Dana-Farber
Cancer Institute

Novel Advances in Head and Neck Cancer: What is after IO?

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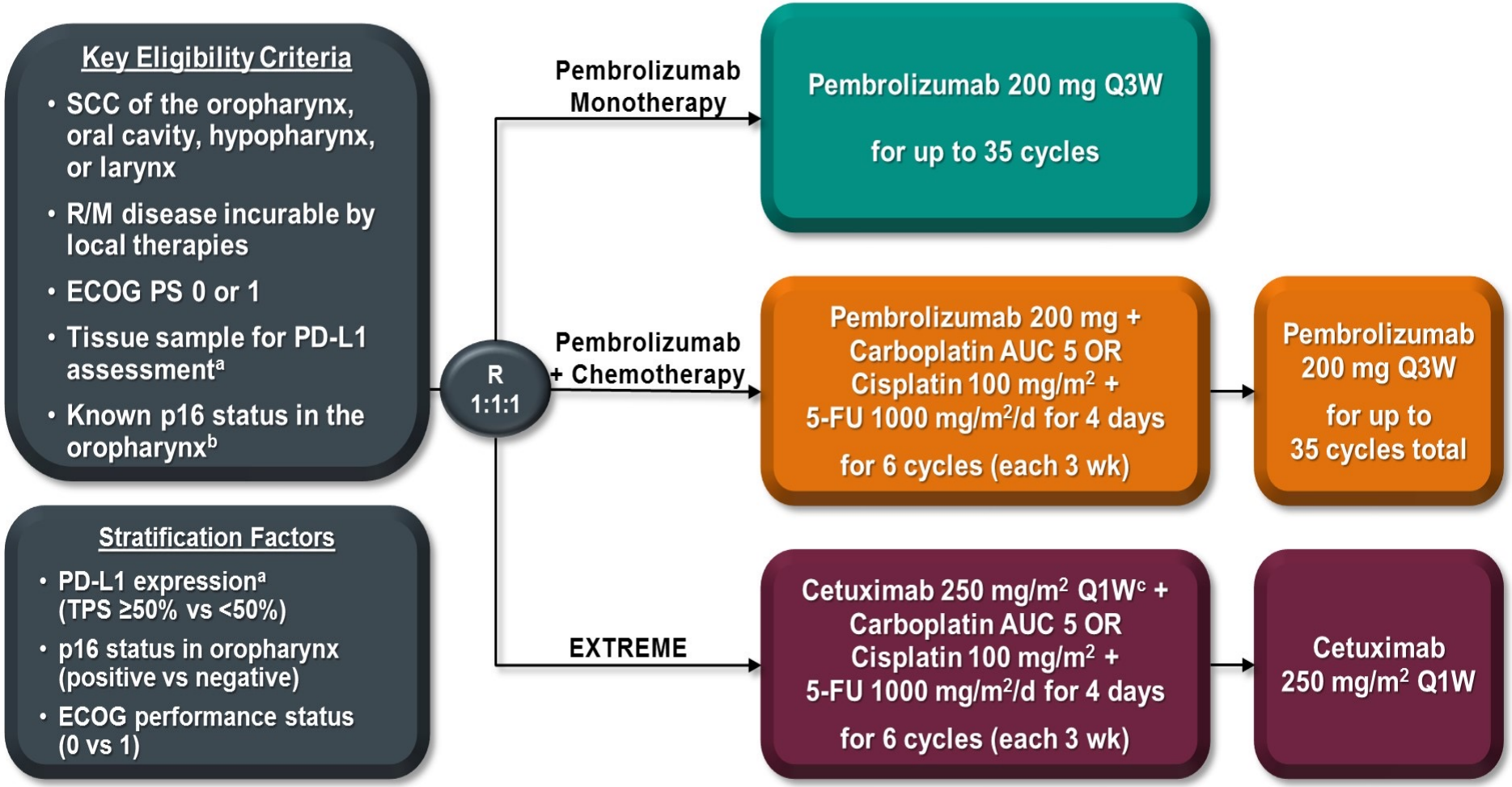
Current Landscape in Recurrent Head and Neck Cancer

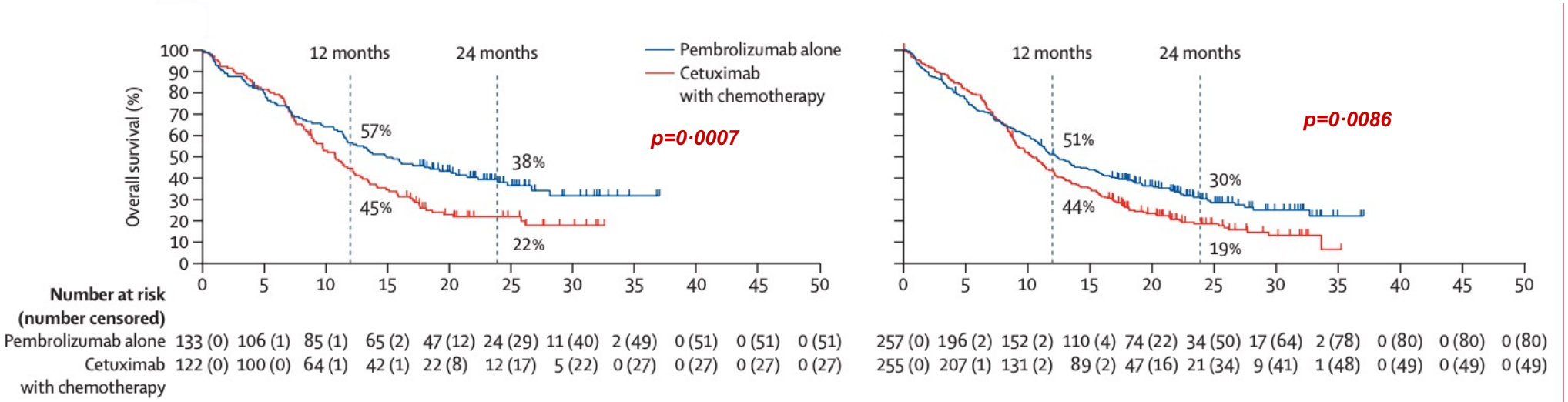
- Checkpoint inhibitors Pembrolizumab and Nivolumab (CPI) approved in first- and second-line (K048, k012, Ck141)
- Benefit appear to be confined to patients with CPS (PDL1) positive disease
- Role of other biomarkers (tTMB, bTMB, GEP, etc) under evaluation
- Response rate 20-40 percent
- Duration of response 20-30 months
- Exceptional responders and cures uncommon
- Beyond CPI: Multiple options , low RR , low OS
    1. Chemotherapy/Cetuximab
    2. Cetuximab
    3. Clinical trials

KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Pembrolizumab vs Extreme



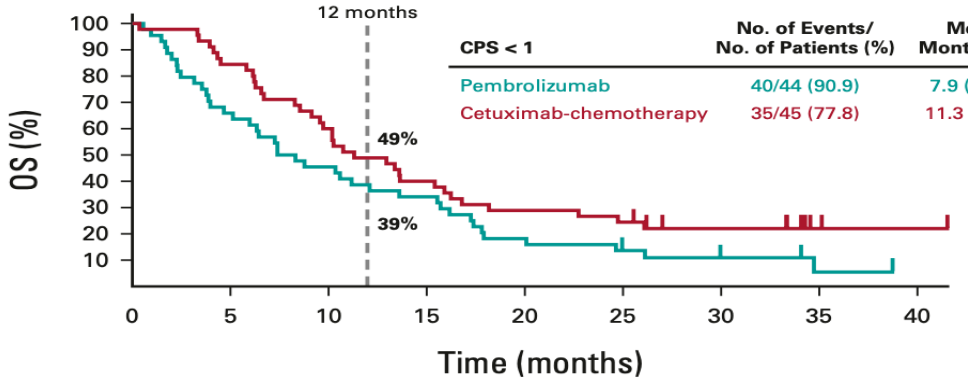
CPS 20

HR 0·61 (95% CI 0·45−0·83, p=0·0007)
Median OS 14·9 months versus 10·7 months

CPS 1

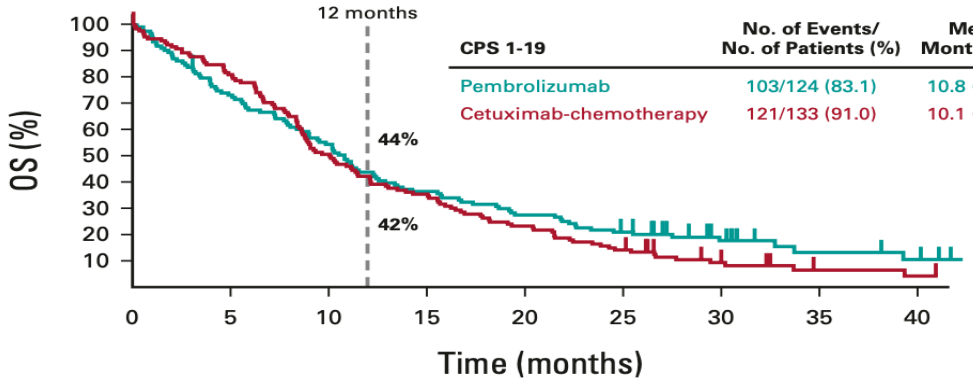
HR 0·78 (95% CI 0·64−0·96, p=0·0086);
Median OS 12·3 months versus 10·3 months

KEYNOTE-048: Subgroup Analysis by CPS



CPS < 1	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab	40/44 (90.9)	7.9 (4.7 to 13.6)	1.51 (0.96 to 2.37)	.96241
Cetuximab-chemotherapy	35/45 (77.8)	11.3 (9.1 to 15.9)		

No. at risk:									
Pembrolizumab	44	29	20	15	8	5	3	1	0
Cetuximab-chemotherapy	45	38	27	18	13	11	7	2	1



CPS 1-19	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)[a]	HR (95% CI)[b]	Nominal *P*[c]
Pembrolizumab	103/124 (83.1)	10.8 (9.0 to 12.6)	0.86 (0.66 to 1.12)	.12827
Cetuximab-chemotherapy	121/133 (91.0)	10.1 (8.7 to 12.1)		

No. at risk:									
Pembrolizumab	124	90	67	45	34	25	14	6	4
Cetuximab-chemotherapy	133	107	67	47	31	19	8	3	2

Burtness B et al: J Clin Oncol. 2022

CheckMate 651 Phase III

Key eligibility criteria

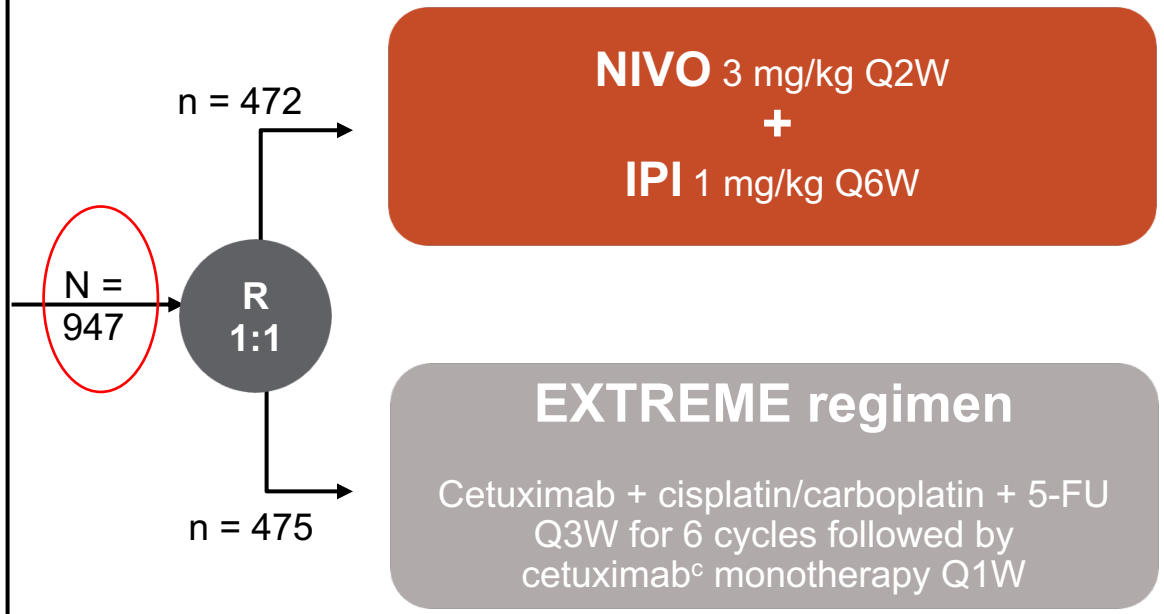
- R/M SCCHN (oral cavity, oropharynx, hypopharynx, or larynx)
- No prior treatment for R/M disease
- Prior chemotherapy for LAD permitted if progression-free ≥6 months post-treatment
- ECOG PS 0−1

