Targeted therapy in HNC

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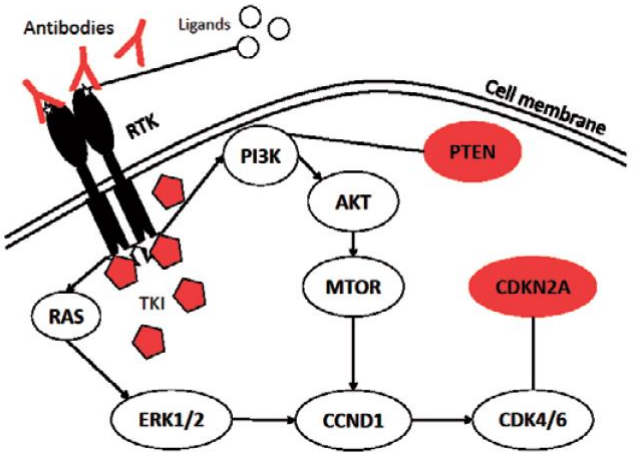
Email: punitalal11@gmail.com

Road map

- Backround of HNC
- Genesis of targeted therapy esp in HNC
- EGFR inhibitor/ EGFR TKI
- Role in HPV positive cancers
- Role in Rec/ Mets setting
- Future of targeted therapy
- Take home message



Background

- HNC 7th Common cancer – heterogeneous disease
- Addition of chemotherapy to loco-regional treatment – 4.5% benefit at 5 years *(Pignon MACHNC update Radiother Oncol2009)*
- Significant toxicity
- With improving local controls – systemic spread being witnessed
- Recurrent/ metastatic – poor prognosis

Side effect profile of active chemotherapeutic agents

- Marrow suppression
- Mucositis and dysphagia
- Sensori neural hearing loss
- Polyneuropathy

Mitigating toxicity – an important goal

The ERBB receptor family network, comprising EGFR (HER1, ERBB1), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4), plays an important part in tumorigenesis

Introduction of Targeted agents in Head Neck Cancer treatment

- Several driver mutations and genetic aberrations have been identified in HNSCC
- Eg; EGFR over expression and amplification
- Majority of mutations are in squamous epithelium (90%)
- No predictive biomarker identified to guide therapy
- Other pathways like p13K – being explored
- HPV tumors – distinct molecular tumor entity; consequences for targeted therapy merits exploration

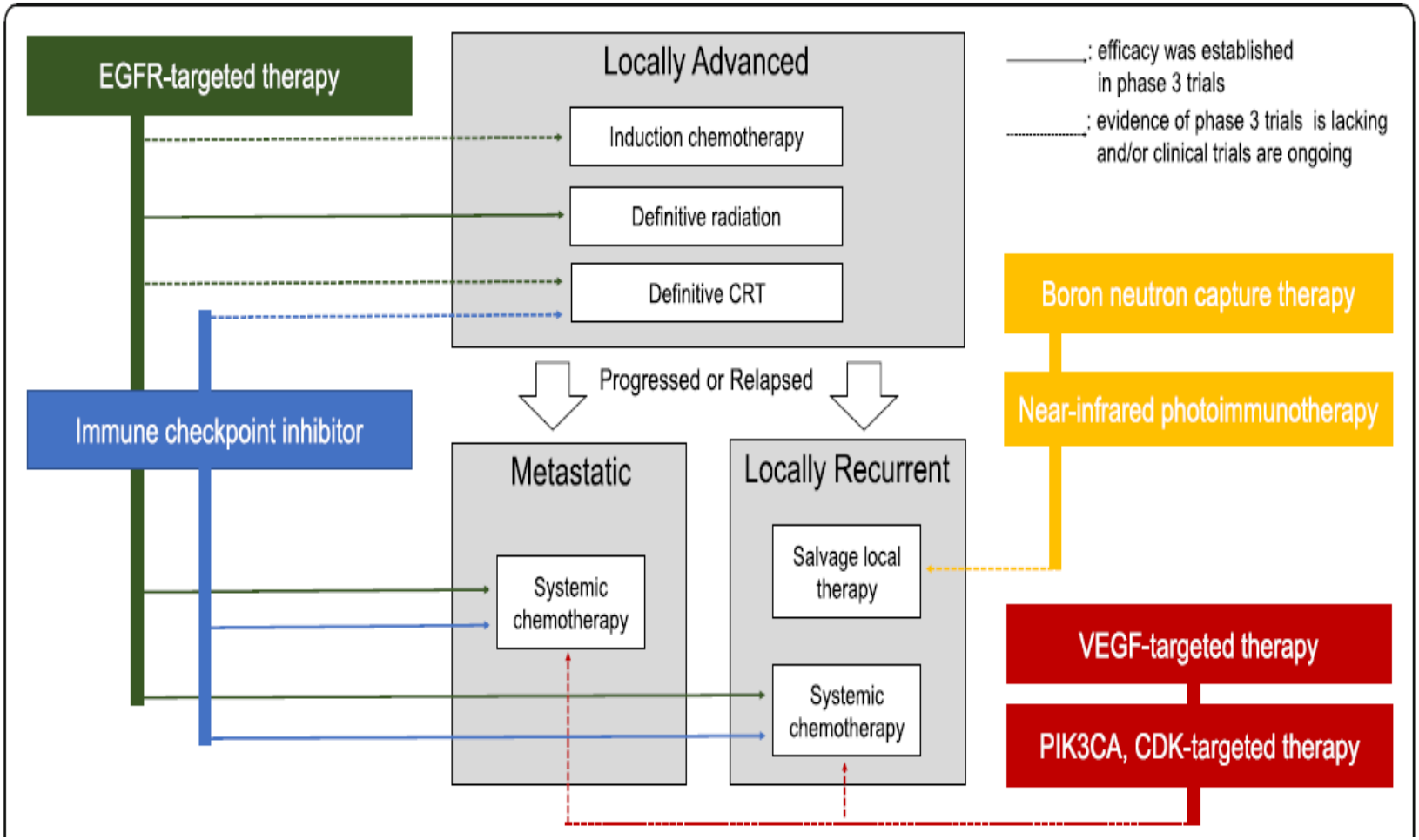
Targeted therapy in HNC - types

Table I. Examples of molecular-targeted therapies in the treatment of head and neck squamous cell carcinoma.

Mechanism of action	Molecular targeted therapy
EGFR monoclonal antibodies	Cetuximab, panitumumab, zalutumumab and nimotuzumab
EGFR tyrosine kinase inhibitors	Gefitinib, erlotinib, lapatinib, afatinib and dacomitinib
VEGF inhibitors	Bevacizumab
VEGFR inhibitors	Sorafenib, sunitinib and vandetanib
PI3K/AKT/mTOR pathway inhibitors	Rapamycin, temsirolimus, everolimus, torin1, PP242 and PP30
Anti-PD-1 antibodies	Pembrolizumab and nivolumab

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; PI3K, phosphatidylinositol 3-kinase; AKT, serine/threonine-specific protein kinase; mTOR, mammalian target of rapamycin; PD-1, programmed death receptor 1.

