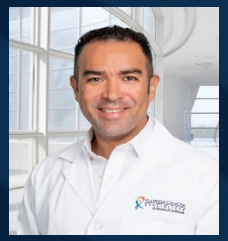
11th Annual WCS™ WINTER CANCER SYMPOSIUM

PROGRAM DIRECTORS:
William Caceres, MD
Luis E. Raez, MD, FACP, FCCP
Edgardo S. Santos Castillero, MD, FACP

MARCH 4–6, 2022
La Concha Renaissance Hotel
San Juan, Puerto Rico

Accredited by: MEC · CANCER EXPERT NOW · MEC VLearning MedPro · MECC GLOBAL MEETINGS

Targeted Therapy & Immunotherapy in HNSCC



Cesar A. Perez, M.D.
Director of Drug Development
Sarah Cannon Research Institute
Florida Cancer Specialists
Associate Professor of Medicine
University of Central Florida

Edgardo S. Santos, M.D., FACP
Medical Director of Research Services
Florida Precision Oncology/a Division of Genesis Care
Clinical Affiliate Associate Professor of Medicine
Charles E. Schmidt College of Medicine
Florida Atlantic University

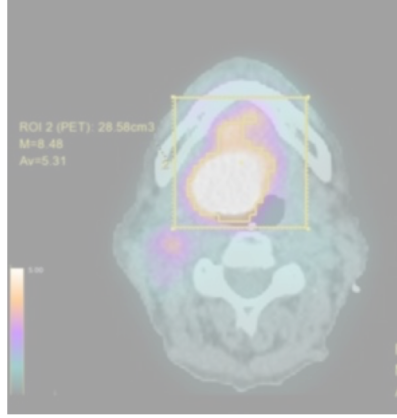
SARAH CANNON Research Institute at Florida Cancer Specialists | FLORIDA CANCER SPECIALISTS & Research Institute

GenesisCare

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

FLORIDA PRECISION ONCOLOGY
A Division of Genesis Care

Head and Neck Cancer

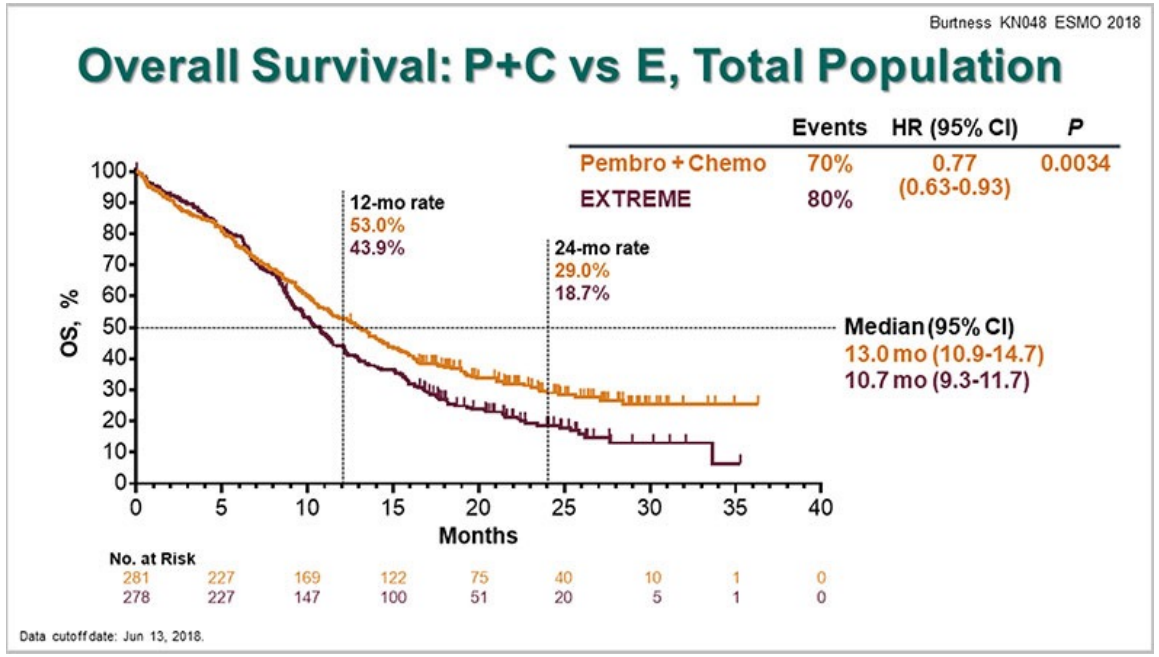


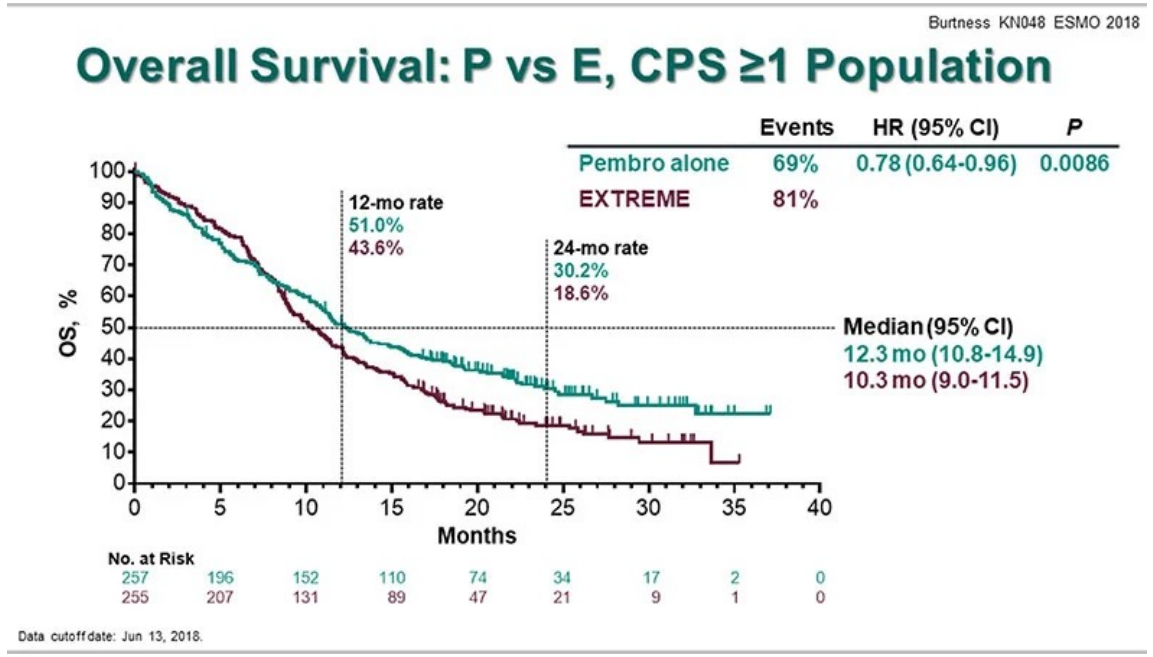
- About 4% of all cancers in the United States.
  - Estimated 66,630 people (48,740 men and 17,890 women) will develop head and neck cancer.

- Aprox. 14,620 deaths (10,640 men and 3,980 women) from head and neck a year in US.

Head and Neck Cancer

A decade of advances, so much more to do…





11th Annual WCS™
WINTER CANCER SYMPOSIUM

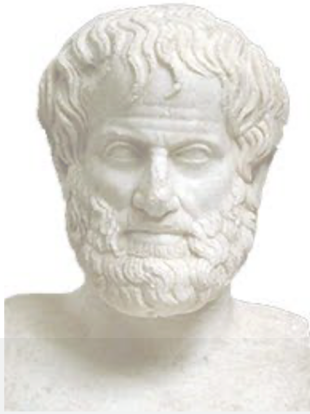
PROGRAM DIRECTORS:
William Caceres, MD
Luis E. Raez, MD, FACP, FCCP
Edgardo S. Santos Castillero, MD, FACP

MARCH 4–6, 2022
La Concha Renaissance Hotel
San Juan, Puerto Rico

Accredited by: MEC · CANCER EXPERT NOW · MEC VLearning MedPro · MECC GLOBAL MEETINGS

Targeted Therapy in Head & Neck Cancer

Targeted Therapy???



Sledge 2005:

"A targeted therapy should attack a biologically important process (usually, though not necessarily, a single molecule), preferably one central to a hallmark of cancer"

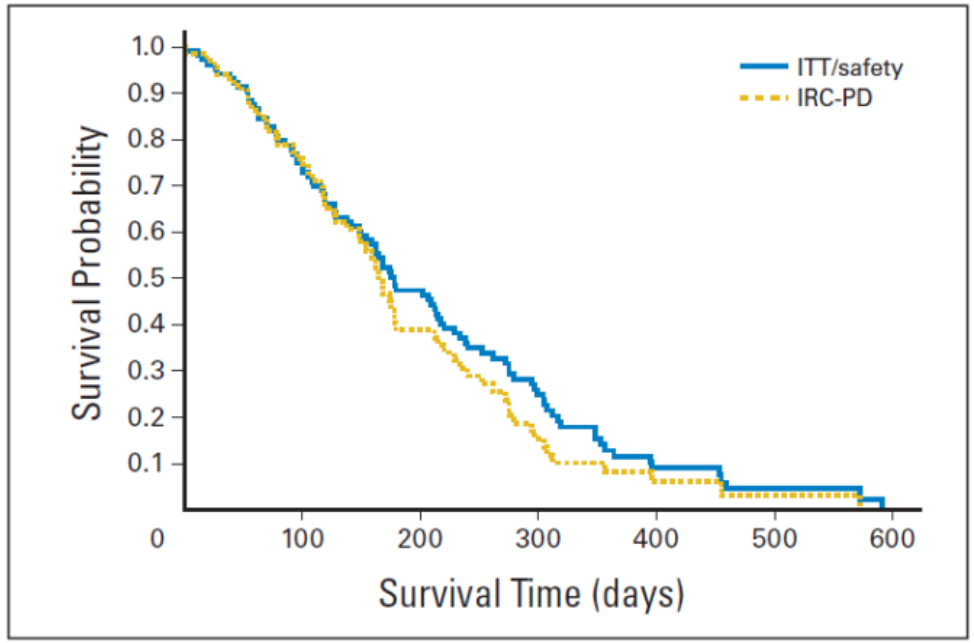
→ Is **Methotrexate** a targeted therapy, since it only inhibits dihydrofolate reductase?

→ Are Aromatase inhibitors targeted therapies?

Peters GJ. *From 'Targeted Therapy' to Targeted Therapy.* Anticancer Res. 2019 Jul;39(7):3341-3345

Head and Neck Cancer

A decade of advances, so much more to do…



- **Cetuximab is only "targeted therapy" currently approved for FDA**
- **Low single agent ORR and DOR**

Cetuximab in platinum-refractory SCCHN.

- ORR 13%

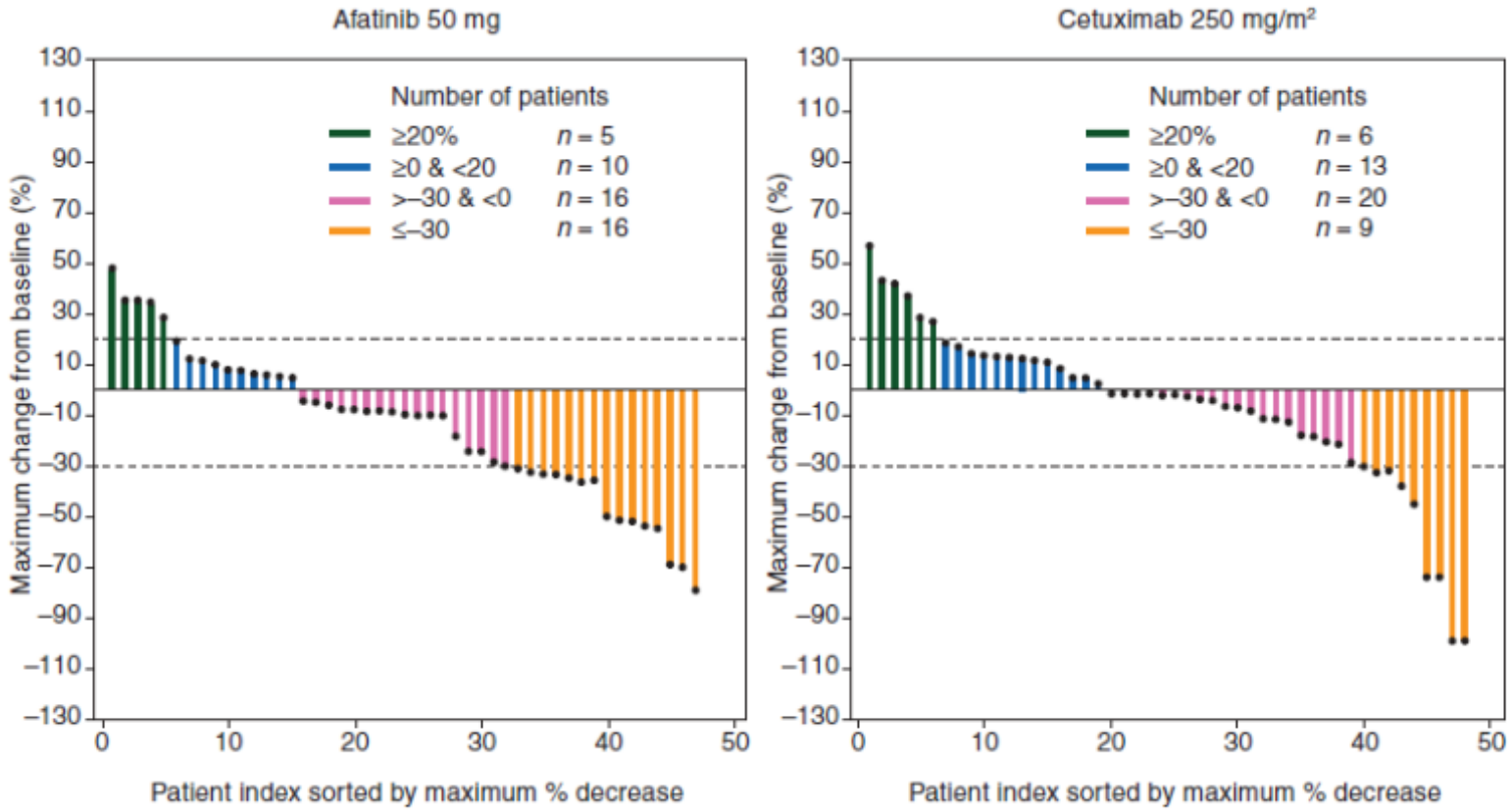
J Clin Oncol 2007 25:2171-2177.

Afatinib vs cetuximab in unselected R/M SCCHN

ORR 16.1% with Afat vs 6.5% with Cetux. (Investigator reported)

DRAEs leading to Tx discontinuation

23% with Afat vs 5% with Cetux



Annals of Oncology 25: 1813–1820, 2014

Head and Neck Cancer

So what are the targets?