Stratified by:

p16 expression (OPC p16+ vs p16−/non-OPC)

Tumor PD-L1[a] status (<1% vs ≥1%)

Prior chemotherapy (yes vs no)



Until disease progression, unacceptable toxicity, *or* 2 years for NIVO + IPI

Primary endpoints (independently tested)

- OS in all randomized
- OS in PD-L1 CPS ≥20

Secondary endpoints

- OS in PD-L1 CPS ≥1
- PFS by BICR (all randomized, PD-L1 CPS ≥20)
- ORR/DOR by BICR (all randomized, PD-L1 CPS ≥20)

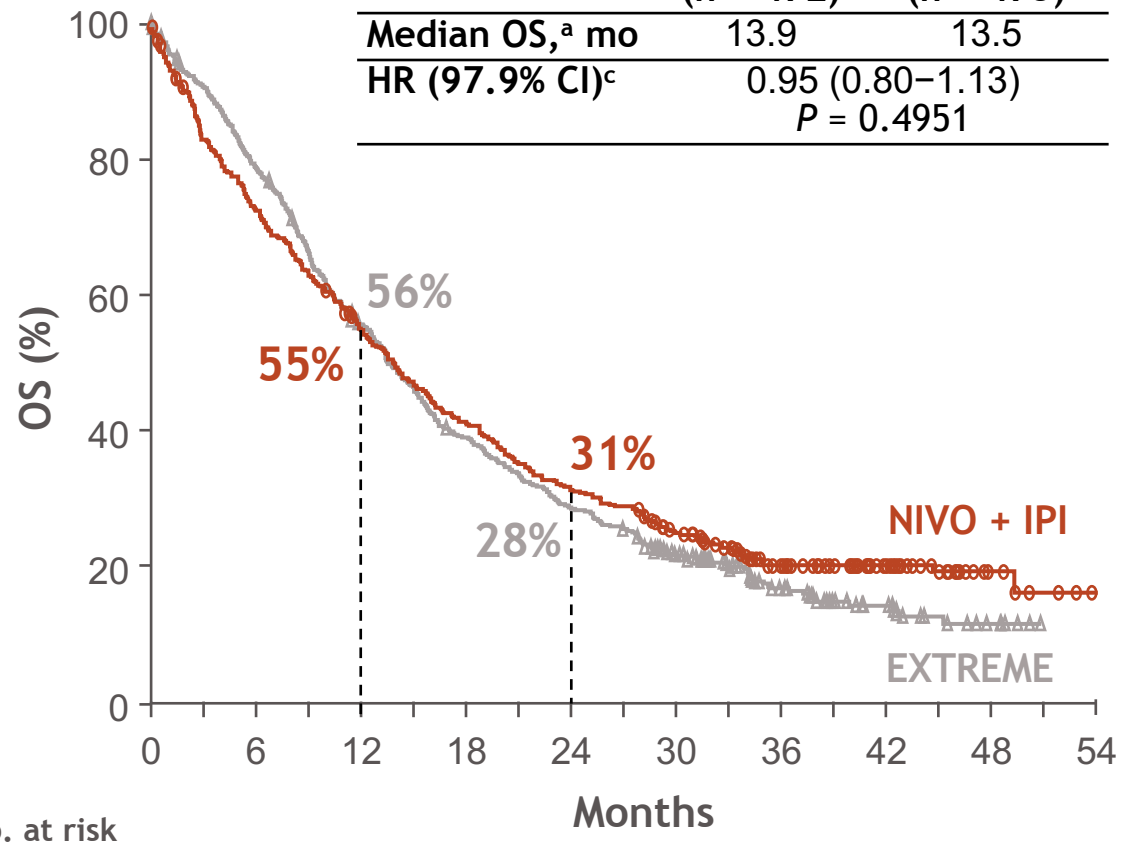
Exploratory endpoints

- PFS and ORR/DOR in PD-L1 CPS ≥1
- Patient-reported outcomes
- Safety

Primary endpoints: OS with NIVO + IPI vs EXTREME

All randomized

	NIVO + IPI (n = 472)	EXTREME (n = 475)
Median OS,[a] mo	13.9	13.5
HR (97.9% CI)[c]	0.95 (0.80–1.13) *P* = 0.4951	

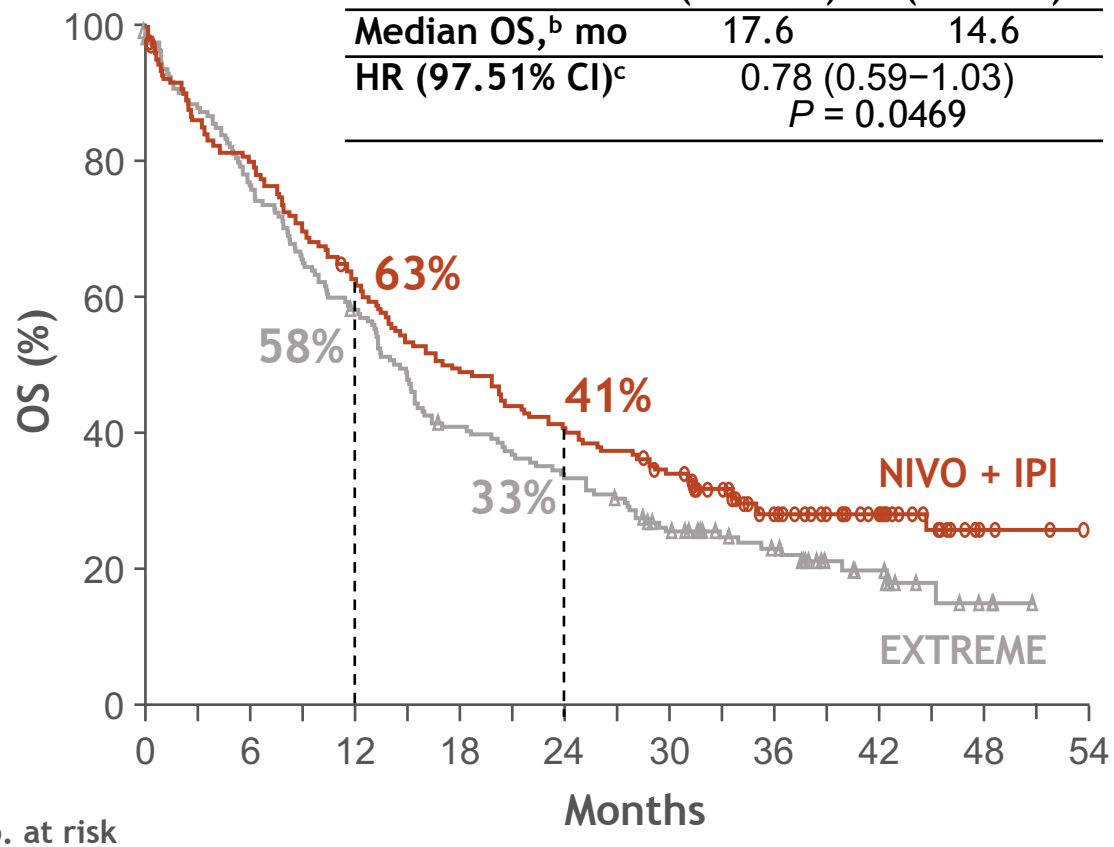


No. at risk

NIVO + IPI	472	340	254	190	144	108	58	32	8	0
EXTREME	475	366	255	177	129	88	47	21	6	0

PD-L1 CPS ≥20

	NIVO + IPI (n = 185)	EXTREME (n = 178)
Median OS,[b] mo	17.6	14.6
HR (97.51% CI)[c]	0.78 (0.59–1.03) *P* = 0.0469	



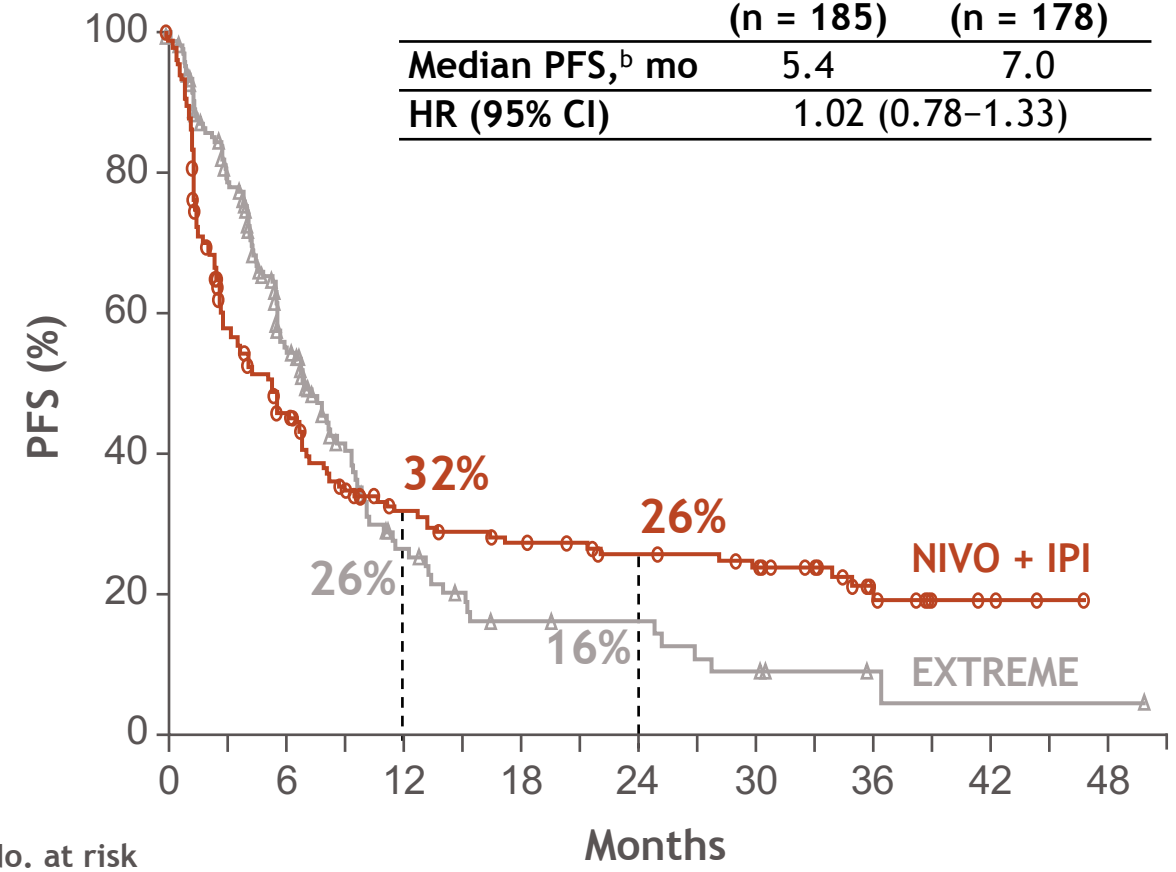
No. at risk

NIVO + IPI	185	147	114	89	74	60	36	21	4	0
EXTREME	178	135	101	70	57	40	26	12	3	0

Efficacy in PD-L1 CPS ≥20 population

PFS

	NIVO + IPI (n = 185)	EXTREME (n = 178)
Median PFS,[b] mo	5.4	7.0
HR (95% CI)	1.02 (0.78–1.33)	

