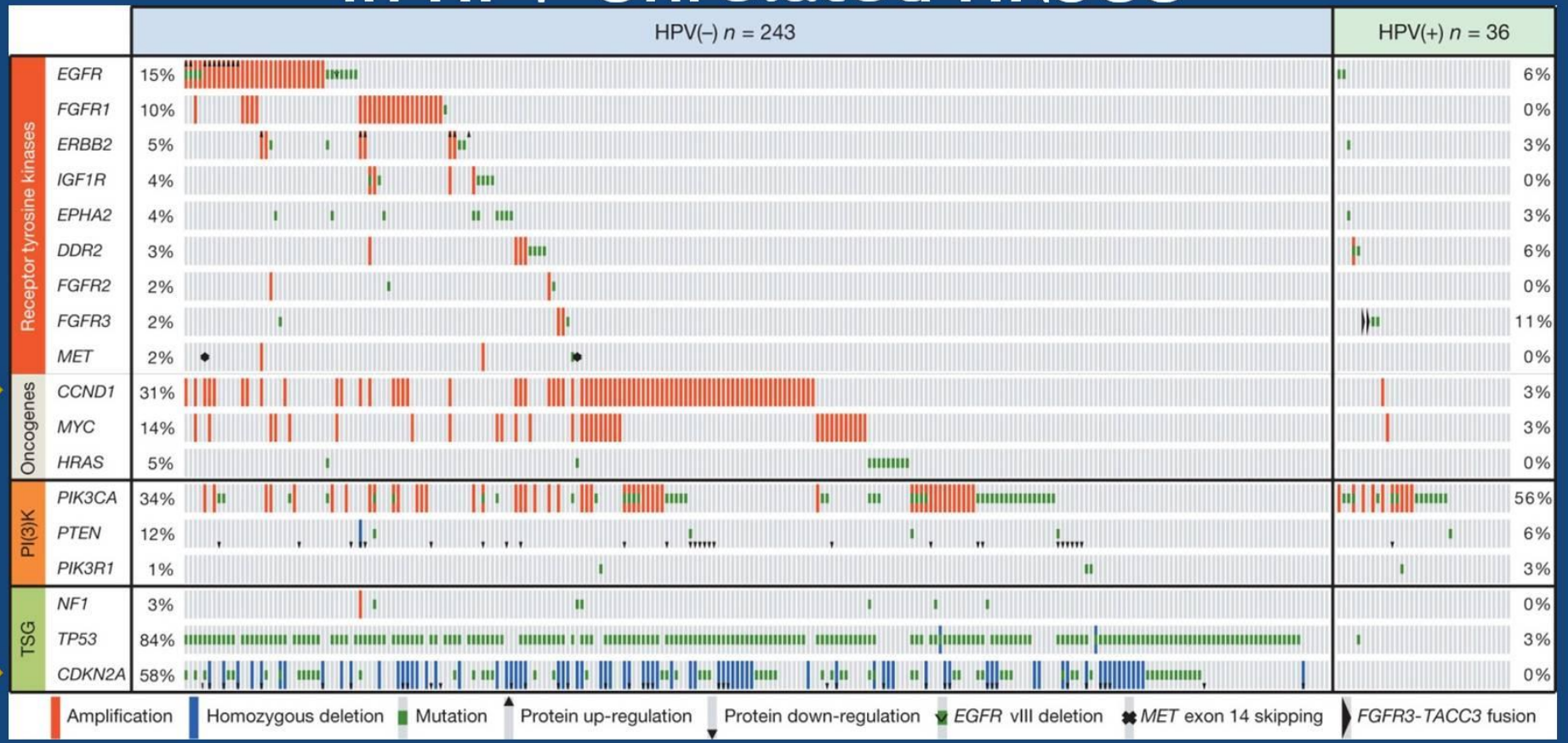
Cetuximab
CDDP 100 q 21 x2
OP 70%
OP 37% HPV, 48% unk
XRT 100% accelerated

We no longer study p16+ and p16 – together: Lessons from RTOG 0522, Bonner, etc.



