ASCO / ESMO updates

Developments in Head and Neck Cancers

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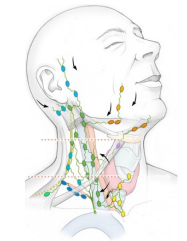
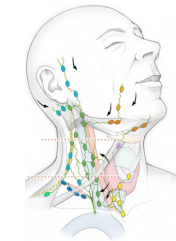
12/01/2023

COMPREHENSIVE CANCER CENTER



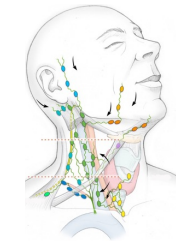
ASCO

- Abstract 6003 - Phase II FRAIL-IMMUNE trial evaluating the efficacy and safety of durvalumab combined with weekly paclitaxel carboplatin in first-line in patients with (R/M SCCHN) not eligible for cisplatin-based therapies.
- Abstract 6005 - Dose expansion results of the bifunctional EGFR/TGFβ inhibitor BCA101 with pembrolizumab in patients with recurrent, metastatic head and neck squamous cell carcinoma.
- Abstract 6029 – TACTI-002 Part C : Phase II study of eftilagimod alpha (soluble LAG3) and pembrolizumab in patients with metastatic second line H/N SCC unselected for PD-L1.
- Abstract 6083 - Combined pulse radiotherapy (QUAD shot regimen) with ICI to enhance immune responses for LAHNSCC in patients considered ineligible for curative intent therapy.



ESMO

- HCC 15-132: A randomized phase II study of concurrent vs. sequential pembrolizumab with chemoradiation (CRT) in locally advanced head and neck cancer (LA HNSCC): 4-year results and tumor-immune microenvironment analysis.
- LBA 46 - SAKK 11/16, a phase II trial evaluating Overall Survival (OS) of recurrent/metastatic Head & Neck Squamous Cell Carcinoma (R/MHNSCC) patients (pts) progressing after ≥ 1line of systemic therapy, treated with MVX-ONCO-1, a novel, first in class cell encapsulation-based immunotherapy.
- A phase 2 study evaluating tipifarnib in m*HRAS,* recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) (AIM-HN)



Treatment landscape R/M HNSCC

First Line →

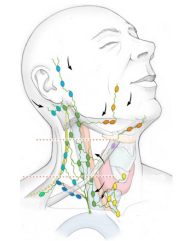
PD1 Monotherapy	PD1 + Chemotherapy
- PDL1 + disease - CPS score 1 & >20	PDL1 – or unknown High tumor burden

Second Line →

No standard of care
- Depends on first line therapy. - Performance status
1. No previous PDL1 → PD-1 therapy 2. Single agent vs doublet chemotherapy 3. EGFR naïve → Cetuximab/platinum

Third Line →

No standard of care
- Depends previous lines of therapy. Likely single agent chemotherapy



[Head / Neck cancer]

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Abstract 6003 – Frail Immune

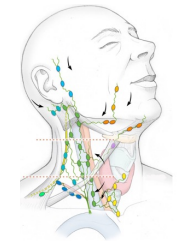
- Phase II FRAIL-IMMUNE trial evaluating the efficacy and safety of durvalumab combined with weekly paclitaxel carboplatin in first-line in patients with (R/M SCCHN) not eligible for cisplatin-based therapies. (GORTEC 2018-03)

✓ Objective : Efficacy and tolerance of PDL-1 inhibition (durvalumab) combined with weekly carboplatin (AUC2) + Paclitaxel as first line for patients R/M ineligible for cisplatin

✓ Prospective, multicenter, single arm phase II, N=64 patients

✓ Primary End Point: OS at 12 months

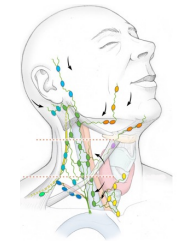
✓ Secondary End Points: PFS, ORR, DoR, QoL.



Abstract 6003 – Frail Immune trial

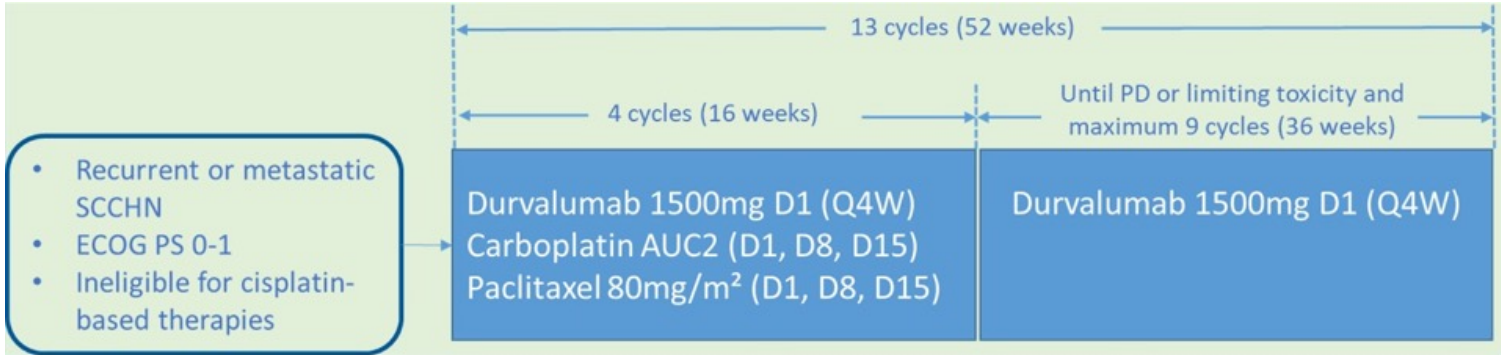
Patients and disease characteristics (N=64)			
Sex	Female	6	(9.4%
	Male	58	(90.6%
Age	Median (min; max)	69.5 (54.0; 90.0)	
ECOG	0	24	(37.5%
	1	40	(62.5%
Localization of the primary tumor	Oral cavity	9	(14.1%
	Oropharynx	24	(37.5%
	Hypopharynx	11	(17.2%
	Larynx	18	(28.1%
	Isolated cervical lymphnodes, unk primary site	2	(3.1%
Status of the disease at inclusion	Primary metastatic	5	(7.8%
	Metastatic only, recurrence	19	(29.7%
	Locoregional only, recurrence	26	(40.6%
	Primary locoregional and metastatic	1	(1.6%
	Locoregional and metastatic recurrence	13	(20.3%
PDL1	Missing	8	
	<1	13	(23.2%
	>=1	43	(76.8%
	>=20	17	(30.4%
HPV (oropharynx)	Missing	4	
	Negative	11	(55.0%
	Positive	9	(45.0%

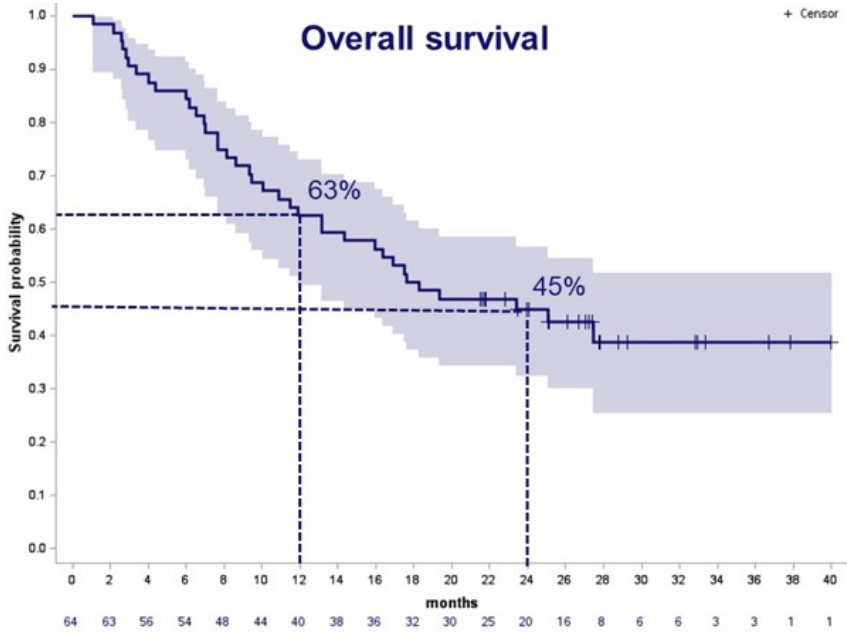
Criteria for Cisplatin ineligibility
Older than 70 years old (N=30)
Creatinine clearance: 40< Creat Cl <60ml/min (N=18)
Comorbidities (N=18)



Slides images from ASCO2023 Abstract presentation. Fayette MD, et al.

