

XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

**BOLOGNA,
27-29 OTTOBRE 2023**

PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

RADIO-IMMUNOTHERAPY FOR HEAD AND NECK CANCER IN 2023: WHERE DO WE STAND?

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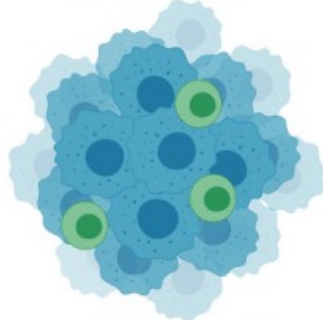


Associazione Italiana
Radioterapia e Oncologia clinica

COI: None relevant to this presentation

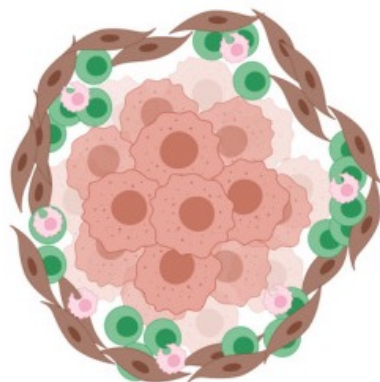


Immune-desert
(cold tumor)

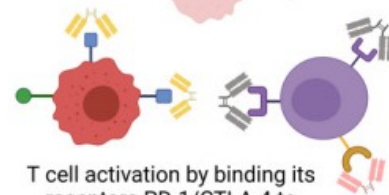


T cell inactivation by binding its receptors PD-1/CTLA-4 to PD-L1 and CD80/86 on tumor cells

Immune-excluded



Immune-inflamed
(hot tumor)



T cell activation by binding its receptors PD-1/CTLA-4 to anti-PD-1/CTLA-4 antibodies



Gene	Cytogenetic location	Mutation type	Function in	Role
<i>TP53</i>	17p13.1	Missense	DNA damage	TSG
		Allelic loss		
<i>NOTCH1</i>	9q34.3	Inactivating mutation	Signal transduction pathways	TSG
<i>PIK3CA</i>	3q26.32	Amplification	Signal transduction pathways	Oncogene
		Activating mutation		
<i>FAT1</i>	4q35.2	Inactivating mutation	Cell-cell connection	TSG
		Deletion		
<i>HRAS</i>	11p15.5	Activating mutation	Signal transduction pathways	Oncogene
<i>CDKN2A</i>	9p21.3	Loss of function	Cell cycle	TSG
<i>NSD1</i>	5q35.3	Inactivating mutation	Epigenetic regulation	TSG
<i>KMT2D</i>	12q13.12	Inactivating mutation	Epigenetic regulation	TSG