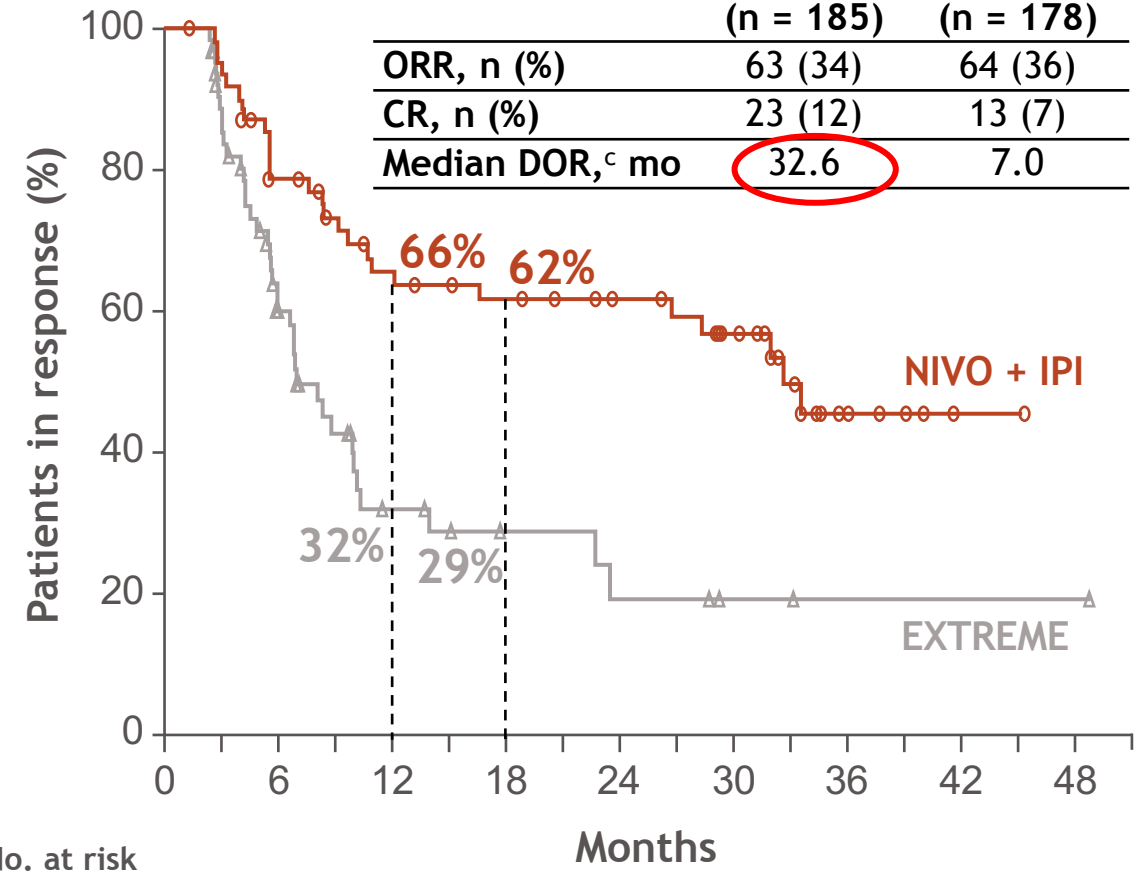


No. at risk

NIVO + IPI	185	73	43	35	29	25	11	4	0	0
EXTREME	178	70	22	10	9	5	2	1	1	0

ORR[a] and DOR[a]

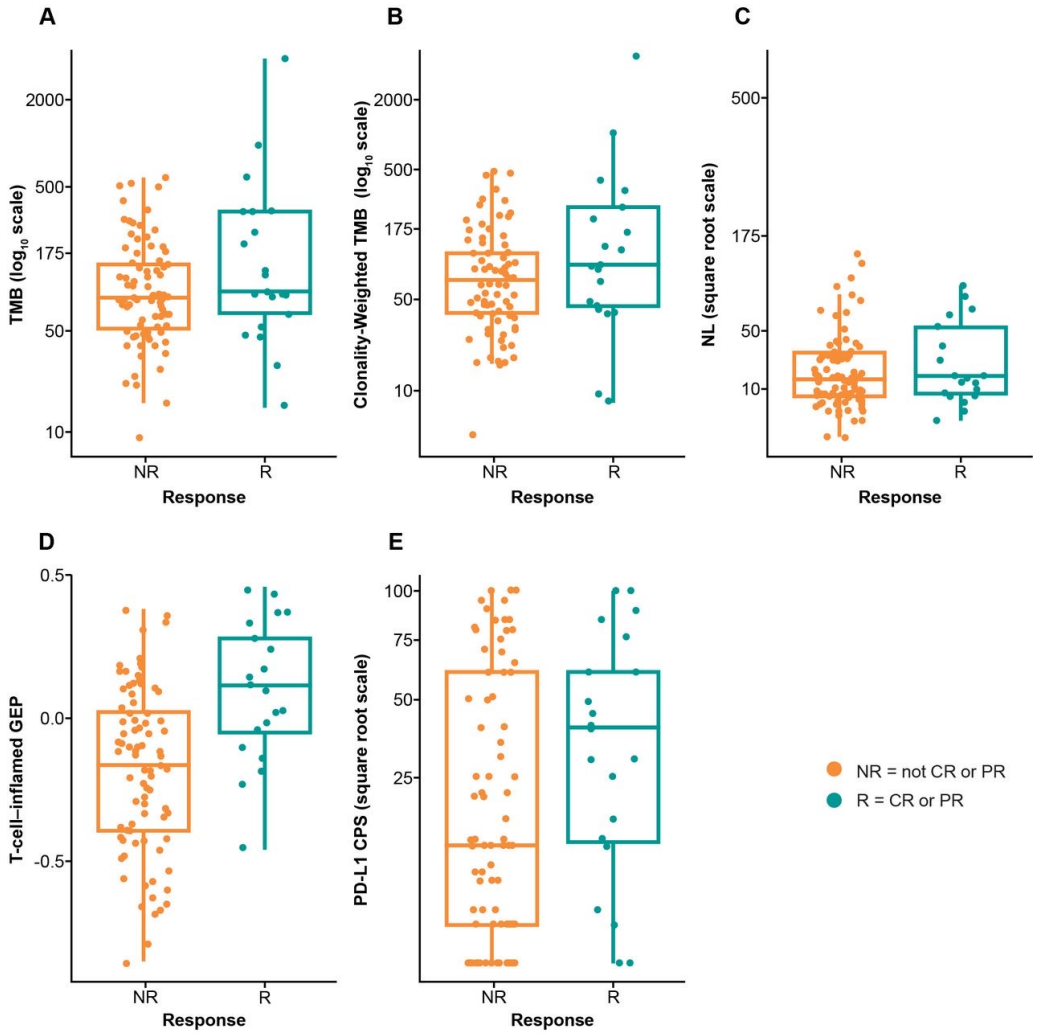
	NIVO + IPI (n = 185)	EXTREME (n = 178)
ORR, n (%)	63 (34)	64 (36)
CR, n (%)	23 (12)	13 (7)
Median DOR,[c] mo	32.6	7.0



No. at risk

NIVO + IPI	63	46	34	30	26	20	7	2	0	0
EXTREME	64	30	11	6	4	2	1	1	1	0

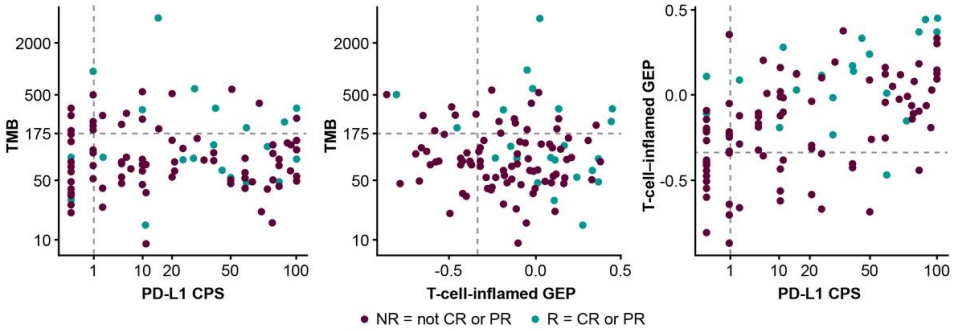
Keynote 012 :Association between biomarkers and response



Haddad et al. J Immunother Cancer 2022

Keynote 012 :Correlation Studies

A



B

	CPS <1	CPS ≥1
TMB ≥175 mut/exome	n/N=0/4 0% (0-49.0)	n/N=8/22 36.4% (19.7-57.0)
TMB <175 mut/exome	n/N=2/14 14.3% (4.0-39.9)	n/N=11/66 16.7% (9.6%-27.4)

C

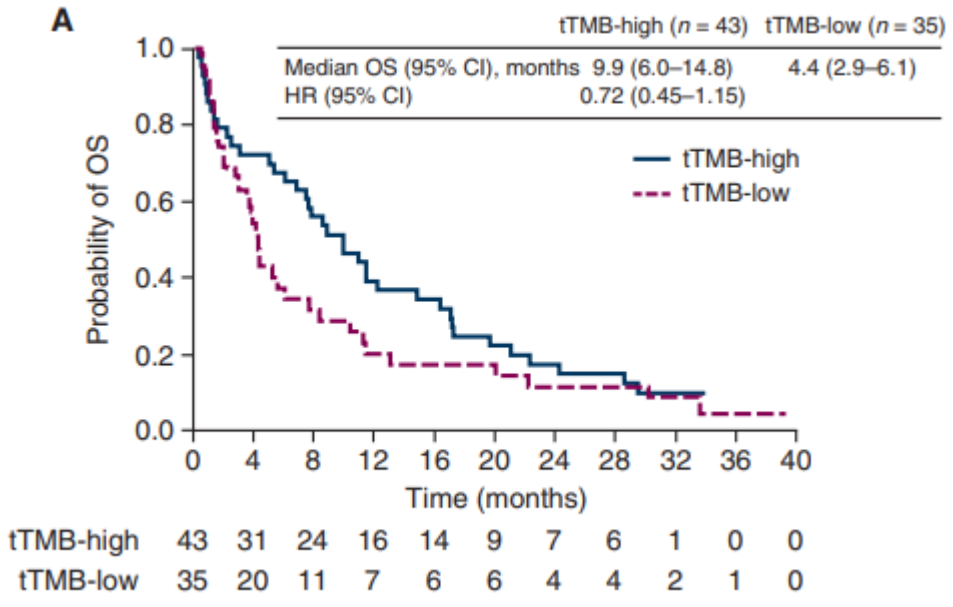
	GEP^{low}	GEP^{nonlow}
TMB ≥175 mut/exome	n/N=1/7 14.3% (2.6-51.3)	n/N=7/18 38.9% (20.3-61.4)
TMB <175 mut/exome	n/N=0/23 0% (0-14.3)	n/N=13/59 23.2% (14.1-35.8)

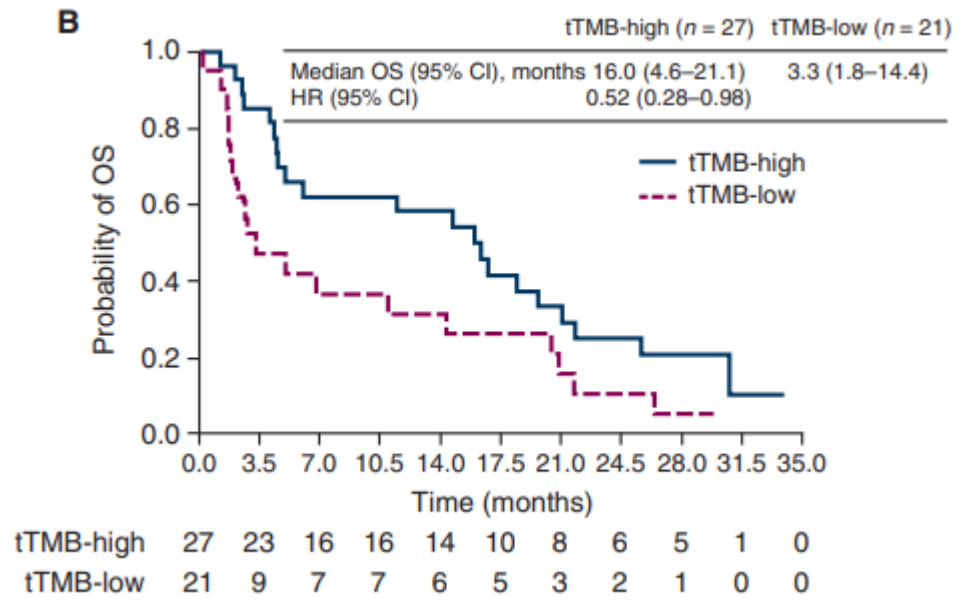
D

	CPS<1	CPS ≥1
GEP^{nonlow}	n/N=2/7 28.6% (8.2-64.1)	n/N=18/67 26.9% (17.7-38.5)
GEP^{low}	n/N=0/10 0% (0-27.8)	n/N=1/20 5% (0.9-23.6)

