Challenges in Targeting Head and Neck Squamous Cell Carcinoma

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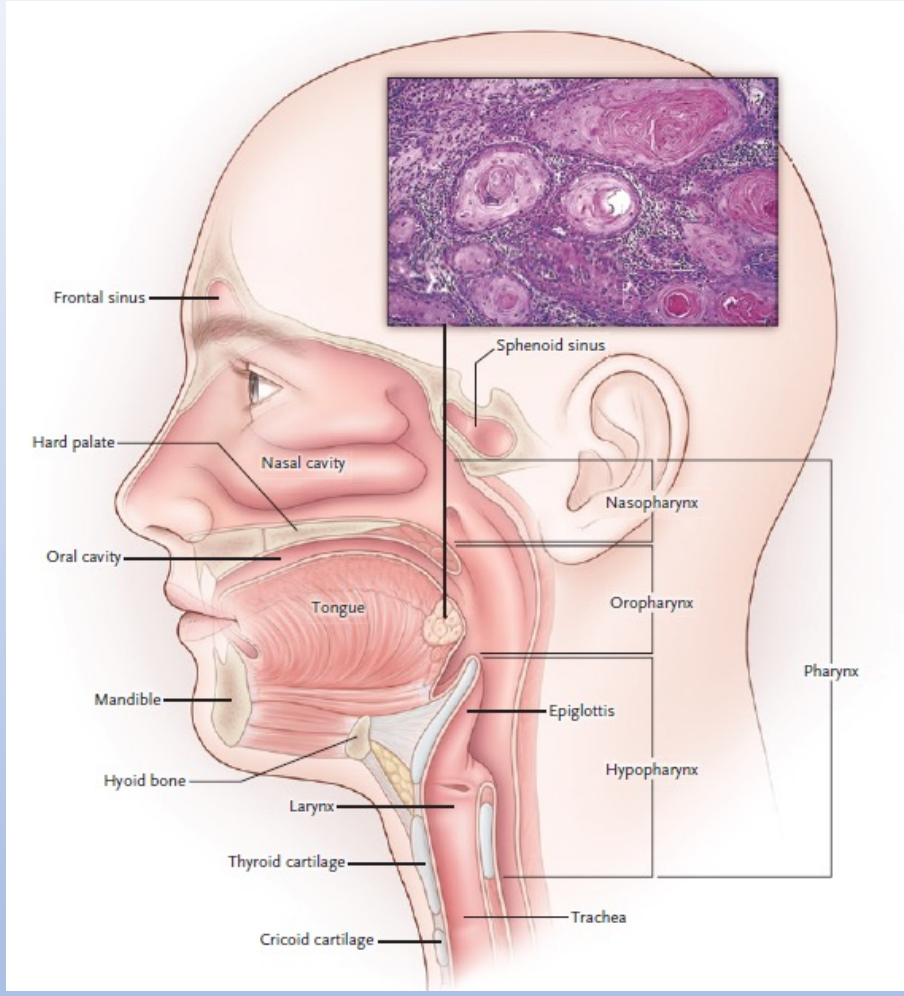
Head and Neck Cancer

- Global
  - 7th most common cancer worldwide
  - 890,000 new cases/year
  - 450,000 annual deaths
- USA (2023)
  - Incidence 66,920
  - Deaths 15,400

