Systemic Therapies for Head and Neck Cancer

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Ochsner™ Health System

Disclosures

- Speaker – BMS, Pfizer, Astrazeneca
- Advisory Board/Consultant – Nektar Therapeutics, Xenthera

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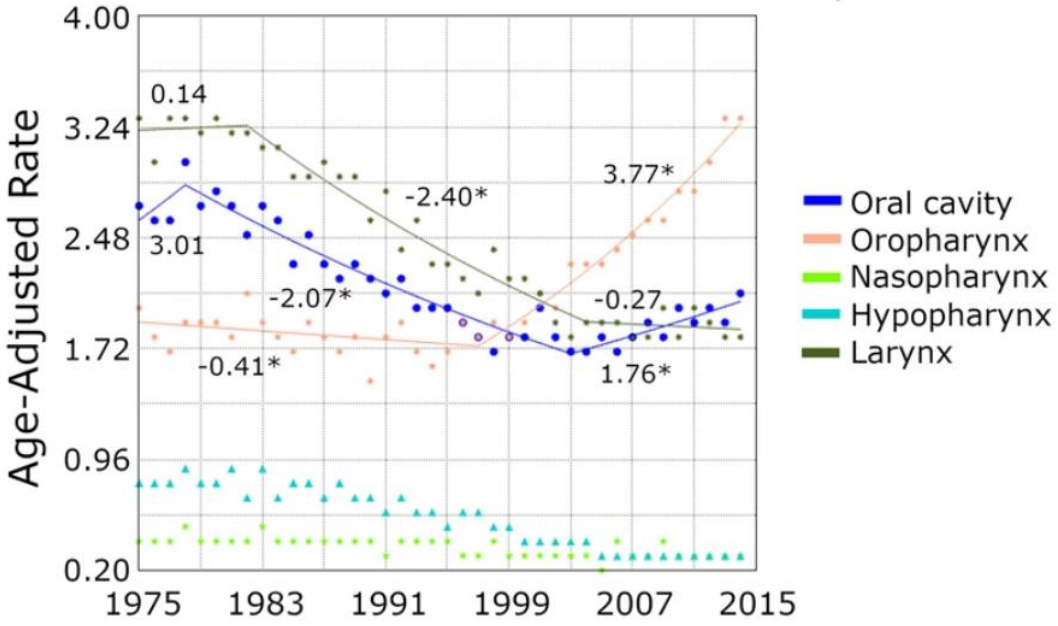
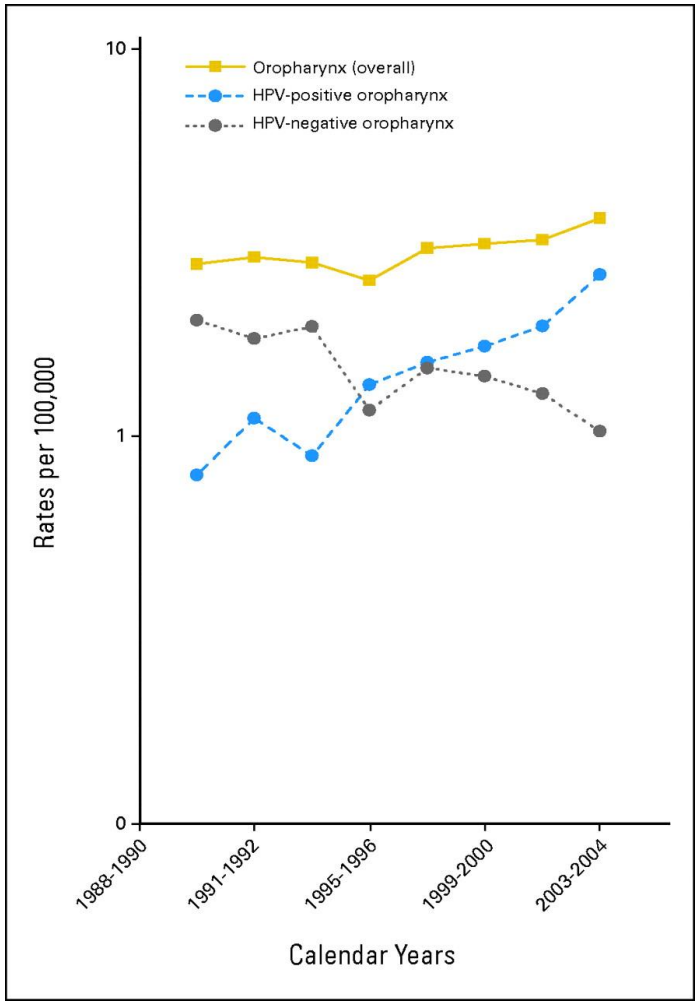
Epidemiology and Etiology – HPV on the rise



Kim, YJ., Kim, J.H. *Sci Rep* 10, 7877 (2020)



Chaturvedi A K et al. JCO 2011;29:4294-4301

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Principles of Treatment

- Stage/Intent of Treatment
  - Curative intent – multimodality
  - Palliative intent – Immunotherapy based

- Anatomical Primary Site
  - Expected Pattern of Failure
  - Organ Preservation

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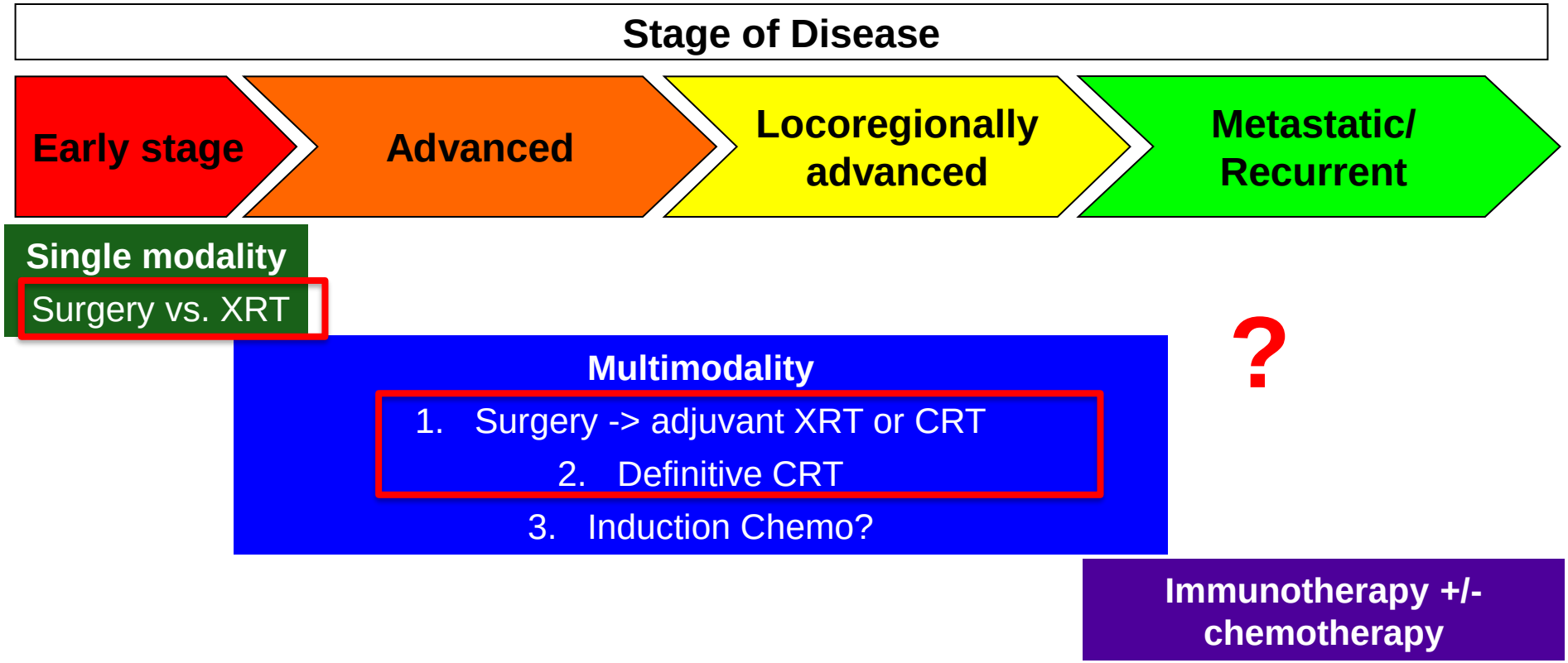
Principles of Treatment

Stage



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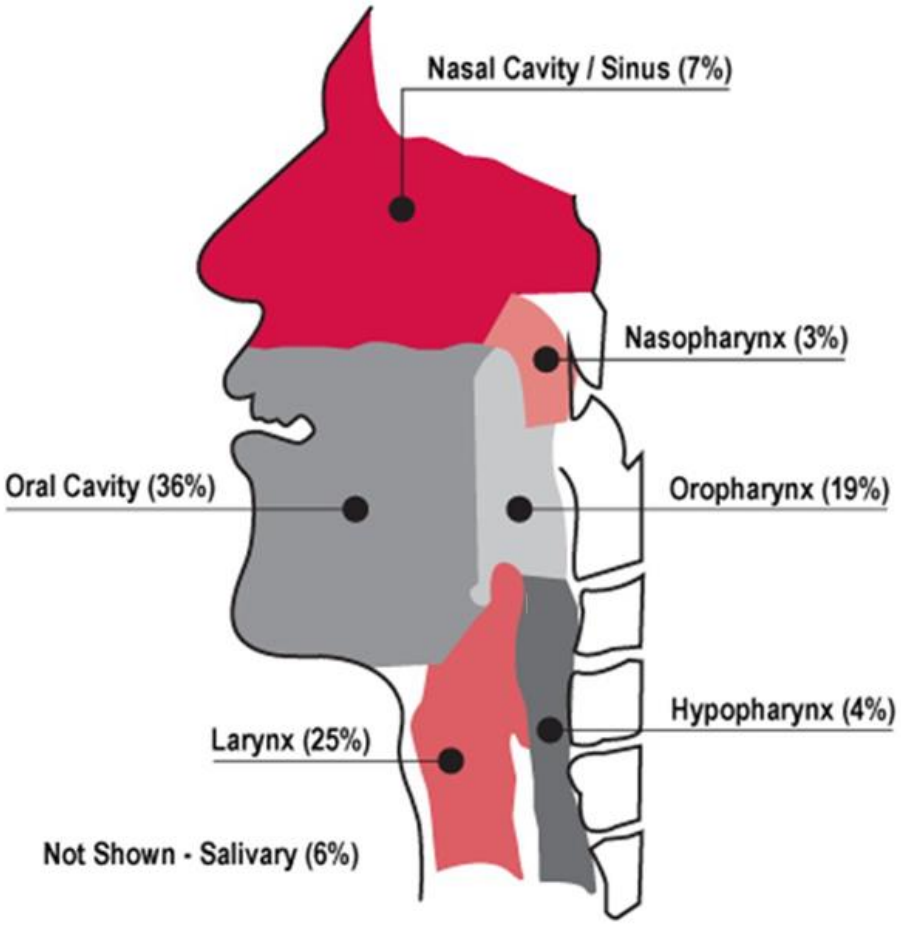
Principles of Treatment

