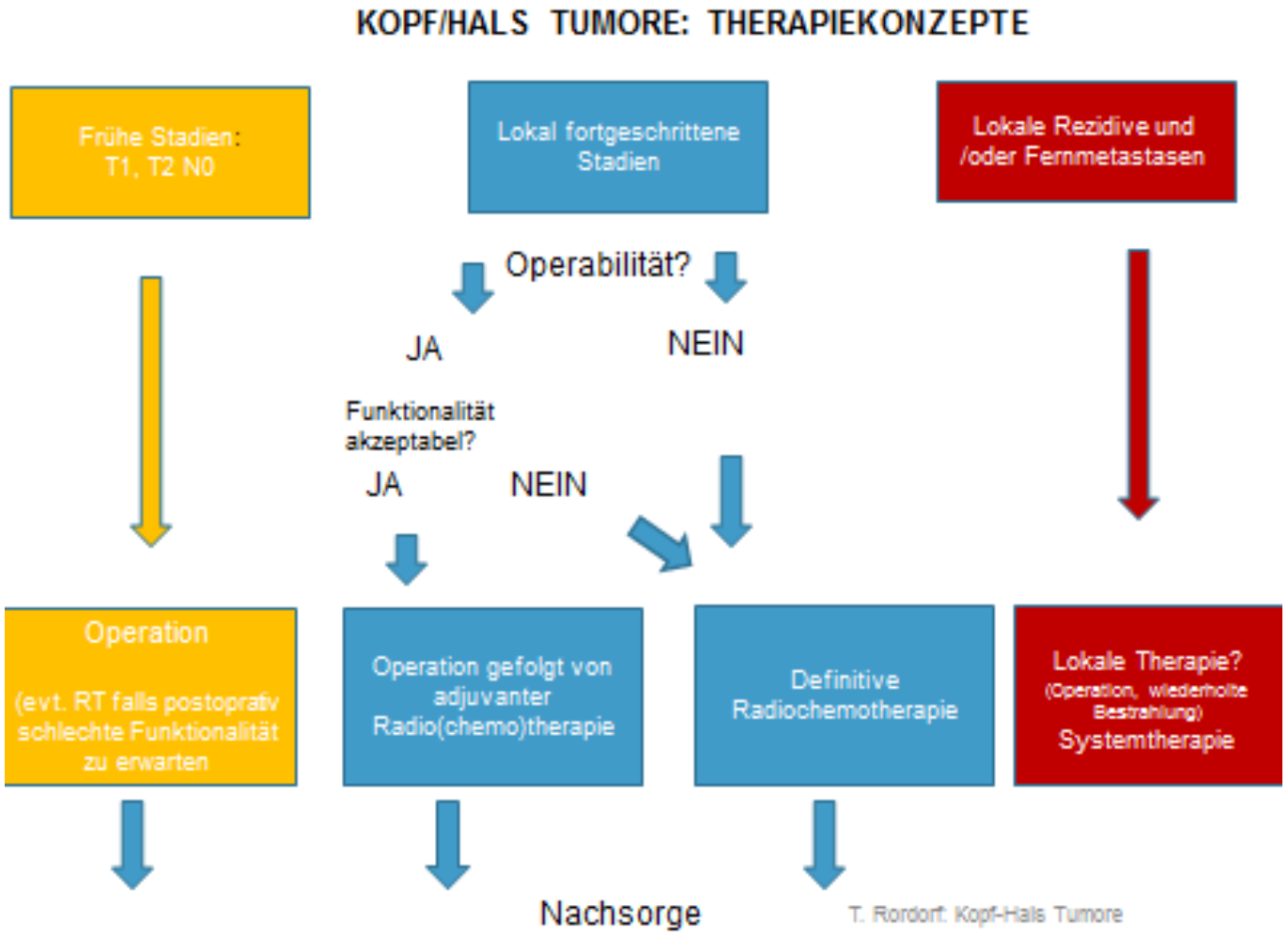
Systemic treatement of head and neck cancer

Tamara Rordorf

25.8.2017

- Role of chemotherapy in curative setting
- Recurrent/metastatic HNSCC: first line therapy and beyond
- Immunotherapy in HNSCC

Therapeutic concepts



- Role of chemotherapy in curative setting (multimodal treatment)
  - primary (concurrent) radiochemotherapy
  - postoperative (adjuvant) radio(chemo)therapy
  - neoadjuvant chemotherapy

- r/mHNSCC: first line therapy and beyond
- Immunotherapy in HNSCC

LASCCHN: concomittant RCT

B.H, male, 68 y

LA HNSCC of hypopharynx cT3c, N2-3,G3

comorbidities: coronary heart disease

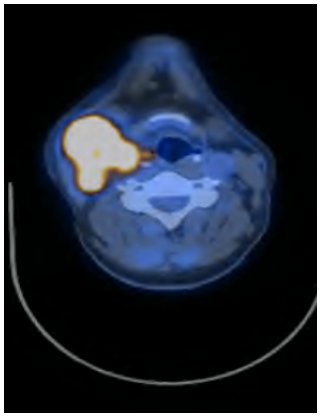
RT total dose 69.6 Gy

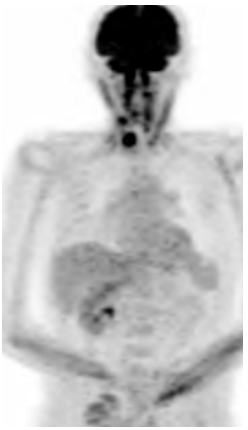
concomitant cisplatin 40 mg/m2 weekly, for 5 weeks

Very good parital remission, rest FDG activity

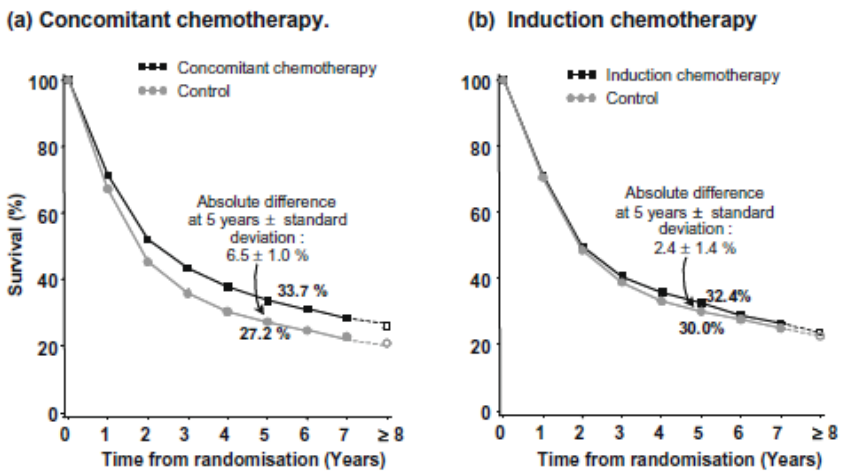
Neck-dissection 10/10

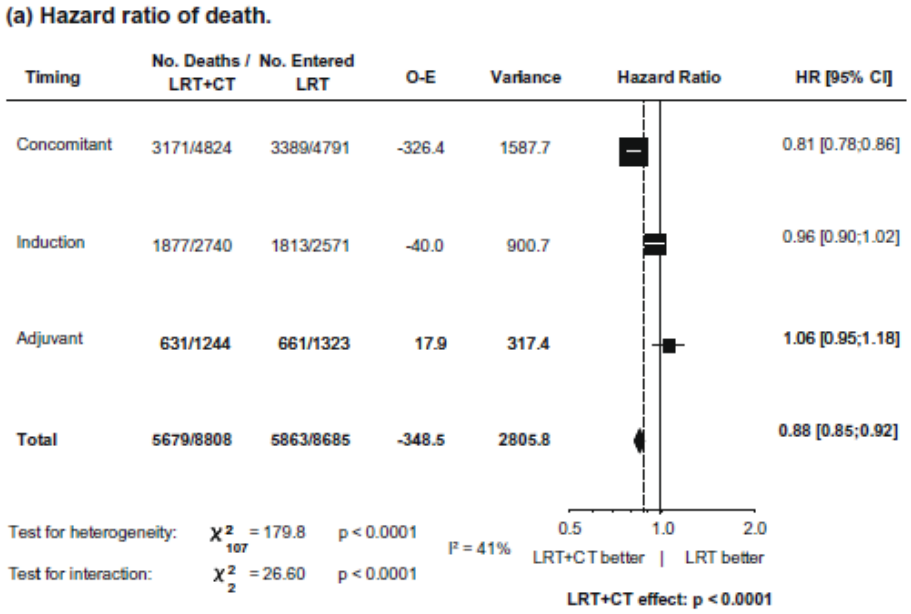
follow up: complete remission





Pignon et al, 2009: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients





concurrent chemotherapy: decrease in the risk of death (HR 0.81, 95%CI 0.78-0.86)

Absolute survival benefit: 6.5 %

No survival benefit

for concurrent chemotherapy in pts over 70

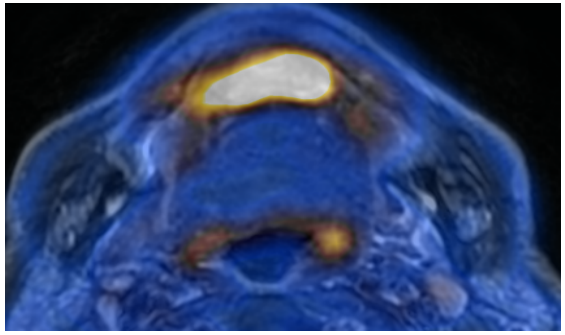
for adjuvant or neoadjuvant chemotherapy

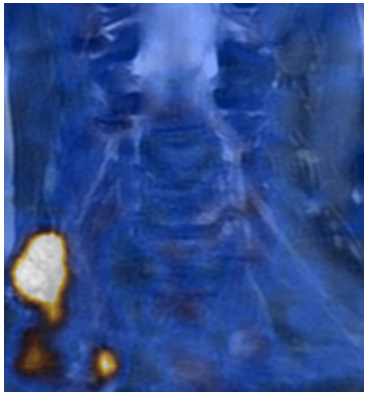
LASCCHN:
primary surgery followed by adjuvant radiochemotherapy

79 yo male patient, current smoker

SCC floor of the mouth,, pT4a (3.5 cm), pN2c (7/42), M0, G2-3, L1, p16 positive; surgery:

Mandibula resection, parital ressection of the tongue, reconstruction with fibular transplant 6/14





-> ad RT oder RCT?

