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Emerging Role of Immunotherapy in Head and Neck Cancer

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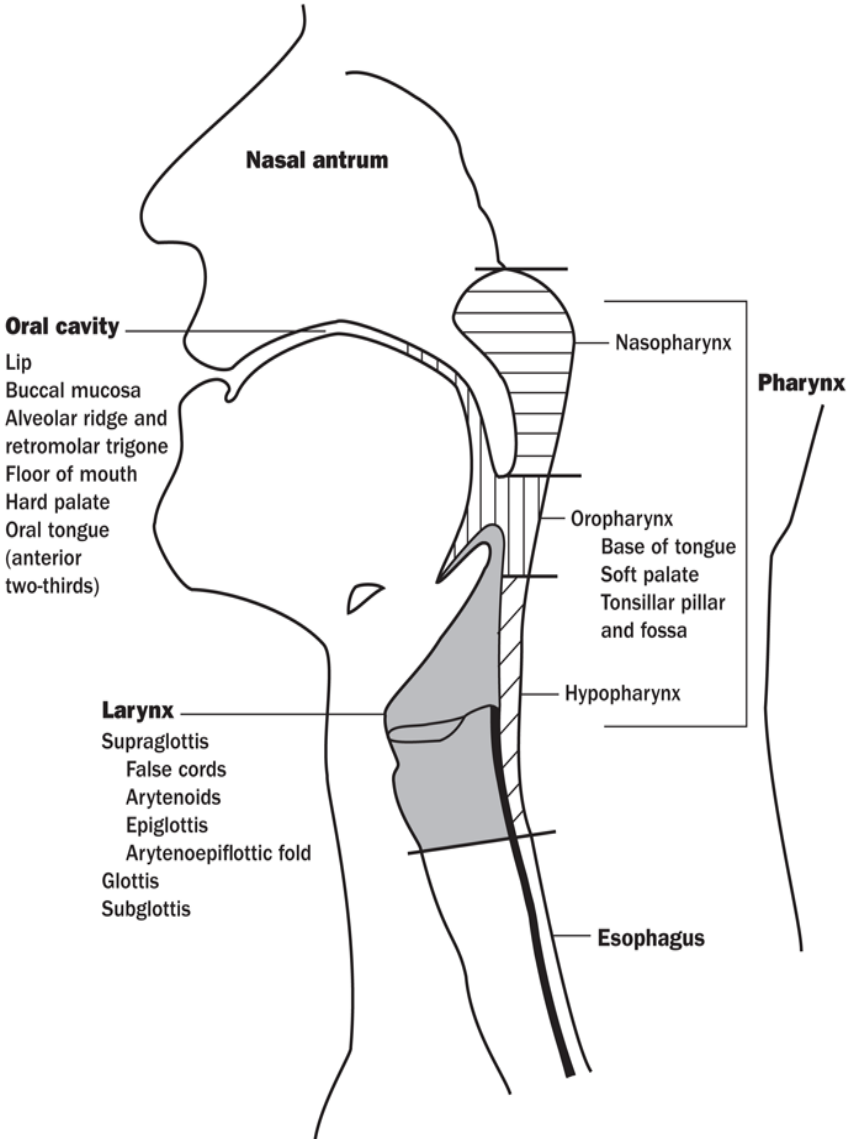
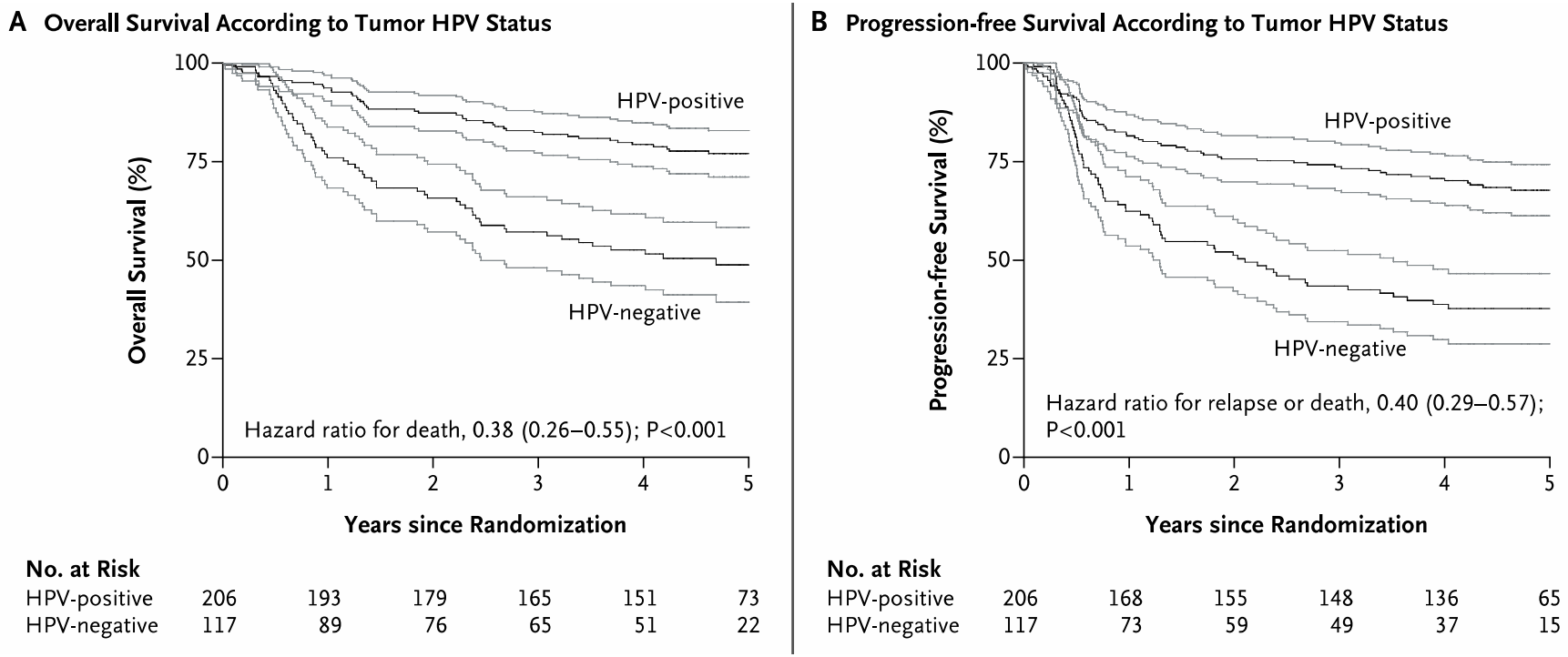
Outline of Talk

I. Introduction: Basics of incurable SCCHN in the pre-IO era
II. New IO data: Nivolumab and Pembrolizumab
III. A look to the future—integration into cure!

What is Head and Neck Cancer?



HPV



Ang. *N Engl J Med.* 2011

Case

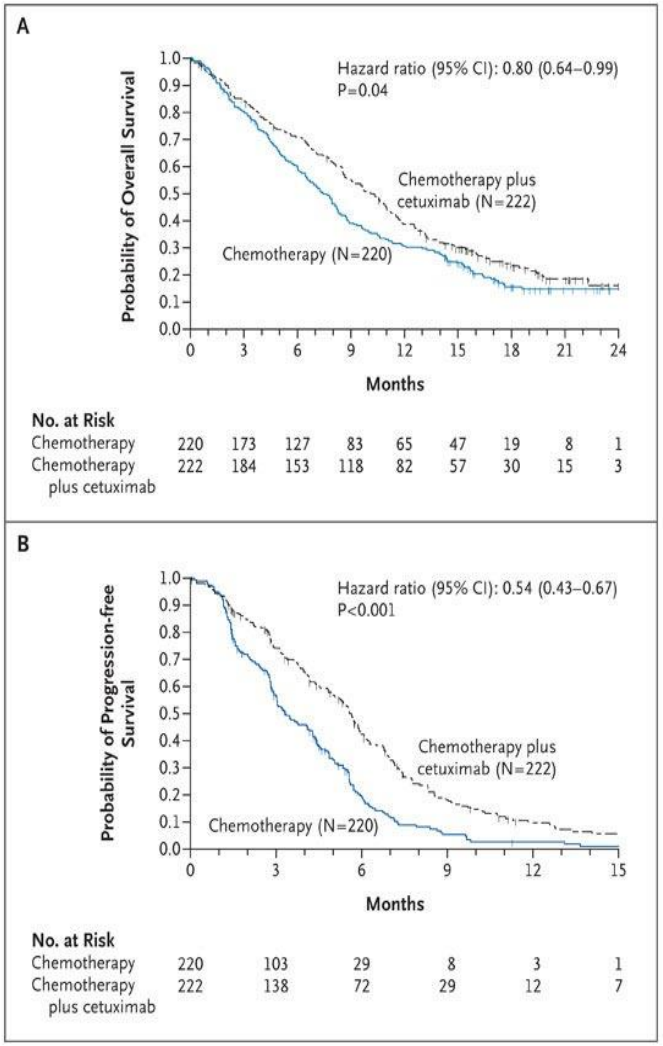
- A 60-year-old man with 40 pack year smoking history who was treated with partial laryngectomy 2 years ago presents with biopsy-proven metastases to his lungs.

Historic Options for this Patient

Author	Drugs	Patients	Median Survival (months)
Jacobs, et al.	Cisplatin 5-FU Cisplatin + 5-FU	83 83 79	5.0 6.1 5.5
Forastiere, et al.	Methotrexate Carboplatin + 5-FU Cisplatin + 5-FU	88 86 87	5.6 6.0 6.6
Burtness, et al.	Cisplatin Cisplatin + C225	57 60	8 9.2
Vermorken, et al. (EXTREME)	Cisplatin (or carboplatin) + 5-FU Cisplatin (or carboplatin) + 5-FU + C225	220 222	7.4 10.1

EXTREME: Current SOC for this patient

C225 Adds to Cis-5FU



Why "EXTREME" was a very good name

Table 3. Grade 3 or 4 Adverse Events in the Safety Population.*

Event	Cetuximab plus Platinum–Fluorouracil (N=219)		Platinum–Fluorouracil Alone (N=215)		P Value†
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4	
	number of patients (%)				
Any event	179 (82)	67 (31)	164 (76)	66 (31)	0.19
Neutropenia	49 (22)	9 (4)	50 (23)	18 (8)	0.91
Anemia	29 (13)	2 (1)	41 (19)	2 (1)	0.12
Thrombocytopenia	24 (11)	0	24 (11)	3 (1)	1.00
Leukopenia	19 (9)	4 (2)	19 (9)	5 (2)	1.00
Skin reactions‡	20 (9)	0	1 (<1)	0	<0.001
Hypokalemia	16 (7)	2 (1)	10 (5)	1 (<1)	0.31
Cardiac events§	16 (7)	11 (5)	9 (4)	7 (3)	0.22
Vomiting	12 (5)	0	6 (3)	0	0.23
Asthenia	11 (5)	1 (<1)	12 (6)	1 (<1)	0.83
Anorexia	11 (5)	2 (1)	3 (1)	1 (<1)	0.05
Hypomagnesemia	11 (5)	8 (4)	3 (1)	1 (<1)	0.05
Febrile neutropenia	10 (5)	2 (1)	10 (5)	4 (2)	1.00
Dyspnea	9 (4)	2 (1)	17 (8)	5 (2)	0.11
Pneumonia	9 (4)	3 (1)	4 (2)	1 (<1)	0.26
Hypocalcemia	9 (4)	5 (2)	2 (1)	0	0.06
Sepsis (including septic shock)	9 (4)	6 (3)	1 (<1)	1 (<1)	0.02
Tumor hemorrhage	3 (1)	2 (1)	6 (3)	4 (2)	0.33
Decreased performance status	2 (1)	1 (<1)	4 (2)	4 (2)	0.45
Respiratory failure	1 (<1)	0	5 (2)	4 (2)	0.12

Key Take-Home Points

- Old school chemotherapy not very effective
- “Standard” cytotoxic backbone of CDDP/5FU based on poor evidence
- CDDP/5FU +/- cetuximab is toxic

Case Revisited

- A 60-year-old-man with 40 pack year smoking history who was treated with partial laryngectomy 2 years ago presented with biopsy-proven metastases to his lungs.