Abstract 6003 – Frail Immune trial





Analysis population N=64	
Number of deaths (%)	37 (57.8%)
Median OS, months [min-max]	18.0 [11.9-NR]
12-month OS-rate (95%CI)	63% [49-73]
24-month OS-rate (95%CI)	45% [32-57]

Median duration of follow-up was 27.1 months (21.5-40.1)

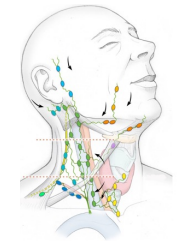
12 months OS 63%, mOS 18 months, PFS 7.0 months, ORR 71%

Slides images from ASCO2023 Abstract presentation. Fayette MD, et al.

Abstract 6003 – Frail Immune trial

Summary of AEs		
All grades AEs	64	(100.0%)
All grade AEs related to Durvalumab	54	(84.4%)
All grade AEs related to chemotherapy	62	(96.9%)
Grade ≥ 3 AEs	54	(84.4%)
Grade ≥ 3 AEs related to Durvalumab	13	(20.3%)
Grade ≥ 3 AEs related to chemotherapy	43	(67.2%)
Grade 5 AEs	11	(17.2%)
Grade 5 AEs related to Durvalumab	0	(0.0%)
Grade 5 AEs related to chemotherapy	1*	(1.6%)
AEs having led to Durvalumab modification	36	(56.3%)
AEs having led to chemotherapy modification	54	(84.4%)
Durvalumab definite discontinuation due to toxicity	2	(3.1%)
Chemotherapy discontinuation due to toxicity	13	(18.8%)

Slides images from ASCO2023 Abstract presentation. Fayette MD, et al.



[Head / Neck cancer]

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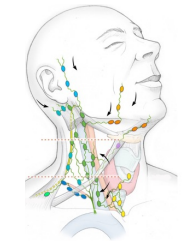
Abstract 6003 – Frail Immune trial

Discussion

- Durvalumab plus weekly Carboplatin (2AUC) + Paclitaxel (80 mg/m2) could serve as a potential option for cis-ineligible patients.
- ?KEYNOTE-B10 (ESMO 2022) → Pembrolizumab+Carboplatin + Paclitaxel (3 weekly). ORR 43%, PFS 5.6 months and OS 12.1.
- Better tolerance for weekly schedule administration



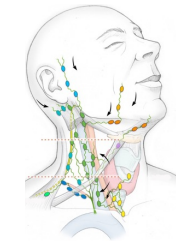
Abstract 6005 - BCA101 with pembrolizumab

Dose expansion results of the bifunctional EGFR/TGFβ inhibitor BCA101 with pembrolizumab.

- ✓ R/M HNSCC (oral cavity, oropharynx, hypopharynx and larynx)
- ✓ CPS > or equal 1.
- ✓ No prior systemic therapy.

Stage 1 → 18 patients , >4 responses required to proceed stage 2.

Stage 2 → 21 patients (total 39).



[Head / Neck cancer]

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Abstract 6005 - BCA101 with pembrolizumab

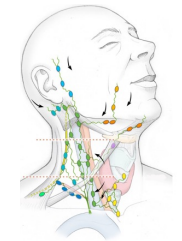
- BCA101 mechanism of actions:

TGF-b inhibitor (trap) to the tumor microenvironment through EGFR directed approach.

Increase antitumor activity via ADCC and increased NK cell activation.

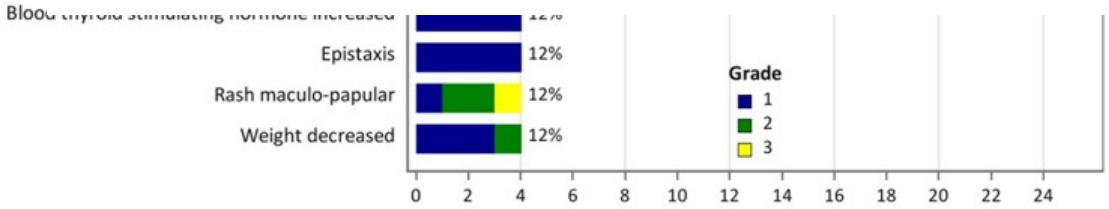
Dual inhibition of EFR and TGF-B prevents epithelial-mesenchymal transition and metastasis.

Slides images from ASCO2023 Abstract presentation. Hanna et al.



Abstract 6005 - BCA101 with pembrolizumab

		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%)



f subjects (two G3 events)

manageable without the
ns
heal hemorrhage

ng to:
6%)
ted reaction

natase increased

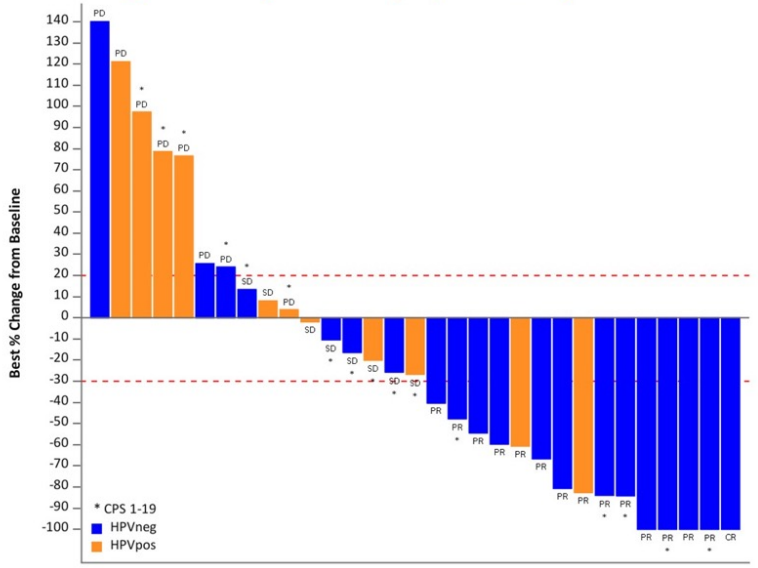
- Permanent discontinuation: 3/33 (9%)
  - G3 tracheal hemorrhage
  - G4 pericarditis
  - G3 blood alkaline phosphatase increased

Total n=33

Slides images from ASCO2023 Abstract presentation. Hanna et al.

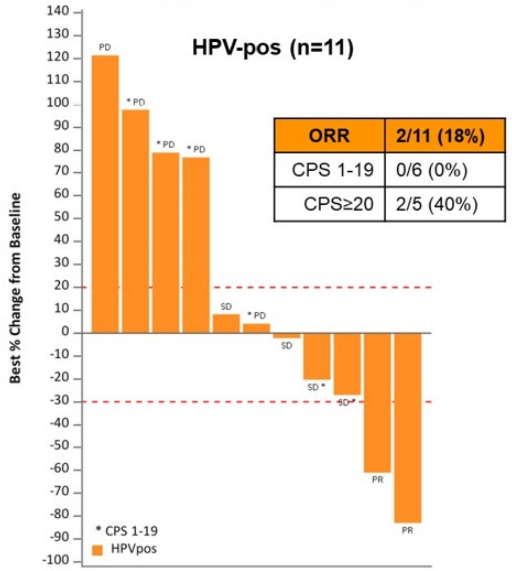
Abstract 6005 - BCA101 with pembrolizumab

Preliminary Efficacy – Total population (N=31 evaluable)