LAHNSCC:
Adjuvante RT vs RCT

EORTC 22931

ORIGINAL ARTICLE

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèbvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, Ir., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931

ABSTRACT

BACKGROUND
We compared concomitant cisplatin and irradiation with radiotherapy alone as adjuvant treatment for stage III or IV head and neck cancer.

METHODS
After undergoing surgery with curative intent, 167 patients were randomly assigned to receive radiotherapy alone (66 Gy over a period of 6½ weeks) and 167 to receive the same radiotherapy regimen combined with 100 mg of cisplatin per square meter of body-surface area on days 1, 22, and 43 of the radiotherapy regimen.

RESULTS
After a median follow-up of 60 months, the rate of progression-free survival was significantly higher in the combined-therapy group than in the group given radiotherapy alone (P=0.04 by the log-rank test; hazard ratio for disease progression, 0.75; 95 percent confidence interval, 0.56 to 0.99), with 5-year Kaplan–Meier estimates of progression-free survival of 47 percent and 36 percent, respectively. The overall survival rate was also significantly higher in the combined-therapy group than in the radiotherapy

RTOG 95-01

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2004 VOL. 350 NO. 19

Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck

Jay S. Cooper, M.D., Thomas F. Pajak, Ph.D., Arlene A. Forastiere, M.D., John Jacobs, M.D., Bruce H. Campbell, M.D., Scott B. Saxman, M.D., Julie A. Kish, M.D., Harold E. Kim, M.D., Anthony J. Cmelak, M.D., Marvin Rotman, M.D., Mitchell Machtay, M.D., John F. Ensley, M.D., K.S. Clifford Chao, M.D., Christopher J. Schultz, M.D., Nancy Lee, M.D., and Karen K. Fu, M.D., for the Radiation Therapy Oncology Group 9501/Intergroup

ABSTRACT

BACKGROUND
Despite the use of resection and postoperative radiotherapy, high-risk squamous-cell carcinoma of the head and neck frequently recurs in the original tumor bed. We tested the hypothesis that concurrent postoperative administration of cisplatin and radiotherapy would improve the rate of local and regional control.

METHODS
Between September 9, 1995, and April 28, 2000, 459 patients were enrolled. After undergoing total resection of all visible and palpable disease, 231 patients were randomly assigned to receive radiotherapy alone (60 to 66 Gy in 30 to 33 fractions over a period of 6 to 6.6 weeks) and 228 patients to receive the identical treatment plus concurrent cisplatin (100 mg per square meter of body-surface area intravenously on days 1, 22, and 43).

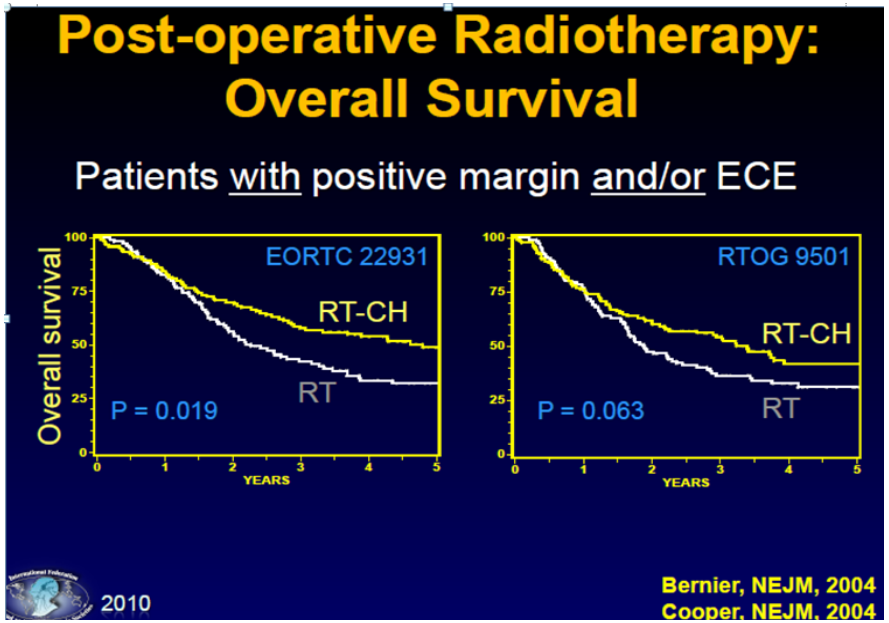
RESULTS
After a median follow-up of 45.9 months, the rate of local and regional control was significantly higher in the combined-therapy group than in the group given radiotherapy alone (hazard ratio for local or regional recurrence, 0.61; 95 percent confidence interval,

From New York University Medical Center, New York (J.S.C.); Radiation Therapy Oncology Group Headquarters, Philadelphia (T.F.P.); Johns Hopkins Oncology Center, Baltimore (A.A.F.); Wayne State University School of Medicine, Detroit (J.J., H.E.K., J.F.E.); Medical College of Wisconsin, Milwaukee (B.H.C., C.J.S.); National Cancer Institute, Bethesda, Md. (S.B.S.); H. Lee Moffitt Cancer Center, Tampa, Fla. (J.A.K.); Vanderbilt Cancer Center, Nashville (A.J.C.); State University of New York Health Center at Brooklyn, Brooklyn (M.R.); University of Pennsylvania Health System, Philadelphia (M.M.); Mallinckrodt Institute of Radiology, St. Louis (K.S.C.C.); and the University of California, San Francisco, San Francisco (N.L., K.K.F.).

N Engl J Med 2004;350:1937-44.

LASCC: postoperative RT vs RCT

Combined analysis of EORTC and RTOG 95-01 trial: only patients with ECE and R1 benefit from RCT (vs RT)



G.E., 1937. histology report

B 2014.30481 Neck dissection rechts Level II: Muskel- und Gewebsanteile ohne Lymphknotenstrukturen.

B 2014.30482 Neck dissection-Anteil III rechts: Metastase des Plattenepithelkarzinoms (0,4cm, ohne extrakapsuläres Wachstum) in einem Lymphknoten (1/1).

B 2014.30483 Neck dissection-Anteil IV rechts: Metastasen des Plattenepithelkarzinoms in zwei von zehn Lymphknoten (1,6 und 0,8cm, jeweils mit extrakapsulärem Wachstum) (2/10).

B 2014.30484 Neck dissection-Anteil V rechts: Sieben tumorfreie Lymphknoten (0/7).

B 2014.30485 Neck dissection Ib links: Zwei tumorfreie Lymphknoten (0/2).

B 2014.30486 Neck dissection II links: Metastase des Plattenepithelkarzinoms (1,3 cm, mit extrakapsulärem Wachstum) in einem von zwei Lymphknoten (1/2).

LAHNSCC:
adjuvante RT vs RCT

RTOG 95-01 (Cooper et al, NEJM 2004)

- > RCT besser: 2 LK oder mehr; R1, oder extrakapsuläre Ausbreitung

EORTC trial (Bernier et al, NEJM 2004)

Combined Analysis

extranodal spread, R1 benefit from RCT vs RT

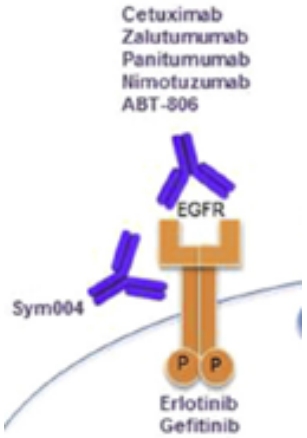
possible adverse risk factors:

vascular/lymphatic/perineural infiltration, pT3/4, oral/oropharynx with positive level 4 or 5 nodes: no beniefit in joined analysis, benefit in EORTC trial (-> consider rCT)

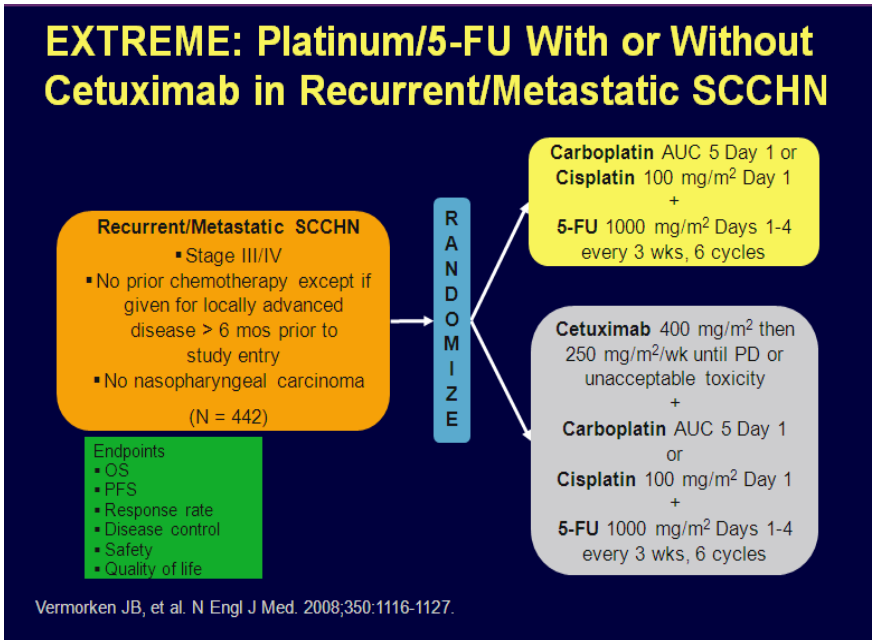
EGFR signaling and inhibition

- epidermal growth factor receptor (EGFR) overexpressed in 90% of HNSCC; higher expression is associated with poor prognosis
- Activation: ligand binding on extracellular domain leads to activation of signalling pathways
- Blockade: monoclonal antibodies
- Cetuximab: chimeric IgG1 antibody against extracell. domain
- Improved of OS when cetuximab added to standard of care