Primary Site



Distribution of Head & Neck Cancers by Subsite

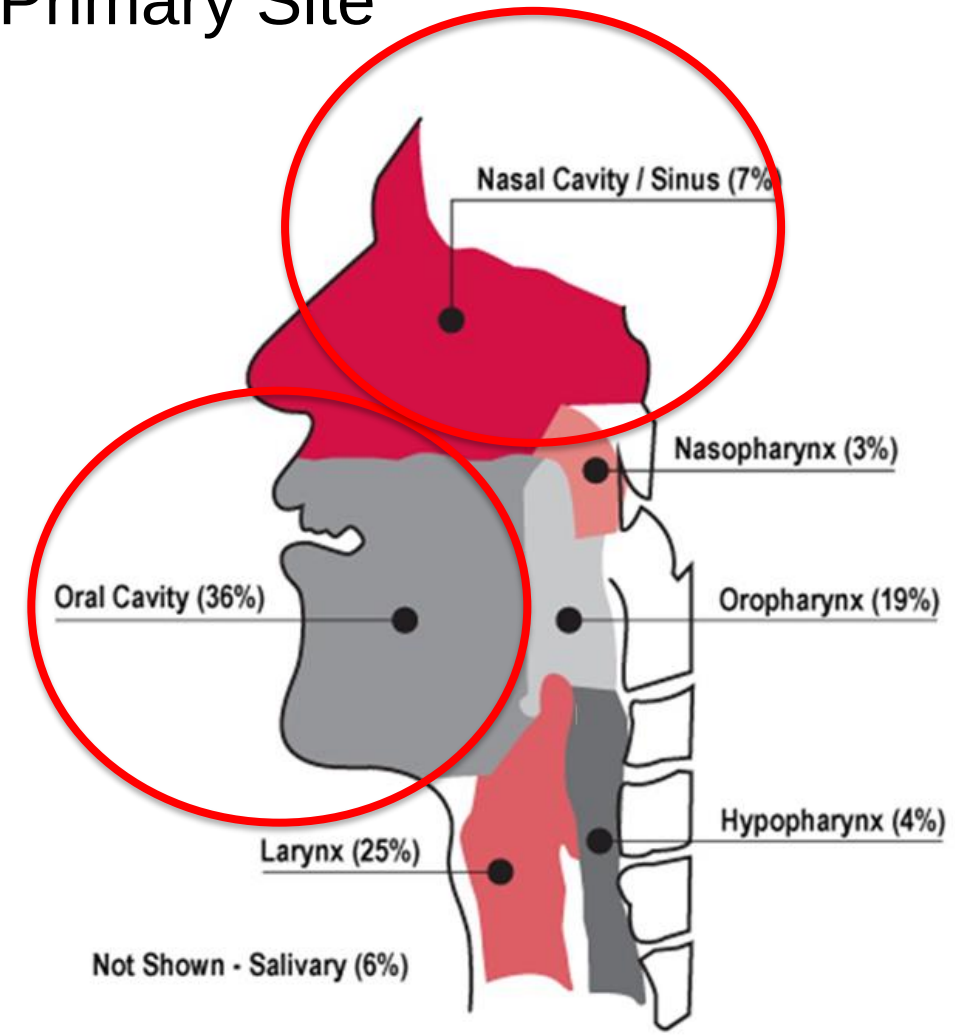
https://health.mo.gov/living/families/oralhealth/head-neck-cancer-hpv.php

Principles of Treatment

Primary Site

Predominant pattern of failure - **Locoregional**

Surgery (preferred) +/- RT or CRT



Distribution of Head & Neck Cancers by Subsite

https://health.mo.gov/living/families/oralhealth/head-neck-cancer-hpv.php

Adjuvant Treatment

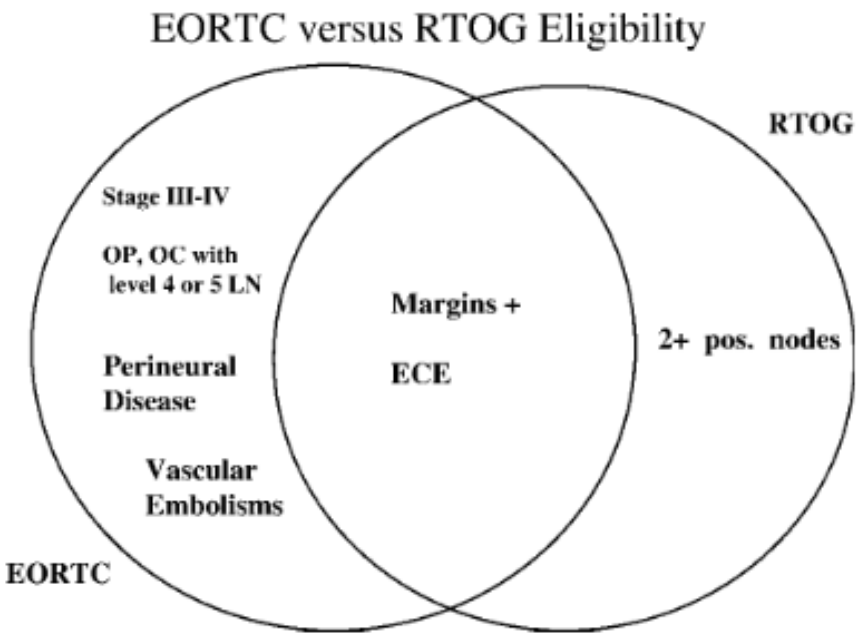
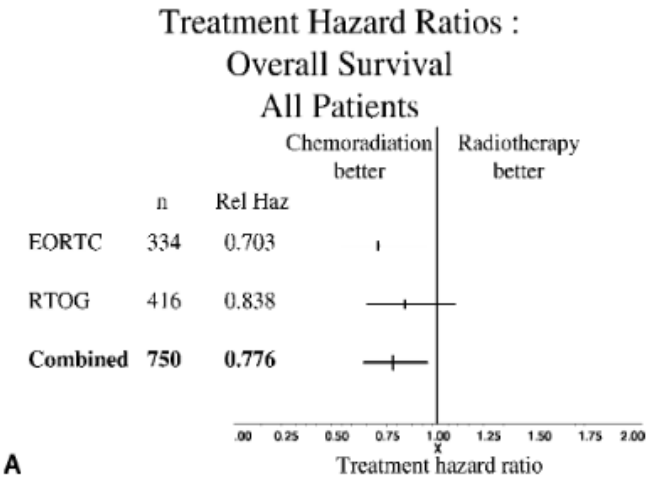


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.



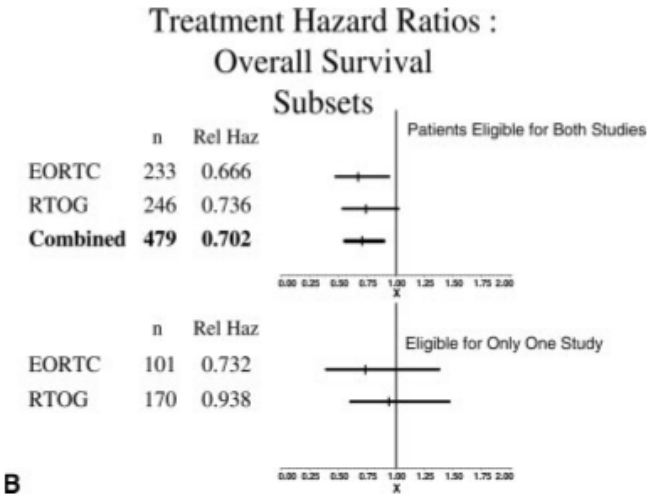


FIGURE 5. (A) Impact of adjuvant chemoradiation on overall survival in EORTC and RTOG trials. **(B)** Comparative analysis of hazard ratio values in patients eligible for both trials or one trial only.

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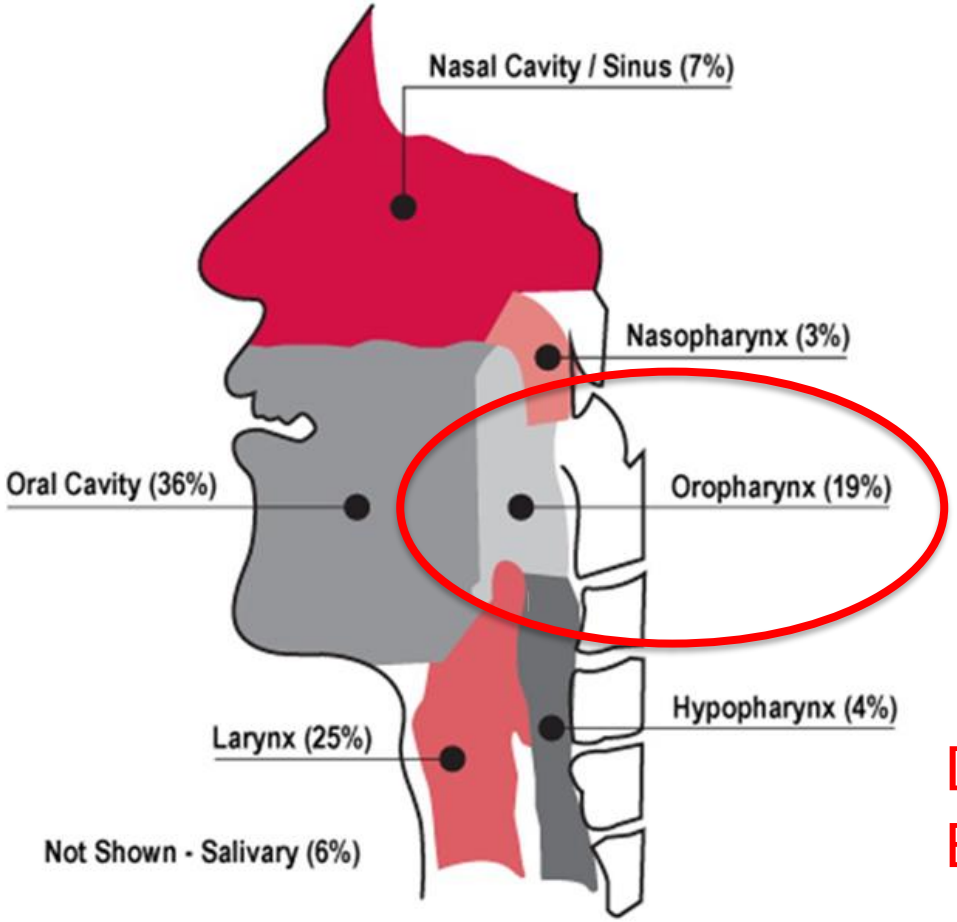
Principles of Treatment

