Novel Advances in Head & Neck and Thyroid Cancers

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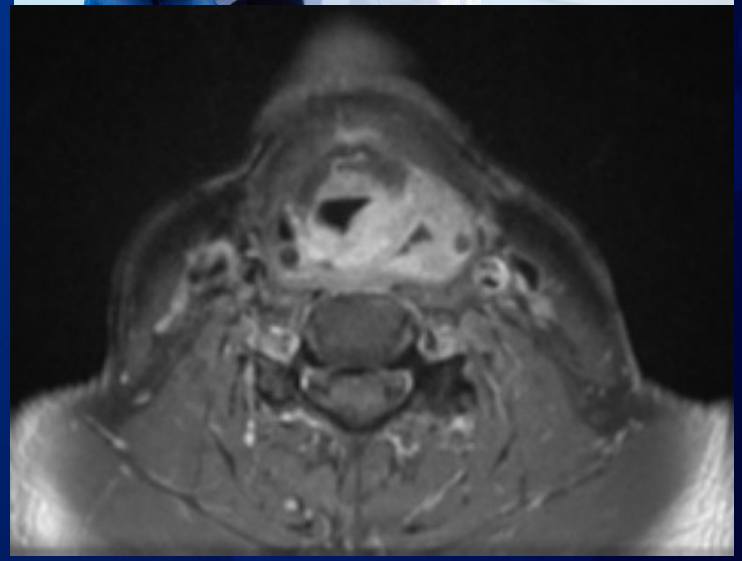
Associate Professor of Medicine, University of Central Florida

Dr. R

- He is a married 55 yo community physician. He is married and has a 12-year-old daughter
- Developed hoarseness and diagnosed with a hypopharyngeal SCC
- He read the 10-year survival rate for hypopharyngeal tumors is 10%
- Referred for definitive therapy…

Very anxious about his new diagnosis and inquiring about immunotherapy



Head and Neck Cancer Treatment approach

Current Landscape…

Upfront - Curative intent

50-65% Long term DFS

- ✓ Surgical Resection + PORT ± Ctx
- ✓ ChemoRT

Salvage - Curative intent?

10-25% DFS

- ✓ Sx or ChemoRT

R/M Disease - Palliative intent

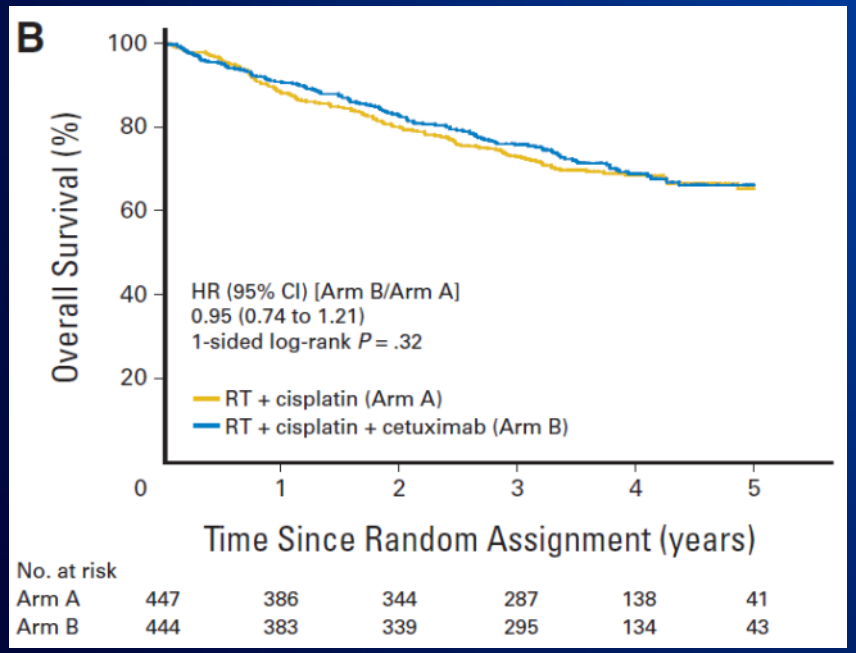
OS 13 mo

- ➢ Pembrolizumab for pts PD-L1 CPS >1%
- ➢ Chemo-Pembrolizumab (regardless of PD-L1)

Locally Advanced SCCHN

Cisplatin-based chemoRT CONTINUES to be our standard

RTOG 0522 → adding Cetuximab to Cisplatin-RT failed to improve OS



Can we do better by adding a Checkpoint inhibitor?

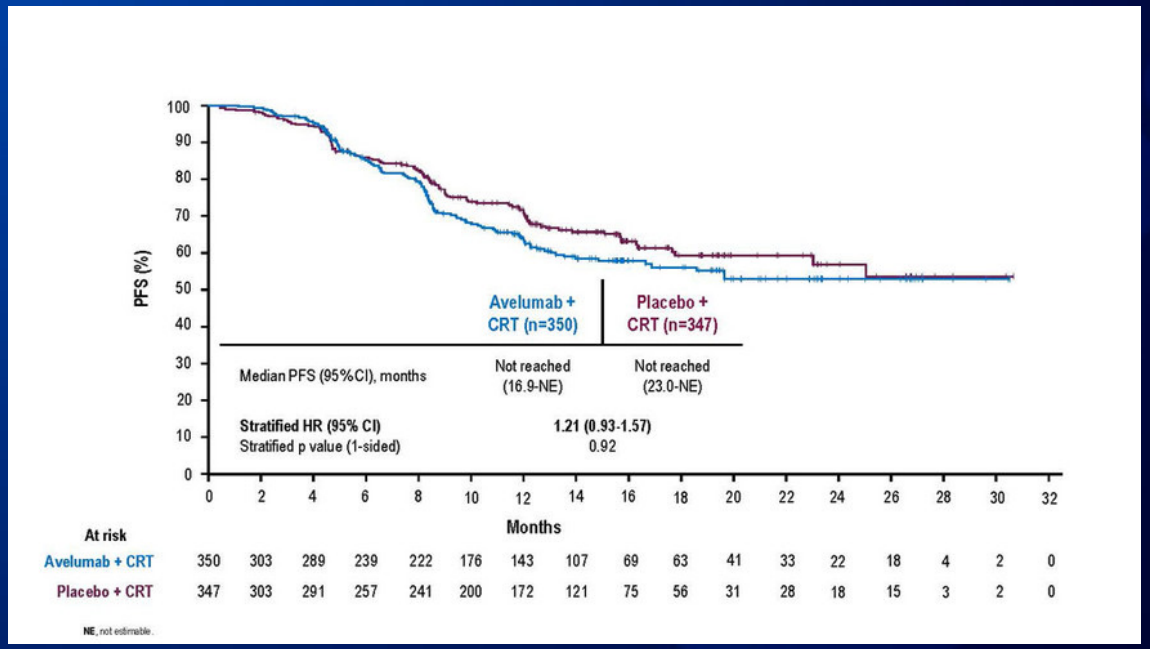
Can we do better by adding a checkpoint inhibitor?