Age

Gender

HLA Polymorphisms

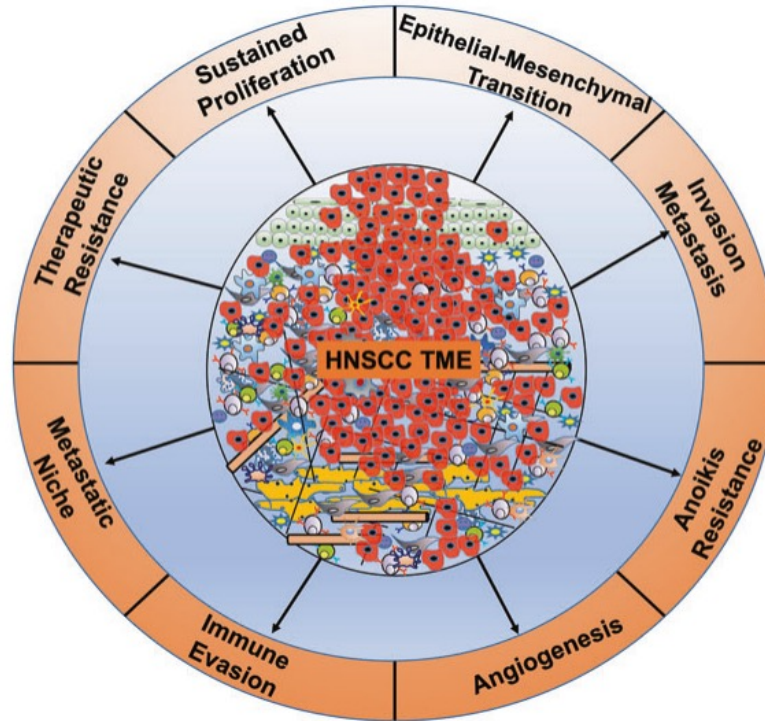
Previous therapies

Concurrent medications

Smoking

Disease site

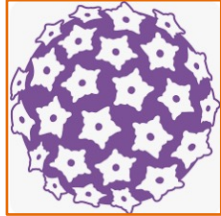
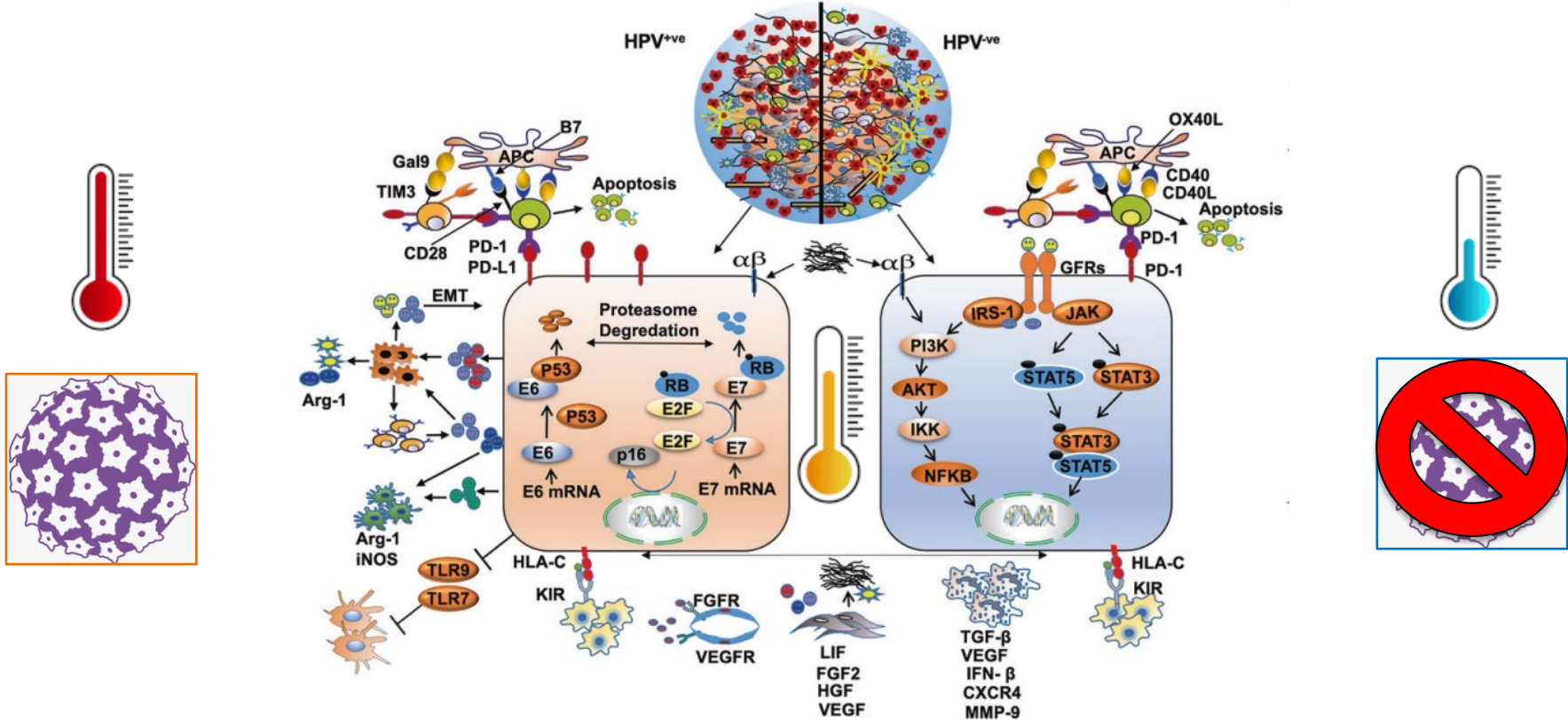
Viral Infections