Primary Site



Distribution of Head & Neck Cancers by Subsite

Predominant pattern of failure - **Locoregional**

HPV associated – **Better responses to RT**

Definitive RT or CRT vs. Endoscopic/Robotic Sx

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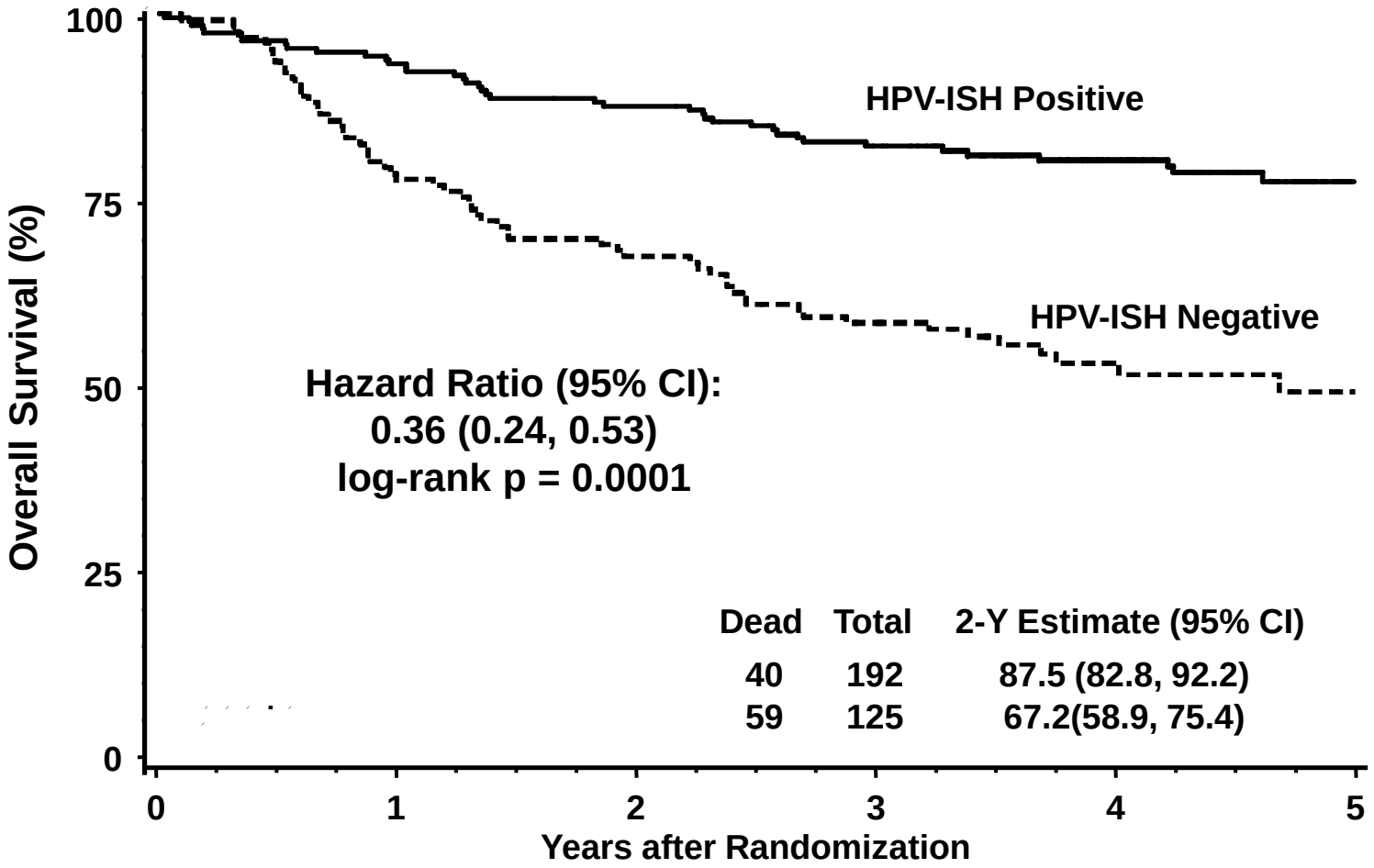
https://health.mo.gov/living/families/oralhealth/head-neck-cancer-hpv.php

Etiology Affects Outcomes

Phase III Trial RTOG 0129 – Survival by HPV Status



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Ang KK NEJM , 2010

Which Radiosensitizing Agent?

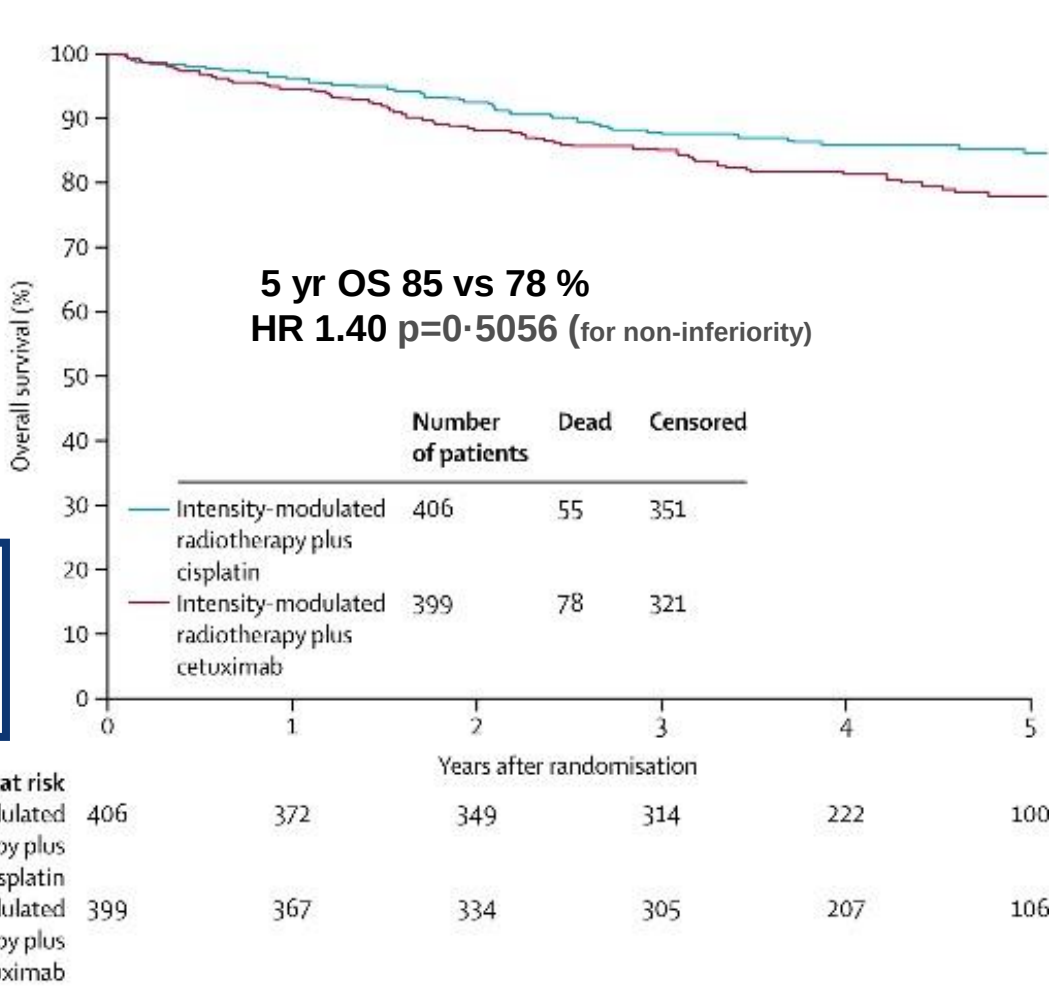
*NRG Oncology RTOG 1016 – **HPV positive only***

AJCC 7 Stage III or IV

RANDOMIZED

IMRT 70Gy + Cisplatin 100 mg/m2 x 2 q 3 week

IMRT 70 Gy + 8 doses cetuximab



5 yr OS 85 vs 78 %
HR 1.40 p=0·5056 (for non-inferiority)

Gillison M. et al. Lancet 2018

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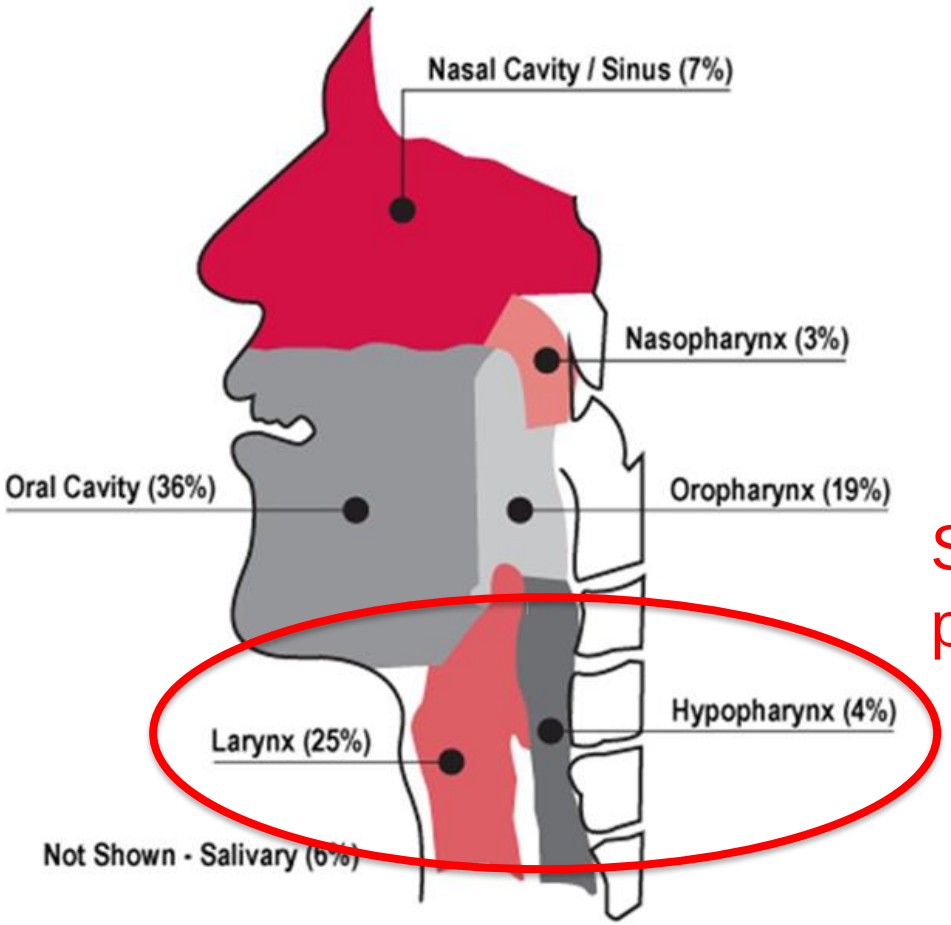
Principles of Treatment

Primary Site



Distribution of Head & Neck Cancers by Subsite

Predominant pattern of failure - **Locoregional**

Surgery or CRT – organ preservation?

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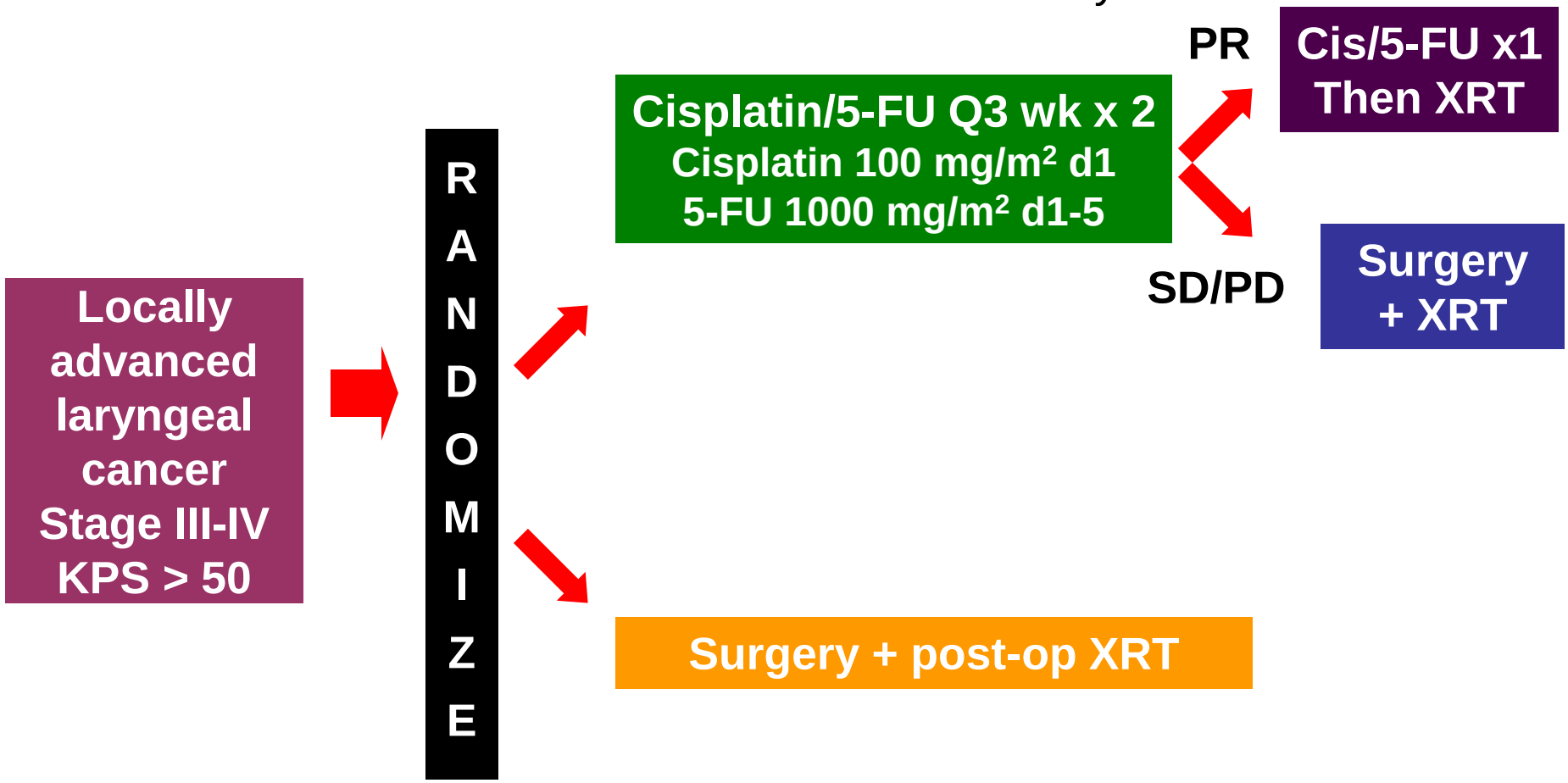
https://health.mo.gov/living/families/oralhealth/head-neck-cancer-hpv.php