Landscape of non surgical treatment of HNSCC



Epidermal Growth Factor

- Transmembrane protein belonging to ErbB1 or HER1 family of receptor tyrosine kinase (RTK) activity – most well described cancer drug target
- EGFR overexpression seen in 90% HNSCC

- Extracellular signals lead to altered intracellular responses such as cell proliferation, apoptosis, angiogenesis, metastasizing potential.
- EGFR binds – homodimers/heterodimers with other members of ERB Family → activate signaling pathway

EGFR over expression - negative prognostic factor

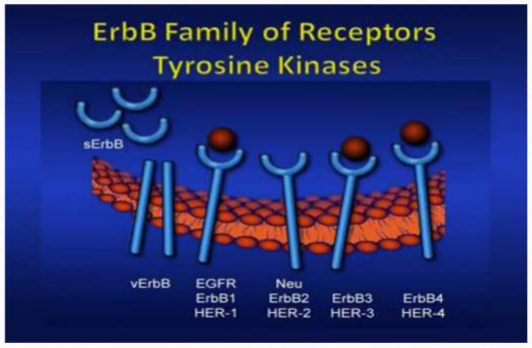
Clinical implication –
Size ↑
↓radiosensitivity
↑ risk of recurrence

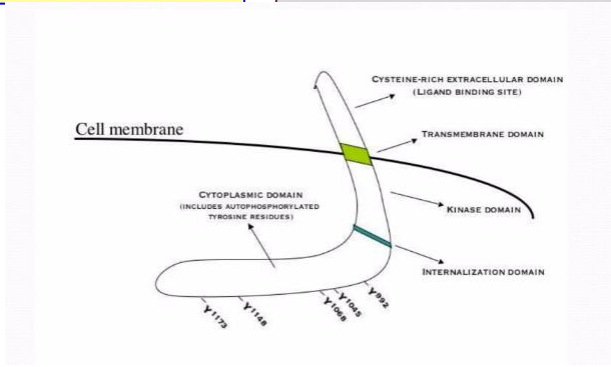
EGFR inhibitors – tumor activity / tolerable profile

- Monoclonal anti EGFR antibodies – attach to extracellular domain – interferes with signal transmission inside the cell

- TKI act at cytoplasmic level. Inhibit autophosphorylation of EGFR. Interferes with transmission at lower intracellular level

Erb B family of receptor





- In rec/ mets setting -to be given until progression/ unacceptable side effects

Cetuximab

- IgG1 monoclonal antibody exclusively against EGFR
- Binds to extracellular domain - inhibits ligand binding → block receptor dimerization, TK phosphorylation, signal transduction
- Preclinical studies – synergism with RT
  - Induction of apoptosis
  - Inhibit proliferation
  - Inhibits angiogenesis
  - Enhance response to chemoradiotherapy
- Does not add to radiation related toxicities
- High level of EGFR – worse prognosis
- Only clinical predictor – skin rash

EGFR TKI

- Modest clinical benefit
- Small molecules
- Gefitinib, Erlotinib, Afatinib, lapatinib
- Lack of biomarkers

Gefitinib and Erlotinib

- Oral quinazoline
- Highly selective EGFR TKI
- Dose schedule – 250mg daily
- 1-11% response rate
- Oral Erlotinib – 150mg daily – high toxicity rate

Historical seminal publication

Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival

James A Bonner, Paul M Harari, Jordi Giralt, Roger B Cohen, Christopher U Jones, Ranjan K Sur, David Raben, Jose Baselga, Sharon A Spencer,

- N=450 LAHNSCC
- RT+Cetuximab vs RT
- 45% vs 36% 5yr OS
- OS advantage -9%
- Esp in ≥ Gd2 rash
- No CT arm

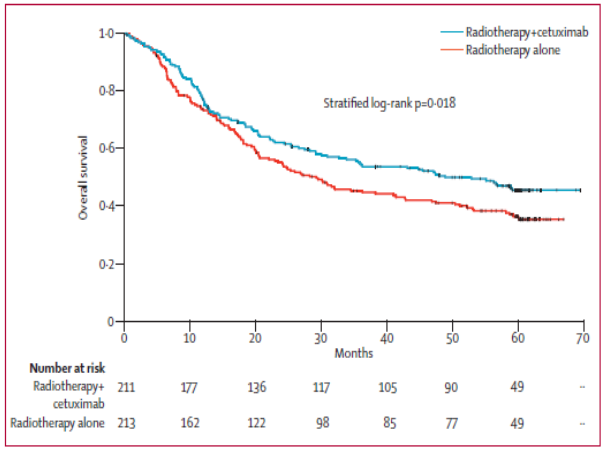


Figure 2: Overall survival by treatment: 5-year update (median follow-up 60 months)

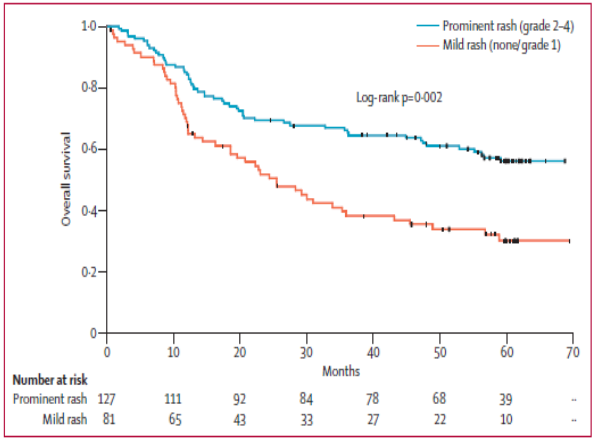


Figure 5: Overall survival by severity of rash in cetuximab-treated patients

Interpretation For patients with LASCCHN, cetuximab plus radiotherapy significantly improves overall survival at 5 years compared with radiotherapy alone, confirming cetuximab plus radiotherapy as an important treatment option

Bonner etal Lancet Oncol 2010

Targeted therapy as 1st line in R/M HNC

Phase III Randomized Trial of Cisplatin Plus Placebo Compared With Cisplatin Plus Cetuximab in Metastatic/ Recurrent Head and Neck Cancer: An Eastern Cooperative Oncology Group Study

Barbara Burtness, Meredith A. Goldwasser, William Flood, Bassam Mattar, and Arlene A. Forastiere

- 117 pts
- CDDP+Cetuximab vs CDDP+Placebo
- Endpoint PFS
- Objective **response rates improved** (26% vs 10%)
- Active as first line agent in RMHNSCC

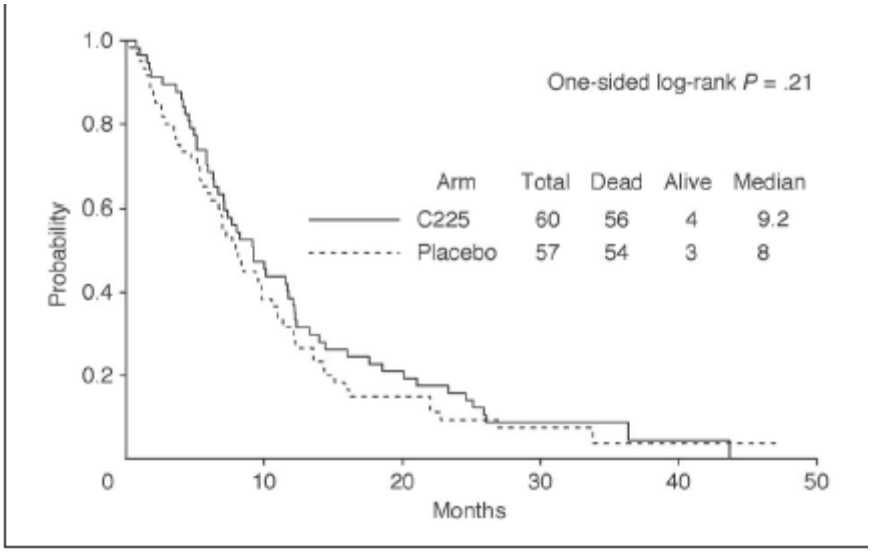


Fig 2. Overall survival by treatment group.