  Phase 3 trial; combination with RT (curative)
  Phase 3 trial; combination with chemotherapy (palliative disease)



LAHNSCC:
RT +/- cetuximab («Bonner» Trial)



Cetuximab:

IgG1 chimerized antibody

Binds exclusively to EGFR and its heterodimers

Prevents repair and survival of tumor cells damaged by the effects of chemotherapy and radiotherapy

- Potentiates apoptosis
- Inhibits cell cycle progression
- Decreases production of angiogenic factors
- Inhibits invasion/metastasis

LAHNSCC:
RT +/- cetuximab («Bonner» Trial)

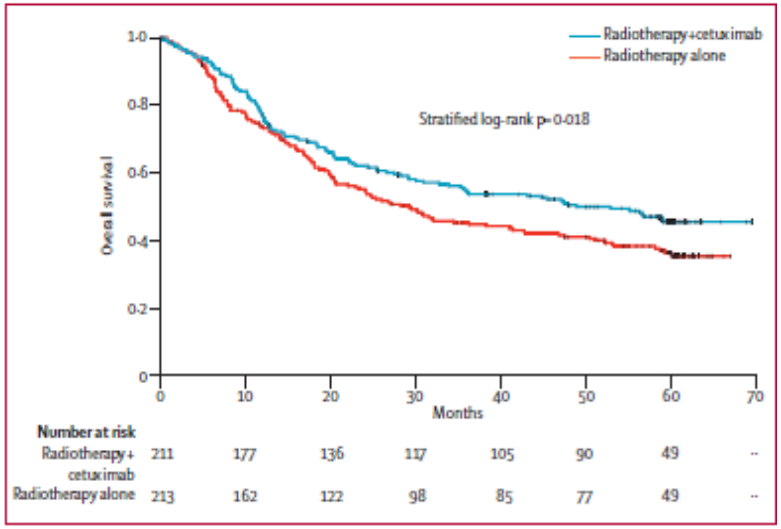


Figure 2: Overall survival by treatment: 5-year update (median follow-up 60 months)

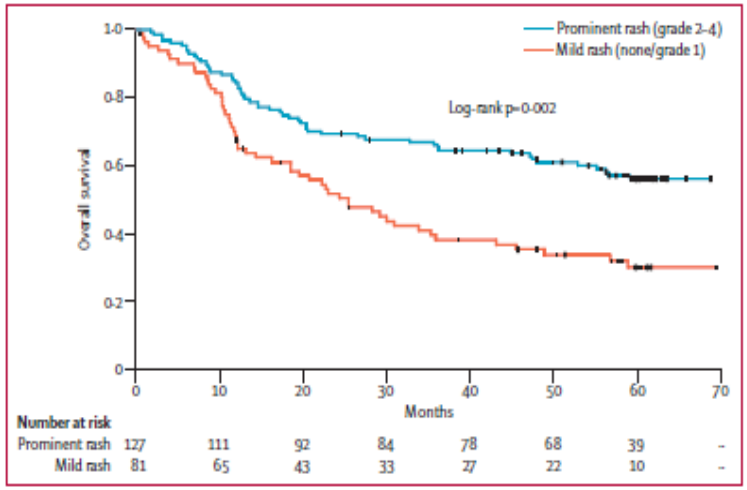


Figure 5: Overall survival by severity of rash in cetuximab-treated patients

	RT (n = 213)	RT + C (N=211)
Median survival,* mos	29.3	49
▪ 95% confidence limits	21-38	36-58+
2 yrs, %	55	62
3 yrs, %	44	57
5 yrs, %	36.4	45.6
Log rank *P* value	.018	
HR (95% CI)	0.71 (0.54-0.95)	

LAHNSCC:
Induction Chemotherapy

Primary chemotherapy followed by local curative treatment (radio(chemo)therapy)

Rationale

HNSCC is chemotherapy-sensitive disease

-> up to 90% response rates in therapy-naive patients

radiation works better in smaller tumor volume

LAHNSCC:
Induction Chemotherapy

O.C, 68 yo male, never smoker

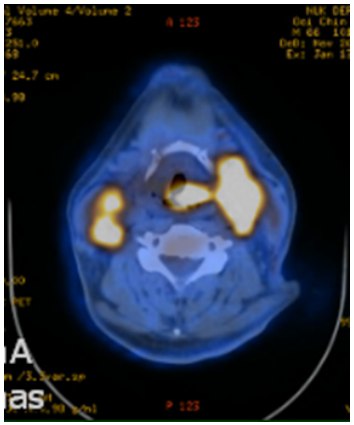
oropharyngeal carcinoma; cT4cN2cN0, HPV positive, diagnosed in1/10

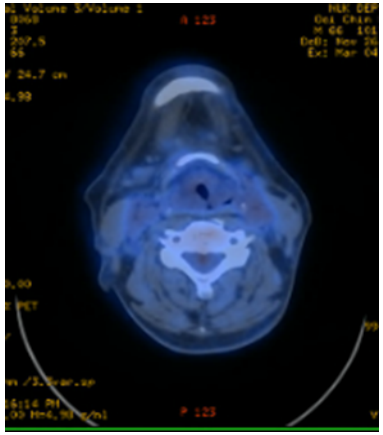
difficulties swallowing, pain

Chemotherapy with docetaxel, cisplatin and 5FU (TCF)

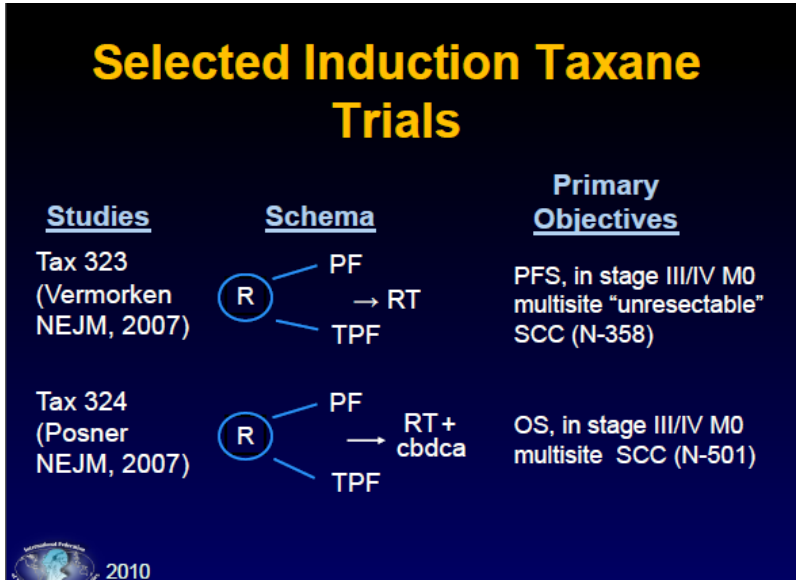
pain and swallowing problems resolved after 1st cyle

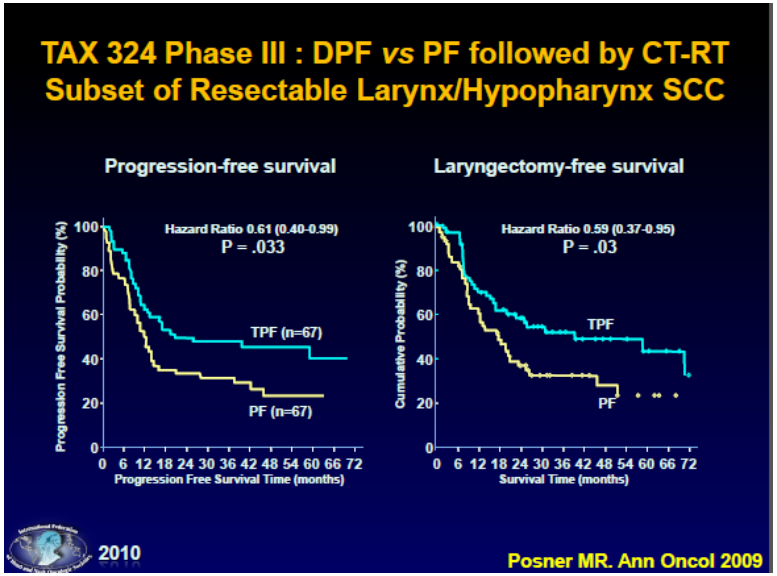
curative RCT - > complete remission





Induction Chemotherapy





But:
No arm included adequate chemoradiotherapy, other trials and meta-analysis showed no survival benefit comapred to RCT

LAHNSCC: Unanswered questions

cisplatin schedule and dosis

is cetuximab equivalent to cisplatin?

role for cetuximab in adjuvant setting?

Is there a patient subroup that benefits from induction chemotherapy?

N Engl J Med. 2008 Sep 11;359(11):1116-27. doi: 10.1056/NEJMoa0802656.

Platinum-based chemotherapy plus cetuximab in head and neck cancer.

Vermorken JB[1], Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R.