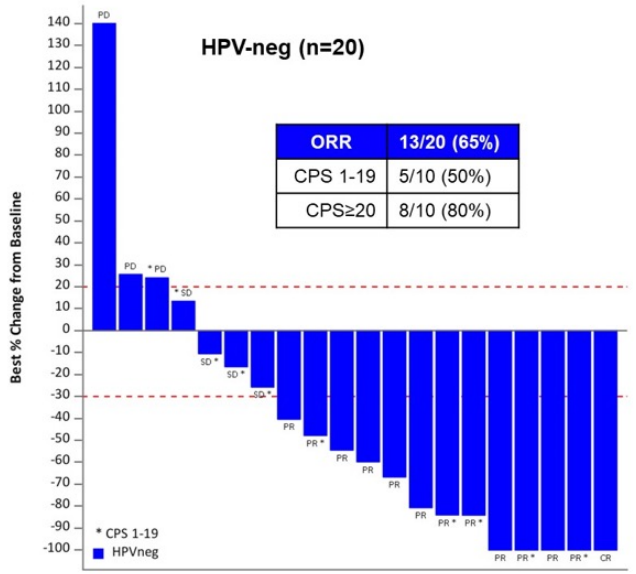


ORR	15/31 (48%)
CR	1 (3%)
PR	14 (45%)
SD	8 (26%)
PD	8 (26%)

Preliminary Efficacy – by HPV status



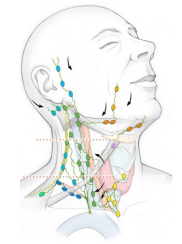
ORR	2/11 (18%)
CPS 1-19	0/6 (0%)
CPS≥20	2/5 (40%)



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

Slides images from ASCO2023 Abstract presentation. Hanna et al.



Abstract 6005 - BCA101 with pembrolizumab

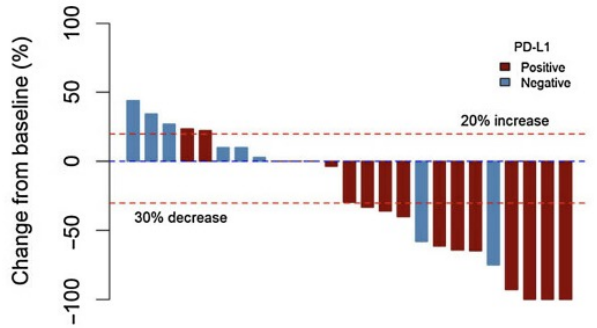
- Discussion

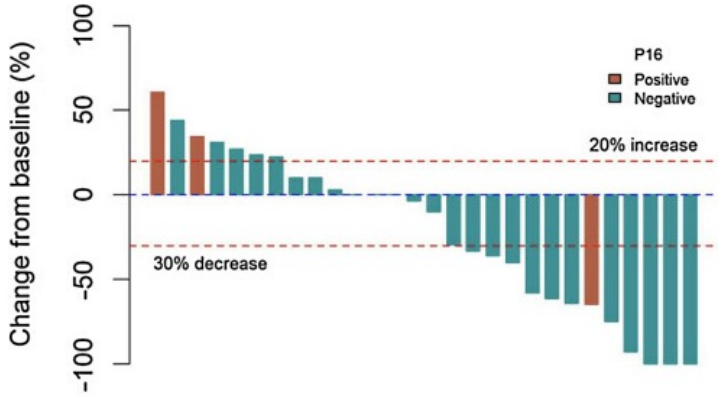
ORR 48%, HPV negative ORR 65%.

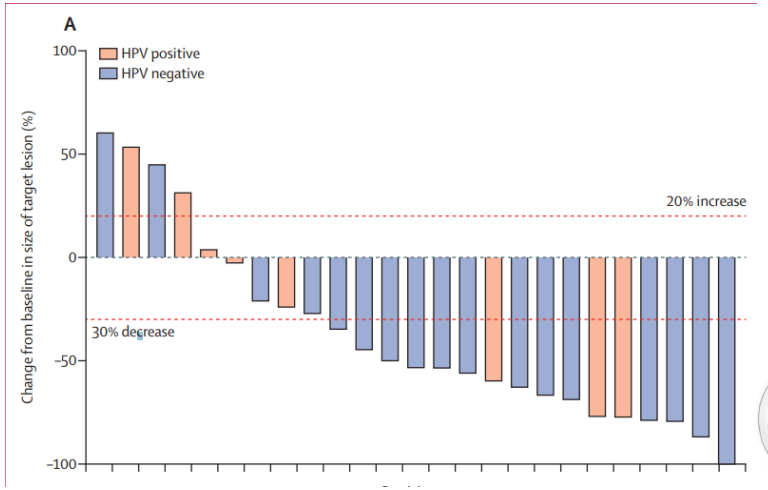
CPS 1-19 (5/10, 50%) & CPS >20 (8/10, 80%)

mPFS HPV negative NR (1.3-14.6, at least 6.6 months)

- Combination warrants larger analysis in randomized study specifically HPV negative population.
- Durvalumab/cetuximab (II) ORR 39% vs Pembrolizumab cetuximab (II) ORR 45%







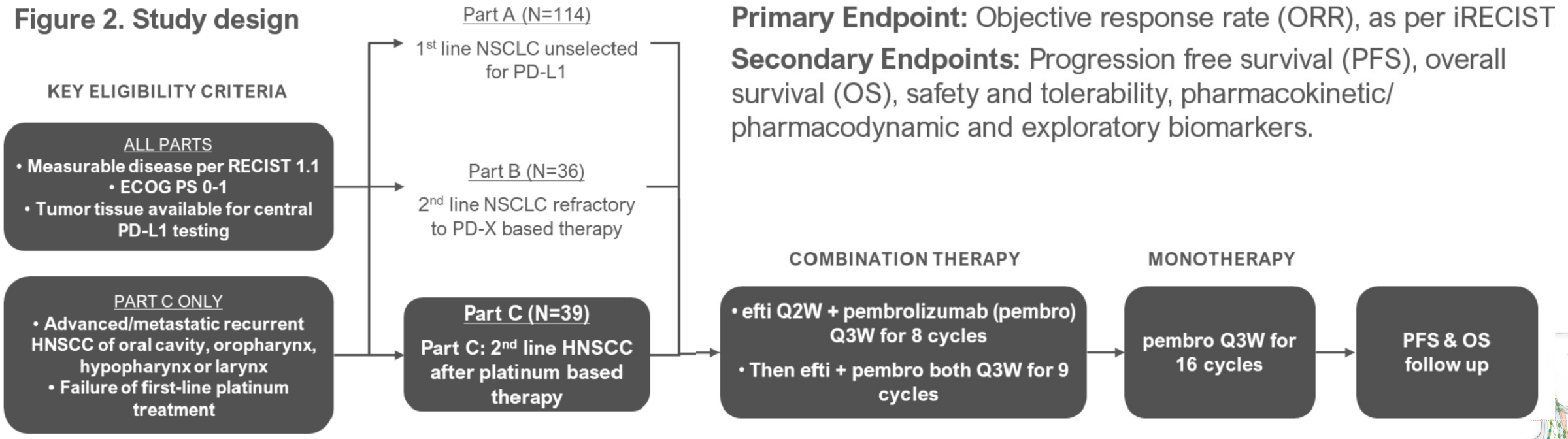
1. Gulati et al. Durvalumab plus cetuximab in patients with recurrent or metastatic head and neck SCC: An open label, nonrandomized, phase II clinical trial. Clin Cancer Res (2023) 29 (10): 1906–1915.
2. Sacco et al. Pembrolizumab plus cetuximab in patients with recurrent or metastatic head and neck SCC: an open label, multi-arm, non-randomized, multicenter, phase 2 trial. Lancet Oncology June 2021, Volume 22, Issue 6, P 883-892

Abstract 6029 – TACTI-002 Part C

Eftilagimod alpha (soluble LAG3) and Pembrolizumab

- Phase II, 2nd line H/N SCC, PDL1 all comers, n=39
- OPC, oral cavity, hypopharynx and larynx. 46% CPS >20, 0 <1%. No P16 status
- Efti 30 mg SC Q2W for 8 cycles and Q3W for 9 cycles + Pembro Q3W for a max of 2 years.

Figure 2. Study design



Doger B et al. Final results of TACTI 002 Part C. ASCO Poster session 2023

Abstract 6029 – TACTI-002 Part C

- Eftilagimod alpha : MH-CII agonist and NOT anti-LAG3 → activate APC → broad CD4/8 activation.