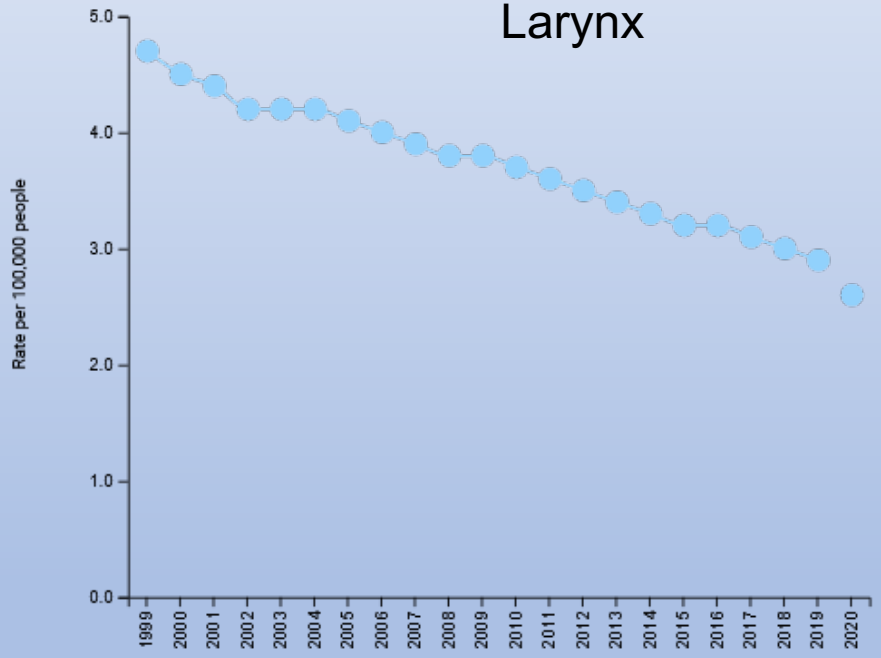
- Histology
- Sites
- Risk factors



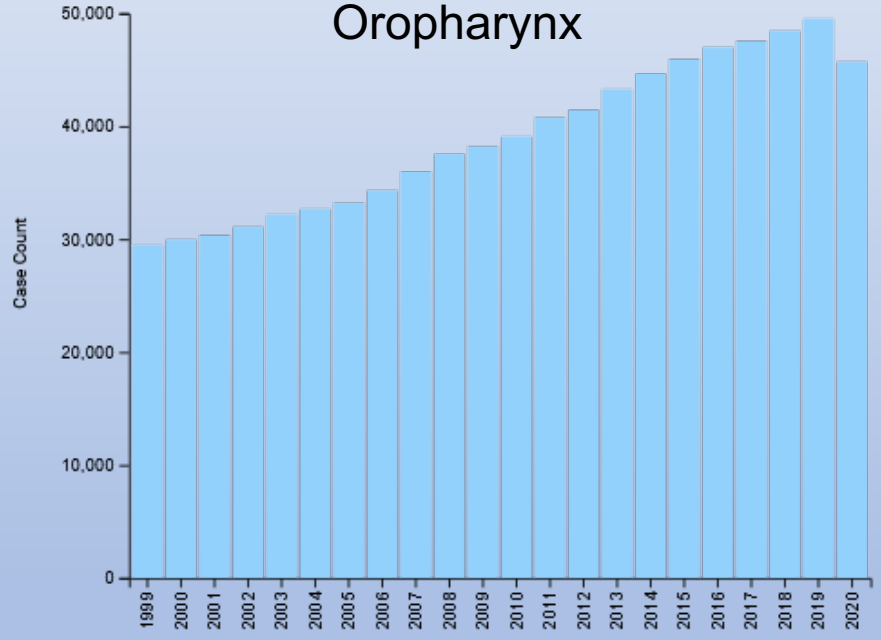
*Sung et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
*Siegel et al. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17-48
* Chow LQM. Head and Neck Cancer. N Engl J Med. 2020 Jan 2;382(1):60-72

Annual rates of new cancers (1999-2020)

Larynx



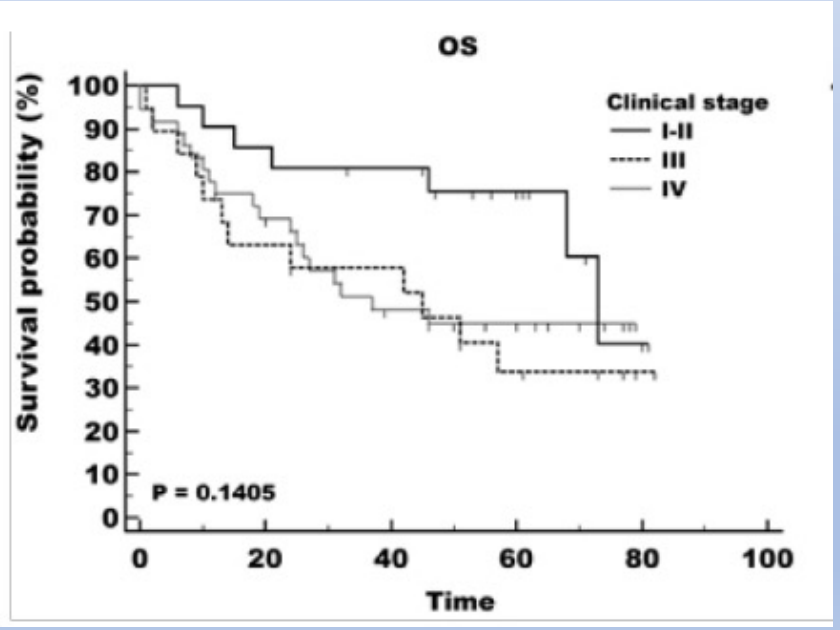
Oropharynx



Source - U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2023.

Challenges in treating head and neck cancer

A. Late presentation
   - Only 30-40% patients present with early-stage disease (Stage I/II)
   - Prognosis is dependent on stage at presentation



**Head and Neck Cancer Patients' Survival According to HPV Status, miRNA Profiling, and Tumour Features-A Cohort Study. Int J Mol Sci. 2023 Feb 7;24(4):3344*

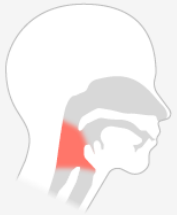
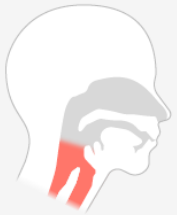
B.Head & neck cancer is n

