HEAD AND NECK CANCER UPDATE

Hyunseok Kang, MD
Associate Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, San Francisco

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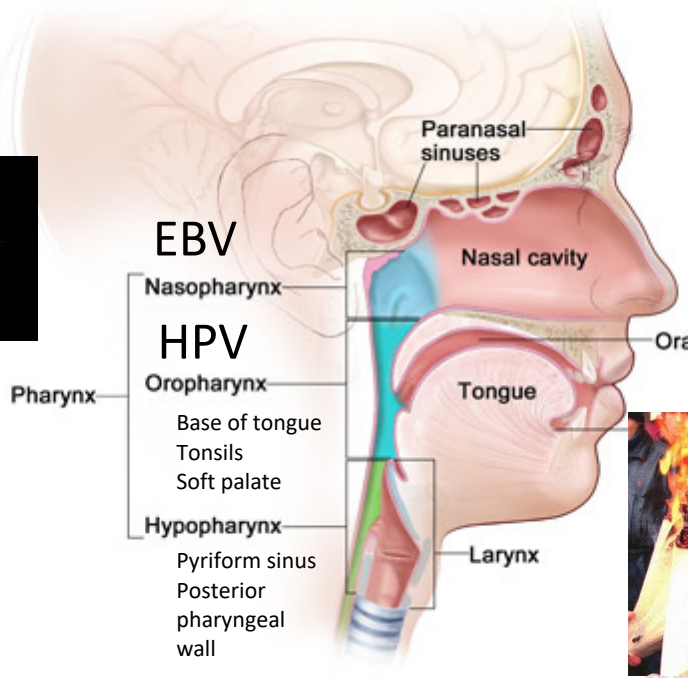
Agenda

- Immune checkpoint inhibitor in locally advanced HNSCC
- Evolving immune therapy options in recurrent/metastatic HNSCC
- Immune checkpoint inhibitor in recurrent/metastatic NPC

Squamous cell carcinoma of head and neck (SCCHN)



Oral tongue
Floor of mouth
Buccal mucosa

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Current treatment approach

No approved therapy

Multimodality therapy

- Surgery → RT or CRT
- Concurrent chemoRT (cisplatin)

Systemic Immunotherapy +/- chemotherapy

- PD-L1 positive: Pembrolizumab
- PD-L1 negative: Pembrolizumab + platinum based chemo

Systemic Chemotherapy and/or targeted therapy

- Chemotherapy
- Cetuximab
- Clinical trial

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Case Study

- 59-year-old male with 15 PY smoking history, quitted 5 years ago
- Past medical history includes hypertension
- Presents with 3 months history of neck mass, FNA confirms HPV positive squamous cell carcinoma

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Case Study

- PET/CT reveals 2.5 cm primary disease in right base of tongue and multiple FDG avid bilateral neck LNs
- Tumor board recommends definitive radiotherapy given bilateral neck involvement
- Radiation oncology plans to offer IMRT with 70 Gy

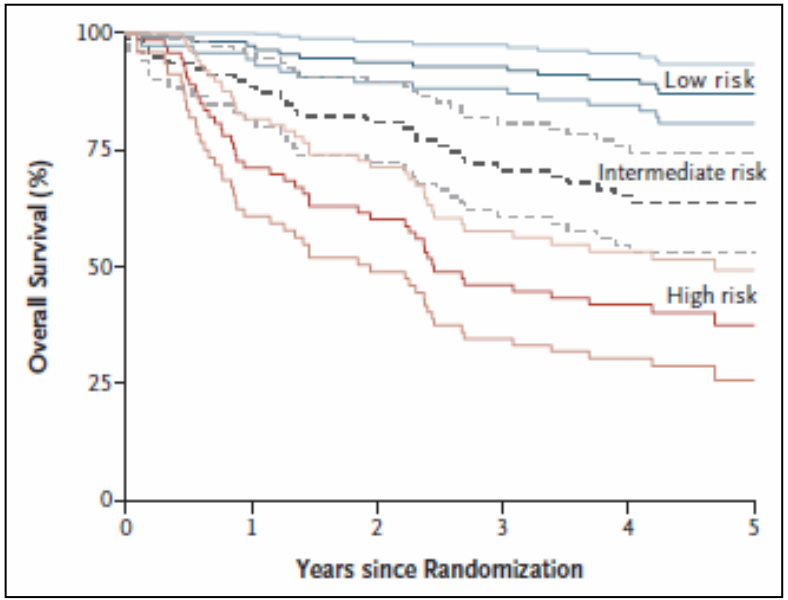
Question 1

The patient comes in for medical oncology consultation. What would you recommend?

1. Radiotherapy alone
2. Concurrent pembrolizumab
3. Concurrent avelumab and cisplatin followed by 1 year of avelumab
4. Concurrent cisplatin
5. Concurrent cetuximab

Better survival of HPV positive SCCHN

(when treated with concurrent chemoradiation)



HPV+/< 10PY : 93% at 3 yr

HPV+/> 10PY : 70% at 3 yr

HPV neg : 46% at 3 yr

Ang KK et al. *New Engl J Med* 2010;363:24-35

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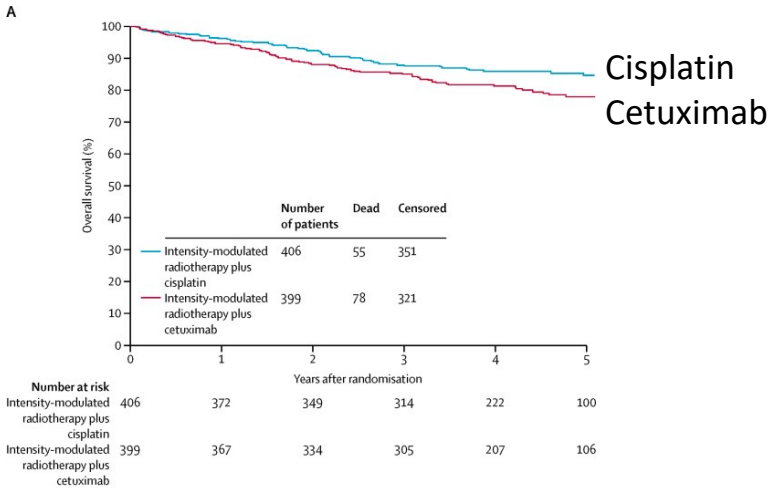
Can we replace cisplatin with cetuximab?

RTOG 10-16 : Cetux versus cisplatin in HPV positive SCCHN

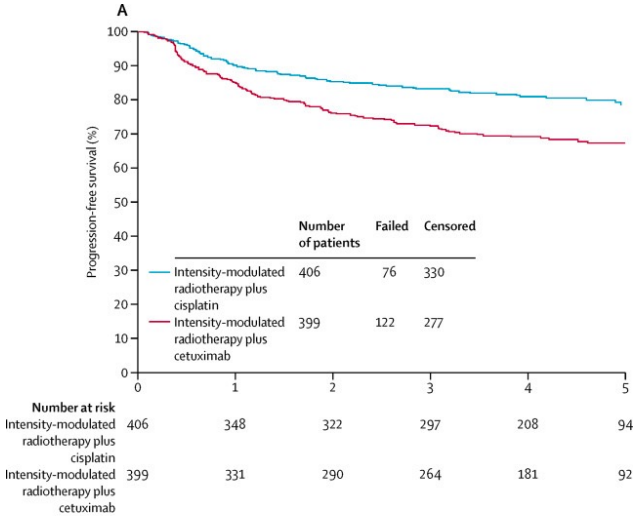
Overall Survival



Cisplatin

Cetuximab

Progression Free Survival



Gillison ML et al. Lancet 2019;393:P40-50

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Can we de-intensify RT for HPV positive patients