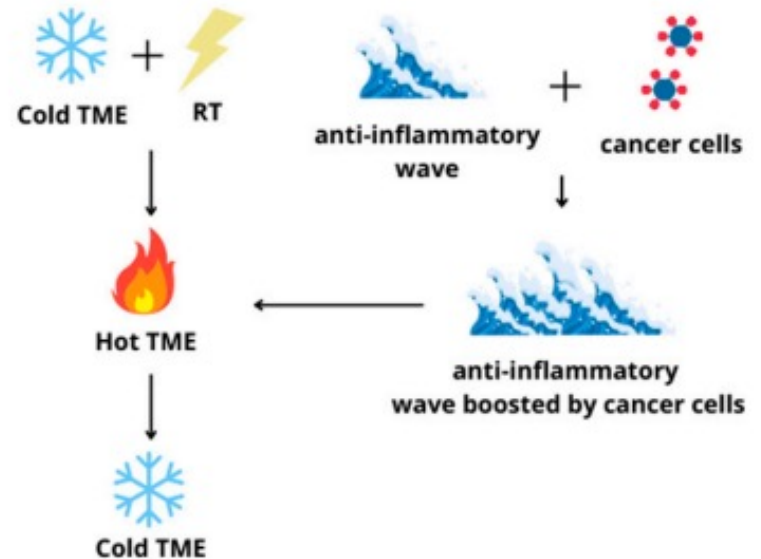
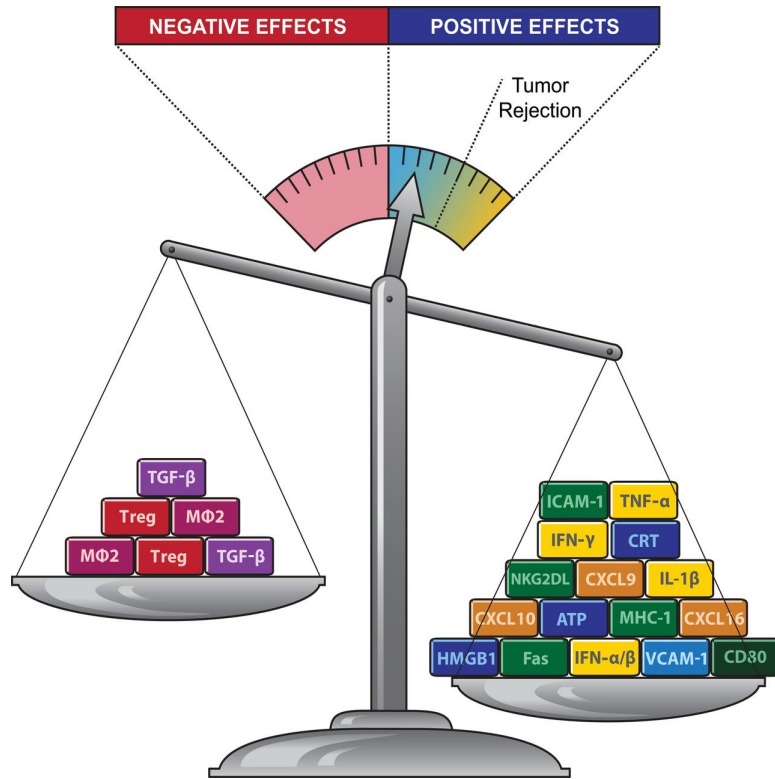
- Cancer cell
- Normal cell
- Tregs
- CD8⁺ T cell
- CD4⁺ T cell
- MDSC
- M2 Macrophages
- NK Cells
- Neutrophils
- APS
- Fibroblasts
- Dendritic cell
- Langerhans cells
- Endothelial cells
- Proteolytic enzymes
- Blood vessels
- Muscle cells
- ECM
- TGFβ
- CCL2
- IL-10
- EGF
- IL6

Bhat et al., Sign Transd and Targeted Ther, 2021

Bhat et al., Sign Transd and Targeted Ther, 2021; adapted

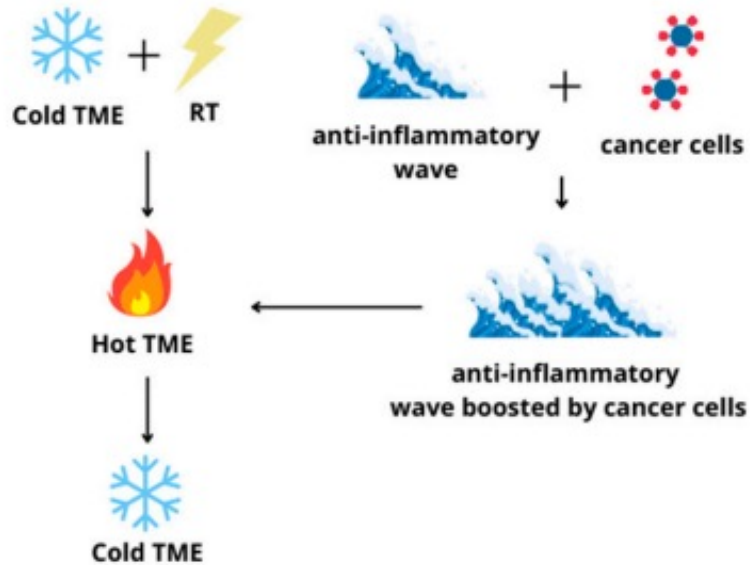


What about radiotherapy?