- You treated with EXTREME. This was c/b severe fatigue, febrile neutropenia, nausea, vomiting and mild neuropathy, but resulted in 6 months response.

- His cancer has now progressed.

Case Revisited: What should you do?

- Methotrexate
- 5FU
- Nivolumab or Pembrolizumab
- Nivolumab or Pembrolizumab, as long as PD-L1 is +
- Nivolumab or Pembrolizumab as long as PD-L1 is + and HPV is +

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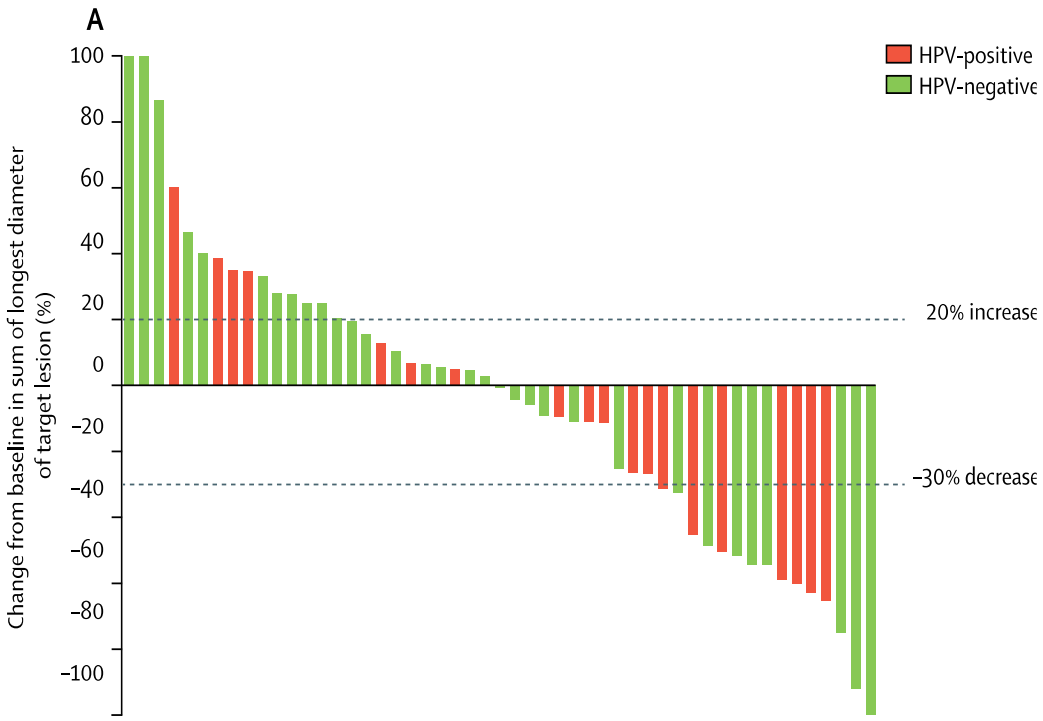
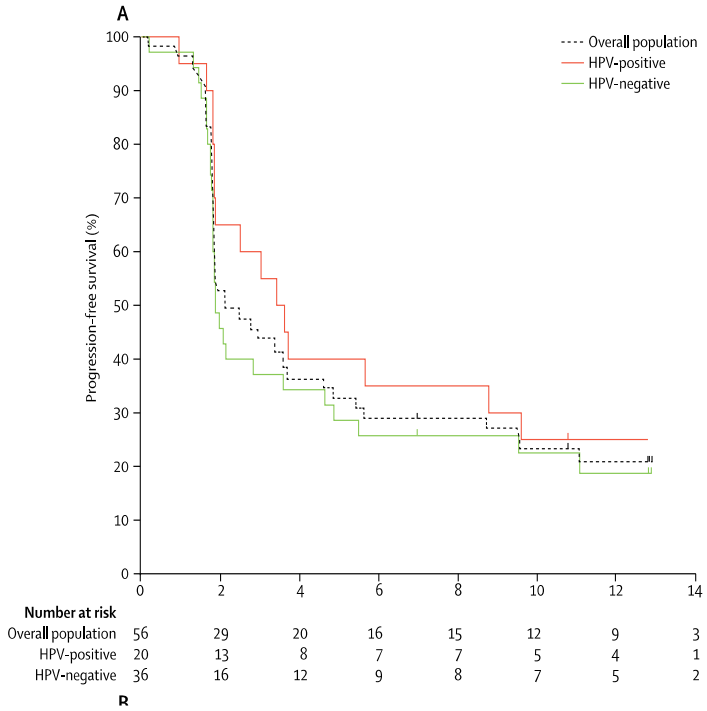
KEYNOTE-012a – Pembrolizumab in PD-L1+ SCCHN





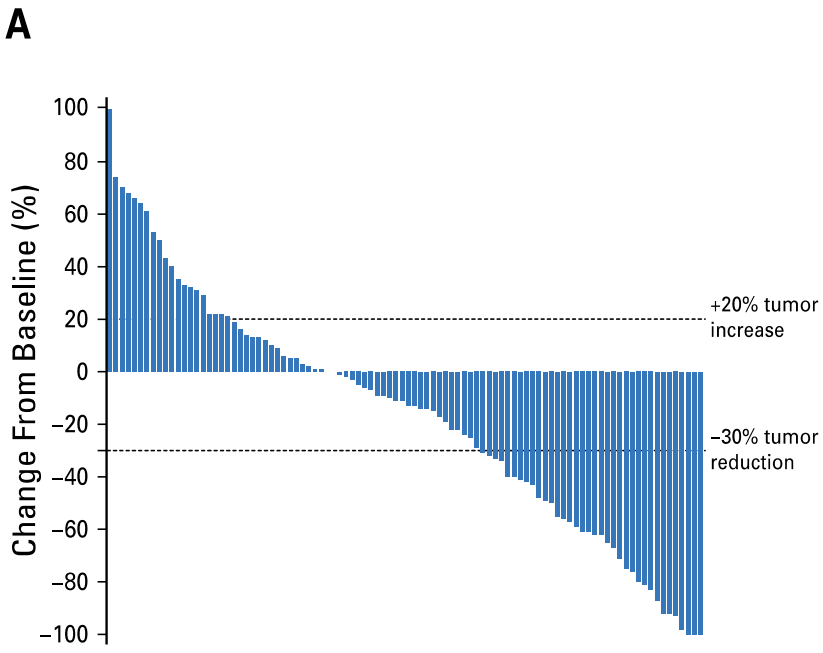
Seiwert, Weiss, et al. *Lancet Oncology.* 2016

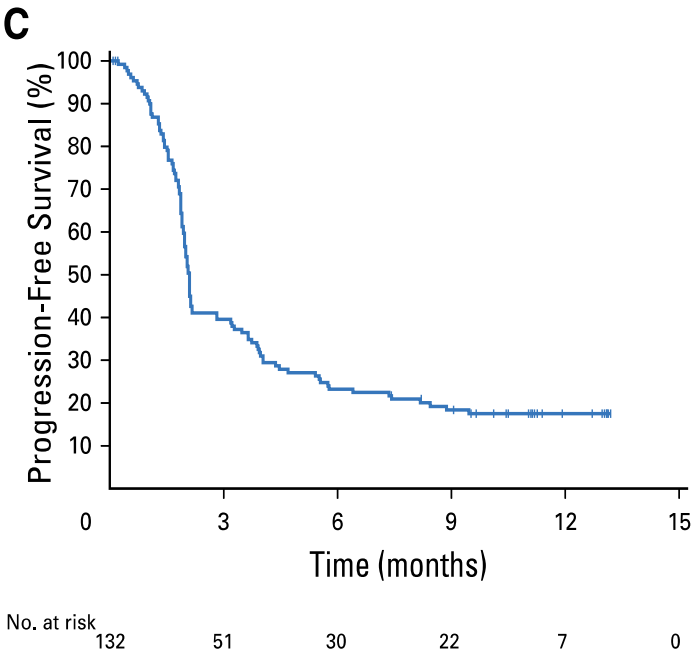
Case

A 50-year-old man is treated with cisplatin and radiation for T2N1 larynx cancer and recurs with metastatic disease to lung 3 months later. PD-L1 is negative. How should he be treated?

- Pembrolizumab
- Cetuximab

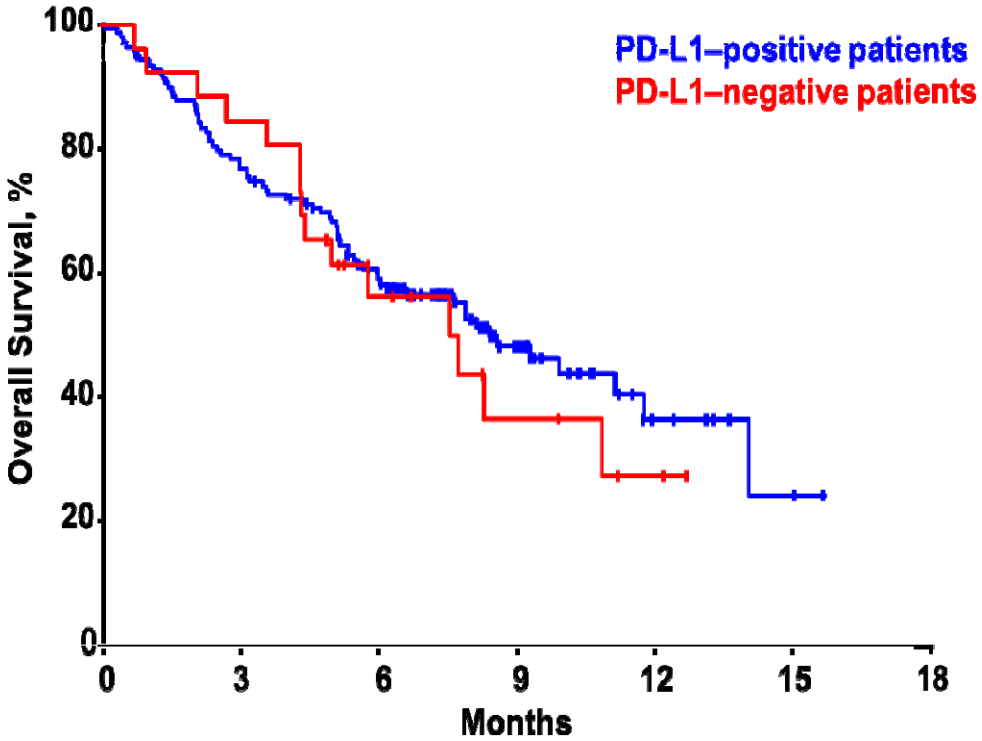
Keynote 12b—unselected by PD-L1





Chow, Weiss, et al. *J Clin Oncol.* 2017.