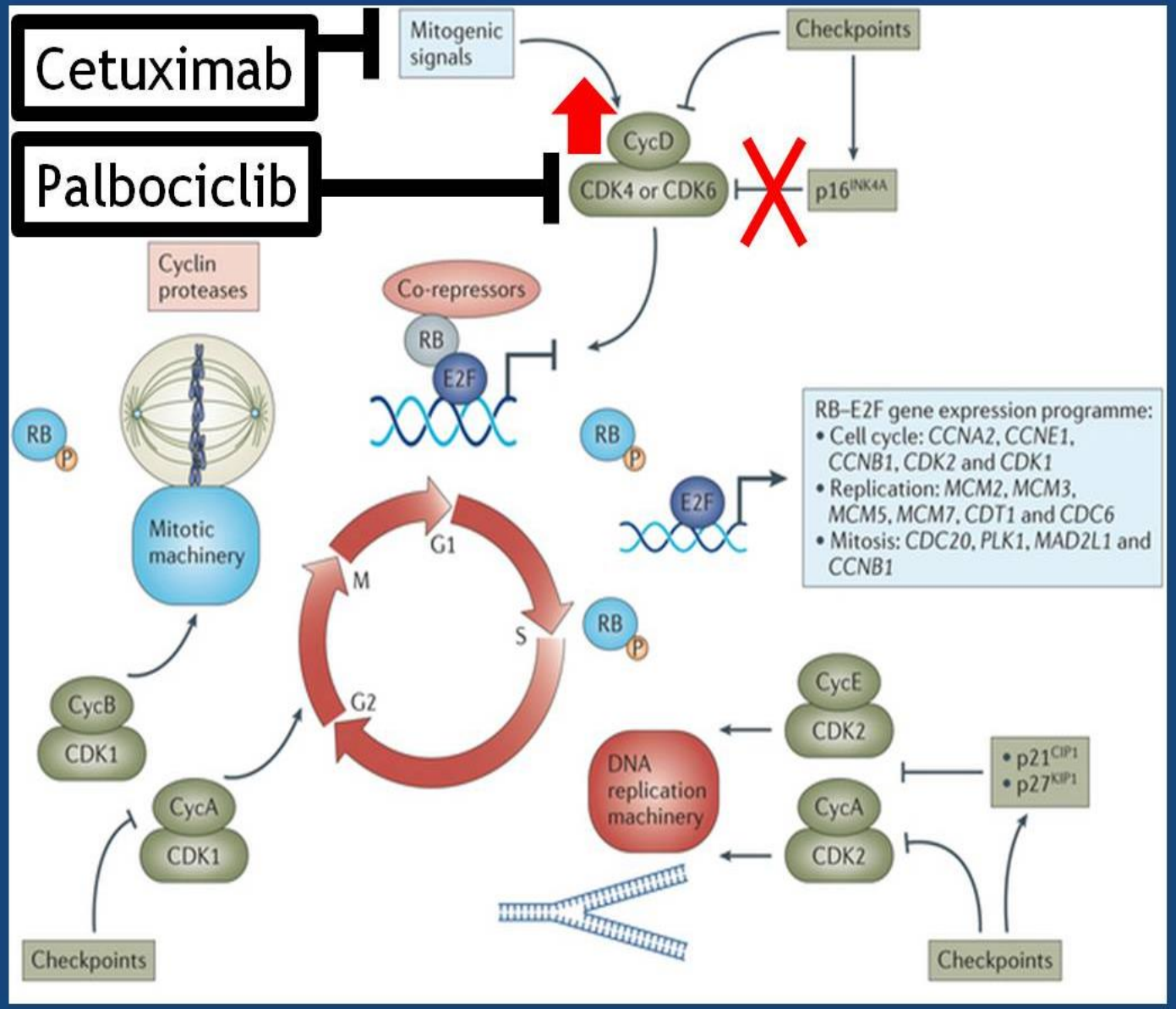
PH 2 palbociclib (CDK4/6i) and cetuximab in CDDP resistant HPV- SCCHN

Mechanism of Cell Cycle Deregulation in HPV-Unrelated HNSCC*



*Nature 2015.