- Primarly of tumors from the oral cavity (62%)
- Only 13% HPV-related
- Most male and heavy smokers

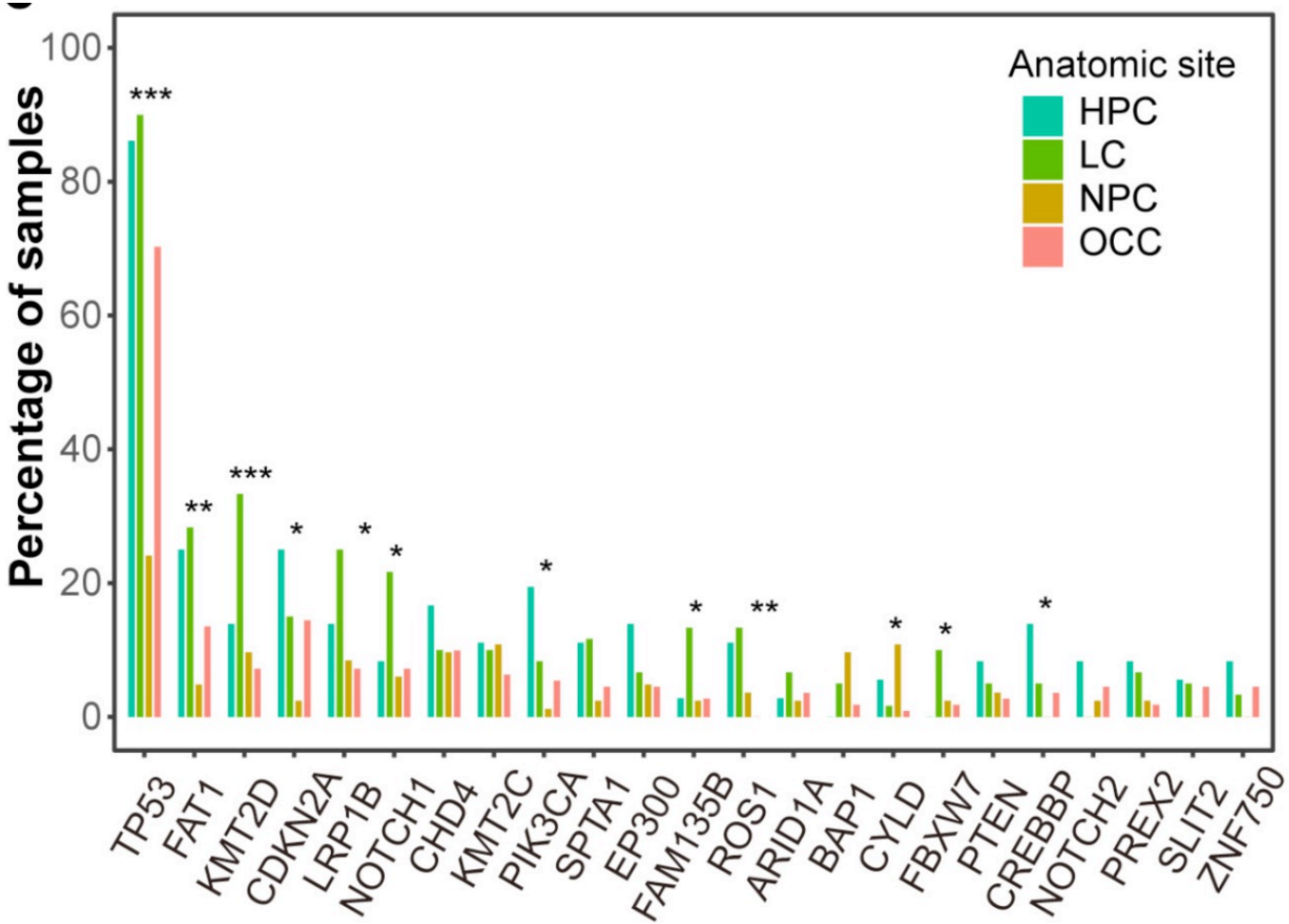
Results:

- TP53 (84%)
- CDKN2A (58%)
- CCDN1 (31%)

- ***HRAS 5%***
- ***PIK3CA (34%)***

The Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* **517,** 576–582 (2015).

Genomic Landscape of Head and Neck Squamous Cell Carcinoma Across Different Anatomic Sites in Chinese Population



Front Genet 2021 Jun 14;12:680699

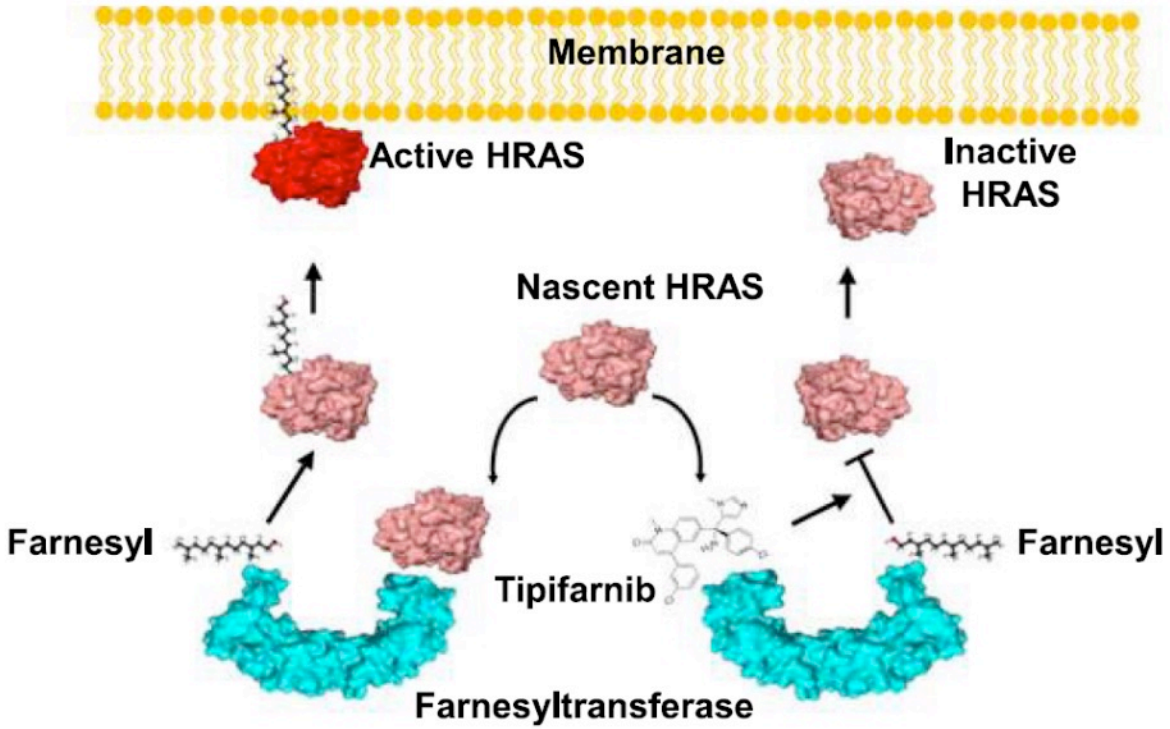
HRAS and Farnesyltransferase inhibitors in SCCHN

RAS proteins require posttranslational modifications to associate with intracellular membranes

HRAS is only dependent on farnesylation for its membrane localization

Overral 3-5% of SCCHN have HRAS mutation

Tipifarnib is a farnesyltransferase inhibitor (FTI)



Mol Cancer Ther 2020 Sep;19(9):1784-1796.

Tipifarnib in HRAS+ SCCHN

Stage 1

Patients with HRAS-mutant solid tumor

Cohort 1: Thyroid Cancer
13 patients dosed
11 evaluable
9 patients with SD
No PRs observed

Cohort 2: Solid tumors other than thyroid cancer
13 patients dosed
12 evaluable
7 patients with SD
2 PRs observed in 3 patients with HNSCC

Cohort 3: SCC other than HNSCC
Up to 20 patients

Stage 2

HNSCC only
Primary objective met with 5 PRs in a total of 9 patients with HNSCC

Cohort Expansion

Cohort expanded to further characterize safety and tolerability in indication(s) of interest

Total patients with HNSCC enrolled
(N = 31)
(30 from KO-TIP-001 and 1 expanded access)

HRAS VAF ≥ 20%
serum albumin ≥ 3.5g/dL or HRAS ≥ 35%
(n = 22)

HRAS VAF ≤ 20%
HRAS VAF 20%-35% with serum albumin ≤ 3.5g/dL
(n = 9)

Patients Received Treatment
(n = 22)

Patients evaluable for efficacy
(n = 20)
PR (n = 11)
SD (n = 9)

Patients not evaluable for efficacy
(n = 2)

Patients evaluable for efficacy
(n = 4)
SD (n = 2)
PD (n = 2)

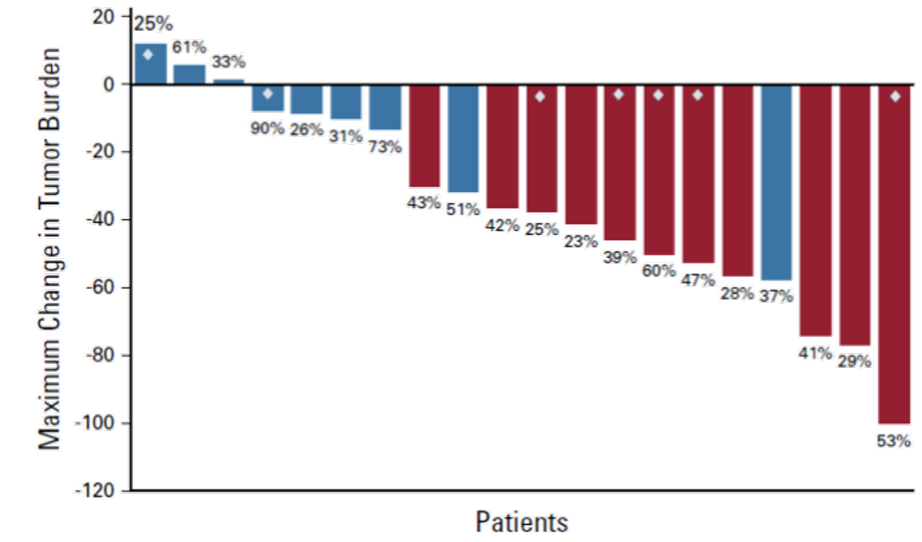
Patients not evaluable for efficacy
(n = 5)

VAF, variant allele frequency

[1]Ho AL, Brana I, Haddad R, et al. Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations. *J Clin Oncol*. 2021;39(17):1856-1864. doi:10.1200/JCO.20.02903.

Tipifarnib in Head and Neck Squamous Cell Carcinoma With HRAS Mutations

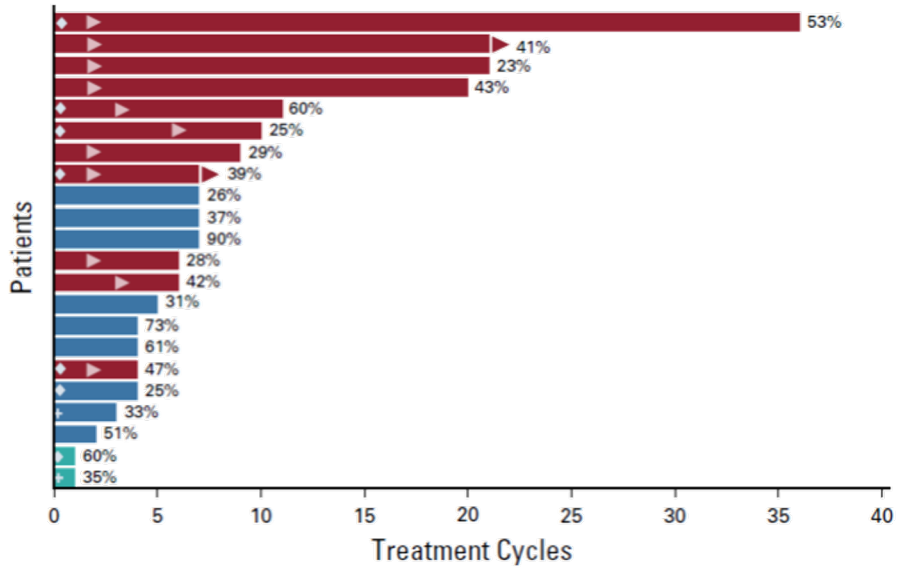
Maximal change in tumor size



PR
SD
Not evaluable for efficacy
Patient initiated treatment at 600 mg bid
Patient withdrew consent
Start of Response
Active treatment

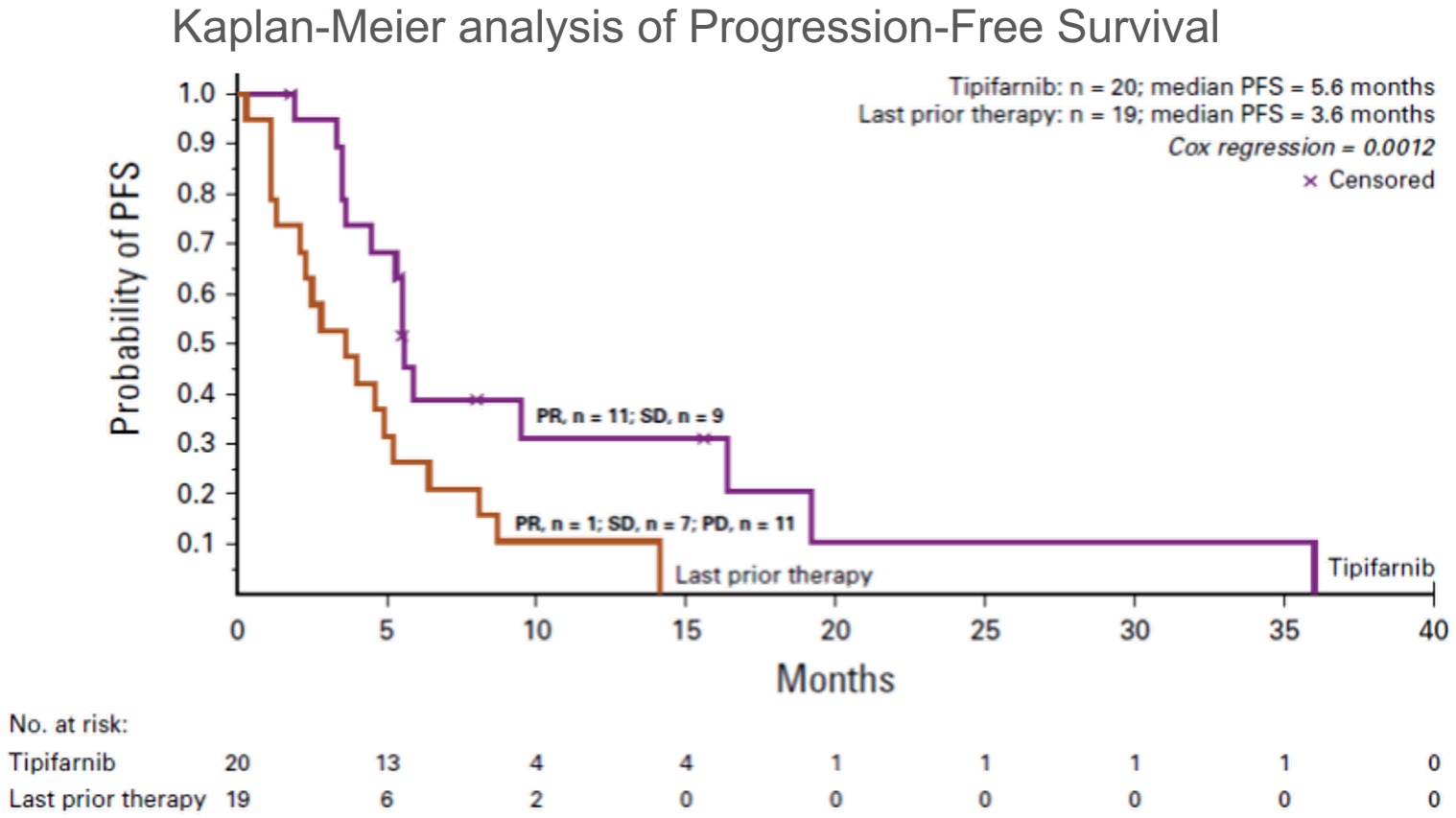
% Numbers at the end of bars represent VAF for each patient

Duration of response to treatment



ORR in pts VAF > 20: 55%

Tipifarnib in Head and Neck Squamous Cell Carcinoma With HRAS Mutations - PFS



Ho AL, et al. Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations. *J Clin Oncol*. 2021;39(17):1856-1864.