Keynote 55

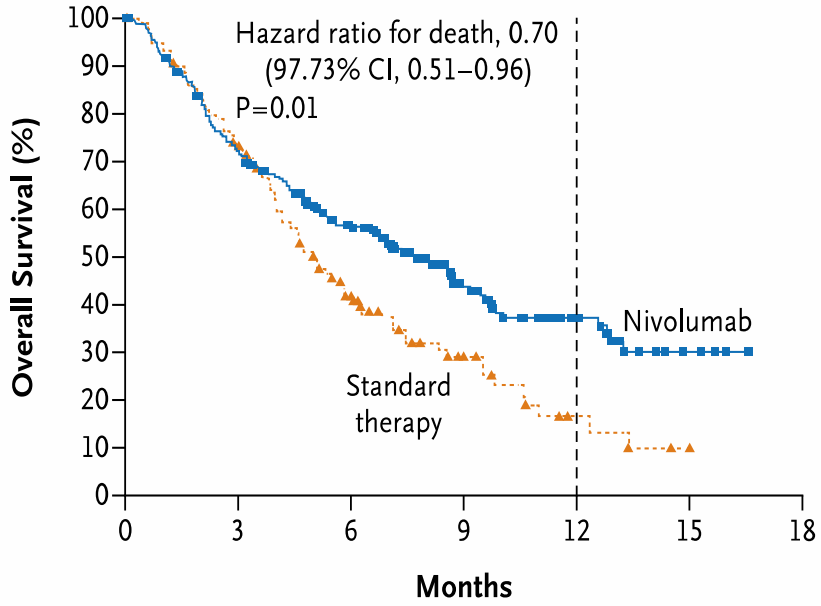


PD-L1 positive	140	107	75	29	7	2	0
PD-L1 negative	26	22	11	5	2	0	0

Checkmate 141

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

Ferris. *N Engl J Med.* 2016.

Checkmate 141

Table 3. Treatment-Related Adverse Events Occurring in at Least 5% of the Patients in Either Group.

Event	Nivolumab (N=236)		Standard Therapy (N=111)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any event	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)
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Decreased appetite	17 (7.2)	0	8 (7.2)	0
Pruritus	17 (7.2)	0	0	0
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)
Vomiting	8 (3.4)	0	8 (7.2)	0
Dry skin	7 (3.0)	0	10 (9.0)	0
Stomatitis	5 (2.1)	1 (0.4)	10 (9.0)	3 (2.7)
Weight loss	4 (1.7)	0	6 (5.4)	0
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Peripheral neuropathy	1 (0.4)	0	7 (6.3)	0
Alopecia	0	0	14 (12.6)	3 (2.7)
Neutropenia	0	0	9 (8.1)	8 (7.2)

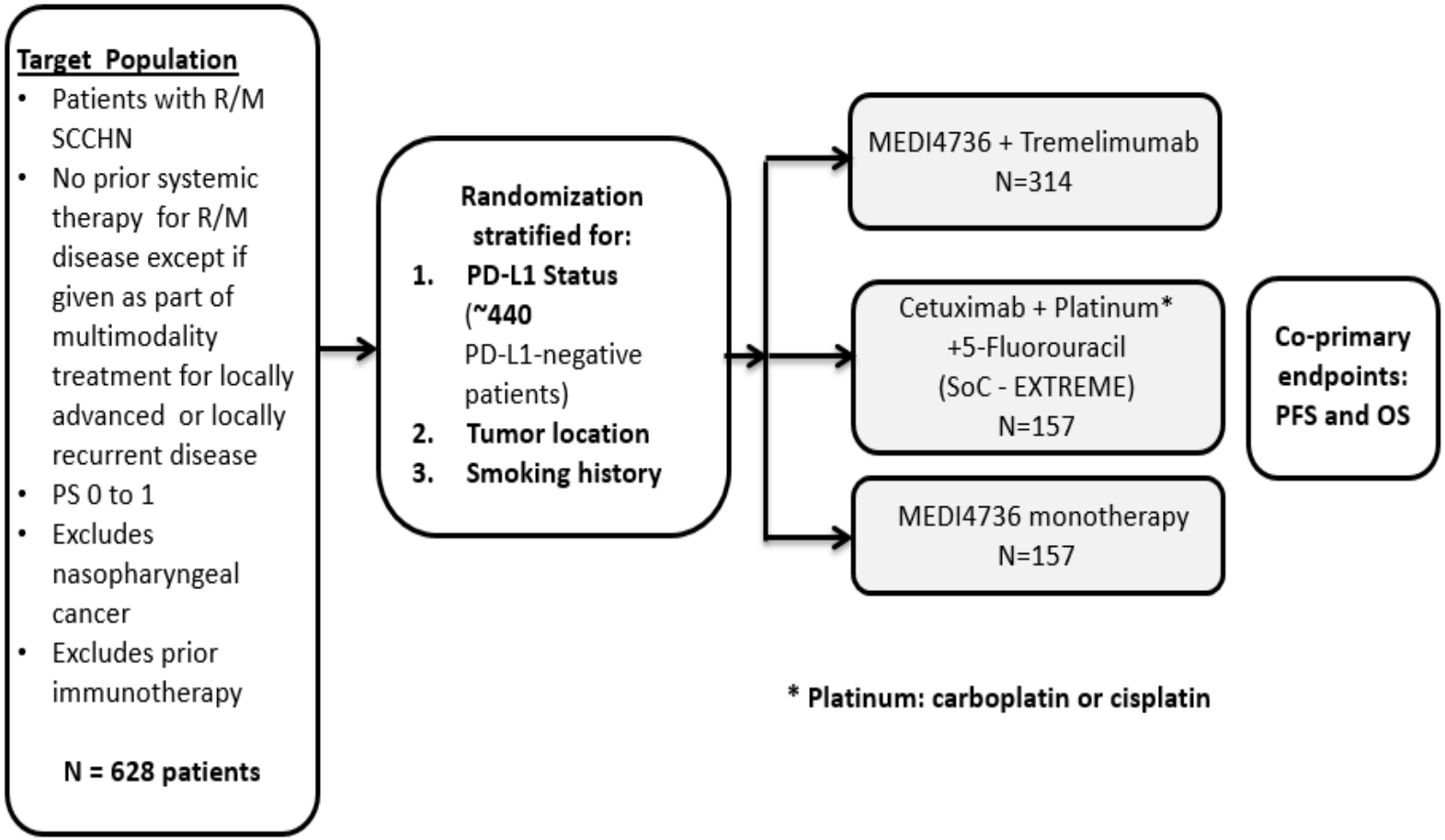
Ferris. *N Engl J Med.* 2016.

Checkmate 141

Variable	Nivolumab (N=240)		Standard Therapy (N=121)		Hazard Ratio for Death (95% CI)
	Patients	Median Survival	Patients	Median Survival	
	no. (%)	*mo*	*no. (%)*	*mo*	
All patients	240 (100.0)	7.5	121 (100.0)	5.1	0.69 (0.53–0.91)
PD-L1 expression level					
≥1%	88 (36.7)	8.7	61 (50.4)	4.6	0.55 (0.36–0.83)
≥5%	54 (22.5)	8.8	43 (35.5)	4.6	0.50 (0.30–0.83)
≥10%	43 (17.9)	8.7	34 (28.1)	5.2	0.56 (0.31–1.01)
<1%	73 (30.4)	5.7	38 (31.4)	5.8	0.89 (0.54–1.45)
<5%	107 (44.6)	7.0	56 (46.3)	5.1	0.81 (0.55–1.21)
<10%	118 (49.2)	7.2	65 (53.7)	4.6	0.73 (0.50–1.06)
Not quantifiable	79 (32.9)	7.8	22 (18.2)	5.8	0.79 (0.44–1.44)
p16 status					
Positive	63 (26.2)	9.1	29 (24.0)	4.4	0.56 (0.32–0.99)
Negative	50 (20.8)	7.5	36 (29.8)	5.8	0.73 (0.42–1.25)
Combined subgroup					
PD-L1 ≥1% and p16-positive	23 (9.6)	8.8	14 (11.6)	3.9	0.50 (0.21–1.19)
PD-L1 ≥1% and p16-negative	17 (7.1)	8.8	16 (13.2)	5.6	0.44 (0.18–1.10)
PD-L1 <1% and p16-positive	24 (10.0)	10.0	10 (8.3)	6.4	0.55 (0.22–1.39)
PD-L1 <1% and p16-negative	14 (5.8)	7.1	12 (9.9)	7.4	0.82 (0.31–2.19)

Ferris. *N Engl J Med.* 2016.

Kestrel



Take-Home Points

- Nivolumab and pembro FDA approved for platinum-refractory SCCHN
- Nivolumab and pembrolizumab are effective and less toxic than alternative options
- In platinum-refractory context, use is independent of PD-L1 or HPV; other biomarkers may have promise (ex. Interferon gamma and mutational burden)
- PD-1 alone or with CTLA-4 is challenging chemo for platinum-sensitive patients

Clinical Case

A 45-year-old woman is treated with cisplatin and radiation for T2N2b oropharyngeal cancer. Two years later, she has recurrence to the tumor bed. How should she be treated?