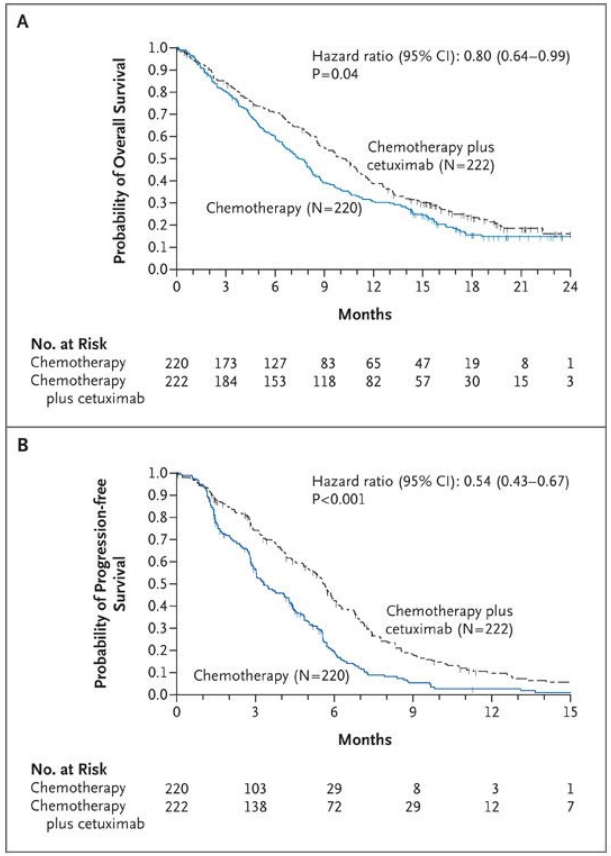


Table 2. Responses to Treatment and Survival.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Survival — mo†				
Overall	10.1 (8.6–11.2)	7.4 (6.4–8.3)	Hazard ratio, 0.80 (0.64–0.99)	0.04‡
Progression-free	5.6 (5.0–6.0)	3.3 (2.9–4.3)	Hazard ratio, 0.54 (0.43–0.67)	<0.001‡
Best response to therapy — %				
Overall	36 (29–42)	20 (15–25)	Odds ratio, 2.33 (1.50–3.60)	<0.001§
Disease control¶	81 (75–86)	60.0 (53–67)	Odds ratio, 2.88 (1.87–4.44)	<0.001§
Time to treatment failure — mo†	4.8 (4.0–5.6)	3.0 (2.8–3.4)	Hazard ratio, 0.59 (0.48–0.73)	<0.001‡
Duration of response — mo‖	5.6 (4.7–6.0)	4.7 (3.6–5.9)	Hazard ratio, 0.76 (0.50–1.17)	0.21‡

- Role of chemotherapy in curative setting
- *r/mHNSCC: first line therapy and beyond*
- Immunotherapy in HNSCC: phase 3 data

Beyond the first line (until 2016):

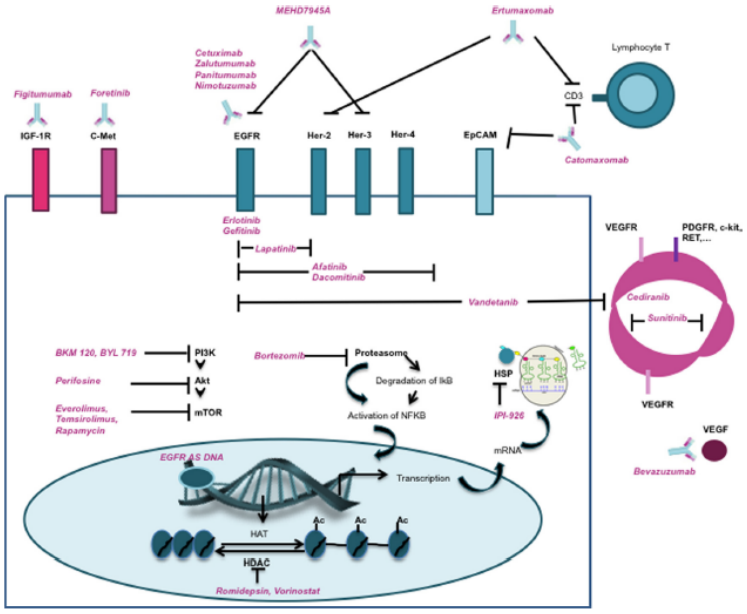
Chemotherapy: taxanes, methotrexate, vinorelbine, cetuximab, monotherapy or combinations…

Selected chemotherapy trials

Study [ref]	Number of patients (# pts)	Treatment line/agent	RR	Disease stabilization/ control rate	TTP	OS	Note
Grau[112]	60	• Paclitaxel 80 mg/m² weekly for 6 weeks; until progression for responders	43%	15%	6.2 months (responding patients only)		
Leon[113]	151 total 43 chemotherapy 68 best supportive care (BSC) 40 radiotherapy	• Diverse	0	9.3%	N/A	107 days for chemotherapy group	
Cho[114]	23	• Docetaxel 35 mg/m² for 3 weeks of 4-week cycle, total 6 cycles	13%	34.7%	9 weeks	29 weeks	
Fayette[54]	66	• Paclitaxel first line 46 pts • Paclitaxel second line 26 pts • Paclitaxel monotherapy 60–80 mg/m² qw • Paclitaxel/carboplatin 175 mg/m²/AUC 5q3w	30% 20% 19% 36%	36%	3.9 months	7.2 months	
Tahara[53]	74	• Paclitaxel 100 mg/m² qw	29%	N/A	3.4	14.3	
Specenier[115]	30	• Docetaxel 36 mg/m² qw for 6 weeks	6.7%	33%	7.4 weeks	17.9 weeks	
Zenda[116]	22	• Docetaxel 60 mg/m² q3–4 w	10%	25%	1.7 months	4.6 months	
Numico[117]	18	• Docetaxel 80 mg/m² q3w	11%	33%	19 weeks	26 weeks	
Vermorken[55]	103	• Erbitux monotherapy followed by • Erbitux-cis at progression	13% (Erbitux mono) 0% (additional cisplatin at progression)	46%	70 days	178 days	
Herbst[54]	51 with SD after cisplatin-based therapy 25 pts with progression under cisplatin 54 progressive within 90 days (amendment)	• Erbitux/Cisplatin	18% 20% 6%		7.4 months 4.2 months 4.1 months	11.7 months 6.1 months 4.3 months	
Baselga[55]	96 platinum-refractory	• Erbitux/Cisplatin	10%	53%	85 days	183 days	
Machiels[54]	191 95	• Zalutumumab • Best supportive care (BSC) (± Mtx)	6.3% 1.1%	48% 27%	9.9 weeks 8.4 weeks	6.7 months 5.2 months	

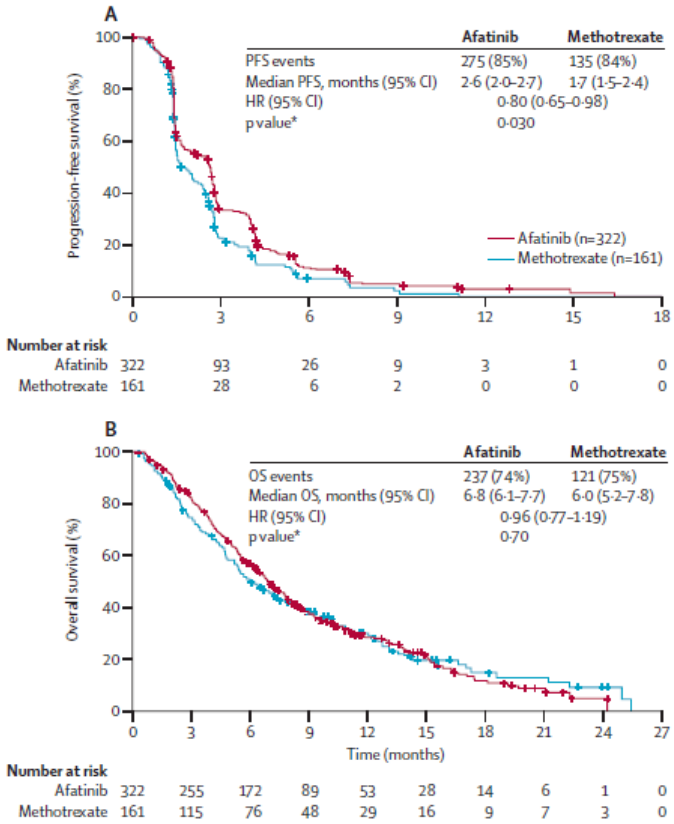
(RR: Response rate; TTP: Time to progression; OS: Overall survival; SD: Stable disease; AUC: Area under the concentration curve).