NRG HN002 study : randomized phase 2 non-smokers, p16 positive OPSCC

HPV positive oropharyngeal cancer
< T4, < N2c, < 10 pack years

P16 status confirmed by IHC

R

Arm A
Weekly cisplatin 40mg/m2
x 6 weeks
+
60 Gy IMRT

2-year PFS : 90.5%

Arm B

60 Gy IMRT

2-year PFS : 87.6%

Target 2-year PFS of 91% versus null hypothesis of 85%

Yom SS et al. *J Clin Oncol* 2021; 39:956-965

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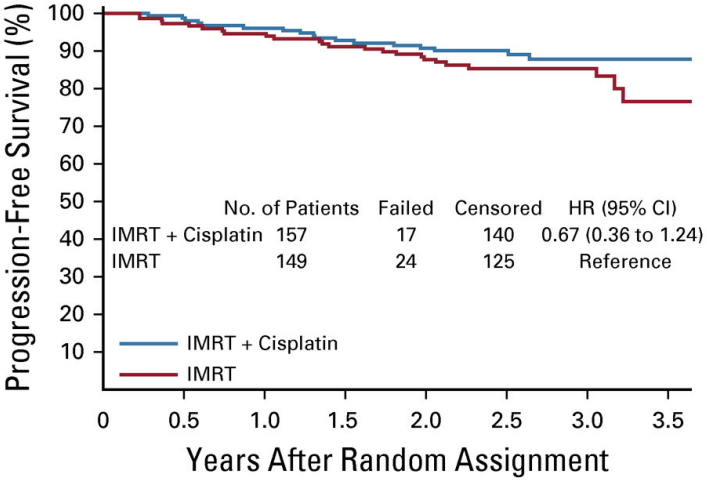
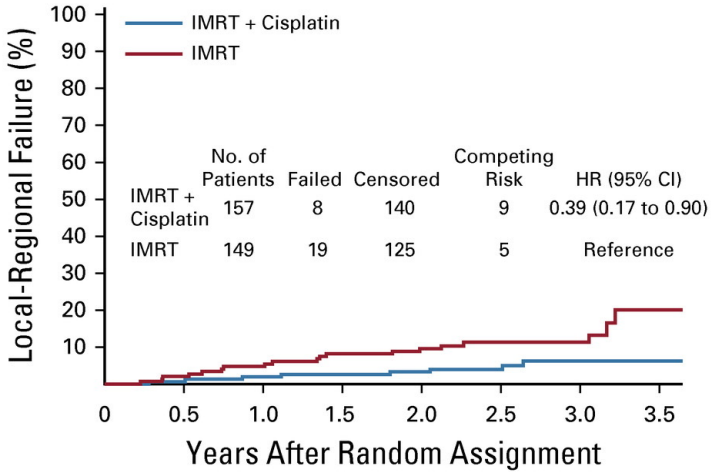
Can we de-intensify RT for HPV positive patients

NRG HN002 study : randomized phase 2 non-smokers, p16 positive OPSCC





Yom SS et al. *J Clin Oncol* 2021; 39:956-965

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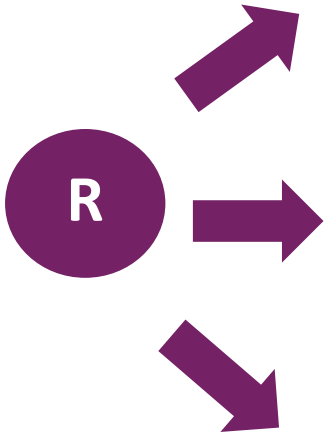
Alternative for HPV positive SCCHN

NRG HN005 study (phase 2/3, n=711)

HPV positive oropharyngeal cancer
T1-2 N1 M0 or T3 N0-1 M0
< 10 PY smoking history

P16 status confirmed by IHC



Arm 1
Cisplatin 100mg/m2 q3wk x 2
+
70 Gy IMRT

Arm 2
Cisplatin 100mg/m2 q3wk x 2
+
60 Gy IMRT

Arm 3
Nivolumab q2wk x 6
+
60 Gy IMRT

Completed enrollment as of 2/2023

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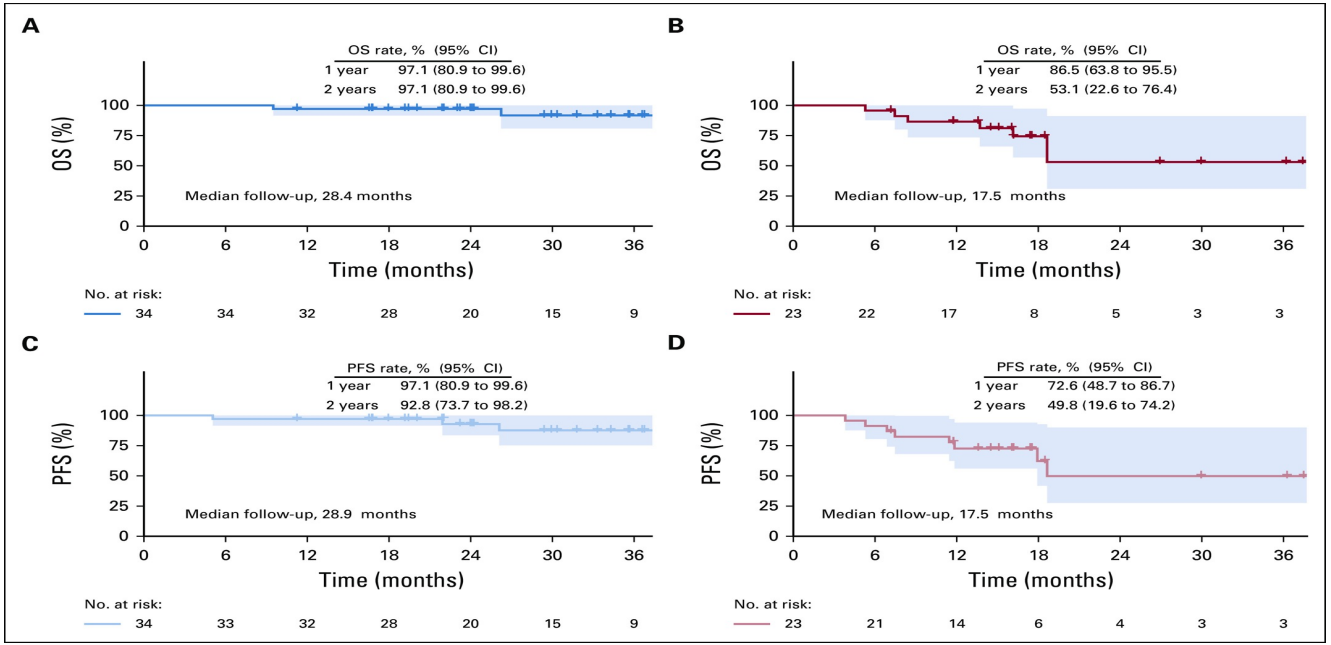
Immune checkpoint inhibitor and (chemo)radiation

Pembrolizumab and RT in SCCHN

HPV positive

HPV negative



Powell SF et al. *J Clin Oncol* 2020; 38:2427-2437

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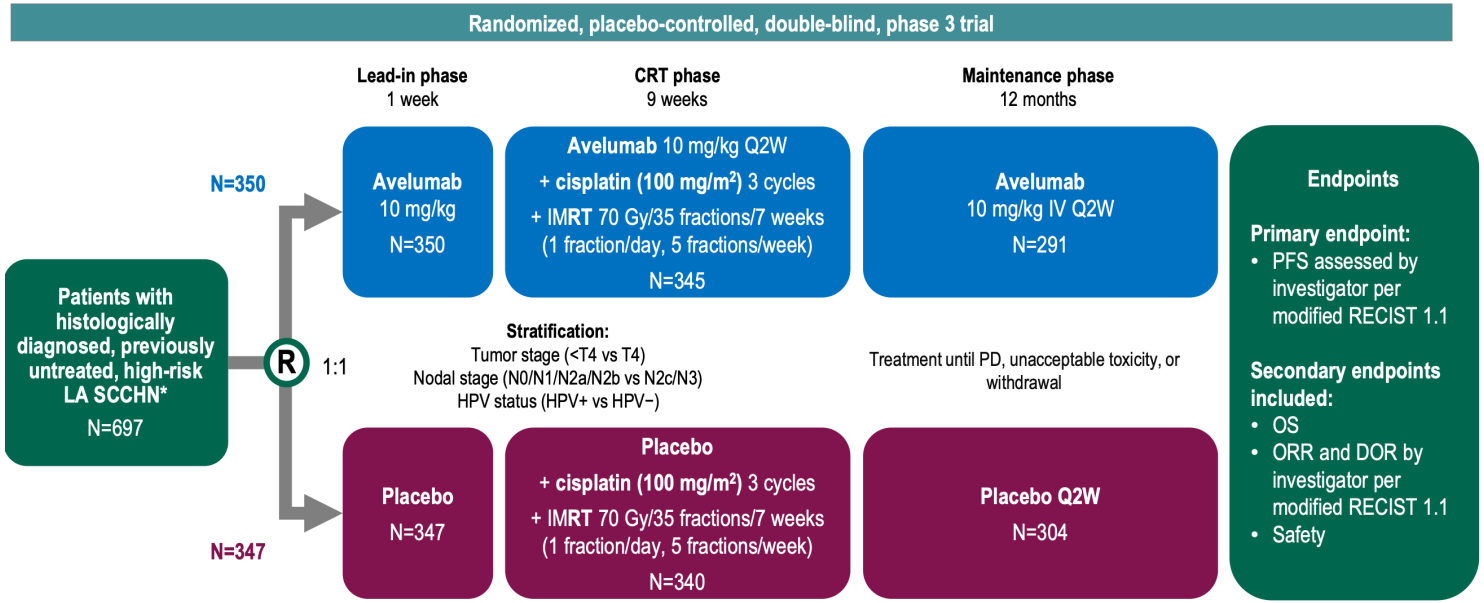
Immune checkpoint inhibitor and (chemo)radiation

