The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2018

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Current Concepts in Head and Neck Surgery and Oncology 2018

Head and Neck Squamous Cell Cancer
Advances in systemic therapy

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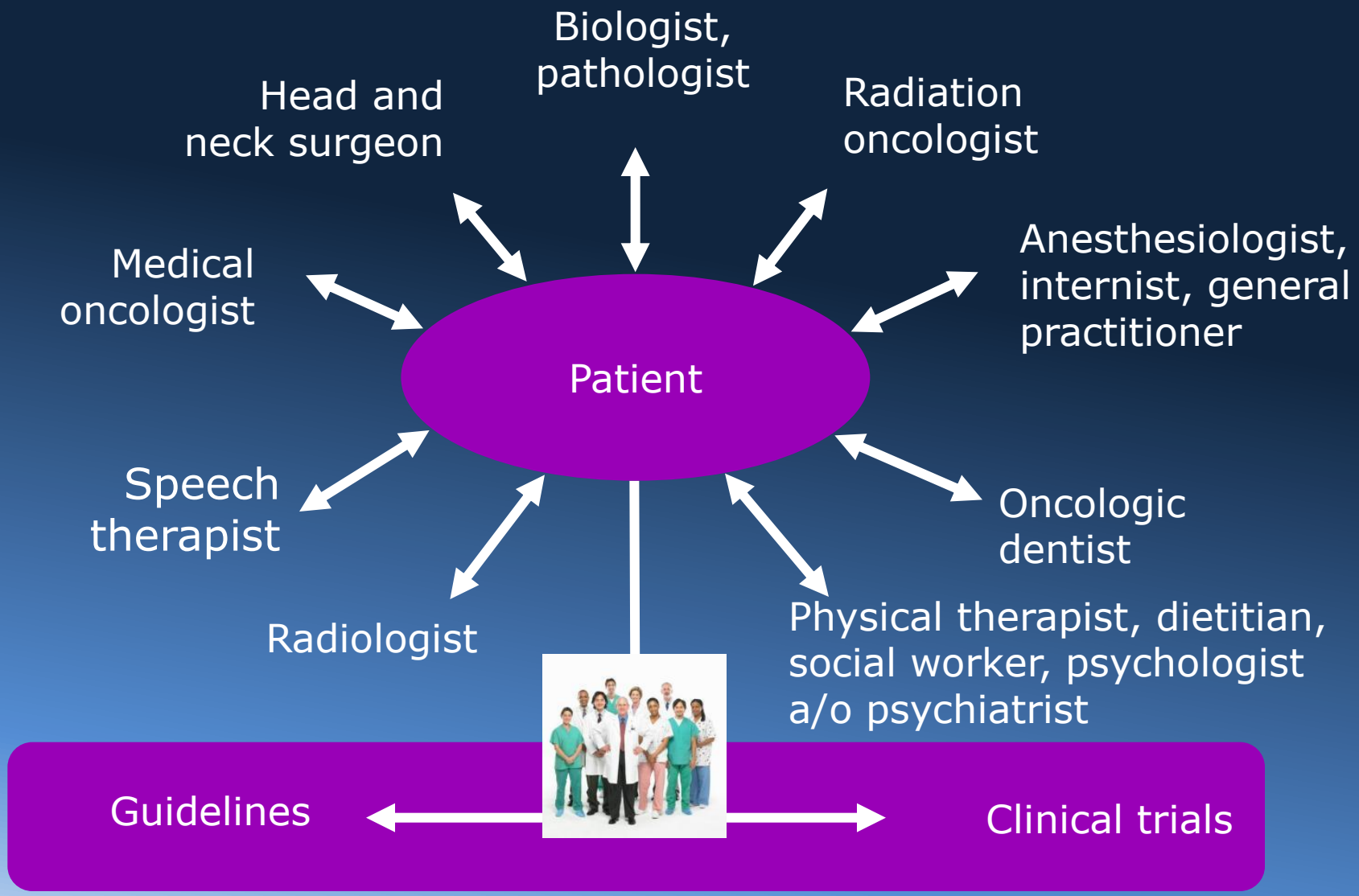
IFHNOS 2018 World Tour

Outline of Presentation

- Importance of MDT meetings
- Standard treatment options for LA-SCCHN
  - The downside of concurrent chemoradiation (CCRT)
  - How to reduce the toxicity of CCRT
  - How to further increase the efficacy of CCRT
  - A new role for induction chemotherapy (ICT)
- Standard treatment options for R/M-SCCHN
  - First and second line phase III trials (targeted agents)
  - The potential benefit of immune checkpoint inhibitors
- Future expectations with immune checkpoint inhibitors

Multidisciplinary Team (MDT) Meetings



Decision Making during MDT Meetings SCCHN patients

- Disease factors (e.g. site, stage, biology [HPV, EGFR], specific risk factors for locoregional or distant relapse)
- Patient factors (e.g. age, sex, performance status, nutritional status, comorbidities, oral health, lifestyle habits, socio-economic status [marital status])
- Treatment factors (surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy)
- Communication / information / support / taking into account the wish of the patient

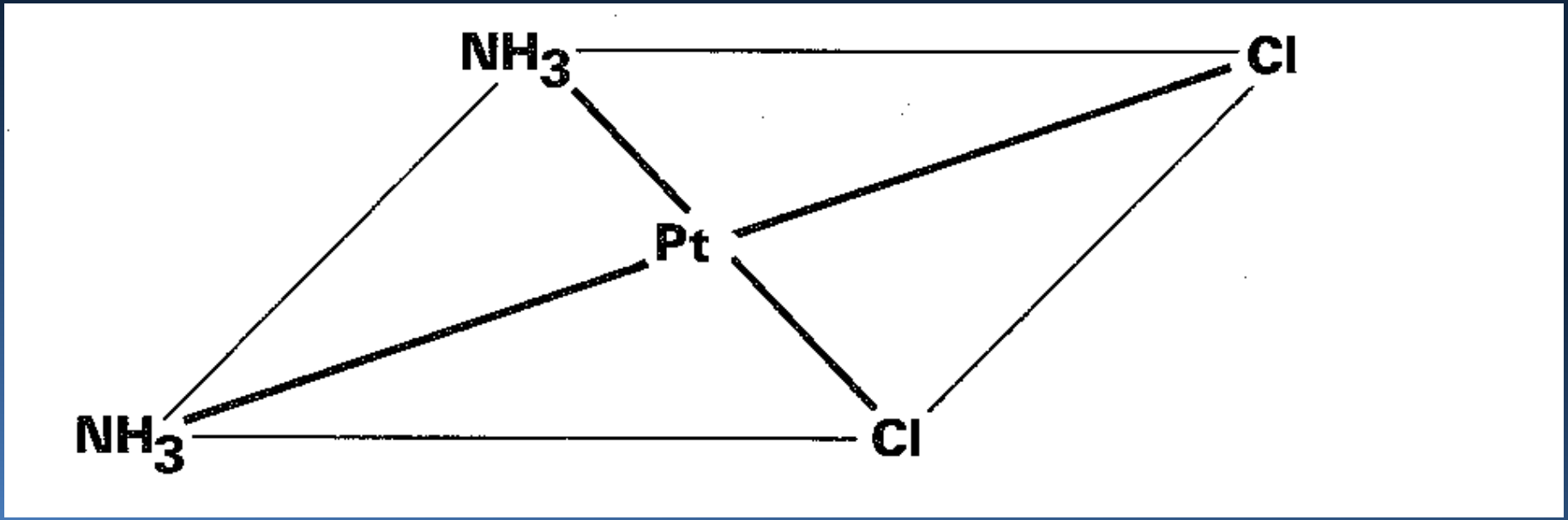
Clinical Practice Guidelines for Patients with Locoregionally Advanced SCCHN
Standard options

	Level of evidence	Grade of recommendation
Surgery → RT or CCRT	I	A
Concomitant CT and RT*	I	A
Cetuximab plus RT	II	B
CCRT or ICT → RT for organ preservation	II	A
ICT → CCRT (sequential therapy)		Still under evaluation

in case of mutilating surgery and in nonresectable disease ;* ***Cisplatin dose: 100 mg/m² x3 during CF-RT*

Gregoire V et al, Ann Oncol 2010: 21 (suppl 5): VI84-VI86

Cisplatin in the Treatment of SCCHN
Crucial role



Cis-diamminedichloroplatinum (II)

Key Features of Cisplatin: Toxicity

Toxicity*:

- Nausea/vomiting
- Renal insuff. (+ Mg^{2+} wasting)[a]
- Neurotoxicity[b]
- Ototoxicity[c]
- Myelosuppression
- Liver toxicity (transaminases ↑)
- Pyrexia

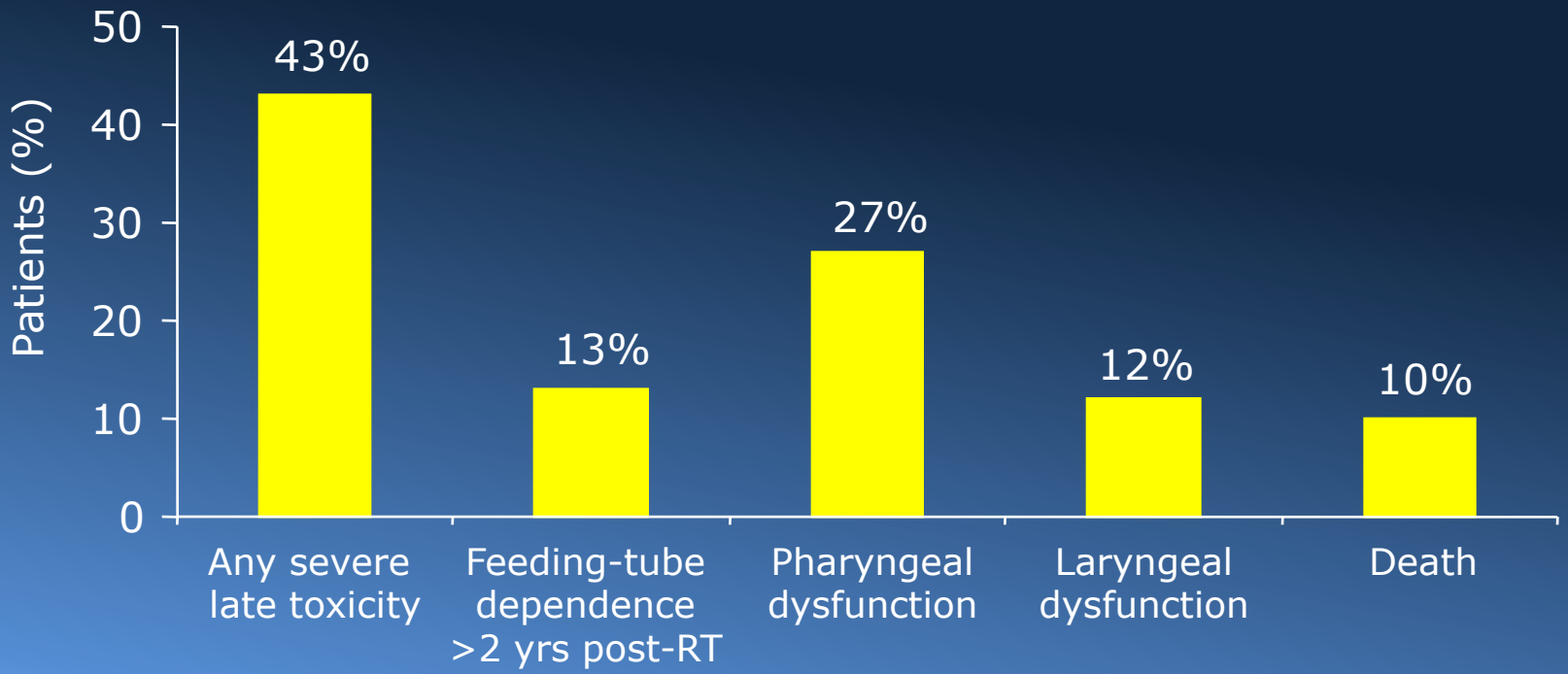
Rarely

- Hypersensitivity
- Visual impairment[+]
- Hemolytic anemia
- Raynaud
- Hypertension
- Cardiac events
- Microangiopathy