«targeted agents»



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,*



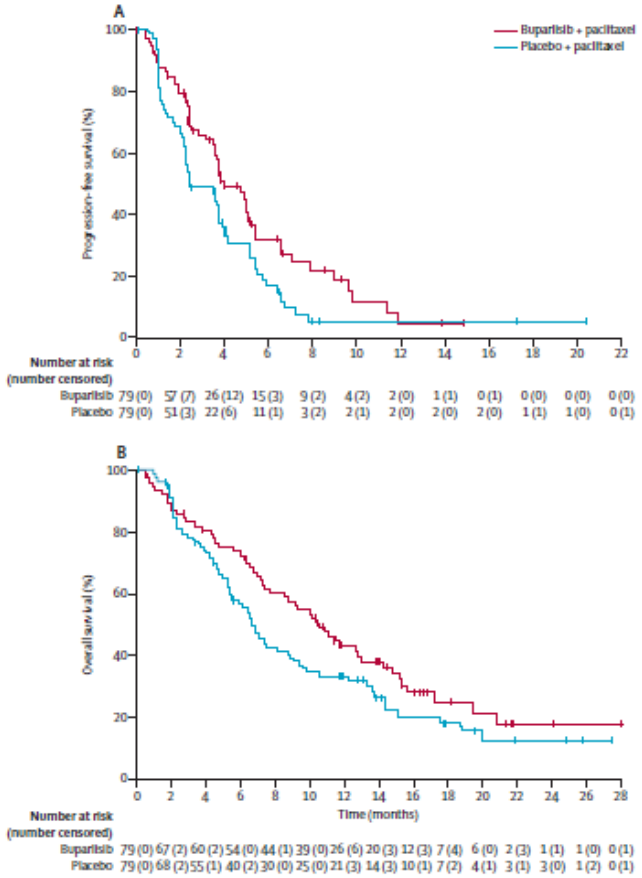
mPFS, months: 2.6 vs 1.7;
HR 0.80, P 0.03

Adverse events higher in afatinib arm:

Rash (10% in afatinib arm, vs 0)
Diarrhoea (9% vs 2%)
Stomatits 6 % vs 8%

Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial

Denis Soulières, Sandrine Faivre, Ricard Mesía, Éva Remenár, Shau-Hsuan Li, Andrey Karpenko, Arunee Dechaphunkul, Sebastian Ochsenreither, Laura Anna Kiss, Jin-Ching Lin, Raj Nagarkar, László Tamás, Sung-Bae Kim, Jozsef Erfán, Anna Alyasova, Stefan Kasper, Carlo Barone, Sabine Turri, Arunava Chakravartty, Marie Chol, Paola Aimone, Samit Hirawat, Lisa Licitra



	Buparlisib and paclitaxel (n=79)	Placebo and paclitaxel (n=79)
Complete response	3 (4%)	1 (1%)
Partial response	28 (35%)	10 (13%)
Stable disease	26 (33%)	44 (56%)
Progressive disease	10 (13%)	19 (24%)
Unknown	11 (14%)	5 (6%)
Not assessed*	1 (1%)	0
Overall response†	31 (39%; 28·4–50·9)	11 (14%; 7·2–23·5)
Median duration of overall response (months)	4·5 (3·1–6·7)	7·1 (2·8–NE)
Disease control‡	57 (72%; 60·9–81·7)	55 (70%; 58·2–79·5)

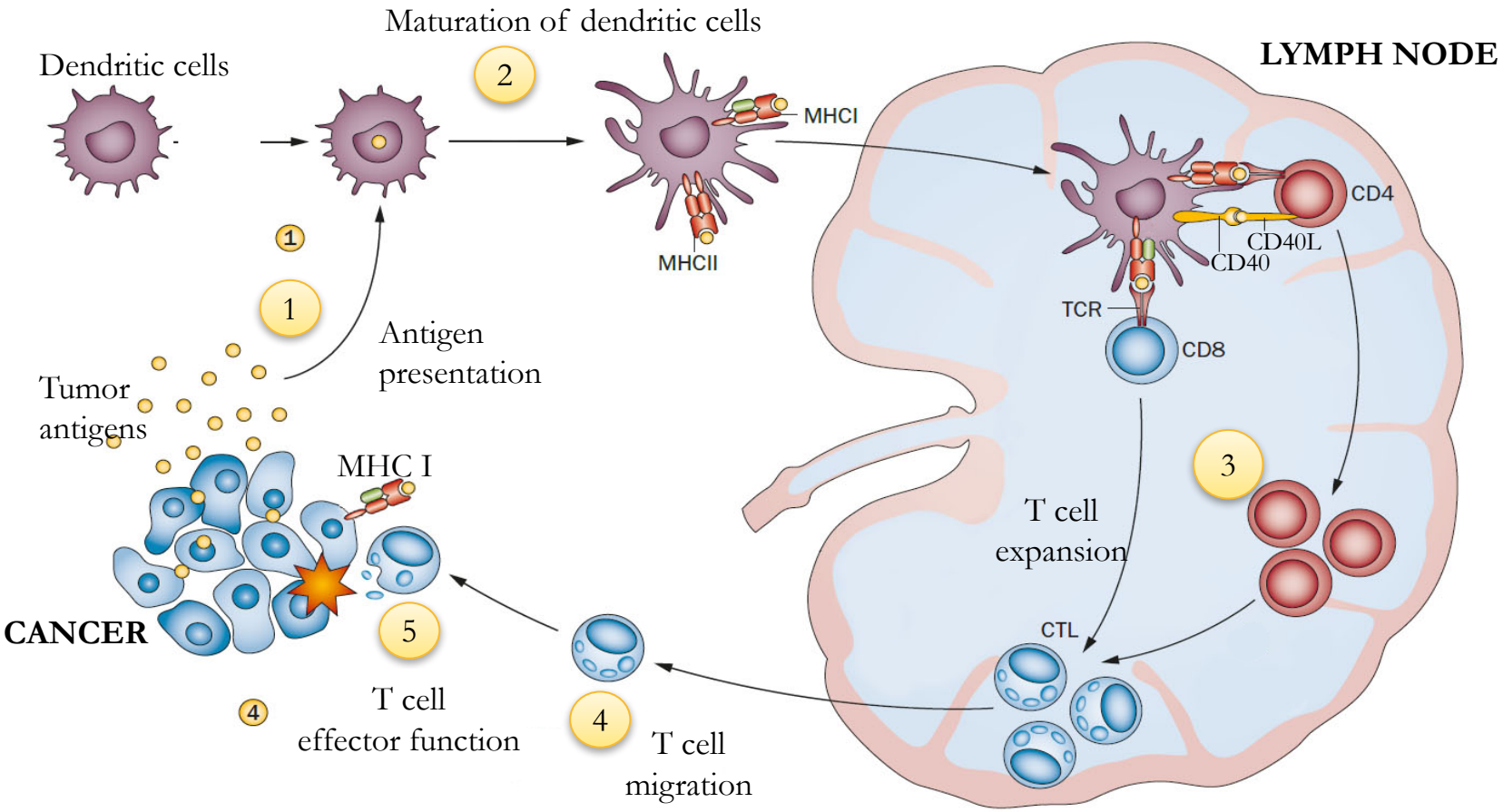
Data are n (%), n (%; 95% CI), or median (95% CI). NE=not evaluable. *One patient did not have a baseline or post-baseline assessment. †Complete response and partial response. ‡Complete response, partial response, or stable disease.

Table 2: Best overall response to therapy

mPFS: 4.6 months vs. 3.5 months; HR 0.65, p=0.01

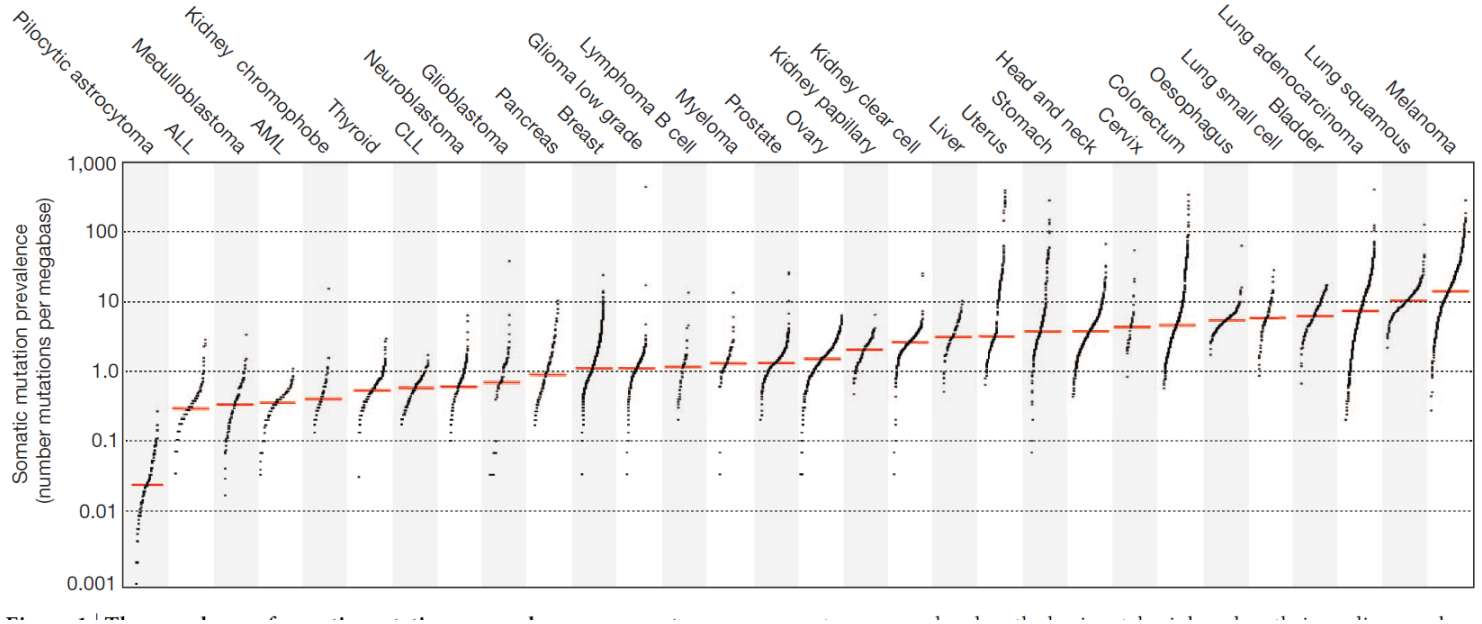
- Chemotherapy in curative setting
- r/mHNSCC: first line therapy and beyond
- Immunotherapy in HNSCC