VIRTUAL 2020 ESMO congress

JAVELIN Head & Neck 100: study design



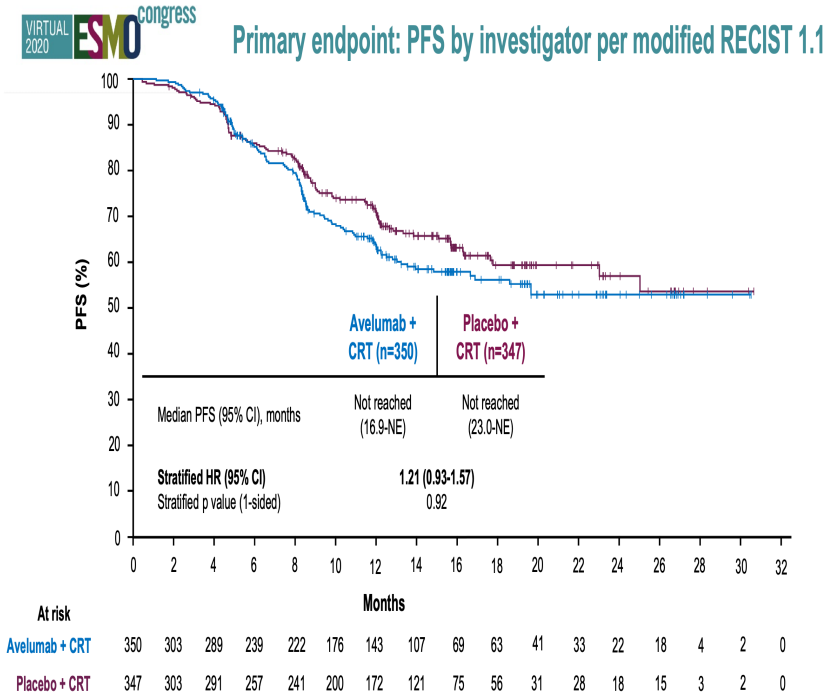
DOR, duration of response; **HPV**, human papillomavirus; **IMRT**, intensity-modulated radiation therapy; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomized; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

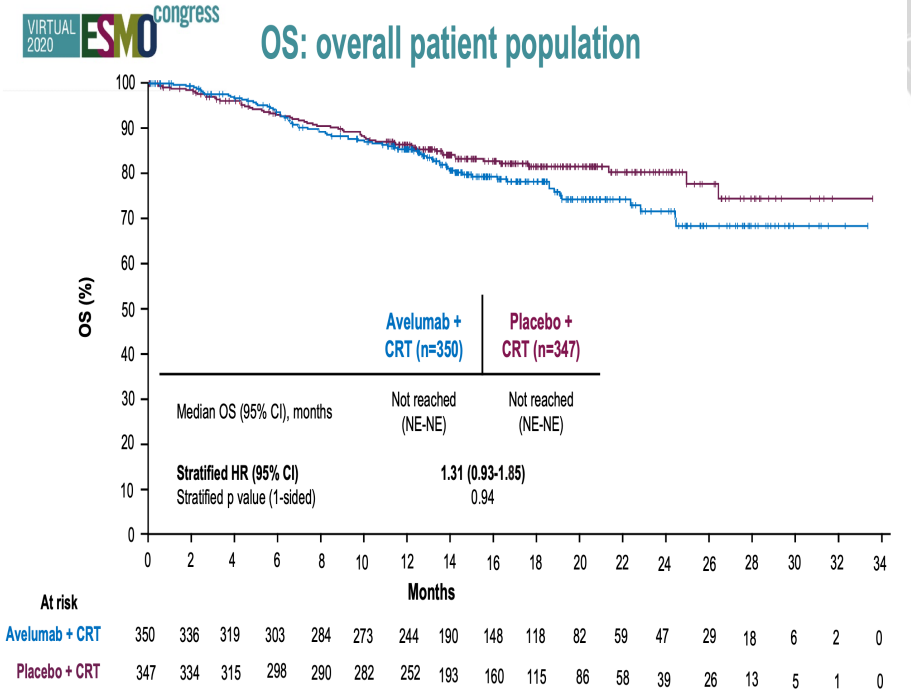
* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

Cohen EW et al. ESMO 2020 Annual Meeting

Immune checkpoint inhibitor and (chemo)radiation

Javelin head and neck 100





Cohen EW et al. ESMO 2020 Annual Meeting
Lee NY et al. *Lancet Oncol* 2021;22(4):450-462

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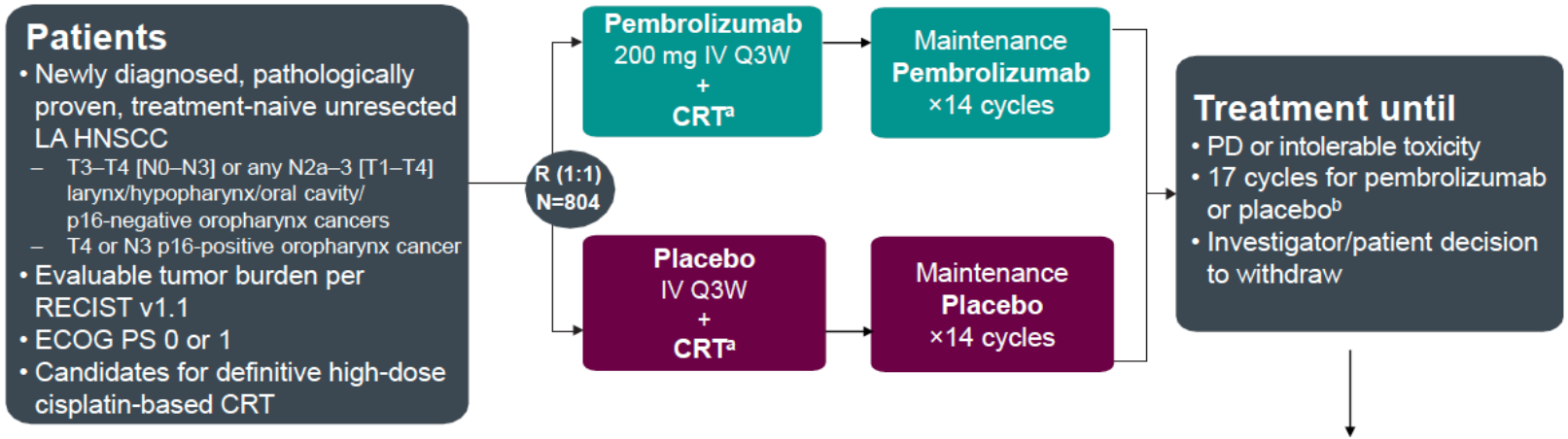
Why did it fail?