•Most toxicities are dose and schedule dependent; [a]ameliorated by hydration, not completely prevented and cumulative; [b]Dose dependent, symptoms typically after a cumulative dose of 300 mg/m^2. Symptoms begin and often progress up to 4 months after stopping cisplatin; in 30-50% it is irreversible.
[c]Cumulative and irreversible.
[+]Papilledema, retrobulbar neuritis, retina dysfunction, transient cortical blindness

CCRT: Late Toxicity

- Analysis of 230 patients receiving CRT in 3 studies (RTOG 91-11, 97-03, 99-14)



MVA: significant variables correlating with severe late toxicity were: older age (OR, 1.05 per year; p=.001), advanced T-stage (OR, 3.07; p=.0036), larynx/hypopharynx primary site (OR, 4.17; p=.0041) and neck dissection (OR, 2.39; p=.018)

Machtay M, et al. J Clin Oncol 2008; 26: 3582–3589

CCRT Standard Nonsurgical Therapy
What next in LA-SCCHN?

- **Should all patients be treated with CCRT?**

- Is further treatment intensification feasible and worth considering?
  - *adding more cytotoxic chemotherapy (ICT)*
  - *adding targeted therapy*
  - *adding a hypoxic sensitizer to CCRT*
  - *immunotherapy*

- Can we select patient who might need less intensive therapy (de-escalation of locoregional therapy) ?

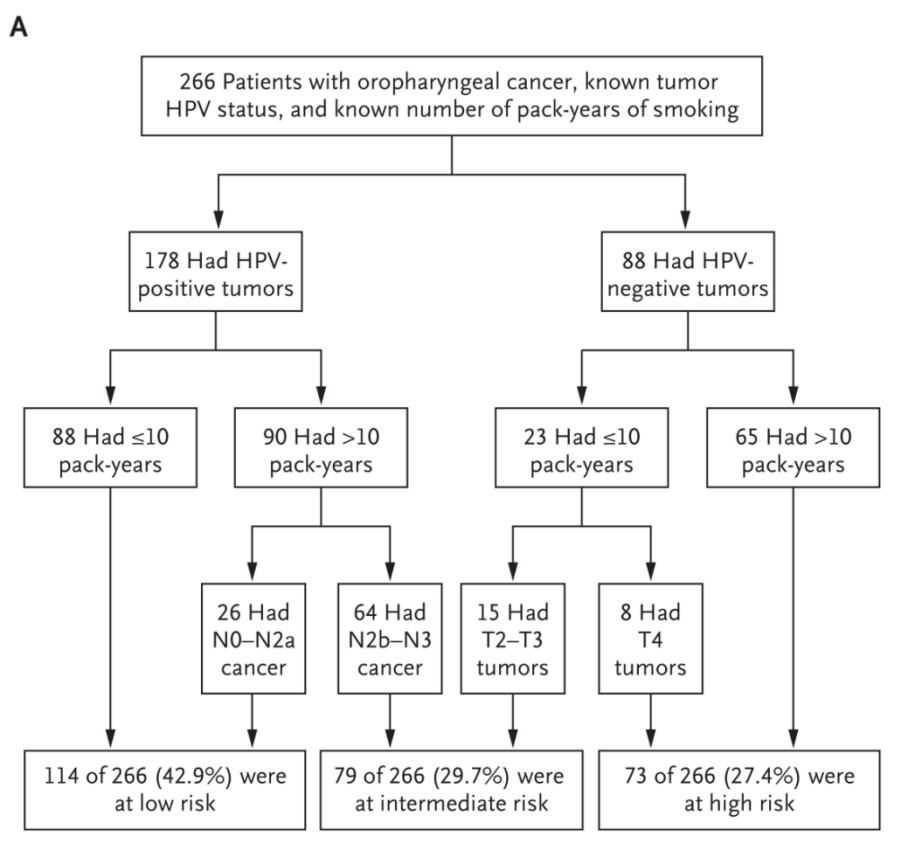
Effectiveness of Chemoradiation in HNC in an Older Patient Population*
SEER Database

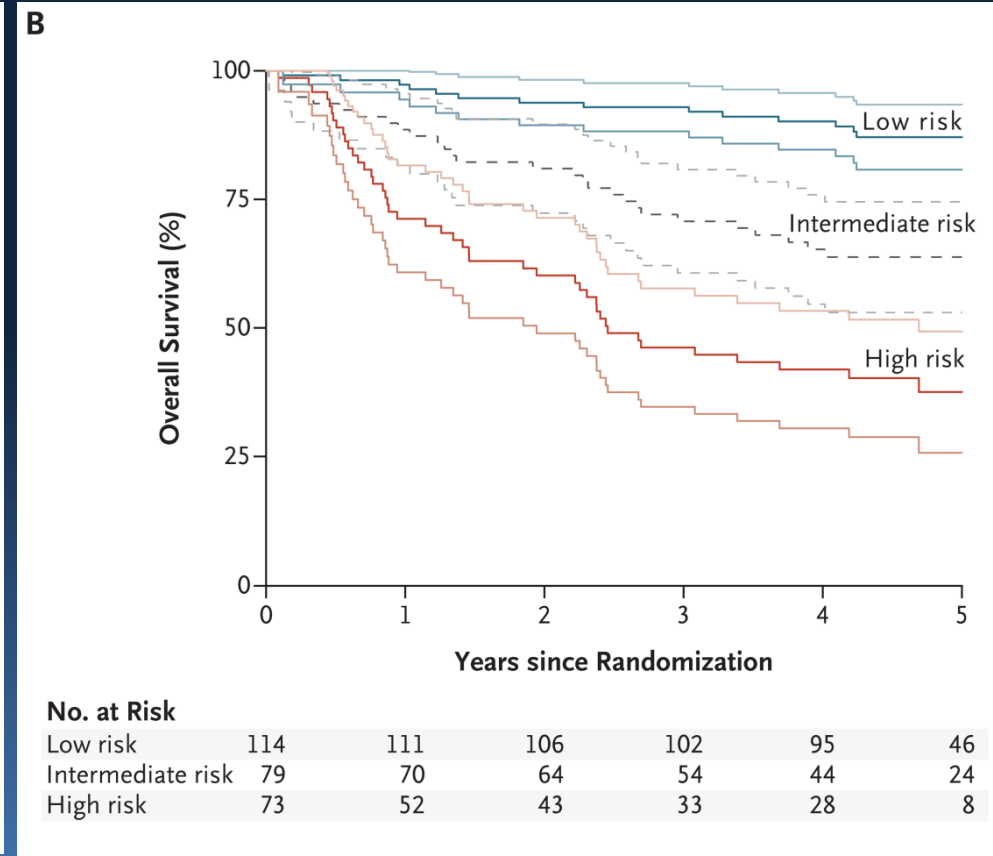
- The unadjusted multivariate Cox regression model for the entire cohort demonstrated no benefit for CCRT over RT (HR 1.134, 95% CI: 1.017-1.203, P<.001)

- Significantly associated with overall survival were:
  - Comorbidities
  - Medicare eligibility
  - Stage
  - Lymph node status
  - IMRT receipt
  - Marital status
  - Cancer site
  - Grade
  - Diagnostic era
  - Age

* VanderWalde et al. Int J Radiation Oncol Biol Phys 2014: 89: 30-37 (10,599 patients treated outside randomized control setting. SEER-Medicare linked database (1992-2007) : 68% male, 89% white, 54% no comorbidities, 55% married. 74% were treated with RT, 26% with CCRT

The Prognostic Significance of Human Papillomavirus in OPC





The 3-year rates of overall survival were 93.0% (95% CI, 88.3 to 97.7) in the low-risk group, 70.8% (95% CI, 60.7 to 80.8) in the intermediate-risk group, and 46.2% (95% CI, 34.7 to 57.7) in the high-risk group.

Ang K et al. N Engl J Med 2010;361:24-35

Methods to Reduce the Toxicity of Cisplatin-based CCRT in SCCHN: Treatment Factors

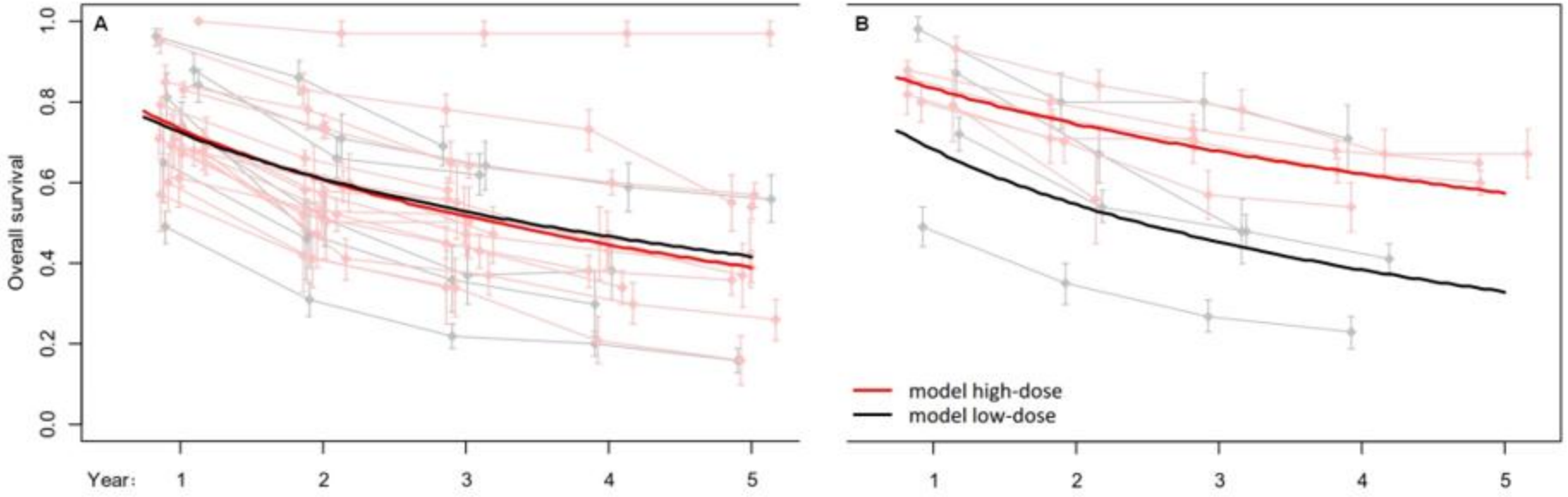
Better targeting of RT
- CT – MRI – (PET)
- IGRT