Javelin HN100

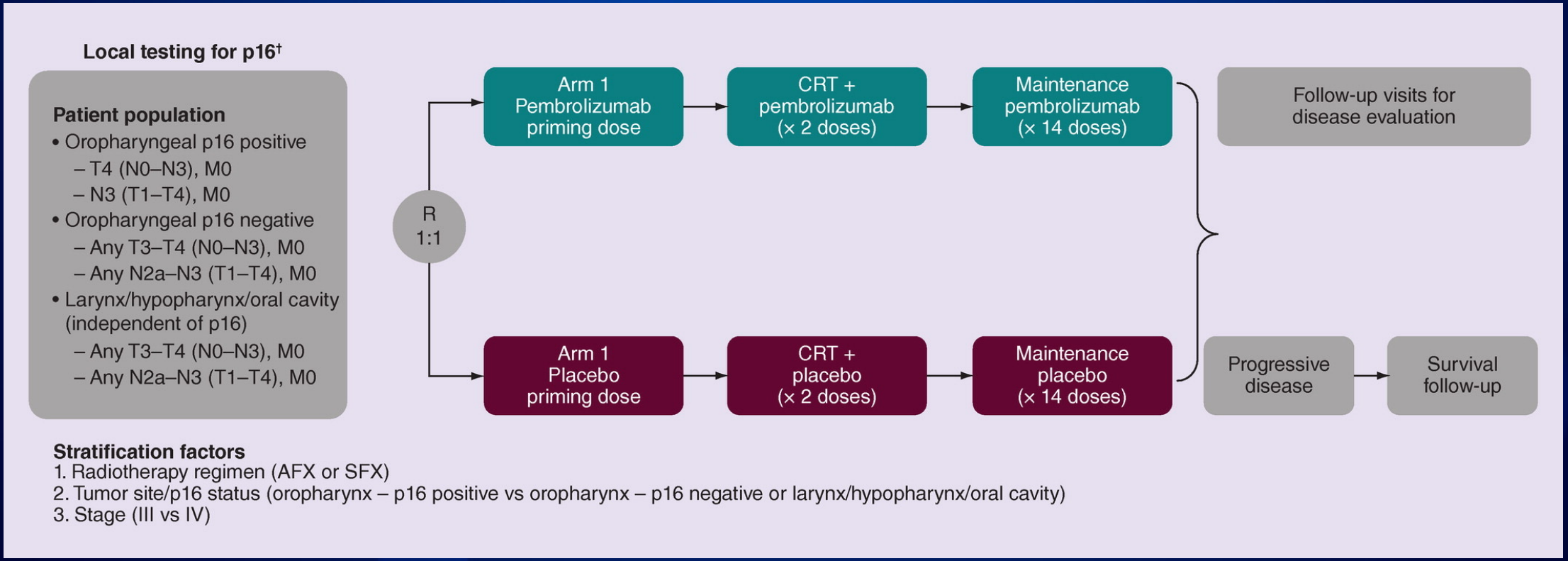
- Cisplatin-based definitive ChemoRT with or without Avelumab
- Median PFS was NOT improved by the addition of Avelumab when compared to placebo

  (*trend in favor of the placebo group*)

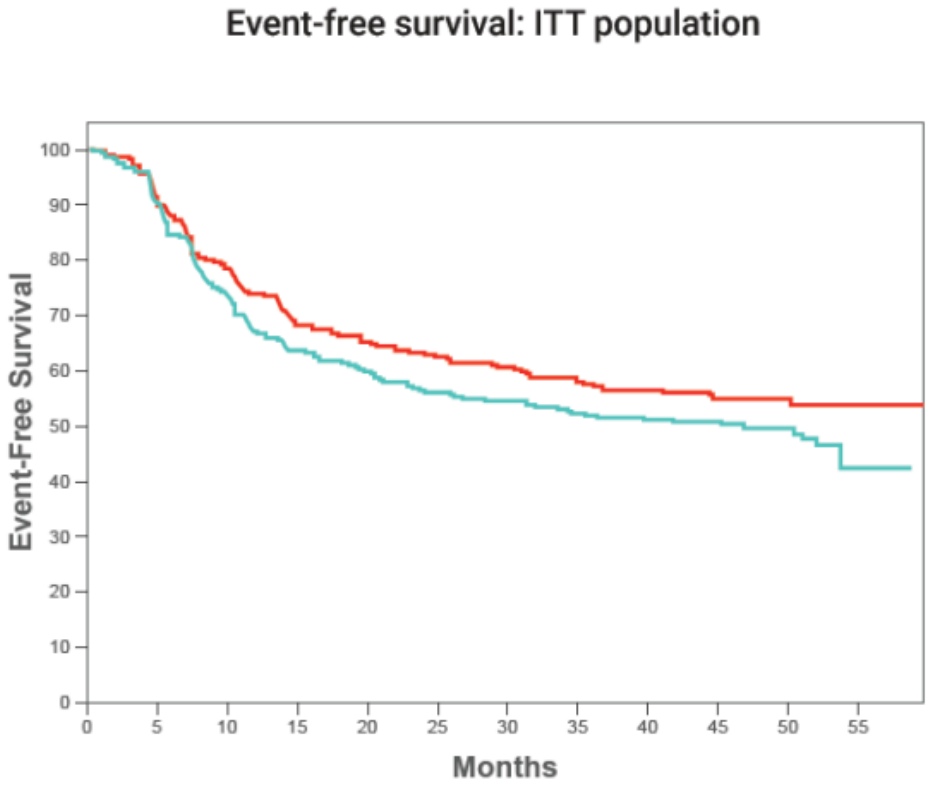
Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial



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) *JP Machiels et al. ESMO 2022 Presidential Symposium II*



Phase III KEYNOTE-412 study



	HR (95% CI)	P-value
Pembrolizumab + Chemoradiation therapy vs Placebo + Chemoradiation therapy	0.83 (0.68 - 1.03)	0.0429

Pembro + CRT → Favorable trend toward improved EFS vs placebo + CRT

… but not statistically significance

Checkpoint inhibitors in the curative setting

- In pts with NSCLC → PACIFIC trial demonstrated that adding Durvalumab consolidation after CRT has an OS benefit (not concurrently)
- Negative results for **Javelin100** and **Keynote-412**
  - Trend towards better outcome in PD-L1 positive pts

  → *T cell dysfunction/suppression during concurrent therapy?*

- "*Throwing the kitchen sink*" to our High-Risk pts doesn't work!

- How about consolidation tx in PD-L1 positive pts??

Dr. R

- He is a married 55 yo community physician.

- He received induction chemotherapy with PCC (weekly Carboplatin-Paclitaxel-Cetuximab) achieving a CR

- Received Definitive RT + Cisplatin

- PD-L1 CPS was 10… “Doc, what else can we do?”