The immune system can eliminate cancer



Adapted from Melero I. et al., Nature Reviews Clinical Oncology, 2014

Mutational load in carcinogen associated HNSCC



Alexandrov et al Nature 2013

Immunotherapy for HNSCC

Interleukin-2 given peritumoral, intranodal, intraarterial

Fishman Clin Cancer res. 2011; Rosenberg Ann surg.1989

Interleukin-12 intratumoral

Rapidis, JCO 2009

Interferon-gamma

conflicting data on tumor response

Richtsmeier WJ, Arch Otholaryngol 1990; Mahfoubi R, 1993, Head and neck

Monoclonal Antibodies

inhibit signalling pathway and initiate cell-mediated cytotoxicity

Immunotherapy for HNSCC

Conjugated Antibodies

mAb+ radioactive substance (Borjesson, Clin Cancer Res 2003

Adoptive cell transfer

mostly in NPC (Smith et al 2012, Chia et al 2014)

patient's own ag-specific effector cells harvested; enginered and re-introduced to the patient (To, Arch Otolayngol HN surgery2000)

Anti-tumor vaccines

Dendritic-cell based (Bontkes Clin Immunol 2008, Gholamin BMC 2010)

peptide based (MAGE 3) (Voskens, 2012); whole tumor vaccines

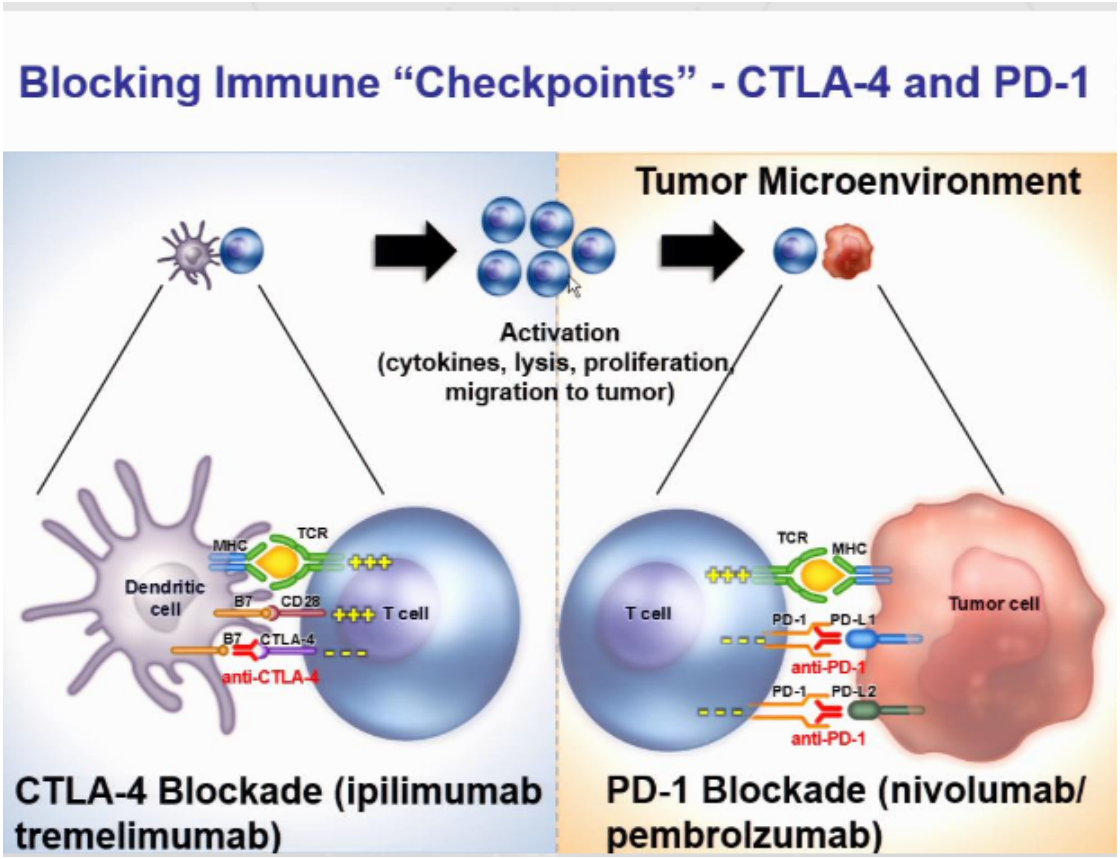
Checkpoint inhibitors in HNSCC

Single substances:

- Nivolumab
- Pembrolizumab
- Darvolumab
- Avelumab

Combinations (clinical trials)

- Vaccines
- Immunotherapy/chemotherapy
- Two checkpoint inhibitors
- Radiation



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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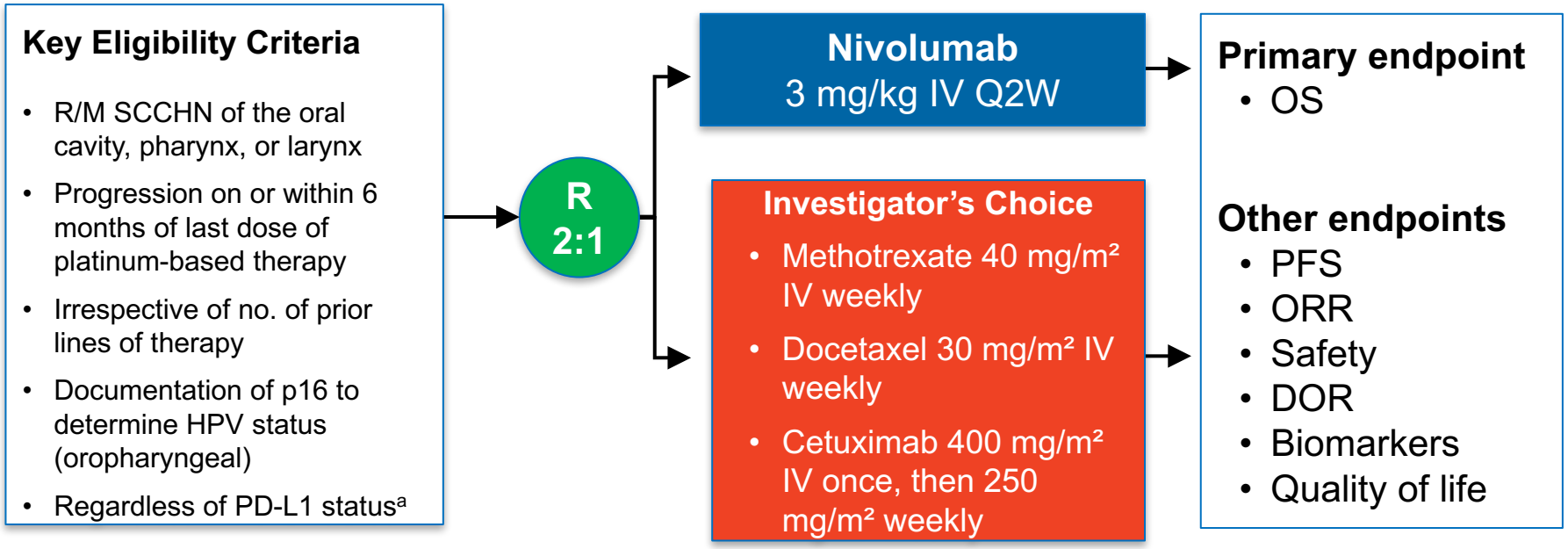
November 8 2016

Phase 3 CheckMate 141 Study Design

Nivolumab in R/M SCCHN After Platinum Therapy

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN



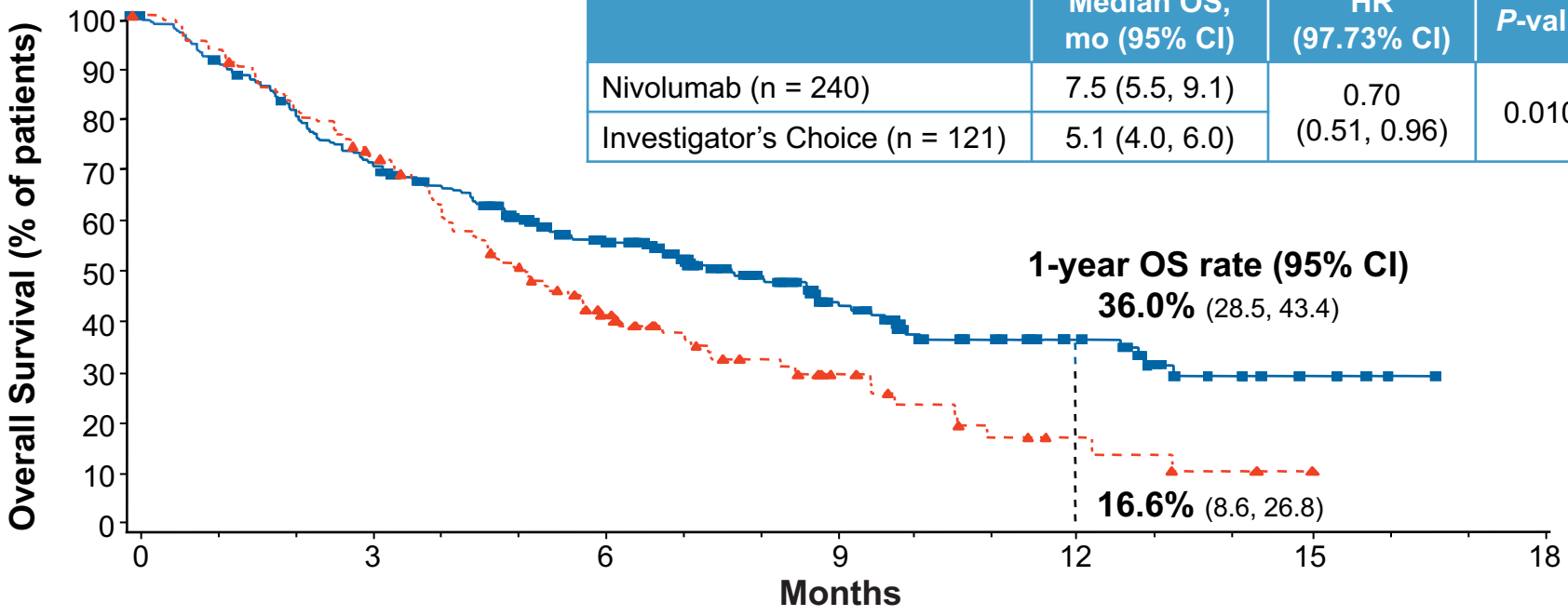
[a]Tissue required for testing

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

Overall Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	7.5 (5.5, 9.1)	0.70 (0.51, 0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0, 6.0)		