New radiotherapy techniques
- IMRT and SW-IMRT
- Stereotactic radiotherapy
- IMPT

Alternatives for high-dose 3-weekly cisplatin
- Other cisplatin dose or schedules
- Other cytotoxics (carboplatin, taxanes, low-dose gemcitabine)
- Biological agents (cetuximab, panitumumab, nimotuzumab)
- Hypoxic modification (nimorazole)

CT= computed tomography; MRI= magnetic resonance imaging; IGRT= image-guided RT; IMPT intensity-modulated particle therapy; IMRT= intensity-modulated RT; PET= positron emission tomography; RT= radiotherapy

Low-dose Weekly vs High-dose 3-Weekly Cisplatin
Two Meta-Analyses



Overall survival analysis comparing high-dose 3-weekly versus low-dose weekly cisplatin concurrently with conventional (A) and altered Fractuionation (B) radiotherapy in the definitive disease setting

JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial

Vanita Noronha, Amit Joshi, Vijay Maruti Patil, Jaiprakash Agarwal, Sarbani Ghosh-Laskar, Ashwini Budrukkar, Vedang Murthy, Tejpal Gupta, Anil K. D'Cruz, Shripad Banavali, Prathamesh S. Pai, Pankaj Chaturvedi, Devendra Chaukar, Nikhil Pande, Arun Chandrasekharan, Vikas Talreja, Dilip Harindran Vallathol, Vijayalakshmi Mathrudev, Aparna Manjrekar, Kamesh Maske, Arati Sanjay Bhelekar, Kavita Nawale, Sadhana Kannan, Vikram Gota, Atanu Bhattacharjee, Shubhada Kane, Shashikant L. Juvekar, and Kumar Prabhash

J Clin Oncol 35.

Trial Design-W3W

ELIGIBILITY CRITERIA

- Age ≤ 70 yrs
- SCC of oral cavity/ pharynx/ larynx/ cervical lymphadenopathy of unknown primary
- Stage III / IV, no distant mets
- Adjuvant or definitive CRT
- If postop: high-risk features: ECE, close or + margins, T4 primary, > 2 LNs +
- No induction chemotherapy
- Adequate organ function

Stratify

- **T-group** (T0,1,2 vs T3,4)
- **N-group** (N0,1 vs N2,3)
- **Therapy intent** (adjuvant vs definitive)

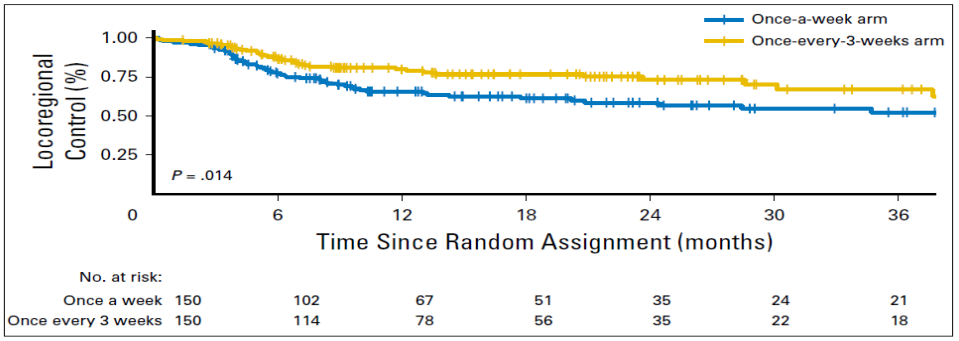
Randomized 1:1 Open Label

n=150 → **3-weekly cisplatin 100mg/m² D1,22,43 of RT**

RT: 60 Gy/30 fr/6 wks (adj)
70 Gy/35 fr/7 weeks-(def)

n=150 → **Weekly cisplatin 30mg/m² with RT**

Follow-up: Weekly during CRT, then Q3 mths x 2 yrs, then Q6 mths



Chemotherapy Details	Weekly cisplatin (n=150)	3-wkly cisplatin (n=150)
Cycles of chemotherapy-no. (%)	< 5: 17 (11.3) ≥6: 133 (88.7) P=0.1	0/ 1: 7 (4.7) ≥2: 143 (95.3)
Days from surgery to CRT start (n=276)-Median (IQR)	42 (36-50)	42 (35-49)
Total treatment time in days (n=276)-Median (IQR)	85 (79-96)	86 (79-95)
Dose reduction in chemotherapy-no. (%)		
Yes	14 (9.3)	12 (8)
No	136 (90.7)	138 (92)
Dose delay > 2 days-no. (%)		
Yes	37 (24.7)	42 (28)
No	113 (75.3)	108 (72)
Days between planned and actual chemo cycle-median (IQR)	0 (0-3)	0 (0-3)
Cumulative cisplatin dose in mg/m²- Median (IQR)	210 (180-210)	300 (200-300)

Methods to Reduce the Toxicity of Cisplatin-based CCRT in SCCHN: Treatment Factors

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CT= computed tomography; MRI= magnetic resonance imaging; IGRT= image-guided RT; IMPT intensity-modulated particle therapy; IMRT= intensity-modulated RT; PET= positron emission tomography; RT= radiotherapy

Can Cetuximab Replace Cisplatin in CCRT?
No large phase III comparison

50 trials, 9615 pts (MA)*	1 trial, 424 patients (Bonner et al)**
HR of death 0.74 (0.67-0.82)[+]	HR of death 0.74 (0.57-0.97)
Main effect on local failure Modest effect on DM	Only effect on local failure No effect on DM
Efficacy irrespective of site and of fractionation schedule	Effect may be site and RT schedule specific
Significant acute toxicity which may inflict on late toxicity, in particular swallowing dysfunction	Grade 3-4 mucositis and radiation dermatitis not significantly increased. Late toxicity seems not increased. High compliance. QoL BRT ~ RT[†]

** Pignon et al, Radioth Oncol 2009: 92; 4-14 (level I evidence); **Bonner et al. N Engl J Med 2006; 354: 567-578 (level II evidence); [+]with mono Platin therapy; [†] Curran D, et al. J Clin Oncol 2007; 25: 2191–2197*

Cisplatin versus Cetuximab with Definitive Concurrent Radiotherapy for HNSCC: An Analysis of Veteran's Health Data

	Median OS (yrs)				
	CET	CIS	HR	95% CI	p-value
Unadjusted (n=3.986)	1.5	3.8	1.78	1.63-1.95	<0.001
PS matched (n=2.114)	1.8	4.2	1.66	1.48-1.86	<0.001
Oral cavity (n=135)	0.8	1.0	1.62	1.07-2.44	0.02
Oropharynx (n=1.485)	1.0	4.6	1.63	1.42-1.88	<0.001
Larynx/HypoPh (n=477)	1.4	3.2	1.87	1.49-2.34	<0.001
Low dose Cis, PS*(n=902)	1.6	3.9	1.53	1.30-1.80	<0.001

Bauml J, et al. ASCO 2018; abstract #6073
**PS matched*

Randomized Trials of CCRT vs BRT

Study	Country	Drug (exp)	Comparator	Phase (no pts)
NCT 1302834	USA	Cetuximab	Cisplatin	III (987)[1]
NCT 01874171	UK	Cetuximab	Cisplatin	III (304)[2]
NCT 01855451	Australia	Cetuximab	Cisplatin	III (200)[3]
NCT 00169247	France	Cetuximab	Cisplatin	II (156)[4]
NCT 00716391	Spain	Cetuximab	Cisplatin	III (458)[5]
NCT 01216020	Italy	Cetuximab	Cisplatin	II (140)
NCT 00547157	"Concert 2"	Panitumumab	Cisplatin	II (150)
NCT 00820248	Canada	Panitumumab	Cisplatin	III (320)[6]
NCT 00496652	Denmark	Zalutumumab	Cisplatin	III (600)[7]

[1]in HPV(p16)+OPC (RTOG-1016);[2]De-Escalate study in HPV(p16)+OPC; [3]TROG 12.01 study in HPV(p16)+OPC; [4]Tremplin (after TPF); [5]after TPF; [6]AF (in exp. arm) vs SF (comparator);[7]6 fraction/week (RT ± Zalutumumab or CCRT ± zalutumumab)

CCRT Standard Nonsurgical Therapy
What next in LA-SCCHN?

- Should all patients be treated with concurrent CRT?
- Is further treatment intensification feasible and worth considering?
  - *adding more cytotoxic chemotherapy (ICT)*
  - *adding targeted therapy*
  - *adding a hypoxic sensitizer to concurrent CRT*
  - *immunotherapy*
- Can we select patient who might need less intensive therapy (de-escalation of locoregional therapy) ?

Adding More Cytotoxic Chemotherapy to CCRT
Role of induction chemotherapy*

- ICT does not have a clear established frontline role in the routine treatment of head and neck carcinomas of the major non-nasopharyngeal sites
- ICT→RT has an established role for organ preservation in advanced laryngeal and hypopharyngeal cancer
- ICT→cisplatin-based CCRT reduces distant metastases, but it does not increase OS and is more toxic than cisplatin-based CCRT alone.