- Different histology
- Different sites
- Different treatment options

** Head and neck cancer. Lancet. 2021 Dec 18;398(10318):2289-2299.*

Treatment strategies

An overview of strategies by cancer type

	Radiography	Surgery	Chemotherapy
Oropharyngeal cancers 	Recent prominence of younger patients who respond better to non-surgical therapies has fuelled an evolution towards methods of deintensifying treatment via reduced radiotherapy doses or volumes.	There has been a renewed interest in surgical management of these cancers to spare patients with papillomavirus-related curable disease treatment-related toxicities of other treatments.	Combined with radiation to treat locally advanced oropharynx cancer; it has also been the standard of care for metastatic disease until recently; with the approval of immunotherapy, PD-1 inhibitors are now the standard of care for a large number of patients with metastatic disease.
Oral cavity cancers 	Radiotherapy, with or without chemotherapy, is reserved for advanced stage disease.	Surgery remains the primary treatment strategy for oral cavity cancers.	Tumours in oral cavity frequently border, or invade, the mandible and maxilla (jawbones), which creates a substantial risk for complications from the use of primary chemoradiotherapy.
Cancers of the larynx and hypopharynx 	Radiation is a cornerstone for treating larynx cancer for the purpose of organ preservation and to treat early stage larynx cancer.	Upfront, definitive surgical therapy is often limited to early-stage disease. However salvage surgery is sometimes necessary for later-stage cancers.	Chemotherapy is often combined with radiation for the purpose of organ preservation, it has also been the standard of care for metastatic disease until recently; with the approval of immunotherapy, PD-1 inhibitors are now the standard of care for a large number of patients with metastatic disease.
Nasopharyngeal cancers 	Radiotherapy is the primary and only curative treatment for early-stage carcinoma.	Surgery is reserved for management of early stage disease.	Chemoradiotherapy is the standard care in patients with locally advanced disease or those at risk of distant metastasis.

C. Multidisciplinary treatment

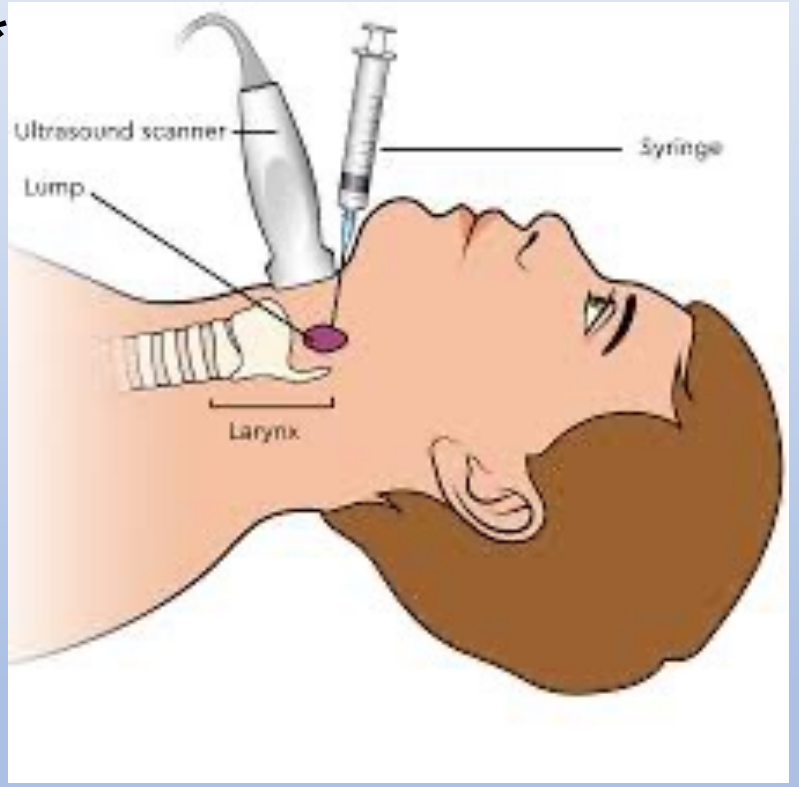
- It takes a village
  - ENT surgeon
  - Radiation oncologist
  - Medical oncologist
  - Radiologist
  - Pathologist
  - Audiologist
  - Dietician
  - Speech & language pathologist

- *Treatment at high volume centers improves survival

** Institutional clinical trial accrual volume and survival of patients with head and neck cancer. J Clin Oncol. 2015 Jan 10;33(2):156-64.*

D. Lack of tissue

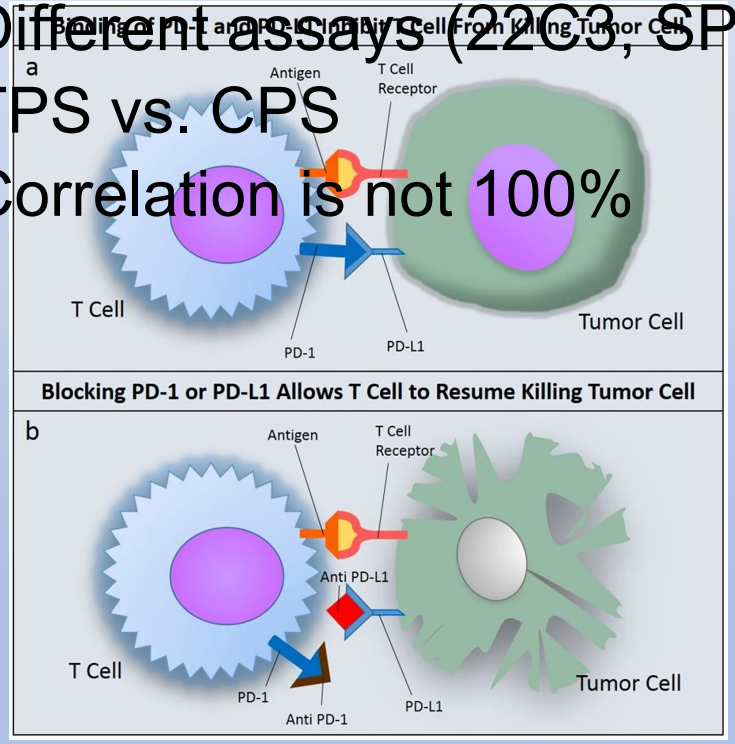
- FNA is the preferred diagnostic modality*

