ESCALATION/DE-ESCALATION THERAPEUTIC STRATEGIES IN HNSCC

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Dep. Radiation-Oncology
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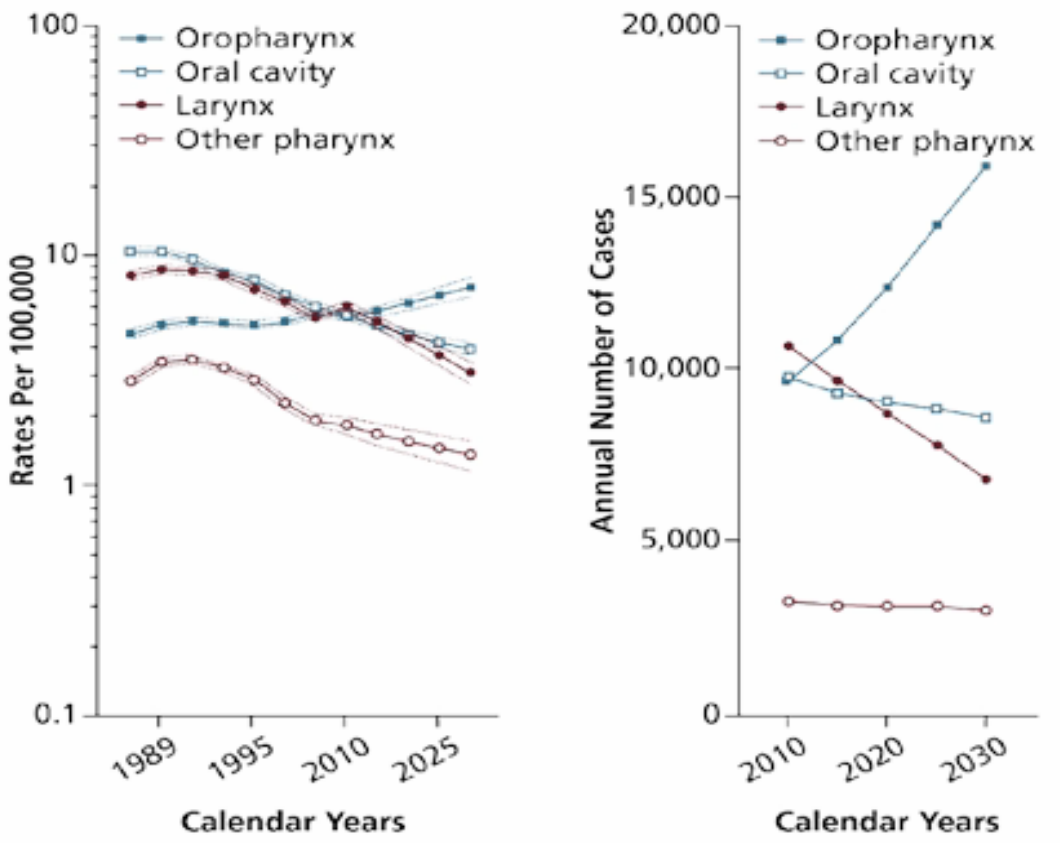
HEAD AND NECK CANCER -HPV

Change in incidence:



Chaturvedi AK J Clin Oncol 2011

TWO DISTINCT HEAD AND NECK CANCERS

	HPV-Positive	HPV-Negative
Anatomic site	Tonsil / BOT	All sites
Histology	Basaloid	Keratinized
Age	Younger	Older
Gender	3:1 men	3:1 men
SE status	High	Low
Risk factors	Sexual behavior	Alcohol / tobacco
Cofactors	Marijuana, immunosuppression	Diet, hygiene
Genetics	p53WT, p16+	p53Mu, p16-
Incidence	Increasing	Decreasing
Survival	High	Worse

Gillison M J Natl Cancer Inst 2008

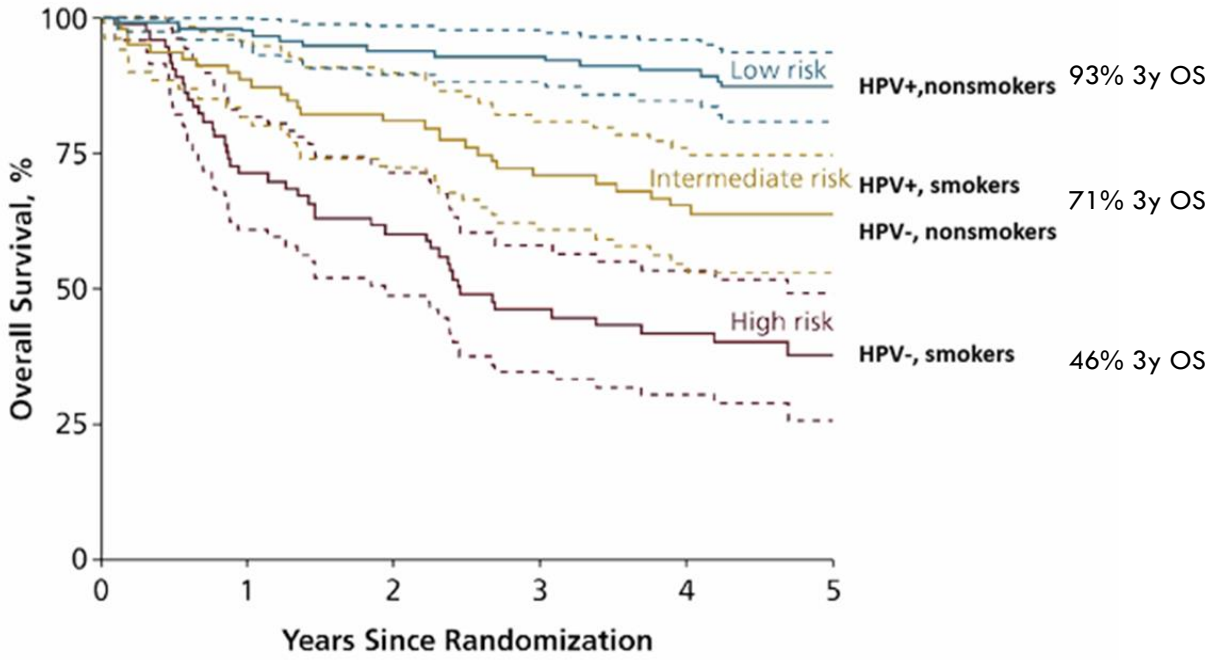
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