- Received Pembrolizumab (off label) for 12 months as maintenance

Remains on remission after 3 years

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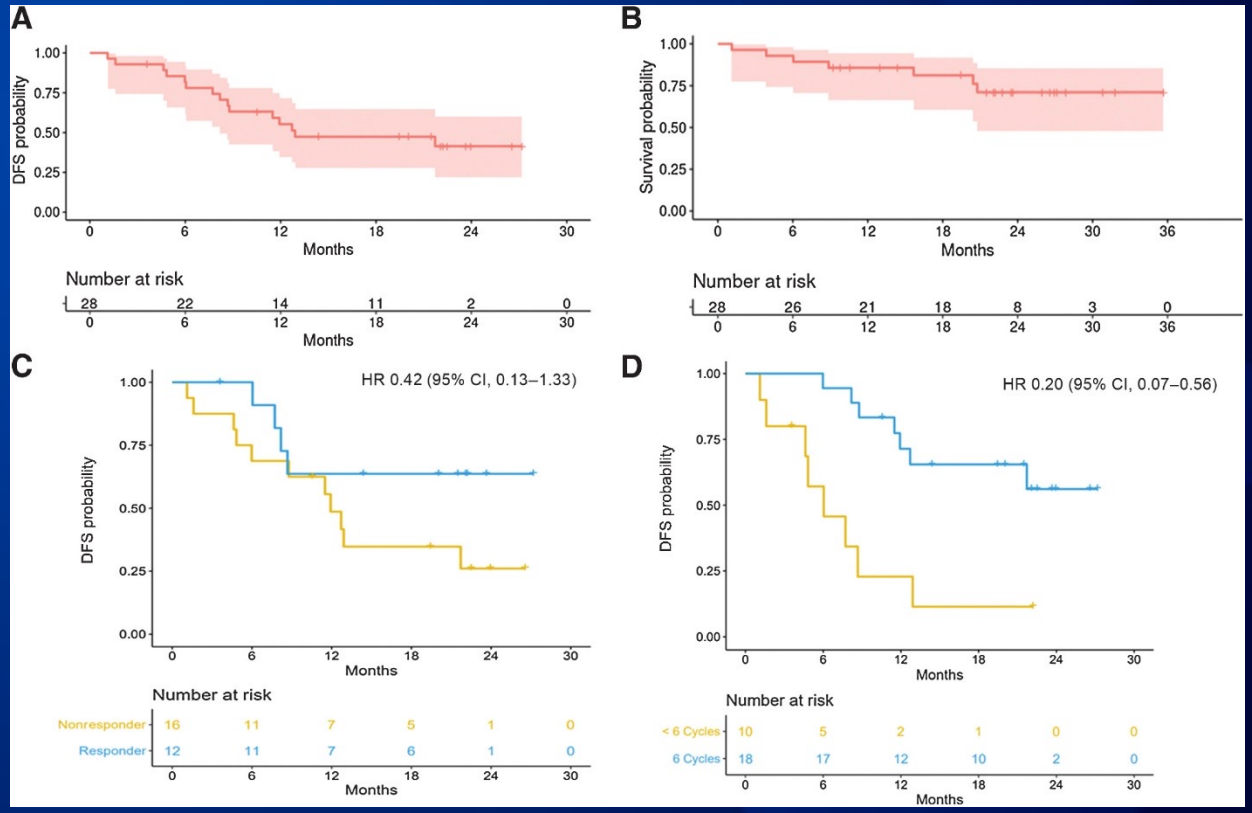
Neoadjuvant and Adjuvant Nivolumab and Lirilumab in Patients with Recurrent, Resectable Squamous Cell Carcinoma of the Head and Neck *Hanna et al Clin Cancer Res (2022) 28 (3): 468–478*

- Lirilumab is a mAb against KIR2DL
- 28 patients, 96% previously radiated
- Nivo + Liri one cycle before, and 6 cycles after Sx
- 43% pathologic response rate

- Two-year DFS and OS of 64% and 80% among pathologic responders



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KEYNOTE-048: Pembrolizumab ± Chemotherapy

Key eligibility criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification factors

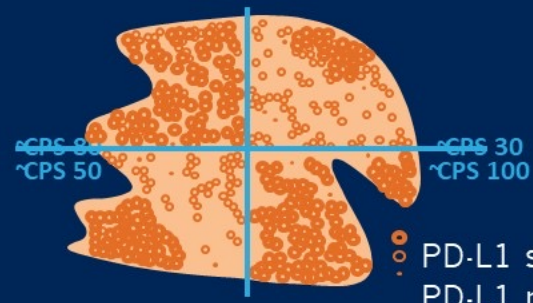
- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R 1:1:1

Pembrolizumab
Pembrolizumab 200 mg Q3W for up to 35 cycles

Pembrolizumab + chemotherapy
Pembrolizumab 200 mg + carboplatin AUC 5 OR cisplatin mg/m² + 5-FU 1,000 mg/m²/d for 4 days for 6 cycles (each 3 wk)
→ Pembrolizumab 200 mg Q3W for up to 35 cycles total

EXTREME
Cetuximab 250 mg/m² Q1W[c] + carboplatin AUC 5 OR cisplatin 100 mg/m² + 5-FU 1,000 mg/m²/d for 4 days for 6 cycles (each 3 wk)
→ Cetuximab 250 mg/m² QW



PD-L1 staining tumor
PD-L1 non-staining tumor
PD-L1 staining mononuclear inflammatory cell