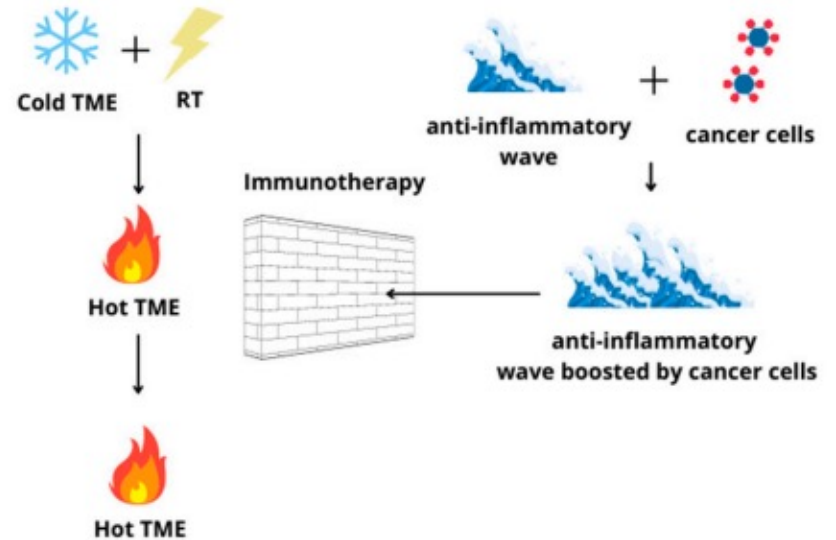


Iori et al., *Curr Oncol*, 2022

Radiotherapy alone



Radiotherapy + Immunotherapy



Recurrent/ Metastatic Setting

ClinicalTrials.gov Identifier	Title	Phase	Patient Population	Interventional Arms	RT Prescription	Timing of ICI to RT
NCT02684253	Screening Trial of Nivolumab With Image Guided, Stereotactic Body Radiotherapy (SBRT) Versus Nivolumab Alone in Patients With Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)	II	Metastatic HNSCC, including HPV+	SBRT + nivolumab	27 Gy in 3 fractions, single lesion	Concurrent + maintenance
NCT04830267	The Efficacy of Camrelizumab Plus Stereotactic Body Radiotherapy in R/M HNSCC	II	Recurrent/metastatic HNSCC, including HPV+	SBRT + Camrelizumab	27 Gy in 3 fractions, single lesion	Neoadjuvant + concurrent + maintenance
NCT04576091	Testing the Addition of an Anti-cancer Drug, BAY 1895344, With Radiation Therapy to the Usual Pembrolizumab Treatment for Recurrent Head and Neck Cancer	I	Recurrent, unresectable HNSCC, including HPV+	SBRT + pembrolizumab + elimusertib	Unspecified dose in 3 fractions	Neoadjuvant + concurrent

Zhou and Wang, Biomedicine, 2022

Locally-Advanced Setting: neoadjuvant IT



Meeting Abstract | 2021 ASCO Annual Meeting I

HEAD AND NECK CANCER

Interim analysis of IMMUNEBOOST-HPV: A multicenter, randomized, open label, phase II study evaluating the feasibility, and tolerance of neoadjuvant nivolumab in high-risk HPV driven oropharynx cancer.

ABSTRACT | VOLUME 33, SUPPLEMENT 7, S840-S841, SEPTEMBER 2022

6530 Neoadjuvant nivolumab (N) before chemoradiation (CRT) in high-risk HPV driven oropharynx cancer (OPC) - IMMUNEBOOST-HPV: A multicenter randomized phase II trial

H. Mirghani • C. Even • A. Larive • ... F. Garic • A. Auperin • P. Blanchard • Show all authors

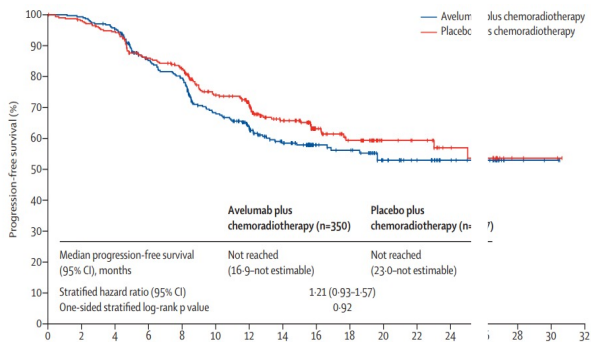
Open Archive • DOI: <https://doi.org/10.1016/j.annonc.2022.07.777>

- In the EA, four pts received $< 200\text{mg}/\text{m}^2$ Cis (2 kidney failures, 2 ototoxicity)
- One pt had RT-delay (day 38, logistical issues).
- All pts received the planned RT dose
- 14 N-related Adverse Events (AE) occurred in 8 pts including 5 serious AE (ankylosing spondylitis flare-up, hepatic cytolysis, 2 colitis, diabetic ketoacidosis).

Locally-Advanced Setting: concomitant immuno-CRT

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

Nancy Y Lee*, Robert L Ferris*, Amanda Psyrry, Robert I Haddad, Makoto Tahara, Jean Bourhis, Kevin Harrington, Jin-Ching Lin, Mohammad Abdul Razaq, Maria Margarida Teixeira, József Lövey, Jerome Chamois, Antonio Rue, Mikhail Vladimirovich Dvorkin, Steven De Beukelaar, Dmitri Pavlov, Holger Thurm, Ezra Cohen*
eter Mu-Hsin Chang, Chaosu Hu, Lara A Dunn,



Number at risk (number censored)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Avelumab plus chemoradiotherapy	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
(0)	(45)	(47)	(67)	(68)	(84)	(105)	(131)	(168)	(172)	(191)	(199)	(210)	(214)	(228)	(230)	(232)	
Placebo plus chemoradiotherapy	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0
(0)	(38)	(39)	(47)	(53)	(70)	(90)	(130)	(172)	(187)	(212)	(215)	(224)	(226)	(238)	(239)	(241)	