RTOG 0129

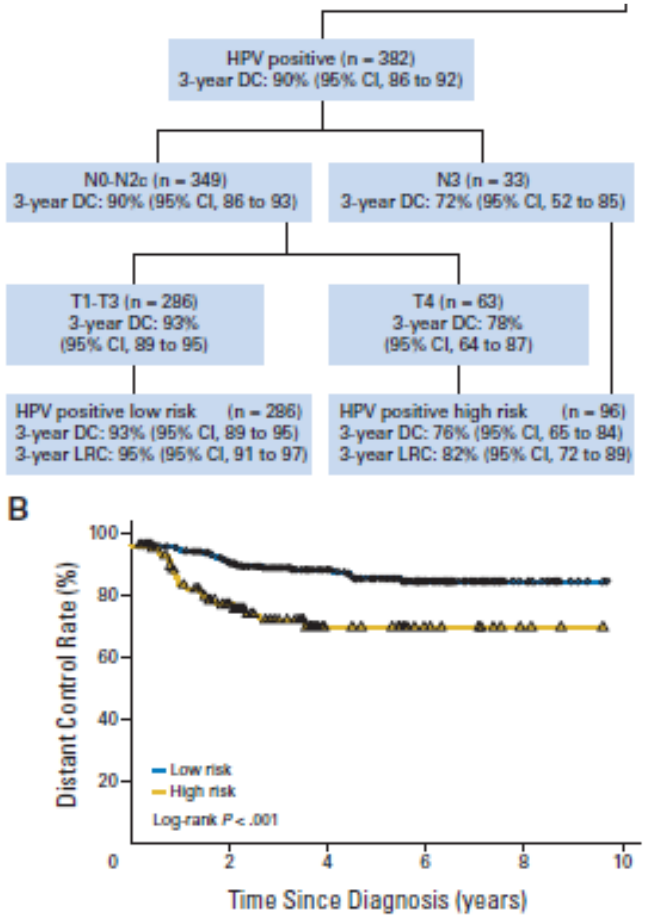


Ang NEJM 2010

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Deintensification Candidate Subgroups in Human Papillomavirus–Related Oropharyngeal Cancer According to Minimal Risk of Distant Metastasis

Brian O'Sullivan, Shao Hui Huang, Lillian L. Siu, John Waldron, Helen Zhao, Bayardo Perez-Ordonez, Ilan Weinreb, John Kim, Jolie Ringash, Andrew Bayley, Laura A. Dawson, Andrew Hope, John Cho, Jonathan Irish, Ralph Gilbert, Patrick Gullane, Angela Hui, Fei-Fei Liu, Eric Chen, and Wei Xu

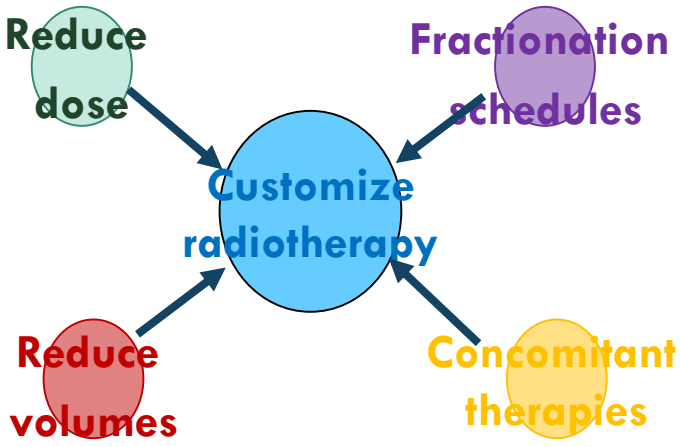


O'Sullivan JCO 2013

WHAT'S NEXT? SEPARATE TRIALS FOR HPV+ AND HPV- DISEASE:

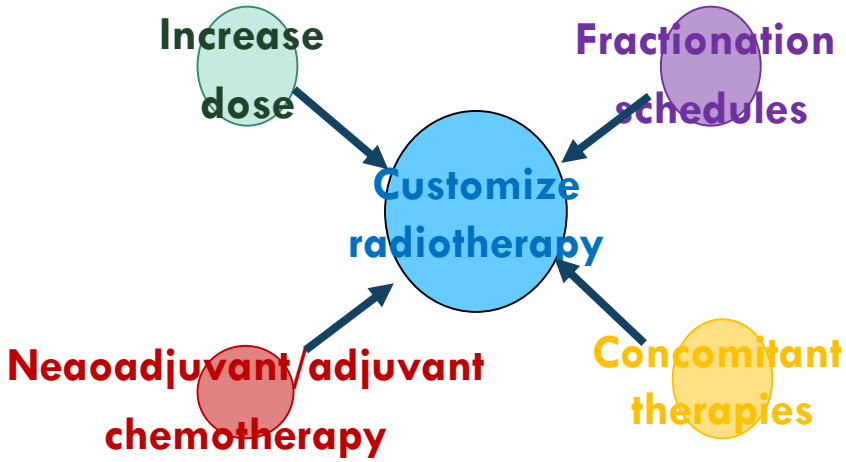
-Can we de-intensify treatment in low risk HPV+/ nonsmokers

- mainting overall survival
- decrease toxicity



-Can we intensify treatment in HPV- high risk patients to increase outcome

- increase overall survival
- 'limit' toxicity



De-intensification trials in HPV-associated OPSCC.

Trial	Phase	N	Inclusion criteria	Treatment
Chemotherapy de-intensification trials				
RTOG 1016 (NCT01302834)	III	706	T1–2, N2a–3, or T3–4, any N, HPV-positive OPSCC	Cetuximab versus high-dose cisplatin concurrent with accelerated IMRT (70 Gy in 6 weeks)
De-ESCALaTE HPV (NCT01874171)	III	304	Stage III–IVA HPV-positive OPSCC (T3N0–T4N0, T1N1–T4N3). Excludes > N2b, >10 PY	Cetuximab versus high-dose cisplatin concurrent with RT (70 Gy)
TROG 12.01 (NCT01855451)	III	200	Stage III (excluding T1–2, N1) or IV (excluding T4, N3, or M1) HPV-positive OPSCC if ≤10 PY. If >10 PY, only N0–2a	Cetuximab versus weekly cisplatin concurrent with RT (70 Gy) once per week
Radiotherapy de-intensification trials				
NRG HN-002 (NCT02254278)	II	296	T1–2, N1–2b, or T3, N0–2b disease and <10 PY HPV-positive OPC	Reduced-dose IMRT (60 Gy) with/without weekly cisplatin
NCT01530997	II	40	T1–3, N0–2c HPV-positive OPSCC if <10 PY or >5 years of abstinence	IMRT (54–60 Gy) with weekly cisplatin (30 mg/m^2)
ECOG 1308 (NCT01084083)	II	80	Resectable stages IIIA/IIIB and IVA/IVB HPV-positive OPSCC (p16-high or HPV-16 ISH positive)	IC, then response-adapted RT (54 or 66–70 Gy) with cetuximab
The Quarterback Trial (NCT01706939)	III	365	Stage III/IV (M0) HPV-associated OPSCC/unknown primary/nasopharynx. Excludes active smokers/>20 PY	IC with TPF: patients with CR/PR randomly assigned 2:1 to carboplatin with RT (56 versus 70 Gy) per week. Non-responders receive standard RT.
De-intensification of surgery/adjuvant therapy				
ECOG 3311 (NCT01898494)	II	377	Resectable stage III–IVB p16-positive OPSCC	TORS then risk-adapted post-operative treatment (observation/50 versus 60/66 Gy with weekly platinum)
PATHOS trial (NCT02215265)	II/III	242	Resectable T1–T3, N0–2b HPV-positive OPSCC. Excludes active smokers with N2b disease	TORS then re-adapted post-operative treatment (observation/50 versus 60Gy/60 Gy with or without weekly cisplatin)
ADEPT (NCT01687413)	III	500	Transoral resected p16-positive OPSCC (R0 margin), T1–4a, pN positive with ECE	Post-operative adjuvant 60-Gy RT with or without weekly cisplatin
NCT01932697	II	40	P16-positive OPSCC (R0 margin), stage I–IVB. Excludes ≥10 PY or smoking within 5 years	Surgery followed by hyperfractionated IMRT (36 Gy/20 fractions BID) + weekly docetaxel