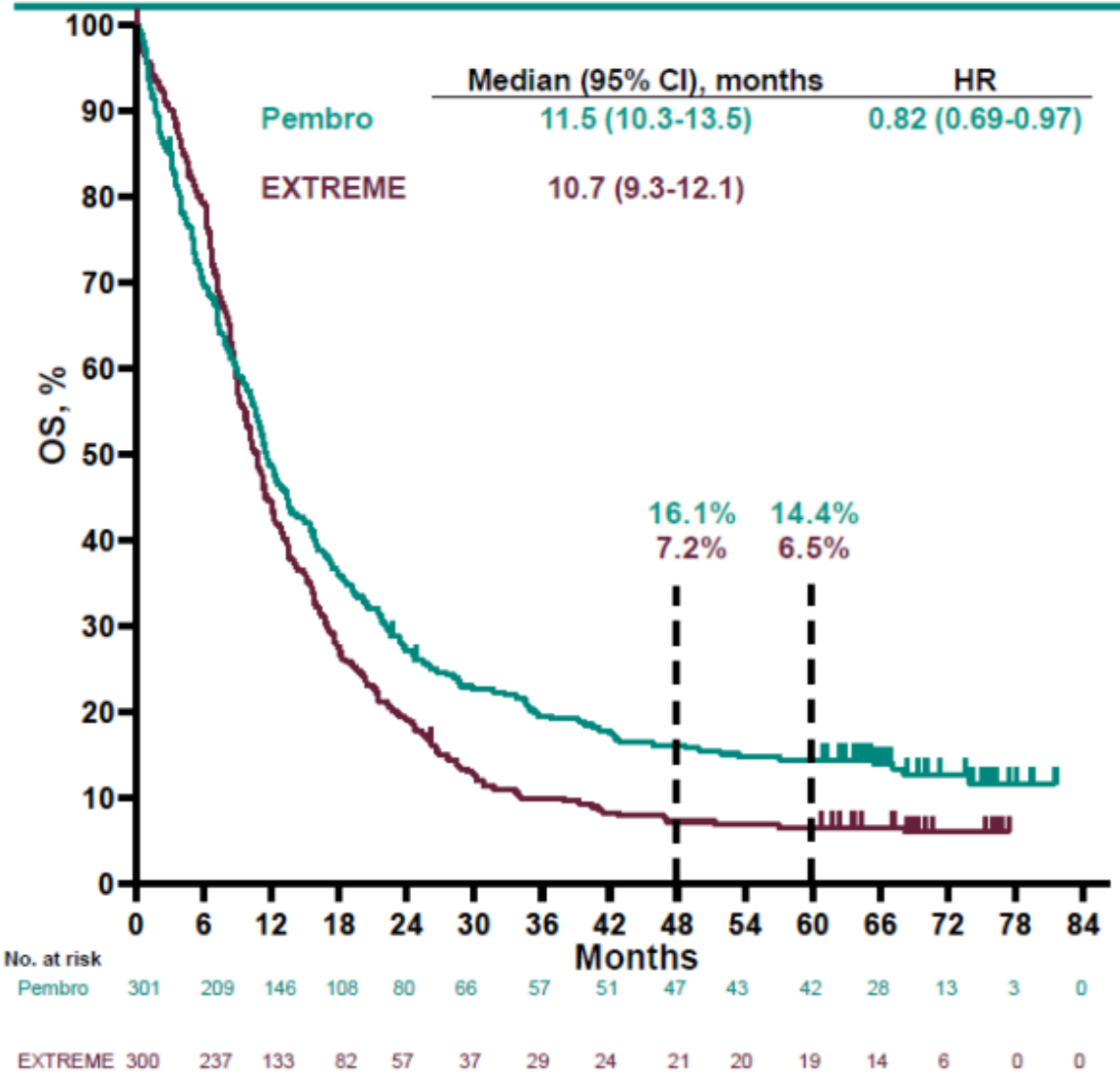
Burtness et al, *Lancet* 2019

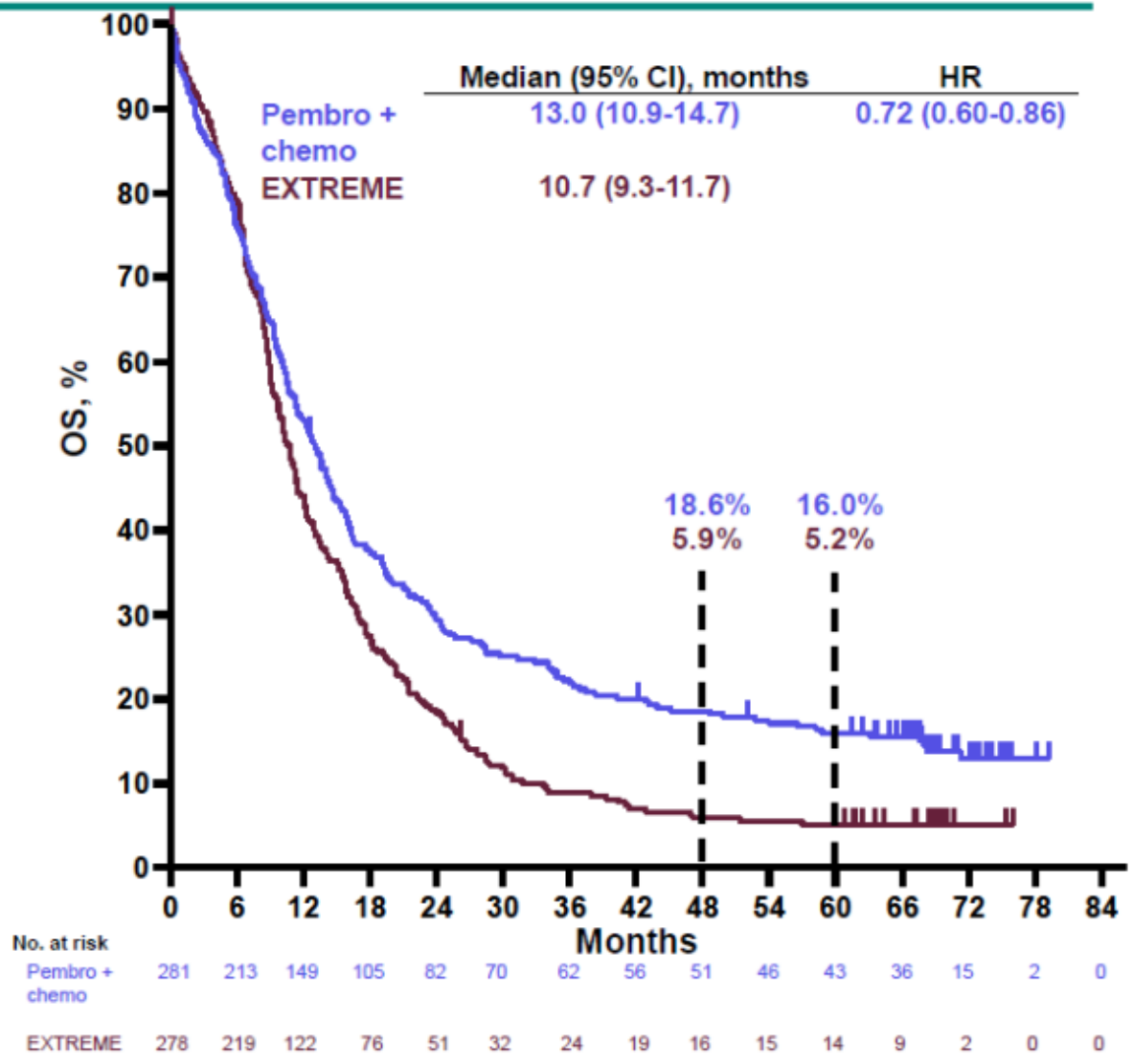
Pembrolizumab With or Without Chemotherapy For First-Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: 5-year Results from KEYNOTE-048

Makoto Tahara[1]; Richard Greil[2]; Danny Rischin[3]; Kevin J. Harrington[4]; Barbara Burtness[5]; Gilberto de Castro[6]; Amanda Psyrri[7]; Irene Brana[8]; Prakash Neupane[9]; Åse Bratland[10]; Thorsten Fuereder[11]; Brett G.M. Hughes[12]; Ricard Mesia[13]; Nuttapong Ngamphaiboon[14]; Tamara Rordorf[15]; Wan Zamaniah Wan Ishak[16]; Jianxin Lin[17]; Burak Gumuscu[17]; Nati Lerman[17]; Denis Soulières[18]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Paracelsus Medical University Salzburg Cancer Research Institute and Cancer Cluster, Salzburg, Austria; [3]Peter MacCallum Cancer Institute University of Melbourne, Melbourne, VIC, Australia; [4]The Institute of Cancer Research, London, United Kingdom; [5]Yale School of Medicine, New Haven, CT, USA; [6]Instituto do Cancer de Sao Paulo—ICESP, São Paulo, Brazil; [7]National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [9]University of Kansas Medical Center, Kansas City, MO, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna/General Hospital Vienna, Vienna, Austria; [12]Royal Brisbane & Women's Hospital, and University of Queensland, Herston, QLD, Australia; [13]Catalan Institute of Oncology, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Ratchatewi, Bangkok, Thailand, [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Wilayah Persekutuan, Malaysia; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]CHUM, Montréal, Quebec, Canada

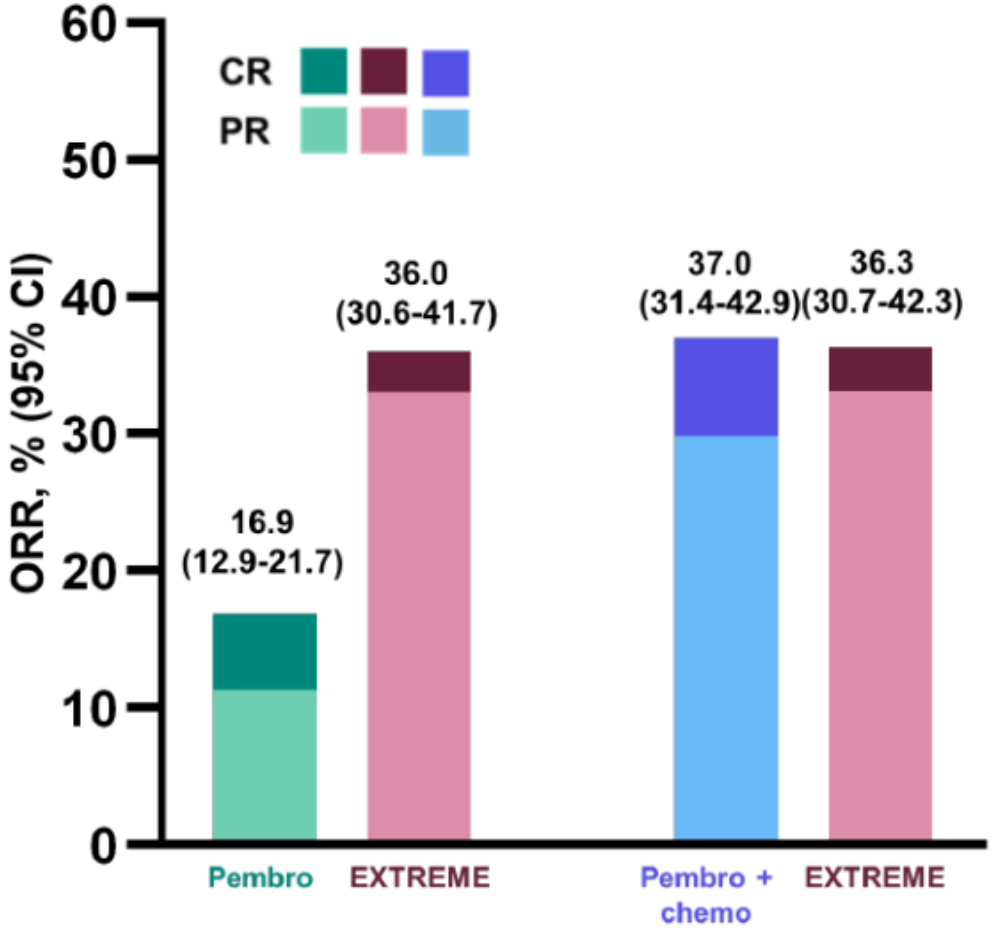
Overall Survival in the ITT Population





Data cutoff date February 21, 2022.