- Nivolumab or pembrolizumab
- Cisplatin, 5FU and cetuximab
- Weekly carboplatin, nab-paclitaxel and cetuximab
- Other

Presentation with Metastatic Disease is Rare

Site	Total in SEER	Number Metastatic at Presentation	Percentage	95% CI
Lip	5,975	20	0.33%	0.20-0.52%
Oral Cavity	16,385	320	1.95%	1.75-2.18%
Oropharynx	17,783	729	4.10%	3.81-4.40%
Hypopharynx	1,866	128	6.86%	5.75-8.10%
Supraglottis	8,114	270	3.33%	2.95-3.74%
Glottis	13,085	87	0.66%	0.53-0.82%
Subglottis	356	12	3.37%	1.75-5.81%
Sinus	1,068	69	6.46%	5.06-8.11%
Nasopharynx	2,610	177	6.78%	5.85-7.81%

Kuperman, ASCO 2008

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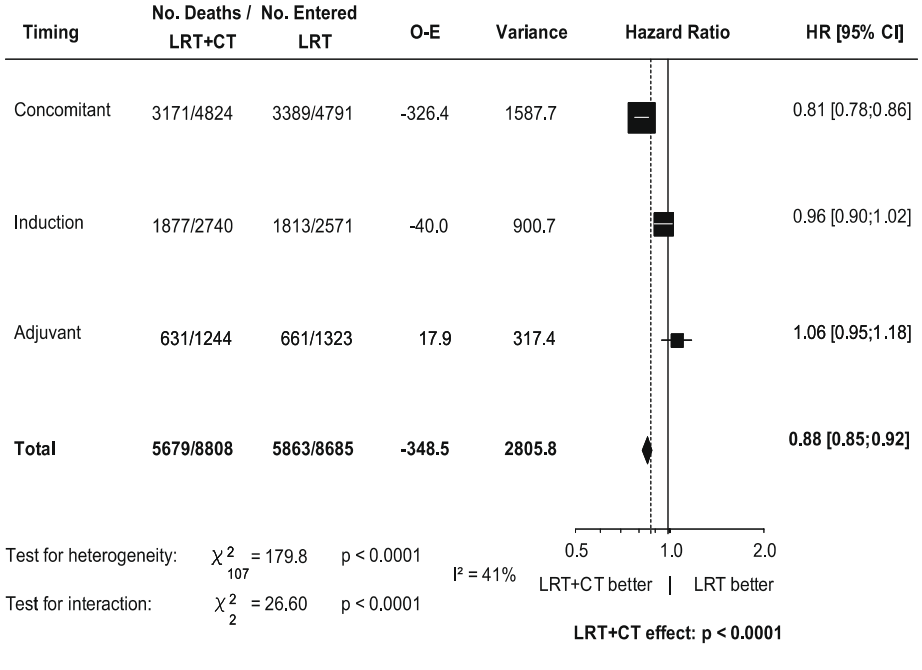
How to Cure LA-SCCHN

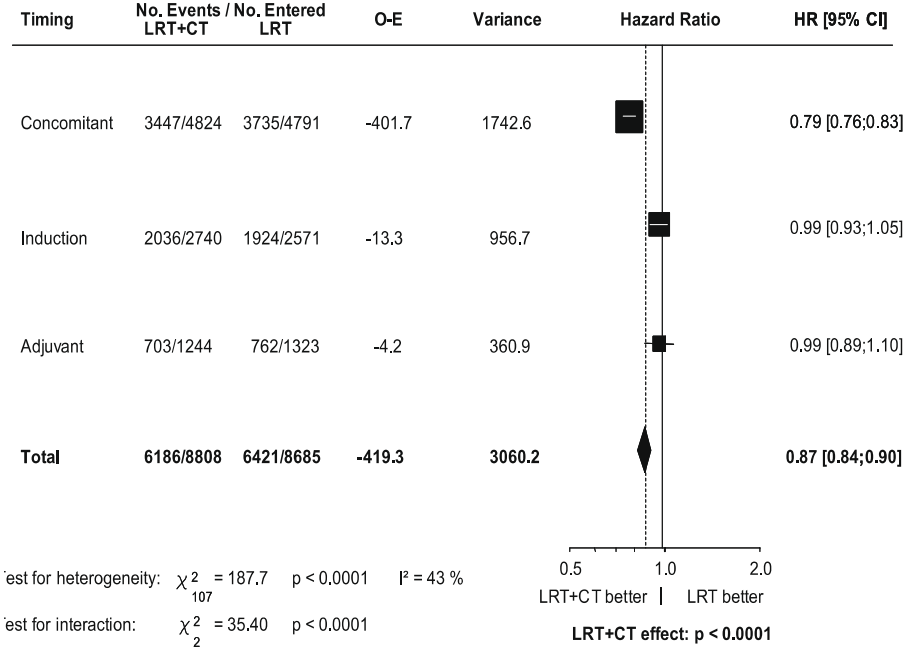
- **Definitive chemo-XRT**
  - Surgery reserved for salvage
- **Surgery followed by XRT**
  - Add chemo for + margins or ECE

MACH-NC

Death



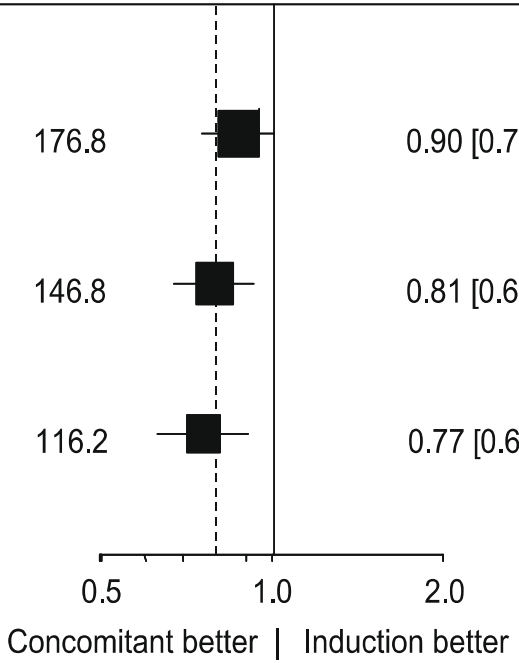
Recurrence or death



Pignon. *Radiotherapy and Oncology.* 2009.

Concurrent vs. Induction

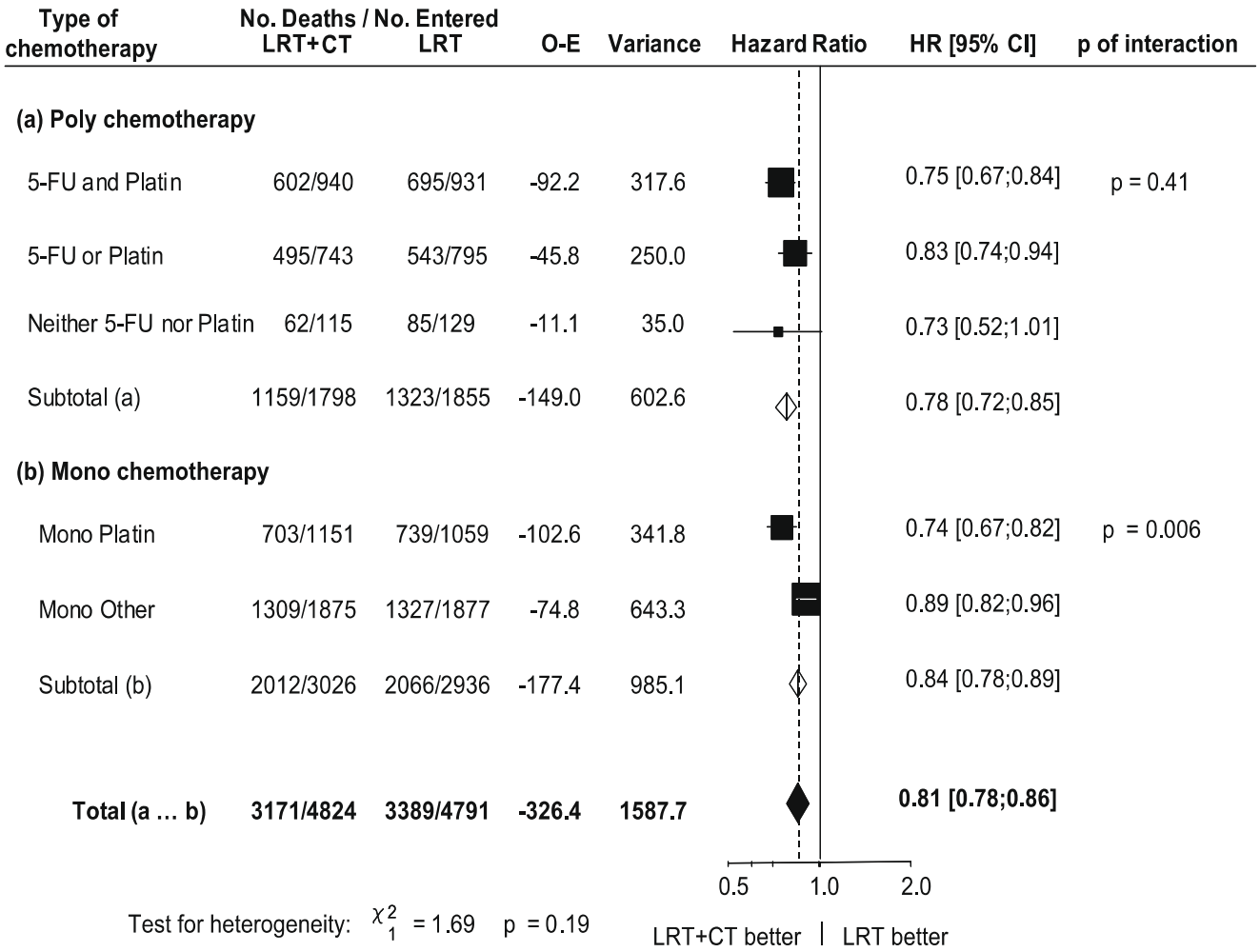
Endpoint	No. Events / No. Entered Concomitant	Induction	O-E	Variance	Hazard Ratio	HR [95% CI]
Overall Survival	349/430	368/431	-19.2	176.8		0.90 [0.77;1.04]
Event free survival	293/354	307/347	-30.1	146.8		0.81 [0.69;0.96]
Loco regional failure	218/343	254/339	-30.4	116.2		0.77 [0.64;0.92]



Concomitant effect: p = 0.0001

Pignon. *Radiotherapy and Oncology.* 2009

Type of Chemo Mattered



Type of chemotherapy	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]	p of interaction
(a) Poly chemotherapy							
5-FU and Platin	602/940	695/931	-92.2	317.6		0.75 [0.67;0.84]	p = 0.41
5-FU or Platin	495/743	543/795	-45.8	250.0		0.83 [0.74;0.94]	
Neither 5-FU nor Platin	62/115	85/129	-11.1	35.0		0.73 [0.52;1.01]	
Subtotal (a)	1159/1798	1323/1855	-149.0	602.6		0.78 [0.72;0.85]	
(b) Mono chemotherapy							
Mono Platin	703/1151	739/1059	-102.6	341.8		0.74 [0.67;0.82]	p = 0.006
Mono Other	1309/1875	1327/1877	-74.8	643.3		0.89 [0.82;0.96]	
Subtotal (b)	2012/3026	2066/2936	-177.4	985.1		0.84 [0.78;0.89]	
Total (a ... b)	**3171/4824**	**3389/4791**	**-326.4**	**1587.7**		**0.81 [0.78;0.86]**	

Pignon. *Radiotherapy and Oncology.* 2009.

RTOG 9911

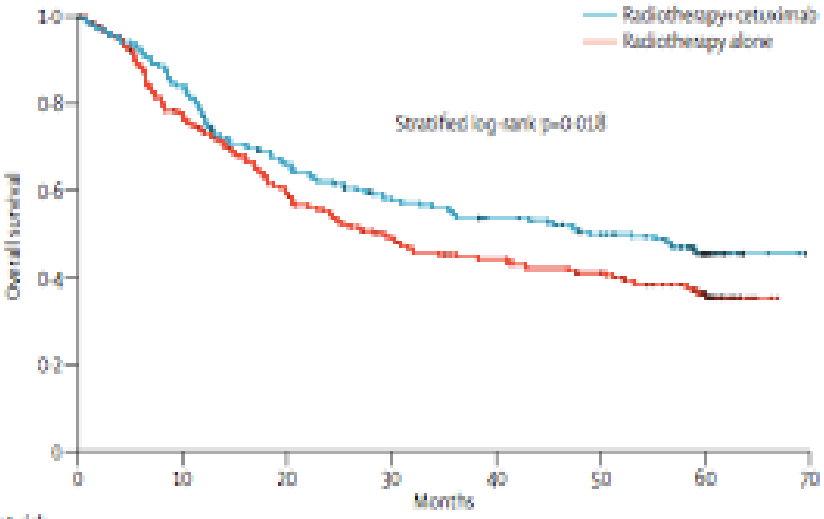
	XRT Alone	Induction→XRT	Chemoradiation
Severe Toxicity	61%	81%	82%
Intact larynx	70%	75%	88%
Locoregional Control	56%	61%	78%
2 year OS	75%	76%	74%
5 year OS	56%	55%	54%

Forastiere. *N Engl J Med.* 2003.