1.DOSE REDUCTION

NCT01520997

Phase II trial

- Univ North Carolina and Florida
- 44 patients
- Low risk HPV+ OPC
- T0-T3, N0-N2C
- Less 10 packyears

De-intensified CRT

- IMRT 60Gy + 6 weekly cisplatin 30mg/m2

Prim Endpoint: pCR

- 86% (98% at primary, 84% at neck)

95% 3y OS

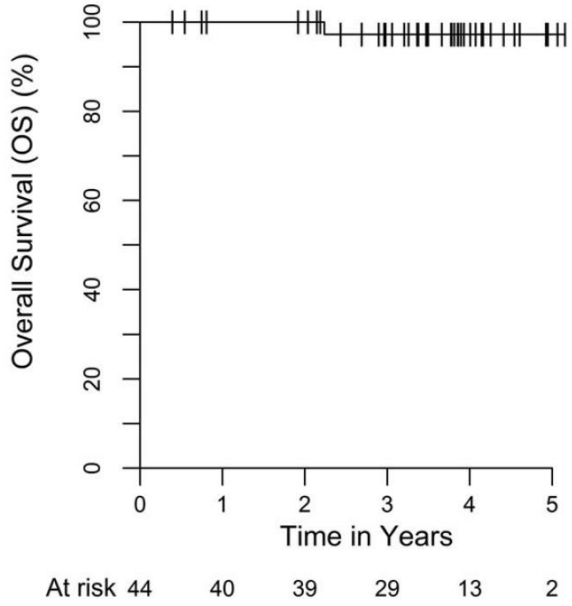


Figure 1. Kaplan-Meier curve for overall survival.

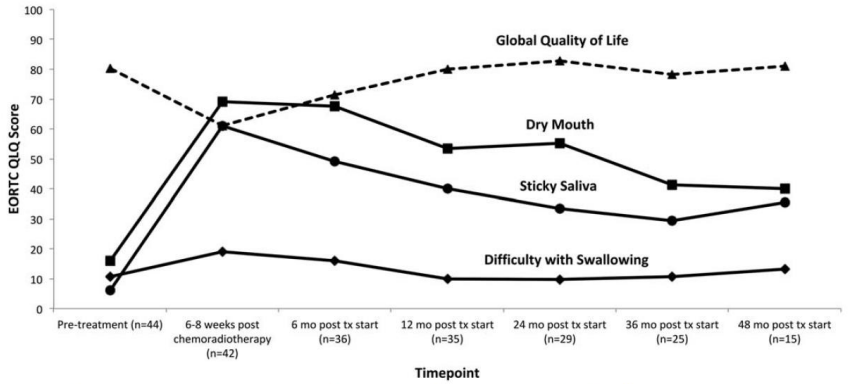
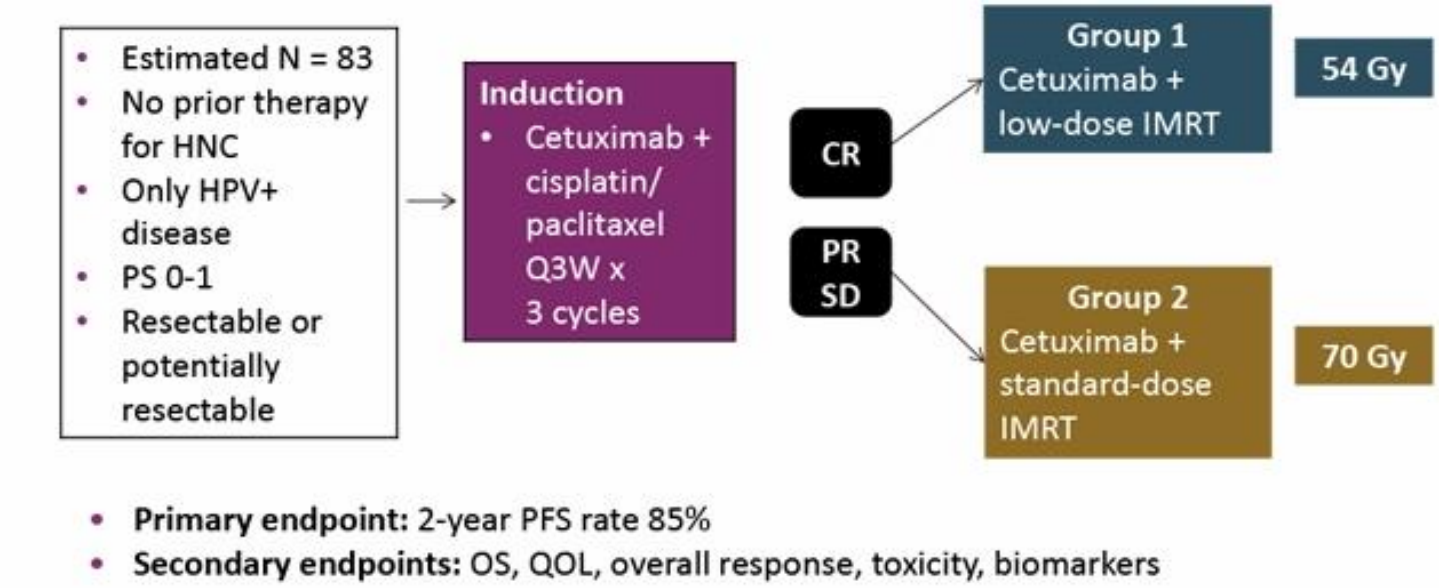


Figure 2. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30) responses (mean scores) for global health status and EORTC QLQ module for head and neck cancer (H&N35) responses (mean scores) for selected symptoms. tx indicates treatment.