SAFETY

- No treatment-related deaths occurred (**Table 2**).
- Immune-related AEs (irAEs[1]) >5%: hypothyroidism (20.5%) and pruritus (10.3%) (**Table 3**).

[1] relationship to efti and/or pembrolizumab could not be ruled out.

Table 2. General overview of AEs

Safety parameter[1]	n (%)
Adverse reactions with fatal outcome[2]	0
Serious adverse reactions[2]	*3 (7.7)*
Grade ≥3 adverse reactions[2]	*5 (12.8)*
Adverse reactions leading to discontinuation of treatment[2]	*2 (5.1)*

PD-L1 CPS[1]	ITT (N=37)	≥20 (N=15)	<20 (N=17)	≥1 (N=25)
Overall response rate (ORR)[2]				
ORR, % [95% CI][3]	29.7 [15.9–47.0]	60.0 [32.3–83.7]	11.8 [1.5–36.4]	38.5 [20.2–59.4]
Progression-free survival (PFS)[2]				
Median, mo [95% CI][4]	2.1 [2.0–4.3]	13.6 [1.6–24.8]	2.0 [1.3–2.7]	2.3 [1.6–13.6]
6-mo PFS rate, %	32.4	53.3	17.7	40.0
Overall survival (OS)				
Median, mo [95% CI][4]	8.7 [4.8–15.6]	15.5 [4.9–31.1]	7.5 [1.9–18.8]	12.6 [4.8–24.8]
12-mo OS rate, %	46.0	66.7	35.3	52.0
Duration of response (DoR)[2]				
Median, mo	NR	NR	16.2	NR
12-mo DoR rate, %	80.0	87.5	50.0	77.8
24-mo DoR rate, %	60.0	62.5	50.0	55.6

Doger B et al. Final results of TACTI 002 Part C. ASCO Poster session 2023

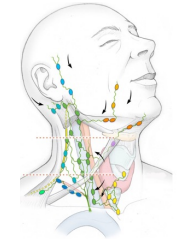
Abstract 6029 – TACTI-002 Part C

Discussion:

- ORR 29.7% with promising responses specially upon CPS>20 (60%).
- mPFS 13.6 months, mOS 15.5 m.
- NO P16 stratification & no CPS <1 included.

AntiLAG 3 H/N cancers

- INCAGN 2385-203: Retifanlimab in Combination With INCAGN02385 anti LAG3 and anti TIM-3 – Abstract ASCO 2023- No results posted.



Abstract 6083 – Combined Pulse Radiotherapy + ICI

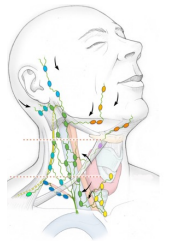
Combination of “Quad shot” with ICI to enhance immune response for elderly patients ineligible for curative intent therapy.

- ✓ Advance cutaneous or mucosal SCC
- ✓ 33 patients → mean age of 81
- ✓ Pulse dose QUAD shot delivered to gross disease excluding elective nodal disease(45 – 59 Gy) spaced 3 weeks + Pembrolizumab or Cemiplimab.

Characteristic	n (%) or mean (SD)
Male, n (%)	20 (60.6%)
Age, mean (SD)	81.27 (8.57)
KPS, n (%)	
50	1 (3.0%)
60	12 (36.4%)
70	18 (54.5%)
80	2 (6.1%)
ECOG, n (%)	
1	3 (9.1%)
2	25 (75.8%)
3	5 (15.2%)

Pathology = SCC, n (%)	25 (75.8.%)
TNM, n (%)	
Recurrent	8 (24.2%)
T0N2M0	2 (6.1%)
T2N0M0	1 (3.0%)
T2N1M0	2 (6.1%)
T2N2M0	4 (12.1%)
T3N0M0	3 (9.1%)
T3N1M0	1 (3.0%)
T3N2M0	2 (6.1%)
T3N2M1	2 (6.1%)

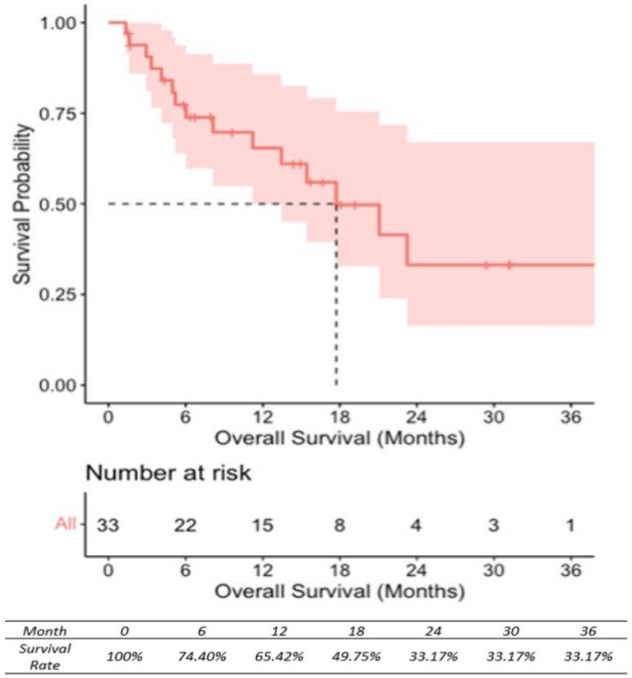
Slides images from ASCO2023 Poster session. J. De Los Santos



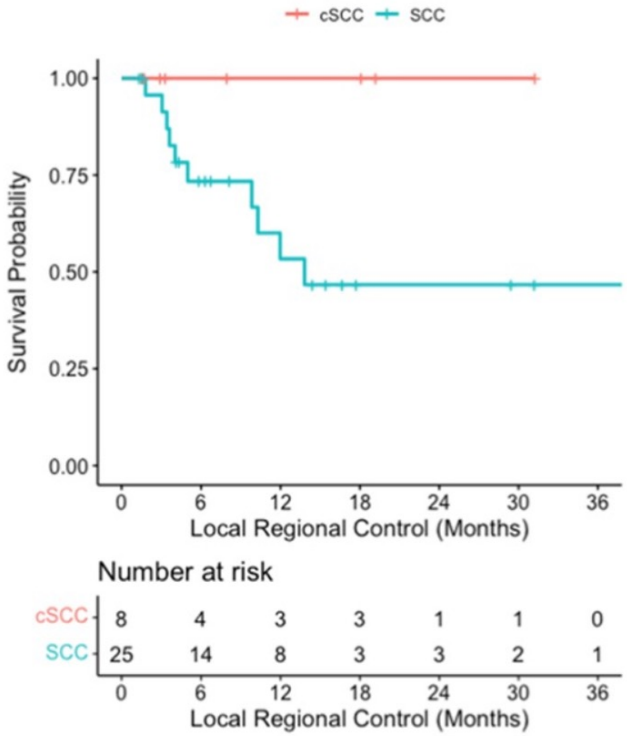
Abstract 6083 – Combined Pulse Radiotherapy + ICI

- Median OS with combination → 17 months vs 5.7 compared to previous series of QUAD
- DFS 1 year 59% , 2 years 37% LRC 61% 1 year and 55.5% 2 years.
- G3/4 = 9% (3/33) Colitis, fatigue, infusion

Figure 1. Kaplan-Meier Curve for Overall Survival (N= 33)

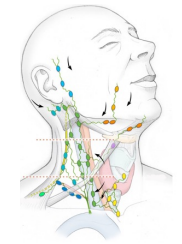


Month	0	6	12	18	24	30	36
Survival Rate	100%	74.40%	65.42%	49.75%	33.17%	33.17%	33.17%



Discussion

- Potential viable options for elderly/frail patients
- Needs to be confirmed with a larger RCT