Conclusion

Addition of cetuximab to cisplatin significantly improves response rate. There was a survival advantage for the development of rash. Progression-free and overall survival were not significantly improved by the addition of cetuximab in this study.

Burtness et al, JCO2005

EGFR expression interpretations –ECOG study

- Tumor tissue assayed for EGFR expression by IHC
- Intensity score -0-3; Density – proportions carrying highest intensity –increments of 10%
- High score – 3+ in ≥80% cells
- Low to moderate – anything less

Subset analysis –
•Response rate 27% EGFR (Low to mod) vs 9% EGFR (High)
•Low to moderate -41% (cetuximab) vs 12% (placebo) 9p=.03)
•High EGFR -12% vs 6% (p=ns)

Explanation for failure of cetuximab in high EGFR –
•Not all targets were covered with the drug. Need high dose?
•Other independent of ligand binding mechanism start to play
• ?Cetuximab resistance

Phase III Randomized, Placebo-Controlled Trial of Docetaxel With or Without Gefitinib in Recurrent or Metastatic Head and Neck Cancer: An Eastern Cooperative Oncology Group Trial

Athanassios Argiris, Musie Ghebremichael, Jill Gilbert, Ju-Whei Lee, Kamakshi Sachidanandam, Jill M. Kolesar, Barbara Burtness, and Arlene A. Forastiere

- Poor PS/ heavily treated 270 R/M pts
- Weekly docetaxel +placebo vs docetaxel +gefitinib
- **No synergism/ improved therapeutic efficacy**
- Outcomes remain poor

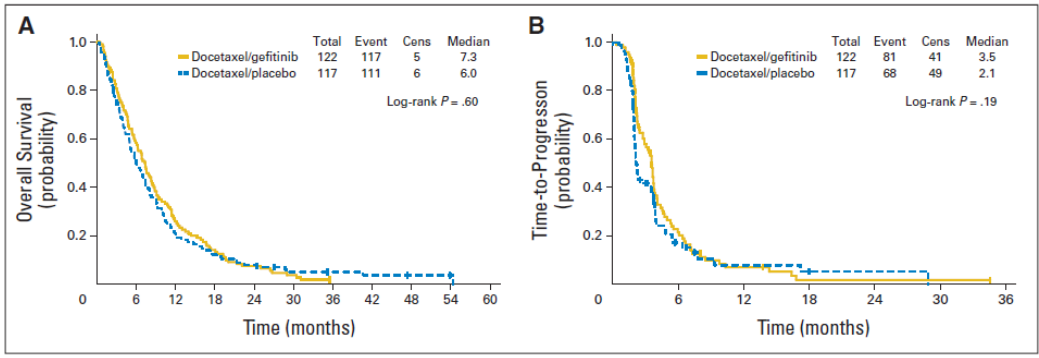


Fig 2. Kaplan-Meier estimates of (A) overall survival by treatment arm (n = 239) and (B) time-to-progression by treatment arm (n = 239). Cens, censored.

Conclusion

The addition of gefitinib to docetaxel was well tolerated but did not improve outcomes in poor prognosis but otherwise unselected patients with SCCHN.

Argiris et al, JCO2013

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., Dmytro Zabolotnyy, M.D., Ph.D., Heinz-Roland Kienzer, M.D., Didier Cupissol, M.D., Frederic Peyrade, M.D., Marco Ber Ihor Vynnychenko, M.D., Ph.D., Dominique De Raucor Carsten Bokemeyer, M.D., Armin Schueler, M.S., Nadia A and Ricardo Hitt, M.D., Ph.D.

- 440 pts untreated RM HNC
- Pr end point -OS
- Median OS - 7.4mo vs 10.1 mo
- Significant OS benefit

•Best outcomes were seen in <65yrs, fit, well to mod diff Oral cavity cancers who recd Cisplatin; EGFR >40% +

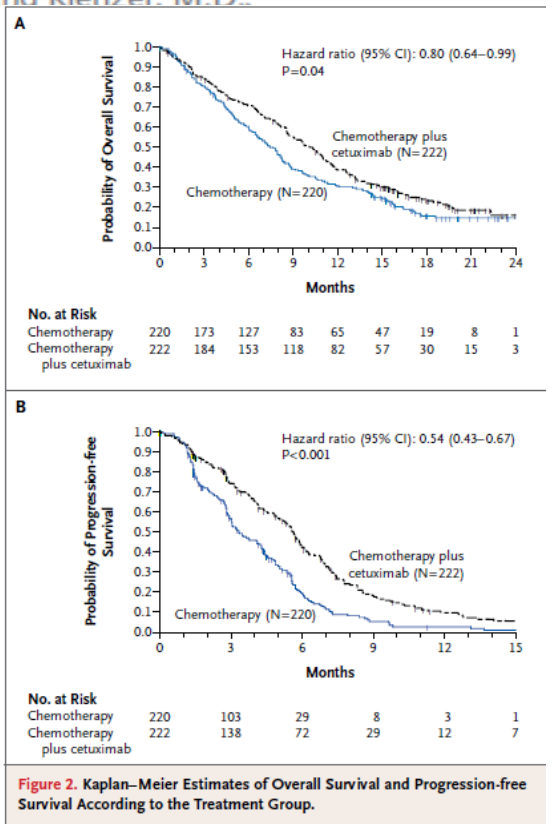


Figure 2. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival According to the Treatment Group.