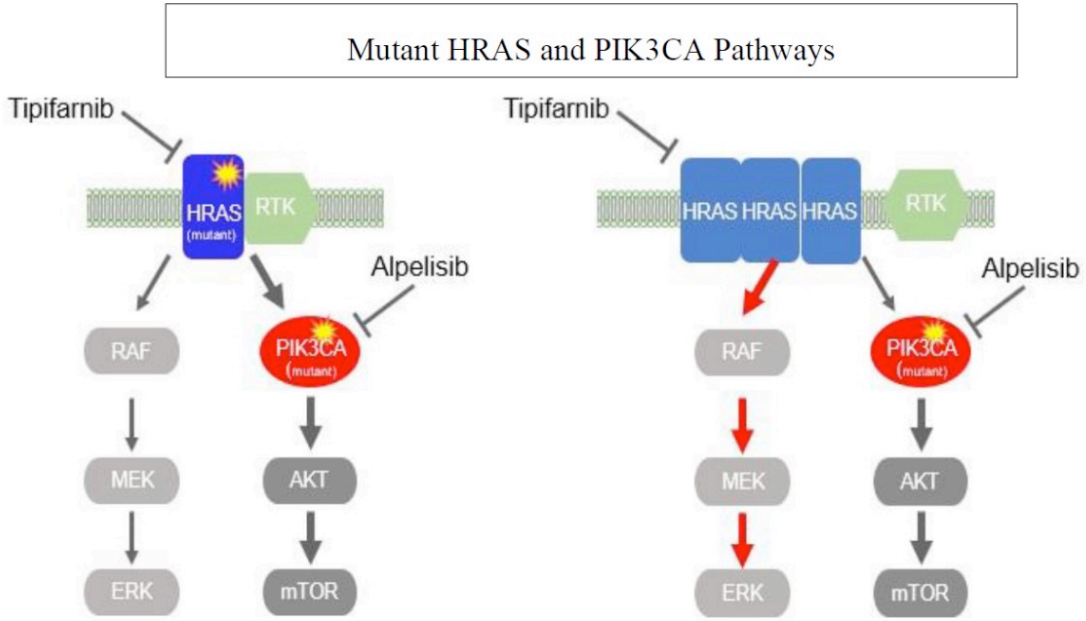
Tipifarnib in Head and Neck Squamous Cell Carcinoma- HRAS Mutation. Toxicity

n = 30

Blood and lymphatic system disorders	15 (50%)	**Metabolism and nutrition disorders**	9 (30%)
• Anemia	11 (37%)	• Hypercalcemia	3 (10%)
• Neutropenia	3 (10%)	• Hypokalemia	3 (10%)
• Lymphopenia	4 (13%)	• Hypophosphatemia	3 (10%)
• Leukopenia	3 (10%)		
Respiratory, thoracic, and mediastinal disorders	9 (30%)	**Gastrointestinal disorders**	6 (20%)
• Pneumonia	3 (10%)	• Nausea	3 (10%)

Ho AL, et al. Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations. *J Clin Oncol*. 2021;39(17):1856-1864.

A Phase 1/2 of tipifarnib and alpelisib in patients with HRAS overexpressing and/or PIK3CA-mutated and/or -amplified recurrent/metastatic head and neck squamous cell carcinoma (the Kurrent trial)



- Two cohorts:
  - PIK3CA mutant
  - HRAS overexpressed
- PIK3CA cohort ongoing

Simultaneous Dosing: 28 Day Cycle			
Week 1	Week 2	Week 3	Week 4
Tipifarnib	Rest	Tipifarnib	Rest
Alpelisib	Alpelisib	Alpelisib	Alpelisib

Immunotherapy in Head & Neck Cancer

→ *NPC*

→ *SCC*

2021 ASCO ANNUAL MEETING

CAPTAIN-1ST: CAMRELIZUMAB VERSUS PLACEBO IN COMBINATION WITH GEMCITABINE AND CISPLATIN AS FIRST-LINE TREATMENT FOR RECURRENT OR METASTATIC NASOPHARYNGEAL CARCINOMA: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

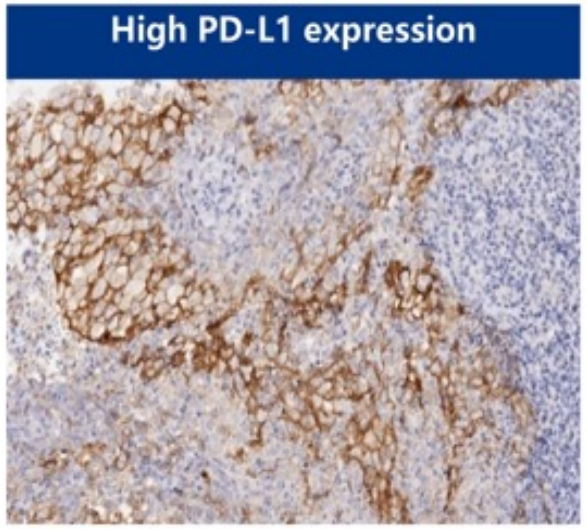
Li Zhang, MD

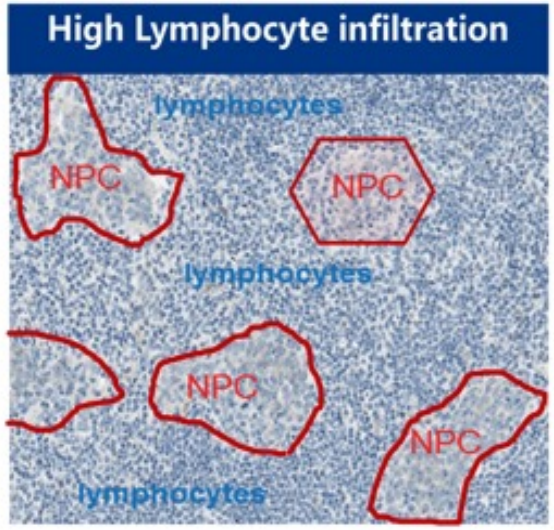
Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China.

June 7, 2021

Background

- Standard first-line treatment for recurrent or metastatic NPC (R/M-NPC) is platinum-based chemotherapy.
  - Gemcitabine + cisplatin (GP): ORR, 64%; median PFS, 7.0 months; median OS, 29.1 months.[3]
- Endemic NPC tumors are characterized by high PD-L1 expression and intensive infiltration of non-malignant lymphocytes.[4]
- First-line camrelizumab plus GP showed encouraging anticancer activity (ORR, 91%; 12-month PFS rate, 61.4%).[5]
- **Objective:** This multicenter, randomized, double-blind, phase 3 study was conducted to investigate camrelizumab plus GP *vs* placebo plus GP for R/M-NPC in the first-line setting.





3. Zhang L, et al. Lancet 2016; 388:1883-92; 4. Larbcharoensub N, et al. Am J Clin Oncol 2018; 41:1204-10; 5. Fang W, et al. Lancet Oncol 2018; 19:1338-50.
Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

Study Design (NCT03707509)

Key eligibility criteria:

- Aged 18-75 years;
- Pathologically confirmed R/M-NPC;
- Had not received previous systemic therapy for R/M-NPC (disease progression at least 6 months after induction, adjuvant, or concurrent chemoradiotherapy were eligible);
- ECOG performance status of 0 or 1;
- At least one measurable lesion according to RECIST version 1.1;

R 1:1

Camrelizumab (200 mg on day 1)
+ gemcitabine (1000 mg/m^2 on days 1 and 8)
+ cisplatin (80 mg/m^2 on day 1)

Q3W for 4-6 cycles

→ Camrelizumab (200 mg on day 1)

Q3W until disease progression, unacceptable toxicity, withdrawal of consent

Stratification factors:

- Liver metastases (yes *vs* no).
- Previous radical concurrent chemoradiotherapy (yes *vs* no).
- ECOG performance status (0 *vs* 1)

Placebo
+ gemcitabine (1000 mg/m^2 on days 1 and 8)
+ cisplatin (80 mg/m^2 on day 1)

Q3W for 4-6 cycles

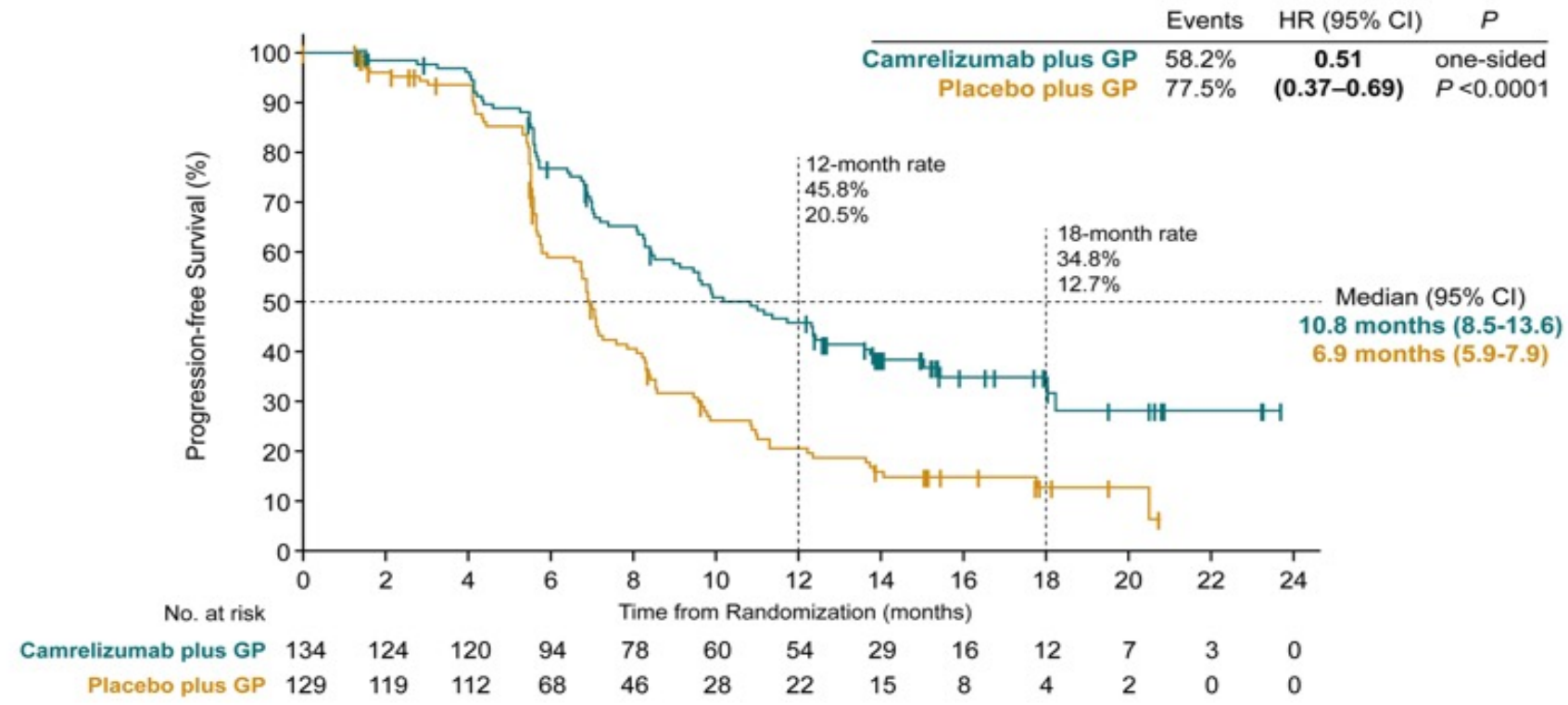
→ Placebo

Q3W until disease progression, unacceptable toxicity, withdrawal of consent

- Primary endpoint: independent review committee (IRC)-assessed PFS
- Secondary endpoints: investigator-assessed PFS, ORR, DCR, DoR, OS and safety

ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; DCR, disease control rate; DoR, duration of response

PFS per IRC



- **Camrelizumab plus GP improved PFS compared with placebo plus GP, with a 49% lower risk of disease progression or death.**

Data cutoff on Dec 31, 2020

Response Summary

	Camrelizumab plus GP (N = 134)	Placebo plus GP (N = 129)
Best overall response, n (%)		
CR	7 (5.2)	2 (1.6)
PR	111 (82.8)	102 (79.1)
SD	11 (8.2)	18 (14.0)
PD	2 (1.5)	4 (3.1)
NA	3 (2.2)	3 (2.3)
ORR		
% (95% CI)	88.1 (81.3–93.0)	80.6 (72.7–87.1)
Treatment difference, % (95% CI)	7.4 (-1.3–16.2); *P* = 0.1063	
DCR		
% (95% CI)	96.3 (91.5–98.8)	94.6 (89.1–97.8)
Treatment difference, % (95% CI)	1.7 (-3.4–6.8); *P* = 0.5469	
DoR		
Median (95% CI), months	9.9 (7.7–12.5)	5.7 (5.2–6.9)
Hazard ratio (95% CI)	0.48 (0.34–0.68); *P* < 0.0001	

- **Camrelizumab plus GP showed superior DoR than placebo plus GP.**

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessable.

Data cutoff on Dec 31, 2020. Assessed by IRC.

Overall Survival

	Camrelizumab plus GP (N = 134)	Placebo plus GP (N = 129)
Events, n (%)	28 (20.9)	38 (29.5)
Median (95% CI), months	NR (NR-NR)	22.6 (19.2-NR)
Hazard ratio (95% CI)	**0.67 (0.41-1.11); *P* = 0.0576**	
12-month rate, % (95% CI)	85.0 (77.7-90.1)	83.4 (75.6-88.8)
24-month rate, % (95% CI)	70.0 (53.9-81.4)	NR (NR-NR)

- **Although the OS was immature in both groups, a trend of survival benefit was observed in the camrelizumab plus GP group.**

NR, not reached.

Data cutoff on Dec 31, 2020.