Chera et al IJROBP 2015
Cancer 2018

2. SELECTION BASED ON INDUCTIONCHEMO

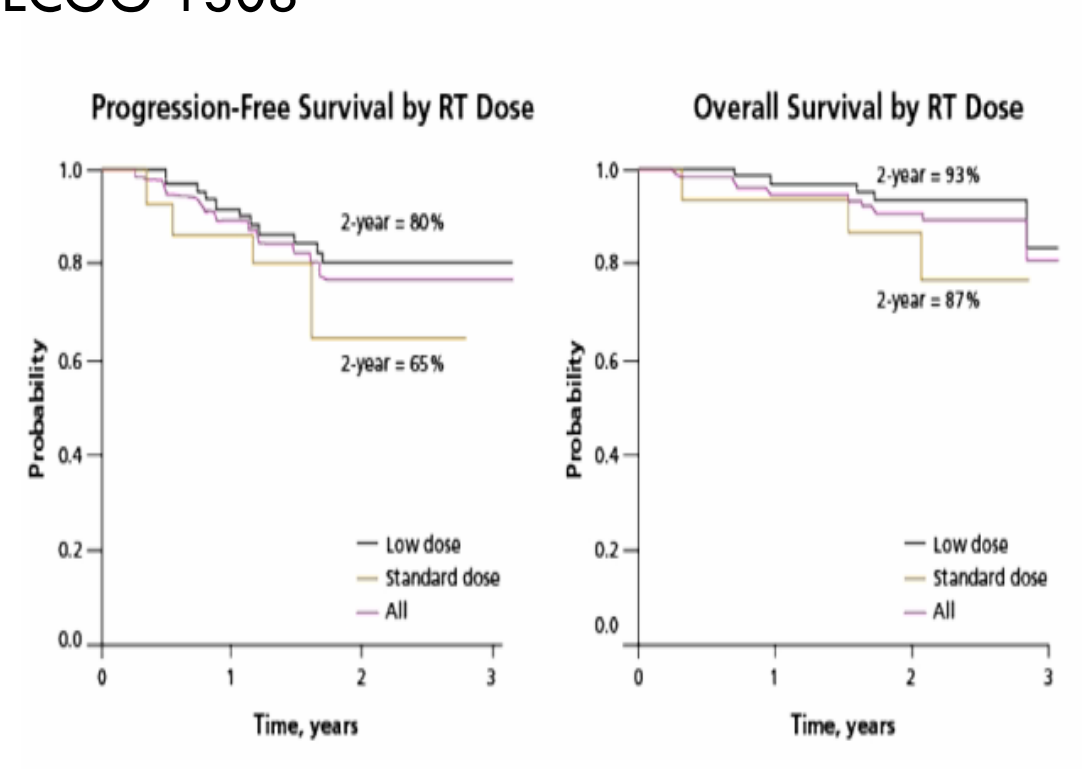
ECOG 1308: randomized Phase II trial

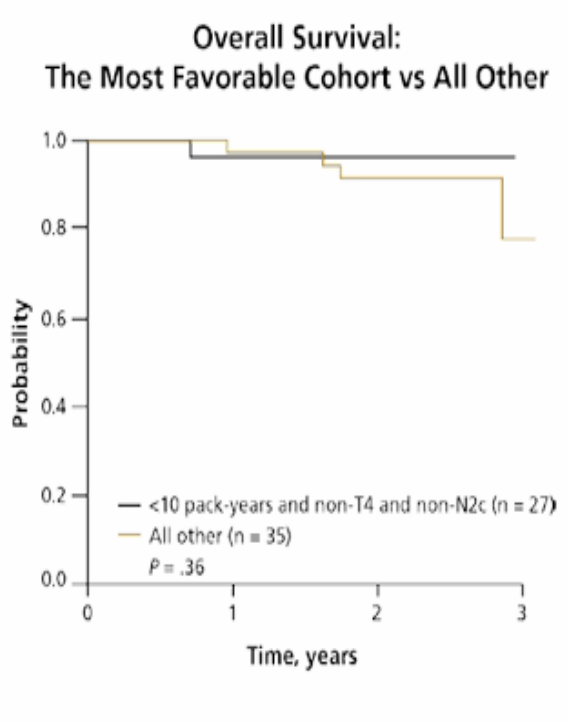


70% CR at primary
58% CR at nodal site

Cmelak A ASCO 2014, abstract LBA6006

ECOG 1308

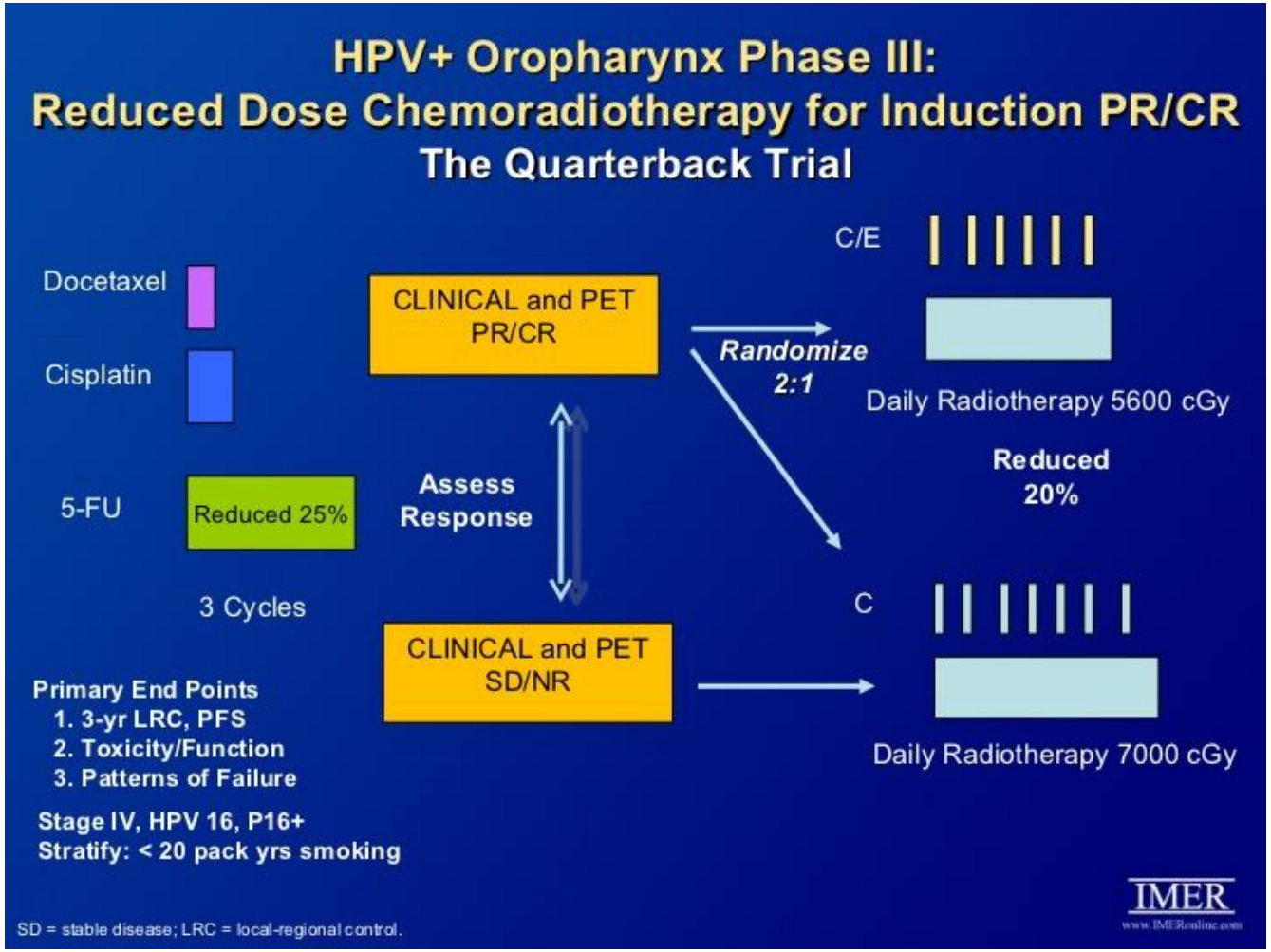




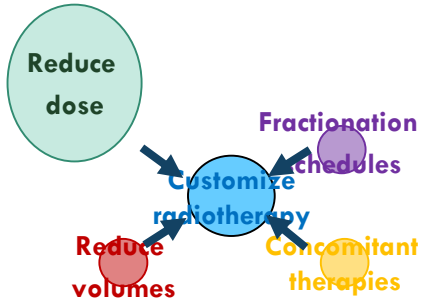
Cmelak A ASCO 2014, abstract LBA6006
Marur JCO 2017