	Events/patients (n/N)		2-year progression-free survival rate, % (95% CI)		Hazard ratio (95% CI)*	p value†
	Avelumab plus chemoradiotherapy	Placebo plus chemoradiotherapy	Avelumab plus chemoradiotherapy	Placebo plus chemoradiotherapy		
Tumour stage‡						
<T4	56/198	51/193	57 (47-66)	58 (45-68)	1.17 (0.80-1.71)	0.87
T4	62/152	55/154	48 (38-57)	56 (46-65)	1.22 (0.85-1.75)	
Nodal stage‡						
NO-N2b	55/184	49/181	59 (48-67)	53 (34-69)	1.09 (0.74-1.60)	0.44
N2c-N3	63/166	57/166	46 (36-56)	56 (46-65)	1.33 (0.93-1.91)	
HPV status‡						
Positive	29/121	26/117	67 (56-76)	72 (61-80)	1.26 (0.74-2.15)	0.80
Negative	89/229	80/230	45 (36-54)	48 (36-59)	1.16 (0.86-1.57)	
...						
Site of primary tumour						
Hypopharynx	35/87	26/64	46 (32-59)	53 (39-66)	1.07 (0.64-1.78)	0.94
Larynx	20/59	17/65	49 (31-65)	51 (24-73)	1.38 (0.72-2.65)	0.50
Oropharynx	42/157	44/169	64 (53-72)	67 (57-74)	1.16 (0.76-1.78)	0.73
Oral cavity	21/47	19/49	38 (19-56)	33 (13-56)	1.00 (0.54-1.86)	
PD-L1 status at baseline						
PD-L1 low (<25%)	90/249	69/237	52 (43-59)	59 (49-68)	1.37 (1.00-1.88)	0.03
PD-L1 high (≥25%)	10/50	26/73	72 (54-84)	52 (36-65)	0.59 (0.28-1.22)	
All patients (stratified)§	118/350	106/347	53 (46-60)	57 (49-64)	1.21 (0.93-1.57)	
All patients (unstratified)	118/350	106/347	53 (46-60)	57 (49-64)	1.20 (0.92-1.56)	

KEY POINTS

- KEYNOTE-412 evaluated concurrent pembrolizumab plus chemoradiation, followed by pembrolizumab maintenance, in locally advanced head and neck squamous cell carcinoma.
- Although numerical trends were observed with pembrolizumab, the benefit fell short of statistical significance.
- Median event-free survival was not reached with pembrolizumab plus chemoradiation and was 46.6 months with chemoradiation alone (HR = 0.83; $P = .0429$), failing to meet the superiority threshold of .0242.
- The PD-L1 (CPS > 20)-enriched subgroup seemed to derive a higher benefit of the addition of pembrolizumab.

Locally-Advanced Setting: concomitant immuno-CRT

Study of Pembrolizumab (MK-3475) or Placebo With Chemoradiation in Participants With Locally Advanced Head and Neck Squamous Cell Carcinoma (MK-3475-412/KEYNOTE-412)

ClinicalTrials.gov ID ⓘ NCT03040999

“Pembrolizumab plus chemoradiation was associated with a favorable trend toward improved event-free survival vs placebo plus chemoradiation in patients with locally advanced head and neck squamous cell carcinoma, and PD-L1 expression may be an informative predictive biomarker,” said **Jean-Pascal Machiels, MD, PhD**, Head of the Department of Adult and Pediatric Oncology and Hematology at the Cliniques universitaires Saint-Luc (UCLouvain) in Brussels, who presented the findings at a Presidential Symposium.

Jean-Pascal
Machiels, MD, PhD

After a median of almost 4 years of follow-up, median event-free survival was not reached with pembrolizumab plus chemoradiation and was 46.6 months with chemoradiation alone (hazard ratio [HR] = 0.83; $P = .0429$). This difference failed to meet the superiority threshold (efficacy boundary was $P = .0242$), Dr. Machiels reported.