- Are anti-PD-L1 antibodies inferior to anti-PD1 antibodies?
  - Keynote 412

- Does RT negate the benefit of immune checkpoint inhibitors?
  - IMvoke 010 study

Immune checkpoint inhibitor and (chemo)radiation

KEYNOTE-412 Study Design (NCT03040999)



Stratification Factors
- Radiotherapy regimen (AFX vs SFX)
- Tumor site/p16 status (oropharynx [p16+ vs p16-] or larynx/hypopharynx/oral cavity)
- Disease stage (III vs IV)

Primary endpoint
- Event-free survival (EFS)

Secondary endpoints included:
- OS
- Safety/tolerability

Post-treatment follow-up to assess
- Safety
- Disease status
- Survival

Machiels JP et al. ESMO 2022 Annual Meeting

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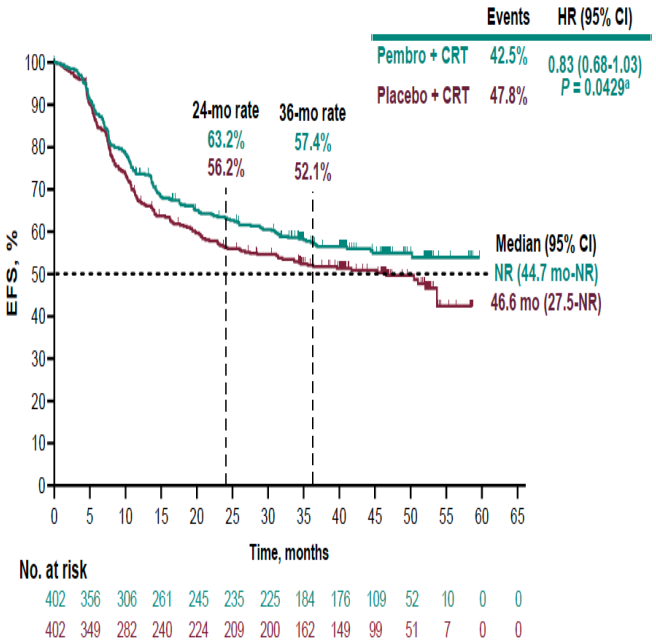
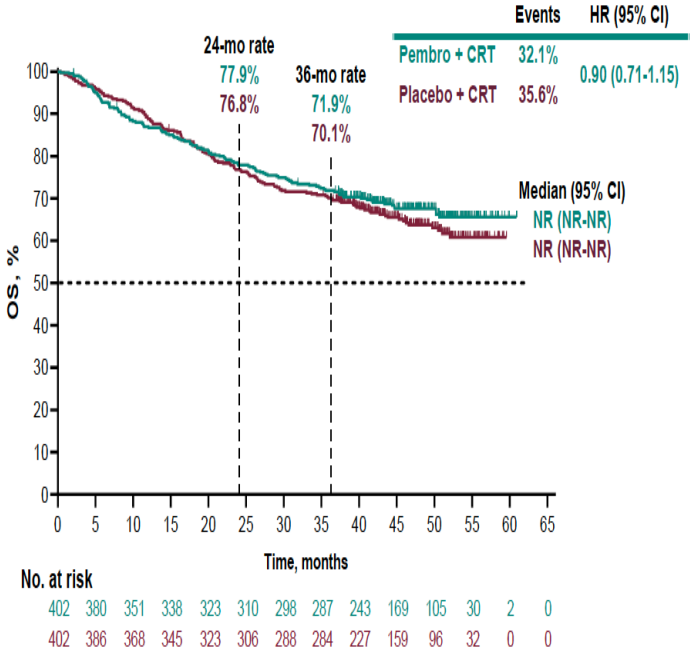
Immune checkpoint inhibitor and (chemo)radiation

Event-Free Survival, ITT Population



Overall Survival, ITT Population



Machiels JP et al. ESMO 2022 Annual Meeting

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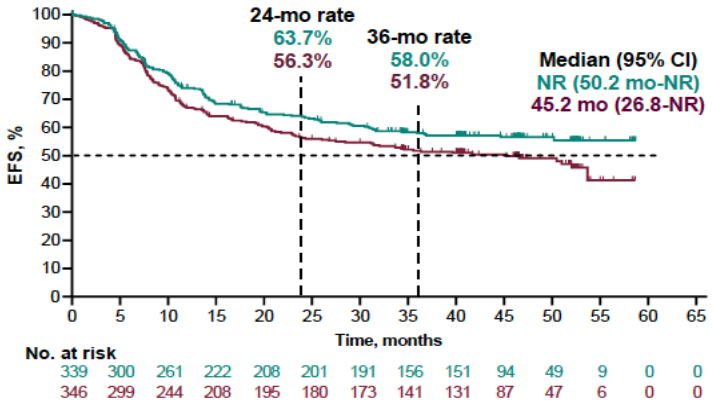
Immune checkpoint inhibitor and (chemo)radiation

EFS and OS in Patients With PD-L1 CPS ≥1 (Prespecified Subgroup Analysis)

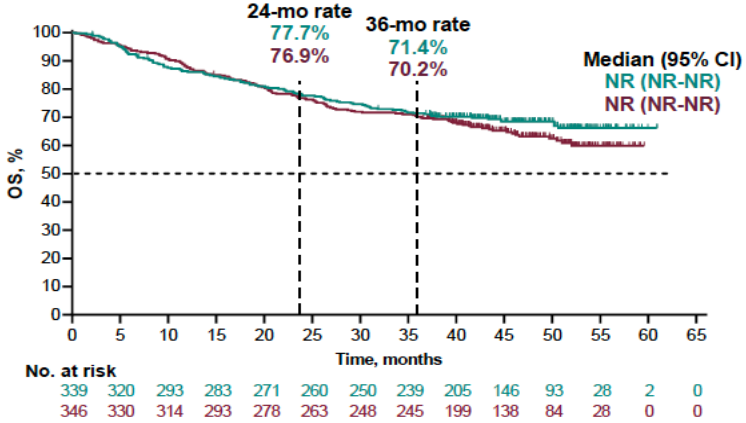
EFS

	Events	HR (95% CI)
Pembro + CRT	41.6%	0.80 (0.64-1.00)
Placebo + CRT	48.6%	



OS

	Events	HR (95% CI)
Pembro + CRT	31.6%	0.88 (0.68-1.14)
Placebo + CRT	36.1%	



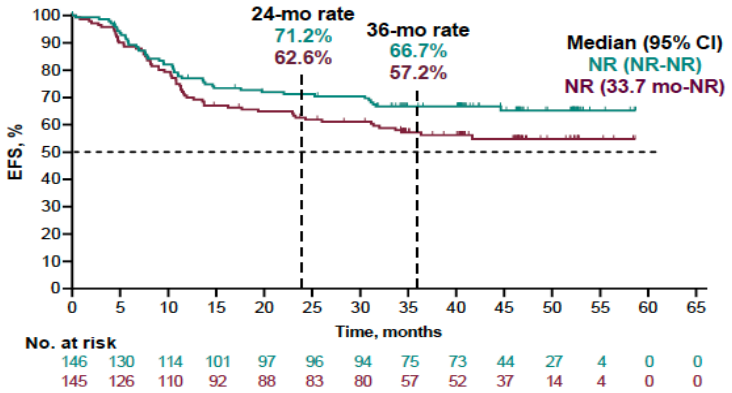
Machiels JP et al. ESMO 2022 Annual Meeting

Immune checkpoint inhibitor and (chemo)radiation

EFS and OS in Patients With PD-L1 CPS ≥20 (Post Hoc Analysis)