Larynx Preservation

VA study

Phase III Trial to Preserve the Larynx



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VA Laryngeal Cancer Study Group. NEJM 324: 1685, 1991

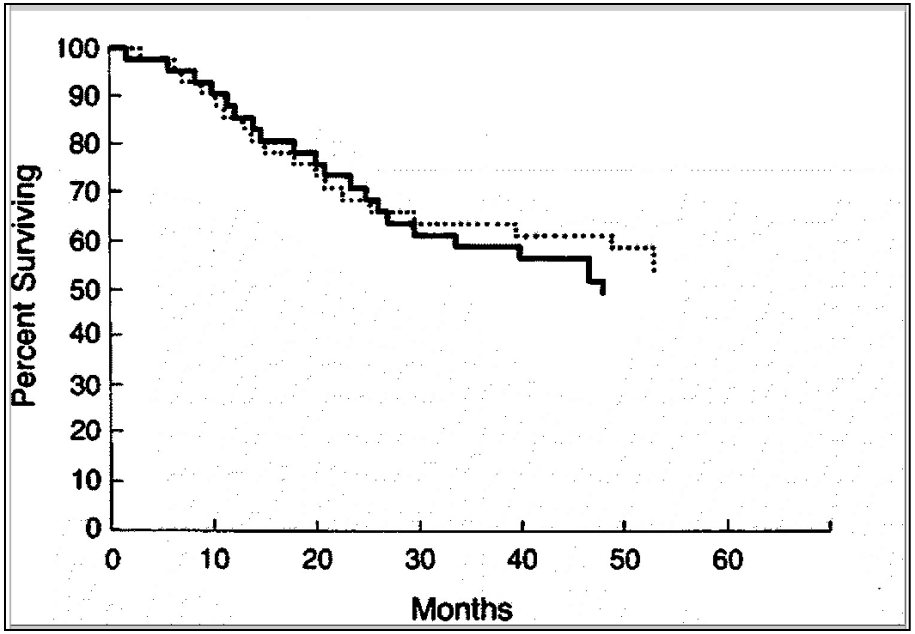
Larynx Preservation

VA study

Patterns of Failure

Site of Recurrence	Surgery (N = 166)	Chemotherapy (N = 166)
	no. of patients (%)	
Primary*	4 (2)	20 (12)
Regional	9 (5)	14 (8)
Distant	29 (17)	18 (11)
All	42 (25)	52 (31)

*Includes recurrences with either positive or negative nodes.



Larynx preserved in 64% of the patients assigned to the chemotherapy group

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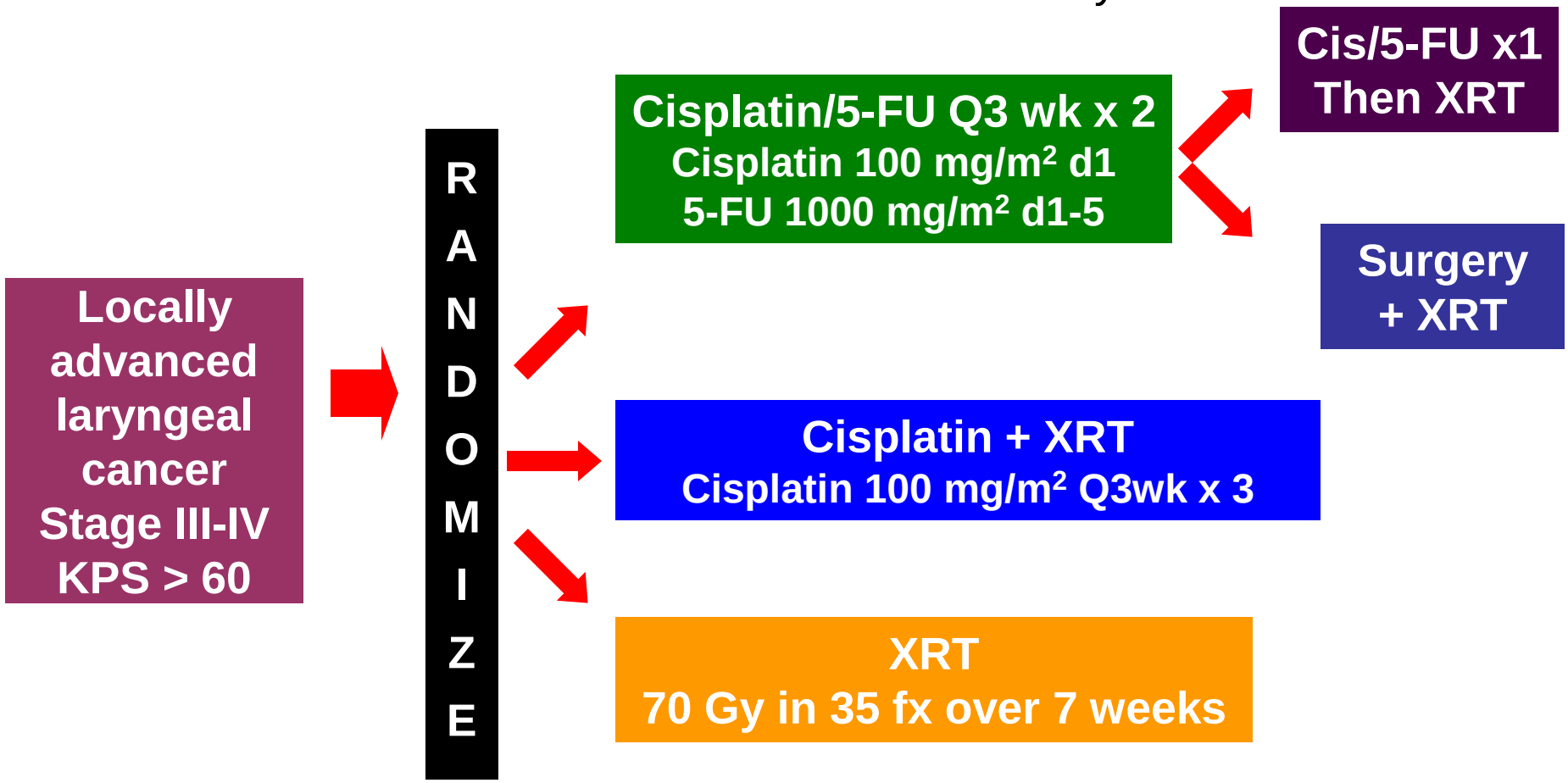
VA Laryngeal Cancer Study Group. NEJM 324: 1685, 1991

Larynx Preservation

RTOG 91-11

Phase III Trial to Preserve the Larynx



Aug 1992 – May 2000; n=518
Primary endpoint: laryngectomy-free survival
Secondary endpoint: OS, DFS, LFS, local-regional control, time to DM

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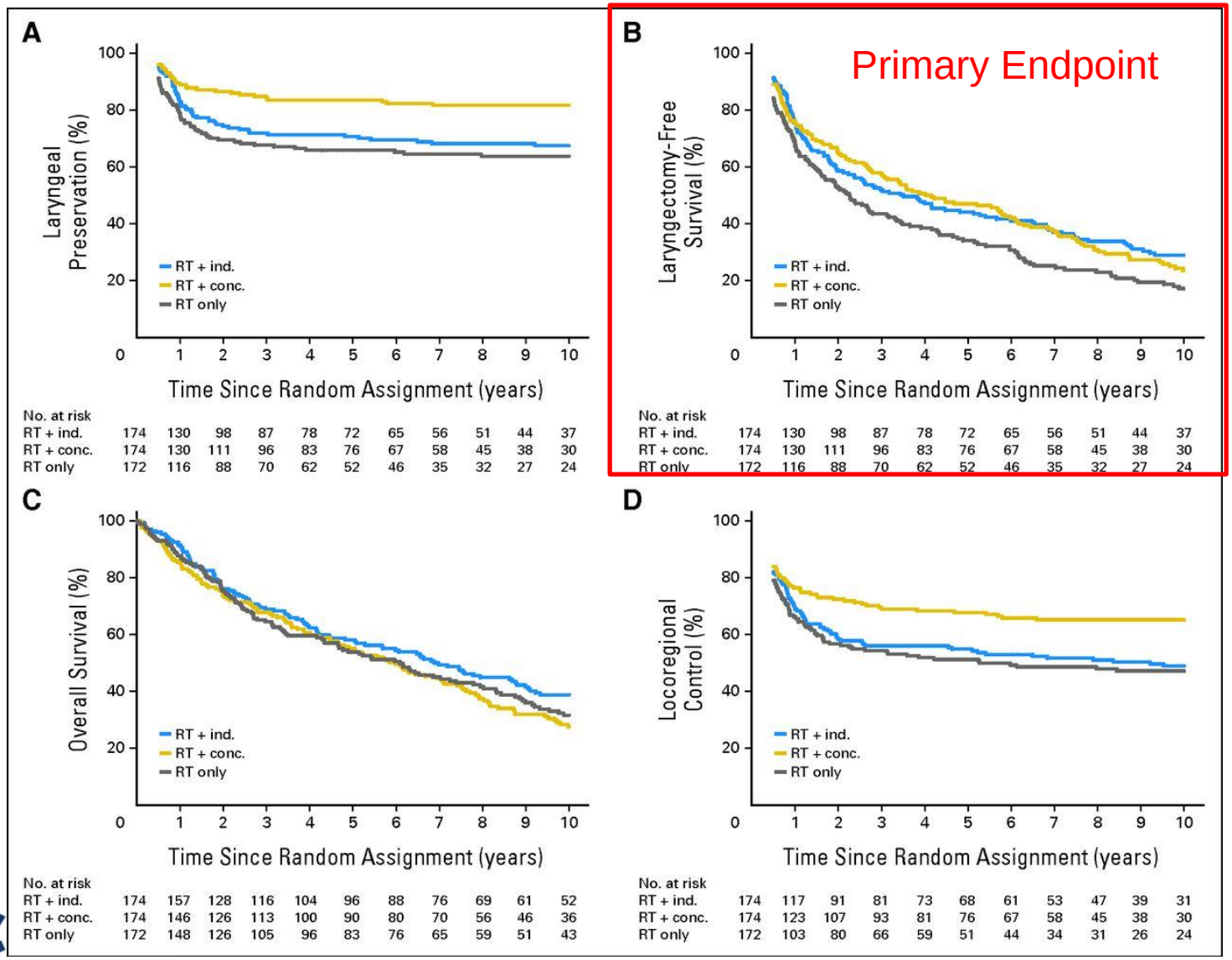
Forastiere et al. NEJM 349 (22): 2091-2098, 2003