Objective Response Rate and Duration of Response per RECIST v1.1 by BICR in the ITT Population



	Pembro vs EXTREME		Pembro + chemo vs EXTREME	
	Pembro n = 301	EXTREME n = 300	Pembro + chemo n = 281	EXTREME n = 278
DOR, median (range), mo	22.6 (1.5+ to 75.5+)	4.5 (1.2+ to 73.9+)	6.7 (1.6+ to 73.8+)	4.3 (1.2+ to 66.5+)

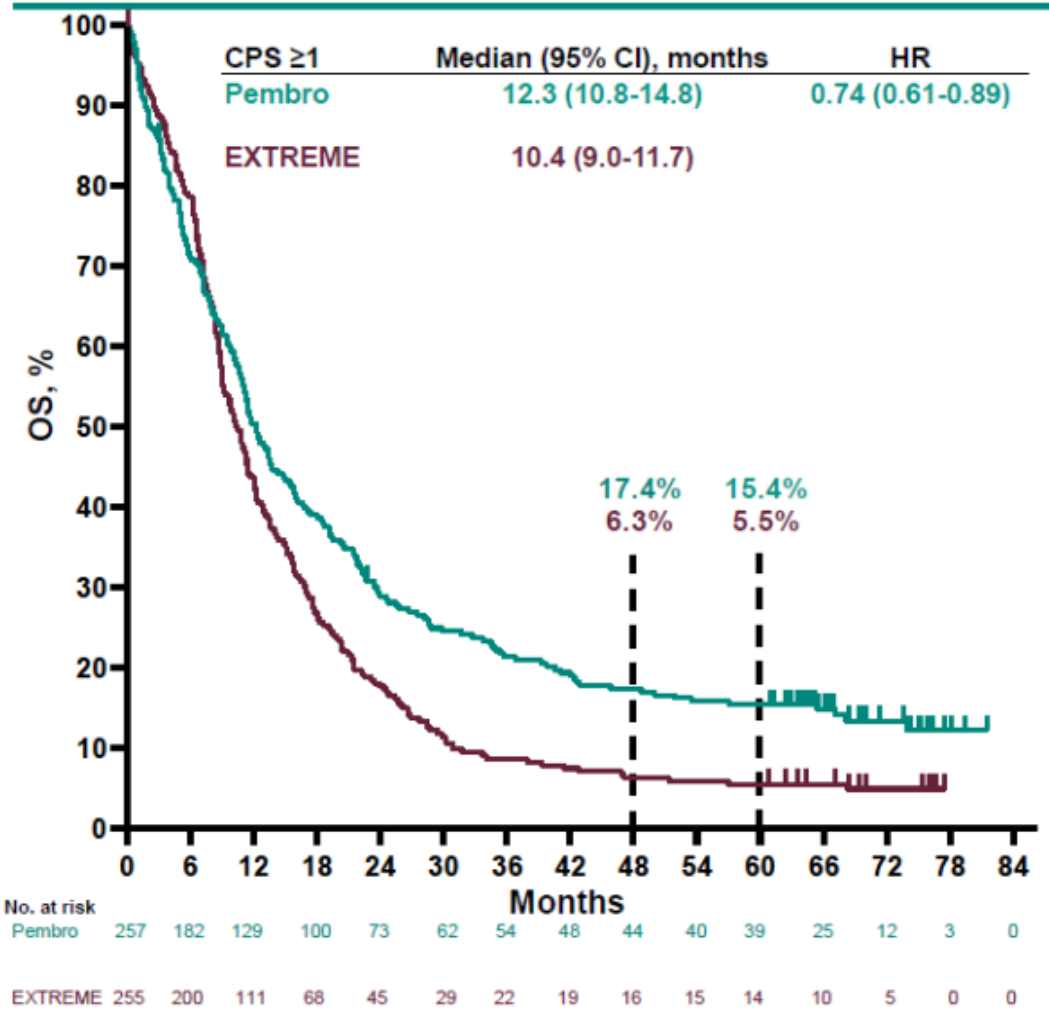
Data cutoff date February 21, 2022.

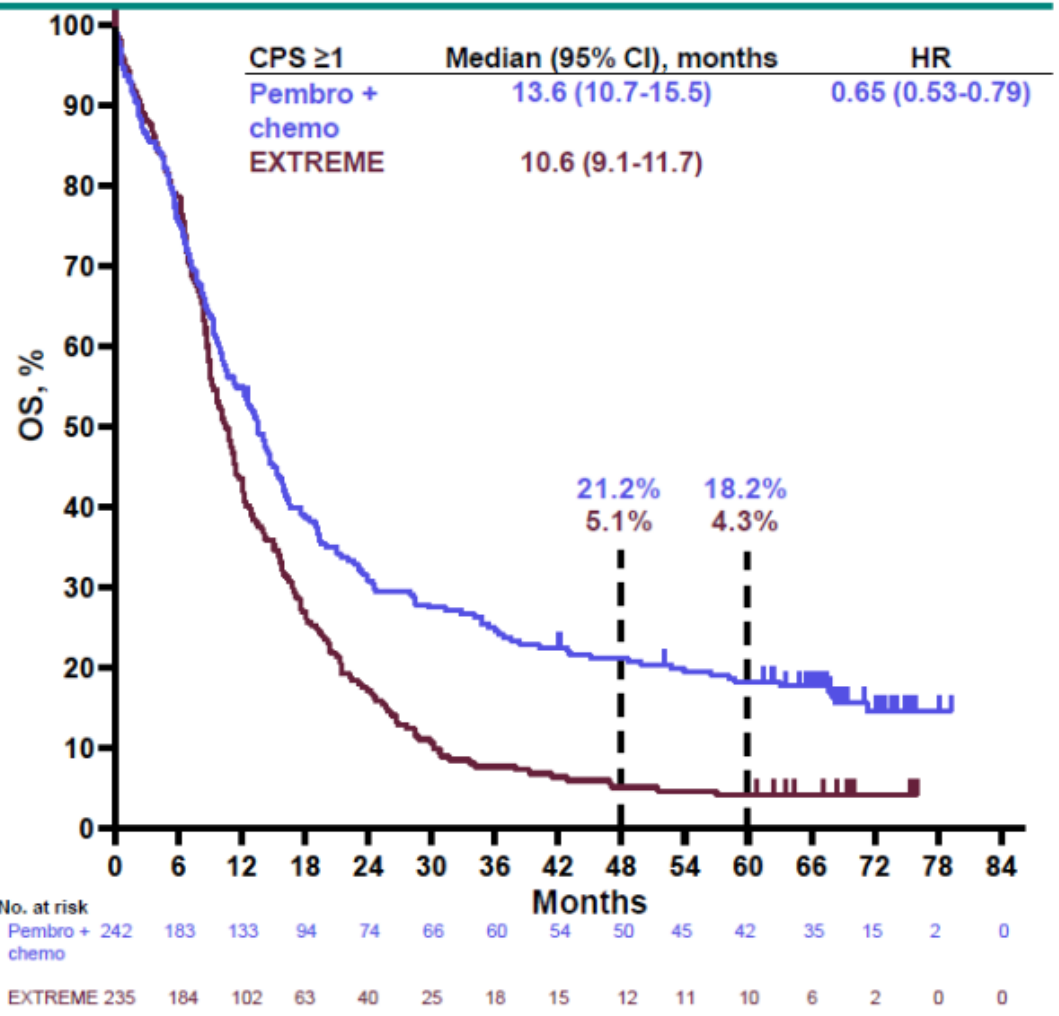
Objective Response Rate and Duration of Response by PD-L1 Status