Locally-Advanced Setting: adjuvant IT

ACTIVE, NOT RECRUITING ⓘ

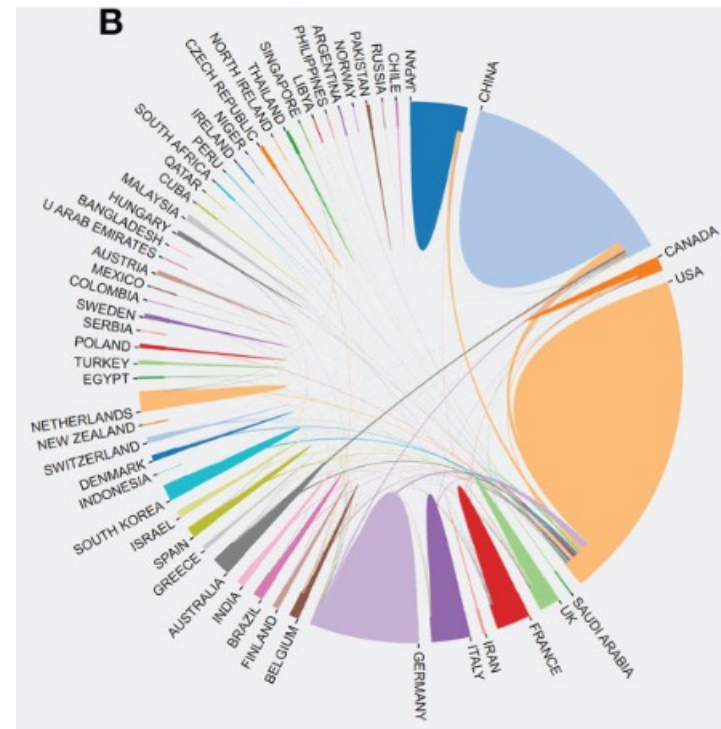
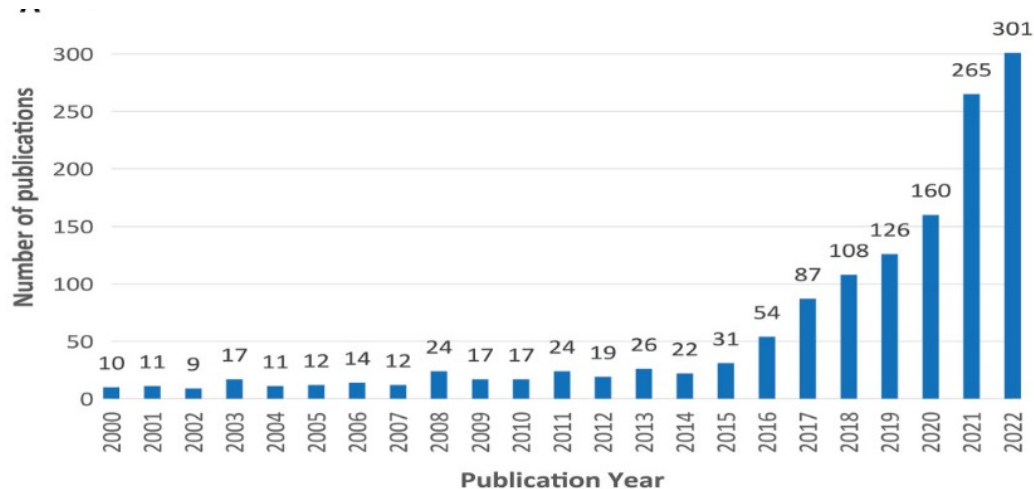
A Study of Atezolizumab (Anti-Pd-L1 Antibody) as Adjuvant Therapy After Definitive Local Therapy in Patients With High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck

ClinicalTrials.gov ID ⓘ NCT03452137

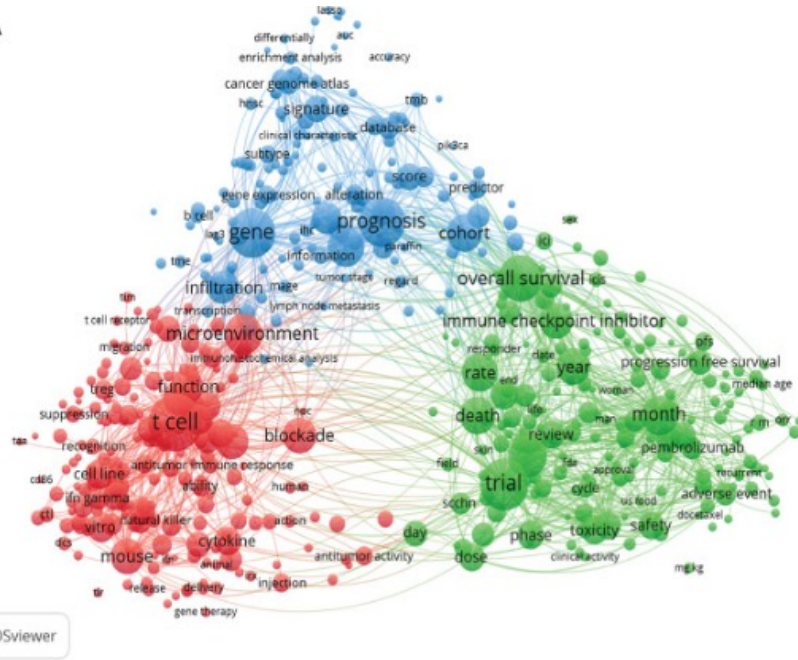


So what?