CONCLUSIONS

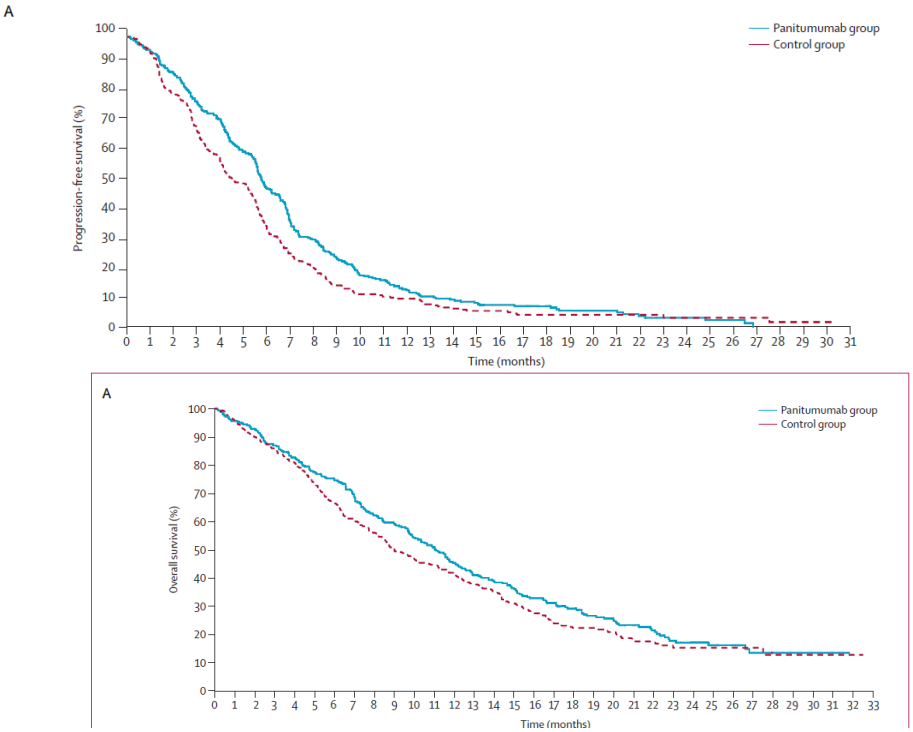
As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum–fluorouracil chemotherapy improved overall survival when given as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck. (ClinicalTrials.gov number, NCT00122460.)

Vermorken et al; EXTREME Trial, NEJM, 2008

Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial

Jan B Vermorken, Jan Stöhlmacher-Williams, Irina Davidenko, Lisa Licitra, Eric Winquist, Cristian Villanueva, Paolo Foa, Sylvie Rottey, Krzysztof Skladowski, Makoto Tahara, Vasant R Pai, Sandrine Faivre, Cesar R Blajman, Arlene A Forastiere, Brian N Stein, Kelly S Oliner,

- 657 patients
- CDDP+5FU+Panitu mumab vs CDDP+5FU



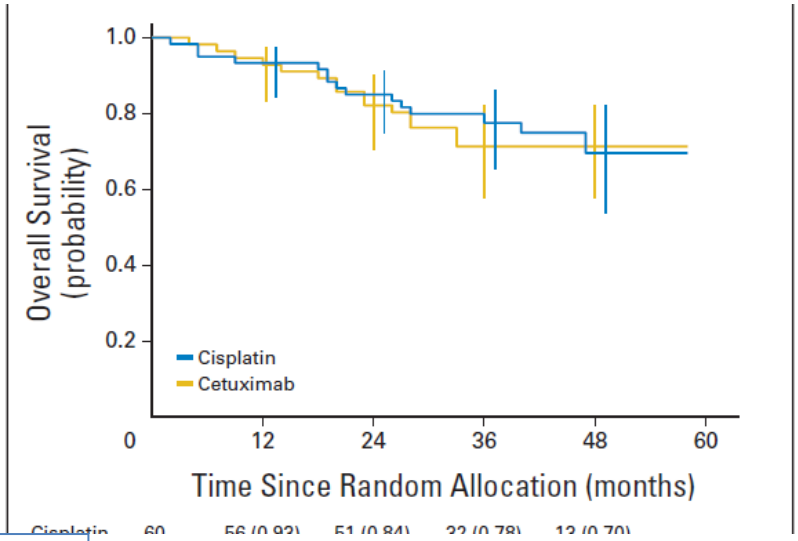
Interpretation Although the addition of panitumumab to chemotherapy did not improve overall survival in an unselected population of patients with recurrent or metastatic SCCHN, it improved progression-free survival and had an acceptable toxicity profile. p16 status could be a prognostic and predictive marker in patients treated with panitumumab and chemotherapy. Prospective assessment will be necessary to validate our biomarker findings.

Vermorken et al; SPECTRUM Trial, Lancet Oncol, 2013

Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation: The TREMPLIN Randomized Phase II Study

Jean Louis Lefebvre, Yoann Pointreau, Frederic Rolland, Marc Alfonsi, Alain Baudoux, Christian Sire, Dominique de Raucourt, Olivier Malard, Marian Degardin, Claude Tuchais, Emmanuel Blot, Michel Rives, Emile Reyt, Jean Marc Tourani, Lionel Geoffrois, Frederic Peyrade, Francois Guichard, Dominique Chevalier,

- Prev untreated LAHNSCC
- Ind CT – responders – CRT vs Cetuximab +RT



Lefebvre et al; TREMPLIN Trial, JCO, 2013

Cetuximab+ RT is comparable to Cisplatin + RT in concurrent setting
Both CRT and BRT are difficult to deliver after Induction CT
Local failures – less in CRT
Salvage surgery – BRT
OS similar

A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck†

T. Y. Seiwert[1*], J. Fayette[2], D. Cupissol[3], J. M. del Campo[4], P. M. Clement[5], R. Hitt[6], M. Degardin[7], W. Zhang[8], A. Blackman[9], E. Ehrnrooth[10] & E. E. W. Cohen[11]

- Oral Afatinib is irreversible small molecule ERB2 family blocker.
- Outcomes comparable to cetuximab – previous experience
- Multicentric phase II included previously treated 128 R/M HNSCC
- Afatinib vs Cetuximab

  - Comparable
  - Can be used sequentially – lack of cross resistance
  - Useful in enteral feeding patient too

Phase III Study of Gefitinib Compared With Intravenous Methotrexate for Recurrent Squamous Cell Carcinoma of the Head and Neck

J. Simon W. Stewart, Ezra E.W. Cohen, Lisa Licitra, Carla M.L. Van Herpen, Chonlakiet Khorprasert, Denis Soulieres, Pavel Vodvarka, Danny Rischin, Avgust M. Garin, Fred R. Hirsch, Marileila Varella-Garcia,

- 486 patients
- Oral Gefitinib 250 vs 500 vs methotrexate
- Favorable toxicity profile with Gefitinib

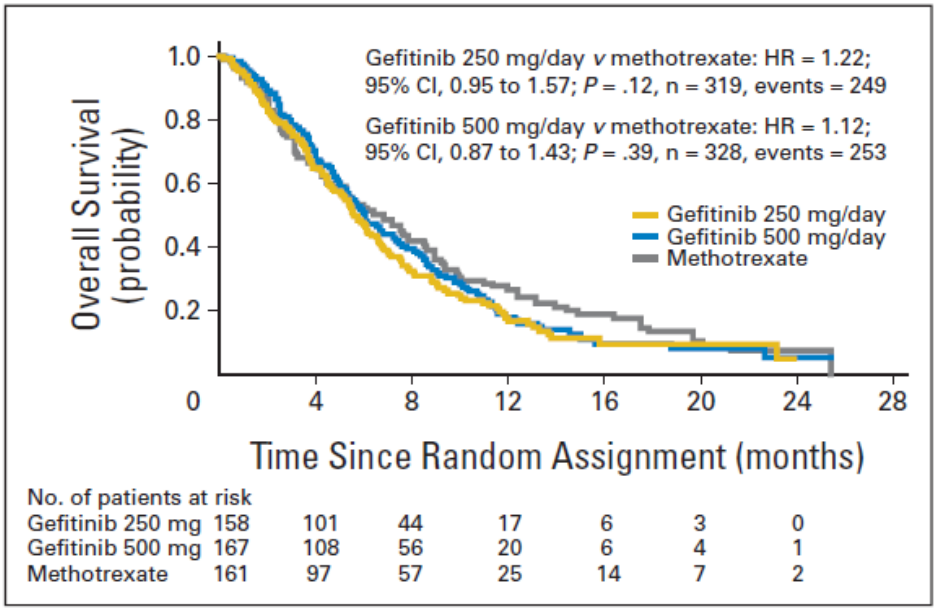


Fig 2. Overall survival.