Haddad et al. J Immunother Cancer 2022

Tissue TMB with Durvalumab and/or Tremelimumab Hawk and Condor Trials

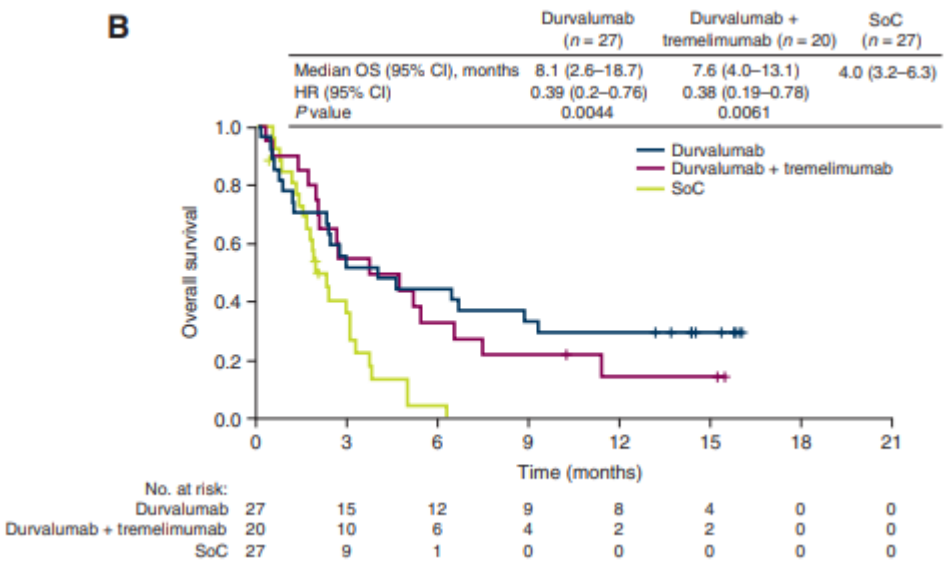


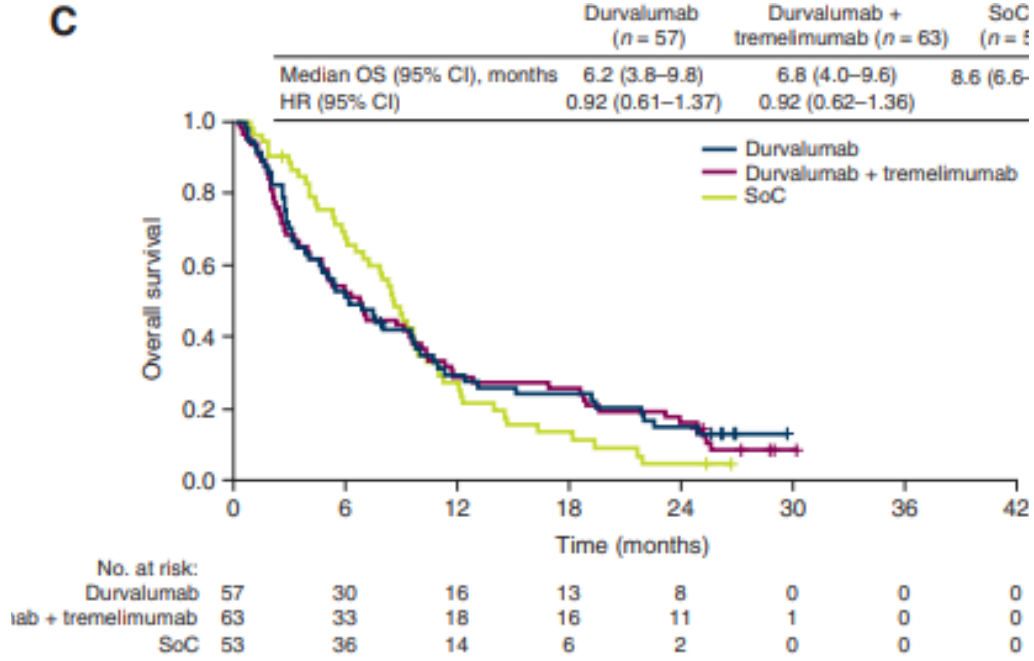


Wildsmith et al CCR 2023

Blood TMB with Durvalumab and/or Tremelimumab

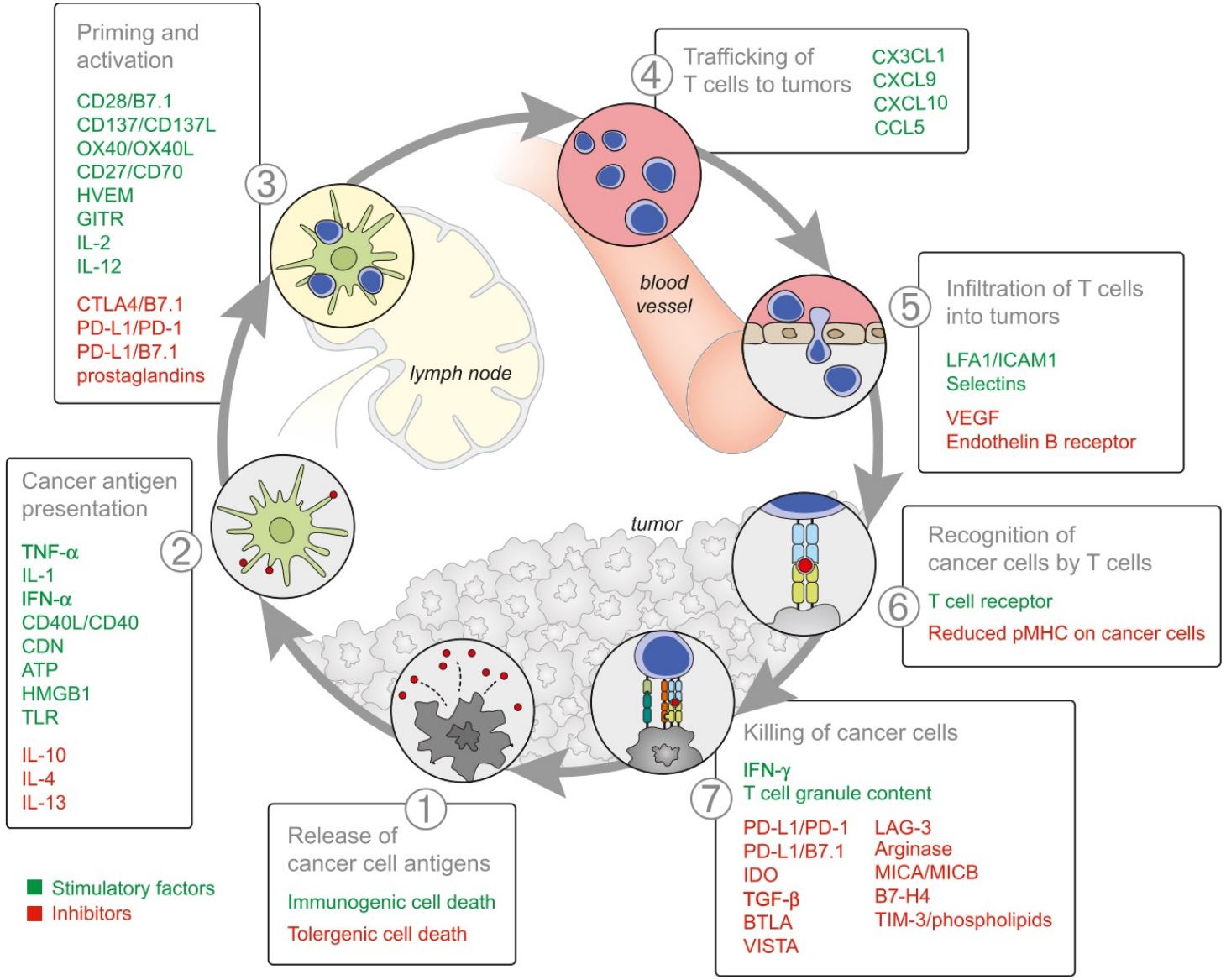
Eagle Phase III trial





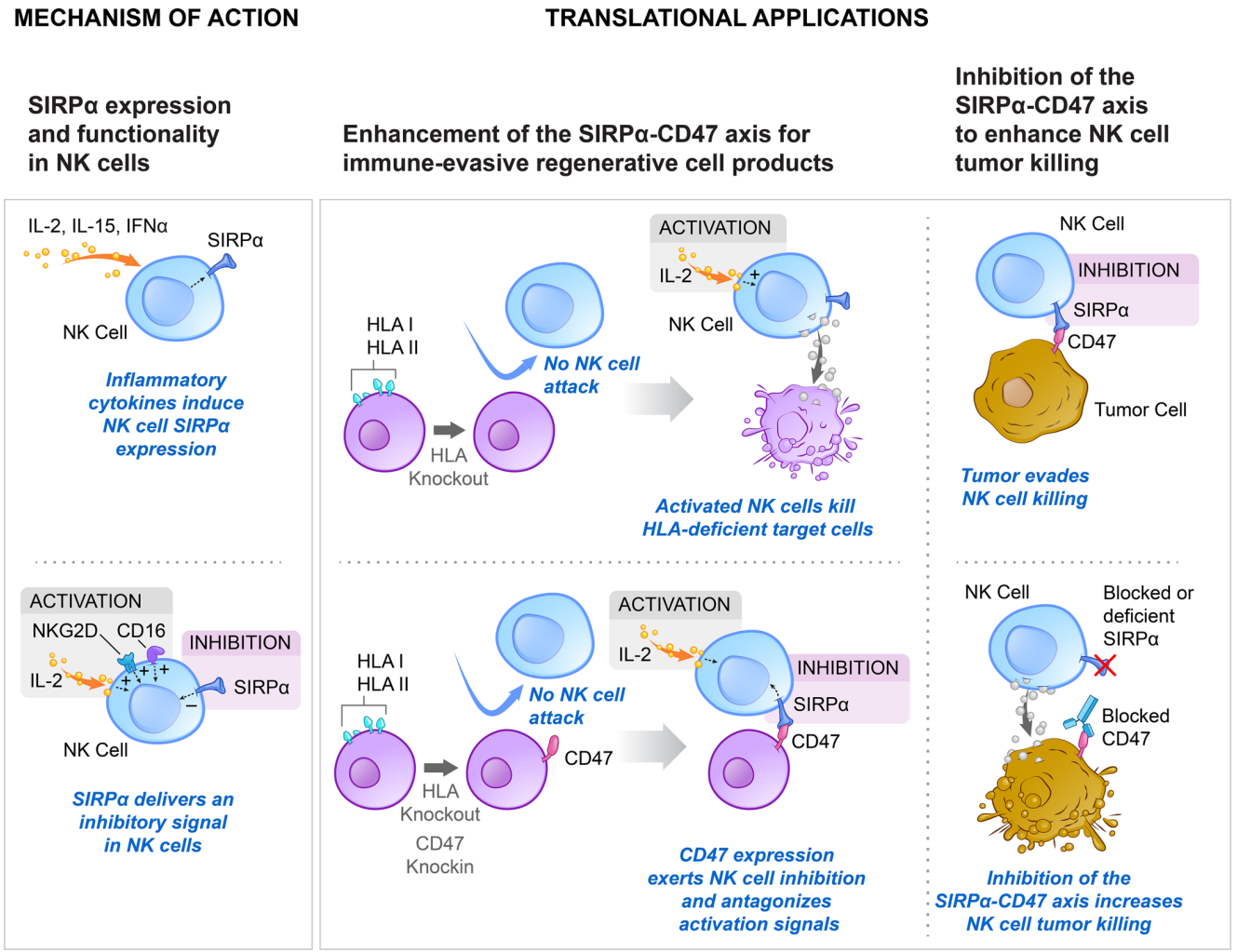
Wildsmith et al CCR 2023

Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



Chen and Mellman 2013

The SIRPα–CD47 immune checkpoint in NK cells



J Exp Med. 2021;218(3). doi:10.1084/jem.20200839

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ASPEN-01 Results[1]