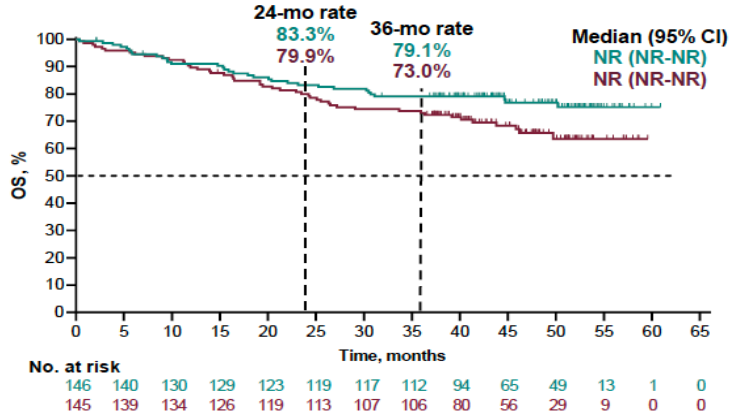
EFS

	Events	HR (95% CI)
Pembro + CRT	32.2%	0.73 (0.49-1.06)
Placebo + CRT	42.1%	



OS

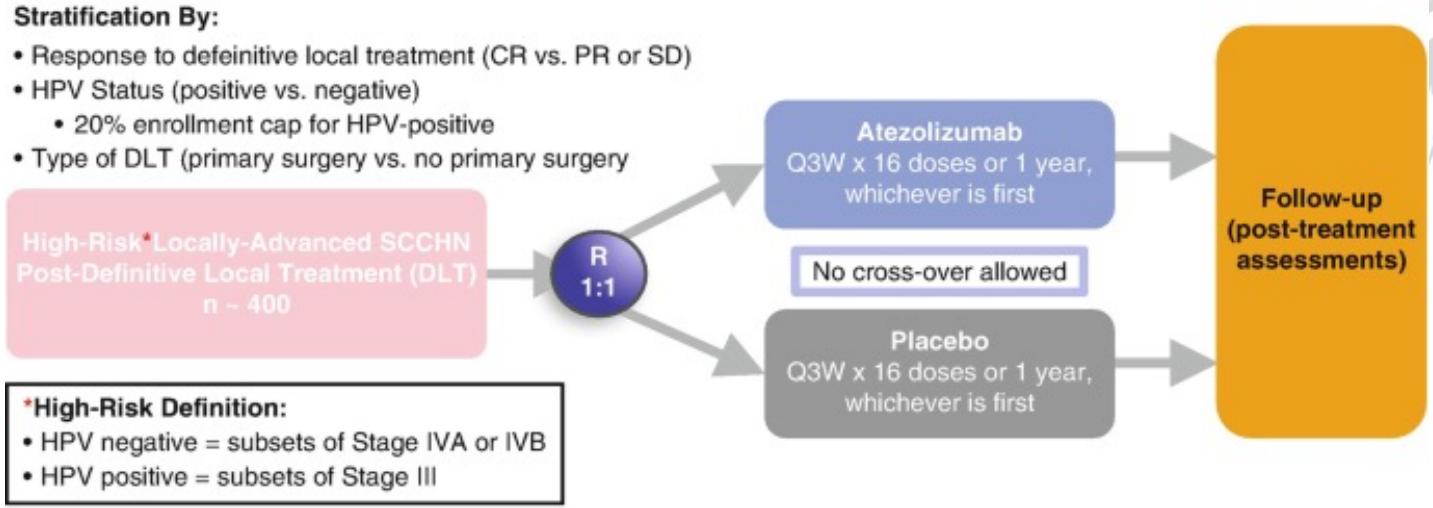
	Events	HR (95% CI)
Pembro + CRT	22.6%	0.67 (0.43-1.04)
Placebo + CRT	32.4%	



Data cutoff date: May 31, 2022.

Machiels JP et al. ESMO 2022 Annual Meeting

Imvoke-010 study (ongoing)



Key: CR – complete remission; DLT – definitive local treatment; HPV – human papillomavirus; PR – partial remission; Q3w – every 3 weeks; R – randomisation; RT - radiotherapy ; SD – stable disease

Harrington KJ et al. Crit Issues Head Neck Oncol 2021
https://doi.org/10.1007/978-3-030-63234-2_14

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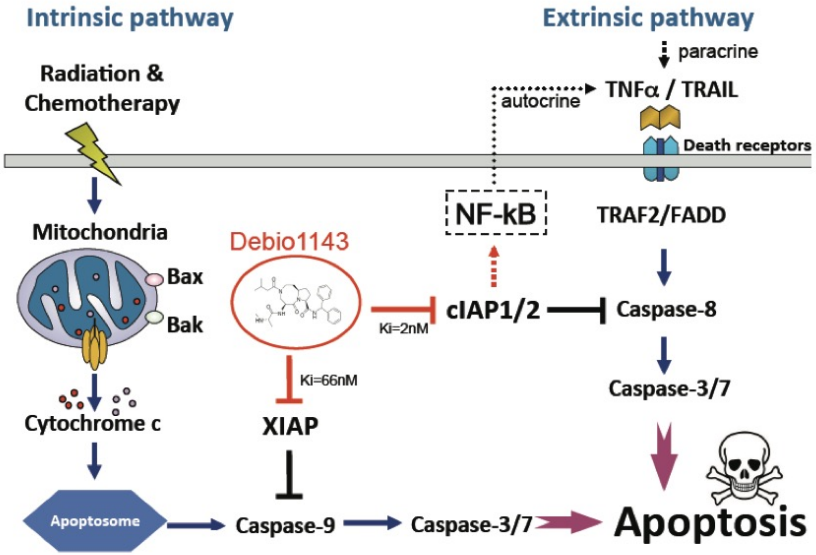
What about HPV negative HNSCC?

IAP inhibitor and chemoradiation – Xevinapant (Debio 1143)



- Members of the Inhibitor of Apoptosis Protein (IAP) family are key negative regulators of programmed cell death
- IAPs are overexpressed in SCCHN
- The oral monovalent SMAC mimetic, xevinapant, functions as an antagonist of multiple IAPs thus facilitating cell death

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IAP inhibitor and chemoradiation

VIRTUAL 2020 ESMO congress

STUDY DESIGN

Double-blind, placebo-controlled, Randomized Phase II

Part A

N=14

Dose escalation Phase I*

Primary endpoint

Definition of MTD/RP2D

RP2D

200mg QD

Part B

N=96 (ITT)

R

1:1

Xevinapant + CRT n=48

Placebo + CRT n=47

- **Xevinapant/Placebo** D1- D14 every 21 days for 3 cycles
- **CDDP** 100mg/m² every 21 days, for 3 cycles
- **IMRT** 2Gy 5d/week over 7 weeks (total dose 70Gy)

Stratified by

- N0-N1 vs N2-N3
- Primary tumor site (OPC vs non-OPC)
  - If OPC, by HPV/p16 status

Primary endpoint

- Locoregional control rate at 18 months after CRT (Δ>20% between arms with 0.8 power at 0.2 significance level)

Main secondary endpoints

- PFS
- Duration of LRC
- Overall survival

Main inclusion criteria:

- Previously untreated, unresectable stage III, IVA & IVB LA-SCCHN
- Oral cavity
- Hypopharynx
- Larynx
- Oropharynx-HPV/p16 both negative or positive

ClinicalTrials.gov Identifier: NCT02022098.
* Tao et al. ESTRO 2016

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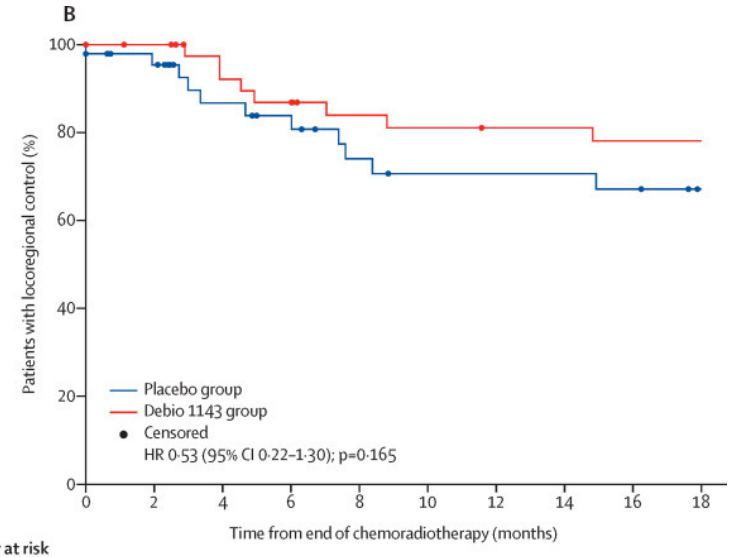
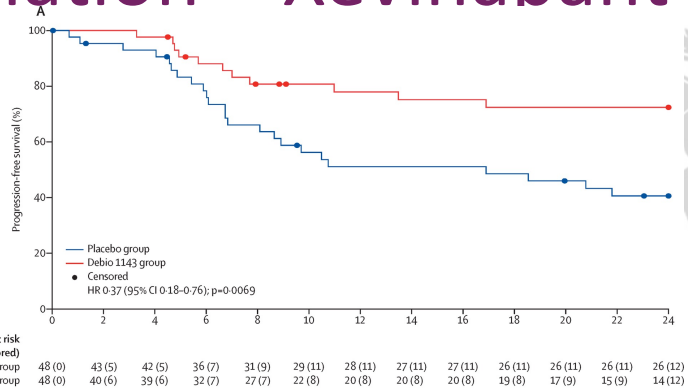
IAP inhibitor and chemoradiation – Xevinapant

Locoregional control



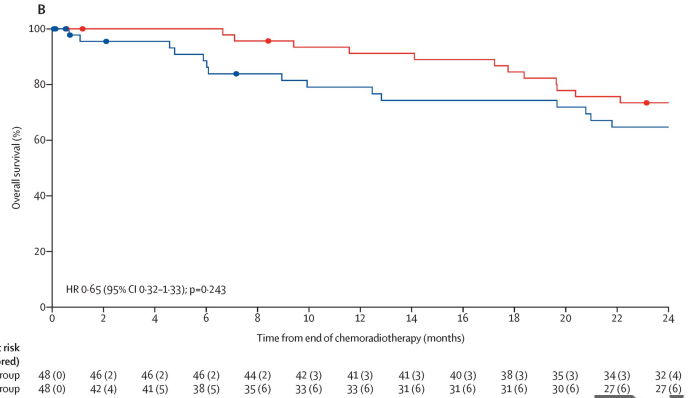
Number at risk (number censored)										
Debio 1143 group	48 (6)	41 (7)	35 (10)	33 (10)	29 (13)	28 (13)	27 (14)	27 (14)	26 (14)	26 (14)
Placebo group	48 (6)	38 (8)	30 (13)	27 (15)	22 (17)	20 (18)	20 (18)	20 (18)	19 (18)	16 (21)