Conclusion

In patients with recurrent or metastatic SCCHN, while responses with gefitinib were seen, neither gefitinib 250 nor 500 mg/day improved overall survival compared with methotrexate. With the exception of tumor hemorrhage–type events with gefitinib, the adverse event profiles were generally consistent with those previously observed.

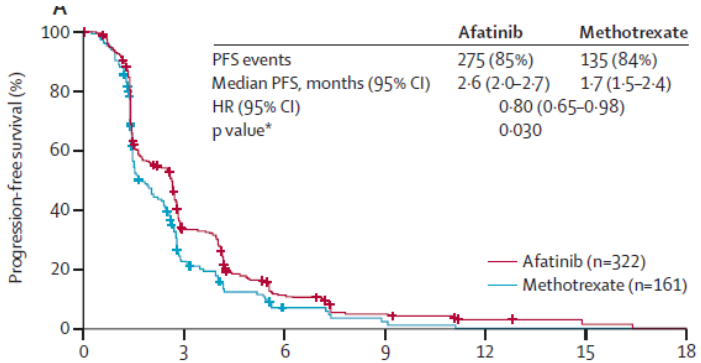
Stewart et al, JCO 2009

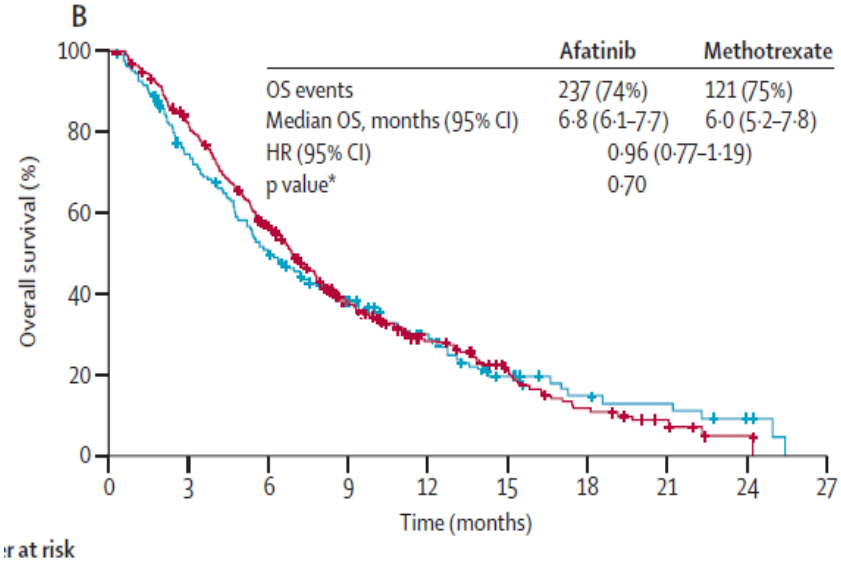
Targeted therapy as 2nd line in R/M HNC

Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial

Jean-Pascal H Machiels, Robert I Haddad*, Jérôme Fayette*, Lisa F Licitra, Makoto Tahara, Jan B Vermorken, Paul M Clement, Thomas Gauler, Didier Cupissol, Juan José Grau, Joël Guigay, Francesco Caponigro, Gilberto de Castro Jr, Luciano de Souza Viana, Ulrich Keilholz, Joseph M del Campo,*

- 483 patients
- Afatinib versus Methotrexate



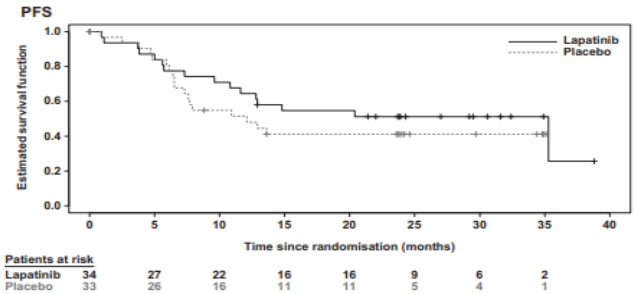


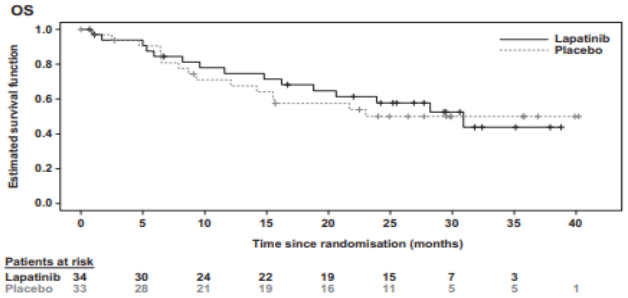
Interpretation Afatinib was associated with significant improvements in progression-free survival and had a manageable safety profile. These findings provide important new insights into the treatment of this patient population and support further investigations with irreversible ERBB family blockers in HNSCC.

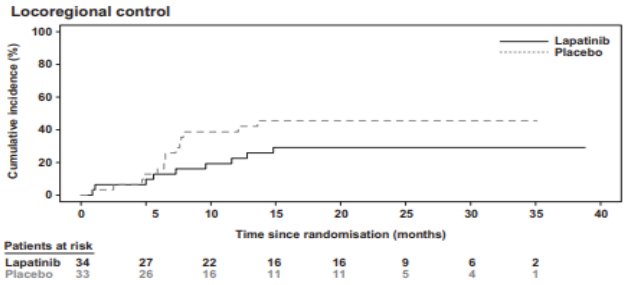
Macials et al; Lux HN 1 Trial, Lancet Oncol, 2015

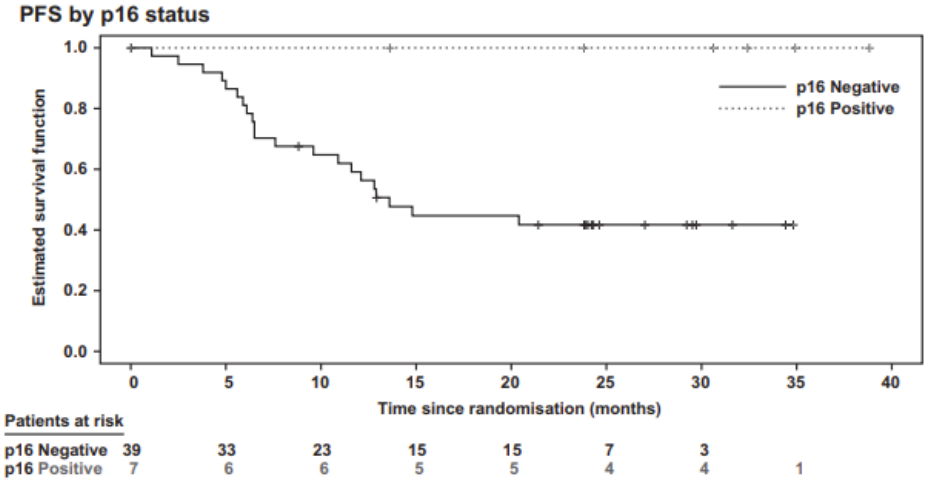
Randomised Phase II study of oral lapatinib combined with chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck: Rationale for future randomised trials in human papilloma virus-negative disease ☆