2021 ASCO ANNUAL MEETING

JUPITER-02: The randomized, double-blind, phase 3 study of toripalimab or placebo plus cisplatin and gemcitabine as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC)

Rui-Hua Xu[1, *], Hai-Qiang Mai[2], Qiu-Yan Chen[2] Dongping Chen[3], Chaosu Hu[4], Kunyu Yang[5], Jiyu Wen[6], Jingao Li[7], Ying-Rui Shi[8], Feng Jin[9], Ruilian Xu[10], Jianji Pan[11], Shenhong Qu[12], Ping Li[13], Chunhong Hu[14], Yi-Chun Liu[15], Yi Jiang[16], Xia He[17], Hung-Ming Wang[18] and Wan-Teck Lim[19], Coherus Biosciences and Shanghai Junshi Biosciences.

[1]Department of Medical Oncology, Sun Yat-Sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; [2] Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center; [3]Affiliated Cancer Hospital & Institute of Guangzhou Medical University, Guangzhou, China; [4]Fudan University Cancer Center, Shanghai, China; [5]Union Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, China; [6]Affiliated Hospital of Guangdong Medical University, Zhanjiang, China; [7]Jiangxi Cancer Hospital, Nanchang, China; [8]Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, China; [9]Guizhou Cancer Hospital of Guizhou Medical University, Guiyang China; [10]Shenzhen People's Hospital, Shenzhen, China; [11]Fujian Provincial Cancer Hospital, Fuzhou, China; [12]The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; [13]West China Hospital of Sichuan University, Chengdu, China; [14]The Second Xiangya Hospital of Central South University, Changsha, China; [15]Taichung Veterans General Hospital, Taichung, Taiwan; [16]Cancer Hospital of Shantou University Medical College, Shantou, China; [17]Jiangsu Cancer Hospital, Nanjing, China; [18]Chang Gung Memorial Hospital, Taoyuan, Taiwan; [19]National Cancer Centre, Singapore City, Singapore

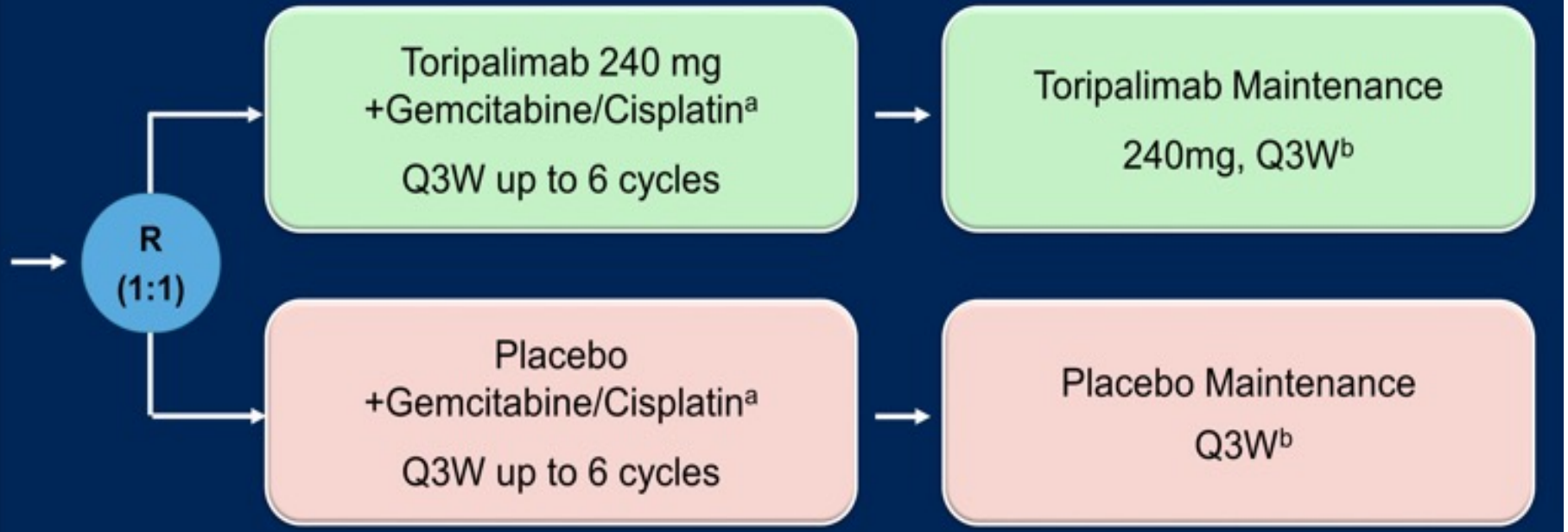
JUPITER-02: Study Design
(ClinicalTrials.gov identifier: NCT03581786)

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



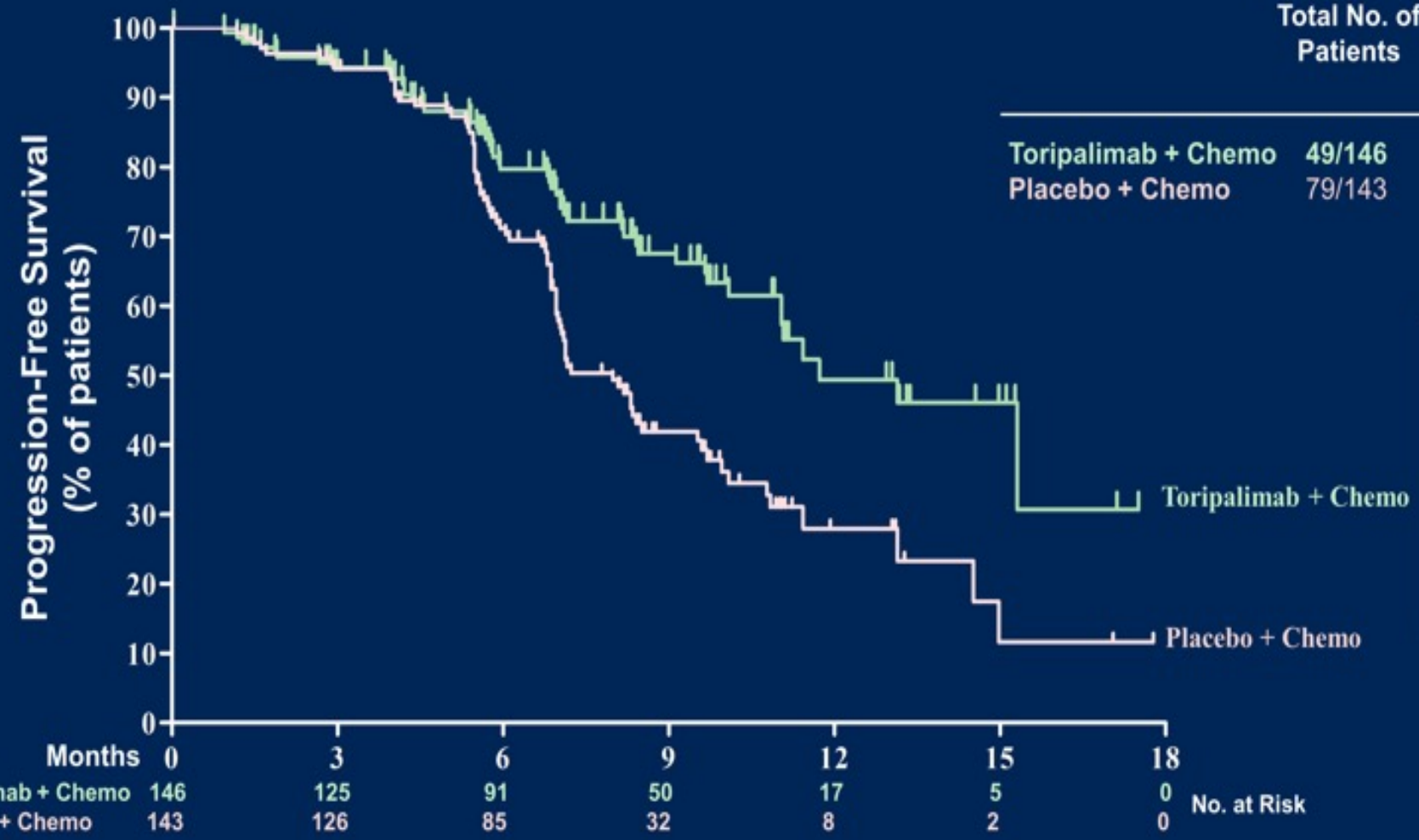
- Primary endpoint: PFS by a blinded independent review committee (BIRC) per RECIST v1.1
- Secondary endpoints: PFS by the Investigator, ORR, DoR, DCR, OS, and PFS & OS 1-year and 2-year rates

[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.

Progression-Free Survival by BIRC per RECIST v1.1

Interim Analysis Data cut-off Date: May 30, 2020

	No. of Events/ Total No. of Patients	Median Progression-free Survival, months (95% CI)	1-Yr Progression-free Survival Rate, % (95% CI)
Toripalimab + Chemo	49/146	11.7 (11.0, NE)	49.4 (36.4, 61.1)
Placebo + Chemo	79/143	8.0 (7.0, 9.5)	27.9 (18.0, 38.8)



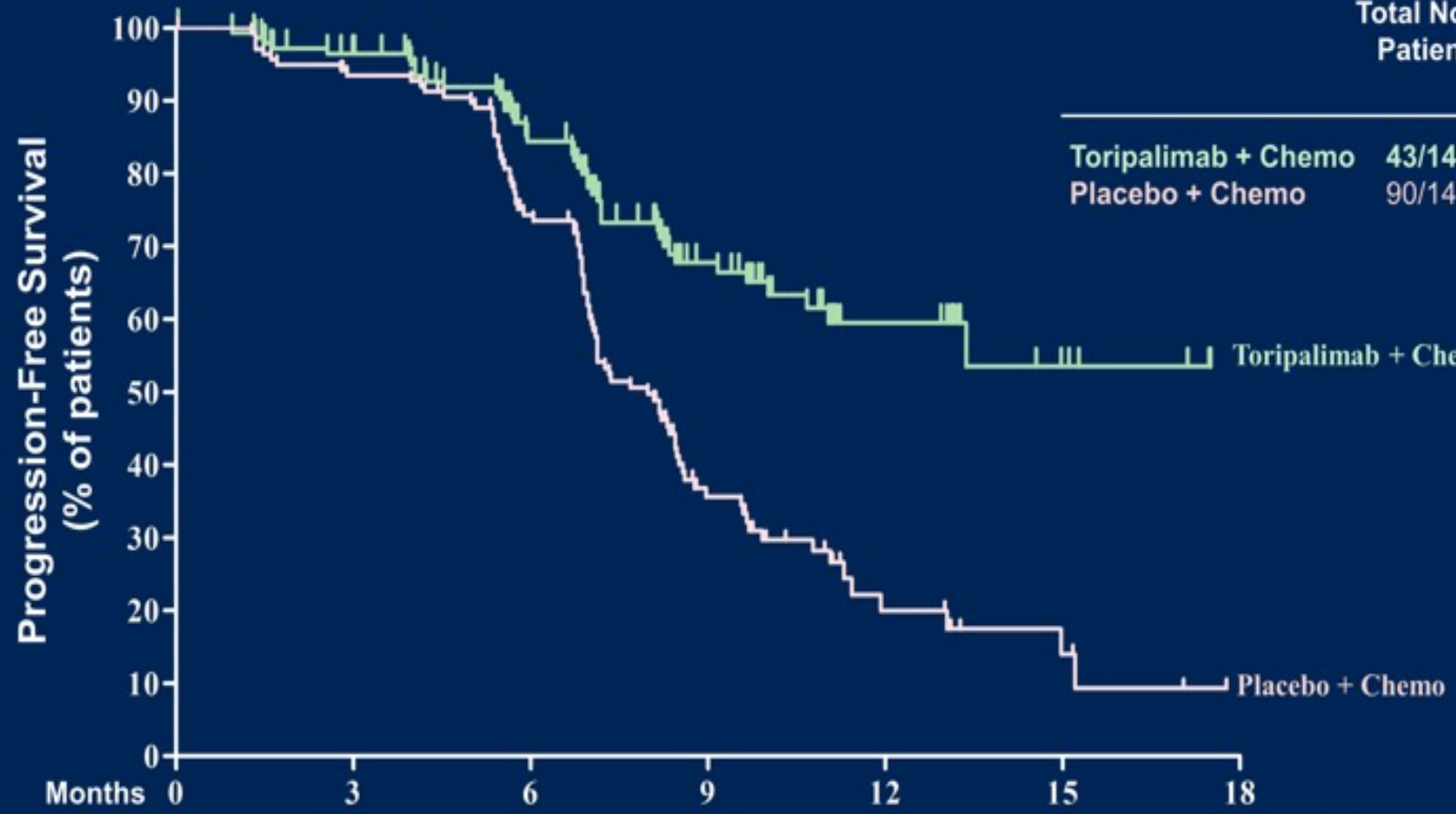
Stratified HR for disease progression or death,

0.52 (95% CI 0.36-0.74); P=0.0003

Progression-Free Survival by PI per RECIST v1.1

Interim Analysis Data cut-off Date: May 30, 2020

	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI) *mo*	1-Yr Progression-free Survival Rate, % (95% CI)
Toripalimab + Chemo	43/146	NE (11.0, NE)	59.5 (48.4, 69.0)
Placebo + Chemo	90/143	8.0 (7.1, 8.5)	20.0 (11.6, 30.0)