Evorpacept: CD47 blocker

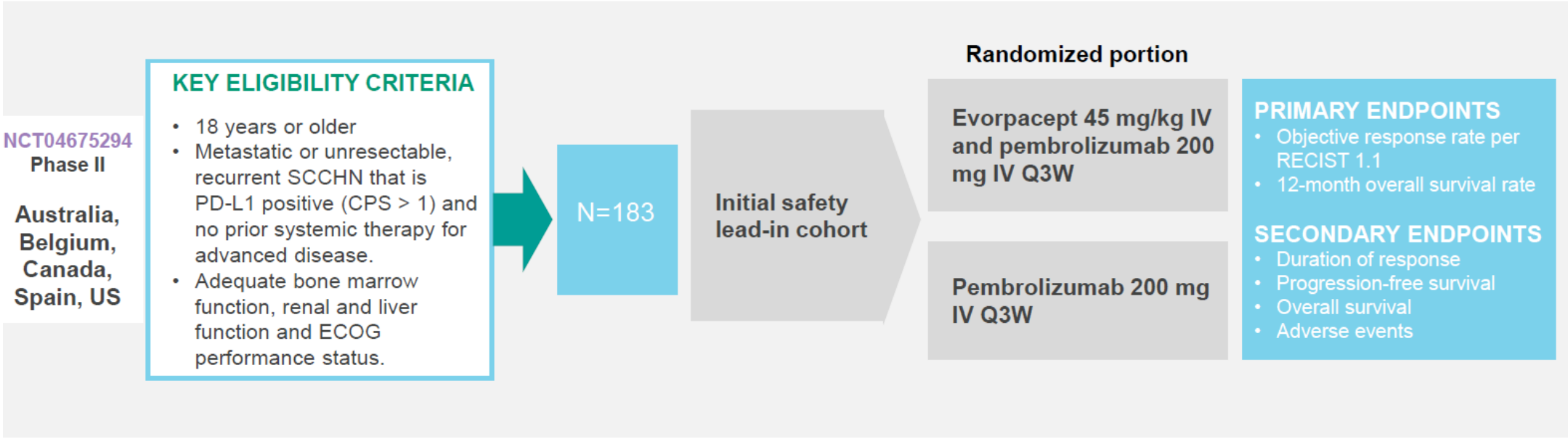
- In patients with 1L SCCHN who have not received prior treatment for their advanced disease (n=13), evorpacept in combination with pembrolizumab + 5-FU + platinum demonstrated:
  - initial ORR of 38.5%
  - 12-month OS rate of 87.5%
  - mOS not reached.
- These results compare favorably with benchmark survival data from standard pembrolizumab + chemotherapy in the 1L SCCHN setting.

5-FU, 5-fluorouracail; ORR, objective response rate; OS, overall survival; SCCHN, squamous cell carcinoma of head and neck.

1. Lee KW, et al. *J ImmunoTher Cancer* 2022;9 (Suppl 2): A530 abstract 498.

ASPEN-03: Phase II Study of Evorpacept (ALX148) in Combination With Pembrolizumab in Patients With Advanced SCCHN

Evorpacept: CD47 blocker



Trial Design:
Randomized, open-label multicenter study, incorporating an initial safety lead-in cohort followed by a randomized portion

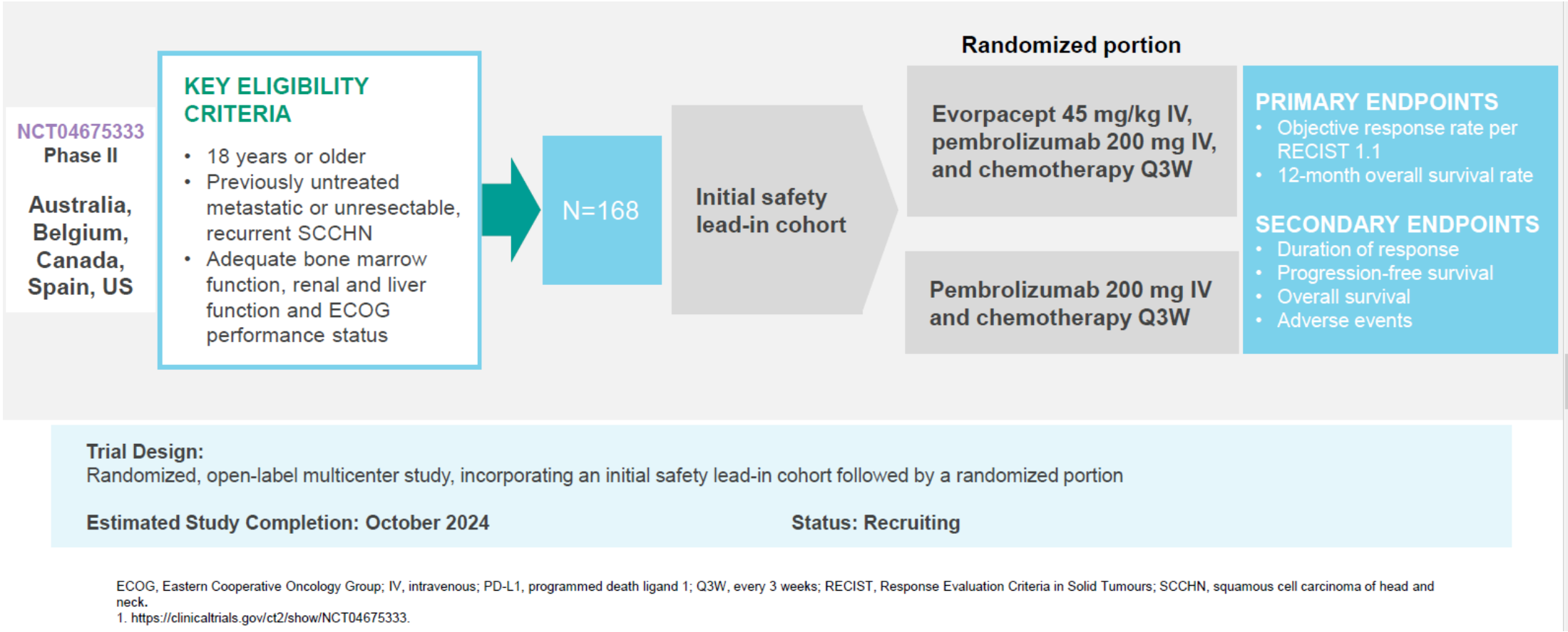
Estimated Study Completion: October 2024 **Status: Recruiting**

CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SCCHN, squamous cell carcinoma of head and neck.

1. https://clinicaltrials.gov/ct2/show/NCT04675294.

ASPEN-04: Phase II Study of Evorpacept (ALX148) in Combination With Pembrolizumab and Chemotherapy in Patients With Advanced SCCHN

Evorpacept: CD47 blocker



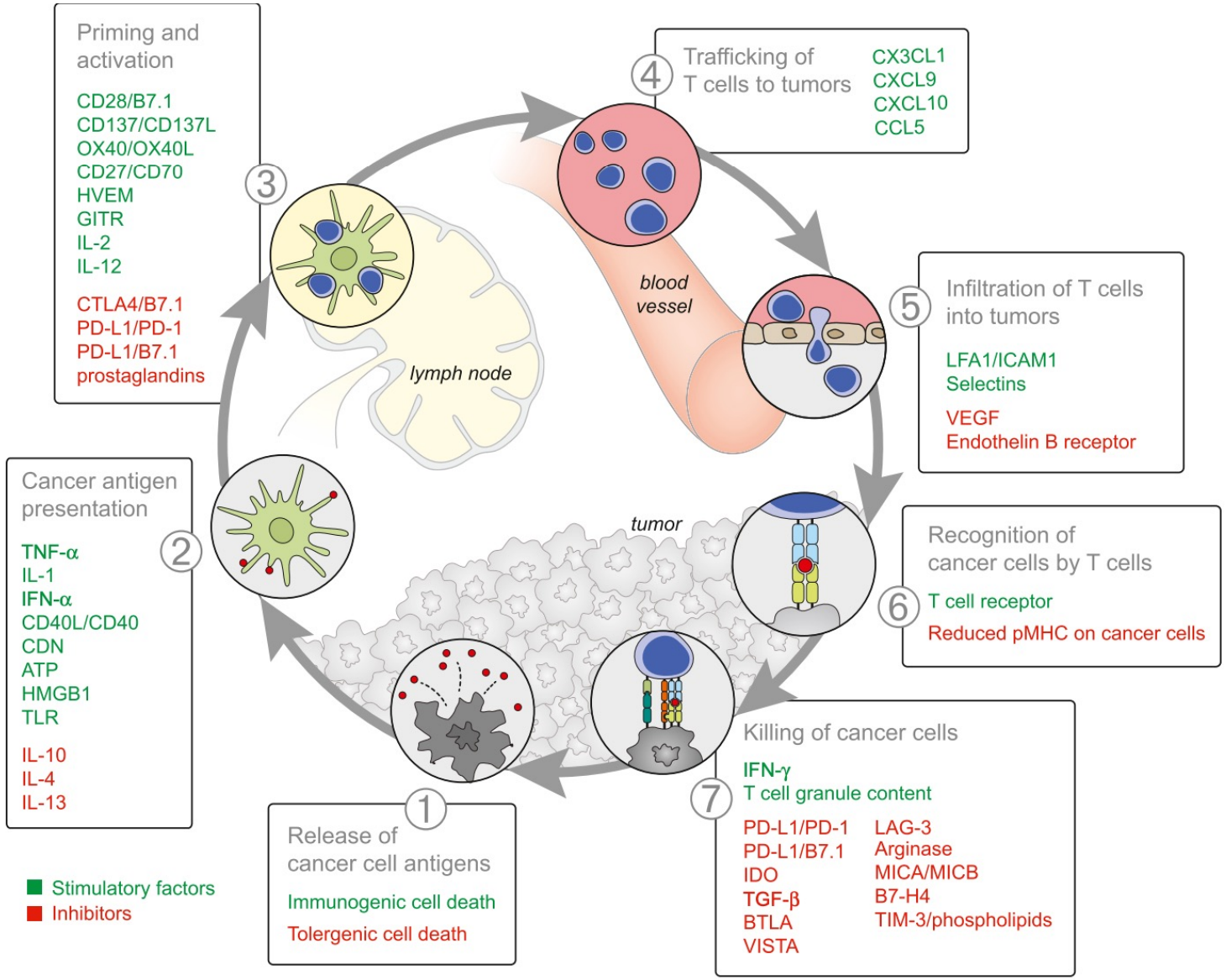
Trial Design:
Randomized, open-label multicenter study, incorporating an initial safety lead-in cohort followed by a randomized portion

Estimated Study Completion: October 2024 **Status: Recruiting**

ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SCCHN, squamous cell carcinoma of head and neck.

1. https://clinicaltrials.gov/ct2/show/NCT04675333.

Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



Chen and Mellman 2013

TACTI-003: Phase II Study of Eftilagimod Alpha (Efti; IMP321) in Combination With Pembrolizumab for 1L Treatment of Unresectable r/m SCCHN

Eftilagimod: soluble lymphocyte activation gene (LAG)-3 (APC activator)

NCT04811027
Phase IIb

Worldwide

KEY ELIGIBILITY CRITERIA

- 18 years or older
- Recurrent/metastatic (disseminated) SCCHN Availability of tissue for PD-L1 biomarker analysis
- Availability of PD-L1 biomarker result using the FDA approved diagnostic test
- Availability of tissue for testing of HPV status for oropharyngeal cancer
- ECOG PS 0-1

N=154

Cohort A
Randomised 1:1 to:

- Efti 30 mg SC Q2W (cycles 1–4) and Q3W (cycles 5 onwards) and pembrolizumab 400 mg IV (30 min) Q6W
- Pembrolizumab 400 mg IV (30 min) Q6W

Cohort B

- Efti 30 mg SC Q2W (cycles 1–4) and Q3W (cycles 5 onwards) and pembrolizumab 400 mg IV (30 min) Q6W

PRIMARY ENDPOINTS

- ORR according to RECIST 1.1

SECONDARY ENDPOINTS

- OS
- ORR according to iRECIST
- Time to and duration of response, DCR and PFS according to RECIST 1.1 and iRECIST
- Occurrence of anti-efti-specific antibodies
- Frequency, severity and duration of (serious) AEs
- Quality of life

Stratification:

- Cohort A: CPS ≥1
- Cohort B: CPS <1

Trial Design:
Randomized, open-label, parallel assignment study

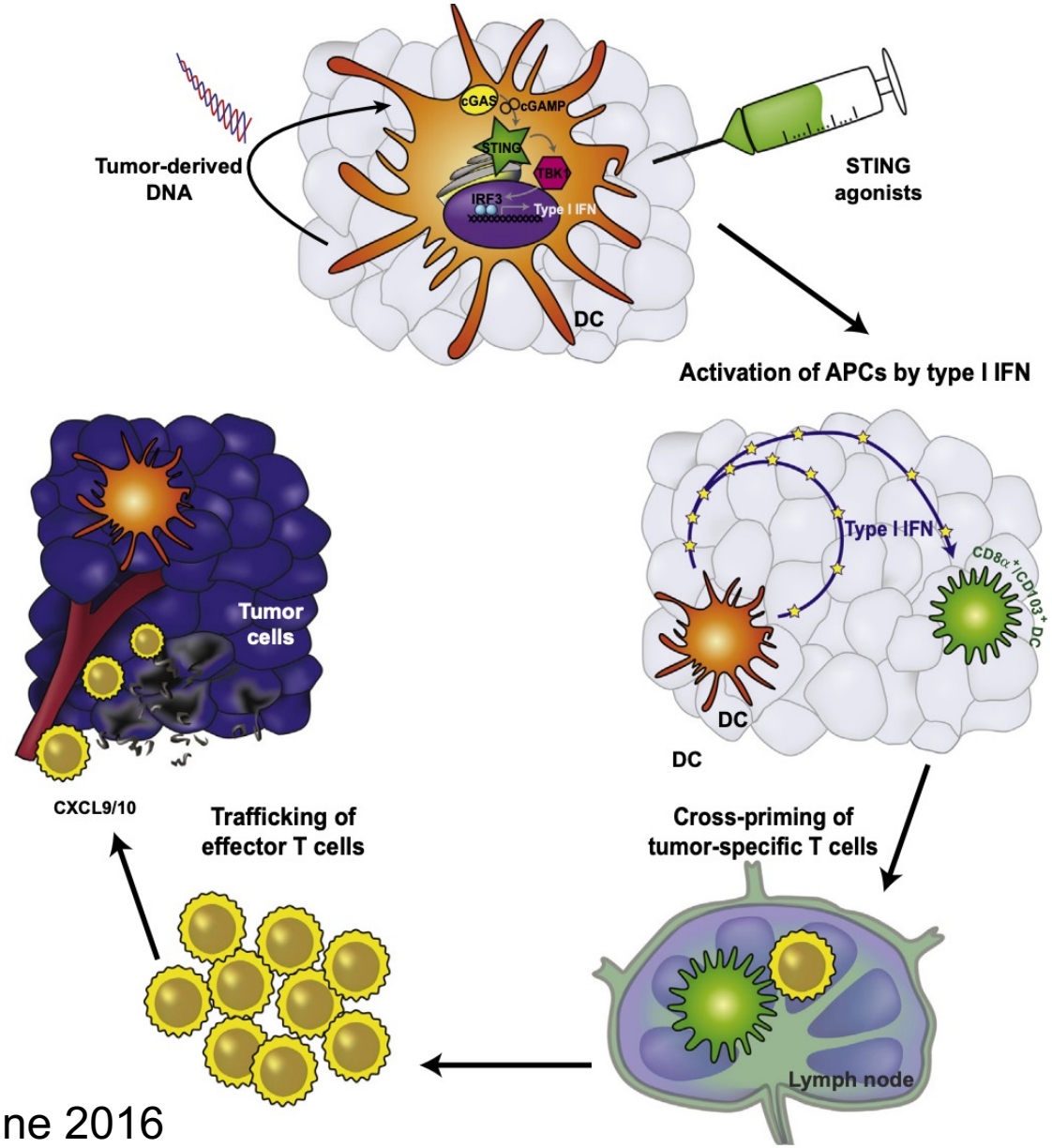
Estimated Study Completion: March 2025

Status: Recruiting

AEs, adverse events; APC, antigen-presenting cell; CPS, combined positive score; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; iRESIST, modified RECIST 1.1 for immune-based therapeutics; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SC, subcutaneous; SCCHN, squamous cell carcinoma of head and neck.

1. https://clinicaltrials.gov/ct2/show/NCT04811027.

STING Pathway Activation



Corrales and Gajewski, Cytokine 2016

Ulevostinag ± Pembrolizumab: Phase II Study to Evaluate Intratumoral Ulevostinag + IV Pembrolizumab vs IV Pembrolizumab Monotherapy in 1L r/m SCCHN

Ulevostinag (MK-1454): Stimulator of Interferon Genes (STING) agonist

NCT04220866
Phase II

Worldwide

KEY ELIGIBILITY CRITERIA

- 18 years or older
- SCCHN considered incurable by local therapies
- No prior systemic therapy administered in the recurrent or metastatic setting
- Tumor PD-L1 expression of CPS ≥1
- Measurable disease per RECIST 1.1
- At least 1 measurable lesion which is amenable to injection
- ECOG PS of 0 or 1
- Adequate organ function ≤7 days prior to treatment initiation

N=200

Ulevostinag 540 µg IT on Day 1 of every week for two 3-week cycles then on Day 1 of each 3-week cycle for up 33 cycles and pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for up to 35 cycles

Pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (up to 35 cycles)

PRIMARY ENDPOINTS

- ORR per RECIST 1.1

SECONDARY ENDPOINTS

- PFS per RECIST 1.1
- DoR per RECIST 1.1
- OS
- Number of participants experiencing an AE
- Number of participants discontinuing due to an AE

Stratification:

- PD-L1 CPS ≥1–19 vs ≥20
- ECOG PS 0 vs 1
- HPV + vs -

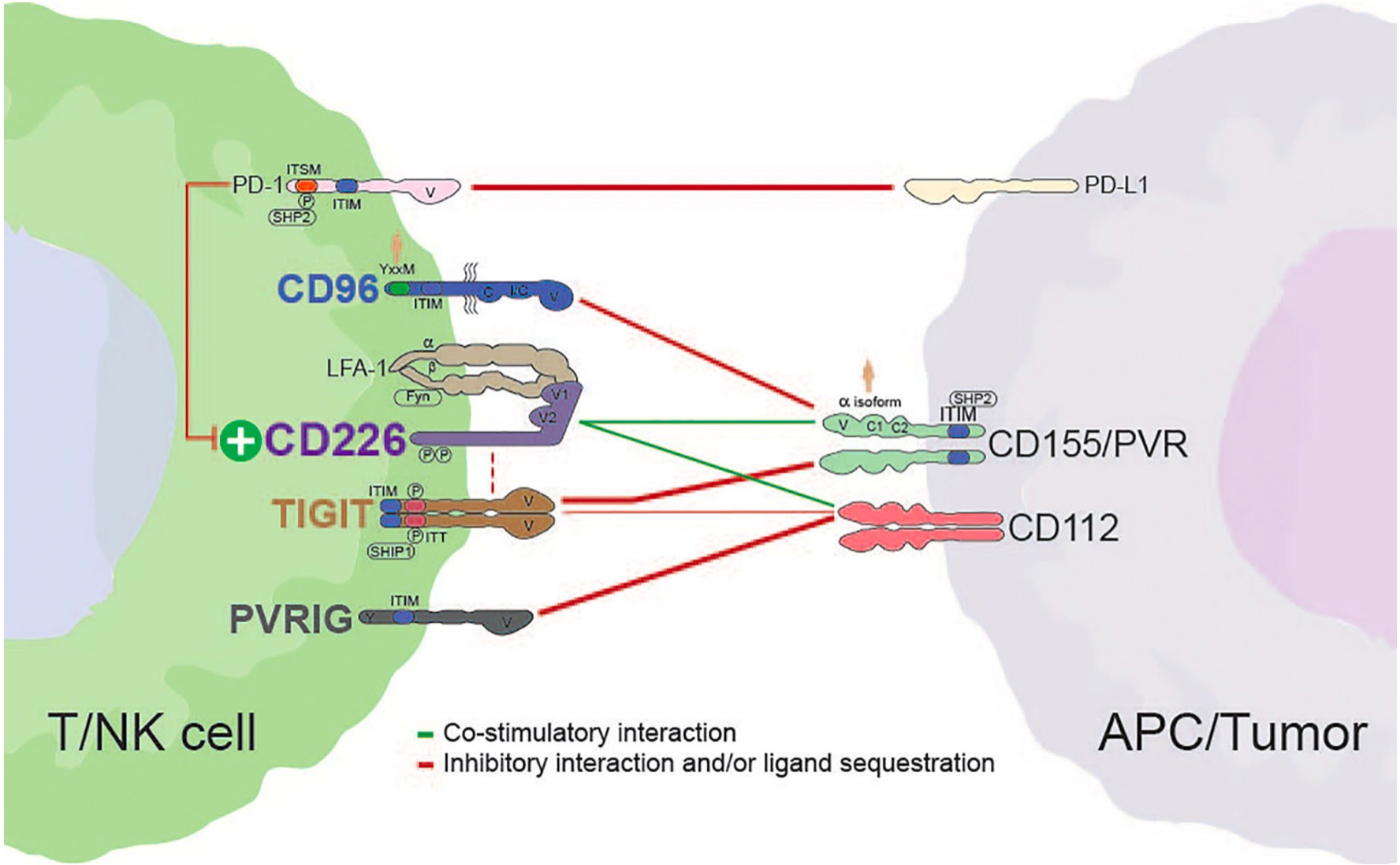
Trial Design:
Randomized, open-label study

Estimated Study Completion: April 2023

Status: Active, not recruiting

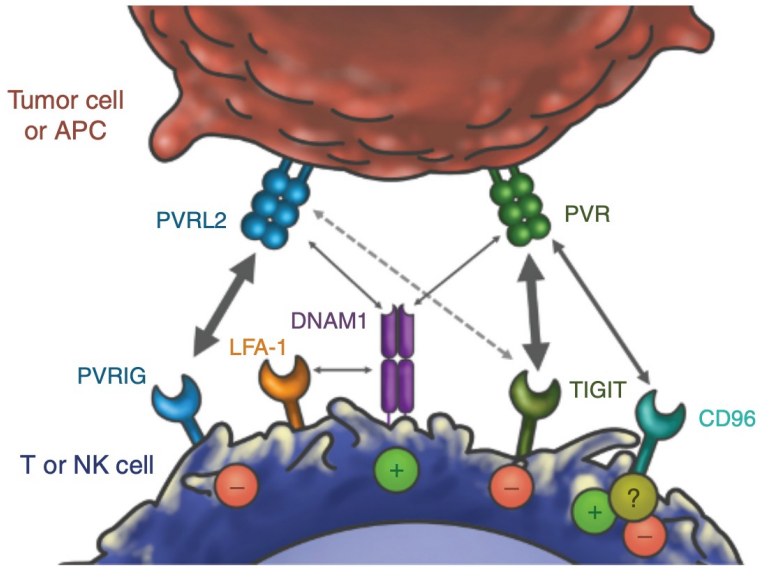
CPS, combined positive score; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IT, intratumoral; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; SCCHN, squamous cell carcinoma of head and neck; RECIST, Response Evaluation Criteria in Solid Tumours.