PFS



Number at risk (number censored)												
Debio 1143 group	48 (0)	43 (5)	42 (5)	36 (7)	31 (9)	29 (11)	28 (11)	27 (11)	27 (11)	26 (11)	26 (11)	26 (12)
Placebo group	48 (0)	40 (6)	39 (6)	32 (7)	27 (7)	22 (8)	20 (8)	20 (8)	20 (8)	19 (8)	17 (9)	15 (9)	14 (12)

OS



Number at risk (number censored)												
Debio 1143 group	48 (0)	46 (2)	46 (2)	46 (2)	44 (2)	42 (3)	41 (3)	41 (3)	40 (3)	38 (3)	35 (3)	34 (3)	32 (4)
Placebo group	48 (0)	42 (4)	41 (5)	38 (5)	35 (6)	33 (6)	33 (6)	31 (6)	31 (6)	31 (6)	30 (6)	27 (6)	27 (6)

Sun XS et al. *Lancet Oncol* 2020;21:1173-1187

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Phase 3 study of Debio 1143 (xevinapant) in combination with platinum-based chemotherapy and radiation

HPV negative SCCHN
Stage III, IVa or IVb

R

Arm A
Cisplatin 100mg/m2 q3wk x 3
+
Debio 1143 orally on days 1-14 q3wk

Arm B
Cisplatin 100mg/m2 q3wk x 3
+
Placebo orally on days 1-14 q3wk

Completed enrollment as of 2/2023

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Summary – PULA SCCHN

- HPV positive SCCHN
  - Concurrent cetuximab is NOT an alternative to cisplatin
  - De-intensification of RT trial (NRG HN005) is on-going

- HPV negative SCCHN
  - Induction chemotherapy is NOT helpful
  - IAP inhibitor + chemoradiation looks promising, a randomized phase 3 study is ongoing

Summary – PULA SCCHN

- Immune checkpoint inhibitor + CRT
  - Concurrent avelumab or pembrolizumab with CRT did NOT improve PFS or OS (Javelin head and neck 100 and Keynote-412 came back negative)
  - IMvoke010 (adjuvant atezolizumab after completion of SOC CRT) study completed accrual

Case Study

- 76 year-old man with 40 PY smoking history presented with progressive weight loss and dysphagia

- Exam revealed a hypopharynx mass, biopsy showed moderately differentiated squamous cell carcinoma, PD-L1 negative

- PET/CT showed bilateral lung metastases

Question 2

You think the patient is too frail for platinum-based chemotherapy. What would be the best next step?

1. Cetuximab + Nivolumab
2. Pembrolizumab alone
3. Cabozantinib + Pembrolizumab
4. Cetuximab + Pembrolizumab
5. Any of the above

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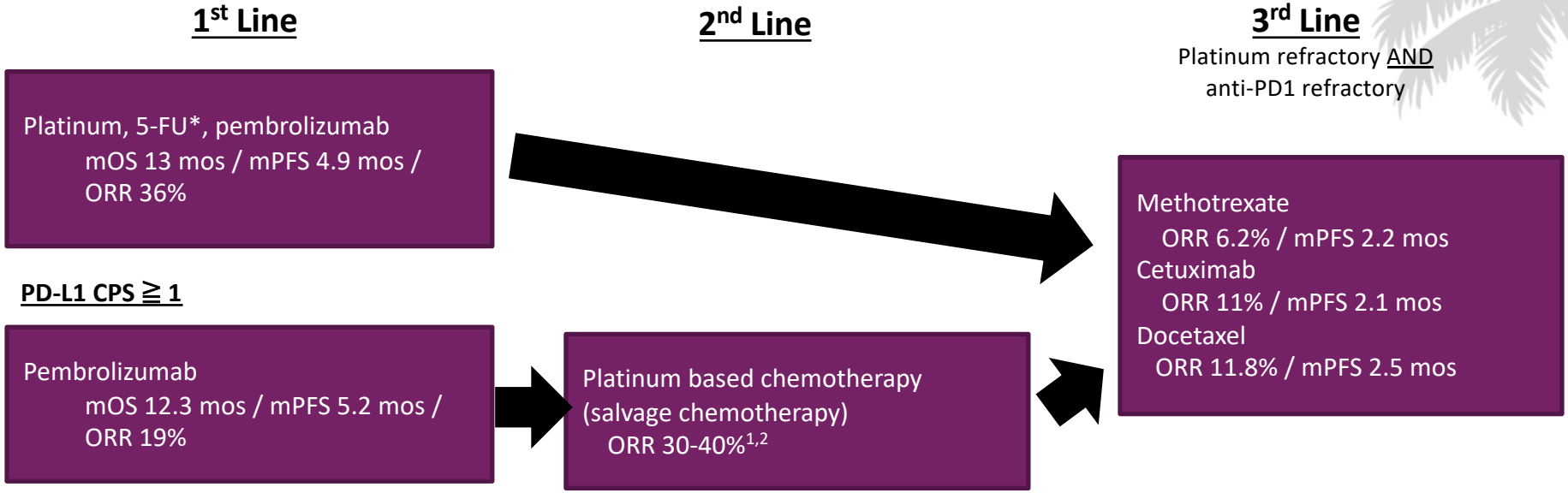
Definition of lines of therapy in R/M HNSCC



* In practice, many clinicians use taxanes (paclitaxel or docetaxel) in place of 5-FU

1. Saleh K et al. Eur J Cancer 2019;121:123-129
2. Fushimi C et al. Anticancer Res 2020;40:5277-83

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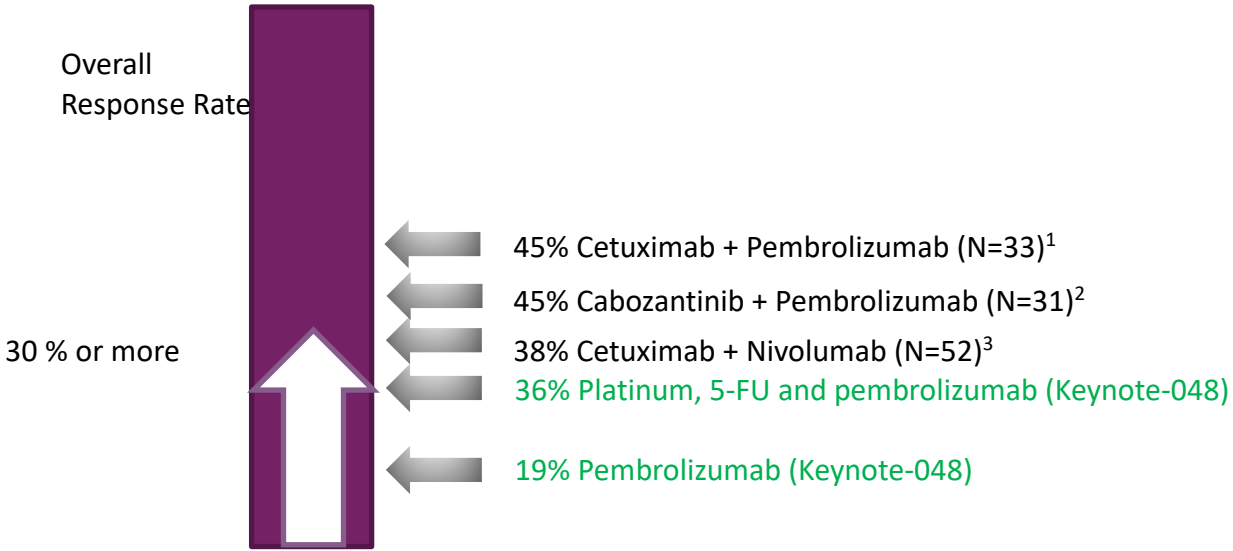
What makes an exciting study?