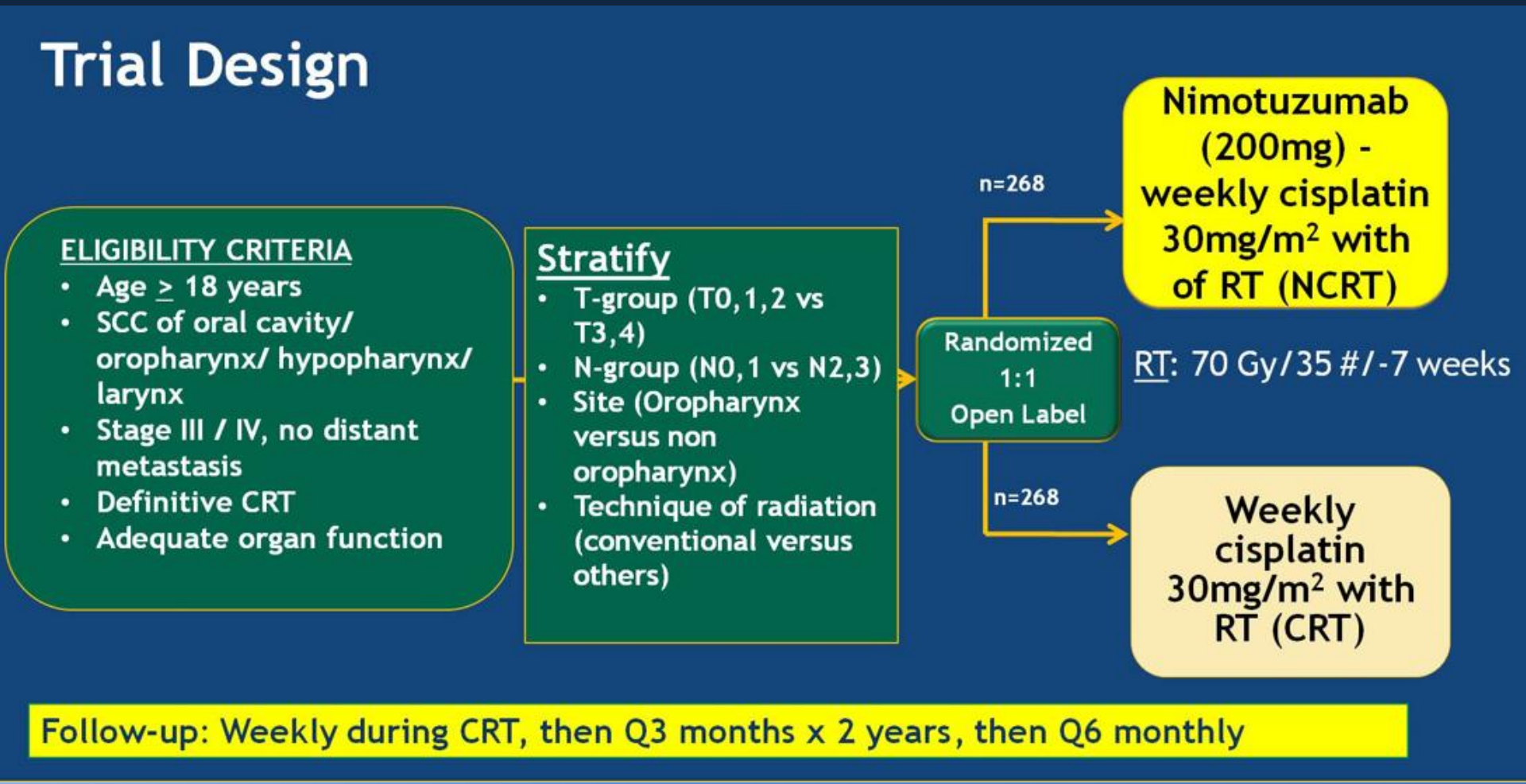
**Haddad RI, Vermorken JB et al.Annals of Oncology 29: 1130–1140, 2018*

Adding Anti-EGFR Drugs to CCRT

Study	Country	Anti-EGFR	CCRT (drug)	Phase (no pts)
NCT 00265941	USA	Cetuximab	Cisplatin	III (895)[1]
NCT 00496652	Denmark	Zalutumumab	Cisplatin	III (619)
NCT 00500760	Concert-1	Panitumumab	Cisplatin	II (153)
NCT 00229723	International	Gefitinib	Cisplatin	II (224)[2]
NCT 00410826	USA	Erlotinib	Cisplatin	II (204)
NCT 01074021	China	Nimotuzumab	Cisplatin	III (480)[3]
NCT 00957086	Singapore	Nimotuzumab	Cisplatin	III (710)[4]
NCT 01516996	China	Nimotuzumab	TP	II (80)[5]

[1]RTOG0522; [2]published (no effect); [3]study (placebo-controlled) in NPC (2008 stages III/IVa); [4]placebo controlled in the postoperative setting; [5]nimotuzumab during 2x ICT and CRT

Adding Anti-EGFR Medication to Chemoradiation

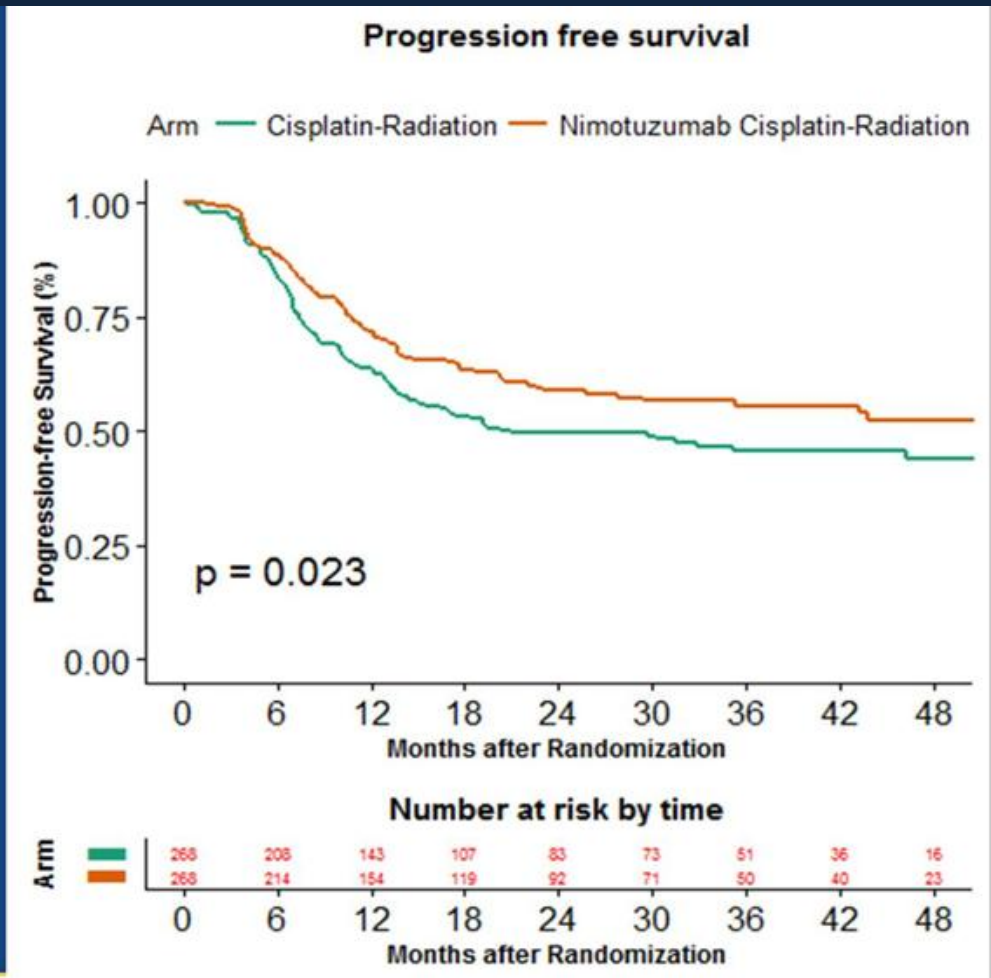


Vijay Maruti Patil, ASCO 2018; abstract #6000

Adding Anti-EGFR Medication to Chemoradiation

PFS

- PFS was significantly longer in the patients treated in the NCRT arm (Hazard ratio, 0.74; 95% CI 0.56-0.95)
- The 2 year PFS was 49.5% (Std.Error =3.3%) in the CRT arm while the corresponding figures was 58.9% (Std.Error =3.4%) in the NCRT arm

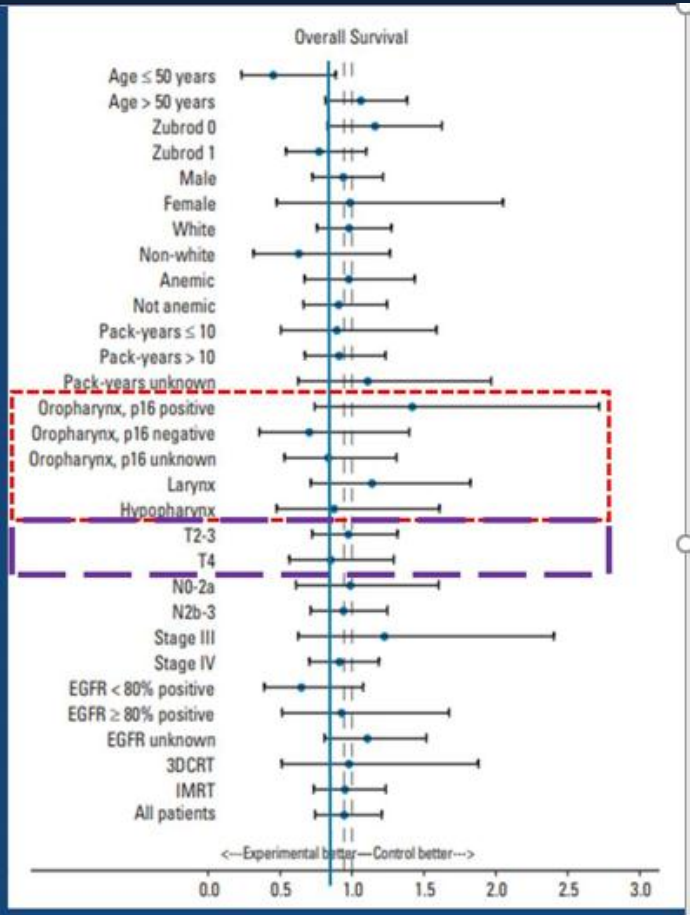


Vijay Maruti Patil, ASCO 2018; abstract #6000

Difference with previous study

Factors	RTOG 0522- Cetuximab arm	Our study- Nimotuzumab arm
Patient characteristics		
HPV Negative	26.8%	94%
Hypo pharynx	6.4%	23.1%
T3-T4	60%	84.7%
Treatment		
Radiation interruptions (any cause)	51.8%	34.3%
Cisplatin 160 or above*	88.5%	92.9%

*-As data in RTOG 0522 available for 160mg/m2



Ang et al. J Clin Oncol. 2014 Sep 20;32(27):2940-50.

Vijay Maruti Patil, ASCO 2018, abstract #6000

Adding Checkpoint Inhibitors to RT or CCRT
Study with ≥100 patients

Trial	Setting	Regimens
PembroRad	IIR (definitive)	Pembro+RT vs Cet +RT
PATHWay	IIR (adjuvant)	Pembro vs placebo
RTOG 3504	I/III (def.+adj)	Nivo+CRT (LD-P) vs Nivo+CRT (HD-P) vs Nivo+Cet+RT vs Nivo+RT
REACH	III (definitive)	P+RT vs Cet+Ave+RT* vs Cet+RT
KEYNOTE-412	III (definitive)	Pembro+P+RT vs Placebo+P+RT
JAVELIN HN-100	III (definitive)	Ave+P+RT vs Placebo+P+RT

*Modified from Szturz and Vermorken, BMC Medicine 2017 (*separately in NPC and Oral cavity cancer)*
Pembro=pembrolizumab (anti-PD1); Cet= cetuximab; P=cisplatin; RT=radiotherapy; CRT=chemoradiation
Nivo= nivolumab (anti-PD1); Ave= avelumab (anti-PD-L1)

CCRT Standard Nonsurgical Therapy
What next in LA-SCCHN?