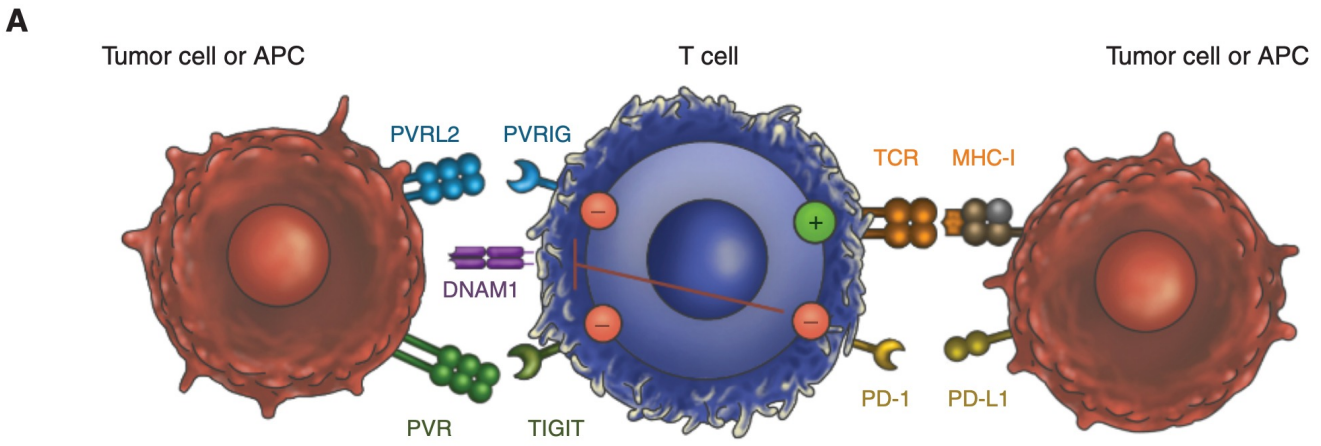
CD226 Axis

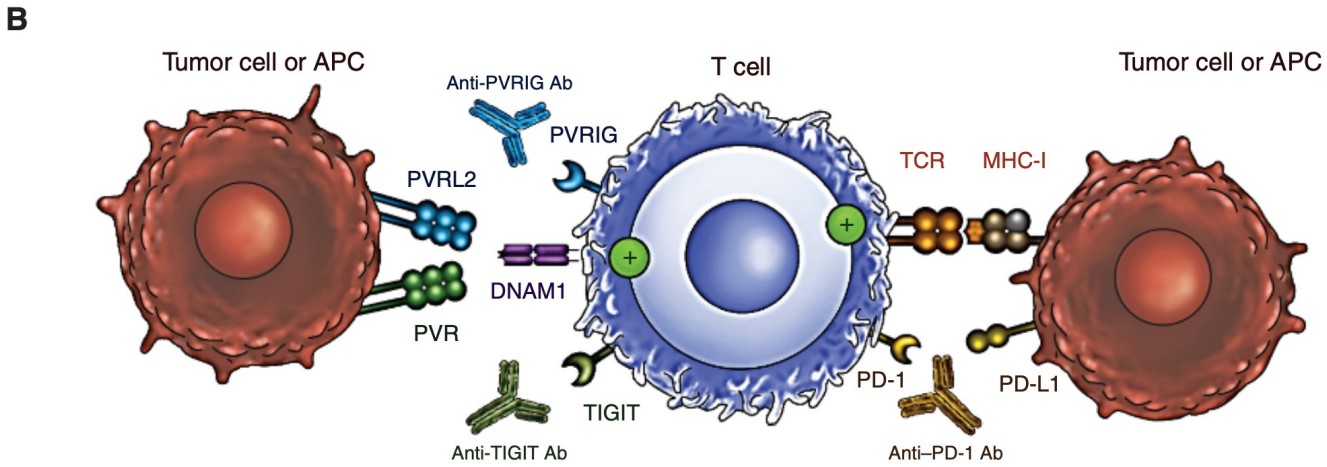


Connor et al Frontiers in Immunology 2022

TIGIT AND PVRIG







Alteber et al, Cancer Discovery 2021

SKYSCRAPER-09: Phase II, Randomized, Double Blind Study of Atezolizumab Plus Tiragolumab and Atezolizumab Plus Placebo as 1L in r/m PD-L1 Positive SCCHN

Atezolizumab: anti-PD-L1

KEY ELIGIBILITY CRITERIA

- 18 years or older
- Recurrent/metastatic SCCHN incurable by local therapies
- Results from HPV status test for oropharyngeal carcinoma
- No prior systemic therapy for metastatic/recurrent SCCHN
- Measurable disease per RECIST v1.1
- Tumour PD-L1 expression
- ECOG PS of 0 or 1
- Life expectancy ≥12 weeks

N=120

Atezolizumab 1200 mg IV and tiragolumab 600 mg IV Q3W on Day 1 of each 21-day cycle

Atezolizumab 1200 mg IV and IV placebo Q3W on Day 1 of each 21-day cycle

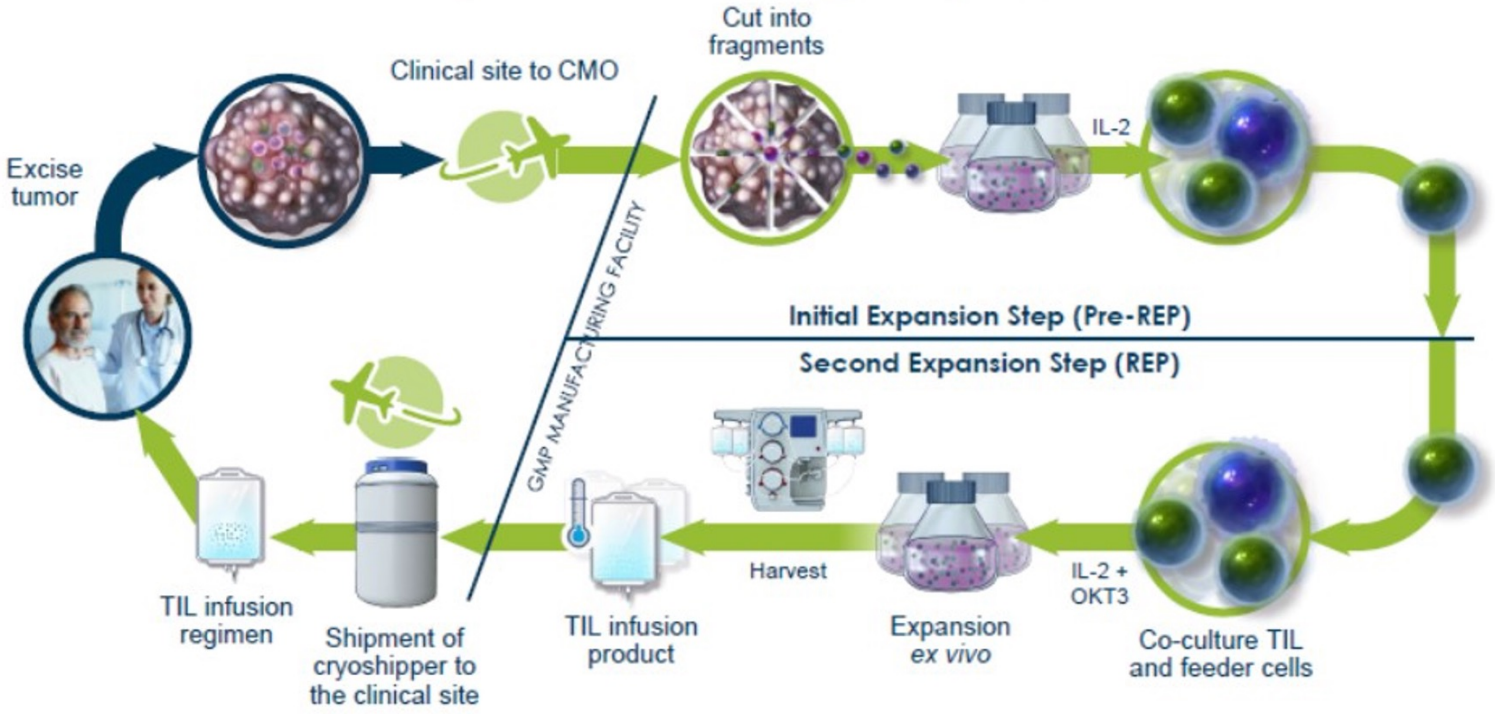
PRIMARY ENDPOINTS

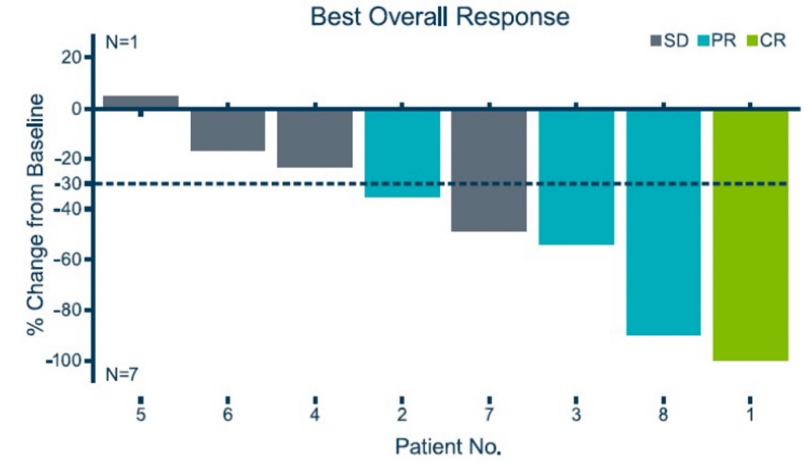
- Confirmed ORR

SECONDARY ENDPOINTS

- DOR
- PFS
- OS
- PFS at 6 months
- OS at 6 and 12 months
- TTCD
- % participants with AEs
- C_{min} and C_{max} of atezolizumab
- C_{min} and C_{max} of tiragolumab
- No. participants with ADAs to atezolizumab and tiragolumab

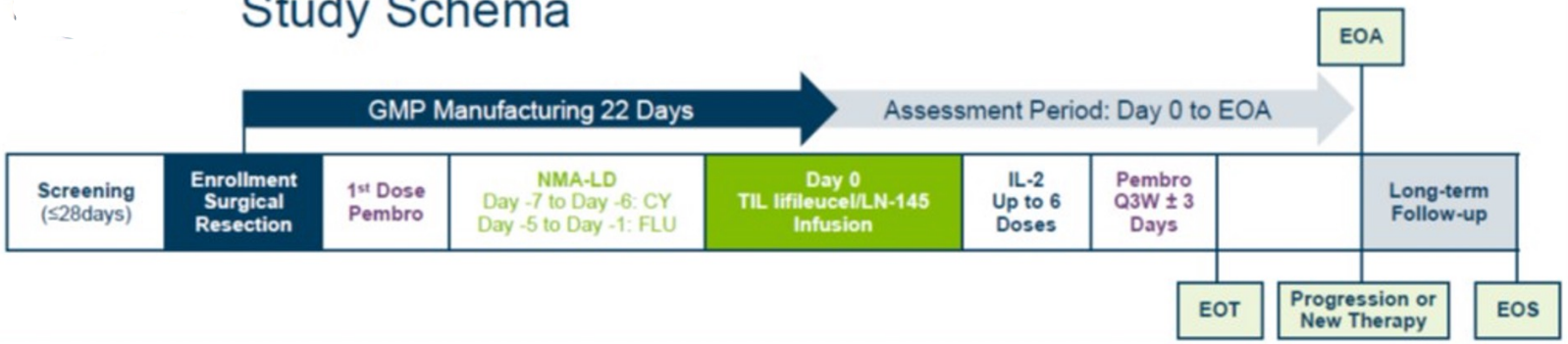
LN-145 Production Method Uses Central GMP Manufacturing in a 22-day Process Yielding a Cryopreserved TIL Product