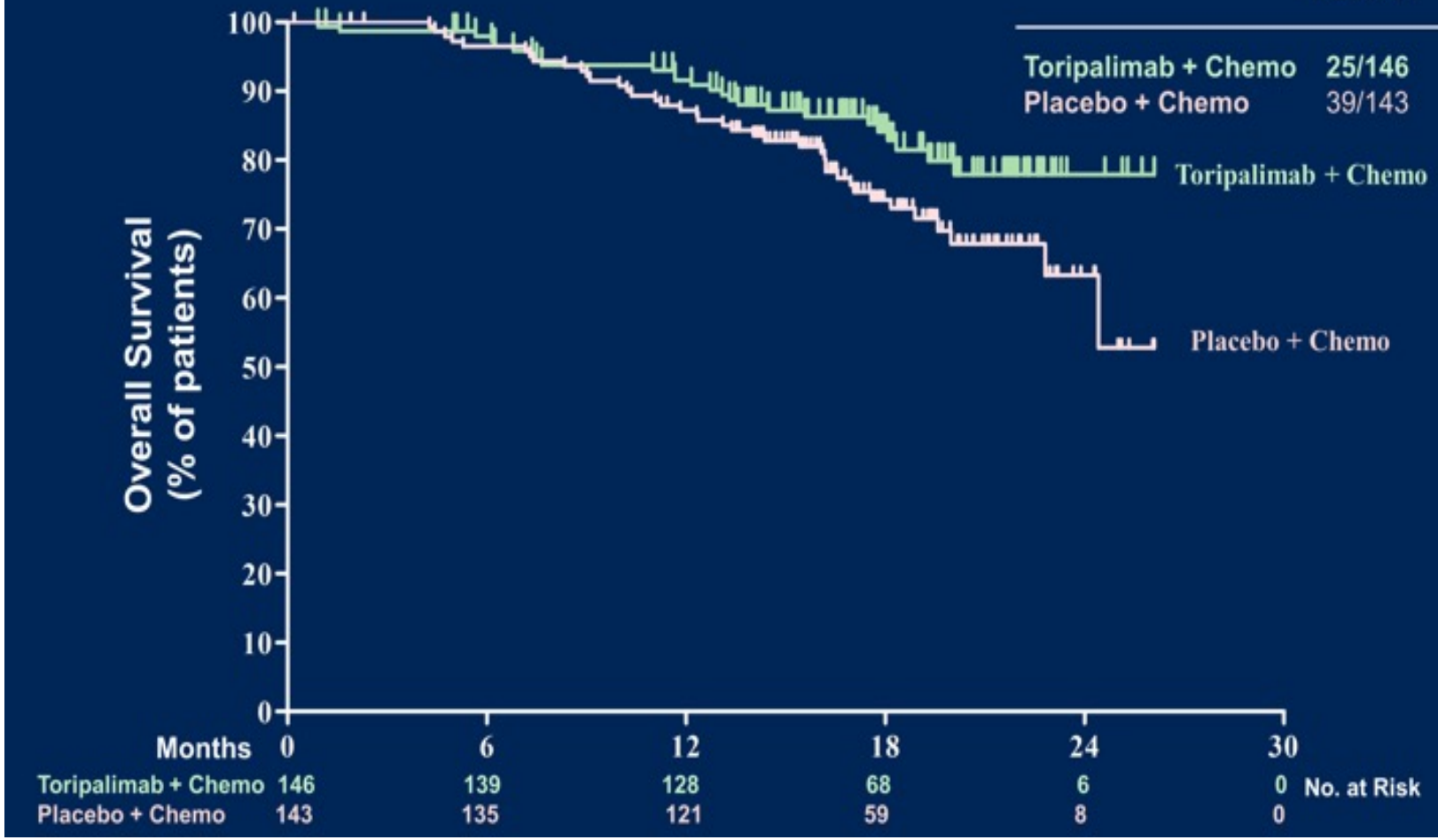
Stratified HR for disease progression or death,

0.41 (95% CI 0.28-0.59); P<0.0001

Overall Survival Update

Nine-month OS update after PFS Interim Analysis on Feb 18, 2021

	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate % (95% CI)	2-Yr Overall Survival Rate % (95% CI)
Toripalimab + Chemo	25/146	NE (NE, NE)	91.6 (85.6, 95.1)	77.8 (68.0, 85.0)
Placebo + Chemo	39/143	NE (22.8, NE)	87.1 (80.4, 91.7)	63.3 (49.8, 74.1)



Stratified HR for death,

0.603 (95% CI 0.364-0.997); P=0.0462

Conclusions

- The addition of toripalimab to GP as a first-line treatment for R/M NPC patients provided superior PFS, OS, ORR and DoR than GP alone.
  - Significant improvement in PFS： mPFS 11.7 vs. 8.0 months, HR=0.52 (95%CI: 0.36-0.74), p=0.0003
  - Although mOS was not mature in either arm, a 40% reduction in risk of death was observed in the toripalimab arm over the placebo arm.
  - A second interim OS analysis will be performed at pre-specified final PFS analysis followed by the final OS analysis
- No new safety signals were identified with toripalimab added to GP.
- Toripalimab plus GP represents a new standard of care as 1st line therapy for patients with R/M NPC.

Squamous Cell Carcinoma of the Head & Neck (SCCHN):

- Novel IO Agents:
  - CTLA-4 (Ipi + Nivo vs EXTREME)
  - HPV+ malignancies (TGF-β/PD-L1 + HPV16 vaccine +NHS/IL-12)
  - LAG3 + Pembro (all HNCa)

- Neoadjuvant Immunotherapy (Pembro)

2021 ESMO congress

Nivolumab + ipilimumab vs EXTREME regimen as first-line treatment for recurrent/metastatic squamous cell carcinoma of the head and neck: final results of CheckMate 651

Athanassios Argiris,[1,2] Kevin Harrington,[3] Makoto Tahara,[4] Robert L. Ferris,[5] Maura Gillison,[6] Jerome Fayette,[7] Amaury Daste,[8] Piotr Koralewski,[9] Ricard Mesia,[10] Nabil F. Saba,[11] Milena Mak,[12] Miguel Angel Álvarez Avitia,[13] Alexander Guminski,[14] Urs Müller-Richter,[15] Naomi Kiyota,[16] Mustimbo Roberts,[17] Tariq Aziz Khan,[17] Karen Miller-Moslin,[17] Li Wei,[17] Robert Haddad[18]

[1]Hygeia Hospital, Marousi, Greece; [2]Thomas Jefferson University, Philadelphia, PA, USA; [3]Royal Marsden Hospital/The Institute of Cancer Research, London, UK; [4]National Cancer Center Hospital East, Kashiwa, Japan; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Centre Léon Bérard, Lyon, France; [8]Hôpital Saint-André, Bordeaux, France; [9]Wojewodzki Szpital Specjalistyczny im. Ludwika Rydygiera w Krakowie, Krakow, Poland; [10]Catalan Institut of Oncology, L'Hospitalet de Llobregat, Barcelona, Spain; [11]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [12]Instituto do Câncer do Estado de São Paulo, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [13]Instituto Nacional De Cancerología, Mexico City, Mexico; [14]Royal North Shore Hospital, Sydney, Australia; [15]University Hospital Würzburg, Bavarian Cancer Research Center (BZKF), Würzburg, Germany; [16]Kobe University Hospital, Kobe, Japan; [17]Bristol Myers Squibb, Princeton, NJ, USA; [18]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Presentation number LBA36

KEYNOTE-048 Study Design (NCT02358031)

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

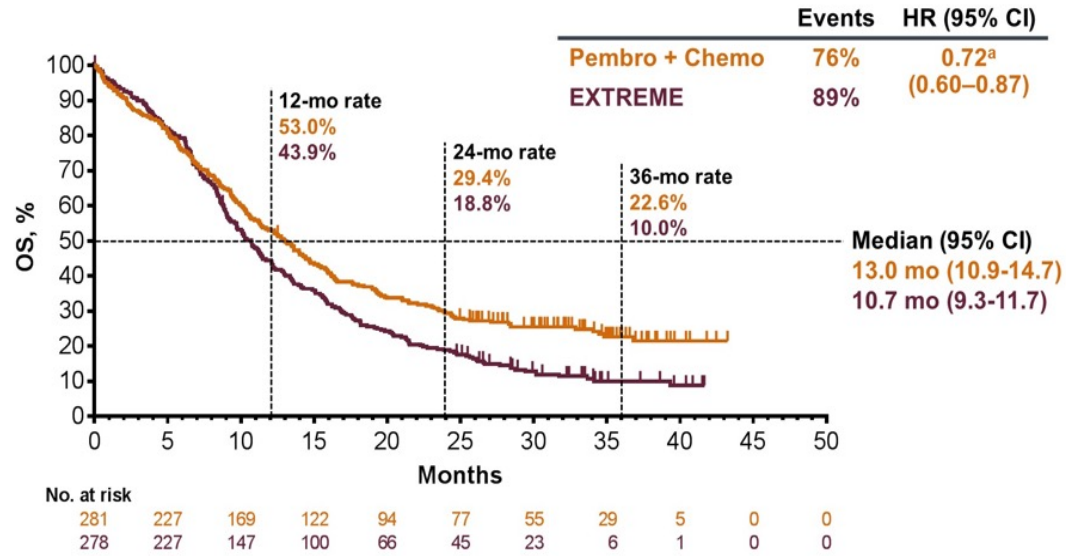
- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R 1:1:1

- Pembrolizumab Monotherapy → Pembrolizumab 200 mg Q3W for up to 35 cycles
- Pembrolizumab + Chemotherapy → Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 35 cycles total
- EXTREME → Cetuximab 250 mg/m^2 Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Cetuximab 250 mg/m^2 Q1W

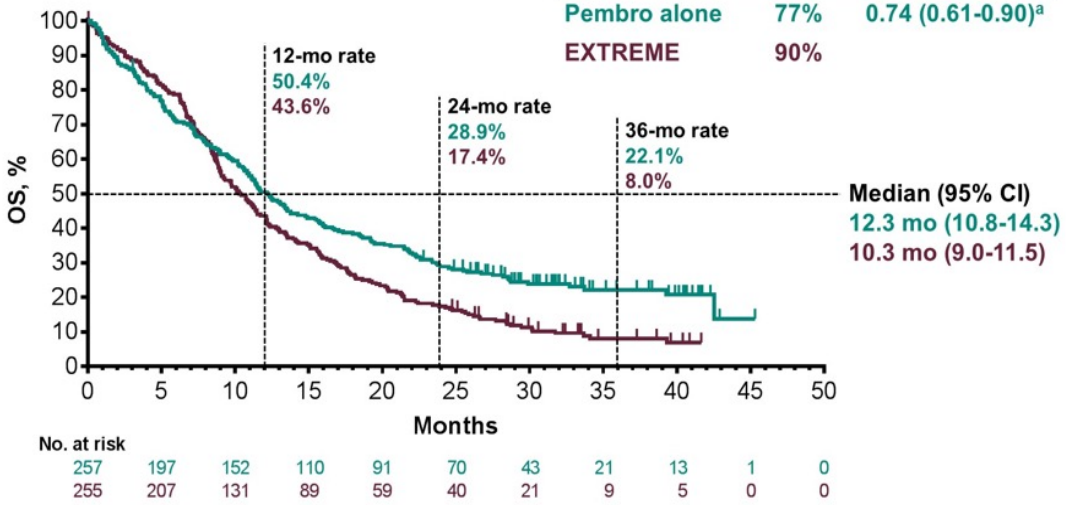
[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m^2.

OS, P+C vs E, Total Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥1 Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.78 (95% CI 0.64–0.96).
FA (data cutoff date: Feb 25, 2019).

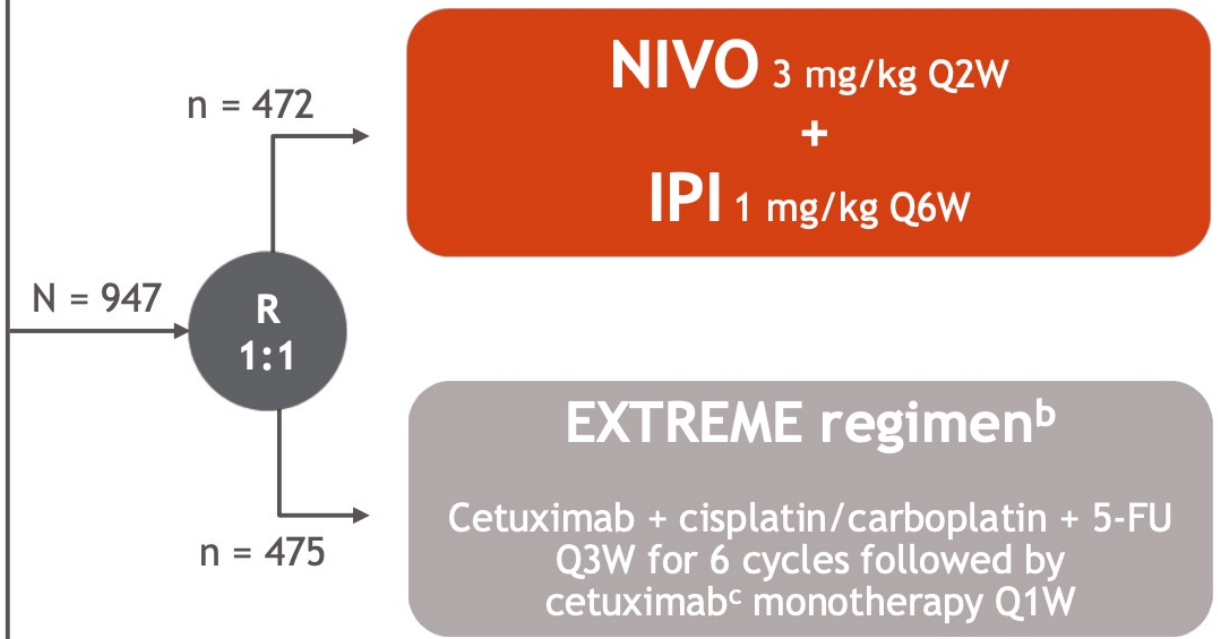
CheckMate 651 study design

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[a] ≥20

Secondary endpoints

- OS in PD-L1 CPS ≥1[d]
- 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

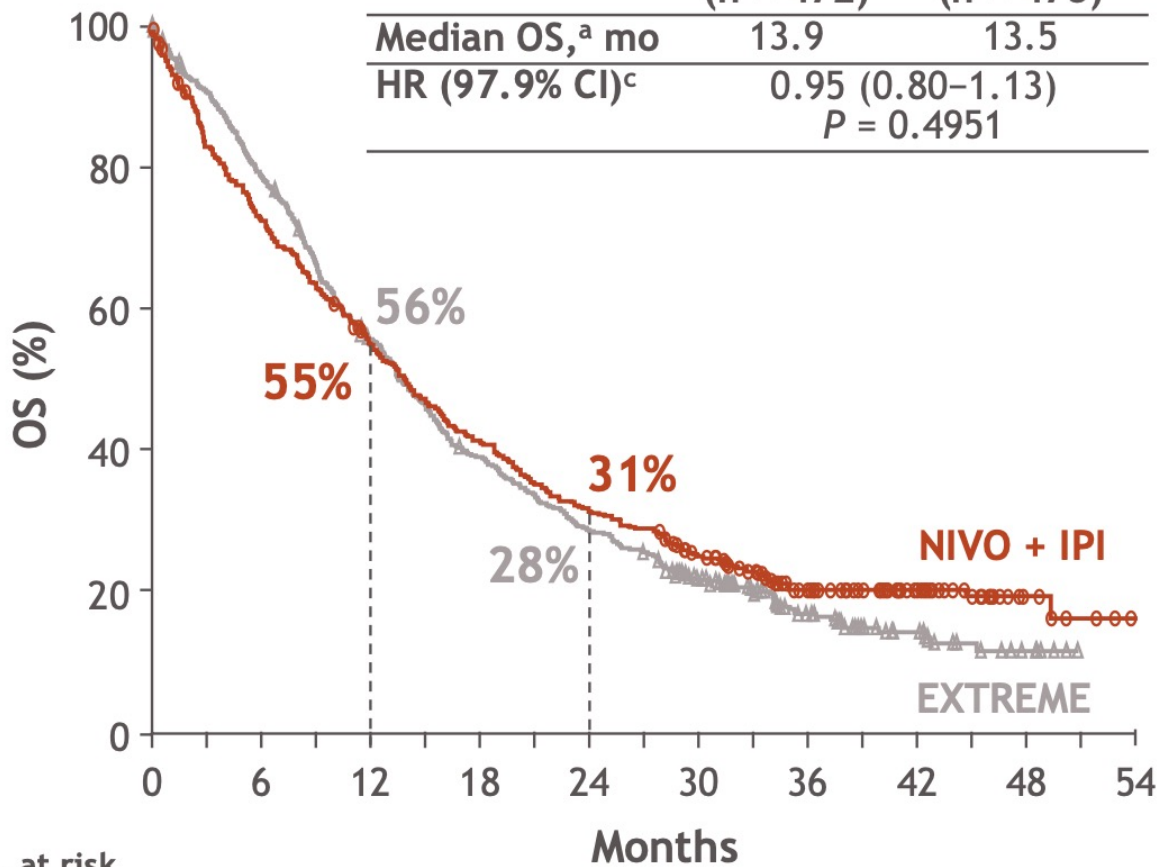
NCT02741570. Database lock: June 21, 2021; minimum / median follow-up: 27.3 months / 39.1 months.