1st line R/M HNSCC



1. Sacco A et al. Lancet Oncol 2021
2. Saba NF et al. ASCO 2022 annual meeting
3. Chung CH et al. ASCO 2021 annual meeting

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Immune checkpoint inhibitor and cetuximab

- Pembrolizumab and cetuximab
  - 33 patients with IO naïve, platinum-refractory or ineligible RM-SCCHN patients
  - Single arm, open-label, phase 2 study
  - Results
    - 1 CR and 14 PR out of 33 patients (ORR 45%)
    - Median duration of response = 14.9 months
    - Median overall survival = 18.4 months

Sscco AG et al. *Lancet Oncol* 2021; 22:883-892

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Immune checkpoint inhibitor and targeted therapy

- Pembrolizumab and lenvatinib (20mg daily)
  - 22 patients with measurable, confirmed SCCHN
  - Single arm, open-label, phase 2 study
  - Results
    - 1 CR and 8 PR out of 22 patients (ORR 36.4%)
    - Median DOR 13.3 months, 1 year PFS 41.9%

Taylor MH NF et al. ASCO 2018 Annual Meeting

- Pembrolizumab and cabozantinib (40mg daily)
  - 31 evaluable patients with IO naïve RM-SCCHN patients
  - Single arm, open-label, phase 2 study
  - Results
    - 0 CR and 14 PR out of 31 patients (ORR 45%)
    - 1-year OS : 67.7% and 1 year PFS : 51.8%

Saba NF et al. ASCO 2022 Annual Meeting

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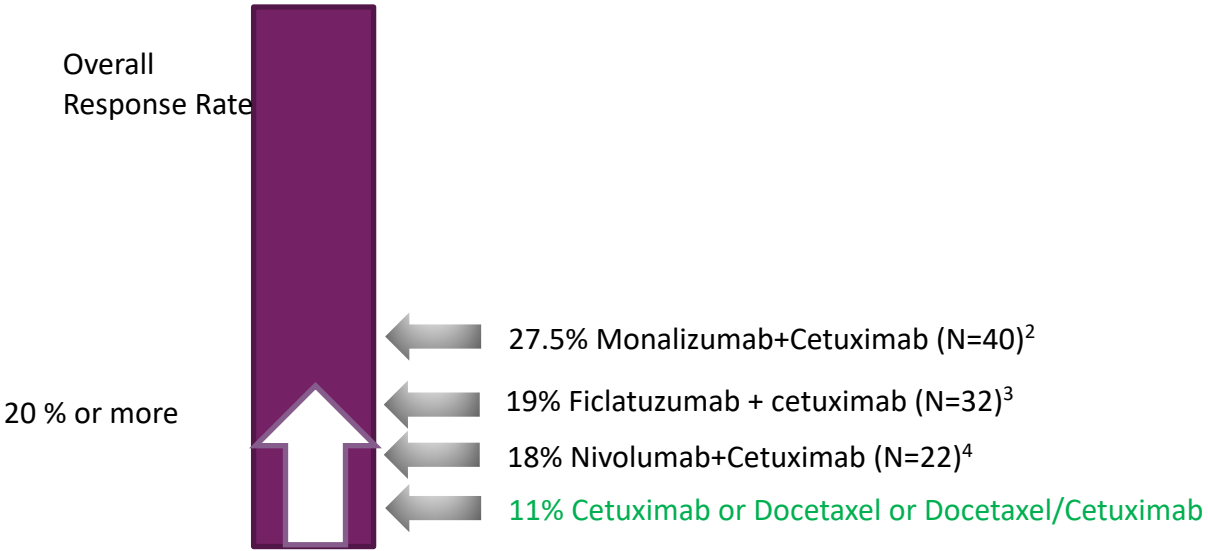
What makes an exciting study?

2nd/3rd line R/M HNSCC



1. Cohen R et al. ASCO 2020 annual meeting
2. Bauman JL et al. ASCO 2021 annual meeting
3. Chung CH et al. ASCO 2020 annual meeting

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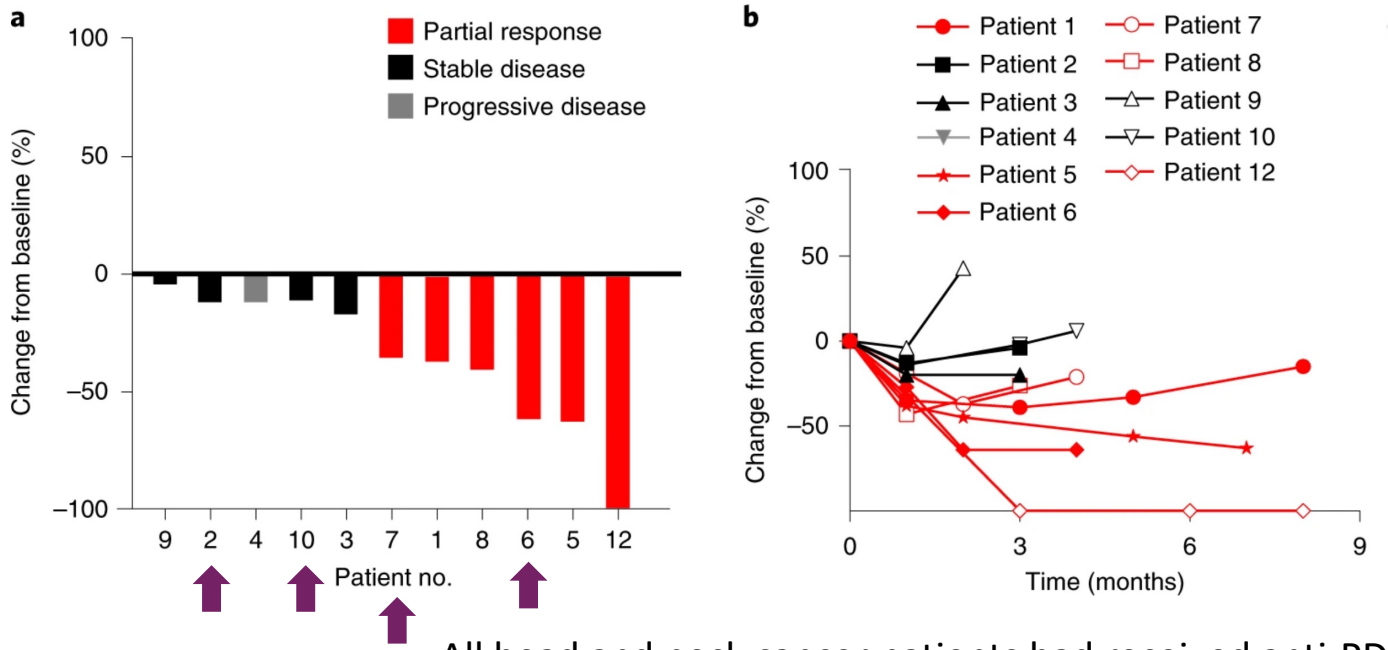
Cell therapy – HPV targeting T cells

E7 TCR-T cells in HPV16 associated cancer patients



All head and neck cancer patients had received anti-PD1

Nagarsheth NB et al. Nat Med 2021;27:419-425

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Summary – RM SCCHN

- Immune checkpoint inhibitor + cetuximab or VEGFR TKI
  - May become an alternative for 1st line treatment for IO naïve patients
  - Seems to have some activity in IO refractory patients

- Emerging options with cell therapy and other targeted agents

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Case Study

- 52 year-old lady, originally from Hong Kong, presented with 2 months of nose bleed

- Found to have a nasopharynx mass, biopsy revealed undifferentiated carcinoma, EBER positive

- PET/CT showed bilateral neck mass, as well as bone metastasis

Question 3

What would be the best treatment option?