Cell Cycle in HPV-Unrelated HNSCC*



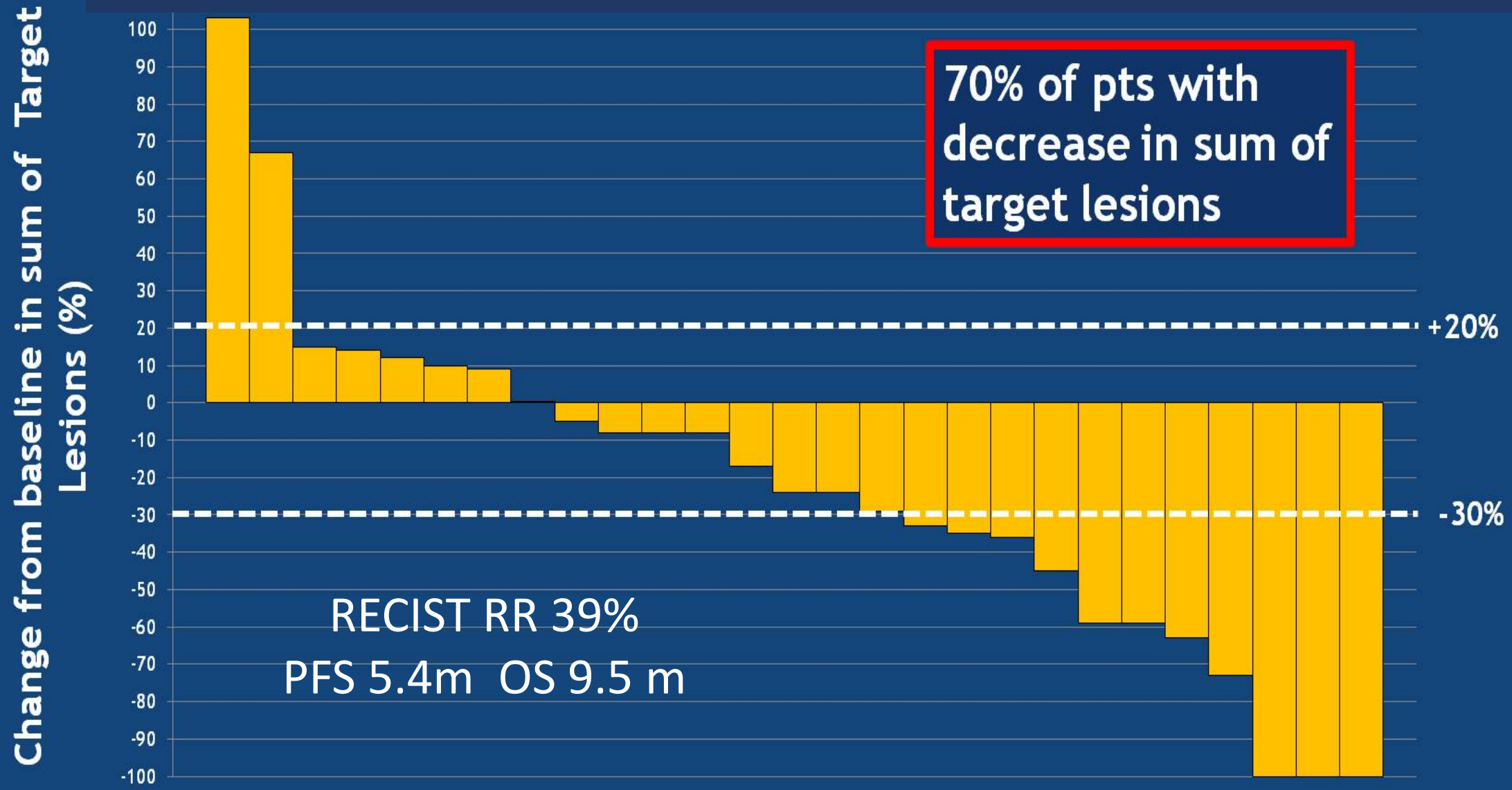
*Nat Rev Drug Discov 2015.

Primary Hypothesis of Phase II Trial

Palbociclib and Cetuximab
would increase the tumor response rate of
platinum-resistant HPV-unrelated RM-HNSCC
from 13% (historical data with
cetuximab monotherapy)* to ≥ 26%.

PRIOR data: virtually no RR to palbo alone,
Ph 1 evidence of combined activity in cetuximab resistant dz.