	Pembro vs EXTREME		Pembro + chemo vs EXTREME	
	Pembro	**EXTREME**	**Pembro + chemo**	**EXTREME**
CPS ≥1, n	257	255	242	235
ORR, % (95% CI)	19.1 (14.5-24.4)	34.9 (29.1-41.1)	38.0 (31.9-44.5)	35.7 (29.6-42.2)
DOR, median, (range) mo	23.4 (1.5+ to 75.5+)	4.5 (1.2+ to 73.9+)	6.7 (1.6+ to 73.8+)	4.3 (1.2+ to 66.5+)
CPS ≥20, n	133	122	126	110
ORR, % (95% CI)	23.3 (16.4-31.4)	36.1 (27.6-45.3)	45.2 (36.4-54.3)	38.2 (29.1-47.9)
DOR, median, (range) mo	23.4 (2.7 to 75.5+)	4.3 (1.2+ to 38.2+)	7.1 (2.1+ to 73.8+)	4.2 (1.2+ to 38.2+)

Data cutoff date: February 21, 2022.

Overall Survival in the CPS ≥1 Population





Data cutoff date February 21, 2022.

Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for R/M SCCHN: KEYNOTE-048

- Median duration of response (DOR) in pts with PD-L1 CPS > 1
  - Pembrolizumab 23.4 months vs 4.5 mo EXTREME

- Median (DOR) in pts with PD-L1 CPS > 1
  - Pembro+Chemo 6·7 months vs 4.3 months in EXTREME

Check PD-L1 on your pts… if CPS > 1 and low disease burden/Symptoms
Use single agent Pembrolizumab

But most are not fans of Carbo-5FU
KEYNOTE-B10 study

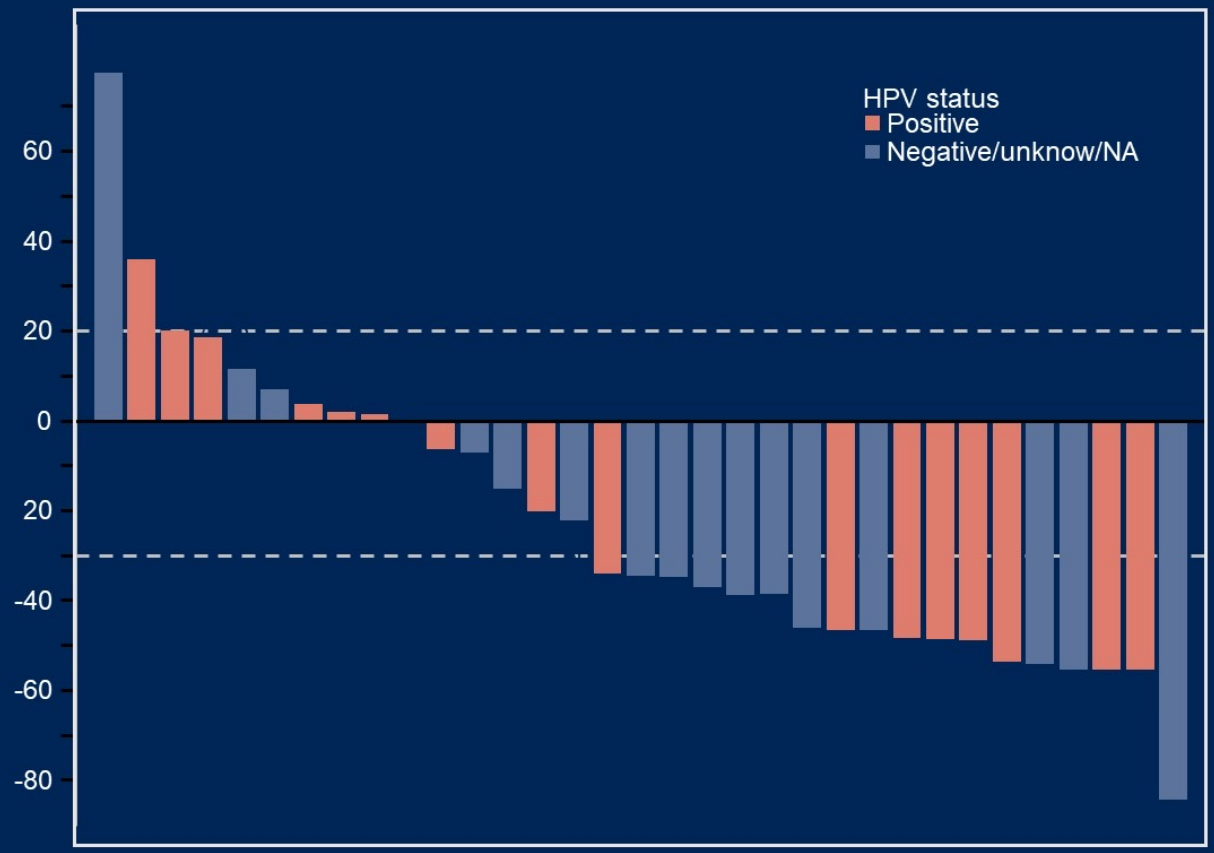
Pembrolizumab (pembro) + carboplatin (carbo) + paclitaxel (pacli) as first-line (1L) therapy in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). *M.R. Dzienis et al. ESMO 2022*

- *100 pts enrolled, 41 still on Tx at data cuttoff*
- *Confirmed ORR was 43% (95% CI, 32-54).*
- *Combination similar efficacy than Keynote048, known safety*

A phase II trial of pembrolizumab and cabozantinib in patients (pts) with recurrent metastatic head and neck squamous cell carcinoma (RMHNSCC)