- Should all patients be treated with concurrent CRT?
- Is further treatment intensification feasible and worth considering?
  - *adding more cytotoxic chemotherapy (ICT)*
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  - *immunotherapy*
- Can we select patient who might need less intensive therapy (de-escalation of locoregional therapy) ?

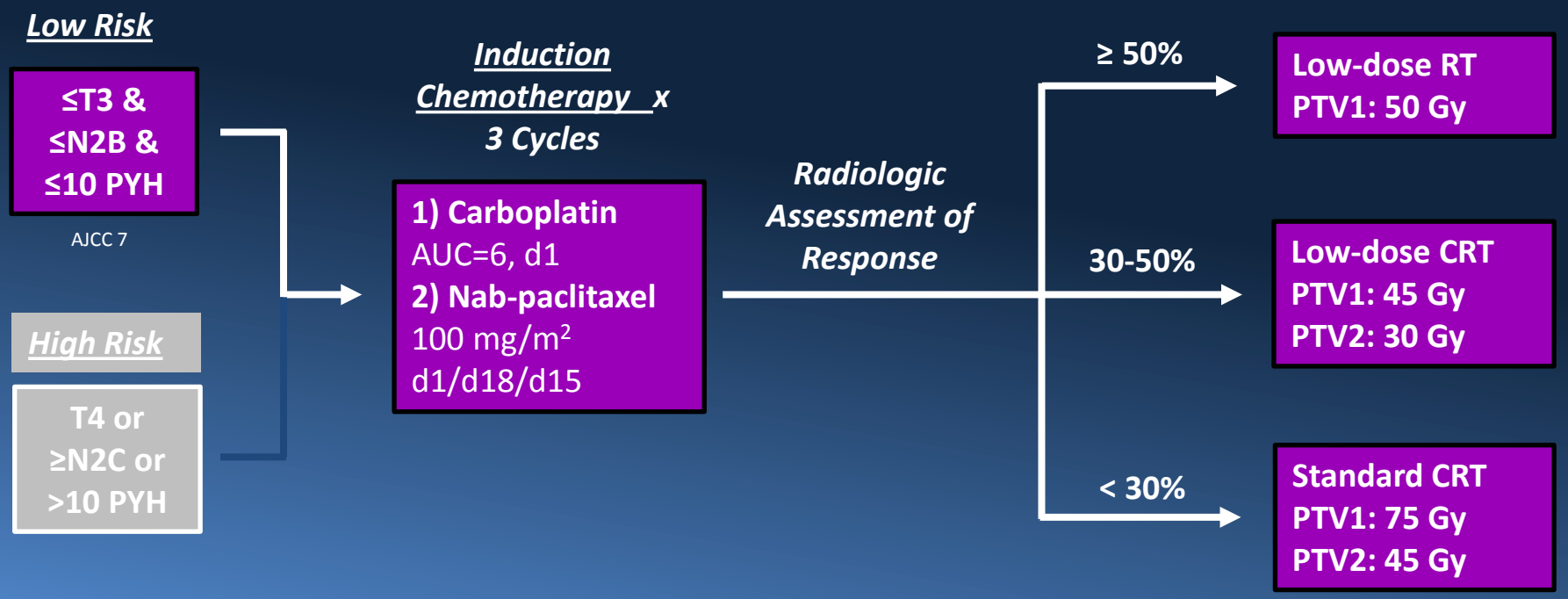
Research Areas of Induction Chemotherapy for Treatment De-intensification

- ICT can be used as a tool to stratefy patients by treatment response
- Applicable to good-prognosis HPV-associated OPC
- Ongoing trials:
  - OPTIMA HPV (NCT02258659)
  - Quarterback trial (NCT01706939)*
  - ECOG 1308 (NCT01084083)**

*Stage III and IV HPVOPC: 3x TPF, when CR/PR randomization between 56 Gy and 70 Gy, when NR standard CCRT
**Stage III-IVB resectable HPVOPC: 3x TCE, when CR-54Gy/27 fr, when PR/SD-69.3 Gy/33fr

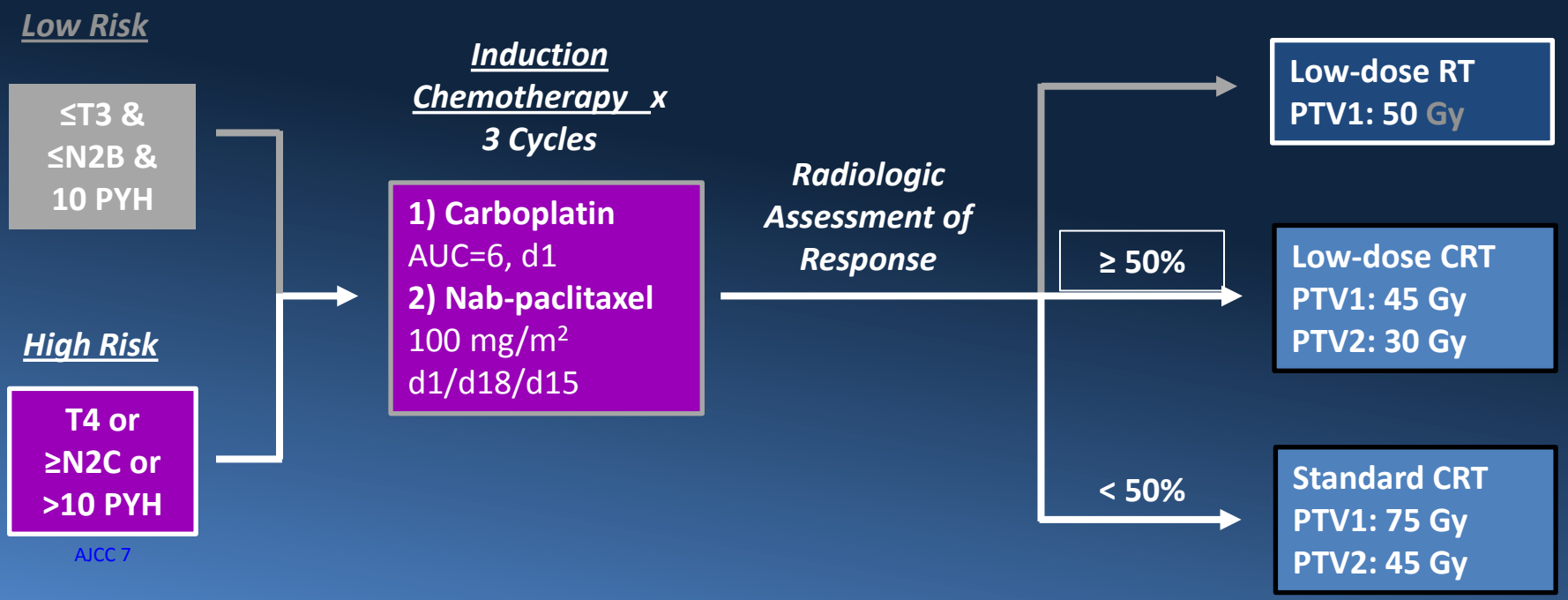
Chapman CH et al. Future Oncol 2017; 13: 469-475

OPTIMA = Oro-Pharynx Tumor Induction Response Stratified Therapy To Minimize Adverse Events



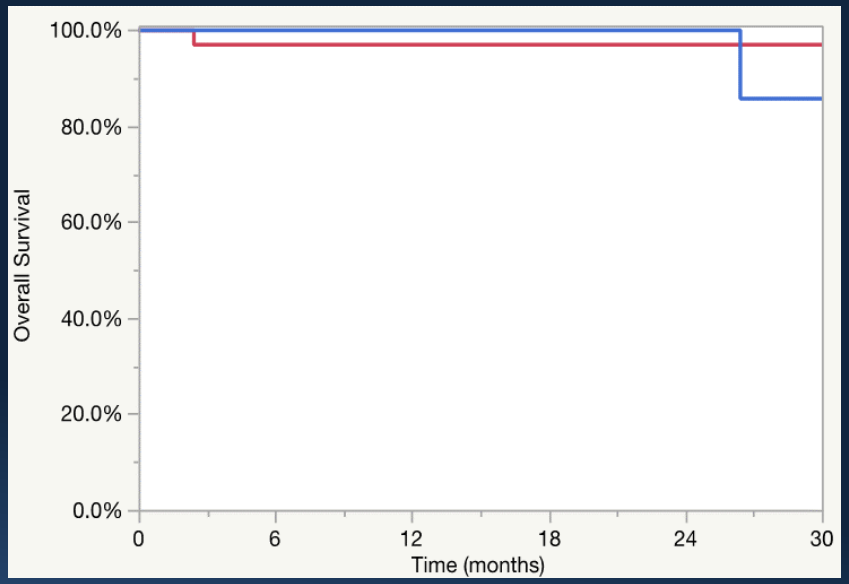
Seiwert et al. MHNCS 2018

OPTIMA = Oro-Pharynx Tumor Induction Response Stratified Therapy To Minimize Adverse Events