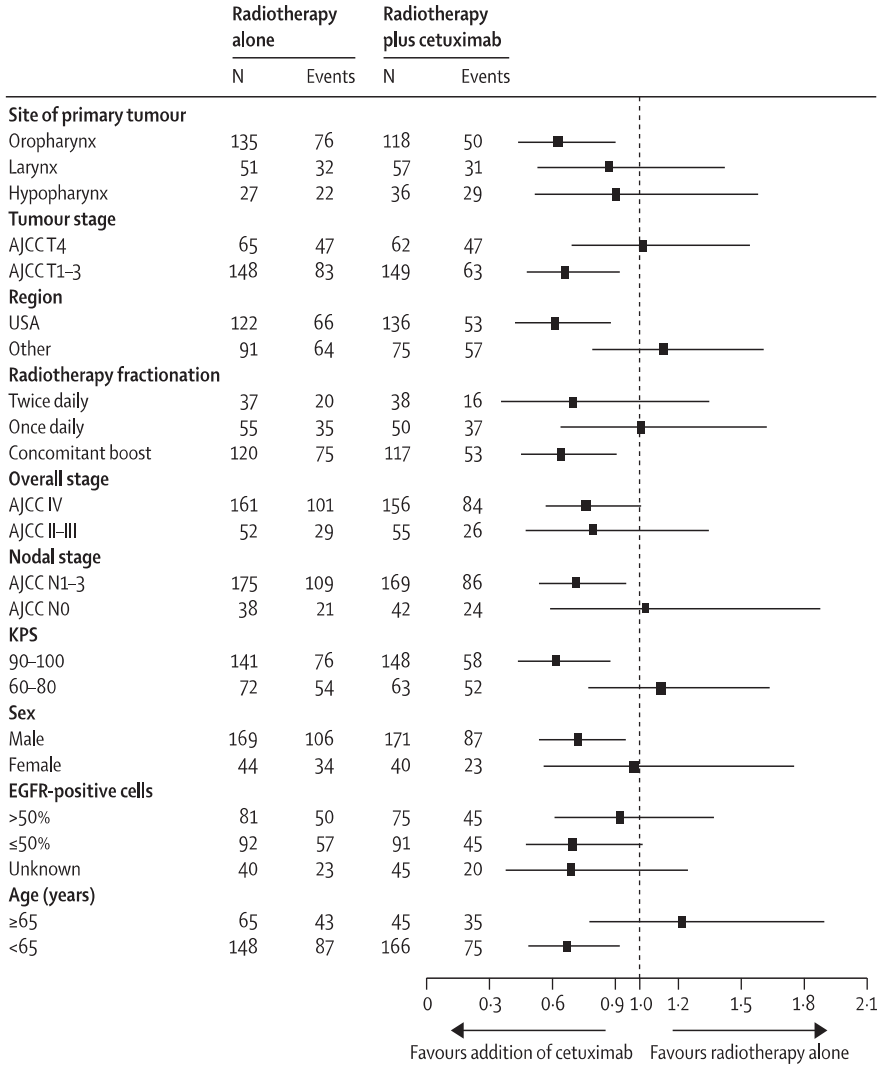
Toxicity of Cisplatin

- Emetogenic—perhaps most of any chemo
- Ototoxic—particularly high freq and tinnitus
- Neurotoxic—mostly peripheral sensory, but also weird autonomic stuff
- Nephrotoxic
- Count suppression: F&N, anemia
- Increased XRT side effects→decreased feasibility

Cetuximab with Radiation

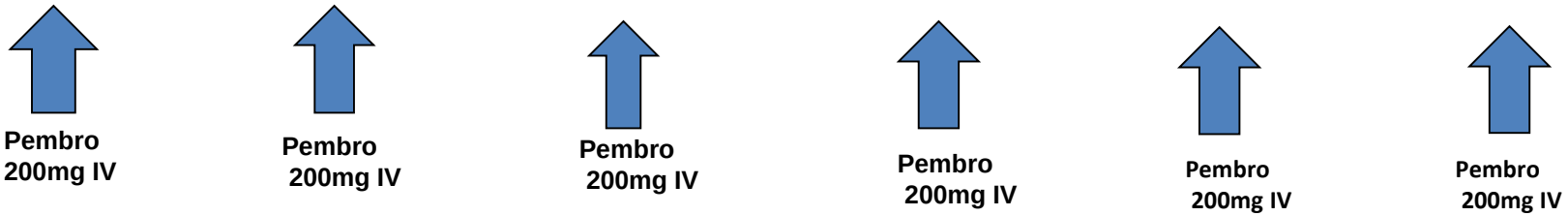


	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	63 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35(16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)



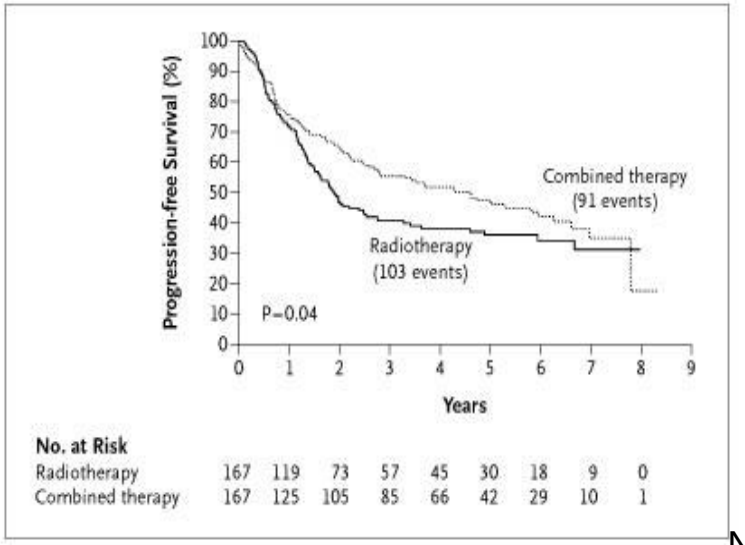
LCCC 1509: Pembrolizumab and Radiation for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN) not Eligible for Cisplatin Therapy

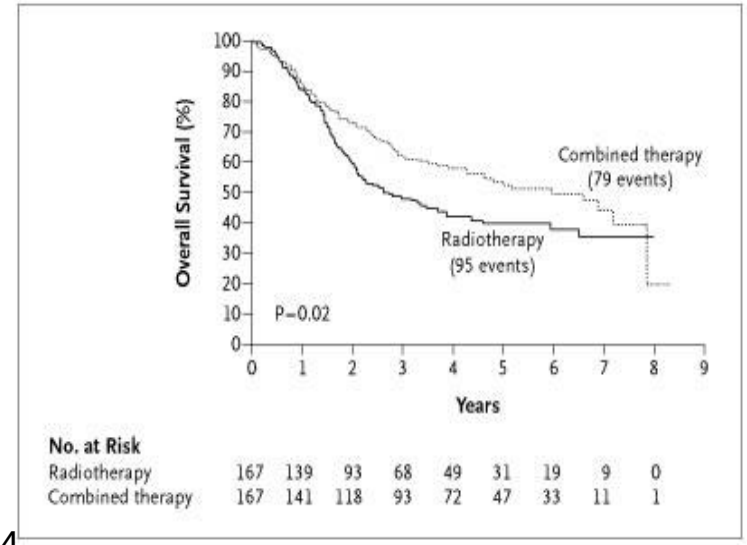
Pembrolizumab (Pembro) Concomitant with and Post 7 weeks of Radiation															
Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16
IMRT 2Gy/d (M-F)	IMRT 2Gy/d (M-F)	IMRT 2Gy/d (M-F)	IMRT 2Gy/d (M-F)	IMRT 2Gy/d (M-F)	IMRT 2Gy/d (M-F)	IMRT 2Gy/d (M-F)									



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



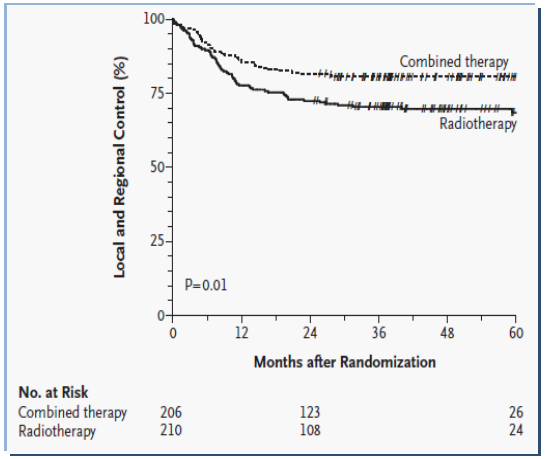


NEJM, 2004

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

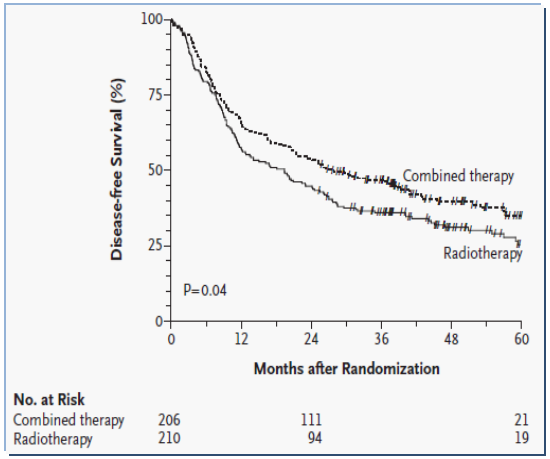
Jay S. Cooper, M.D., Thomas F. Pajak, Ph.D., Arlene A. Forastiere, M.D., John Jacobs, M.D., Bruce H. Campbell, M.D., Scott B. Saxman, M.D., Julie A. Kish, M.D., Harold E. Kim, M.D., Anthony J. Cmelak, M.D., Marvin Rotman, M.D., Mitchell Machtay, M.D., John F. Ensley, M.D., K.S. Clifford Chao, M.D., Christopher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