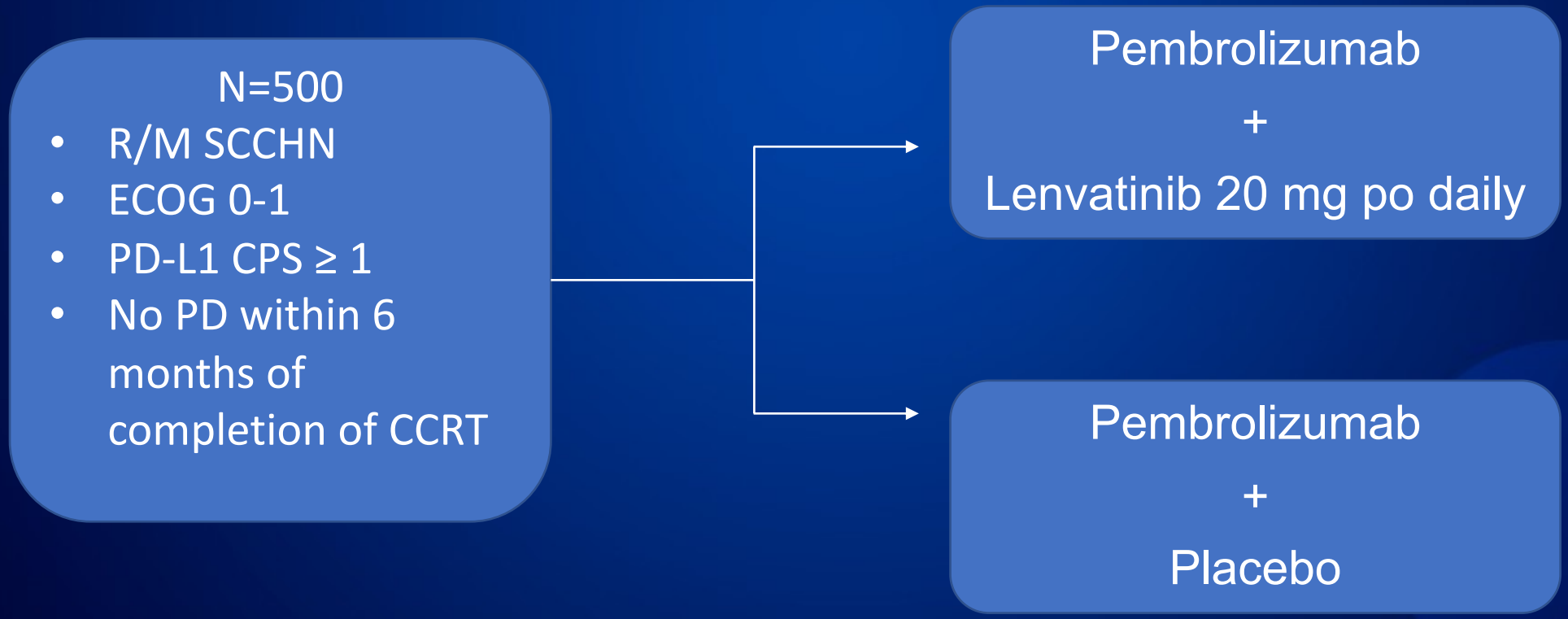
Saba et al ASCO 2022

	N=33 n (%)
ORR	18 (54)
CR	0 (0)
PR	18(54)
SD	12(36)
PD	3(9)
Clinical benefit	30(91)



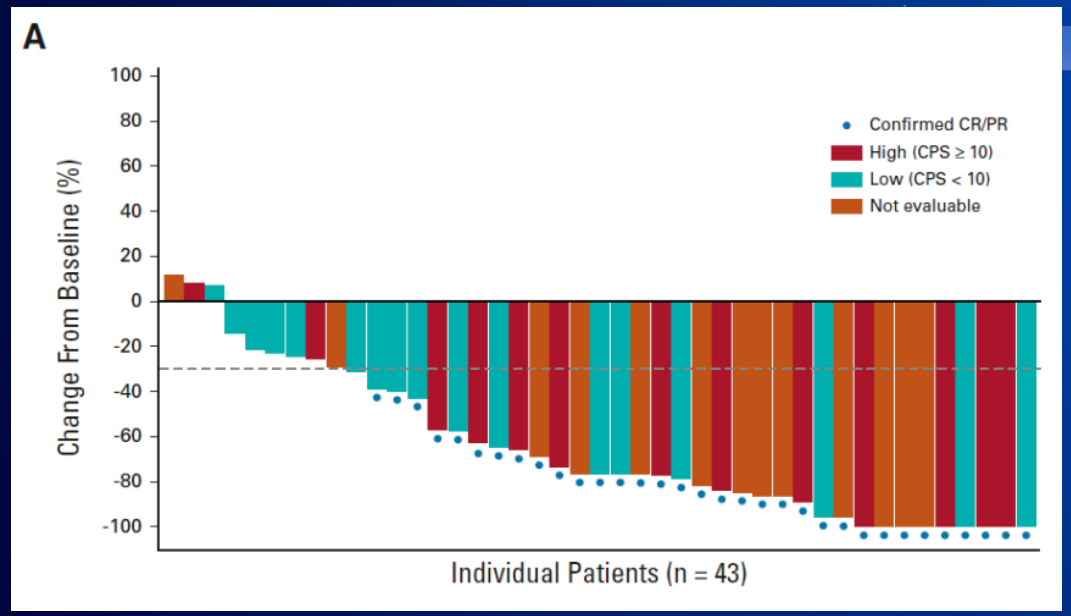
CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Phase III LEAP-010 study: first-line pembrolizumab with or without lenvatinib in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).



What about ADCs?

Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer



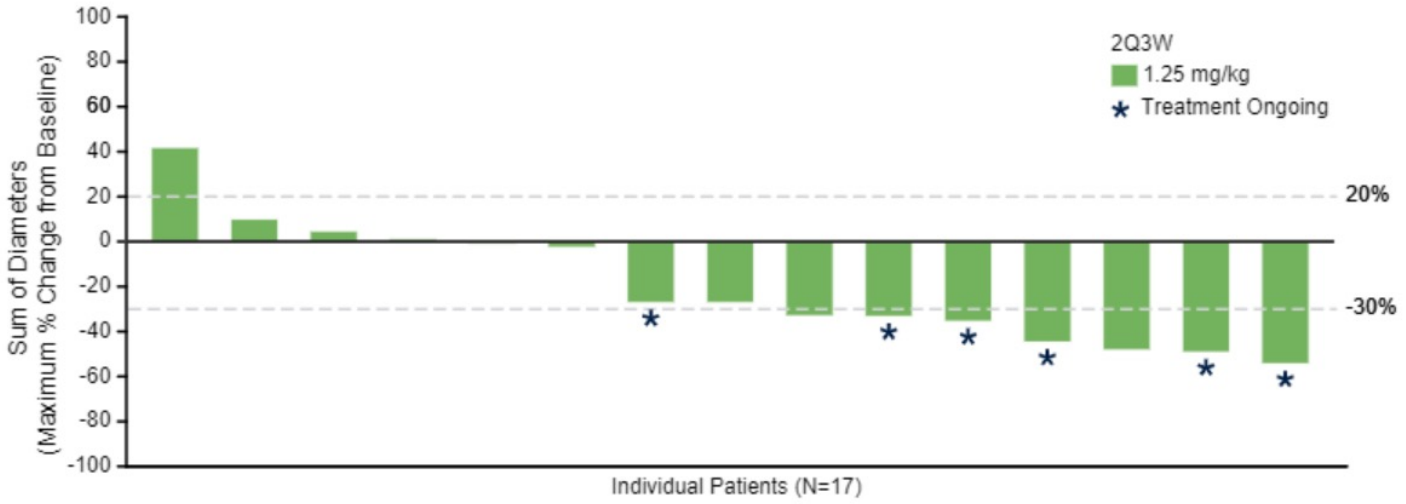
- Impressive responses of Enfortumab plus pembro in BladderCa
- Can we develop a similar approach for R/M SCCHN?