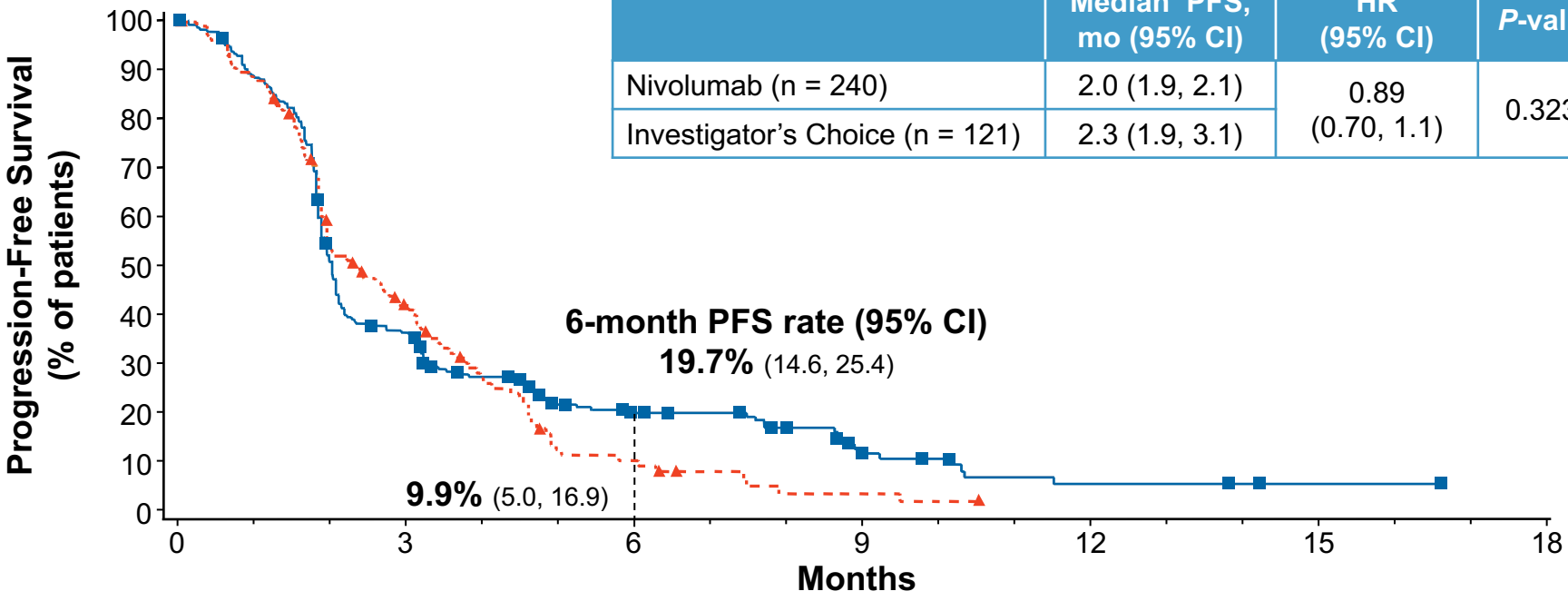
No. at Risk

Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

Progression-Free Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median PFS, mo (95% CI)	HR (95% CI)	*P*-value
Nivolumab (n = 240)	2.0 (1.9, 2.1)	0.89 (0.70, 1.1)	0.3236
Investigator's Choice (n = 121)	2.3 (1.9, 3.1)		



No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Investigator's Choice	121	43	9	2	0	0	0

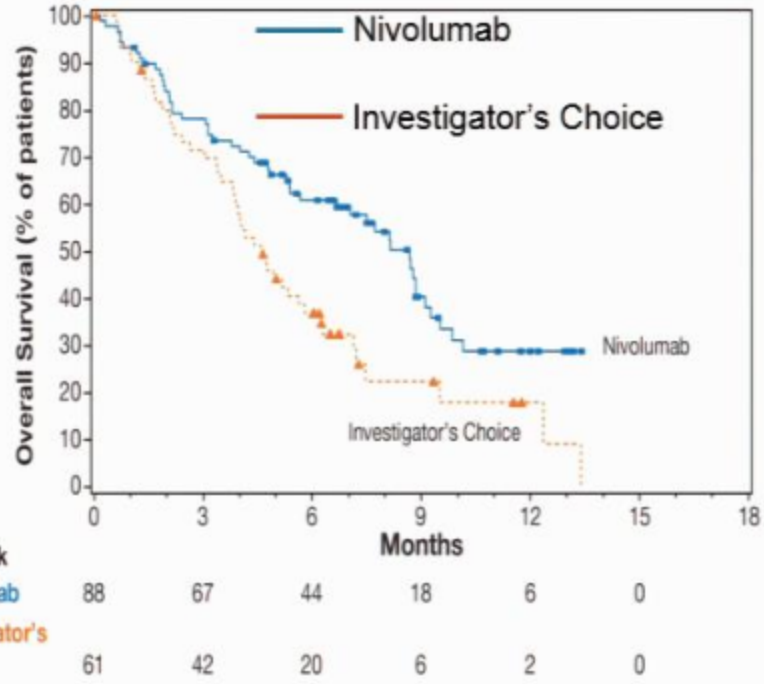
Overall Survival by PD-L1 Expression

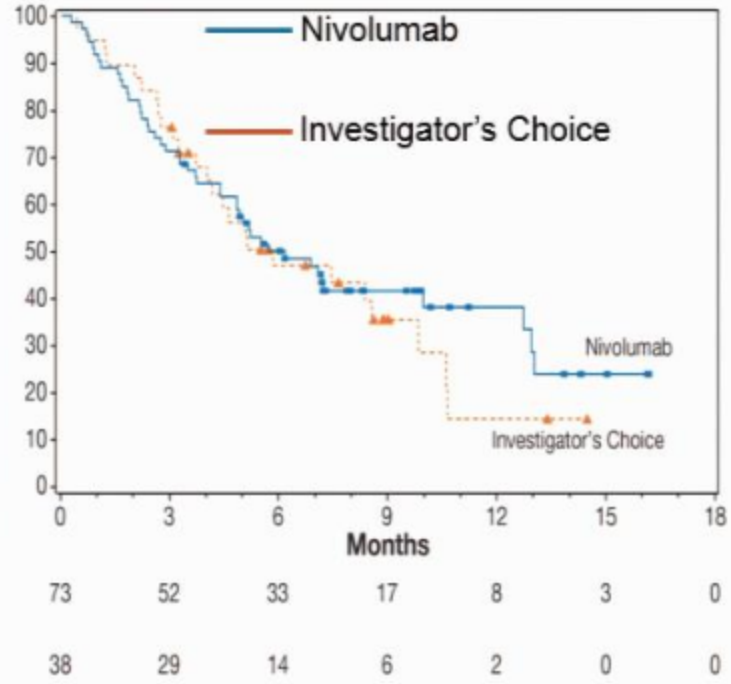
PD-L1 Expression ≥1%

Treatment Arm	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 88)	8.7 (5.7-9.1)	0.55 (0.36-0.83)
Investigator's choice (n = 61)	4.6 (3.8-5.8)	

PD-L1 Expression <1%

Treatment Arm	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 73)	5.7 (4.4-12.7)	0.89 (0.54-1.45)
Investigator's choice (n = 38)	5.8 (4.0-9.8)	





No. at Risk													
Nivolumab	88	67	44	18	6	0	73	52	33	17	8	3	0
Investigator's Choice	61	42	20	6	2	0	38	29	14	6	2	0	0

Ferris RL et al. *NEJM* 2016

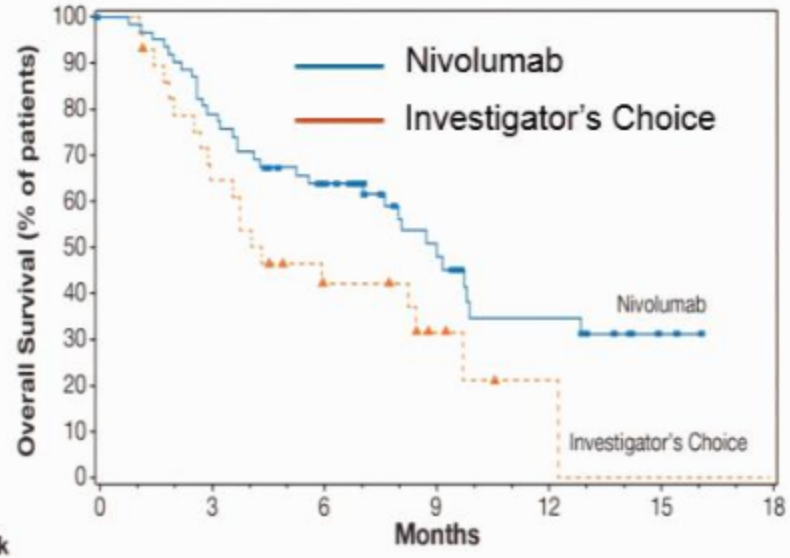
Overall Survival by p16 (HPV) Status

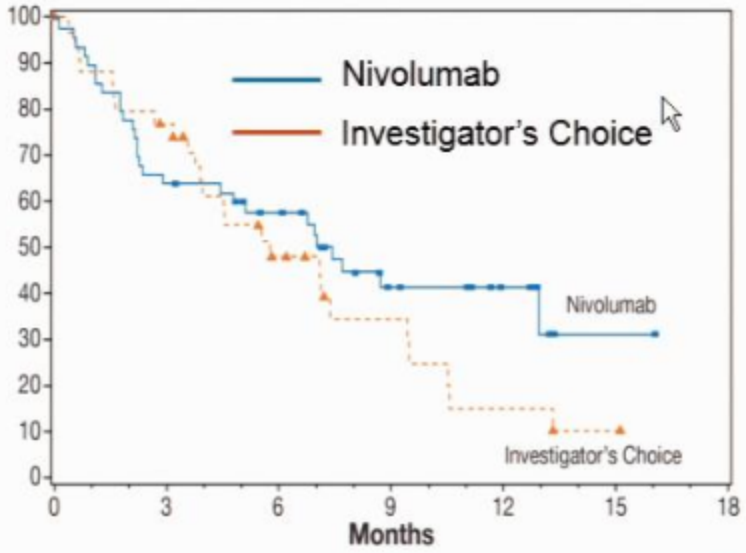
p16-Positive

Treatment Arm	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 63)	9.1 (7.2-10.0)	0.56 (0.32-0.99)
Investigator's choice (n = 29)	4.4 (3.0-9.8)	

p16-Negative

Treatment Arm	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 50)	7.5 (3.0-NA)	0.73 (0.42-1.25)
Investigator's choice (n = 36)	5.8 (3.8-9.5)	