[Head / Neck cancer]
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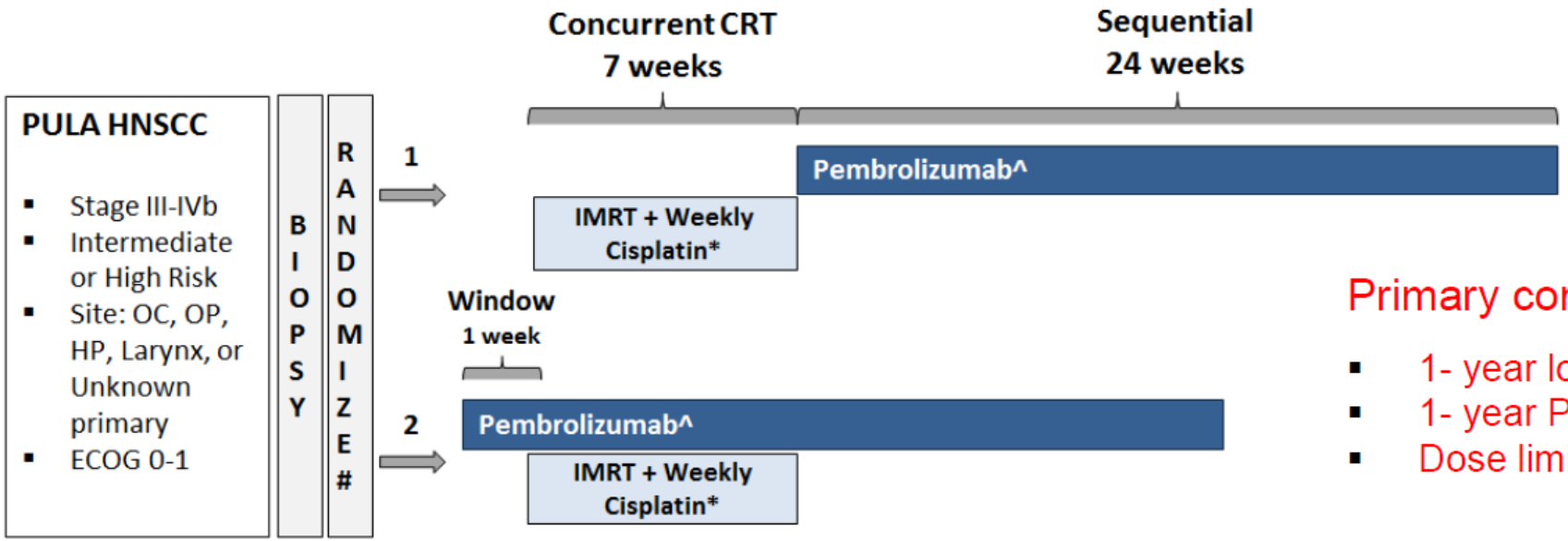
Slides images from ASCO2023 Poster session. J. De Los Santos et. al.

ESMO - HCC 15-132



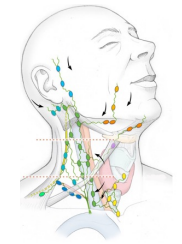
#Stratify:
- HPV status (p16)
- N0-2b vs. N2c-3

*Cisplatin: 40 mg/m²/week x 7 doses
^Pembrolizumab: 200 mg IV q 3 weeks x 8 doses

Primary composite endpoint:

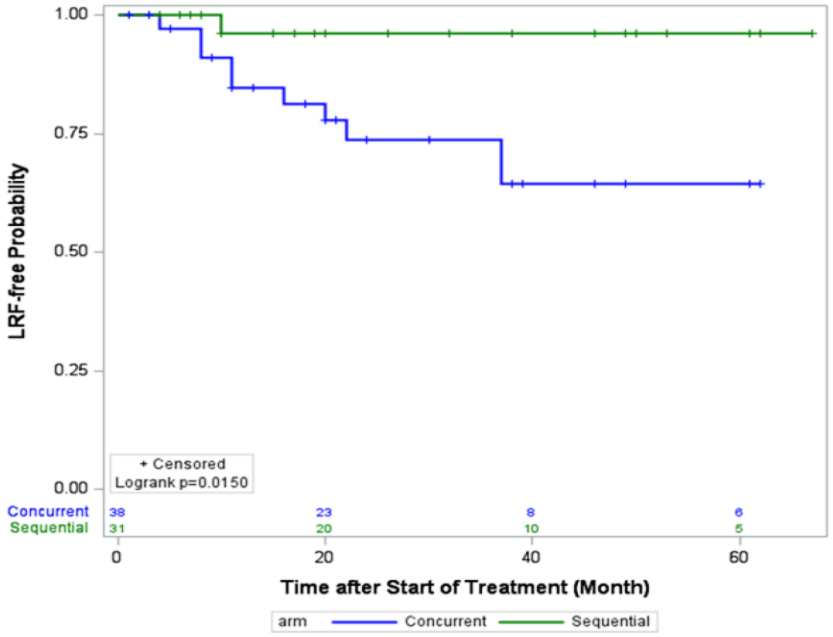
- 1- year local failure rate < 60%
- 1- year PFS ≥60%
- Dose limiting toxicity rate ≤ 20%

Slides images from ESMO2023 Abstract session,. Zandberg et. al.

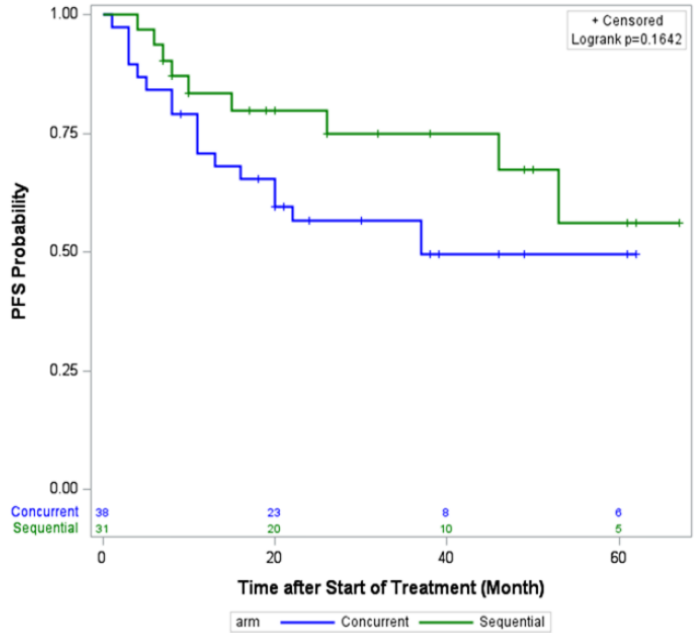


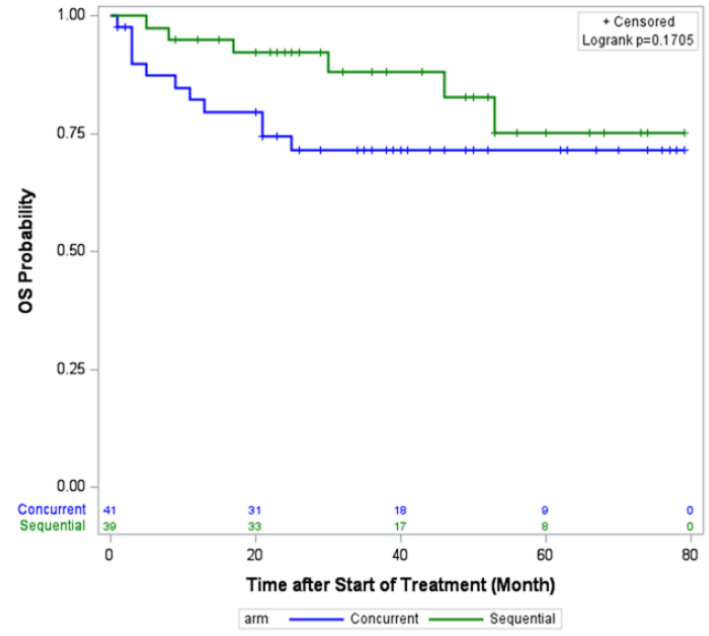
ESMO - HCC 15-132

Locoregional Control Rate



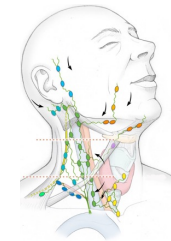
LRC	Concurrent	Sequential	HR (95%CI)	P value
4 Year	64%	95%	0.12 (0.02,0.94)	0.04





		Concurrent	Sequential	HR (95%CI)	P value
PFS	4 Year	49%	67%	0.57 (0.26,1.28)	0.17
OS	4 Year	71%	83%	0.51 (0.19, 1.37)	0.18

MADRID 2023 ESMO congress



Slides images from ESMO2023 Abstract session,. Zandberg et. al.