RTOG 91-11 10-year Update



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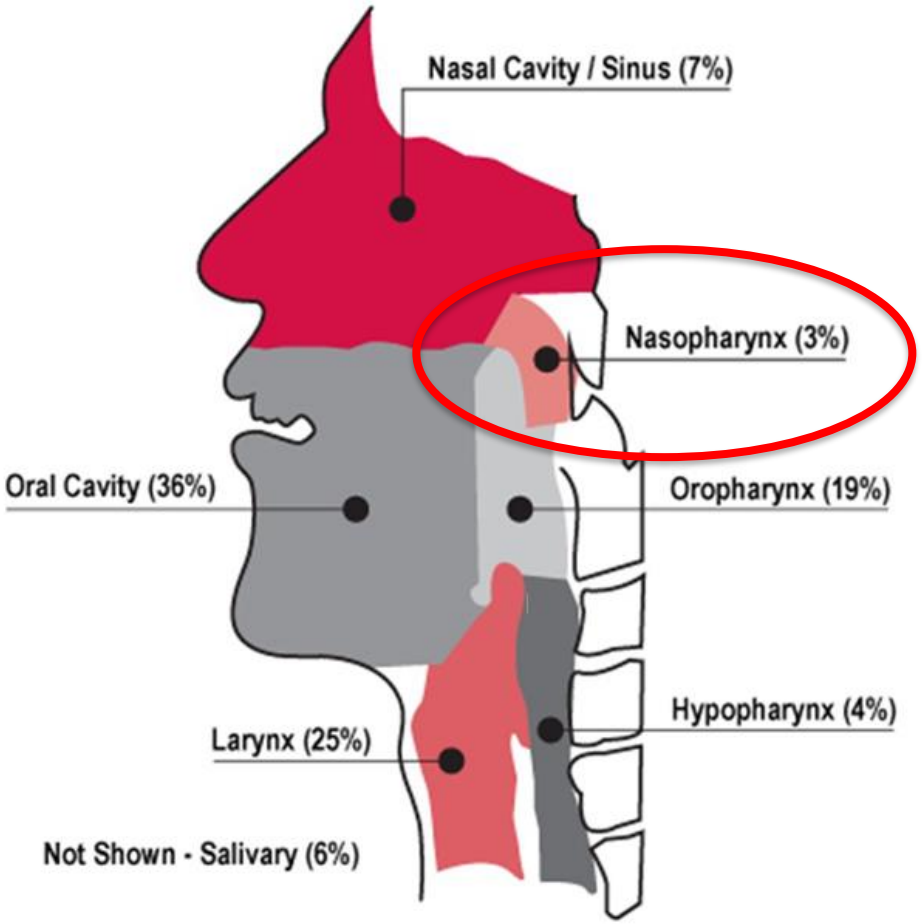
Forastiere A A et al. JCO 2013;31:845-852

Principles of Treatment

Primary Site

Predominant pattern of failure – **Locoregional and Distant**

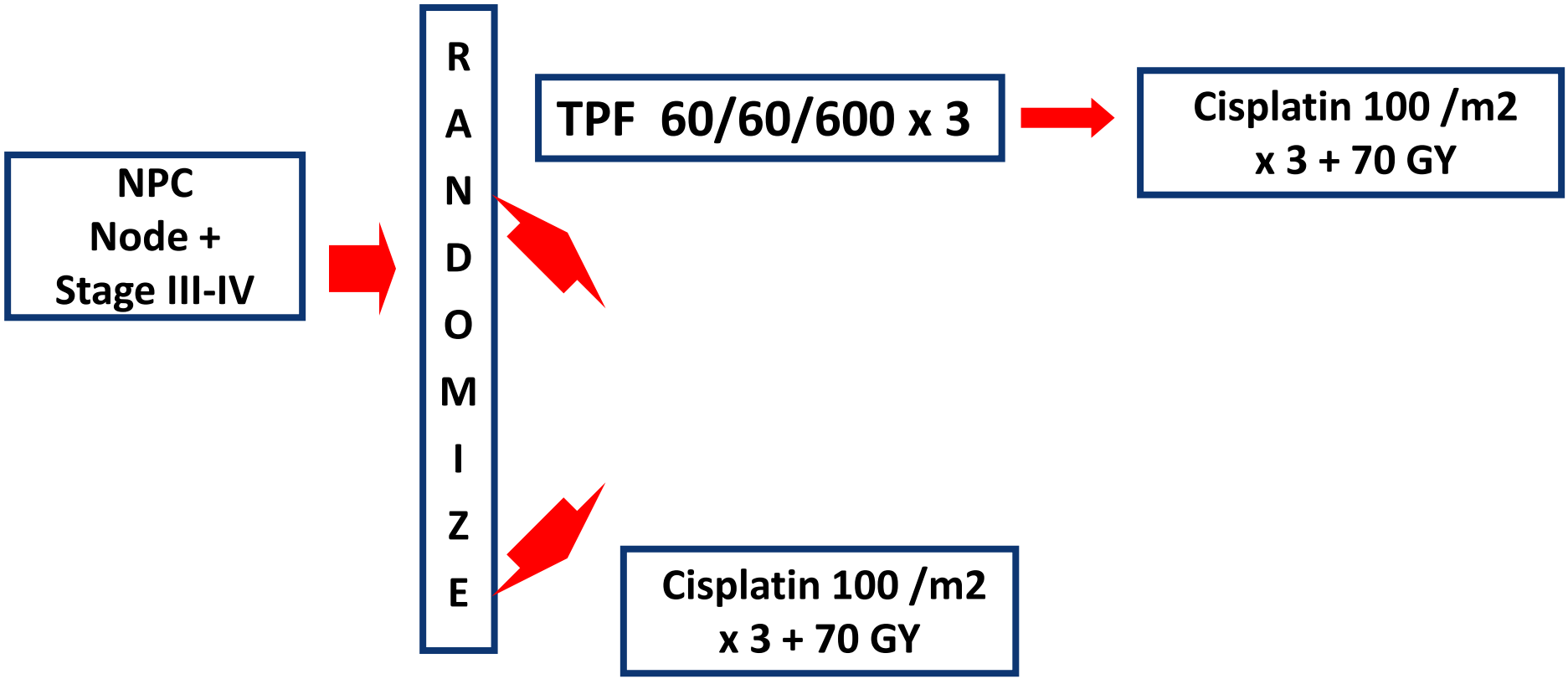
Induction or Adjuvant chemo with CRT



Distribution of Head & Neck Cancers by Subsite

https://health.mo.gov/living/families/oralhealth/head-neck-cancer-hpv.php

Nasopharynx Cancer – Chinese Multicenter Trial



Primary endpoints: at 3 yrs: FFS 80 vs 72% HR 0.68,
OS 92 vs 86% HR 0.59

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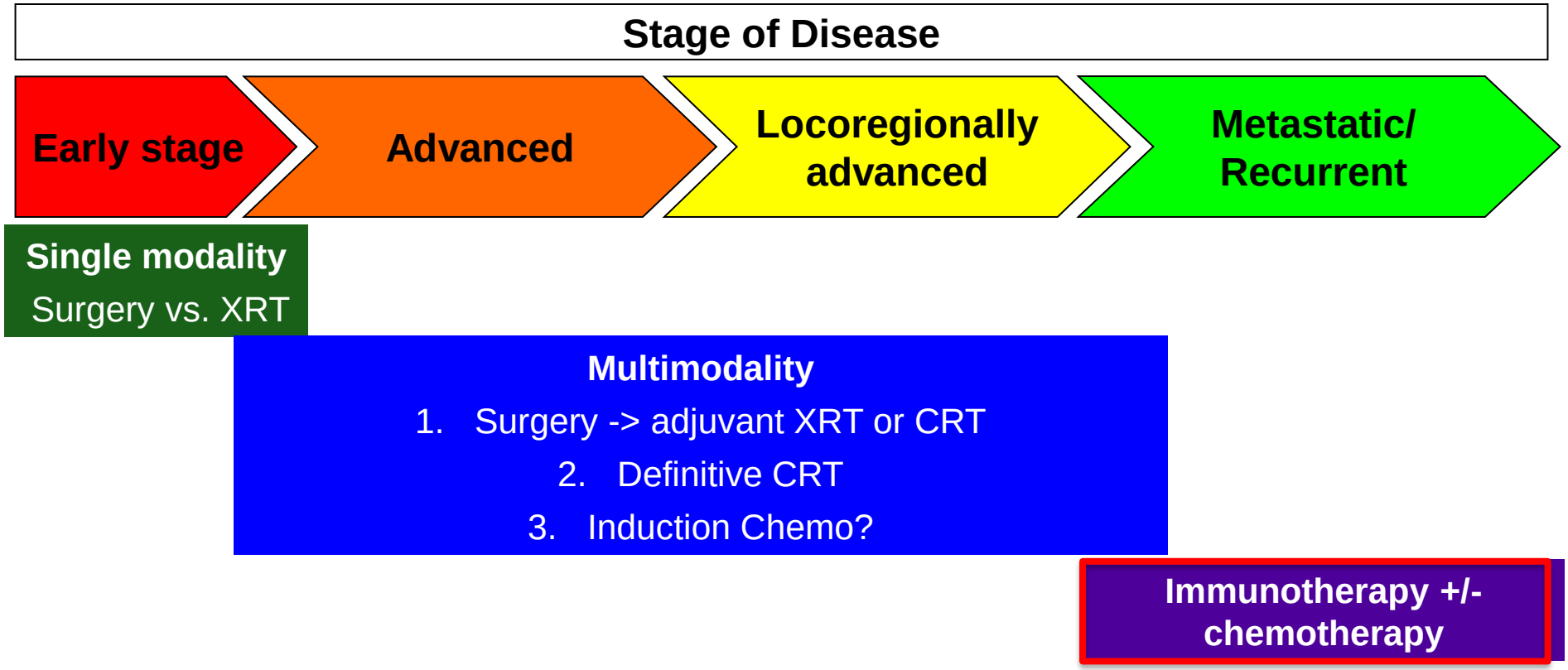
Sun Y et al Lance Oncol 2016