Responses to palbo+ cetuximab



Three patients not included above: followed by clinical exam (1), post treatment scan not evaluable due to lack of IV contrast (1) and early death (1)
Four patients are still on active treatment - The best tumor response to date is reported.

For next year, maybe:
Safety And Efficacy Study Of Palbociclib Plus Cetuximab Versus Cetuximab To Treat Head And Neck Cancer. NCT02499120

- Opened 2015, closed 2018
- HPV negative, PD to platinum
- RP2 trial cetuximab +/- palbo
- OS endpoint
- Readout soon?

Anti PD-1 in cutaneous SCC: it works! ASCO 2018 abstract #9519

- Regeneron Ph 2 (anti PD-1)

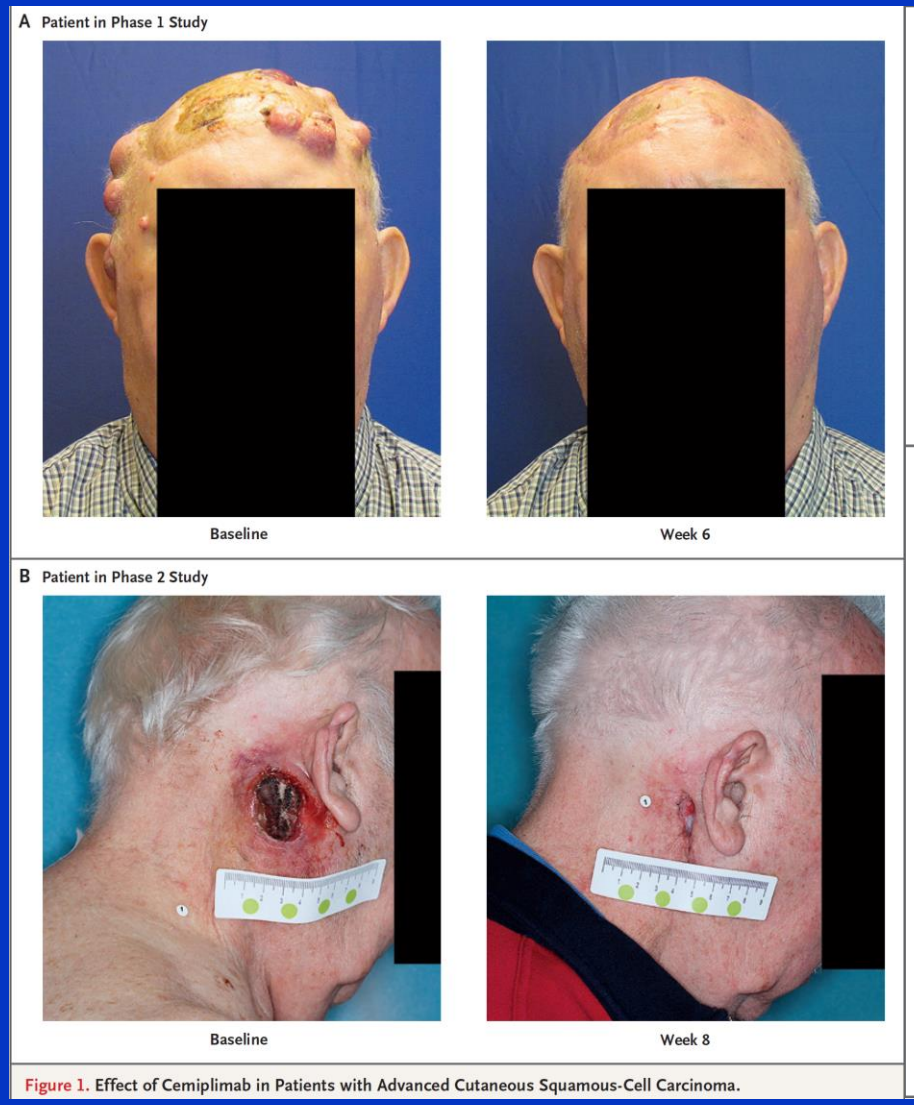
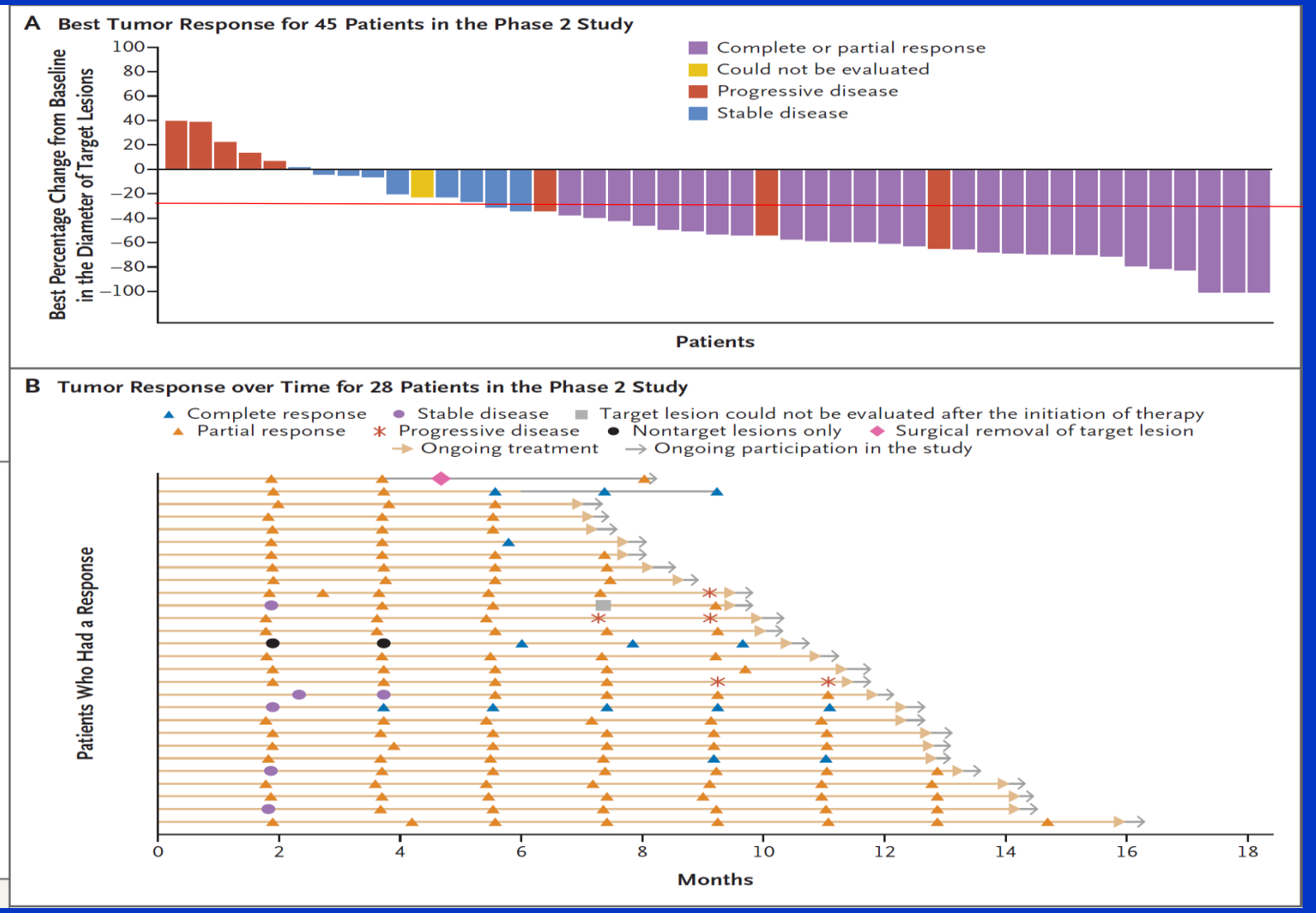