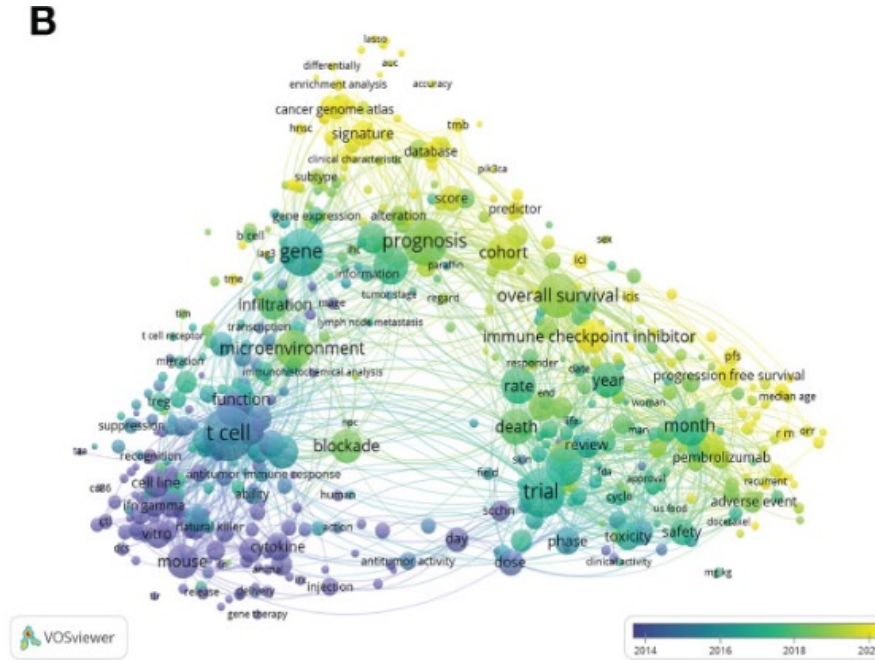
Bibliometric study on the knowledge graph of immunotherapy for head and neck cancer



A

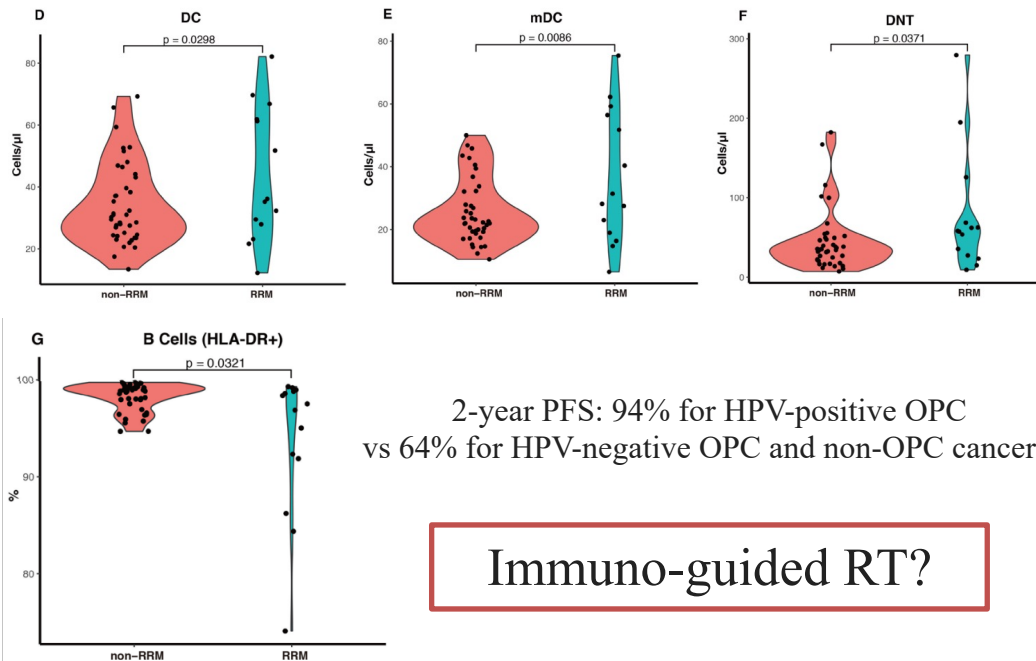
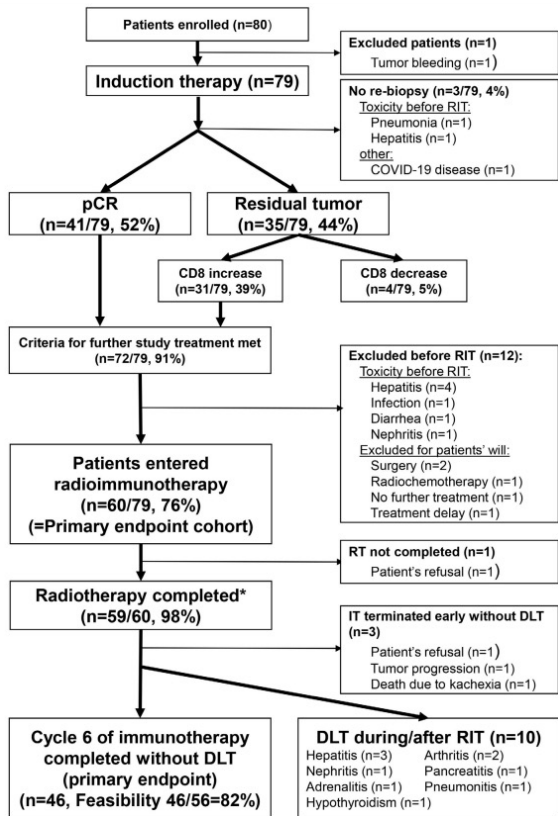