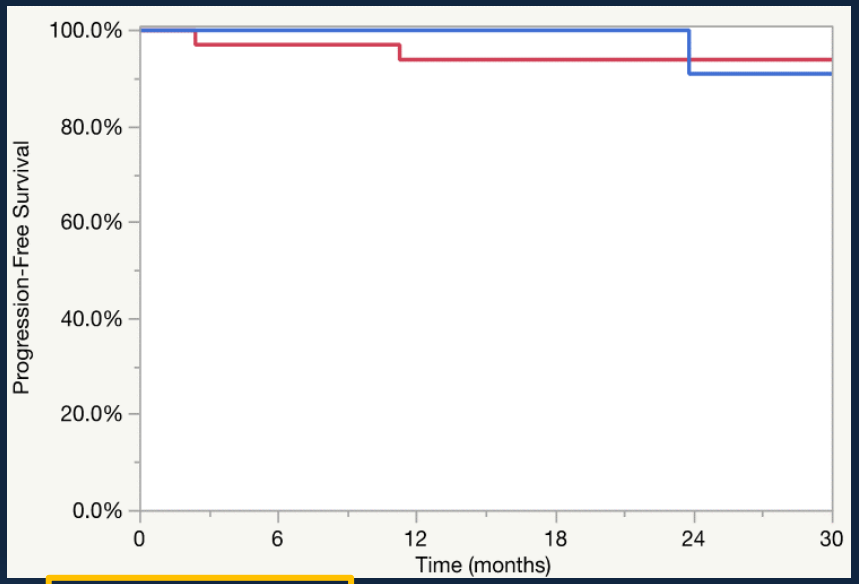
Seiwert et al. MHNCS 2018

Overall Survival



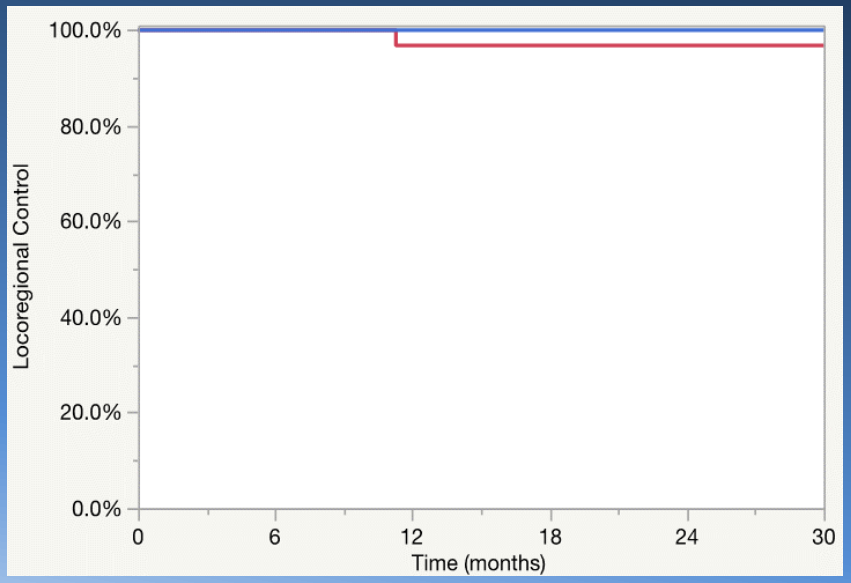
2-year OS: 100% 2.5-year OS: 85.7%
2-year PFS: 93.8% 2.5-year PFS: 93.8%

Progression-Free Survival



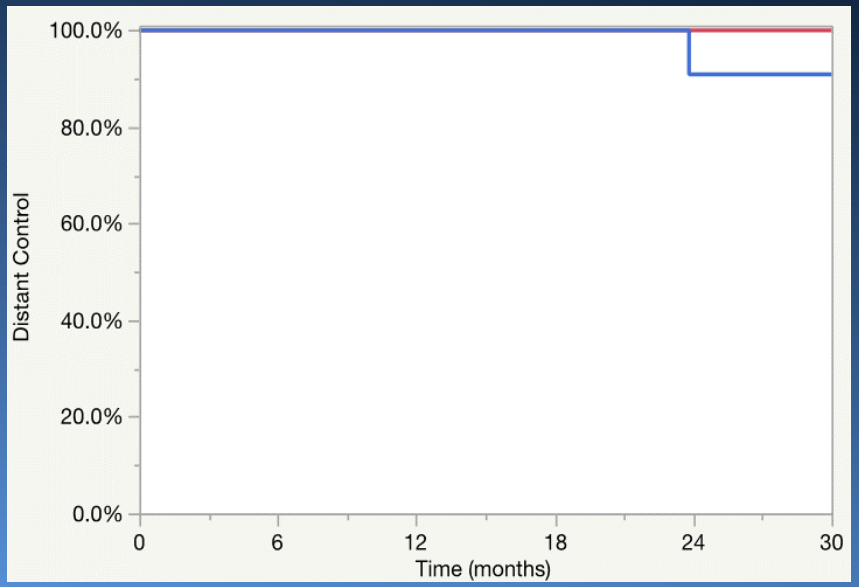
2-year PFS: 91.0% 2.5-year PFS: 91.0%
2-year OS: 97.0% 2.5-year OS: 97.0%

Locoregional Control



2-year LRC: 100% 2.5-year LRC: 100%
2-year DC: 100% 2.5-year DC: 100%

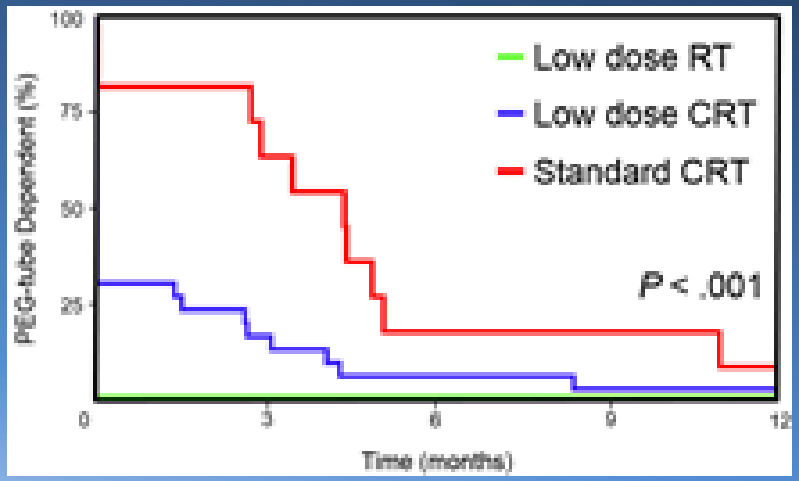
Distant Control



2-year DC: 91.0% 2.5-year DC: 91.0%
2-year LRC: 96.8% 2.5-year LRC: 96.8%

Treatment Arm	Acute Toxicity (%)			
	Grade ≥3 Mucositis	*P-Value*	Grade ≥3 Dermatitis	*P-Value*
Low dose RT	15.0	*0.01*	0	*0.002*
Low dose CRT	46.7		10.0	
Standard CRT	63.6		45.5	

G-tube dependency



Treatment Arm	PEG-Dependency (%)	
	6 Mos.	12 Mos.
Low dose RT	0	0
Low dose CRT	6.9	3.5
Standard CRT	18.2	9.1

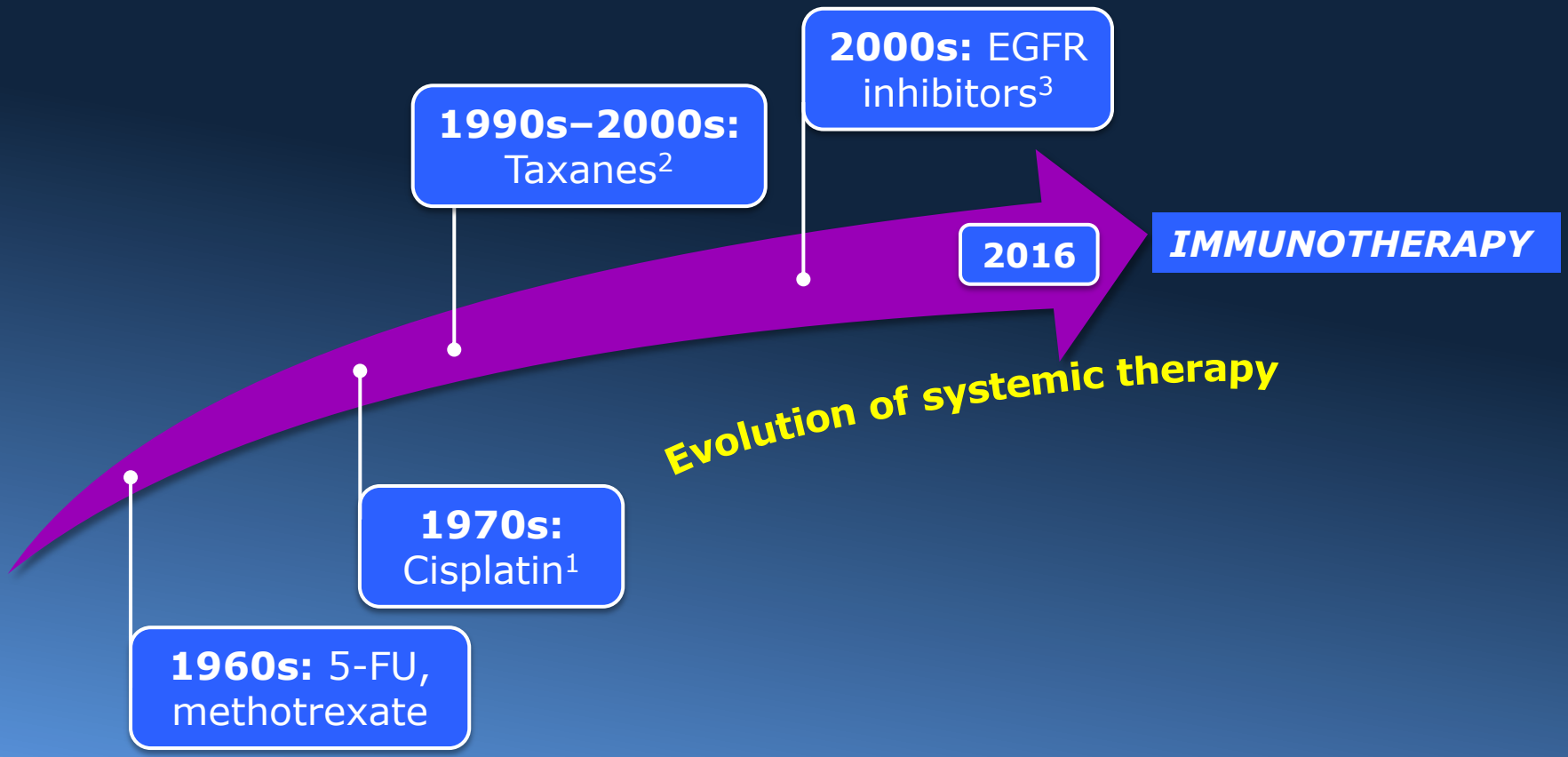
Seiwert et al. MHNCS 2018

Standard Treatment Options in R/M-SCCHN 2018

- Resectable disease
  - Surgery at all times if possible
  - Postop RT or CCRT (if not complete) [1]
- Nonresectable disease
  - RT or CCRT (if no organ dysfunction/morbidiy) [1]
- Recurrent/Metastatic disease
  - First-line: EXTREME (platinum/5-FU/cetuximab)[2,3]
  - Alternatives in unfavorable pts: single agents ± cetuximab
  - Second-line: CheckMate-141 (nivolumab single agent)[3]
  - Pembrolizumab also approved for same indication in the US[3]
  - Best supportive care only (PS3) [2,3]

[1]Strojan et al. Head & Neck- DOI 10.1002/hed.23542; [2]Gregoire V et al, Ann Oncol 2010: 21 (suppl 5): VI84-VI86; [3]NCCN Guidelines

Systemic Therapy Options are Evolving for SCCHN



Courtesy of Ethan Argiris

1. Wittes RE, et al. Cancer Treat Rep 1977;61:359–366;
2. Gibson MK, et al. J Clin Oncol 2005;23:3562–3567;
3. Vermorken JB, et al. N Engl J Med 2008;359:1116–1127