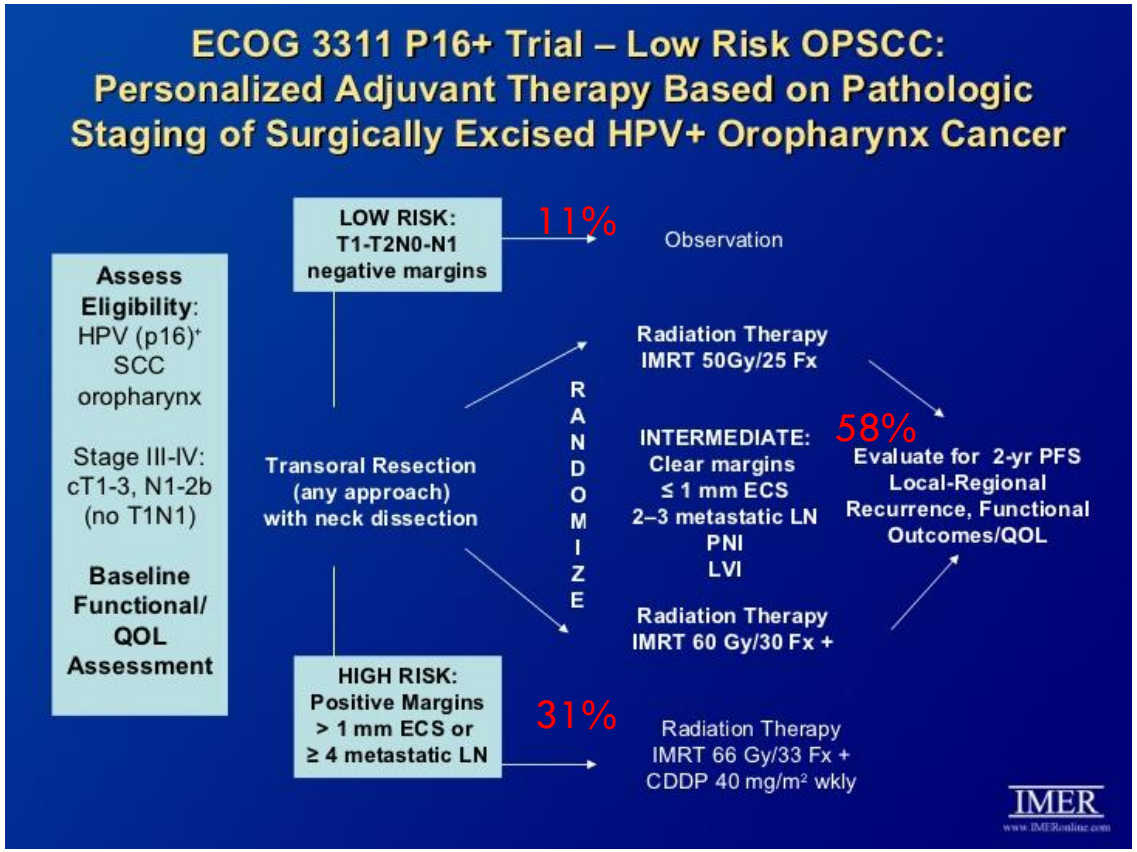
SELECTION BASED ON INDUCTIONCHEMO

Quarterback



3. POSTOP DOSE REDUCTION

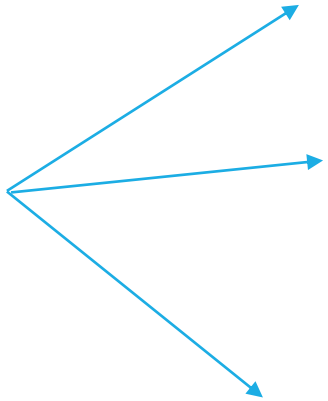




POSTOP DOSE REDUCTION

PATHOS

-Phase II trial
242 pts
- P16+ OPSCC
-T1T3N0N2b
-transoral surgery to primary + neck dissection



Low risk: no adjuvant therapy

Intermediate risk:
T3 tumours (or T1T2 tumours with additional risk factors)
N2a or N2b
perineural and/or vascular invasion or close margins (15mm)

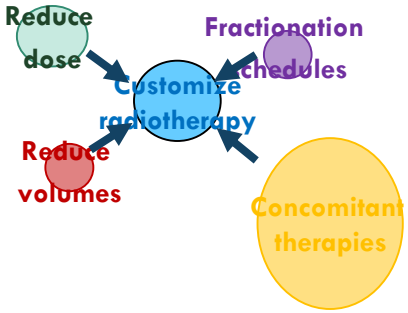
- PORT 60Gy 6 wks
- PORT 50Gy 5 wks

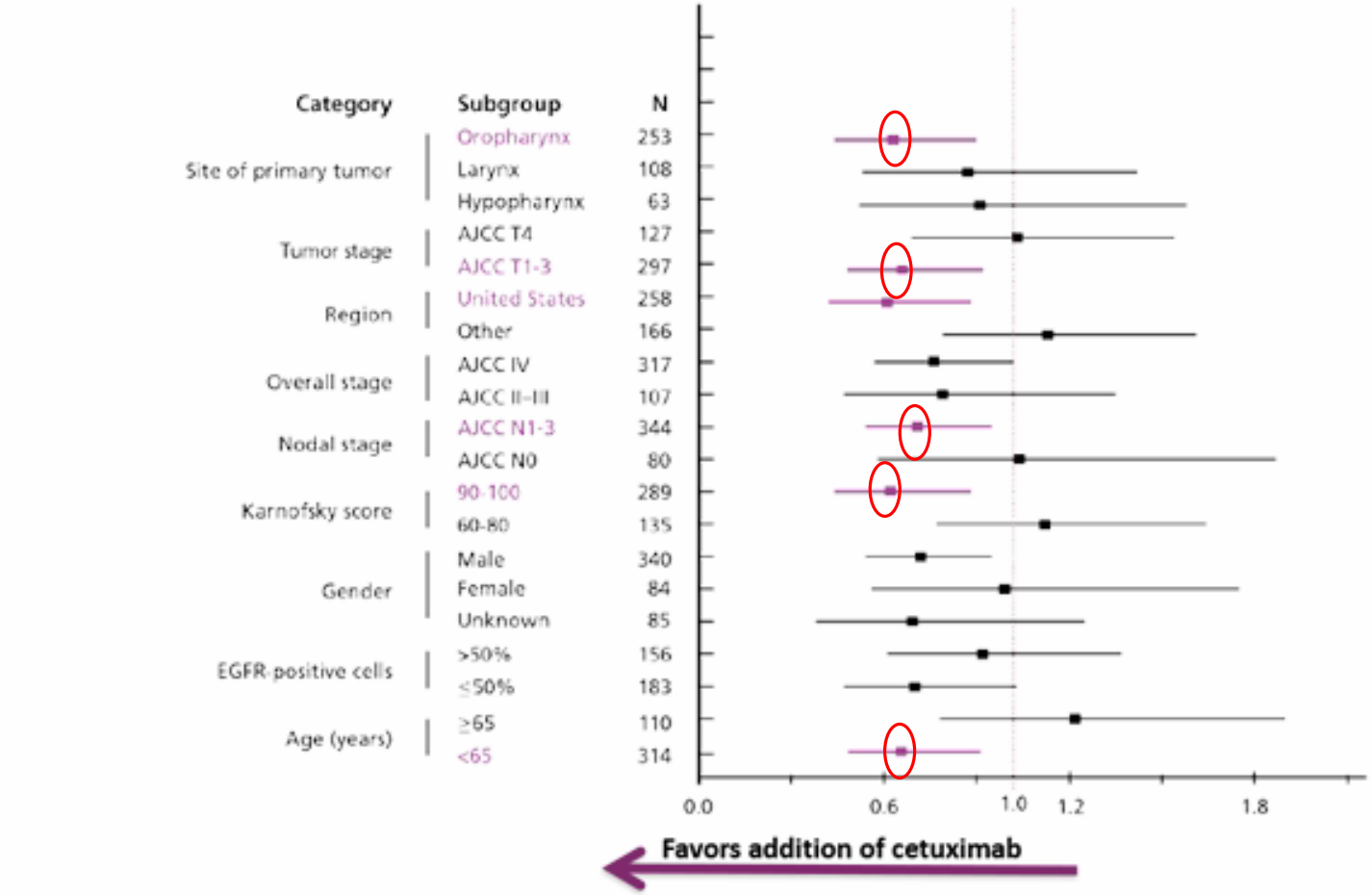
High risk
positive (<1mm) margins
and/or evidence of cervical lymph node extracapsular spread