[a]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [b]Initial cetuximab dose of 400 mg/m^2 once only, then cetuximab 250 mg/m^2 Q1W plus cisplatin 100 mg/m^2 or carboplatin AUC 5 on day 1, plus fluorouracil 1000 mg/m^2/d for 4 days for 6 cycles (Q3W); [c]Cetuximab 250 mg/m^2 Q1W; Q2W maintenance was allowed per local prescribing information; [d]Part of statistical testing hierarchy.
BICR, blinded independent central review; CPS, combined positive score; DOR, duration of response; LAD, locally advanced disease; OPC, oropharyngeal cancer; ORR, objective response rate.

Primary endpoints: OS with NIVO + IPI vs EXTREME

All randomized

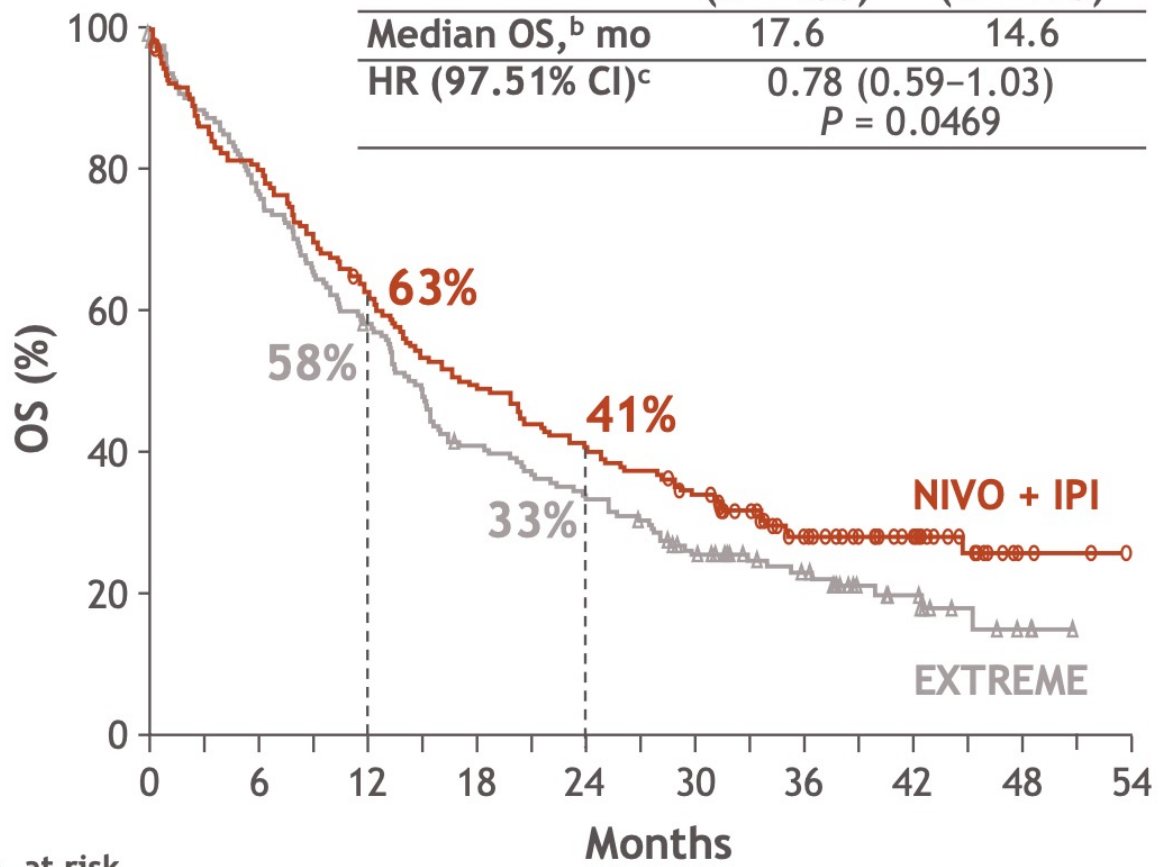
	NIVO + IPI (n = 472)	EXTREME (n = 475)
Median OS,[a] mo	13.9	13.5
HR (97.9% CI)[c]	0.95 (0.80–1.13) *P* = 0.4951	



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

Minimum follow-up: 27.3 months.

[a]95% CI = 12.1–15.8 (NIVO + IPI) and 12.6–15.2 (EXTREME); [b]95% CI = 13.8–22.0 (NIVO + IPI) and 12.3–16.0 (EXTREME); [c]Confidence intervals are adjusted based on the final α levels for each primary endpoint. CPS, combined positive score.

2021 ASCO® ANNUAL MEETING

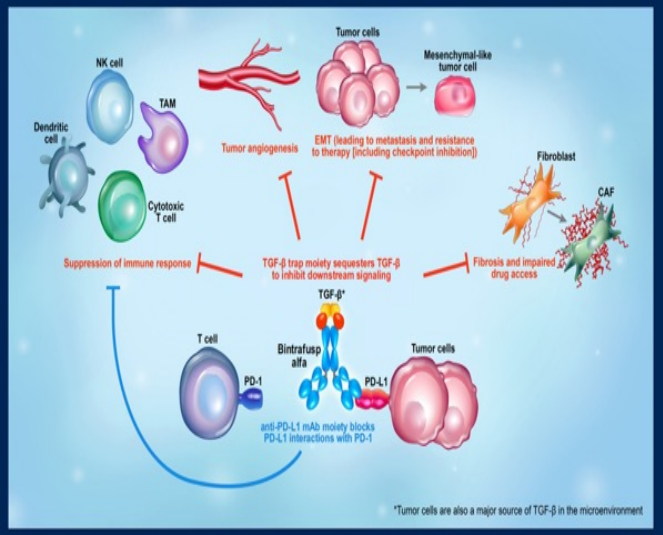
PHASE II EVALUATION OF THE TRIPLE COMBINATION OF PDS0101, M9241, AND BINTRAFUSP ALFA IN PATIENTS WITH HPV 16 POSITIVE MALIGNANCIES

Julius Strauss[1], Charalampos S. Floudas[2], Houssein Abdul Sater[2], Michell Manu[3], Elizabeth Lamping[2], Deneise C Francis[2], Lisa M Cordes[2], Jenn Marte[2], Renee N Donahue[1], Caroline Jochems[1], Jason Redman[2], Ravi A Madan[2], Marijo Bilusic[2], Fatima Karzai[2], Scott Norberg[2], Christian S. Hinrichs[2], Lauren V Wood[4], Frank K Bedu-Addo[4], Jeffrey Schlom[1], James L Gulley[2]

[1]Laboratory of Tumor Immunology and Biology, NCI; [2]Genitourinary Malignancies Branch, NCI; [3]Leidos Biomedical Research, Inc.; [4]PDS Biotechnology, Princeton, NJ

Abstract No. 2501. Presented at the 2021 ASCO Annual Meeting, June 4–8, 2021; Virtual. Presentation No.

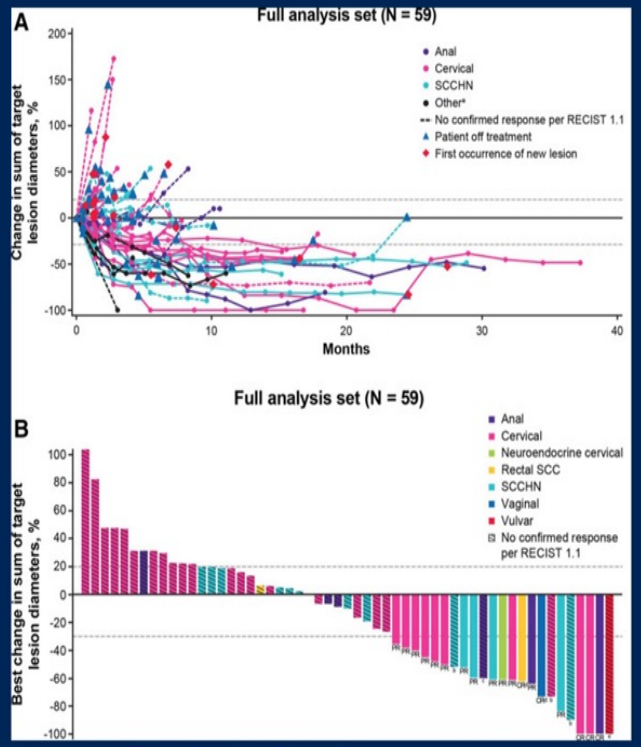
Bintrafusp alfa: a TGF-β and PD-L1 Inhibitor



- Bintrafusp alfa is an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1
- In a phase 1 study, bintrafusp alfa was well tolerated and produced durable responses in several solid tumor types [1-3]

1.Strauss J, et al. *Clin Cancer Res.* 2018;24:1287–95; 2. Paz-Ares L, et al. *J Clin Oncol.* 2018;36(Suppl):Abstract 9017; 3. Cho BC, et al. *Ann Oncol.* 2018;29(Suppl):Abstract 1048O..

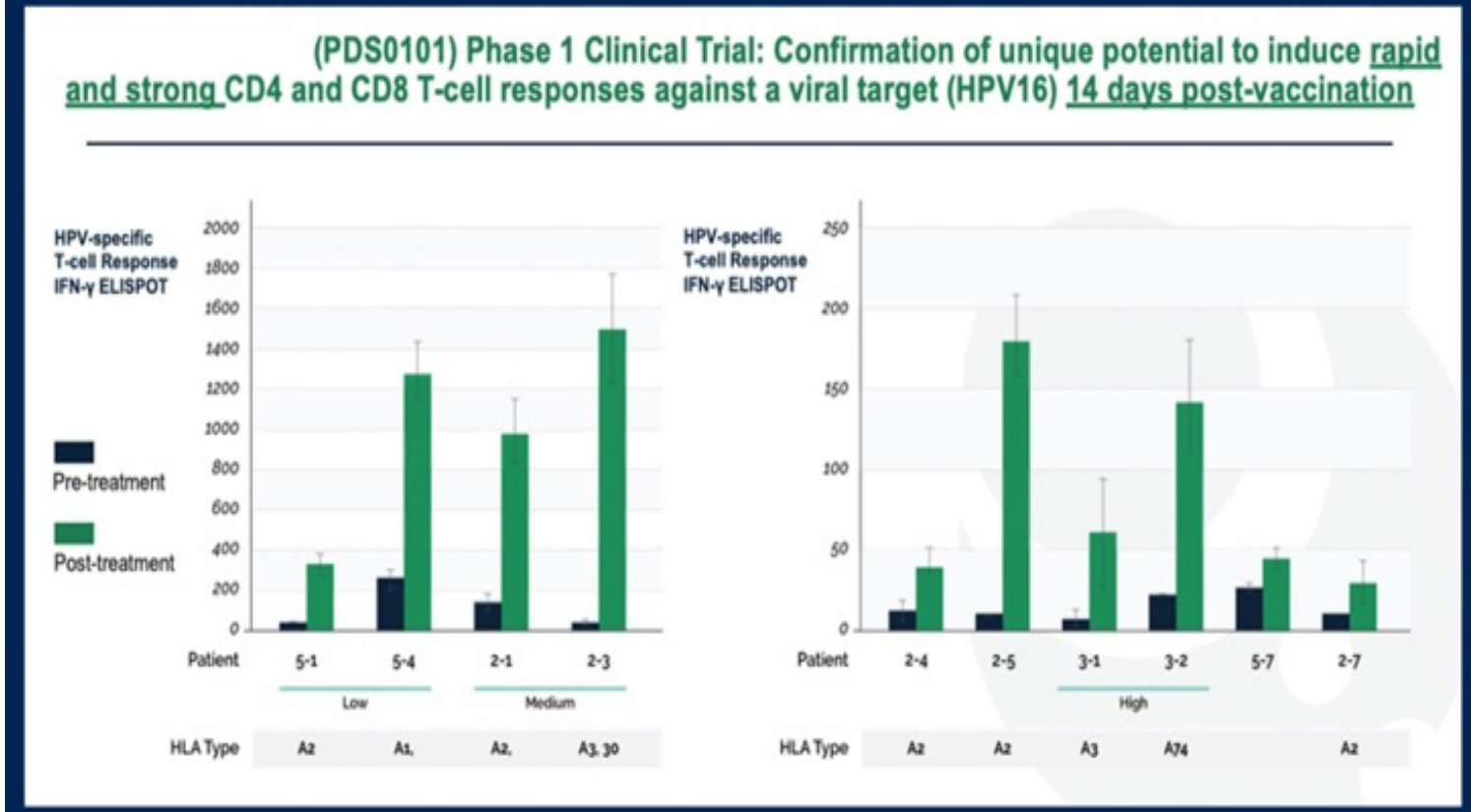
Bintrafusp alfa in HPV-Related Cancers



- 79 patients with advanced HPV-associated cancers (59 checkpoint naïve and 20 checkpoint refractory) received bintrafusp alfa IV every 2 weeks until disease progression or intolerance[1]
- Side effect profile similar to standard anti-PD(L)1 inhibitors with the addition of keratoacanthomas & mucosal bleeding
- ORR was 30.5% in checkpoint naïve disease
- ORR was 10% in checkpoint refractory disease