PF vs Single Agents or Other Pt-Regimens
Randomized trials in R/M-SCCHN

	N	Regimen	ORR (%)	Median OS (months)	Significant OS benefit
Jacobs et al 1992	249	Cisplatin + 5-FU Cisplatin 5-FU	32* 17 13	5.5 5.0 6.1	No
Forastiere et al 1992	277	Cisplatin + 5-FU Carboplatin + 5-FU Methotrexate	32* 21 10	6.6 5.0 5.6	No
Clavel et al 1994	382	CABO Cisplatin + 5-FU Cisplatin	34* 31* 15	7.3 7.3 7.3	No
Gibson et al 2005	218	Cisplatin + 5-FU Cisplatin + paclitaxel	27 26	8.7 8.1	No
Urba et al 2012	795	Cisplatin/Pemetrexed Cisplatin/placebo	12 8	7.3 6.3	No

**Statistically significant*

Jacobs et al. J Clin Oncol 1992; Forastiere et al. J Clin Oncol 1992; Clavel et al. Ann Oncol 1994;; Gibson et al. J Clin Oncol 2005; Urba et al, Cancer 2012

Completed Randomized Phase II/III Trials with Anti-EGFR drugs in First-Line R/M-SCCHN

Study/Reference	N	Regimen	RR (%)	PFS (mo)	OS (mo)
ECOG 5397 Burtness et al J Clin Oncol 2005	117	Cisplatin + cetuximab Cisplatin + placebo	26[a] 10	4.2 2.7	9.2 8.0
EXTREME Vermorken et al N Engl J Med 2008	442	PF[1] + cetuximab PF[1]	36[a] 20	5.6[b] 3.3	10.1[c] 7.4
SPECTRUM Vermorken et al Lancet Oncol 2013	657	PF[2] + panitumumab PF[2]	36[a] 25	5.8[b] 4.6	11.1 9.0

PF[1] = cisplatin or carboplatin plus 5-FU; PF[2] = cisplatin plus 5-FU
[a, b, c]: significant differences

CT plus Cetuximab in First-Line SCCHN
Taxane regimens better partner?

Author	Phase	N	Regimen	ORR (%)	Median PFS (months)	Median OS (months)
Vermorken 2008	III	442	PF PF + cetuximab	20 36*	3.3 5.6*	7.4 10.1*
Burtness 2005	III	117	Cis + Placebo Cis + cetuximab	10 26*	2.7 4.2	8.0 9.2
Buentzel 2007	II	23	Pacli/Carbo + cetuximab	56	5.0**	8.0
Hitt 2011	II	46	Pacli + cetuximab	54	4.2	8.1
Guigay 2015	II	54	Doce/Cis /cetuximab	44	6.2	14.0
Tahara 2018	II	45	Pacl/Carbo + cetuximan	40	5.2	14.7

**Significant; **TTP*

Vermorken et al. NEJM 2008; Burtness et al. JCO 2005; Tahara et al, Ann Oncol 2018
Hitt et al. Ann Oncol 2011; Buentzel et al. ASCO 2007 (abstract 6012); Guigay et al. Ann Oncol 215

Second-line Treatment with Anti-EGFR Drugs
Randomized phase III trials in R/M-SCCHN

Study/Reference	N	Regimen	RR (%)	PFS	OS (mo)
IMEX	486	Gefitinib (250 mg)	3	ND	5.6
Stewart et al, 2009		Gefitinib (500 mg)	8	ND	6.0
		Methotrexate	4	ND	6.7
ZALUTE	286	Z + BSC (-MTX)	6	2.3*	6.7˚
Machiels et al, 2011		BSC (optional MTX)	1	1.9*	5.2˚
LUX HN1	483	Afatinib	10	2.6+	6.8
Machiels et al, 2015		Methotrexate	6	1.7	6.0

BSC = best supportive care; Z = zalutumumab; MTX = methotrexate; ND = no data;
**HR (95% CI): 0.62 (0.47-0.83), p=0,0010; ˚ HR (95% CI): 0.77 (0.57-1.05), p=0.0648; +HR (95% CI): 0.80 (0.65-0.98),p=0.03*

Second-line Treatment with Targeting Drugs
Randomized trials in R/M-SCCHN

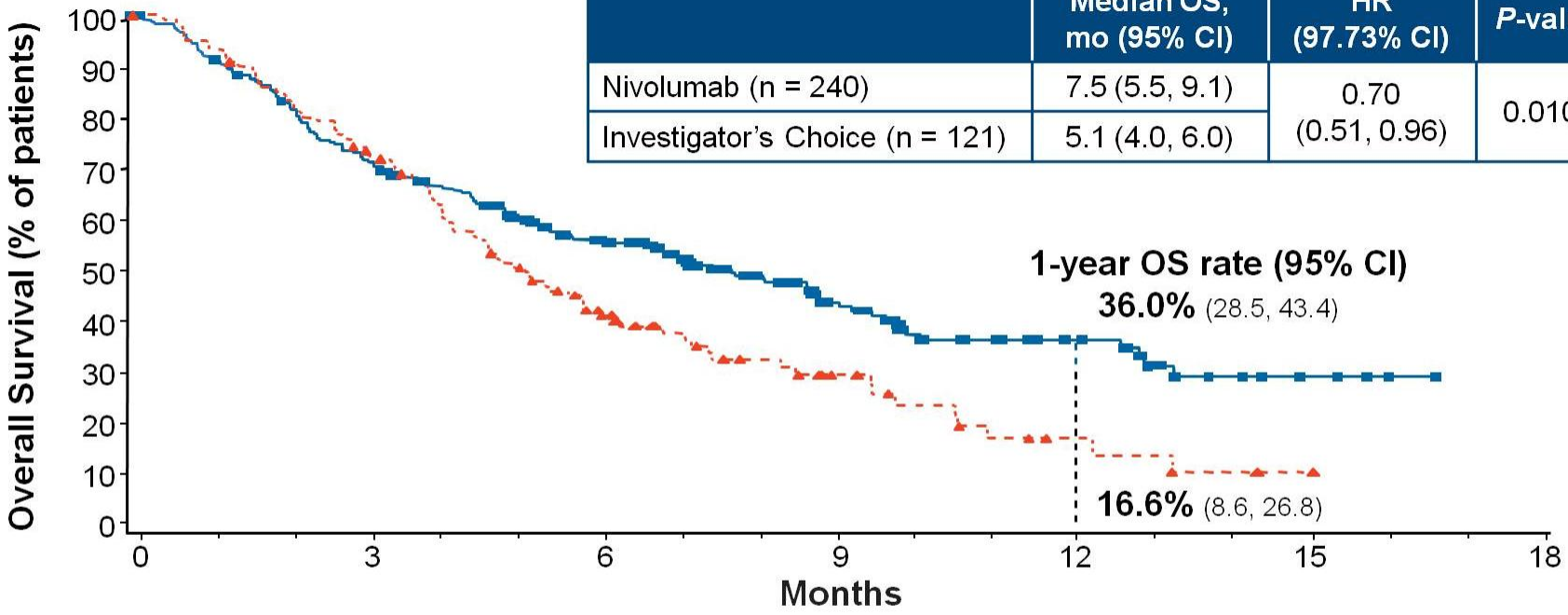
Study/Reference	N	Regimen	RR (%)	PFS	OS (mo)
ECOG 1302	270	D + Gefitinib	12	3.5 (TTP)	7.3
Argiris et al, 2013		D + placebo	6	2.1 (TTP)	6.0
BERIL-1 Trial	158	Buparlisib + paclitaxel	39	4.6*	10.4**
Soulières et al, 2017		Placebo + paclitaxel	14	3.5	6.5
CHECKMATE-141	361	Nivolumab	13	2.0	7.5+
Ferris et al, 2016		Investigator's choice	6	2.3	5.1

TTP= time to progression

**p=0.01 (one-sided); **p= 0.04 (one-sided); +p=0.01*

CheckMate 141: Overall Survival

	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)		

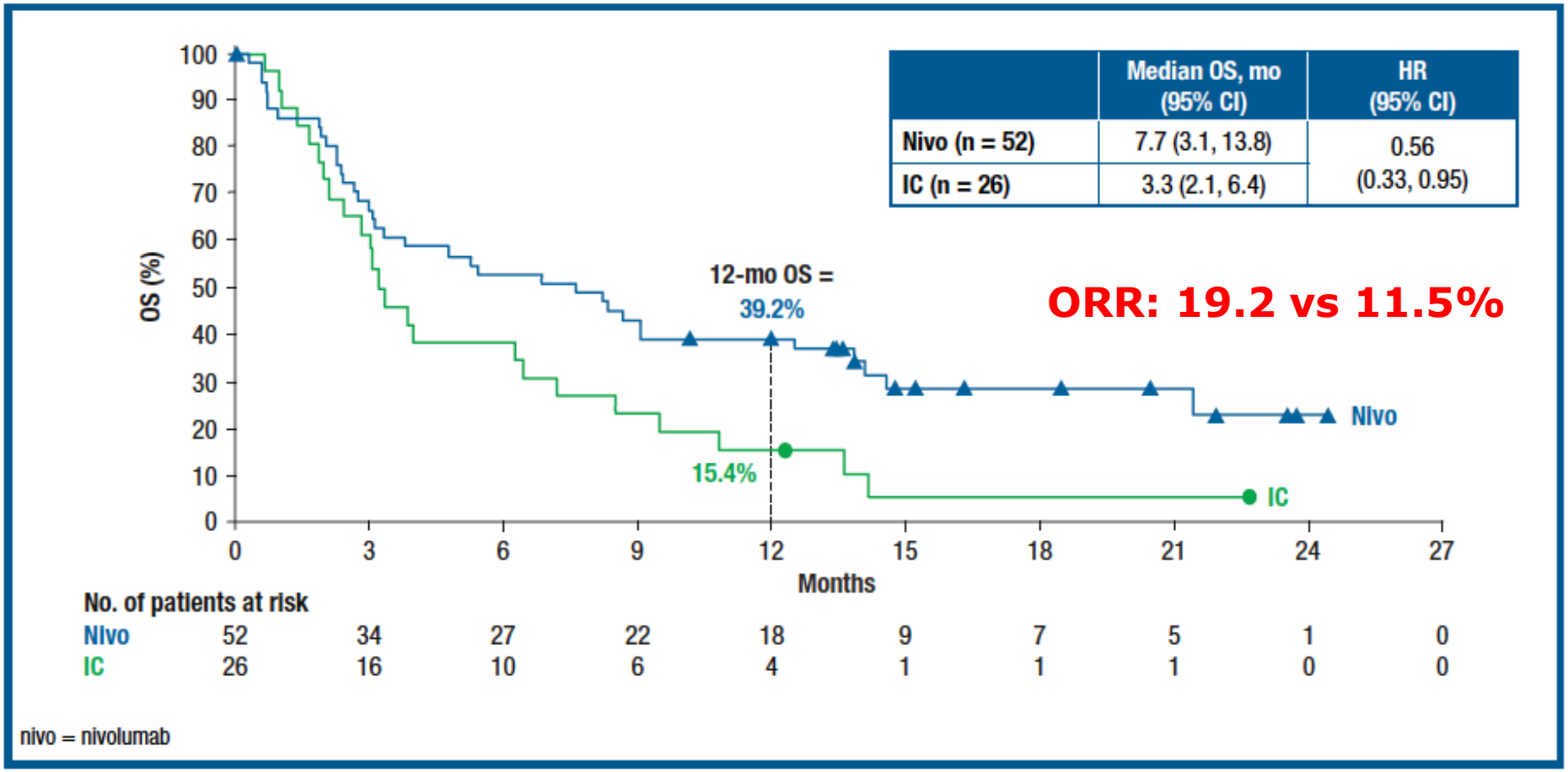


No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

Ferris RL, et al. N Engl J Med. 2016;375:1856-67

CheckMate 141: Outcomes in the First-line R/M-SCCHN

Figure 2. OS among patients receiving 1L R/M nivolumab or IC after platinum-based therapy in the primary/adjuvant setting