- POCRT 60Gy 6 wks + cisplat
- PORT 60Gy 6 wks

4.CONCOMITANT THERAPIES

SUBSTITUTE CETUXIMAB FOR CISPLATIN?





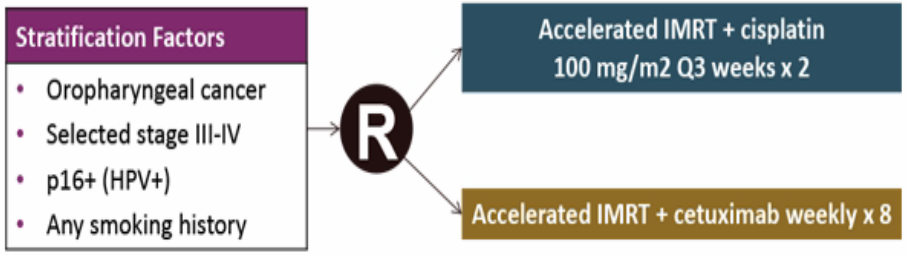
Bonner JA Lancet Oncol 2010

SUBSTITUTE CETUXIMAB FOR CISPLATIN?

Concomitant therapies

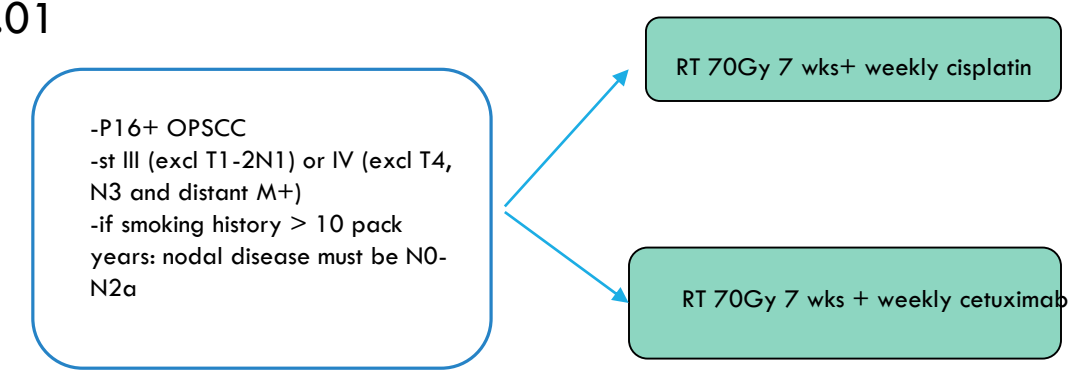
- 805 patients
- Primary outcome: survival (non-inferiority trial)

RTOG 1016

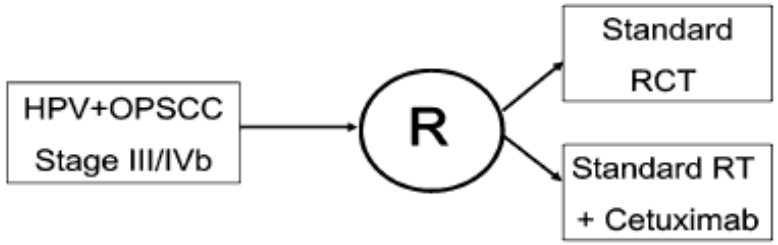


	Cisplatin	Cetuximab	
5Y-LRR	9.9%	17.3%	
5Y-DMR	8.6%	11.7%	
5Y-PFS	78.4%	67.3%	HR: 1.29-2.29
5Y-OS	84.6%	77.9%	

TROG 12.01

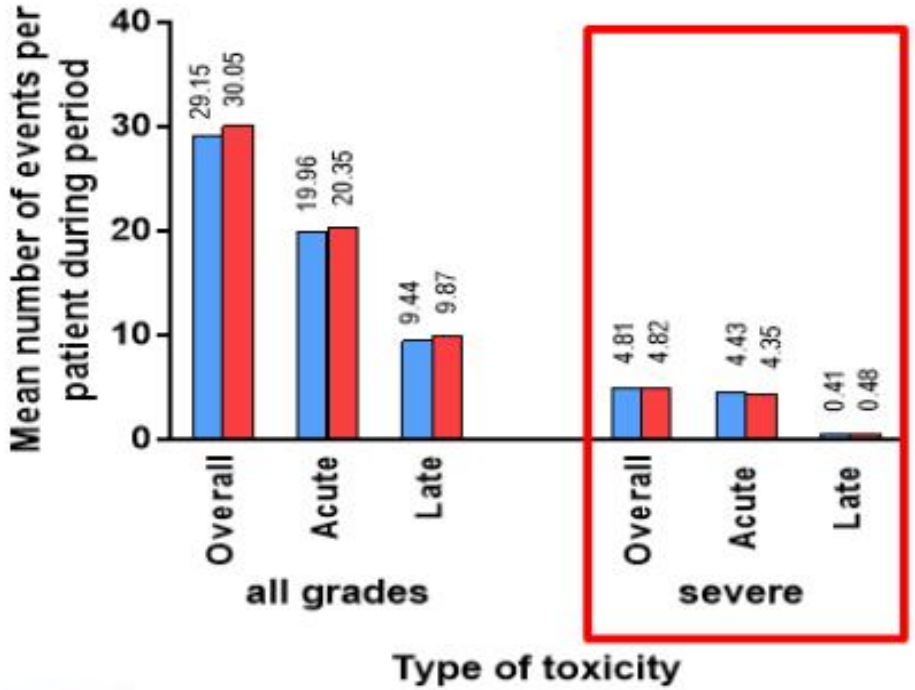


De-ESCALaTE



TOXICITY

Same rates of severe (G3-5) and all grade (G1-5) toxicity between arms



Cisplatin + radiotherapy

Cetuximab + radiotherapy

Overall severe toxicity events per patient:

Cisplatin: 4.81 (4.23 to 5.40)

Cetuximab: 4.82 (95%CI = 4.22 to 5.43)

p= 0.98

MUNICH 2018 ESMO congress

Slide ESMO presentation H. Mehanna

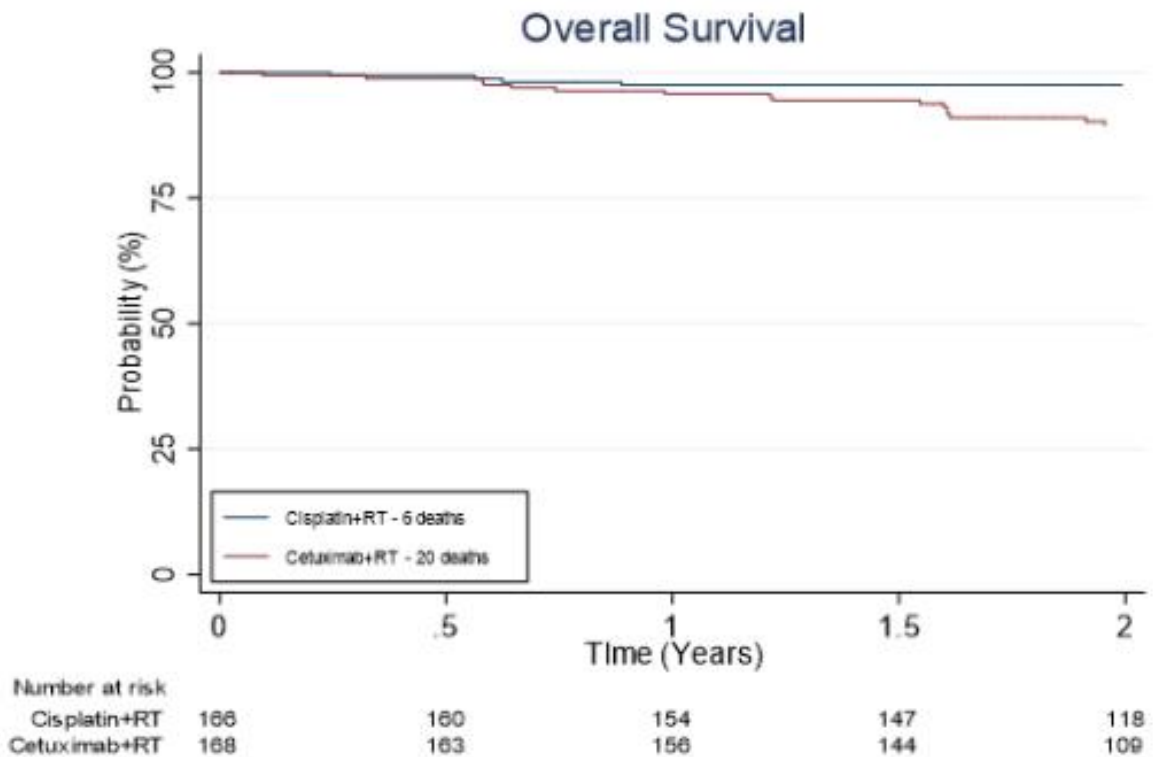
SURVIVAL

Significantly worse overall survival with cetuximab

2 yr OS:
97.5% vs 89.4%
p= 0.001

HR=4.99
95% CI: 1.70 to 14.67

Adjusted HR: 5.94,
95% CI: 1.98-17.79, p=0.001



MUNICH 2018 ESMO congress

Slide ESMO presentation H. Mehanna

WHAT ABOUT ESCALATION TRIALS?

Intermediate-risk HPV+ group and T4 or N3 disease: OS about 70% at 3 years

Escalating treatments in this high risk group?

Phase III

CompARE trial (UK)