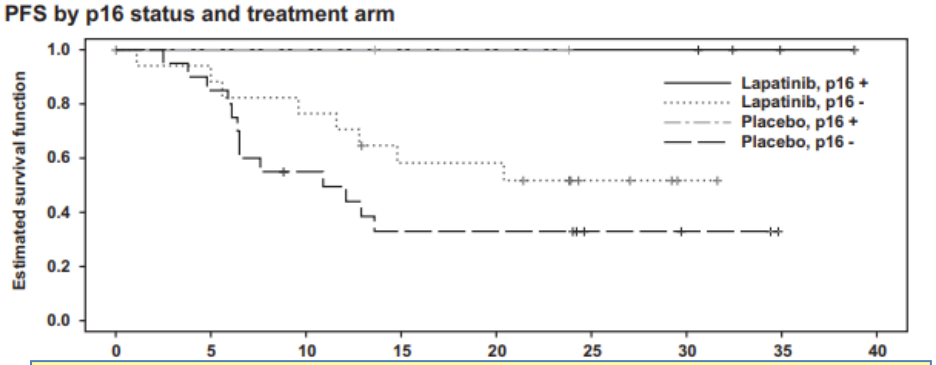
Kevin Harrington [a,*], Alain Berrier [b], Martin Robinson [c], Eva Remenar [d], Martin Housset [e], Fernando Hurtado de, Hisham Mehanna [h], Iman El-Hariry [i], N











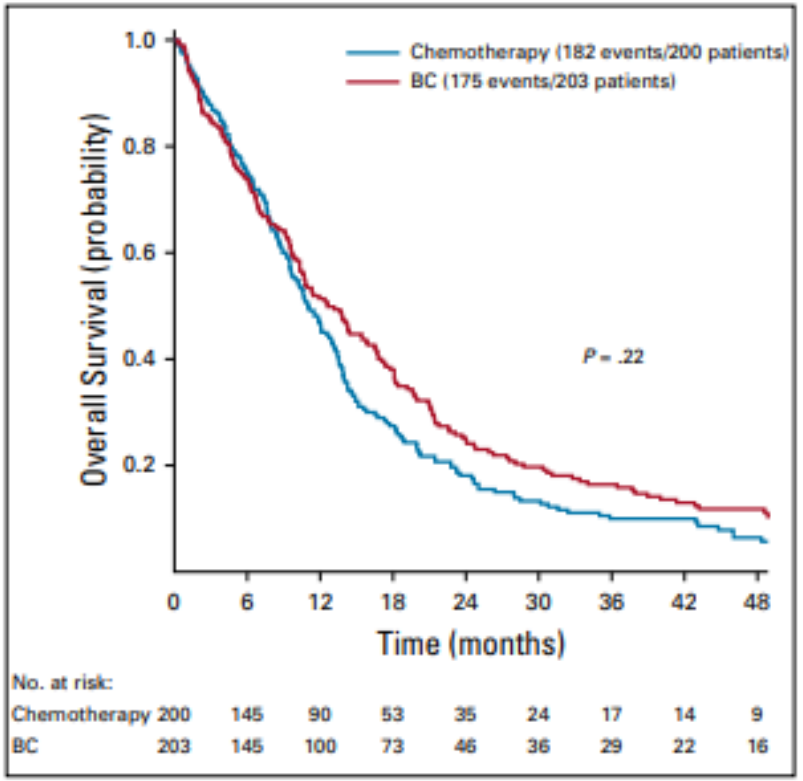
Oral Lapitinib (conc/ maintenance CRT) improves PFS in P16 negative cases

Harrington et al, Eur J Cancer 2013

Phase III Randomized Trial of Chemotherapy With or Without Bevacizumab in Patients With Recurrent or Metastatic Head and Neck Cancer

Athanassios Argiris, MD[1]; Shuli Li, PhD[2]; Panayiotis Savvides, MD[3]; James P. Ohr, MD[4]; Jill Gilbert, MD[5]; Marshall A. Levine, MD[6]; Arnab Chakravarti, MD[7]; Missak Haigentz Jr, MD[8]; Nabil F. Saba, MD[9]; Chukwuemeka V. Ikpeazu, MD, PhD[10]; Charles J. Schneider, MD[11]; Harlan A. Pinto, MD[12]; Arlene A. Forastiere, MD[13]; and Barbara Burtness, MD[14,15]

- 365 RMHNC
- VEGF antibody
- CDDP doublet with or without Bev (till progression)
- ORR- 35% vs 24% (p=.01)
- OS – 12mo vs 11mo (p=ns)
- Treatment related deaths -9%



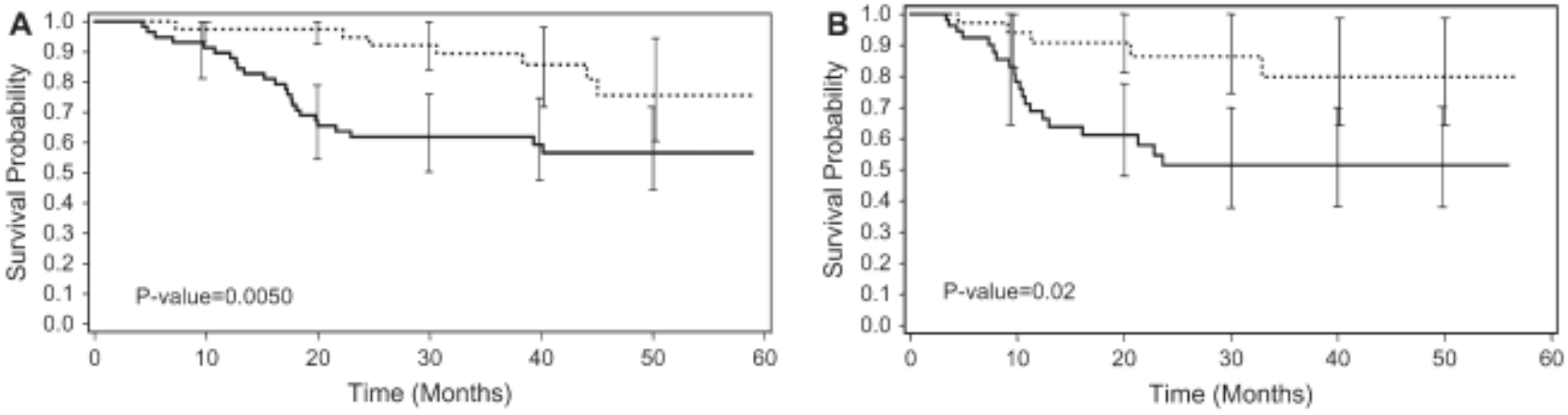
CONCLUSION The addition of bevacizumab to chemotherapy did not improve OS but improved the response rate and progression-free survival with increased toxicities. These results encourage biomarker-driven studies of angiogenesis inhibitors with better toxicity profiles in select patients with SCCHN.