1. Cisplatin + 5-FU
2. Gemcitabine + Cisplatin
3. Gemcitabine + Cisplatin + Pembrolizumab
4. Pembrolizumab

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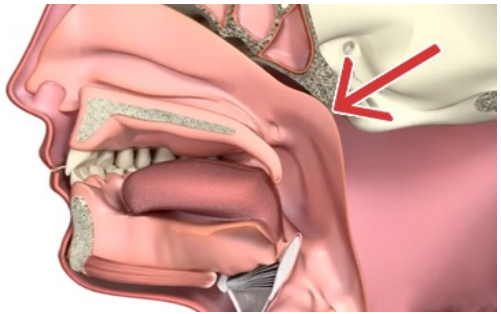
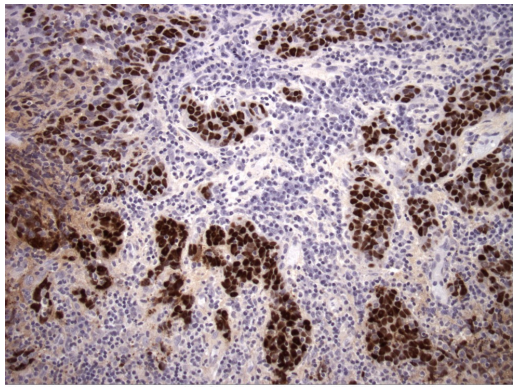
Nasopharyngeal carcinoma





Nasopharyngeal carcinoma (NPC) with positivity for EBER tumor cells

- Affects 130,000 patients worldwide
- Most cases occur in South China, Southeastern Asia and North Africa
- EBV related cancer with undifferentiated histology

How we treat recurrent/metastatic NPC

1st Line

Gemcitabine/Cisplatin

Zhang L et al. *Lancet* 2016;388:1883-92

2nd Line

Include platinum refractory patients (progression within 4-6 months after last platinum)

Pembrolizumab*
ORR 26% (PD-L1+)
Nivolumab
ORR 20%

Pembrolizumab: Keynote 028
Hsu C et al. *J Clin Oncol* 2017;35:4050-4056

Nivolumab: Checkmate 358
DeLoard JP et al. *ASCO 2017 Annual Meeting*

3rd Line

Platinum refractory AND anti-PD1 refractory

Paclitaxel
Docetaxel
5-FU
Xeloda

* A phase 3 trial (Keynote 122) failed to meet the primary endpoint of OS improvement over SOC

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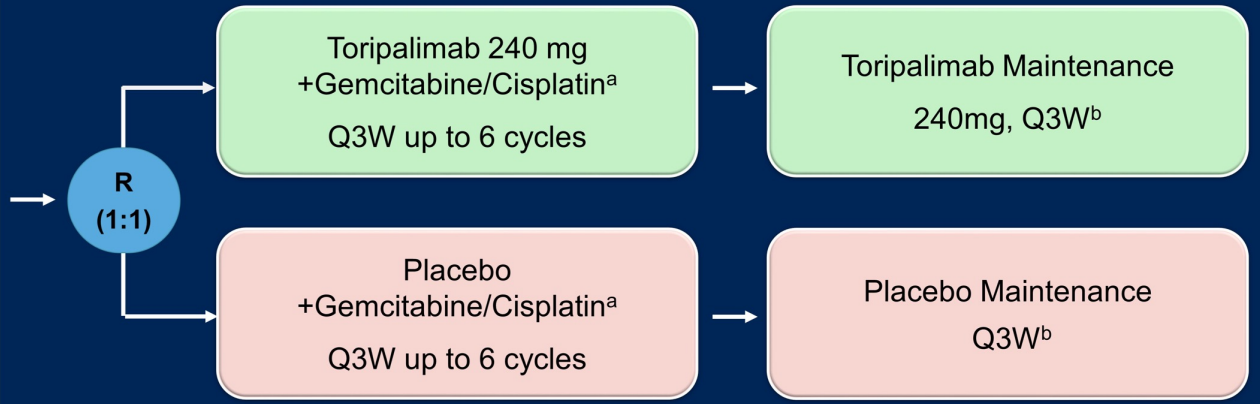
JUPITER-02: Study Design
(ClinicalTrials.gov identifier: NCT03581786)

Key Eligibility Criteria

- Primary metastatic NPC or recurrent NPC after curative-intent therapy
- Treatment naïve for recurrent or metastatic (R/M) disease
- ECOG 0-1
- 18-75 yrs
- Measurable disease per RECIST v1.1

Stratification Factors

- Recurrent vs Primary metastatic
- ECOG PS 0 vs 1

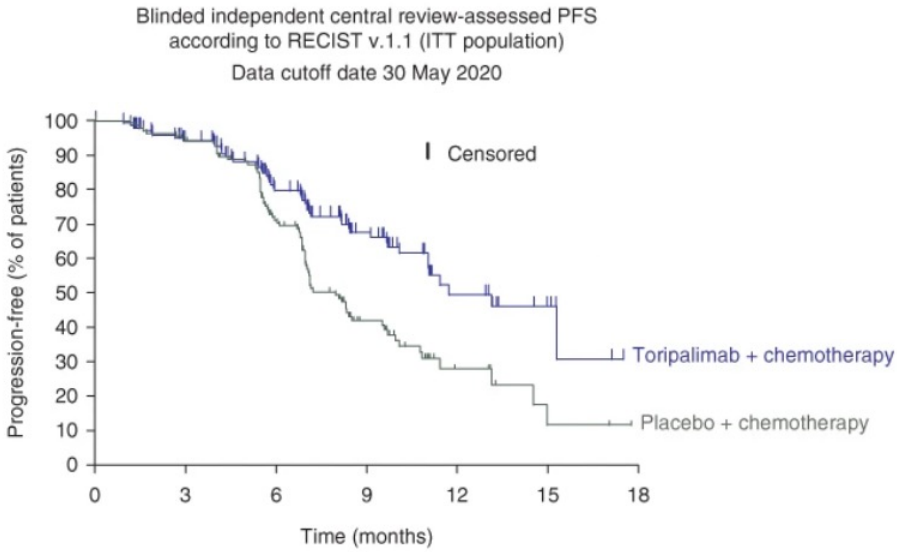


- Primary endpoint: PFS by a blinded independent review committee (BIRC) per RECIST v1.1
- Secondary endpoints: PFS by the Investigator, ORR, DoR, DCR, OS, and PFS & OS 1-year and 2-year rates

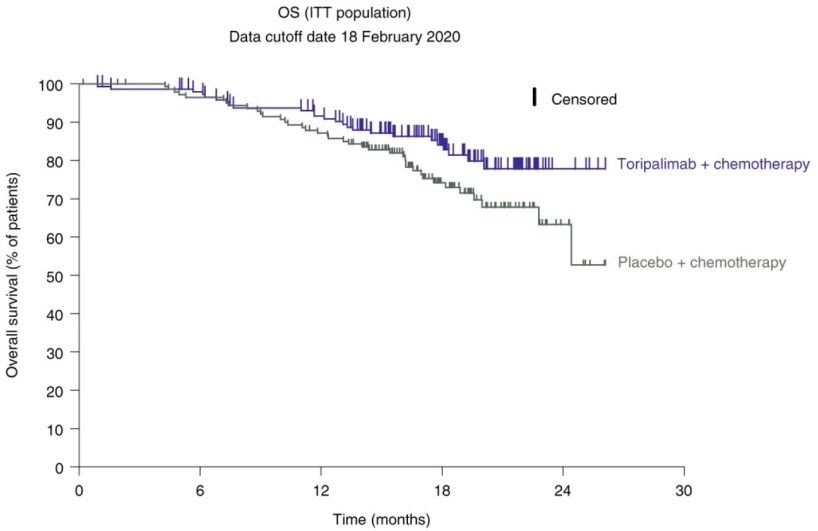
[a] Gemcitabine 1000mg/m^2 D1,8 +Cisplatin 80mg/m^2 D1
[b] Until progressive disease, excessive toxicity, withdrawal of consent or investigator's judgement or a maximum treatment of 2 years.

Immune checkpoint inhibitor in NPC

Toripalimab and chemotherapy prolongs PFS and OS in recurrent/metastatic NPC



mPFS : 11.7 mo vs 8.0 mo
HR 0.52 (95%CI 0.36-0.74)



2-year OS : 77.8% vs 63.3 mo
HR 0.60 (95%CI 0.364-0.997)

Mai HQ et al. Nat Med 2021;27:1536-1543

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Summary – RM NPC

- Gemcitabine/Cisplatin + anti-PD1 should be considered as the standard for 1st line treatment of R/M-NPC

	GC + Toripalimab[1]	GC + camrelizumab[2]	GC + tisleizumab	Gem/Cis[3]	Cis/5-FU[3]
ORR	77.4%	88.1%		64%	42%
DoR	10.0 mo	9.9 mo			
mPFS	11.7 mo	10.8 mo	9.6 mo	7.0 mo	5.6 mo
mOS	NR	NR	NR	29.1 mo	20.9 mo
1-year OS	91.6%				

1. Xu RH et al. ASCO 2021 Annual Meeting
2. Zhang L et al. ASCO 2021 Annual Meeting
3. Zhang L et al. Lancet 2016;388:1883-1892

Summary

- PULA HNSCC
  - ICIs failed to improve outcome when added to concurrent chemoXRT
  - Cisplatin remains to be the SOC for concurrent chemoradiation
- RM HNSCC
  - 1st line immune checkpoint inhibitor (+/- chemotherapy) remains to be SOC
  - Options for different combination (to be explored further)
- RM NPC
  - 1st line immune checkpoint inhibitor + chemotherapy is the new SOC

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Questions?

hyunseok.kang@ucsf.edu