Locoregional Control



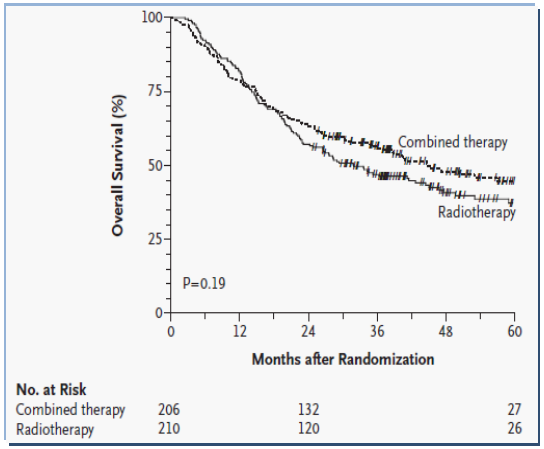
HR 0.61
P=0.01

DFS



HR 0.78
P=0.04

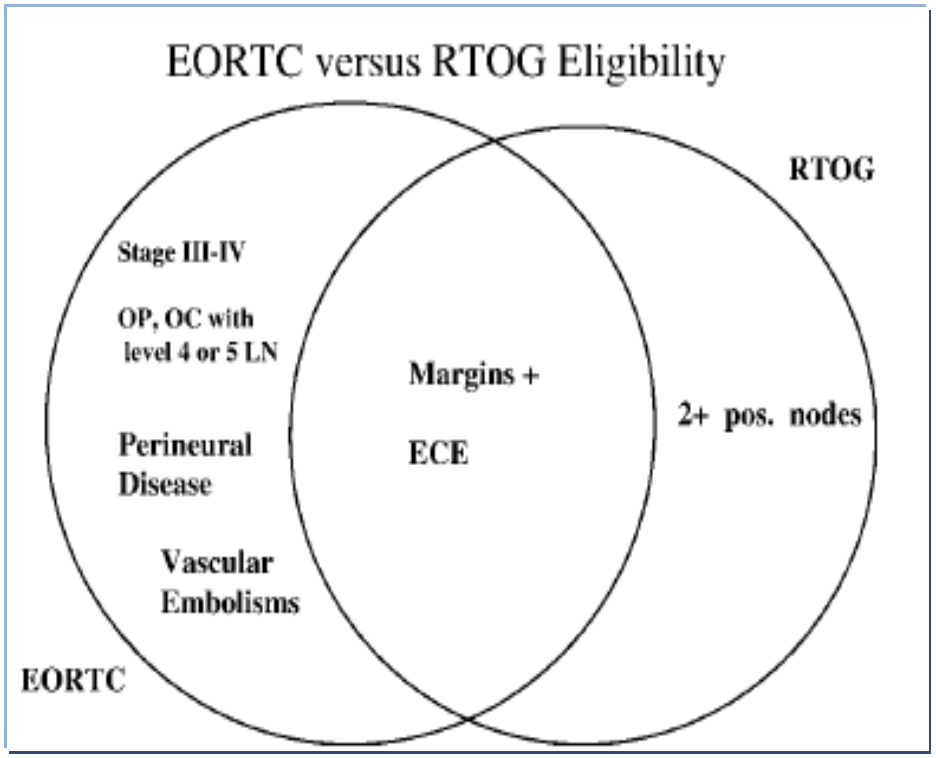
OS

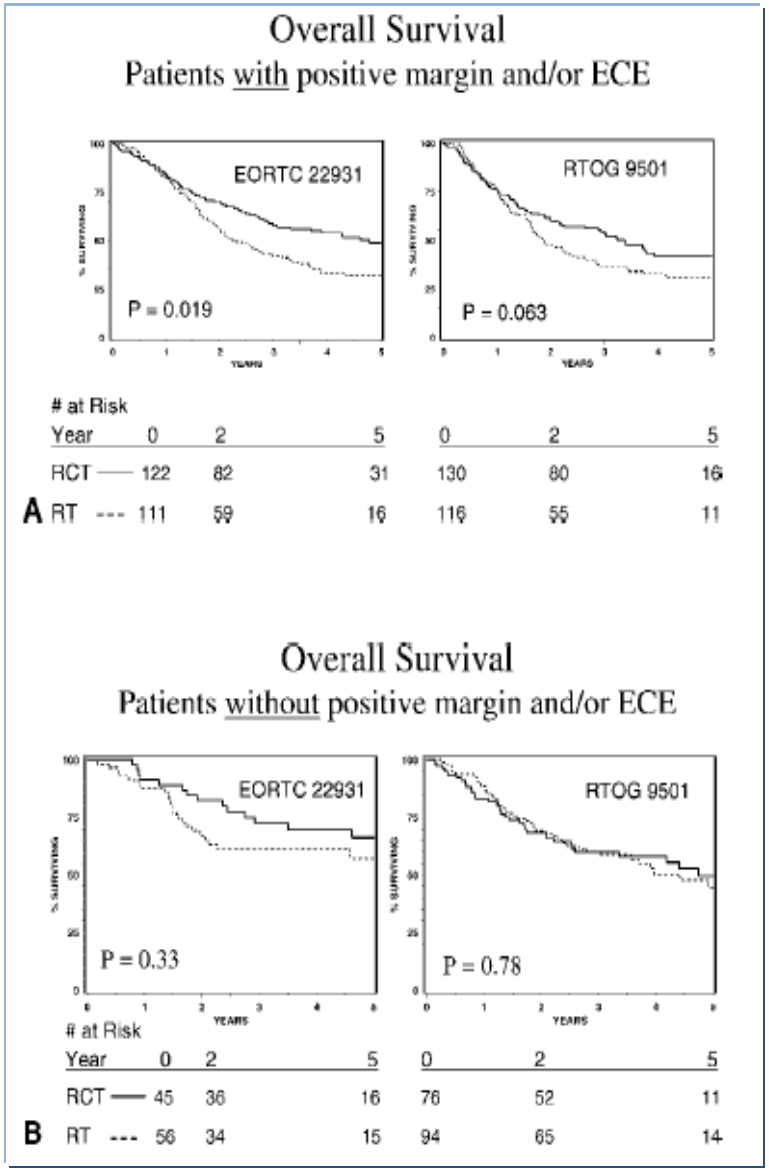


HR 0.84
P=0.19

NEJM, 2004

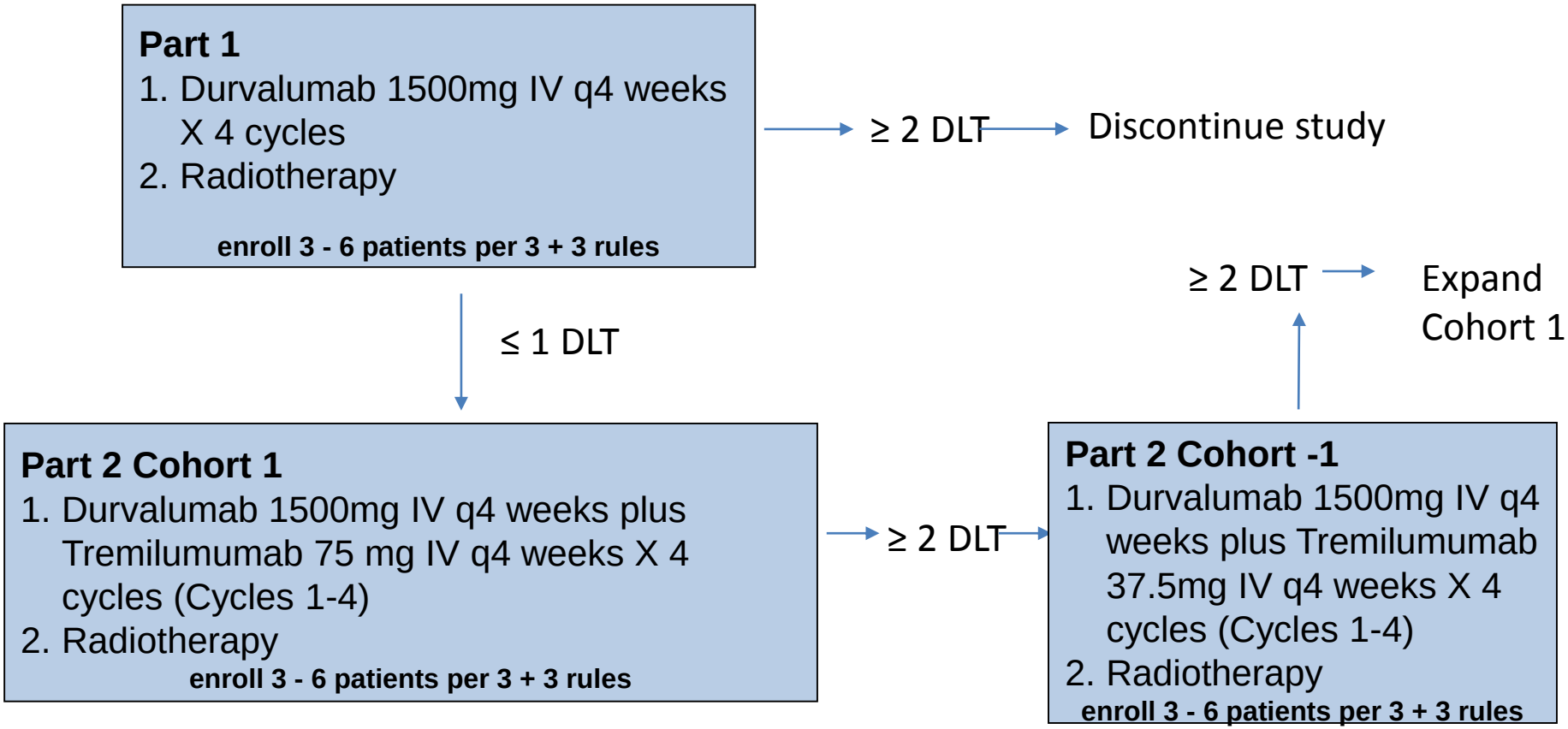
Combined Analysis



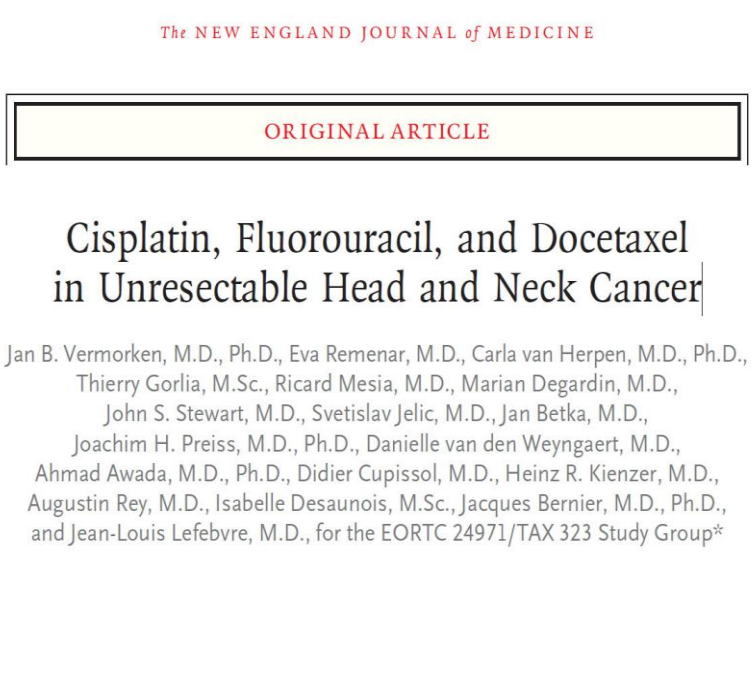


Bernier, et al. *Head and Neck.* 2005.