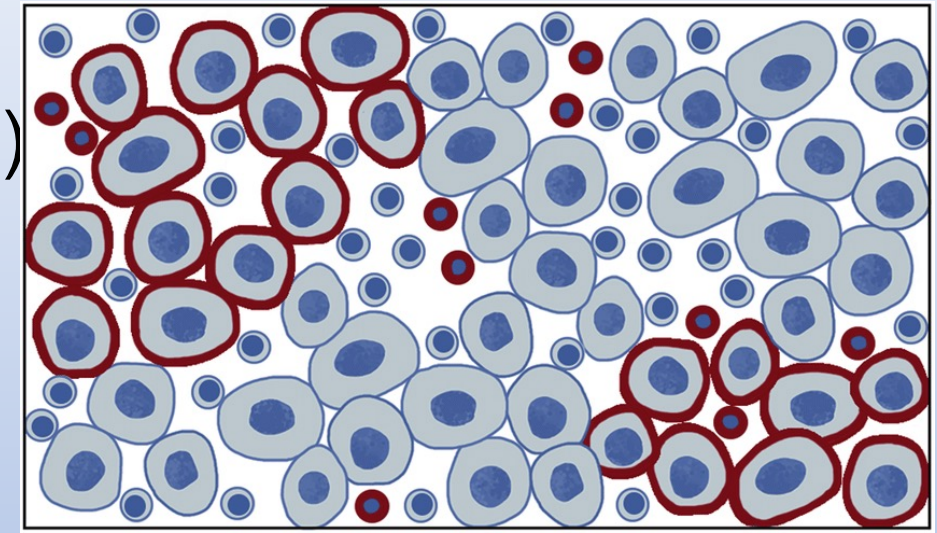


**Fine-needle aspiration cytology in a regional head and neck cancer center: comparison with a systematic review and meta-analysis. Head Neck. 2008 Sep;30(9):1246-52.*

E. Lack of predictive biomarkers

- Programmed death-ligand 1 (PD-L1)
  - Different assays (22C3, SP263)
  - TPS vs. CPS
  - Correlation is not 100%





PD-L1 negative tumor cell

PD-L1 negative immune cell

PD-L1 positive tumor cell

PD-L1 positive immune cell

$$\text{TPS} = \frac{\text{No. PD-L1 positive tumor cells}}{\text{Total No. of viable tumor cells}} \times 100$$

$$\text{CPS} = \frac{\text{No. PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

**Identification and Validation of a PD-L1 Binding Peptide for Determination of PDL1 Expression in Tumors. Sci Rep. 2017 Oct 20;7(1):13682.*
**Comparison of three PD-L1 immunohistochemical assays in head and neck squamous cell carcinoma (HNSCC). Mod Pathol. 2021 Jun;34(6):1125-1132*

KEYNOTE-040
Study Design

- Recurrence or PD after platinum containing regimen for recurrent or metastatic SCCHN
- PD within 3 to 6 mo of multimodal therapy using platinum
- N = 495

R
1:1

- Primary endpoint: OS in the ITT pop
- Secondary endpoints: OS in the PD-L in the ITT and CPS ≥ 1 populations; s
- Prespecified exploratory end points: ≥ 50% population

Cohen EE, et al. ESMO 2017. Abstract LBA45.