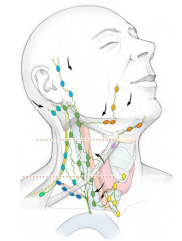
[Head / Neck cancer]
Moises Harari-Turquie, MD.

ESMO - HCC 15-132

- 4 year follow up, patients treated within the sequential arm had significantly higher LRC, and increased in OS and PFS
- Elegant translational TME analysis (30 samples)

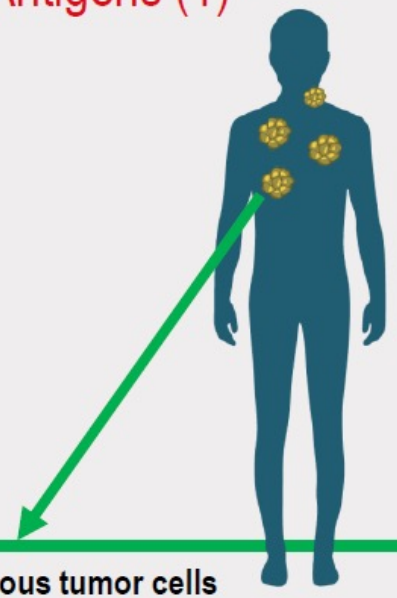
→ PDL1, CD3 pan-CK PDL1, CD8, and reg T cells → PDL1 expression cells were increased in concurrent arm vs sequential arm CD8 + regulatory T cells were decreased near tumor margin and remaining stroma.

- Hypothesis? Changes in TME in concurrent arm may be more immunosuppressive driving radiation resistance.
- ? TME on HPV driven vs HPV negative tumors.



ESMO – LBA 46

Personalized Antigens (1)



Irradiated autologous tumor cells

- Multivalency and patient specificity
- All potential immunogenic epitopes
- 1cm^3 of aseptic tumor
- 3-hour manufacturing process
- No cell culture/expansion/transfection/selection
- Stored frozen
- 4x10^6 irradiated tumor cells / vaccine

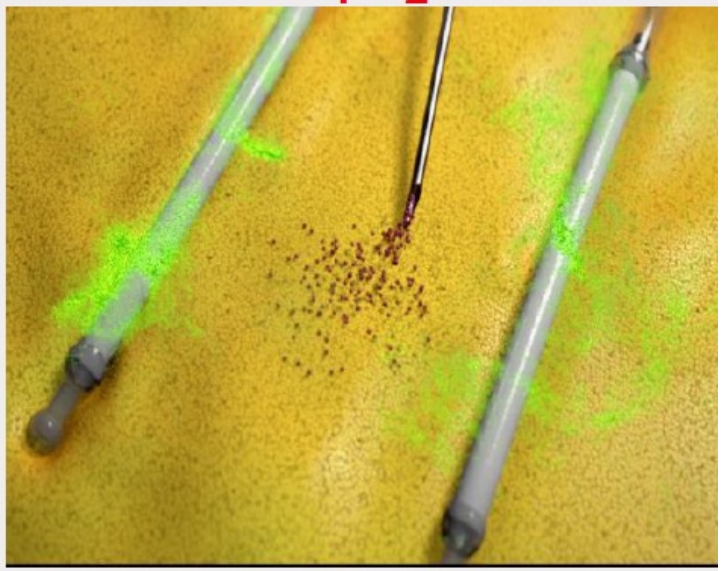
Standardized Adjuvant (2)

Capsule with selective permeability
MVX-ONCO-I Cell line engineered to produce the adjuvant

Sustained delivery of low doses of GM-CSF

- Recruitment and maturation of professional APCs
- Migration, priming & activation of T cells in VDLN
- Same product for all patients
- No systemic effect
- Stored frozen
- 40ng / day / capsule at the vax site for 7 days

1 + 2



Simple procedure

- Co-implanted under normal skin
- Away from any tumor deposit
- Capsules removed after 7 days
- 6 vaccinations over 8 weeks

Slides images from ESMO2023 Abstract session,. Mach et. al.

ESMO – LBA 46

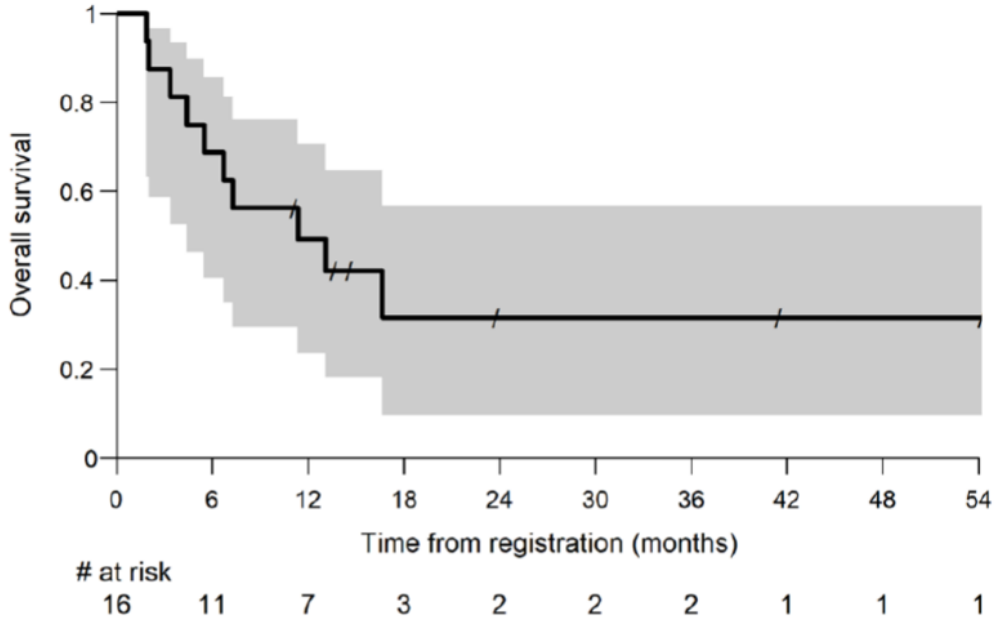
Pts characteristic

Age	59 (range 42-76)
Male / Female	15 / 1
Oral cavity / Oro / Hypopharynx	7 / 7 / 2
P16+ Oropharynx	4
CPS <1 / 1-19 / >20 (1 unknown)	3 / 10 / 2
N° Previous Line (1 / 2 / >2)	5 / 5 / 6
Previous ICI (%)	14/16 (87%)

Safety >80 vaccinations

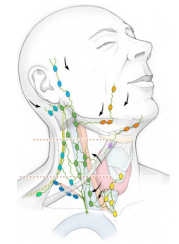
Rx related SAEs	0
Rx related AEs (G1-2)	25.1%
Vaccination site AEs G 3-5	0
Vaccination site AEs G 1-2	43.7%

	Median OS	24mo Survival %
Nivolumab Checkmate 121 NEJM 2018	7.7	16.9%
Pembrolizumab Keynote 040 Lancet 2019	8.4	Est.17%
Durvalumab Eagle AnnOcol 2020	7.6	18.4
Avelumab Javelin BMJ 2021	8	17.1



- **Median OS: 11.4 mo (95% CI: 4.4-NR)**
- **6 months survival 68.8 %**
- **1 year survival 49.2%**
- **2 year survival 31.6%**