J Clin Oncol 37:3266-3274. © 2019 by American Society of Clinical Oncology

Targeted therapy as in HPV positive HNC

HPV tumors of oropharynx

- Favorable histology ; young age at diagnosis
- Independent prognostic value – remains doubtful
- Predictive value - better response to treatment
- Toxicity concerns are greater



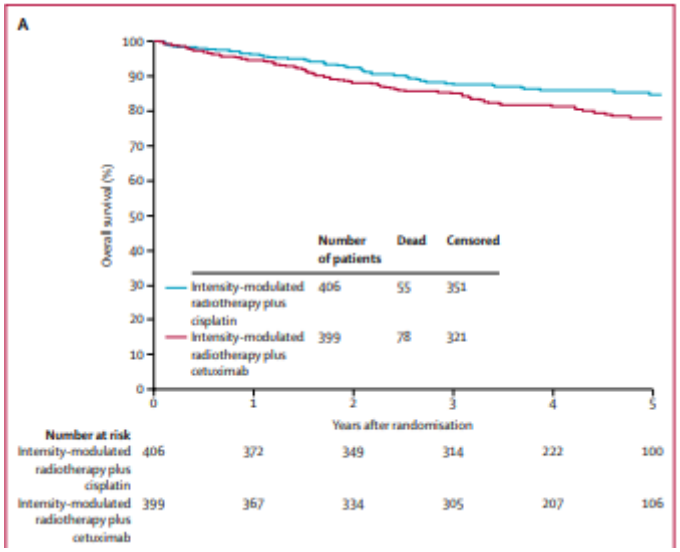
Fakhry et al, JNCI 2008

RTOG 1016 trial

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

Maura L Gillison, Andy M Trotti*, Jonathan Harris, Avraham Eisbruch, Paul M Harari, David J Adelstein, Erich M Sturgis, Barbara Burtness, John A Ridge, Jolie Ringash, James Galvin, Min Yao, Shlomo A Koyfman, Dukagjin M Blakaj, Mohammed A Razaq, A Dimitrios Colevas, Jonathan J Beitler, Christopher U Jones, Neal E Dunlap, Samantha A Seaward, Sharon Spencer, Thomas J Galloway, Jack Phan, James J Dignam,*

- Non inferiority trial; n=987 HPV (+)
- IMRT -70Gy/35fr/6wks
- CDDP replaced by Cetuximab
- End point - OS



RT+ conc Cisplatin – remains the standard of care

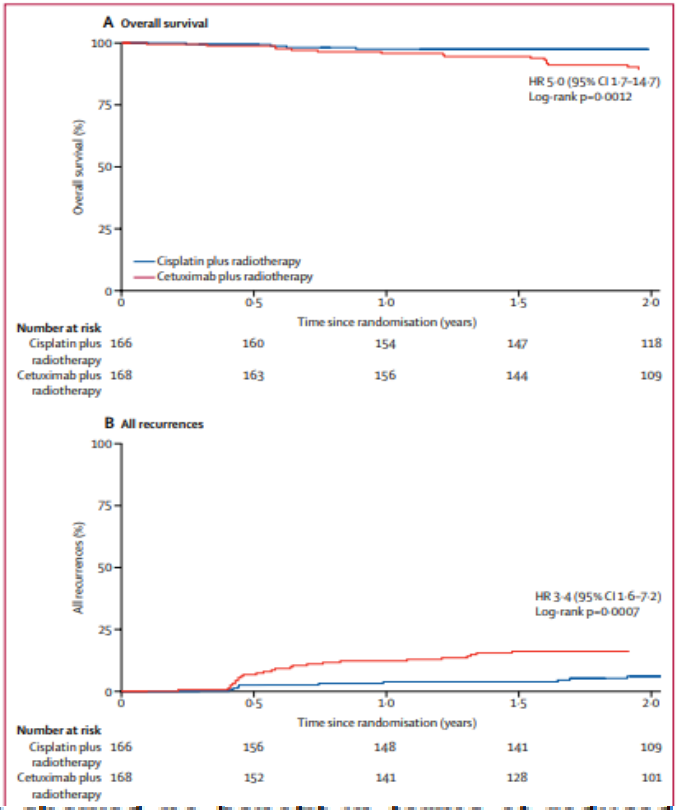
Interpretation For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin. Radiotherapy plus cisplatin is the standard of care for eligible patients with HPV-positive oropharyngeal carcinoma.

Gillison et al, RTOG 1016, Lancet 2018

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

Hisham Mehanna, Max Robinson, Andrew Hartley, Anthony Kong, Bernadette Foran, Tessa Fulton-Lieu… Matthew Dalby, Pankaj Mistry, Mehmet Sen, Lorcan O'Toole, Hoda Al Booz, Karen Dyker, Rafael Moleron, Stephen Whitaker, Sinead Bre… Eleanor Aynsley, Martin Rolles, Emma De Winton, Andrew Chan, Devraj Srinivasan, Ioanna Nixon, Joann… Julia Henderson, Kevin Harrington, Christopher McConkey, Alastair Gray, Janet Dunn, on behalf of the D…

- 334 HNC
- RT+ Cisplatin vs RT+ Cetuximab



•Immediate implications in clinical practice
•Even approved drugs must undergo randomized comparison
RT+ conc Cisplatin – remains the standard of care

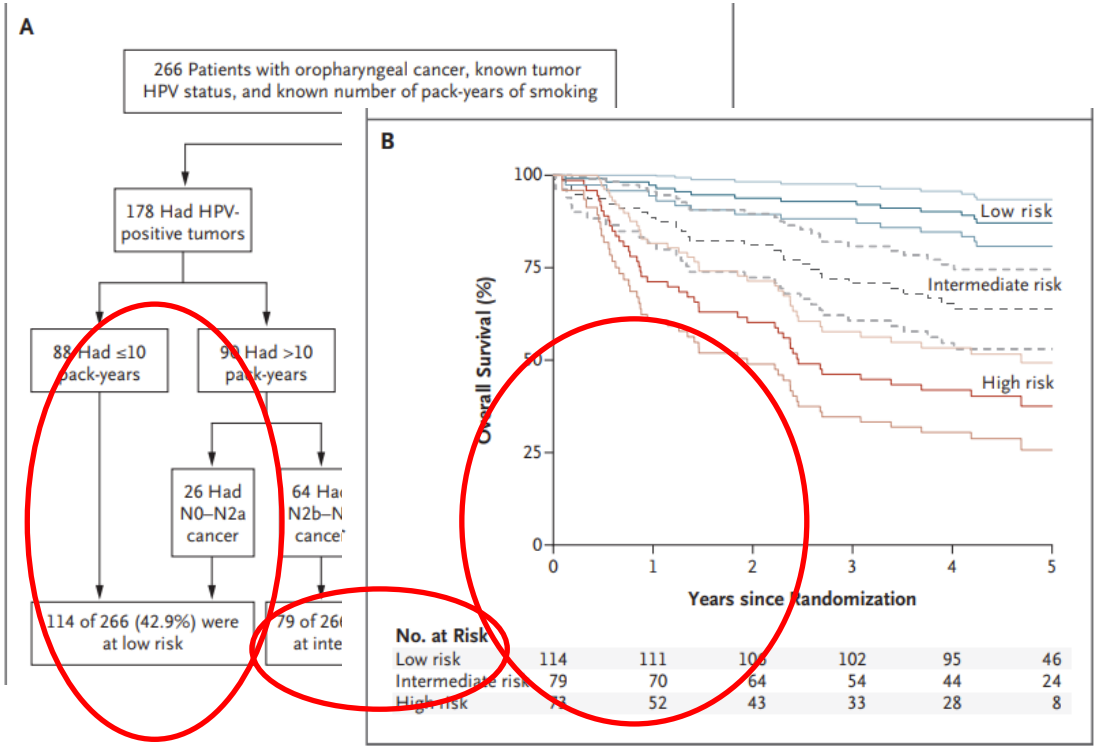
Interpretation Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control. Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