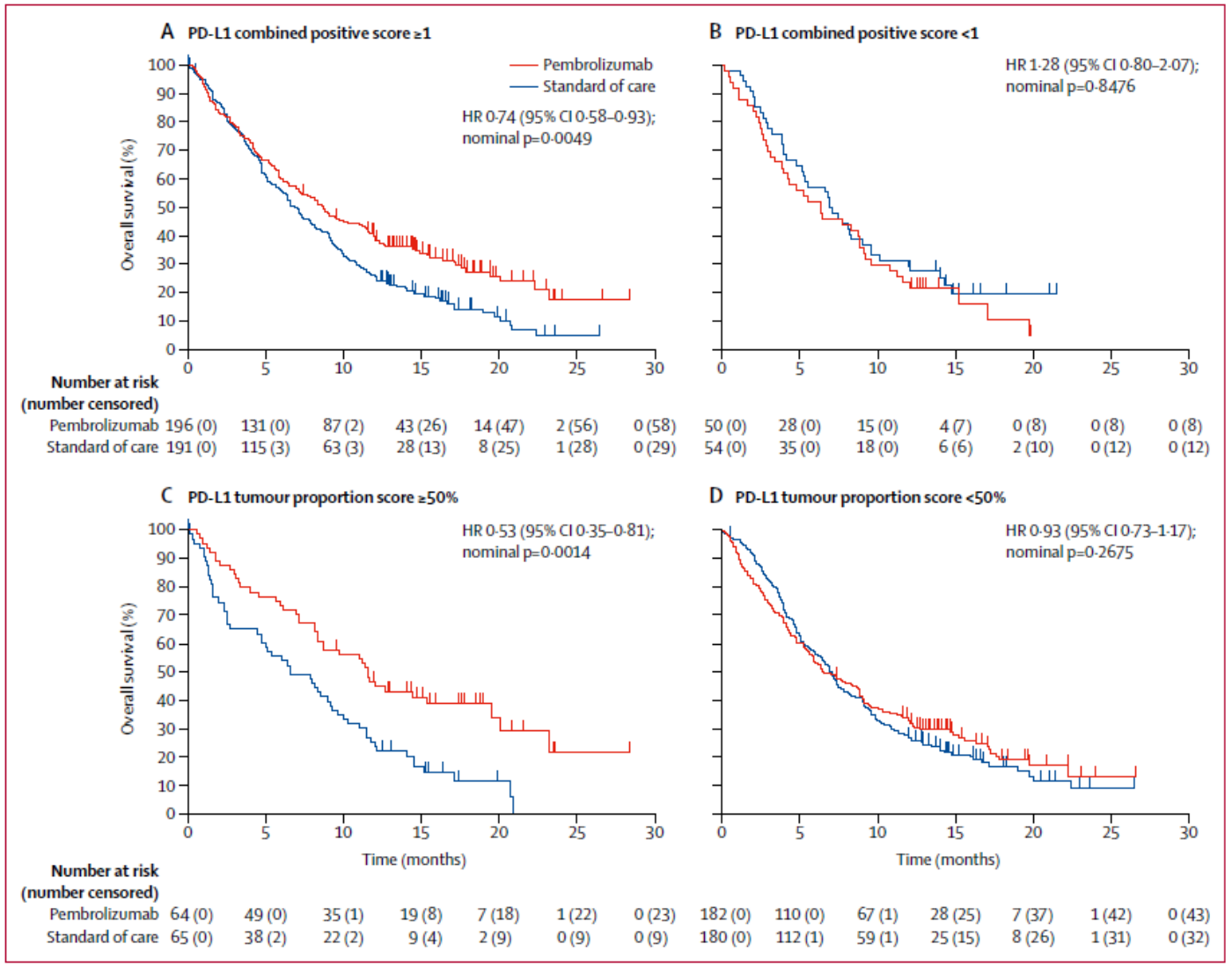


***Figure 3*: Overall survival in the intention-to-treat populations according to PD-L1 expression category**
Kaplan-Meier estimates of overall survival according to treatment group in the population with a combined positive score of 1 or more (A), the population with a combined positive score of less than 1 (B), the population with a tumour proportion score of 50% or more (C), and the population with a tumour proportion score of less than 50% (D). Tick marks represent patients who had data censored at the last time a which they were known to be alive. HR=hazard ratio. PD-L1=programmed death ligand 1.