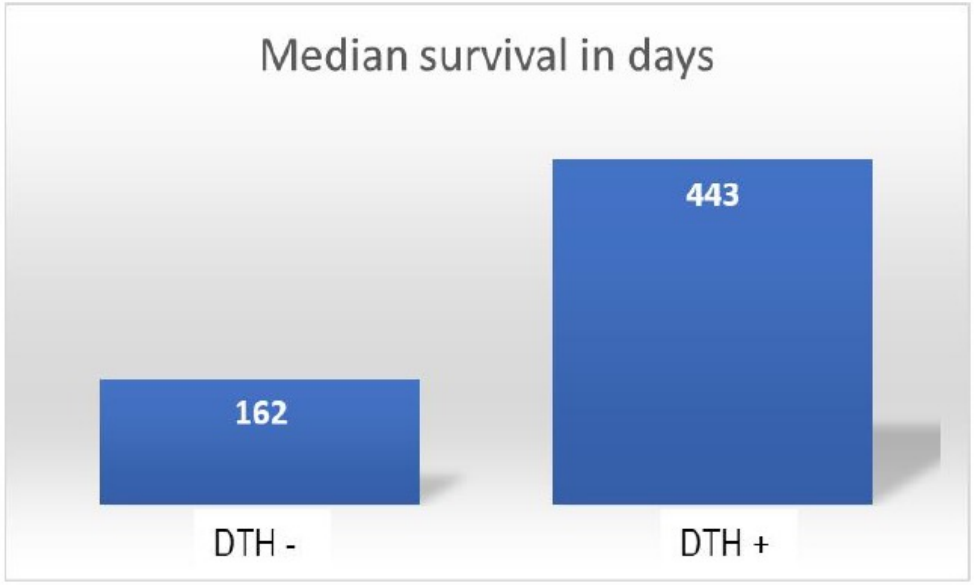
Mach et. al.



ESMO – LBA 46

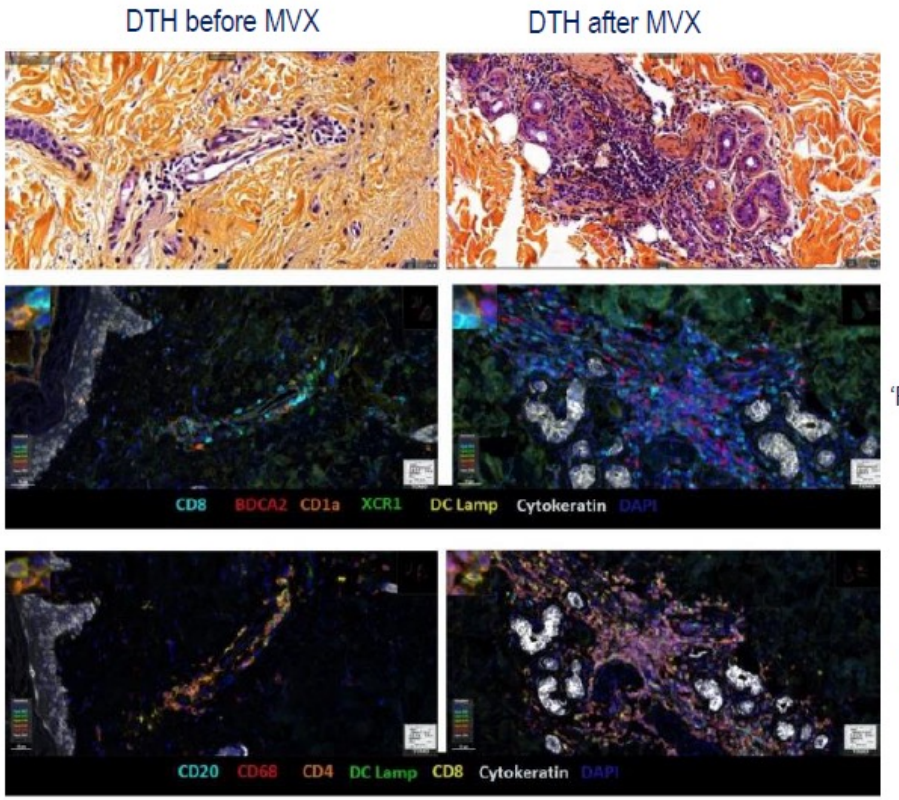
14/16 pts have pre-post Rx DTH. All baseline DTH are negative

	Baseline	Post Vaccine	Alive at 12 mo	% Survival at 12 mo
DTH +	0 /14	7	7	100 %
DTH –	14/14	7	1	14.3 %



DTH: Delayed-type Hypersensitivity

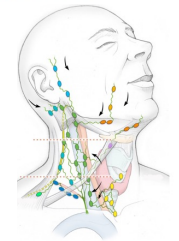
Phenotype of DTH + pre-post Rx



H/Safran stain

'Pan Immuno' panel

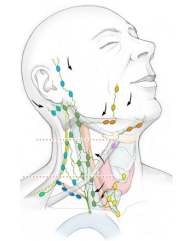
'DCs subset' panel



ESMO – LBA 46

- MVX-ONCO1 – novel mechanism for cancer vaccine with adequate safety profile.
- Meaningful OS, PR in refractory R/M HN SCC.
- DTH to be validated as a potential biomarker

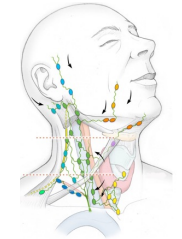
- Needs to be validated in larger phase III, author plans for RCT first line MVX-ONCO1 vs Pembrolizumab.
- First cancer vaccine showing prolonged OS in chemo/IO refractory HNSCC



ESMO – AIM H/N

Phase 2 study evaluating tipifarnib in m*HRAS,* recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) (AIM-HN)

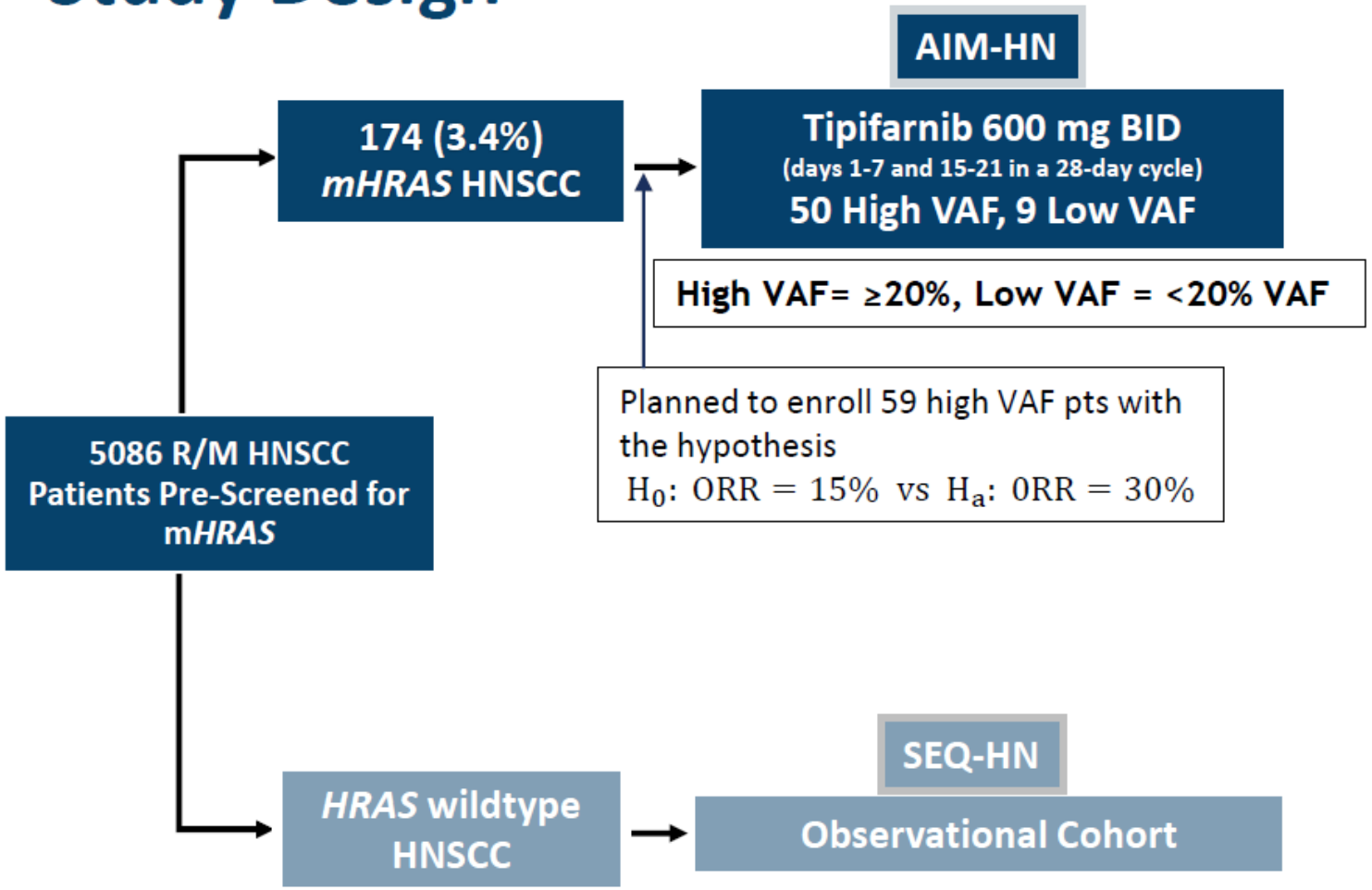
- ✓ MOA: Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FTase)
- ✓ HRAS occurs in 4-8% patients with HN/SCC *
- ✓ Phase 2 KO-TIP-001 (n=20) ORR 50% in mHNSCC VAF >20.