Principles of Treatment

Stage



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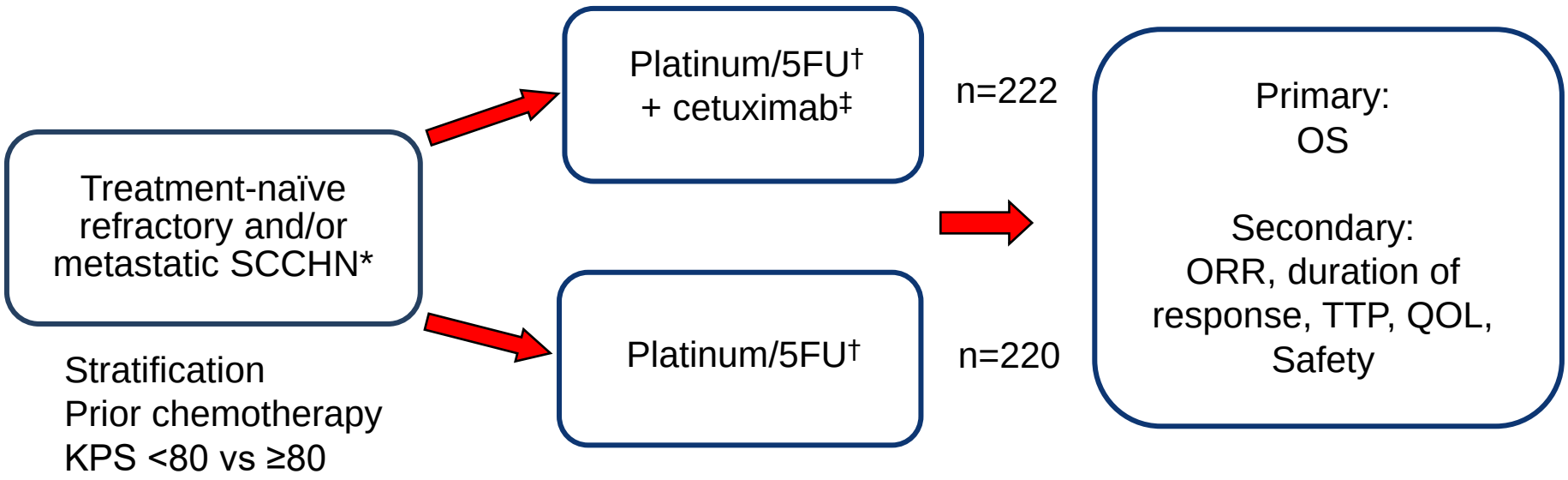
Recurrent/Metastatic HNSCC

EXTREME: Phase III Platinum/5FU ± Cetuximab in 1st Line RM HNSCC



‡Cetuximab 400 mg/m^2 initial dose then 250 mg/m^2 weekly until progression or unacceptable toxicity

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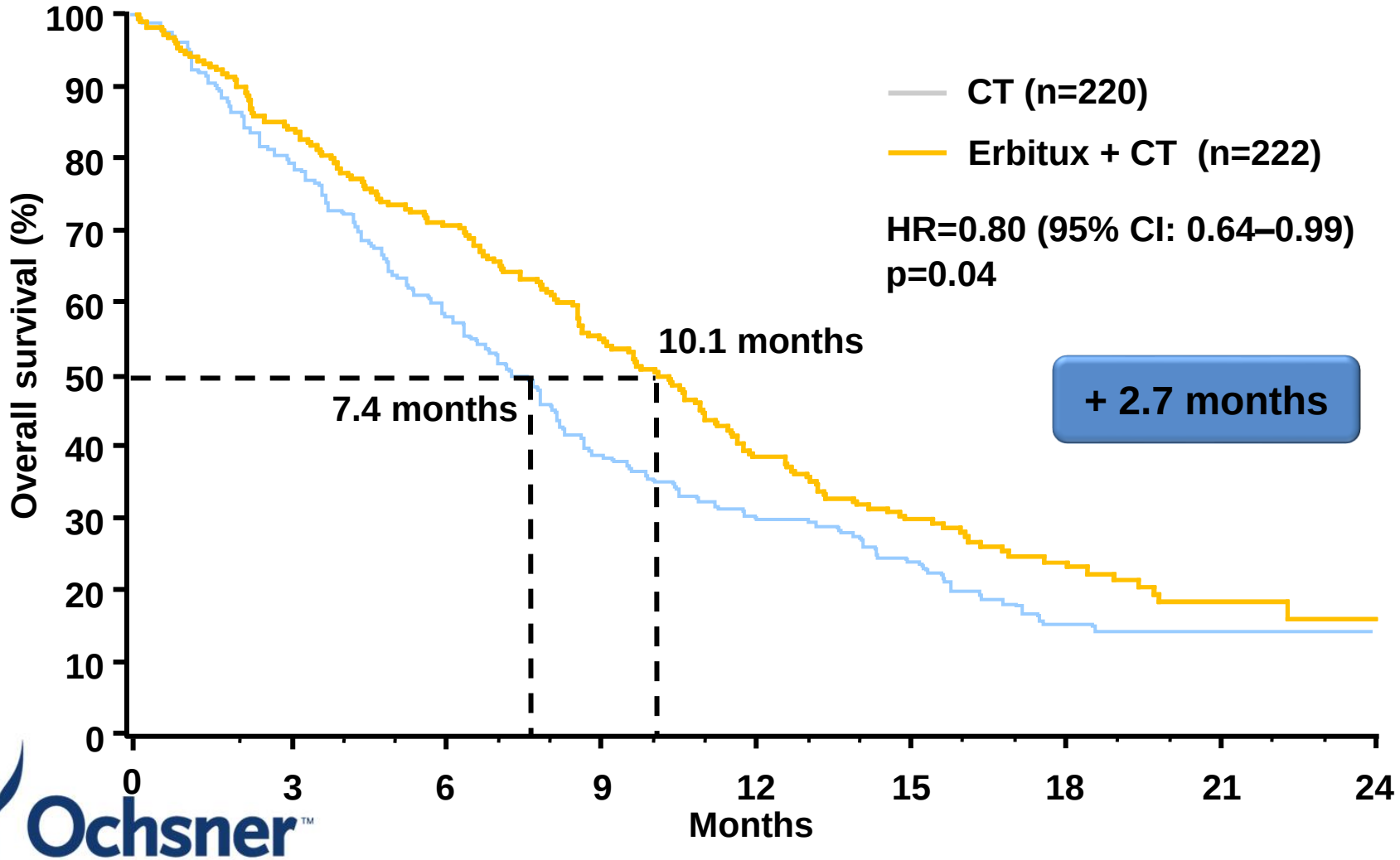
Vermorken NEJM 2008

EXTREME: Overall Survival



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Vermorken NEJM 2008

Phase Checkmate 141

Nivolumab in R/M HNSCC after Platinum

Key Eligibility Criteria

- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status[a]

Stratification factor

- Prior cetuximab treatment

R 2:1

Nivolumab
3 mg/kg IV Q2W

Investigator's Choice

- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint

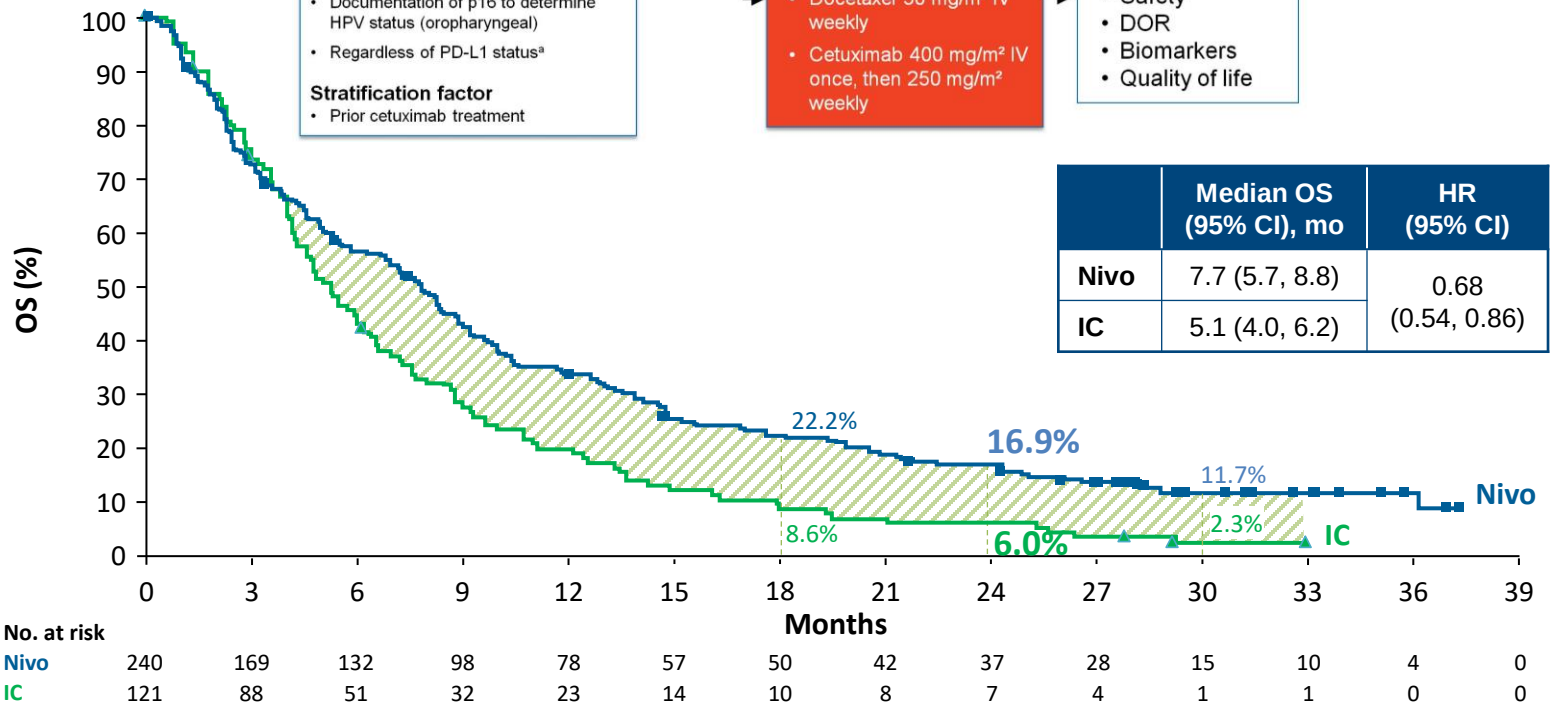
- OS

Other endpoints

- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

Ferris et al., ASCO 2016; NEJM 2016

	Median OS (95% CI), mo	HR (95% CI)
Nivo	7.7 (5.7, 8.8)	0.68 (0.54, 0.86)
IC	5.1 (4.0, 6.2)	



No. at risk													
Nivo	240	169	132	98	78	57	50	42	37	28	15	10	4	0
IC	121	88	51	32	23	14	10	8	7	4	1	1	0	0

Symbols represent censored observations. ITT = intent-to-treat; Nivo, nivolumab

Ferris et al., AACR 2018

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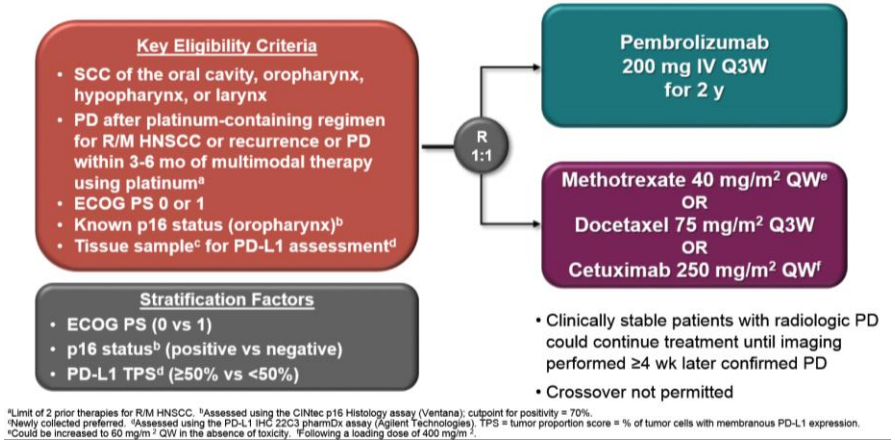
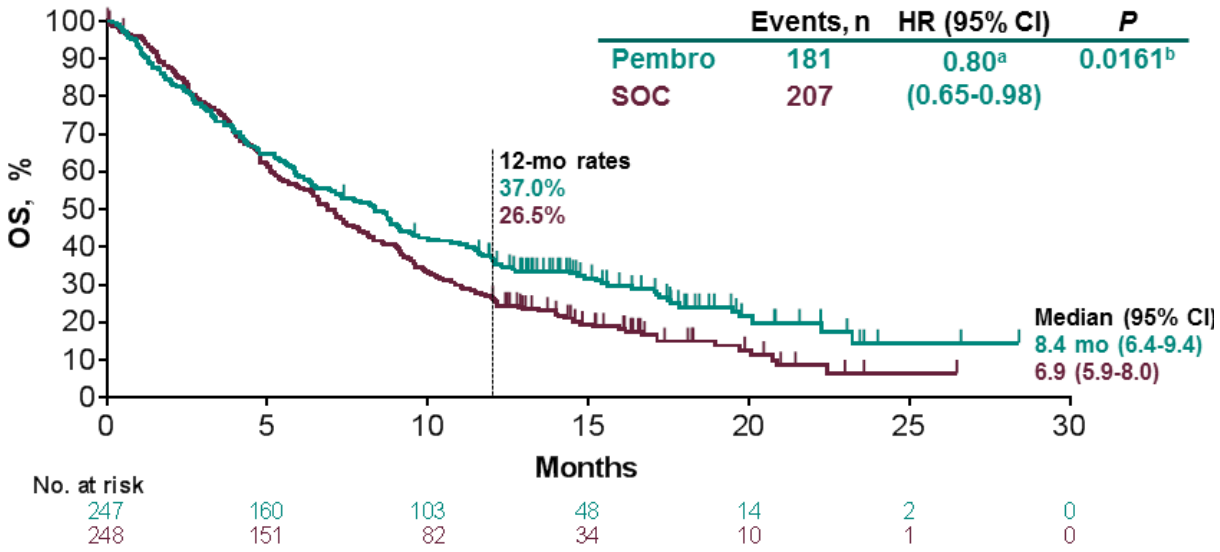
Phase 3 Keynote 040 Study