F. Lack of reliable tumor markers

- EBV DNA
- ctHPV DNA
- ctDNA

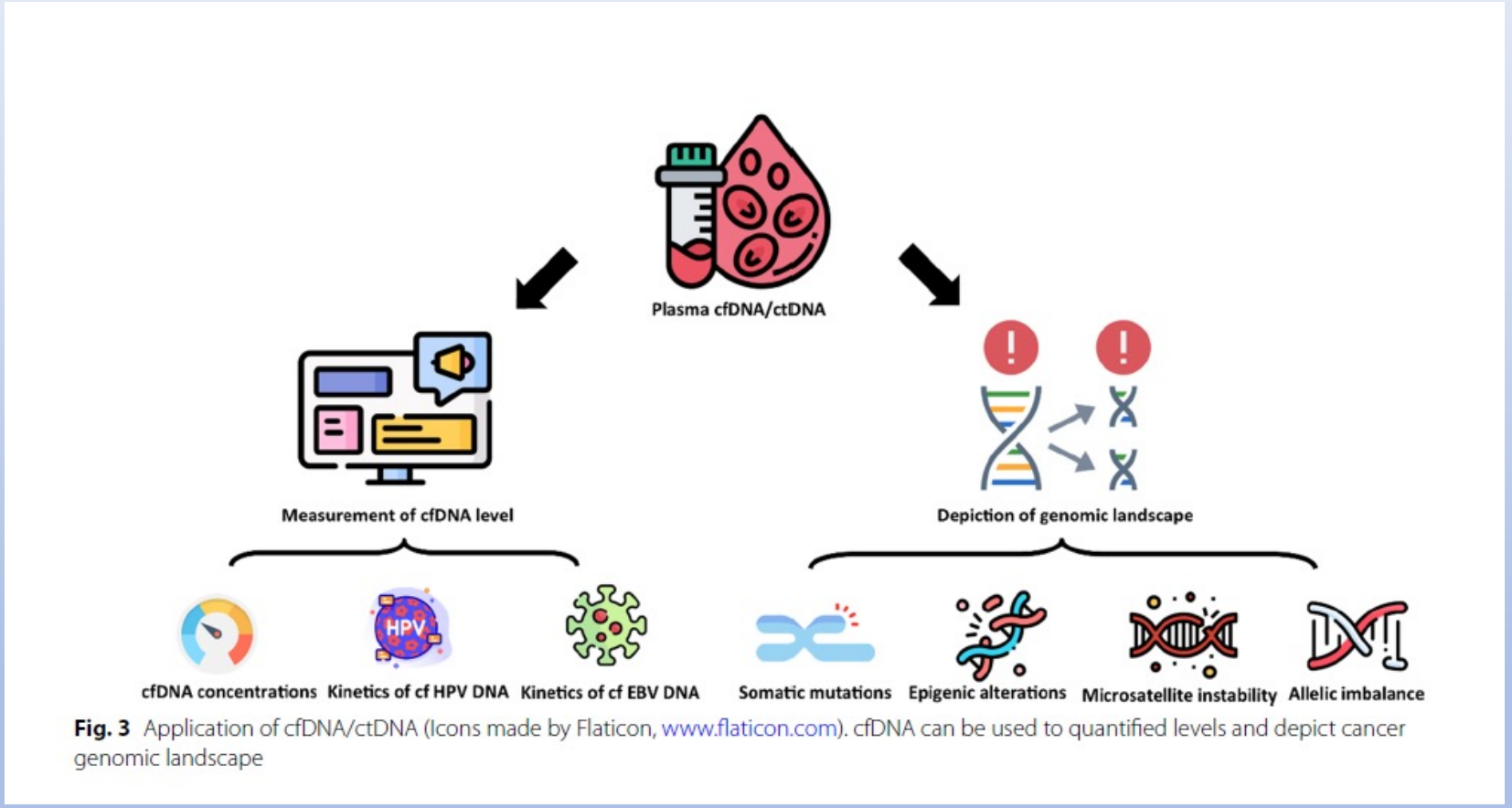
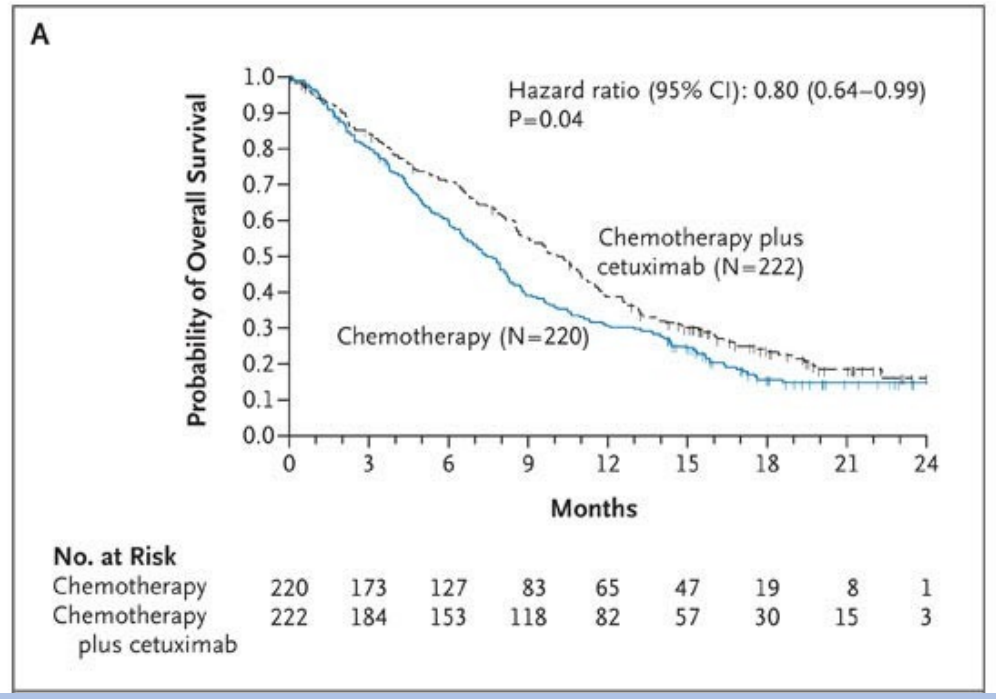


Fig. 3 Application of cfDNA/ctDNA (Icons made by Flaticon, www.flaticon.com). cfDNA can be used to quantified levels and depict cancer genomic landscape