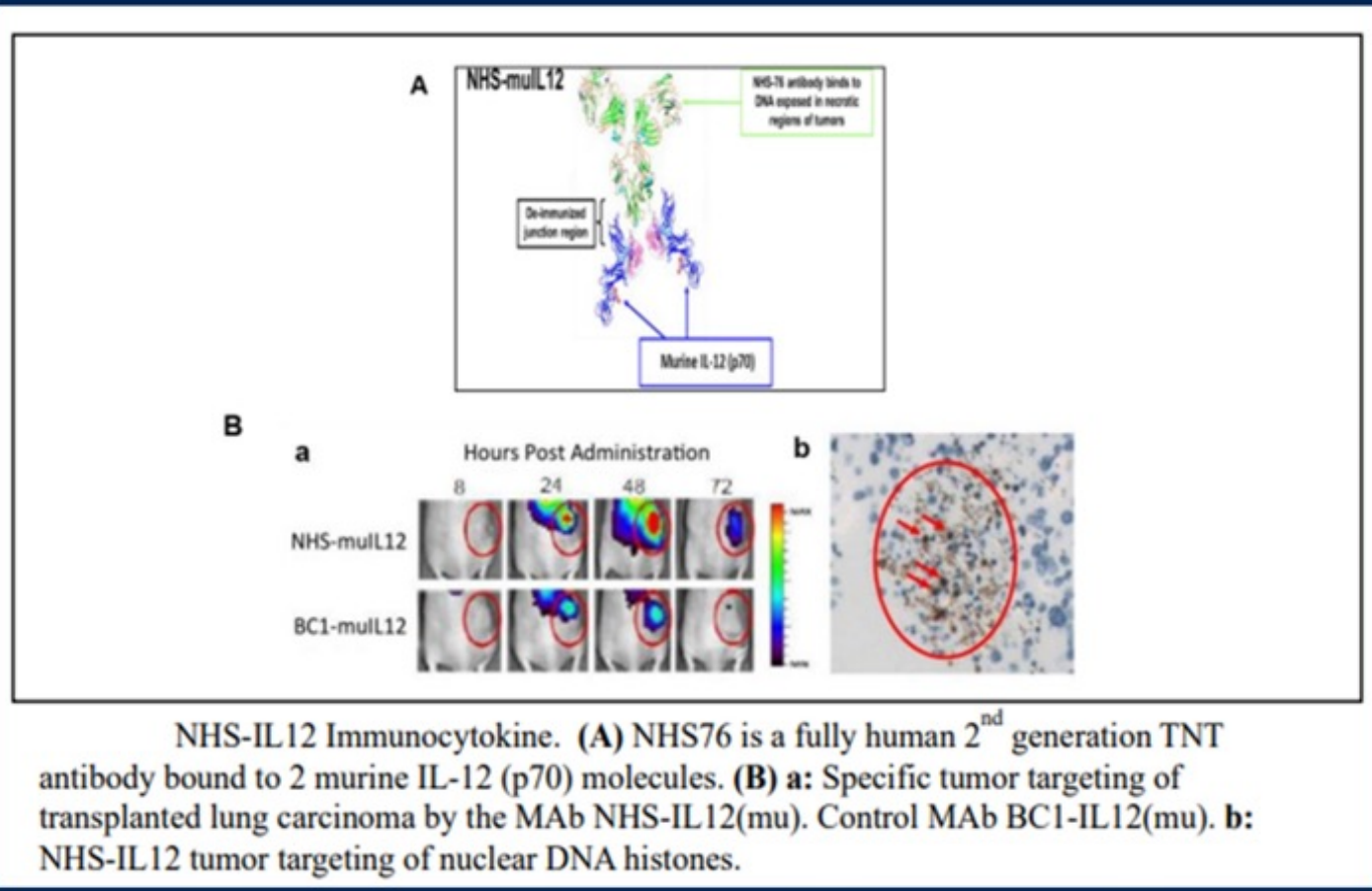
1.Strauss J, et al. J Immunother Cancer. 2020 Dec;8(2):e001395.

PDS0101



- Micellar multi-peptide based therapeutic vaccine targeting HPV 16 E6/ E7 (HPV 16 is the genotype responsible for majority of HPV-related cancers worldwide)
- PDS0101 contain the cationic lipid R-DOTAP which upregulates type I IFNs and promotes antigen cross-presentation
- In a phase I trial patients with cervical intraepithelial neoplasia developed strong HPV-specific CD4+ and CD8+ T cell immune responses[1]
- Was well tolerated with mild transient site reactions and minimal systemic toxicity

M9241 (NHSIL12)



NHS-IL12 Immunocytokine. **(A)** NHS76 is a fully human 2nd generation TNT antibody bound to 2 murine IL-12 (p70) molecules. **(B) a:** Specific tumor targeting of transplanted lung carcinoma by the MAb NHS-IL12(mu). Control MAb BC1-IL12(mu). **b:** NHS-IL12 tumor targeting of nuclear DNA histones.

- Tumor targeting IL12 immunocytokine
- Composed of two IL12 heterodimers fused to NHS76 antibody which binds to histones on free DNA fragments found in areas of tumor necrosis
- In phase 1 trial in patients with advanced solid tumors the most frequently observed AEs included flu like symptoms and asymptomatic lab abnormalities (e.g. mild cytopenias and liver enzyme elevations)[1]
- M9241 treatment resulted in increased T cell infiltration in the TME

1.Strauss J, et al. Clin Cancer Res. 2019 Jan 1;25(1):99-109

Study Design

- Patients with advanced HPV-related cancers received the combination of bintrafusp alfa at 1200 mg flat dose i.v. q 2wks, M9241 at 16.8 mcg/kg s.c. q 4 wks and PDS0101 given as two separate 0.5 ml s.c. injections q 4 wks [NCT04287868]
- Dose reductions of M9241 to 8 mcg/kg were allowed as well as skipped doses of agent(s) for toxicities
- HPV genotyping was done with PCR based assays (BD Onclarity or Molecular MD) if testing not already done

Population

- Cervical
- Anal
- P16+ oropharyngeal
- Other HPV-associated

Endpoints

Primary: ORR
Secondary: safety

Treatment until confirmed progression, unacceptable toxicity, or any criteria for withdrawal; treatment past progression was allowed

Results

	All patients N=25	HPV 16+ N=18	HPV 16+ CPI Naïve N=6	HPV 16+ CPI Refractory N=12
BOR, n (%)				
Complete response (CR)	2 (8)	2 (11.1)	1 (16.7)	1 (8.3)
Partial response (PR)	8 (32)	8 (44.4)	4 (66.7)	4 (33.3)
ORR (CR+PR), n (%)	10 (40)	10 (55.6)	5 (83.3)	5 (41.7)
Disease Reduction, n (%)	13 (52)	12 (66.7)	5 (83.3)	7 (58.3)
Ongoing response, n/n (%)	8/10 (80)	8/10 (80%)	4/5 (80%)	4/5 (80%)
Overall Survival, n/n (%)*	20/25 (80)	16/18 (88.9)	6/6 (100)	10/12 (83.3)

* Median 8 months of follow up

Patient Outcomes

- ORR 55.6% (tumor reduction 66.7%) in HPV 16+ disease
- ORR 83.3% in CPI *naïve* HPV 16+ disease
- ORR 41.7% (tumor reduction 58.3%) in CPI *refractory* HPV 16+ disease
- After a median 8 months of follow up:
  - 80% of responses are ongoing
  - 6/6 (100%) pts with HPV 16+ CPI naïve disease remain alive (historical median OS is 7-11 mo)[1-6]
  - 10/12 (83.3%) pts with HPV 16+ CPI refractory disease remain alive (historical median OS is 3-4 mo)[7]

1. Bauml J, et al. *J Clin Oncol* 2017;35:1542–49; 2. Ott PA, et al. *Ann Oncol*. 2017;28:1036–41; 3. Mehra R, et al. *Br J Cancer*. 2018;119:153–59; 4. Ferris RL, et al. *N Engl J Med*. 2016;375:1856–67; 5. Morris VK, et al. *Lancet Oncol*. 2017;18:446–53; 6. Chung HC, et al. *J Clin Oncol* 2019;37: 1470-8; 7. Strauss J, et al. J Immunother Cancer. 2020 Dec;8(2):e001395

Results

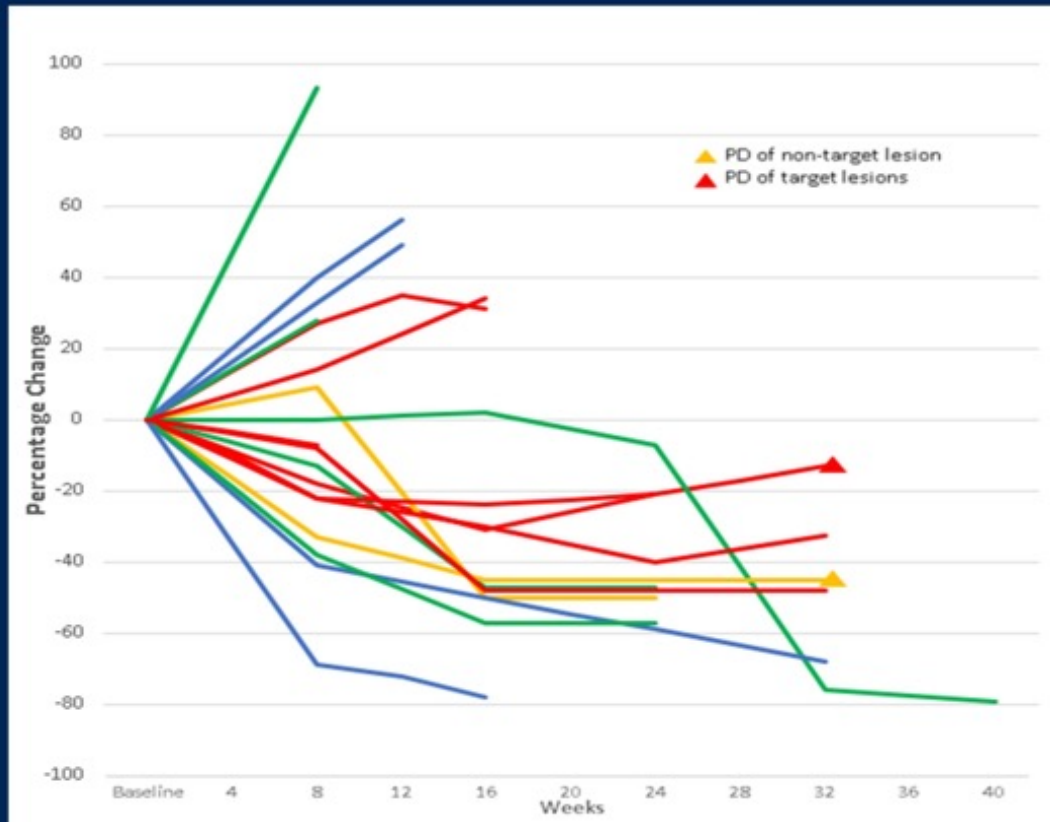
	All patients N=25
	Grade ≥2
Treatment-related adverse events (TRAEs)	23 (92)
TRAEs leading to discontinuation of ≥ 1 drug(s)	5 (20)
Treatment-related serious AEs	7 (28)
TRAEs in ≥5% of patients	
Anemia	12 (48)
Lymphocyte decrease	7 (28)
Flu like symptoms	6 (24)
Injection site reactions	5 (20)
Hematuria	4 (16)
AST/ ALT/ Alk phos elevation	4 (16)
Keratoacanthomas	4 (16)
Leukocyte decrease	3 (12)
Maculopapular rash	3 (12)
Pruritis	3 (12)
Nausea/ vomiting	3 (12)
Mucositis	3 (12)
Hypothyroidism	3 (12)
Peripheral motor neuropathy	2 (8)
Fatigue	2 (8)

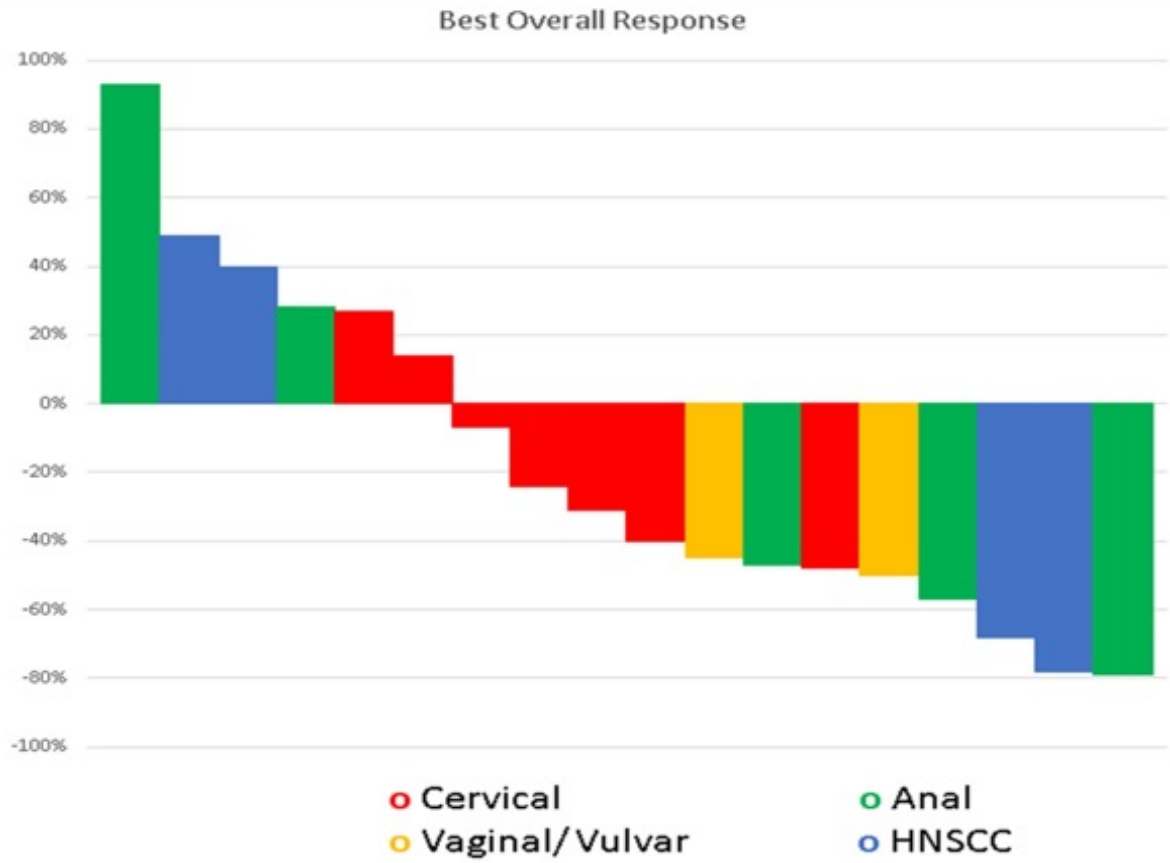
1. Hemophagocytic lymphohistiocytosis

Safety summary

- Grade 3 TRAEs occurred in 10 (40%) patients
  - anemia due to hematuria (n=4), AST/ALT elevation (n=2); flu like symptoms (n=1), nausea/ vomiting (n=1), leukopenia (n=1), lymphopenia (n=2), HLH[1] (n=1)
- All four patients with grade 3 hematuria had cervical ca with prior pelvic RT + brachytherapy
- One patient with transient grade 3 leukopenia and lymphopenia also had transient grade 4 neutropenia
- 4 patients who originally had grade 3 toxicities with the triple combo including M9241 at 16.8 mcg/kg tolerated the triple combo with M9241 at 8 mcg/kg w/o any further grade ≥3 toxicities
- No treatment-related deaths occurred

Results





- Responses in HPV 16+ disease occurred irrespective of tumor type

Conclusions

- Triple combination of PDS0101, M9241 and bintrafusp alfa appears to have a manageable safety profile along with early evidence of notable clinical activity for pts with advanced HPV 16+ malignancies

- Clinical activity noted irrespective of tumor type or CPI status
- ORR was 55.6% (tumor reduction 66.7%) in all pts with advanced HPV 16+ disease
- ORR was 83.3% in patients with CPI *naive* HPV 16+ disease
- ORR was 41.7% (tumor reduction 58.3%) in patients with CPI *refractory* HPV 16+ disease

- After a median 8 months of follow up:
  - 80% of responses are ongoing
  - 6/6 (100%) pts with HPV 16+ CPI naïve disease remain alive
  - 10/12 (83.3%) pts with HPV 16+ CPI refractory disease remain alive

- Accrual is ongoing to the triple combination [NCT04287868]

2021 ASCO ANNUAL MEETING

Abstract #: 6028

Results from a Phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with PD-L1 unselected metastatic 2nd line squamous head and neck carcinoma