Cohen et al., ESMO 2017



Soulieres et al., AACR 2018

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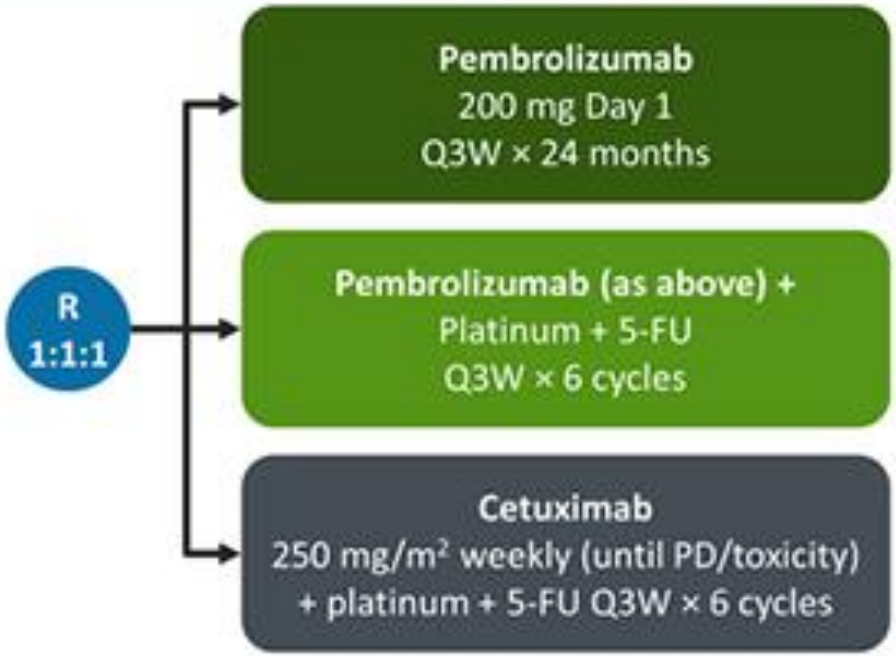
Keynote 048: First-line Study

Phase 3 First-Line Trials
KeyNote 048: pembrolizumab + chemotherapy vs pembrolizumab vs EXTREME (NCT02358031)

Stratified by PD-L1

Primary:
14 Primary Hypotheses

Pembro alone and of pembro + chemo versus Extreme for OS and PFS in CPS≥20, CPS ≥ 1, or total population



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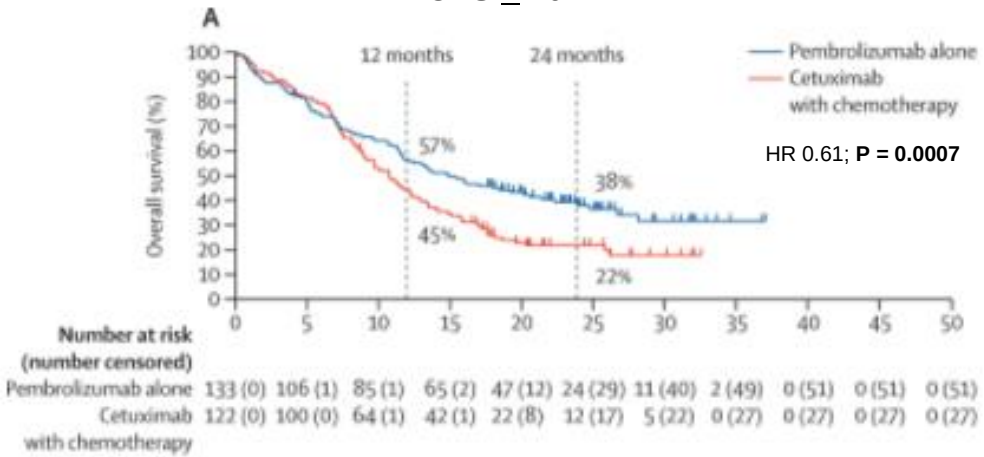
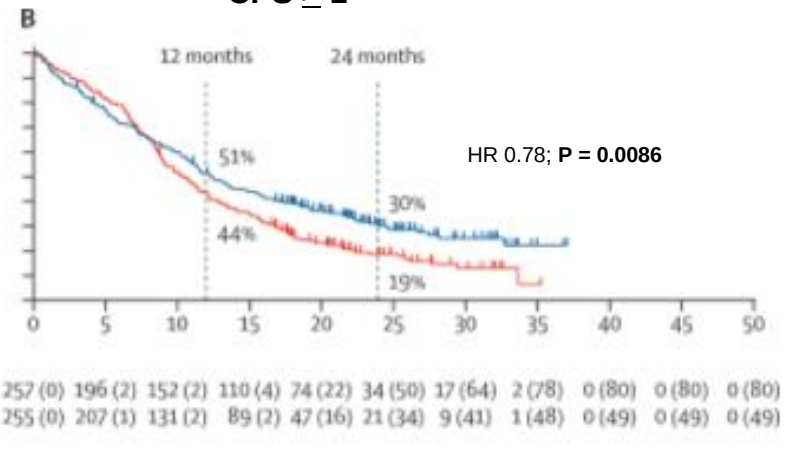
Burtness B, et al. Lancet. 2019

Pembro alone versus EXTREME

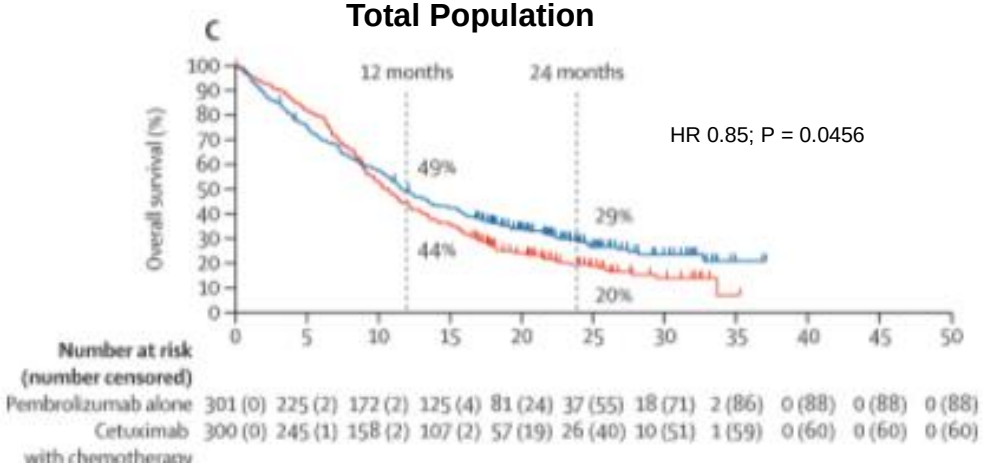
CPS ≥ 20



CPS ≥ 1



Total Population



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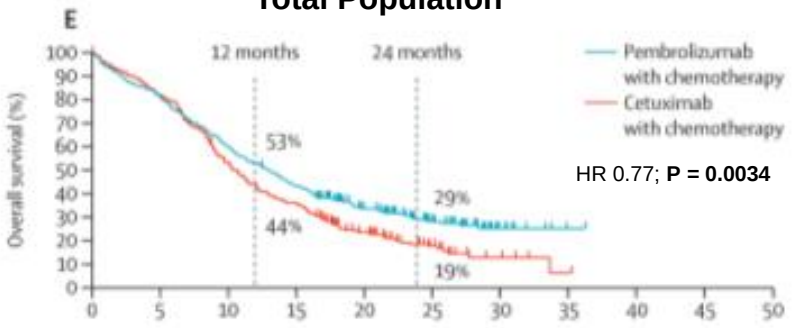
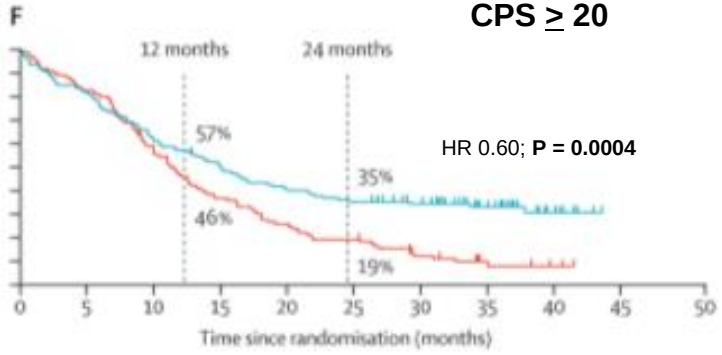
Burtness B, et al. Lancet. 2019

Pembro + Chemo versus EXTREME

Total Population

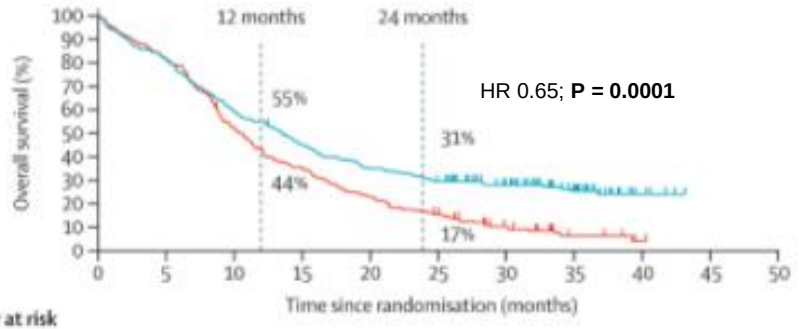


CPS ≥ 20



Number at risk (number censored)												
Pembrolizumab with chemotherapy	281 (0)	227 (0)	169 (0)	122 (1)	75 (22)	40 (47)	10 (74)	1 (83)	0 (84)	0 (84)	0 (84)	
Cetuximab with chemotherapy	278 (0)	227 (1)	147 (2)	100 (2)	51 (19)	20 (40)	5 (51)	1 (54)	0 (55)	0 (55)	0 (55)	
Pembrolizumab with chemotherapy	126 (0)	102 (0)	77 (0)	60 (1)	50 (1)	44 (1)	36 (8)	21 (22)	4 (38)	0 (42)	0 (42)	
Cetuximab with chemotherapy	110 (0)	91 (0)	60 (1)	40 (1)	26 (1)	19 (2)	11 (4)	4 (8)	1 (11)	0 (12)	0 (12)	