Mehanna et al, DeEScalate, Lancet 2018

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.,

- Recursive partitioning analysis
- HPV (+) vs HPV (-) subset
- CBRT+CDDP vs SFRT+CDDP
- 3yr OS – 82% vs 57%



- HPV and smoking are 2 important non-anatomical predictive factors

New kids on the block

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

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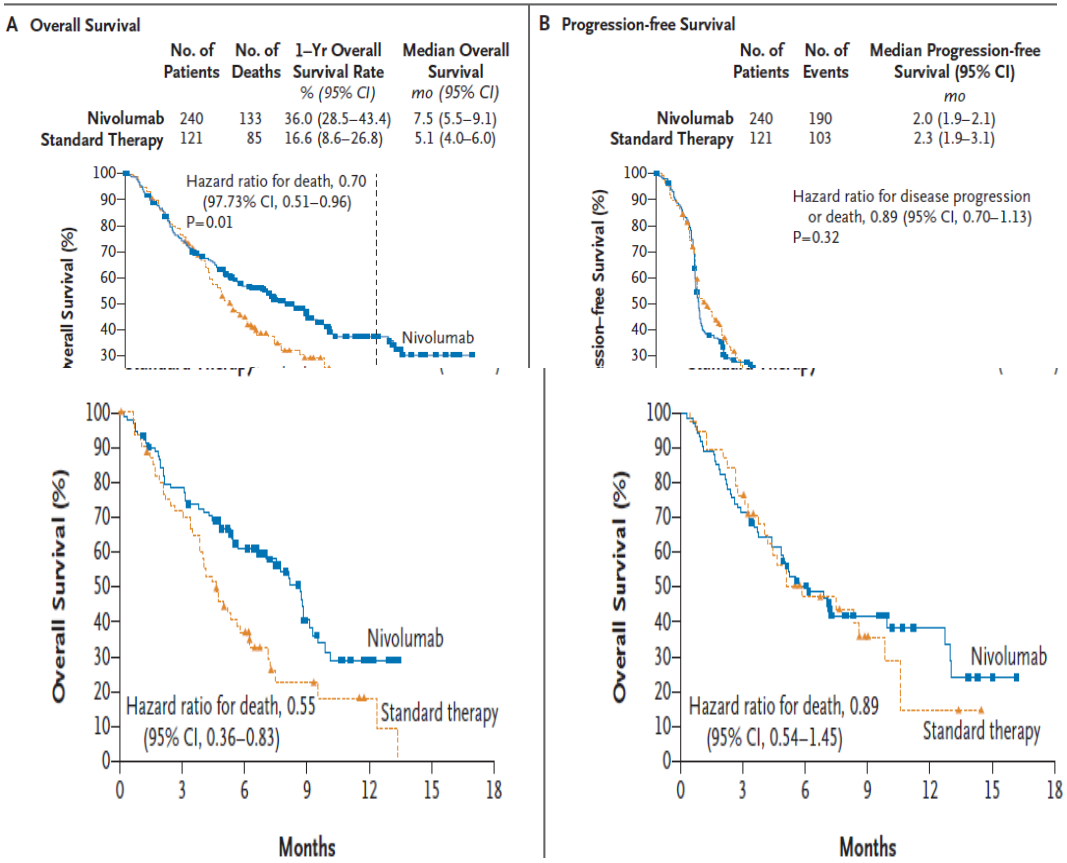
- Check point inhibitor. Anti PD1 monoclonal antibody
- N=361 RMHNC failed within 6 mo of CDDP th.
- End pt-OS; 2:1
- Std th – MTX, Doce etc
- 7.5mo vs 5.6 mo Med OS
- SAE-13% vs 35%
- OS benefit with Nivolumab



Max benefit – Young <65yrs; Fit patients; cetuximab naïve; non DDP failed; prelim
Better outcomes in PD L1 >1% and p-16 positive

Ferris et al, NEJM 2016

Low dose Immunotherapy- Randomized study – TMH study

- Rec HNC or LAHNSCC to be treated with palliative intention
- 160patients; Arm A (metronomic therapy) :MTX+Celecoxib+Erlotinib vs low dose Nivolumab
- 6.7mo vs 10.1mo OS
- SAE 50% in both arms

VM Patil et al JCO 2023

Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study

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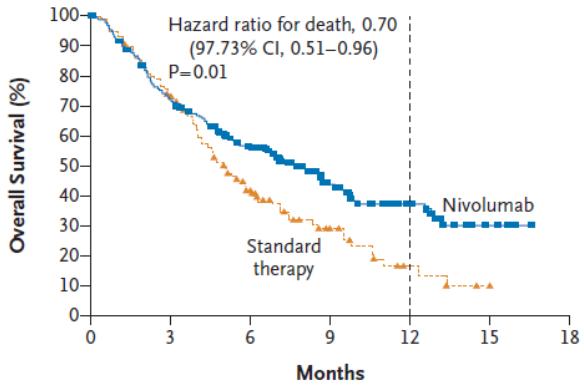
A Overall Survival

	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

CONCLUSION With a 4-year follow-up, first-line pembrolizumab and pembrolizumab-chemotherapy continued to demonstrate survival benefit versus cetuximab-chemotherapy in recurrent/metastatic head and neck squamous cell carcinoma. Patients responded well to subsequent treatment after pembrolizumab-based therapy.

Harrington et al Keynote 048; JCO 2022

Development of resistance with targeted therapy

- Inevitable
- Identification of mechanisms of secondary resistance need to be understood to bypass it.
- Another reason why not so successful in HNC

Take home message

- Host of target molecules
- Hold promise towards personalized medicine
- Heterogeneity in HNC
- Need predictive biomarker driven studies –cMET mutations
- TKI in metronomic therapy
- HPV positive disease needs further exploration – possibly cetuximab +Immunotherapy with checkpoint inhibitors
- Checkpoint inhibitors – a new promise

Thank you