* Li S. A model for RAS mutation patterns in cancers. Nature 2018

ESMO – AIM H/N

Study Design



AIM-HN
KURA KO-TIP-007

Key Eligibility Criteria[1]

- Tumor missense *HRAS* mutation
- Histologically confirmed HNSCC
- Treatment failure from most recent prior therapy and from ≥1 prior platinum-containing regimen
- ≥1 Measurable disease (RECIST v1.1)

Primary Endpoint

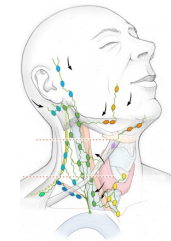
- ORR in high VAF pts by IRF in mITT

Key Secondary Endpoint

- DoR in high VAF pts by IRF in mITT

Key Milestones

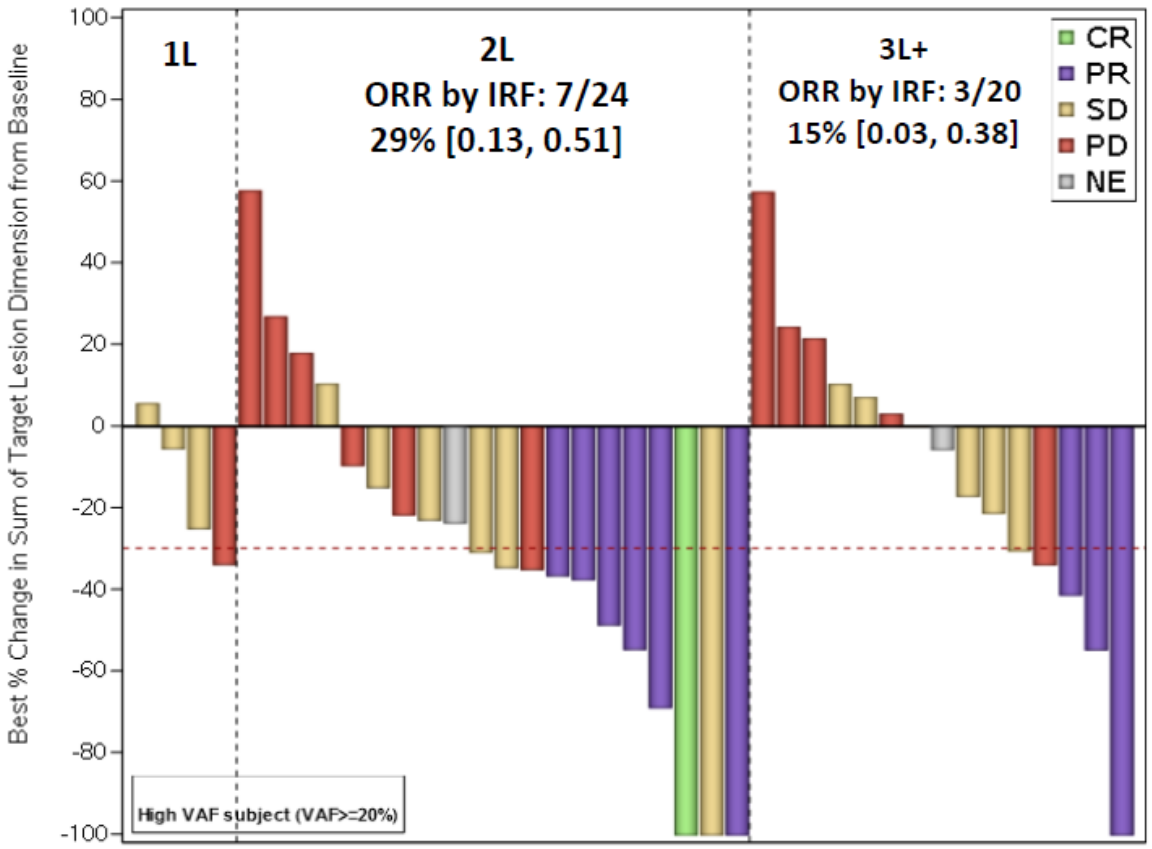
FPI	15 Oct 2019
LPO	2 May 2023
Database Lock	15 Jun 2023



Slides images from ESMO2023 Abstract session,. Ho et. al.

ESMO – AIM H/N

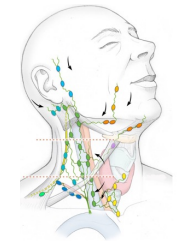
Tipifarnib Shows Antitumor Activity and Clinical Benefit



Patients with **High VAF** in mITT (N=50)	Investigator Assessment	Independent Review Facility
Best Overall Response, n (%)		
Confirmed CR	1 (2)	1 (2)
Confirmed PR	14 (28)	9 (18)
SD	17 (34)	14 (28)
PD	6 (12)	14 (28)
NE	12 (24)	12 (24)
DCR, n (%) [95% CI]	32 (64) [0.49, 0.77]	24 (48) [0.34, 0.63]
ORR, n (%) [95% CI]	15 (30) [0.18, 0.45]	10 (20) [0.10, 0.34]
mDoR, months [95% CI]	5.6 [3.88, 9.23]	6.5 [3.88, -]
mPFS, months [95% CI]	3.7 [2.60, 5.55]	2.6 [1.87, 4.40]

6/10 responders had BOR of PD in the last prior line with IO-based therapies
PFS in these ranged from 1-5 months vs. 6 –27 months on tipifarnib

Slides images from ESMO2023 Abstract session,. Ho et. al.



ESMO – AIM H/N

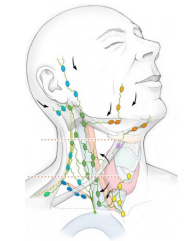
	Safety Analysis Set, N=59	
	Grade ≥3 n (%)	Any Grade n (%)
Patients with Any TRAEs	33 (56)	49 (83)
Anemia	12 (20)	20 (34)
Neutropenia	14 (24)	20 (34)
Fatigue	3 (5)	14 (24)
Leukopenia	8 (14)	13 (22)
Nausea	5 (9)	13 (22)
Thrombocytopenia	3 (5)	10 (17)
Decreased Appetite	1 (2)	10 (17)
Patients with Any Serious TRAEs		13 (22)
Anemia		4 (7)
Febrile Neutropenia		3 (5)
Thrombocytopenia		2 (3)
Patients with TRAEs Leading to Treatment Discontinuation		4 (7)

TRAE, treatment-related adverse event

<u>Discussion</u>

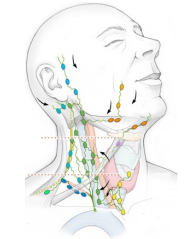
- First targeted therapy for RM/HN SCC
- ORR higher in 2L vs 3L setting
- >56% Grade 3 AE (Cytopenias)

Slides images from ESMO2023 Abstract session,. Ho et. al.



Take home points

- Chemo/IO vs IO alone (CPS score& tumor burden) remains SOC in R/M HN SCC. Multiple therapies are being developed to improve outcomes.
- New development of vaccines, ADC and novel targets such (LAG3, HRAS).
- Unmet needs for 2L and 3L options in the R/M setting.



Thank you!

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