CPS ≥ 1



Number at risk (number censored)												
Pembrolizumab with chemotherapy	242 (0)	197 (0)	144 (0)	109 (1)	84 (1)	70 (2)	52 (17)	29 (37)	5 (60)	0 (65)	0 (65)	
Cetuximab with chemotherapy	235 (0)	191 (1)	122 (2)	83 (2)	54 (2)	35 (3)	17 (11)	5 (18)	1 (21)	0 (22)	0 (22)	

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Burtness B, et al. Lancet. 2019

Response Rate Summary Keynote 048

Table S5: Summary of confirmed objective response at final analysis for the comparison of pembrolizumab vs cetuximab-chemotherapy

Best Response	PD-L1 CPS ≥20 Population		PD-L1 CPS ≥1 Population		Total Population	
	Pembrolizumab N=133	Cetuximab-Chemotherapy N=122	Pembrolizumab N=257	Cetuximab-Chemotherapy N=255	Pembrolizumab N=301	Cetuximab-Chemotherapy N=300
Objective response	31 (23%)	44 (36%)	49 (19%)	89 (35%)	51 (17%)	108 (36%)
Complete response	10 (8%)	4 (3%)	14 (5%)	7 (3%)	14 (5%)	8 (3%)
Partial response	21 (16%)	40 (33%)	35 (14%)	82 (32%)	37 (12%)	100 (33%)
Stable disease	40 (30%)	43 (35%)	72 (28%)	84 (33%)	82 (27%)	102 (34%)
Progressive disease	42 (32%)	12 (10%)	100 (39%)	33 (13%)	122 (41%)	37 (12%)
Non-CR/non-PD*	8 (6%)	6 (5%)	11 (4%)	11 (4%)	14 (5%)	11 (4%)
Not evaluable or assessed†	12 (9%)	17 (14%)	25 (10%)	38 (15%)	32 (11%)	42 (14%)

Table S6: Summary of confirmed objective response at final analysis for the comparison of pembrolizumab-chemotherapy vs cetuximab-chemotherapy

Best Response	PD-L1 CPS ≥20 Population		PD-L1 CPS ≥1 Population		Total Population	
	Pembrolizumab-Chemotherapy N=126	Cetuximab-Chemotherapy	Pembrolizumab-Chemotherapy N=243	Cetuximab-Chemotherapy N=235	Pembrolizumab-Chemotherapy N=281	Cetuximab-Chemotherapy N=278
Objective response	54 (43%)	42 (38%)	88 (36%)	84 (36%)	100 (36%)	101 (36%)
Complete response	12 (10%)	4 (4%)	16 (7%)	7 (3%)	17 (6%)	8 (3%)
Partial response	42 (33%)	38 (35%)	72 (30%)	77 (33%)	83 (30%)	93 (33%)
Stable disease	29 (23%)	38 (35%)	64 (26%)	77 (33%)	78 (28%)	95 (34%)
Progressive disease	19 (15%)	9 (8%)	42 (17%)	29 (12%)	48 (17%)	33 (12%)
Non-CR/non-PD*	4 (3%)	5 (5%)	11 (5%)	9 (4%)	13 (5%)	9 (3%)
Not evaluable or assessed†	20 (16%)	16 (15%)	37 (15%)	36 (15%)	42 (15%)	40 (14%)

Pembro + Chemo versus EXTR...

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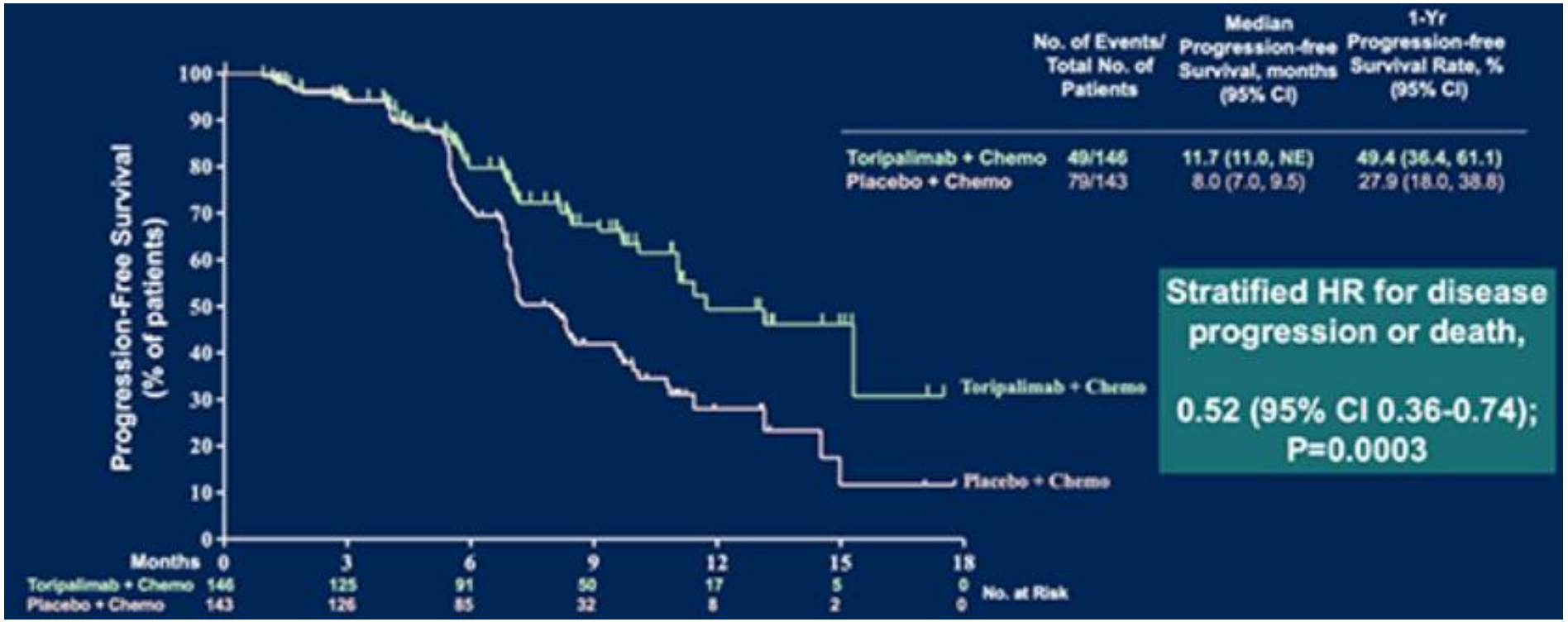
Burtness B, et al. Lancet. 2019

Nasopharyngeal Cancer Left Out?

Jupiter 02 Study – Gem/Cis +/- Toripalimab (PD-1 inhibitor)



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Mai H-Q, et al. Nature Medicine. 2021

2022 Updates

Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial

- Weekly cisplatin 40 mg/m2 concurrent with radiation is **non-inferior** to q 3 week cisplatin 100 mg/m2 for adjuvant.

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2022 Updates

OncologyPRO > Meeting resources > ESMO Congress

Presidential Symposium II

LBA5 - Primary results of the phase III KEYNOTE-412 study: Pembrolizumab (pembro) with chemoradiation therapy (CRT) vs placebo plus CRT for locally advanced (LA) head and neck squamous cell carcinoma (HNSCC)

- Pembrolizumab did **NOT** improve EFS or OS with CRT for LA HNSCC.

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Second Line and Beyond

Can’t we do better than just Cetuximab?

- **Targeted Agents**
  - VEGF agents +/- immune checkpoint blockade.
  - STAT3 inhibitors
  - PI3K inhibitors
- **Novel Combination Immunotherapies**
  - ICOS agonists + PD-1i
  - LAG-3 inhibitors + PD-1i
  - TGF-beta inhibitors + PD-1i
- **Tumor infiltrating lymphocytes**
- **Vaccines**

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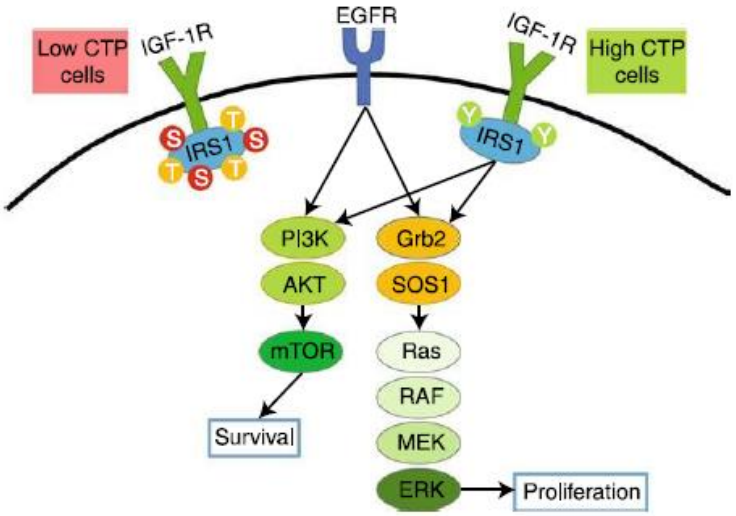
Second Line and Beyond

Can’t we do better than just Cetuximab?

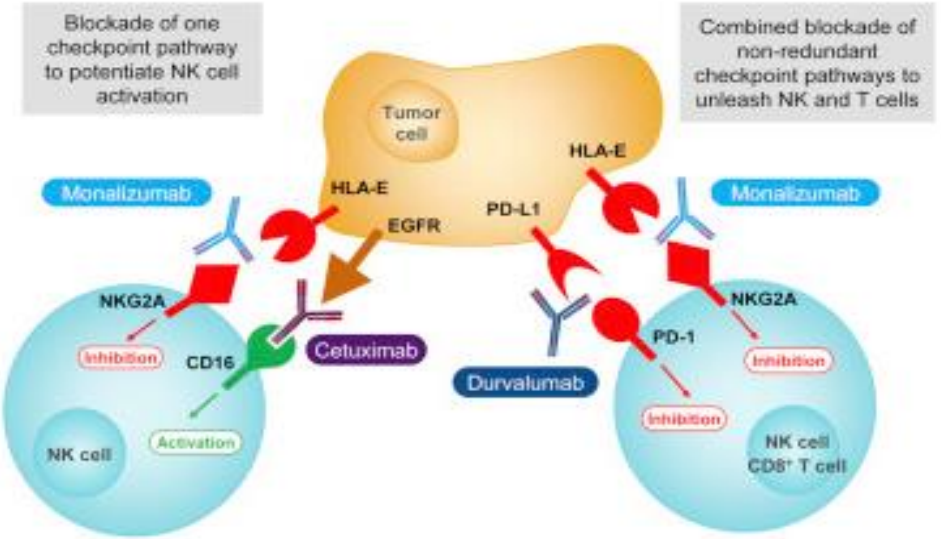
Targeting EGFR inhibitor resistance mechanisms



Berger A, et. al. Nature Cancer, 2021

Trials at Ochsner

Targeting NK Cells



Andre P, et. al. Cell, 2018

Ochsner™ Health System

Summary

- Locally Advanced Disease
  - ChemoRT (Cisplatin preferred) versus Surgery
    - Anatomical site, etiology, organ preservation
  - *Immunotherapy failed to improve ChemoRT in randomized study*

- Frontline Recurrent/Metastatic
  - Pembro or Pembro + Chemo depending on PD-L1
  - *New Immunotherapy combinations?*

- Second Line
  - Cetuximab if not used
  - *Cetuximab combinations?*

Ochsner™ Health System