Planned Phase I Study of PD-L1/CTLA-4 Inhibition with Adjuvant XRT



Induction: What's old is new again (sort of)

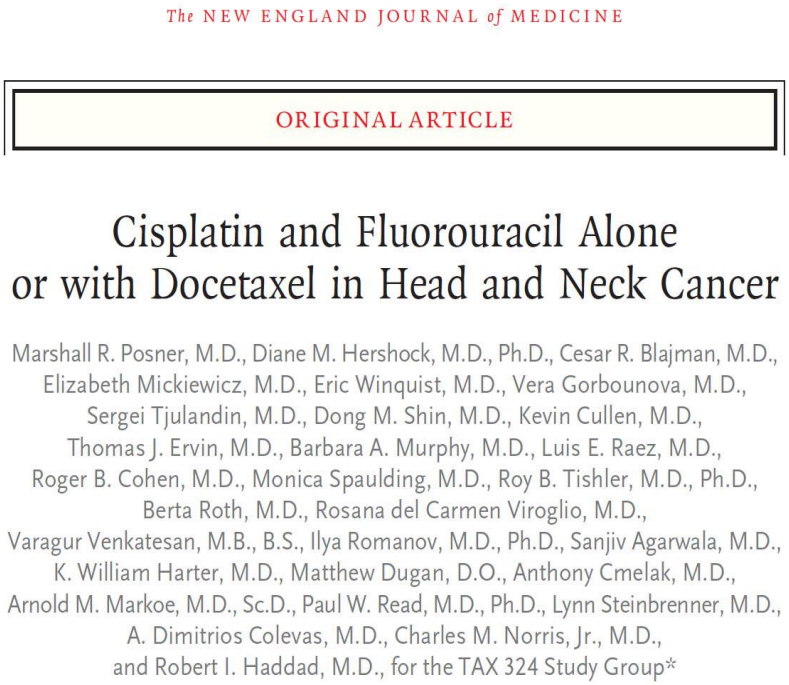


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Eva Remenar, M.D., Carla van Herpen, M.D., Ph.D., Thierry Gorlia, M.Sc., Ricard Mesia, M.D., Marian Degardin, M.D., John S. Stewart, M.D., Svetislav Jelic, M.D., Jan Betka, M.D., Joachim H. Preiss, M.D., Ph.D., Danielle van den Weyngaert, M.D., Ahmad Awada, M.D., Ph.D., Didier Cupissol, M.D., Heinz R. Kienzer, M.D., Augustin Rey, M.D., Isabelle Desaunois, M.Sc., Jacques Bernier, M.D., Ph.D., and Jean-Louis Lefebvre, M.D., for the EORTC 24971/TAX 323 Study Group*

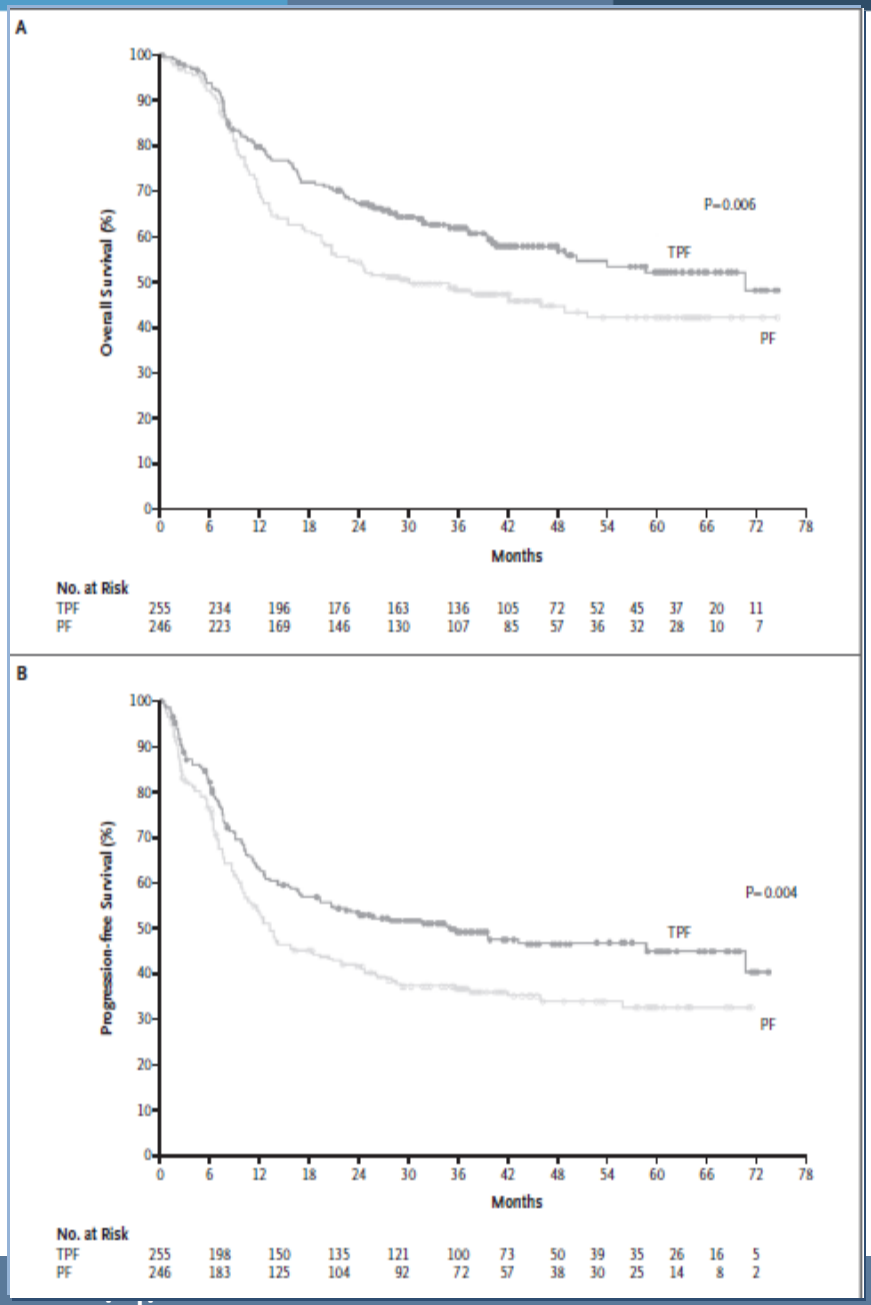


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer

Marshall R. Posner, M.D., Diane M. Hershock, M.D., Ph.D., Cesar R. Blajman, M.D., Elizabeth Mickiewicz, M.D., Eric Winquist, M.D., Vera Gorbounova, M.D., Sergei Tjulandin, M.D., Dong M. Shin, M.D., Kevin Cullen, M.D., Thomas J. Ervin, M.D., Barbara A. Murphy, M.D., Luis E. Raez, M.D., Roger B. Cohen, M.D., Monica Spaulding, M.D., Roy B. Tishler, M.D., Ph.D., Berta Roth, M.D., Rosana del Carmen Viroglio, M.D., Varagur Venkatesan, M.B., B.S., Ilya Romanov, M.D., Ph.D., Sanjiv Agarwala, M.D., K. William Harter, M.D., Matthew Dugan, D.O., Anthony Cmelak, M.D., Arnold M. Markoe, M.D., Sc.D., Paul W. Read, M.D., Ph.D., Lynn Steinbrenner, M.D., A. Dimitrios Colevas, M.D., Charles M. Norris, Jr., M.D., and Robert I. Haddad, M.D., for the TAX 324 Study Group*



TPF vs. PF efficacy: TAX 324

Posner. *N Engl J Med.* 2007.

The TOX of TAX[1,2]

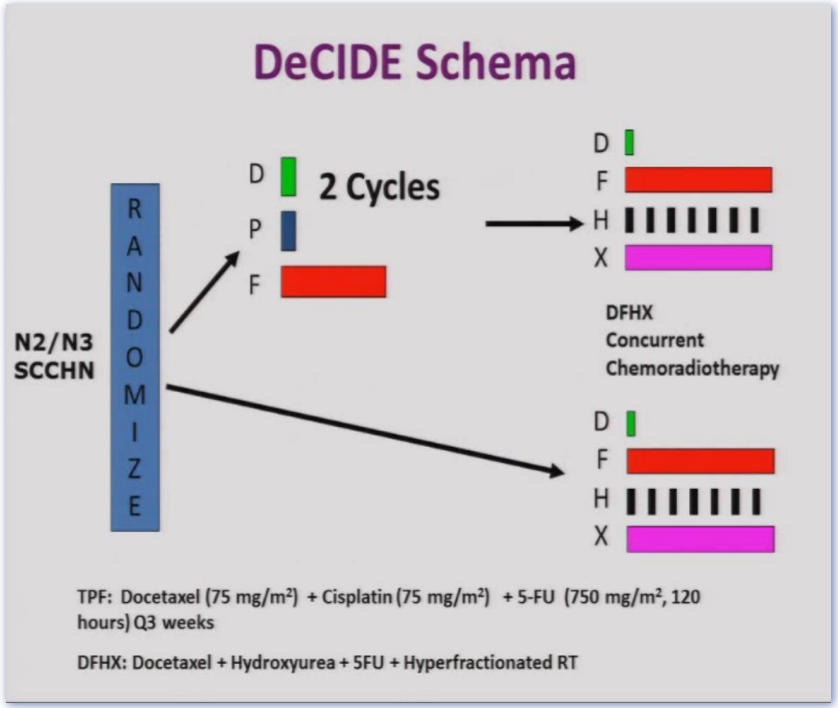
Grade 3/4Toxicity	TAX323[1] (Cis 75,Doc 75 5FU 750/m2 D1–5)	TAX324[2] (Cis 100, Doc 75, 5FU 1g/m2 D1–4
Neutropenia	**76.9%**	**83%**
Febrile neutropenia	**5.2%**	**12%**
Neutropenic infection	**Not reported**	**12%**
Leukopenia	**41.6%**	**Not reported**
Anemia	**9.2%**	**12%**
Thrombocytopenia	**5.2%**	**4%**
Stomatitis	**4.6%**	**21%**
Alopecia	**11.6%**	**Not reported**
Nausea	**.6%**	**14%**
Esophagitis/Dysphagia /Odynophgia	**.6%**	**13%**
Vomiting	**.6%**	**8%**
Anorexia	**.6%**	**12%**
Diarrhea	**2.9%**	**7%**
Infection	**6.9%**	**6%**
Lethargy	**2.9%**	**5%**
Neurotoxicity	**.6%**	**Not reported**
Local toxic effect	**.6%**	**Not reported**