HPV +ve OPC with N2b+ disease >10 pack years

or high risk (HPV–ve OPC) as per Ang classification

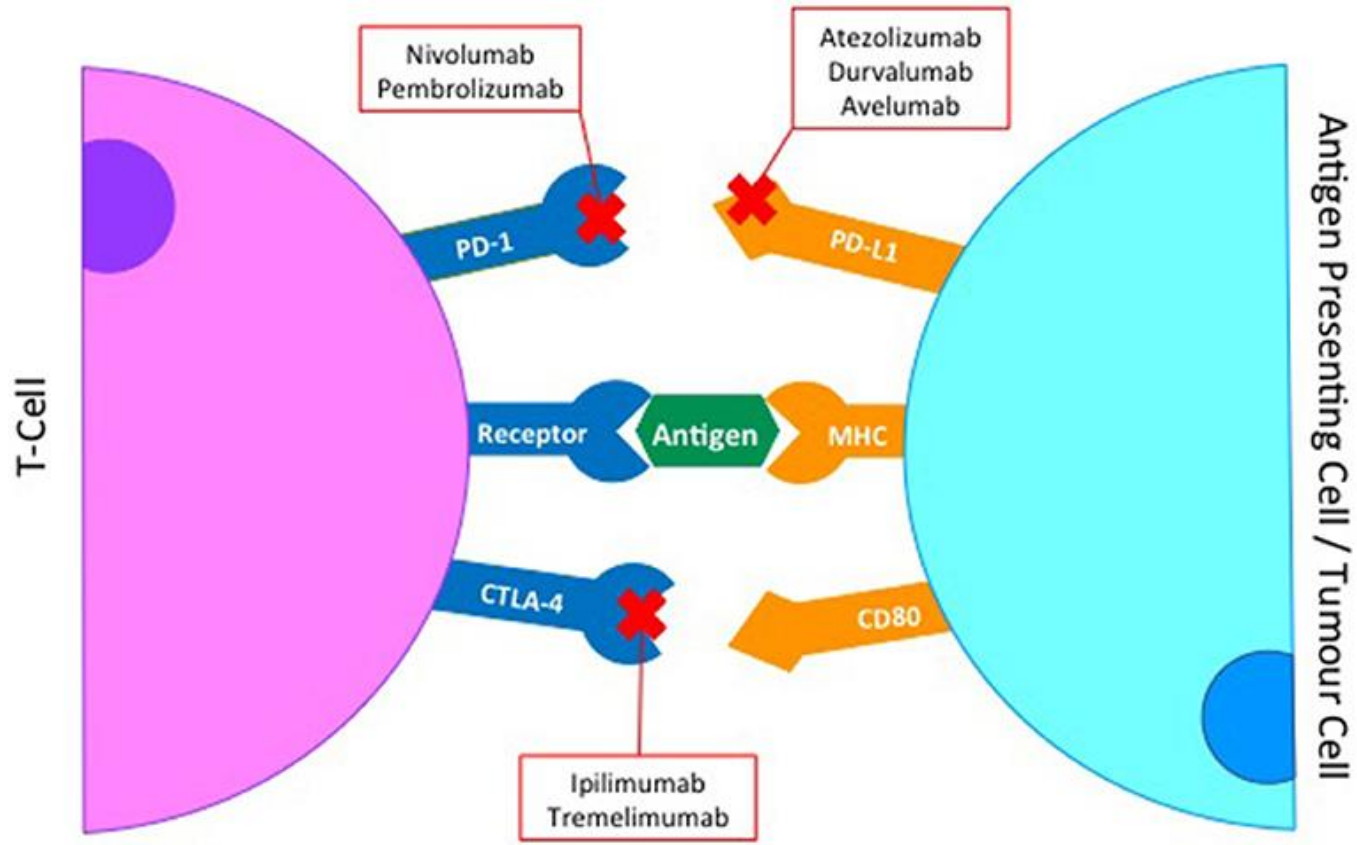
Arm 1 concomitant cisplat+RT

Arm 2 surgery + arm 1

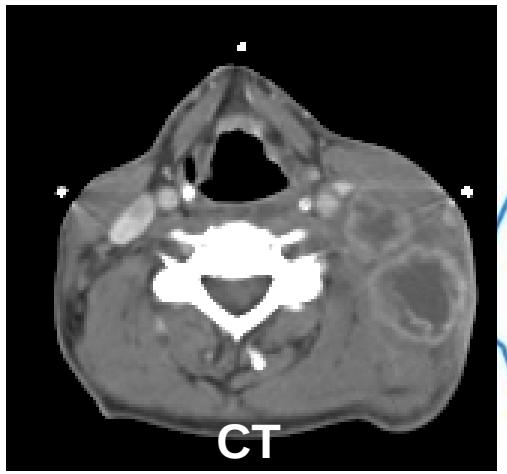
Arm 3 induction TPF+ arm 1

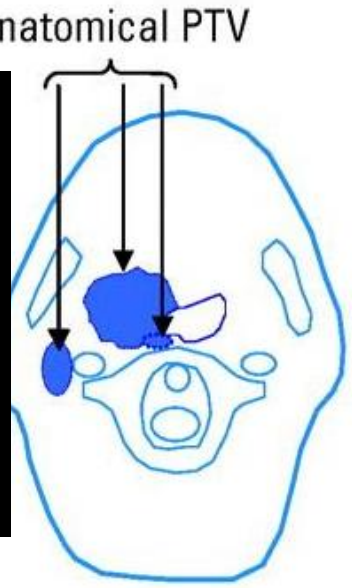
Arm 4 dose-escalated RT

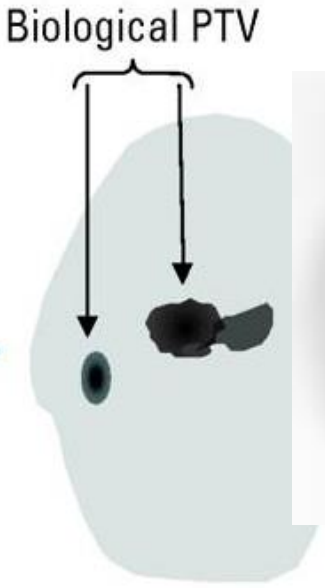
Primary outcome: OS

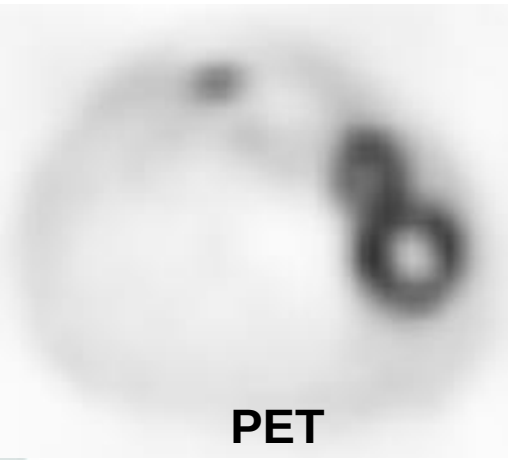

Nivolumab
Pembrolizumab
Atezolizumab
Durvalumab
Avelumab
PD-1
PD-L1
T-Cell
Receptor
Antigen
MHC
Antigen Presenting Cell / Tumour Cell
CTLA-4
CD80
Ipilimumab
Tremelimumab

Increase dose to ‘parts’ of the tumor: Dose-painting on the biological target volume (BTV)

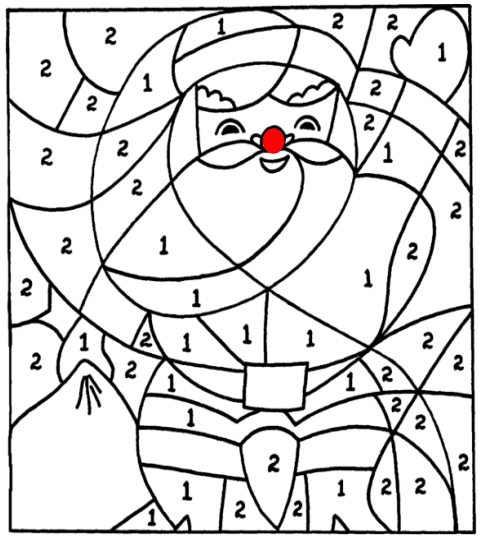


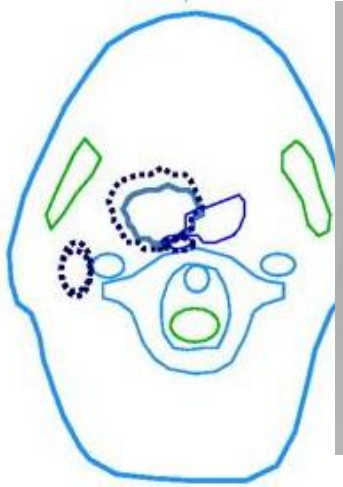


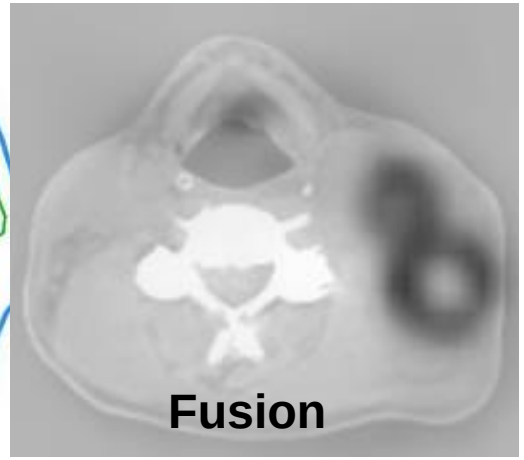




Fusion







Galvin J. et al. J Clin Oncol 2007.

CONCLUSIONS

- Oropharyngeal carcinoma is on the rise with HPV as important causative factor- good prognosis
- Many interesting trials are ongoing de-escalation
  - Results to be awaited, sufficient follow up
  - Risk stratification!
  - Several phase II studies show excellent outcomes
- Poor prognosis HPV+ disease and HPV- disease: 'escalation' trial
- Current recommendations: treat patients according to their stage of disease at presentation, irrespective of HPV status