B



Radiotherapy With Double Checkpoint Blockade of Locally Advanced HNSCC

ClinicalTrials.gov ID [NCT03426657](https://clinicaltrials.gov/ct2/show/study/NCT03426657)



2-year PFS: 94% for HPV-positive OPC vs 64% for HPV-negative OPC and non-OPC cancers

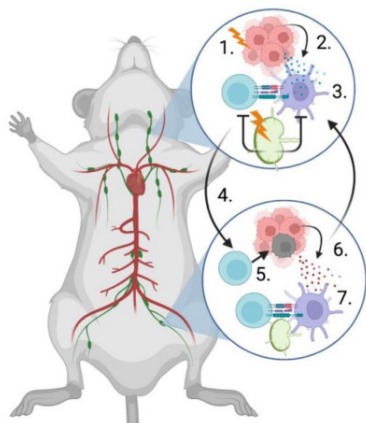
Immuno-guided RT?

nature communications

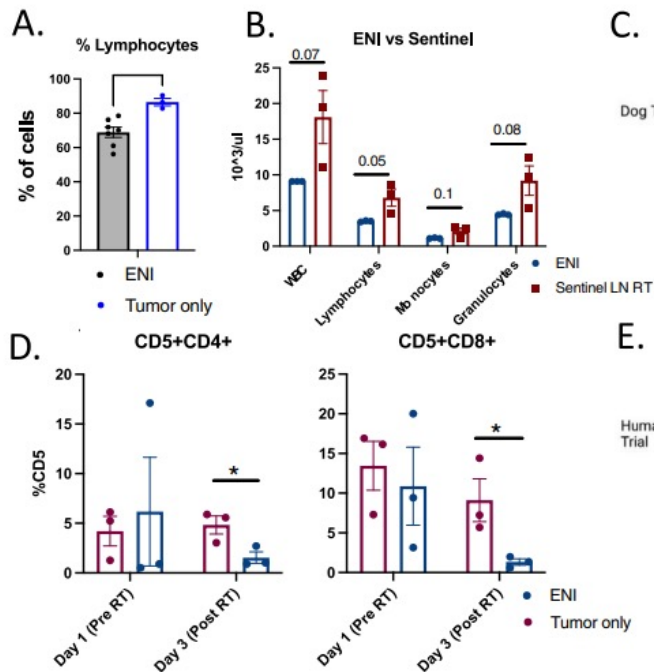


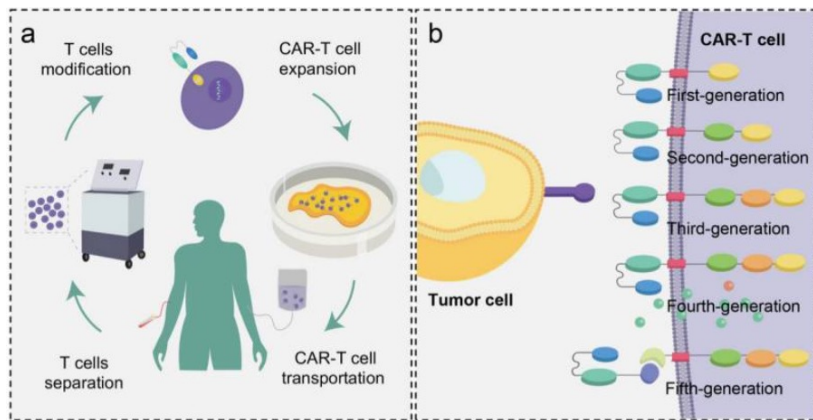
Article <https://doi.org/10.1038/s41467-022-34676-w>

Elective nodal irradiation mitigates local and systemic immunity generated by combination radiation and immunotherapy in head and neck tumors



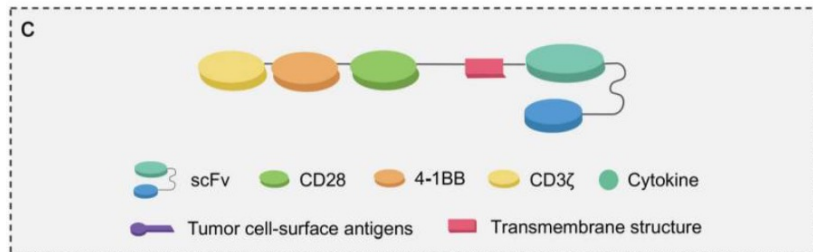
Lymphatic-sparing RT?





CAR-T cell synthesis

CAR-T cell generations



Chimeric Antigen Receptor

Other options?

Target	Introduction
Preclinical study	
HER2	CD28. CD3-ζ/CAd
EGFR	-
CD70	4-1BB.CD3-ζ
MUC1	4-1BB.CD3-ζ/IL-12
CD44v6	CD28. CD3-ζ
B7-H3	-
CD98 + EGFR	UniCAR-T
Clinical trial	
ERBB2/HER2	NCT01818323 NCT03740256
EpCAM	NCT02915445
NKG2DL	NCT04107142
LMP1	NCT02980315

Thanks for your attention!

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