87.5% of evaluable patients had a reduction in tumor burden

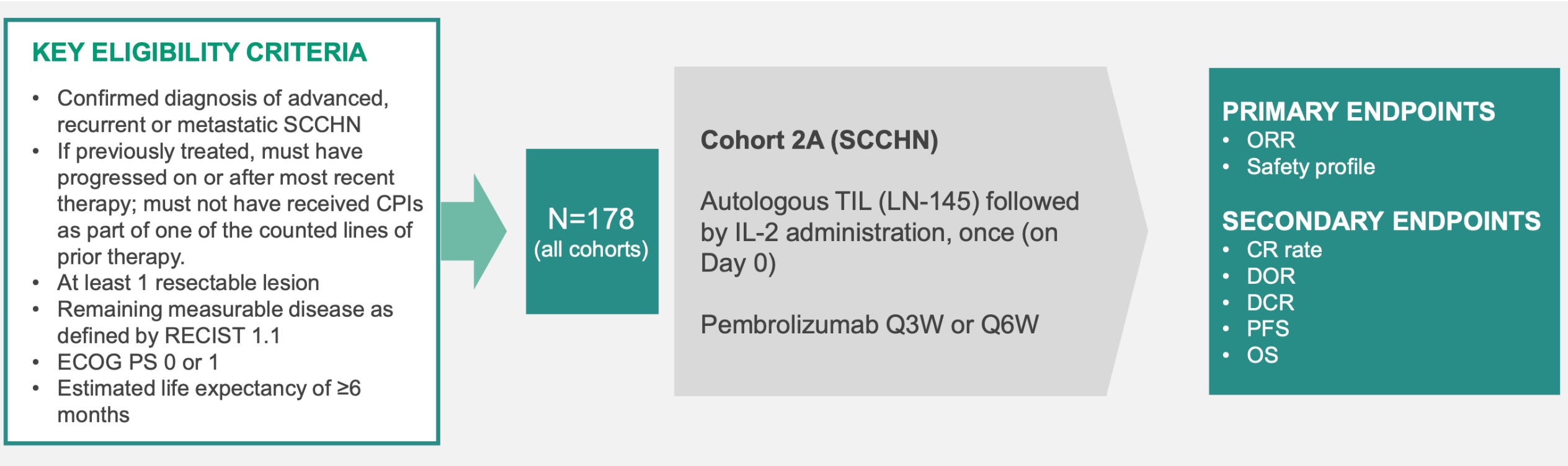
Study Schema



Jimeno et al SITC 2020

LN-145: Phase II Study of Autologous Tumor Infiltrating Lymphocytes (TIL; LN 144/LN-145/LN-145-S1) in Patients With Solid Tumors

LN-145: autologous tumour infiltrating lymphocytes



MCLA-158 (Petosemtamab), An IgG1 Bispecific Antibody Targeting EGFR And LGR5, In Advanced Head And Neck Squamous Cell Carcinoma

Key HNSCC Inclusion Criteria

- Progression on or intolerant to anti-PD-(L)1 and platinum-based therapy in incurable recurrent or metastatic disease
- ECOG PS 0-1
- Measurable disease

Treatment Plan

- Petosemtamab 1500 mg IV, Q2W, 28-day cycle
- Until PD or toxicity
- Tumor assessment Q8W

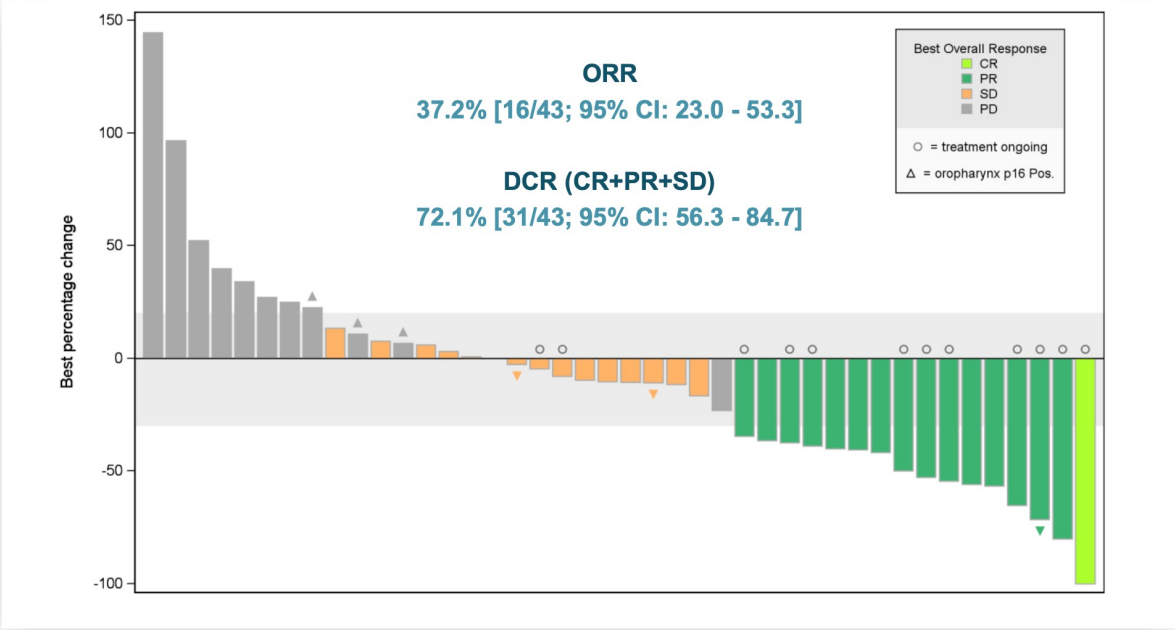
Follow-Up

Survival follow-up for up to 18 months

Demographics and Disease Features	N=49
Age (years), median (range)	63 (31 - 77)
Male / female	38 (78%) / 11 (22%)
ECOG PS 0 / 1	14 (29%) / 35 (71%)
Squamous cell carcinoma histology	48 (98%)[1]
Tumor location	
▪ Oropharynx	17 (35%)
▪ Oral cavity	15 (31%)
▪ Larynx	8 (16%)
▪ Hypopharynx	4 (8%)
▪ Other	5 (10%)[2]
Measurable disease	48 (98%)

1. *One patient had p16-negative epidermoid cancer with unknown origin*
2. *Other: nasal cavity and paranasal sinuses, nasopharynx, supraglottis, vocal cord, unknown origin*

Best Percent Change in Sum of Target Lesions From Baseline (N=43)



One patient with best overall response of not evaluable not included due to no post-baseline tumor assessment
p16 status was available in 9 of the 15 oropharynx patients (6 positive and 3 negative) in the efficacy evaluable population

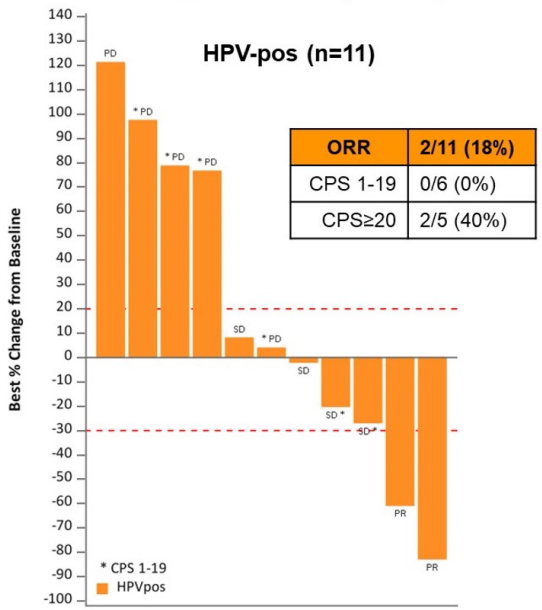
Cohen et al, AACR, 2023

BCA101 (anti-EGFR/TGF-β trap) + pembrolizumab
R/M HNSCC expansion cohort

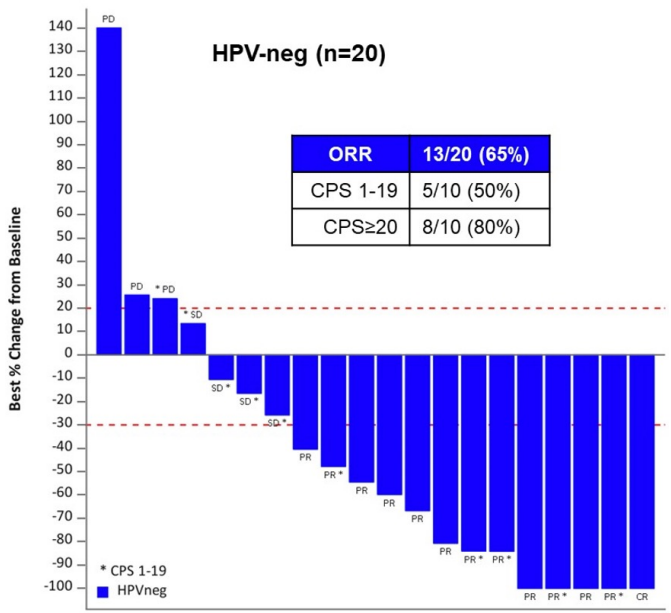
Population

- R/M HNSCC
- Oral cavity, oropharynx, hypopharynx & larynx
- HPV (p16) testing required for oropharyngeal cancer
- CPS≥1
- No prior systemic therapy in R/M setting

		N = 33 (100%)
Age	Median (range)	65 (31-80)
Sex – n (%)	Male/Female	23/10 (70% vs. 30%)
HNSCC Primary site of disease	Oropharynx	18 (55%)
	HPV-pos	12 (67% of Oropharynx)
	HPV-neg	6 (33% of Oropharynx)
	Oral Cavity	10 (30%)
	Hypopharynx	3 (9%)
	Larynx	2 (6%)
CPS - n (%)	≥20	15 (45%)
	1-19	18 (55%)
Distant metastasis – n (%)		25 (76%)
ECOG Performance Status – 0 vs.1 (%)		16 vs. 17 (48% vs. 52%)



ORR	2/11 (18%)
CPS 1-19	0/6 (0%)
CPS≥20	2/5 (40%)



ORR	13/20 (65%)
CPS 1-19	5/10 (50%)
CPS≥20	8/10 (80%)

- ORR 65% in HPV-neg subjects with responses observed in both CPS subgroups

Hanna et al, ASCO 2023

Cabozantinib and Pembrolizumab : Phase II

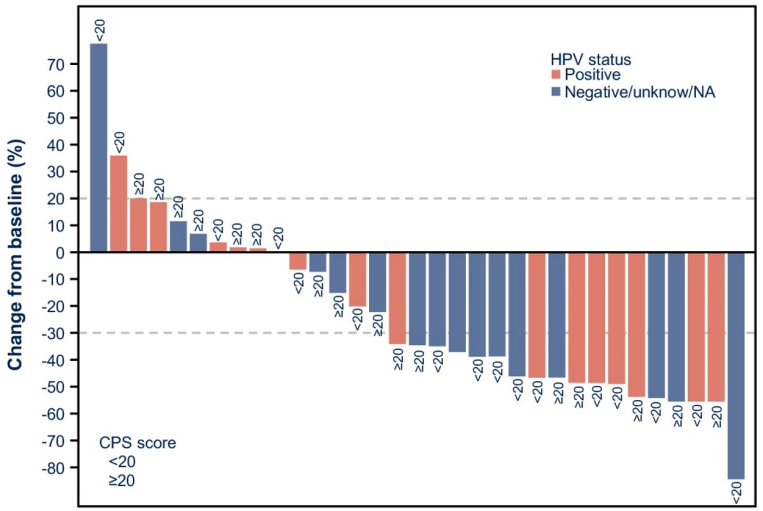
Patients with R/M HNSCC
Inclusion criteria
- Inoperable, refractory or metastatic R/M HNSCC
- RECIST v1.1 measurable disease
- ≤1 prior radiation therapy to the HN allowed
- Life expectancy >3 months
- ECOG performance status 0–1

Exclusion criteria
- HPV negative unknown primary disease
- Cavitating lesions or recent bleeding history

→ **Pembrolizumab 200 mg IV Q3W + Cabozantinib 40 mg PO QD** → Tumors were assessed by RECIST v1.1 criteria by CT/MRI every 9 weeks

Patient Characteristic		N=36 n (%)
Age, median (range), years		62 (54-67)
Gender	Male Female	30 (83) 6 (17)
ECOG performance status, %	0 1	18 (50) 18 (50)
Primary site	Oropharynx Oral cavity Hypopharynx Larynx Nasopharynx	22 (61) 2 (6) 2 (6) 4 (11) 6 (16)
HPV (p16)	Positive Negative Unknown	17 (47) 12 (33) 7 (20)
Prior therapy	Radiation Cisplatin Cetuximab	31 (89) 36 (100) 3 (8)
PD-L1 CPS score (total of 34)	CPS <1 CPS 1-19 CPS ≥20	2 (6) 15 (44) 17 (50)

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



Saba et al, Nat Med 2023

Conclusions

- Checkpoint Blockade current Standard for first line recurrent head and neck cancer
- Post CPI , Chemotherapy with or without cetuximab is current standard
- New targets of interest: LAG3, TIGIT, TIM 3, CD226 axis, PVRIG, STING, CD96
- Synergy with VEGF/PDL1, EGFR/PDL1 , need confirmatory trials