Treatment-Related Adverse Events *Nivolumab in R/M SCCHN After Platinum Therapy*

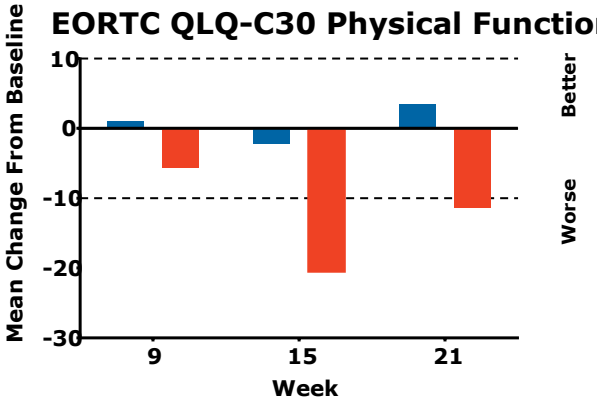
Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Any treatment-related AE in ≥ 10% of patients[a]	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Alopecia	0	0	14 (12.6)	3 (2.7)
Treatment-related select AEs				
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)

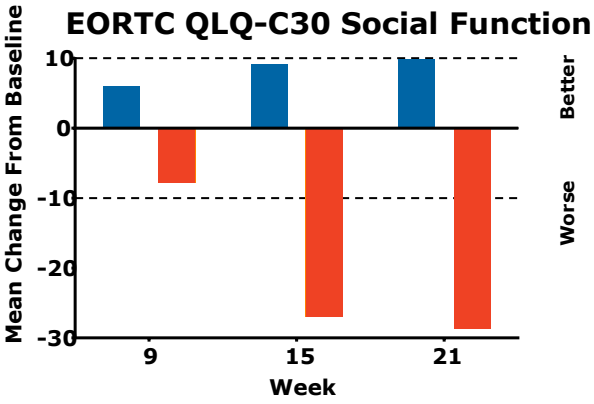
[a]One Grade 5 event (hypercalcemia) in the nivolumab arm and one Grade 5 event (lung infection) in the investigator's choice arm were reported. A second death occurred in the nivolumab arm subsequent to pneumonitis.

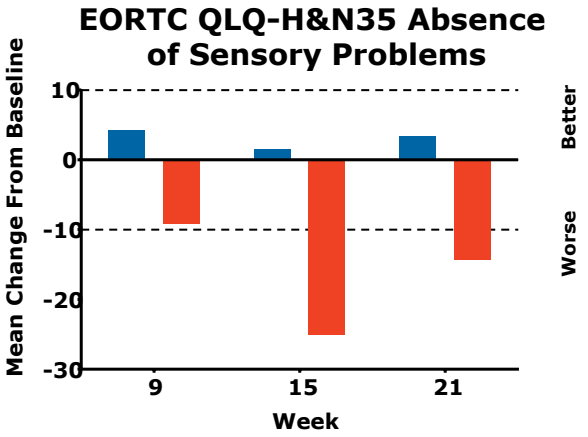
Courtesy of Bob Ferris (ASCO 2016)

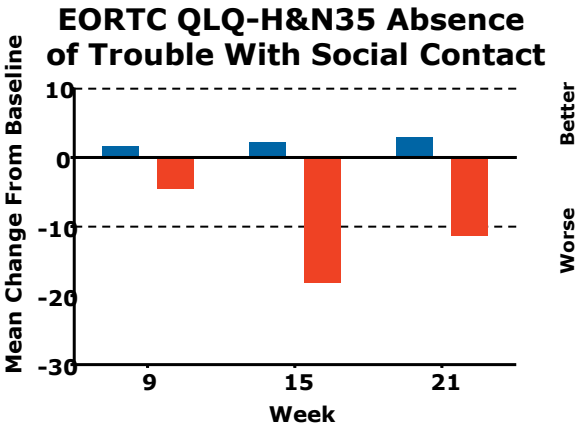
Quality of Life and Symptom Burden

Nivolumab in R/M SCCHN After Platinum Therapy









Nivolumab
Investigator's Choice

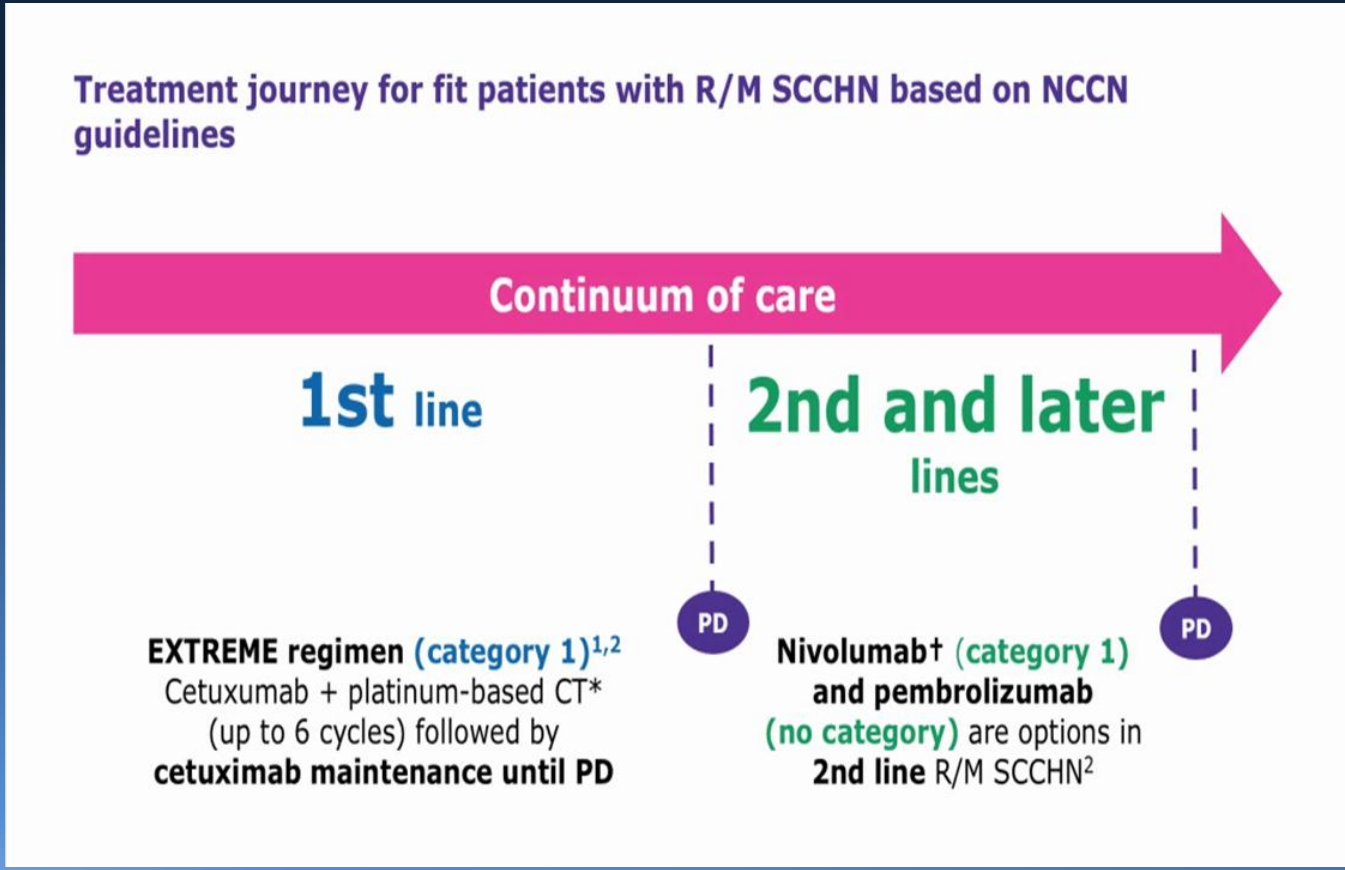
- Nivolumab stabilized PROs while investigator's choice led to meaningful declines in function and worsening of symptoms

Anti-PD-1 MoAb in Second-line R/M-SCCHN

Parameter	Second-line Chemother[1]	Nivolumab Checkmate 141[1]	Pembrolizumab KEYNOTE 040[2]	Second-line Chemother[2]
ORR	5.8%	13.3%	14.6%	10.1%
CR	0.8%	2.5%	1.6%	0.4%
PR	5.0%	10.8%	13.0%	9.7%
Median PFS	2.3 months	2.0 months	2.1 months	2.3
6-month PFS	9.0%	19.7%	25.9%	19.5%
Median OS	5.1 months	7.5 months	8.4 months	7.1 months
12-months	16.6%	36.0%	37.3.0%	27.2%

[1] From Checkmate 141 study (Ferris et al, NEJM 2016; DOI: 10.1056/NEJMMoa1602252)
[2]From KEYNOTE-040 (Cohen et al, ESMO abstract LBA-45, 2017)

New NCCN Guidelines for R/M-SCCHN



Ongoing Randomized first-line Trials with Checkpoint Inhibitors in R/M-SCCHN (≥100 pts)

Trial	Setting	No	Regimens
CheckMate-714	IIR	315	Nivo+Ipi vs Nivo+placebo
KESTREL	III	760	Durva vs Durva+Treme vs PFE
KEYNOTE-048	III	825	Pembro vs Pembro+PF vs PFE
CheckMate-651	III	490	Nivo+Ipi vs PFE

Modified from Szturz and Vermorken, BMC Medicine, 2017

Nivo= nivolumab (anti-PD1); Ipi= ipilimumab (anti-CTLA-4); Durva= durvalumab (anti-PD-L1); Treme= tremelimumab (anti-CTLA-4); Pembro= pembrolizumab (anti-PD1)

Future Expectations with Immune Checkpoint Inhibitors (ICIs)

- ICIs might have repercussions in LA-SCCHN
  - in terms of toxicity (PembroRad study / ASCO 2018)
  - in terms of efficacy (pathology changes after ICI induction)

- ICIs have changed practice in 2nd-line R/M-SCCHN, but
  - will it, combined with cytotoxics or other ICIs, replace the standard EXTREME regimen in first line setting?
  - what will be the optimal sequence when combining ICIs with cytoxics (before, after, at the same time or both)?