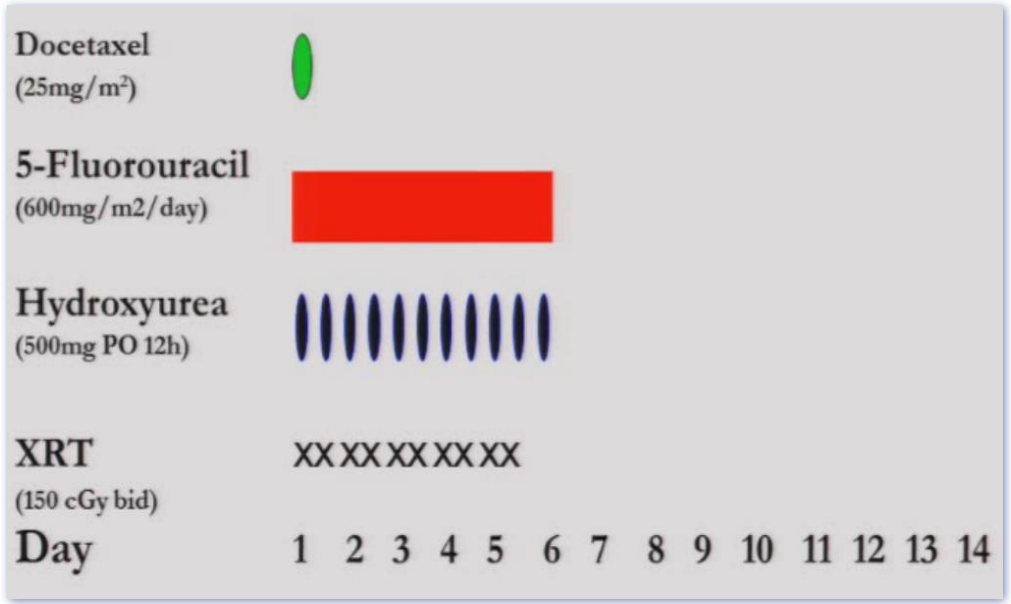
The tax on the TOX[3]

	TPF Arm		PF Arm	
	No.	%	No	%
Entered	255		246	
Rx off prot.	49	21	59	24
Other CRT	20	8	19	8
RT only	9	4	13	5
Chemo only	8	3	16	7
No Rx.	11	4	11	4
Other	1		0	
DefRT/CRT	235	92	219	89

1. Vermorken. *NEJM* 2007.
2. Posner. *NEJM* 2007.
3. Haddad. *JCO* 2009.

DeCIDE: Funky chemorads, +/- TPF induction





Notes on Design:

- DFHX rarely used outside of U Chicago
- BID XRT w/9 days breaks even more unusual
- Underpowered (Original sample size 400 modified to 280)
- TPF insufficiently active, too toxic

Cohen, ASCO 2012.

DeCIDE: Results

Endpoint	IC arm (%)	CRT arm (%)	HR	95% CI	p value
OS	75	73	0.92	0.59-1.42	0.70
DF-free survival	69	64	0.84	0.56-1.26	0.39
RFS	67	59	0.76	0.52-1.13	0.18
Cumulative incidence of DF	10	19	0.46	0.23-0.92	0.025
Cumulative incidence of locoregional failure	9	12	0.79	0.37-1.68	0.55

- RR 73%
- Increased non-cancer deaths
- Decreased cancer deaths
- Much less distant failure
- Trend towards improved OS in OPX
- Trend towards improved OS in N2c/N3

Cohen, ASCO 2012.

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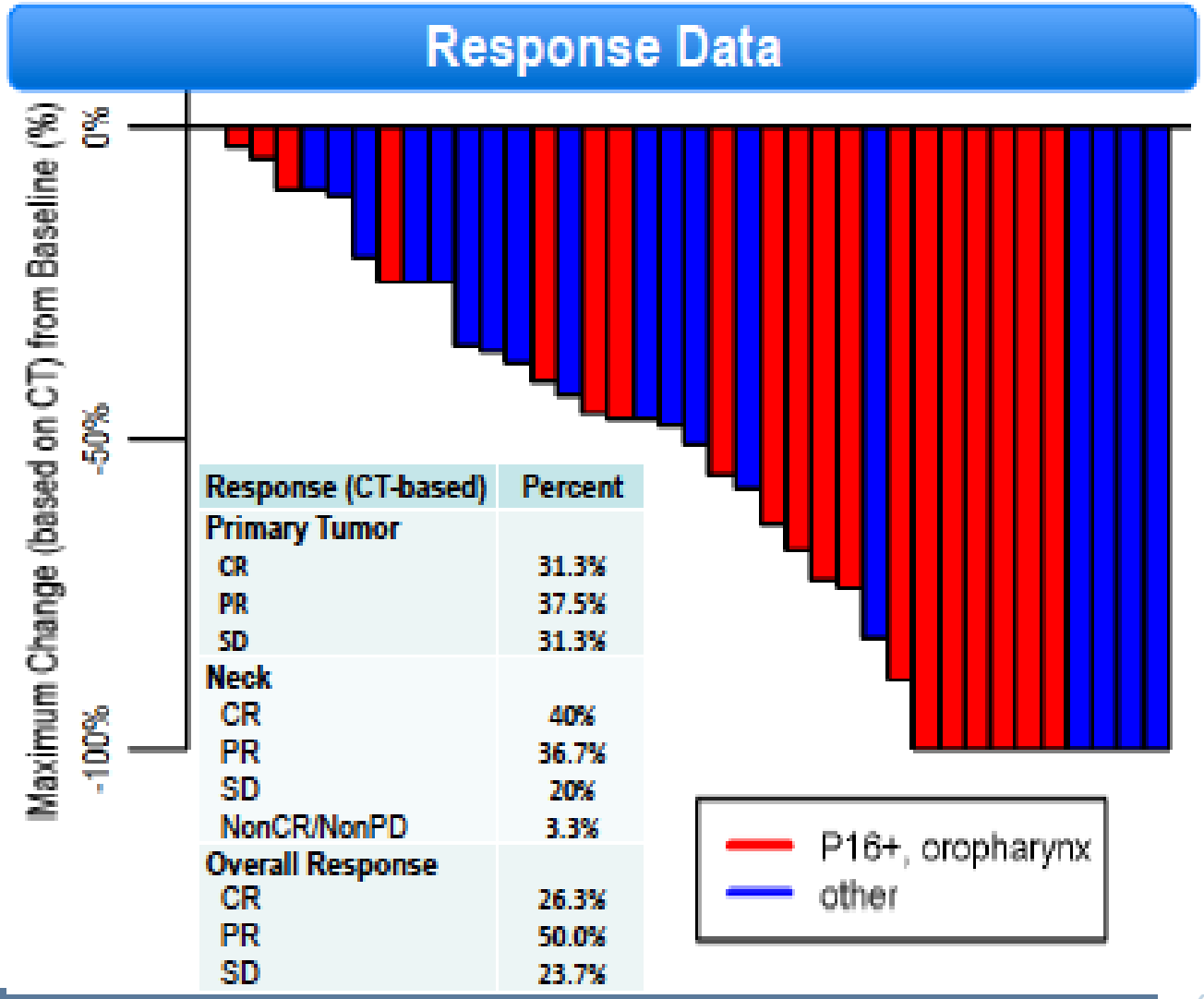
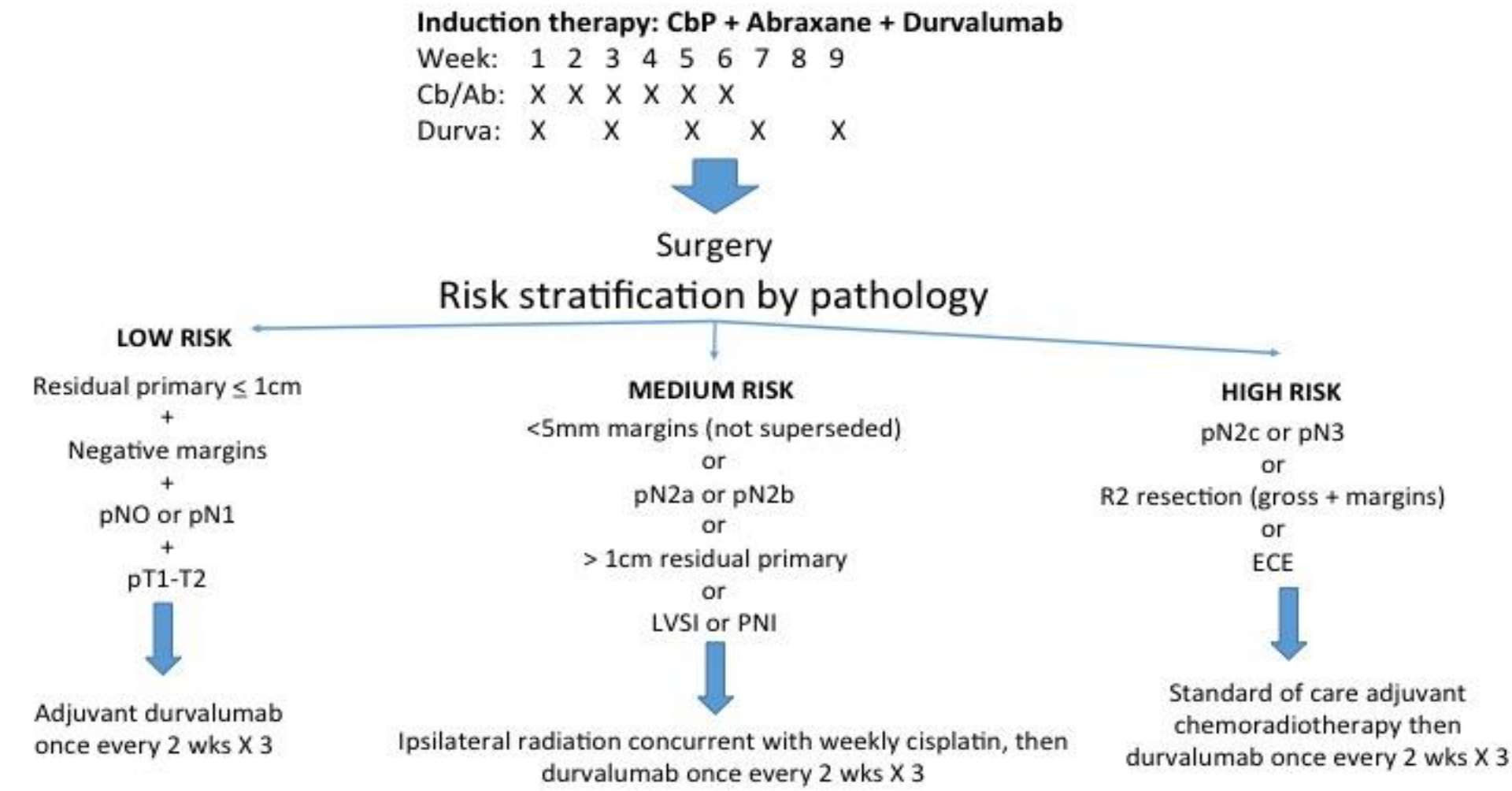
Carboplatin/nab-paclitaxel/C225



Response (CT-based)	Percent
Primary Tumor	
CR	31.3%
PR	37.5%
SD	31.3%
Neck	
CR	40%
PR	36.7%
SD	20%
NonCR/NonPD	3.3%
Overall Response	
CR	26.3%
PR	50.0%
SD	23.7%

Weiss, ASCO 2016.

LCCC1621: Carbo/abraxane/Durvalumab prior to surgical resection



Key Take-Home Points

- Formally approved standard of care for 1L incurable, EXTREME is extremely toxic.
- Nivolumab and pembrolizumab are approved for platinum-refractory patients, regardless of PDL1 or HPV status.
- Most SCCHN is curable. To help the most patients, future advances should evaluate the role of IO in curable disease.
- IO combos and cellular therapeutics and other novel approaches may advance the field.

Questions?

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Thank you for participating in the ICLIO e-Course. Presentation slides and archived recording will be available at accc-iclio.org.

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