**Huang et al. Journal of Biomedical Science (2023) 30:65*

G. Lack of actionable driver mutations

1. EGFR – cetuximab



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

** Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008 Sep 11;359(11):1116-27.*

TABLE 2. Classification of Molecular Alterations According to ESCAT in HNSCC

Gene	Molecular Alterations	Incidence	ESCAT Tier	References
PI3K/AKT/mTOR pathway				
PIK3CA	Hotspot activating mutations (E542K, E545K/A, and H1047R/L)	8.9%	IIIA	48
	Amplifications	21.6%	IIIB	48
	Other activating hotspot missense mutations	4.0%	IIIB	48
PTEN	Homozygous deletions	3.4%	IIIA	49,50
	Known inactivating missense/truncating mutations	2.2%	IIIA	49,50
MAPK pathway				
HRAS	Hotspot-activating missense mutations	6.3%	IB	27,28
Cell cycle and survival pathway				
CDKN2A	Truncating mutations	17.9%	IIA	36
	Known inactivating missense mutations	3.2%	IIA	36
	Homozygous deletions	32.7%	IIA	36
CCND1	Focal amplifications	23.9%	X	36
CDK6	Focal amplifications	5.4%	X	36
IGF1R	Focal amplifications	1.0%	IVA	76,77
EGFR	Focal amplifications	10.7%	IIA	38,39
ERBB2	Focal amplifications	2.0%	IIIA	57-59
FGFR1	Focal amplifications	6.9%	IIIA	61
FGFR3	Known hotspot activating mutations	1.2%	IIIA	60
MET	Focal amplifications	1.0%	IIIA	68-70
NTRK	Oncogenic fusions	0.2%	IC	42-44
DNA repair pathway				
TP53	Inactivating mutations	72%	V	86-88
BRCA1	Truncating mutations	0.2%	IIIA	71-73
BRCA2	Homozygous deletions/truncating mutations	2.0%	IIIA	71-73
Microsatellite instability		1.2%	IC	31-33

Abbreviations: ESCAT, ESMO scale for clinical actionability of molecular targets; HNSCC, head and neck squamous cell carcinoma; mTOR, mammalian target of rapamycin

**Genomic Alterations in Head and Neck Squamous Cell Carcinoma: Level of Evidence According to ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). JCO Precis Oncol. 2021 Nov;5:215-226.*