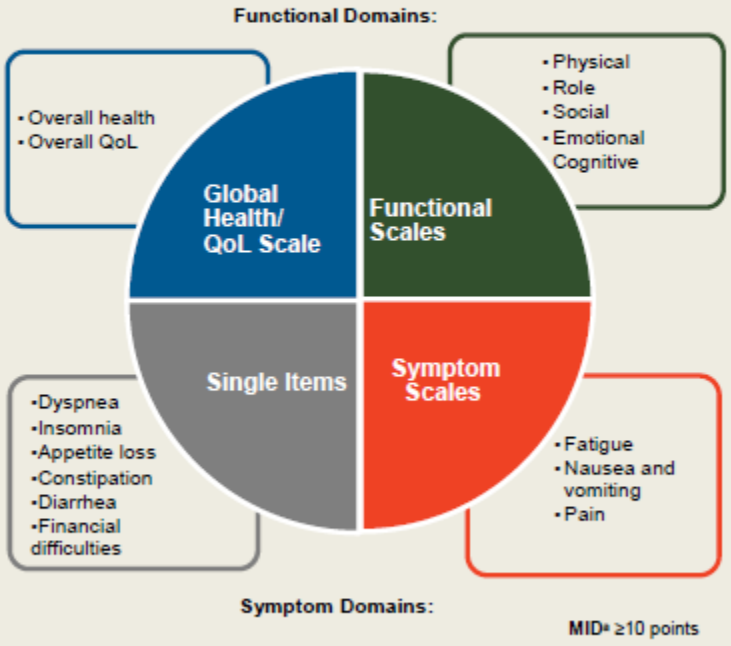




No. at Risk													
Nivolumab	63	49	35	18	10	3	0	50	32	25	12	6	1	0
Investigator's Choice	29	20	11	4	1	0	0	36	26	13	7	3	1	0

Ferris RL et al. *NEJM* 2016

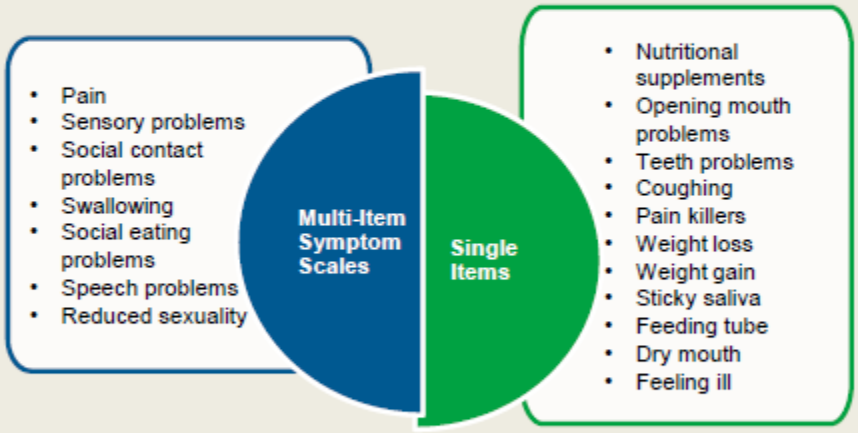
EORTC QLQ-C30



MID* ≥10 points

*10 points is conservative and smaller differences between groups are likely to be clinically relevant[7]

EORTC QLQ-H&N35

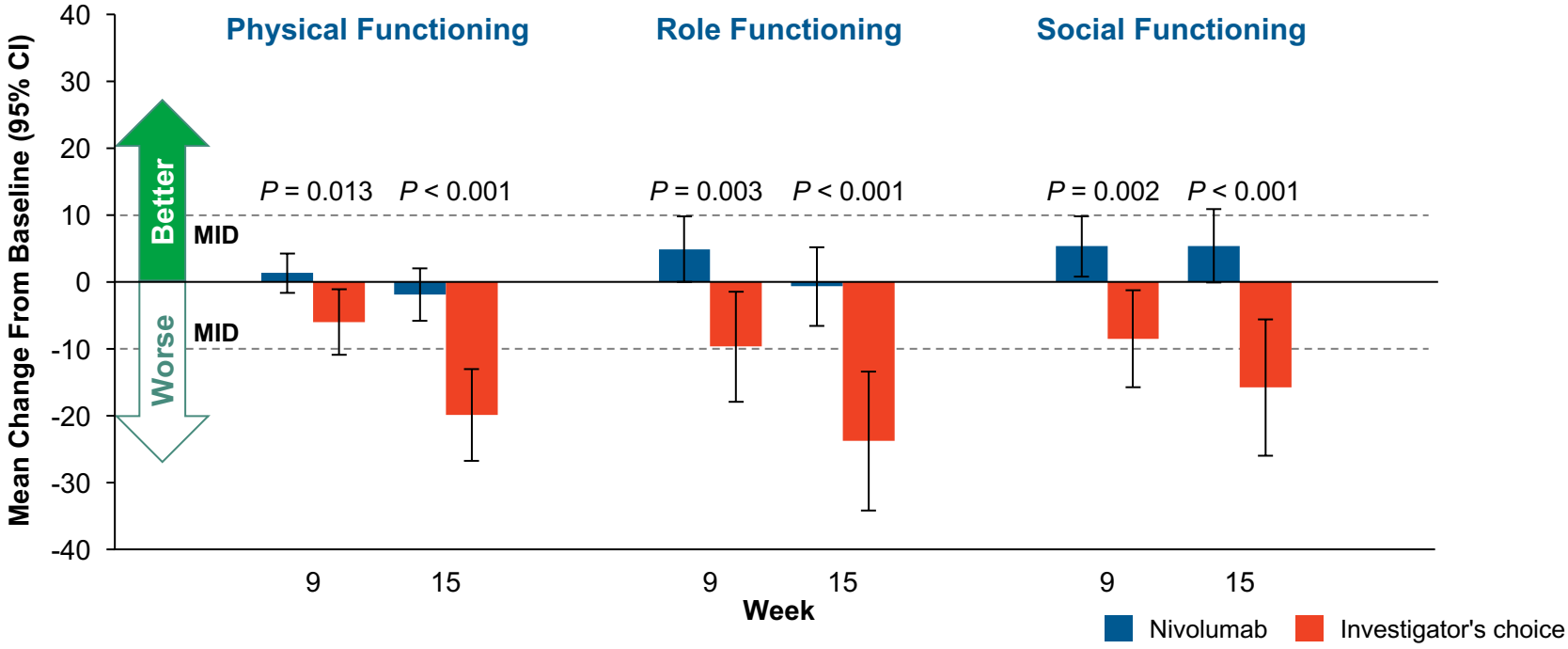


Minimally important difference ≥10 points

EORTC QLQ-C30 Functional Domains

CheckMate 141: Nivolumab vs IC in R/M SCCHN After Platinum Therapy

- Nivolumab-treated patients experienced stable PROs
- Investigator's choice–treated patients had statistically significant and clinically meaningful worsening in physical, role, and social functioning compared with nivolumab



Ongoing immunotherapy trials in HNSCC

Ongoing 2L Phase III trials in R/M HNSCC

Study	Population	Treatment Arms	N
KEYNOTE–040	R/M platinum refractory	• Pembro 200 mg Q3W • SoC (investigator's choice) MTX 40 mg/m2 QW DOC 75 mg/m2 Q3W CET 250 mg/m2 QW	600
EAGLE	R/M platinum refractory	• Durvalumab monotherapy • Durvalumab + Tremelimumab • SoC	720

Ongoing 1L Phase III trials in R/M HNSCC

Study	Population	Treatment Arms	N
CHECKMATE 651	Recurrent / metastatic	• Nivo 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W • CET + 5-FU + plat	490
KEYNOTE–048	Recurrent / metastatic	• Pembro 200 mg Q3W • Pembro + 5-FU + plat • CET + 5-FU + plat	780
KESTREL	Recurrent / metastatic	• Durvalumab monotherapy • Durvalumab + Tremelimumab • SoC	628

Summary

curative setting:

Cisplatin increases overal survival when given concurrently with radiotherapy
Cetuximab is an option for pat that can't recieve cetuximab
in ajduvant setting, chemotherapy increases survial in pts with ENC and R1

metastatic disease:

- 1 st line: Cetuximab, Platin and 5FU is the standard (and standard arm in the phase 3 immuntherapy-trials)

- After platinum-failure:
  - nivolumab is new standard (ranomized phase 3 data showing survival benefit in patients who progresed after platinum containing therapy)

- Multiple trials with immunotherapy in first and second lines; in combination with chemotherapy or other checkpoint inhibitors; oncolytic viruses

Thank you for your attention