Presenting Author: Dr. Irene Braña

Authors: I Braña[1], M Forster[2], A Lopez Pousa [3], B Doger[4], P Roxburgh[5], P Bajaj[6], D Urueta[7], V Quiroga[8], M Krebs[9], C Muellller[10], F Triebel[11]

Affiliates: [1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2] UCL Cancer Institute / University College London Hospitals NHS Foundation, London, UK; [3] Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4] START Madrid- Fundación Jiménez Diaz, Madrid, Spain; [5]Institute of Cancer Sciences, University of Glasgow and The Beatson West of Scotland Cancer Centre, Glasgow, UK; [6] Tasman Oncology, Queensland, Australia; [7] Oncology Consultants, P.A., Houston, USA; [8] Catalan Institute of Oncology Badalona-Hospital Germans Trias i Pujol, B-ARGO group; Badalona, Spain; [9] Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [10] Clinical Development, Immutep GmbH, Berlin, Germany; [11] Research & Development, Immutep S.A.S., Orsay, France

Study Identifiers:
Sponsor: IMP321-P015; MSD: Keynote-PN798; EudraCT: 2018-001994-25; Clinicaltrials.gov: NCT03625323

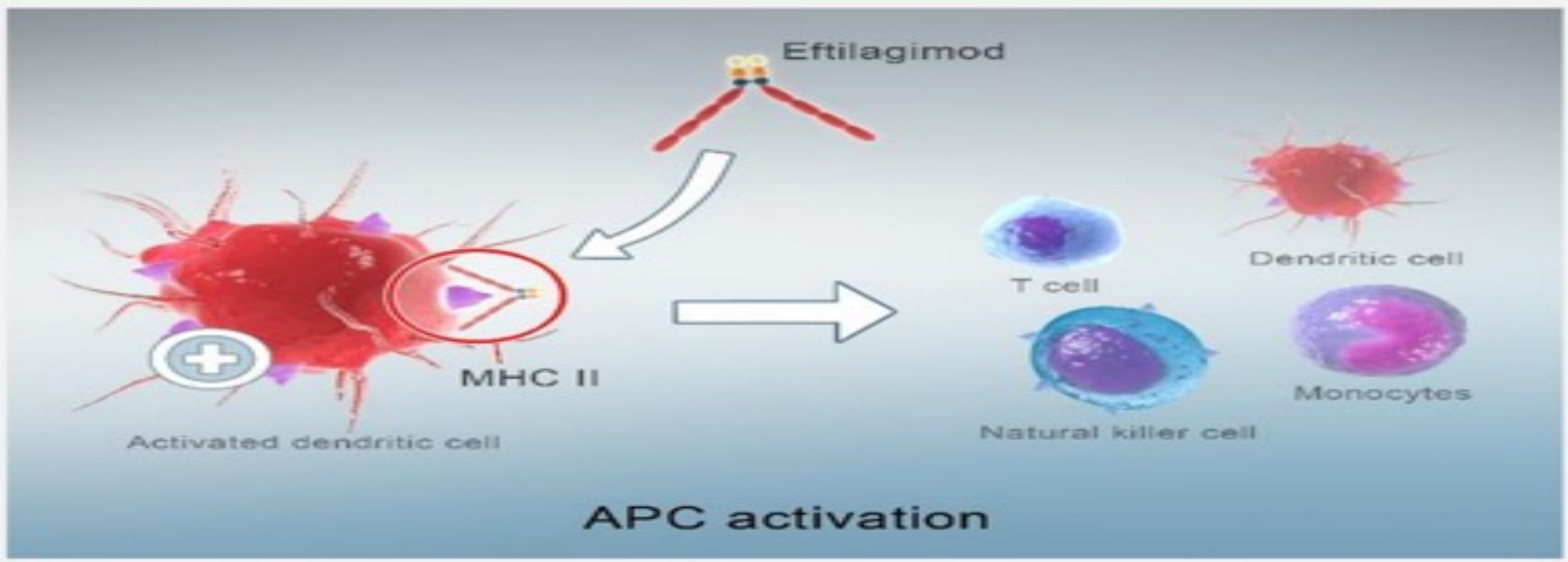
Corresponding author: Frederic Triebel, frederic.triebel@immutep.com

Eftilagimod alpha (efti) MoA

MoA: Efti is a soluble LAG-3 protein targeting a subset of MHC class II molecules to mediate antigen presenting cells (APCs) and CD8 T-cell activation.

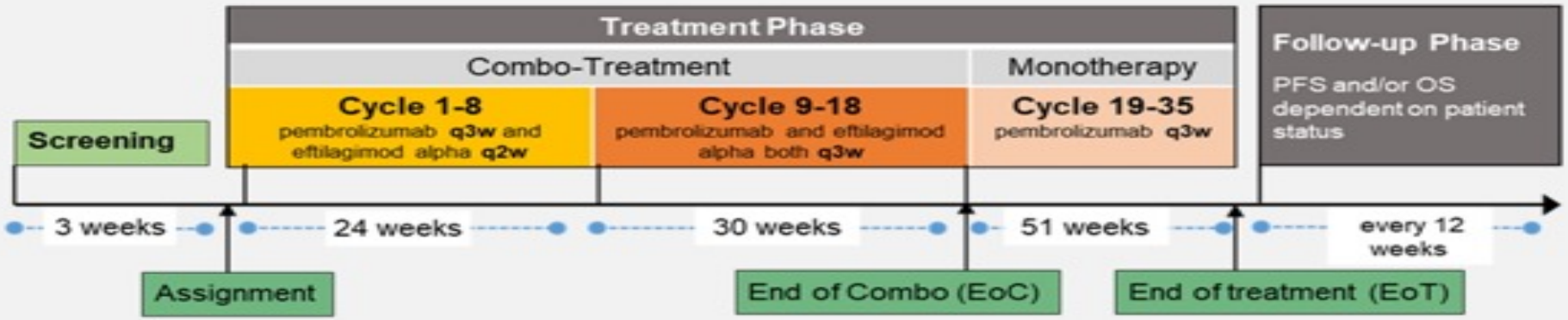
Rationale: Efti activates APCs, leading to an increase in activated T cells, thus potentially reducing the number of non-responders to PD-1/PD-L1 antagonists (e.g. pembrolizumab).

"PUSHING THE ACCELERATOR ON IMMUNE RESPONSES"



TACTI-002
TRIAL DESIGN & INTRODUCTION

- Phase II, multinational, open label, PD-L1 all-comer, multiple indications
- Up to 183 pts in a Simon's optimal two-stage design (NCT03625323)
- Sponsored by Immutep and in collaboration with MSD



Legend: 1 cycle = 3 weeks; q2w – every 2 weeks, q3w every 3 weeks

- Following patients are eligible to part C (2nd line HNSCC):

  *patients **unselected for PD-L1** with recurrent HNSCC disease unamenable to curative treatment with local or systemic therapy, or metastatic (disseminated) disease incurable by local therapies, who progressed on or after 1st line platinum-based therapy*
- 39 patients were enrolled to stage 1 + 2 (LPI in Jan 2021)
- **Primary objective: Overall Response Rate acc. to iRECIST**
- Secondary objectives include PFS, OS, PK, biomarker, PD, safety and tolerability
- Data cut-off: 16th April 2021 (interim data)

Conclusions (Efti + Pembro 2 Line HNSCC-Part C)

SAFETY

- Treatment with efti plus pembrolizumab is well-tolerated with no new safety signals
- Majority of most frequent adverse events are mild to moderate
- Safety profile compares well to KN-040 (pembrolizumab monotherapy)

EFFICACY

- Encouraging ORR (30 % acc. to iRECIST) in patients unselected for PD-L1
- 13.5 % complete responses observed
- Responses were durable with median DOR not yet reached
- In pts with PD-L1 CPS ≥1, ORR was 45.8 % (95 % CI 25.6-67.2), median PFS of 4.1 months and median OS of 12.6 months
- Efficacy in PD-L1 CPS ≥1 encouraging compared to KN-040 (PIII, randomized trial)

The combination of efti plus pembrolizumab is well-tolerated and shows encouraging signs of activity supporting further clinical investigation. A study in 1st line HNSCC patients has been initiated (NCT04811027).

2021 ASCO ANNUAL MEETING

ENHANCED PATHOLOGIC TUMOR RESPONSE WITH TWO CYCLES OF NEOADJUVANT PEMBROLIZUMAB IN SURGICALLY RESECTABLE, LOCALLY ADVANCED HPV-NEGATIVE HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

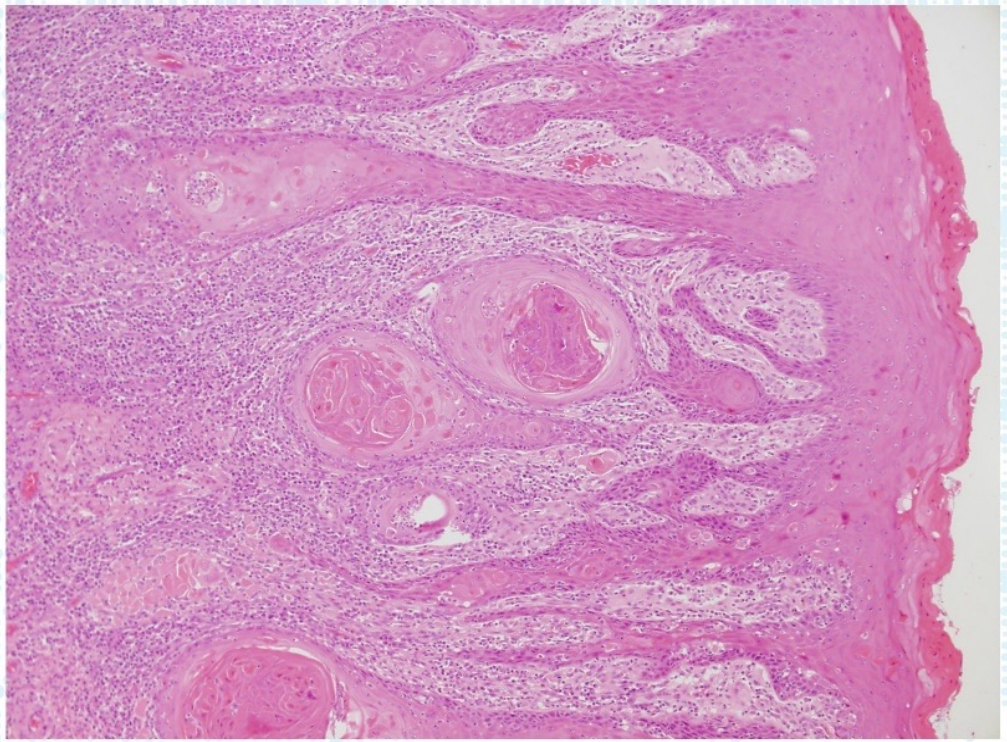
Ravindra Uppaluri, MD/PhD

Dana-Farber/ Brigham and Women's Cancer Center

Douglas Adkins, MD

Siteman Cancer Center/ Washington University in St. Louis

June 7, 2021



Schema for Cohort 2

Endpoints

Cohort 1

Pre-treatment biopsy and blood → Pembrolizumab **(1 dose)** → Surgery (2-3 weeks later) with biopsy and blood → Risk stratified post-op adjuvant + maintenance pembrolizumab → **→1 yr recurrence rate**

Cohort 2

Pre-treatment biopsy and blood → Pembrolizumab **(2 doses)** → Surgery (2-3 weeks later) with biopsy and blood → Risk stratified post-op adjuvant + ~~maintenance pembrolizumab~~ → **→pTR2** **→1 yr recurrence rate**

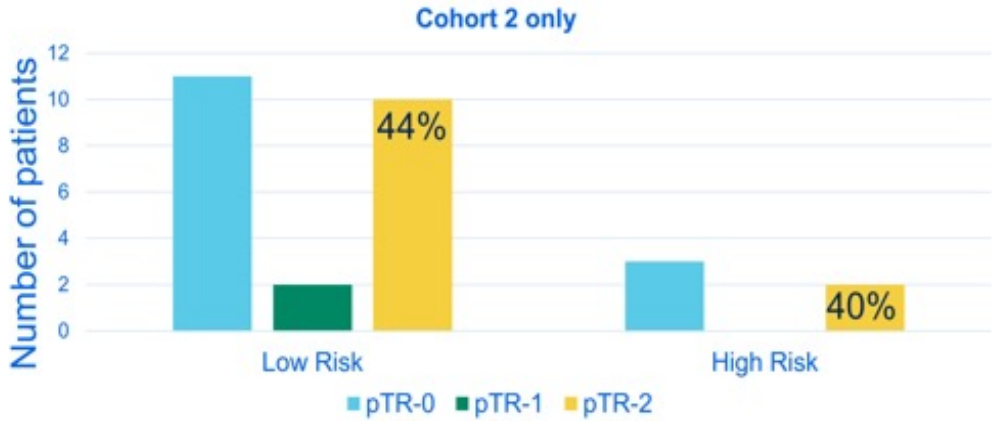
Newly diagnosed, Stage III/IV resectable HNSCC (HPV/p16-)

NCT02296684

Post-surgery findings

Characteristic	Cohort 2 (N=28)*	
pTR Category**		
pTR-0	14	50.0%
pTR-1	2	7.1%
pTR-2	12	42.9%
Pathologic disease Stage, N (%)		
I-II	5	17.9%
III	5	17.9%
IVA-IVB	18	64.3%
Pathologic risk category (positive margins/ENE)		
High risk	5	17.9%
Intermediate/low risk	23	82.1%

*1 patient enrolled but withdrew from trial- did not have surgery
**3 samples with prelim pTR, pending central review for pTR



- Any pTR was seen in 14/28 (50%) of patients
- pTR-2 was seen in 42.9% of patients
  -higher than Cohort 1
- pTR-1 rates (7.1%) were lower than Cohort 1
- pTR distributions were similar across risk categories

Conclusions of NeoAdj Pembro study…

- Neoadjuvant pembrolizumab (two doses) was safe and did not delay surgery
- pTR-2 rates were doubled with two versus one dose of neoadjuvant pembrolizumab
  - Possible explanation includes timing (3 versus 6 weeks) or 2 doses of drug
  - 1-year OS and PFS were excellent
- Further studies are needed to define optimal dosing/timing and relevance of pTR to clinical outcome

Conclusions

- HRAS and PIK3CA mutations/amplifications are potential targets in HNSCC.
- Tipifarnib is promising for HRAS mutant SCCHN, moreover if VAF >20%.
- PIK3CA mutations continue to be targeted, both monotherapy (irreversible PIK3CAi) and combination (with FTI).
- Nasopharyngeal carcinoma: IO + Gem/Cis is emerging as SOC first line.
- SCCHN:
  - Novel IO agents promising: Bintra/PDS/IL-12 for HPV+; LAG3 – eftilagimod.
- SCCHN neoadjuvant studies showed promising results (longer with chemo, with CRT?)

Thank You !

@EdgardoSantosMD
edgardo_ny@hotmail.com
edgardo.santos@usa.genesiscare.com

GenesisCare

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLORIDA PRECISION ONCOLOGY
A Division of Genesis Care