SITC 2022: *A first-in-human trial of an integrin beta-6 targeted antibody-drug conjugate (ADC), SGN-B6A, in patients with advanced solid tumors: Interim results*

HNSCC, 2Q3W (Dose Expansion)[a]

Median 3 (range: 1–6) lines of prior therapy

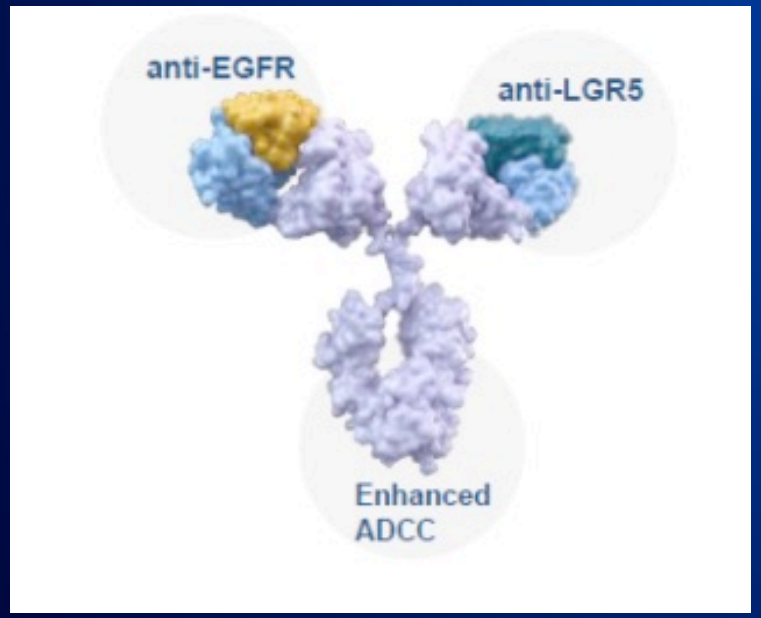
Best Percentage Change in Target Lesion SoD from Baseline per RECIST v1.1



	2Q3W, HNSCC 1.25 mg/kg (N=17)
cORR, n (%)	**5 (29.4)**
95% CI	(10.3, 56.0)
Best Overall Response (Overall, n [%])	
cCR	0
cPR	5 (29.4)
SD	5 (29.4)
PD	5 (29.4)
NE	1 (5.9)
NA	1 (5.9)

- To date, the HNSCC safety profile is consistent with the 2Q3W escalation cohort
- 17 of 18 (94%) treated patients experienced TEAEs and 9 of 18 (50%) treated patients experienced Grade ≥3 TEAEs

CT012 - Clinical activity of MCLA-158 (petosemtamab), an IgG1 bispecific antibody targeting EGFR and LGR5, in advanced head and neck squamous cell cancer (HNSCC)
Cohen EE et al, AACR 2023



- Petosemtamab is a human IgG1 bispecific antibody targeting EGFR and LGR5
- Presented data of the expanded HNSCC cohort treated at the RP2D.
- 49 HNSCC, 42 pts evaluable for efficacy:
  ORR 35.7% (15/42; 1CR, 2 uPR, 12cPR)
- DCR was 71.4%. Median DOR was 6.0 months (95%CI=3.3-not calculable).
- AEs regardless of causality (all grades/G3-4) were rash (33%/0%), hypotension (26%/6%), dyspnea (26%/4%), nausea (26%/1%), dermatitis acneiform (24%/1%),
- IRRs (composite term) were reported in 74%/21% of pts, mostly at the first infusion, and all resolved.

Head and Neck Cancer in 2023

- Cisplatin based Chemo-RT continues to be standard in curative setting

  Adding CPI's has not proven to be beneficial…YET
- Novel CPI combinations in salvage setting might improve outcome
- Pembro-Chemo is standard first line therapy for R/M SCCHN, or Pembrolizumab for pts with PD-L1 CPS > 1
- Watch for TKI+CPI combos in first line (LEAP trial)
- ADCs and Bispecifics are coming for pts with SCCHN…

Whats new for Thyroid Cancer?

Recurrent Thyroid Cancer
Genomic characterization

Altered Gene	PTC	FTC	ATC	MTC
RET	-	-	-	80%
RET/PTC	6.3%	-	-	-
BRAF	59%	-	20%	-
HRAS	4%	18%	3%	
NTRK1,3	0.8%	-	-	-
B-catenin		-	-	-
PAX8:PPARγ		35%	-	-
TP53	1.2%	1.0%	65%	-
other	20%	20%	25%	19%

PTC: Papillary Thyroid Cancer
FTC: Follicular Thyroid Cancer
ATC: Anaplastic Thyroid Cancer
MTC: Medullary Thyroid Cancer

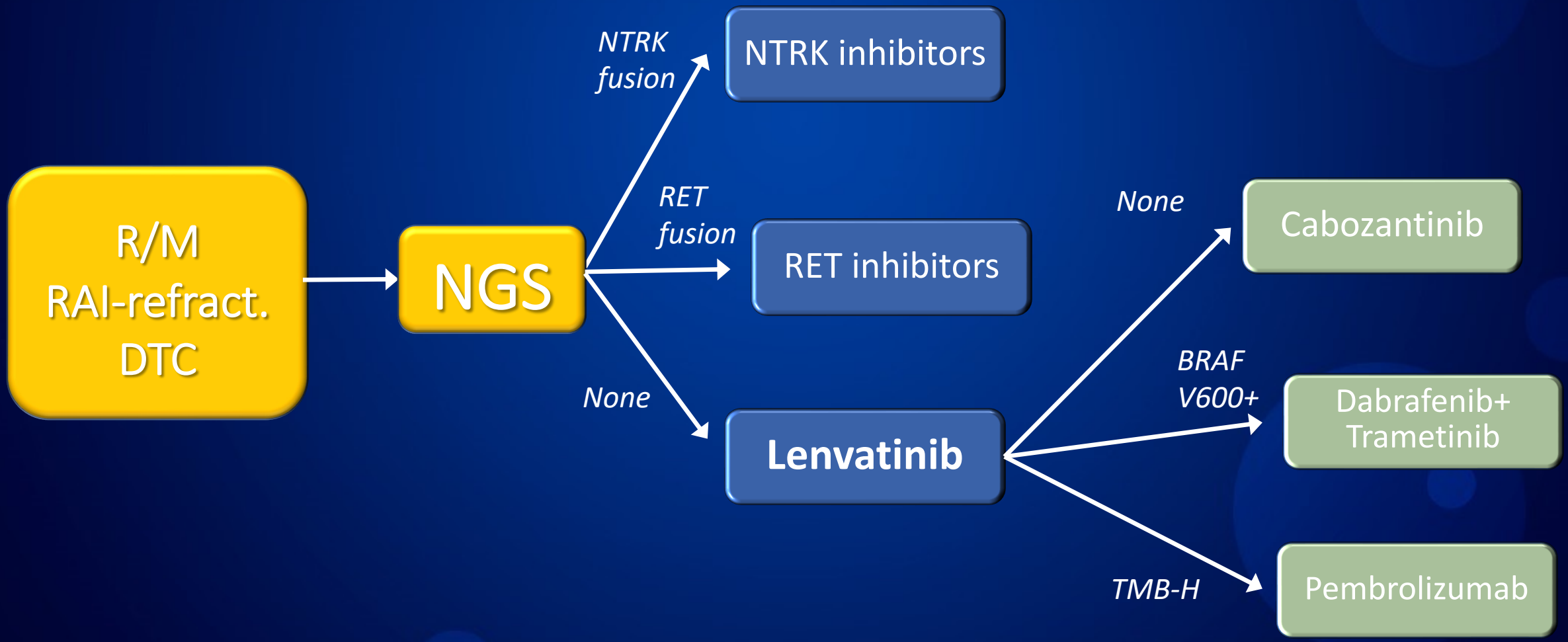
Clin Cancer Res 2018 Jul 1;24(13):3059-3068.

> 70% of DTC tumors have a driver mutation sensitive to an approved agent

> 80% of MTC patients have RET+ tumors

Always do NGS for Recurrent Thyroid Cancer pts!!

Progressive RAI-refractory Thyroid Cancer



2023 ASCO® ANNUAL MEETING

Educational program

Session Type	Session Title
Case-Based Panel	Multidisciplinary Management of Salivary Gland Cancers
Education Session	Current Treatment Strategies and Risk Stratification for Oral Carcinoma
Education Session	How to Approach Advanced Thyroid Cancer in 2023
Education Session	Personalizing Surveillance in Head and Neck Cancer