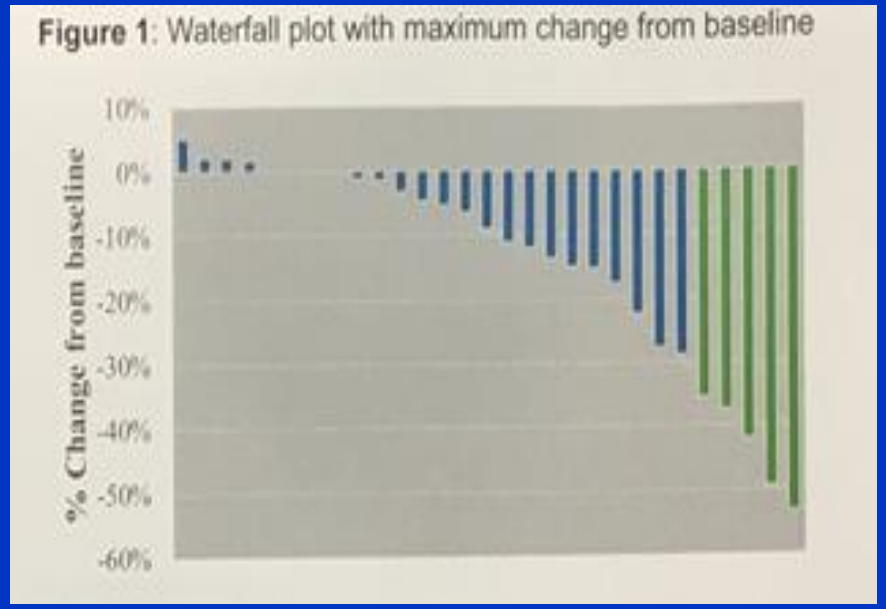
Figure 1. Effect of Cemiplimab in Patients with Advanced Cutaneous Squamous-Cell Carcinoma.

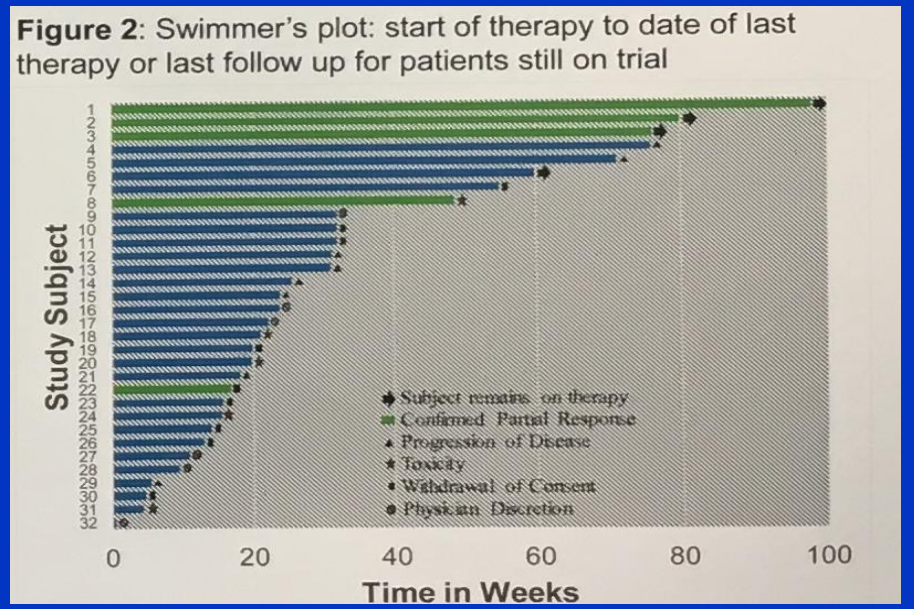


N Engl J Med. PMID: 29863979

Is there any effective systemic therapy for adenoid cystic carcinoma? MAYBE…. ASCO2018 abs #6022

- MSKCC: lenvatinib in ACC
- Swimmer's plot difficult to interpret in disease with typically very long time to progression at baseline





And a second group reported an 11.5% RR in ACC as well . BUT 24 mg/ day!?!?!
Locati et al. U of Milan

END

EBNA-1 inhibition

Mu;ti agent checkpoint

EBNA-1 inhibition

Atara

Ph 1 with Eben

biomarkers

HPV cellular tyherapy

RTOG 1016

Practice change by SEC release. EXTREME is dead

"Merck's anti-PD-1 therapy, for first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), met a primary endpoint of overall survival (OS) as monotherapy in patients whose tumors expressed PD-L1 (Combined Proportion Score (CPS) ≥20)[versus EXTREME].

Merck news release

25 July 2018