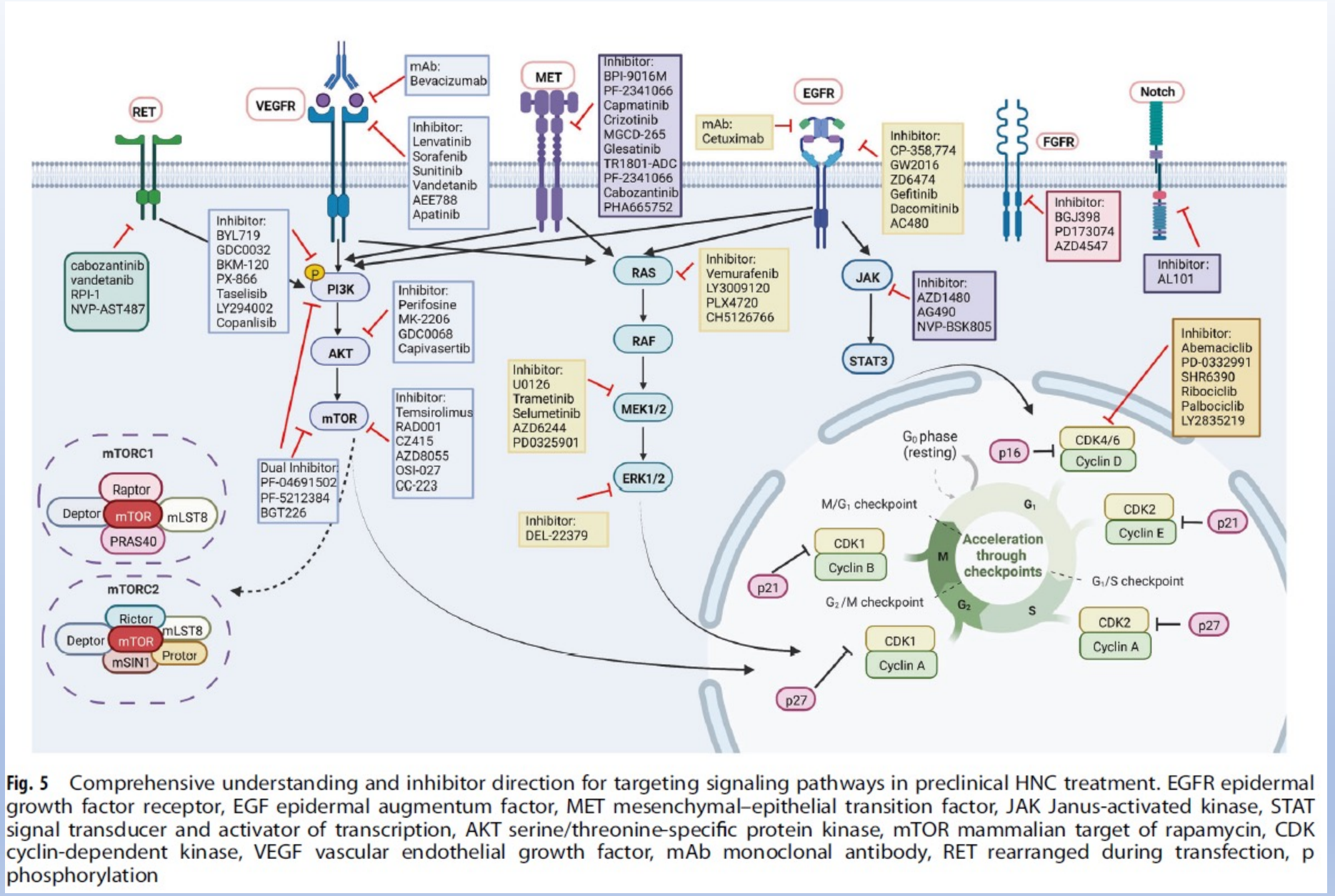


Fig. 5 Comprehensive understanding and inhibitor direction for targeting signaling pathways in preclinical HNC treatment. EGFR epidermal growth factor receptor, EGF epidermal augmentum factor, MET mesenchymal–epithelial transition factor, JAK Janus-activated kinase, STAT signal transducer and activator of transcription, AKT serine/threonine-specific protein kinase, mTOR mammalian target of rapamycin, CDK cyclin-dependent kinase, VEGF vascular endothelial growth factor, mAb monoclonal antibody, RET rearranged during transfection, p phosphorylation

*Targeted therapy for head and neck cancer: signaling pathways and clinical studies. Signal Transduct Target Ther. 2023 Jan 16;8(1):31

2. Cell Cycle – CDK4/6 pathway

6044 **Poster Session**

Abemaciclib in recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC) harboring *CDKN2A* loss, and/or *CCND1* and/or *CDK6* amplification: A phase II multicenter trial.

Jerome Fayette, Esma Saada-Bouzid, Claire Cropet, Amaury Daste, Isabelle Treilleux, Daniel Pissaloux, Frank Pilleul, Charles Mastier, Eve-Marie Neidhardt, Andy Karabajakian, Elodie Grinand, Romaine Mayet, Mathilde Bernardin, Clothilde Celse, Gwenaelle Garin, David Pérol; Centre Léon Bérard, Lyon, France; Centre de Lutte Contre le Cancer Antoine Lacassagne, Nice, France; Centre Léon Bérard, and GINECO, Lyon, France; Department of Medical Oncology, Hôpital Saint-André, University of Bordeaux-CHU Bordeaux, Bordeaux, France; Deeplink Medical, Lyon, France

- >50% patients with HPV negative HNSCC harbor mutations
- Single arm phase II
  - Abemaciclib 200mg BID (2nd line - after platinum and cetuximab)
  - 26 patients – HPV negative RM-HNSCC - CDKN2A loss, and/or CCND1 and/or CDK6 amplification
  - ORR – 0%, SD 32%, progression 50%
  - Median OS – 4.8 months

- "Abemaciclib had limited antitumor activity in RM-HNSCC harboring molecular alteration in CDK4/6 pathway"

*ASCO 2023 - DOI: 10.1200/JCO.2023.41.16_suppl.6044 *Journal of Clinical Oncology* 41, no. 16_suppl (June 01, 2023) 6044-6044

3. Homologous recombination deficiency (HRD)

6016 **Poster Discussion Session**

Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with pembrolizumab and carboplatin as first-line treatment of recurrent or metastatic head and neck squamous-cell carcinoma (RM-HNSCC): A single-arm, phase 2 trial.

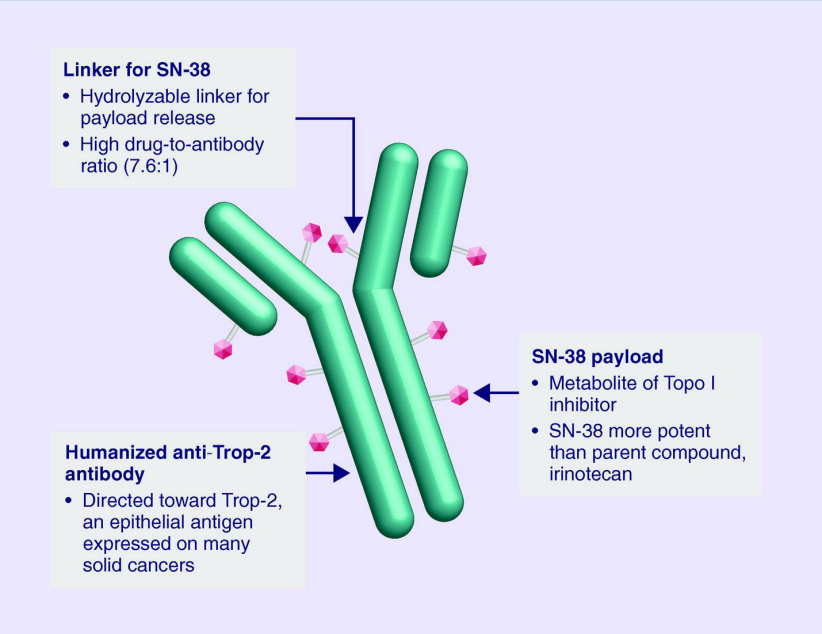
Jared Cohen, Jessica C. Ley, Jingxia Liu, Emma Haselhorst, Peter John Oppelt, Douglas Adkins; Washington University Siteman Cancer Center, St. Louis, MO; Washington University School of Medicine, St. Louis, MO

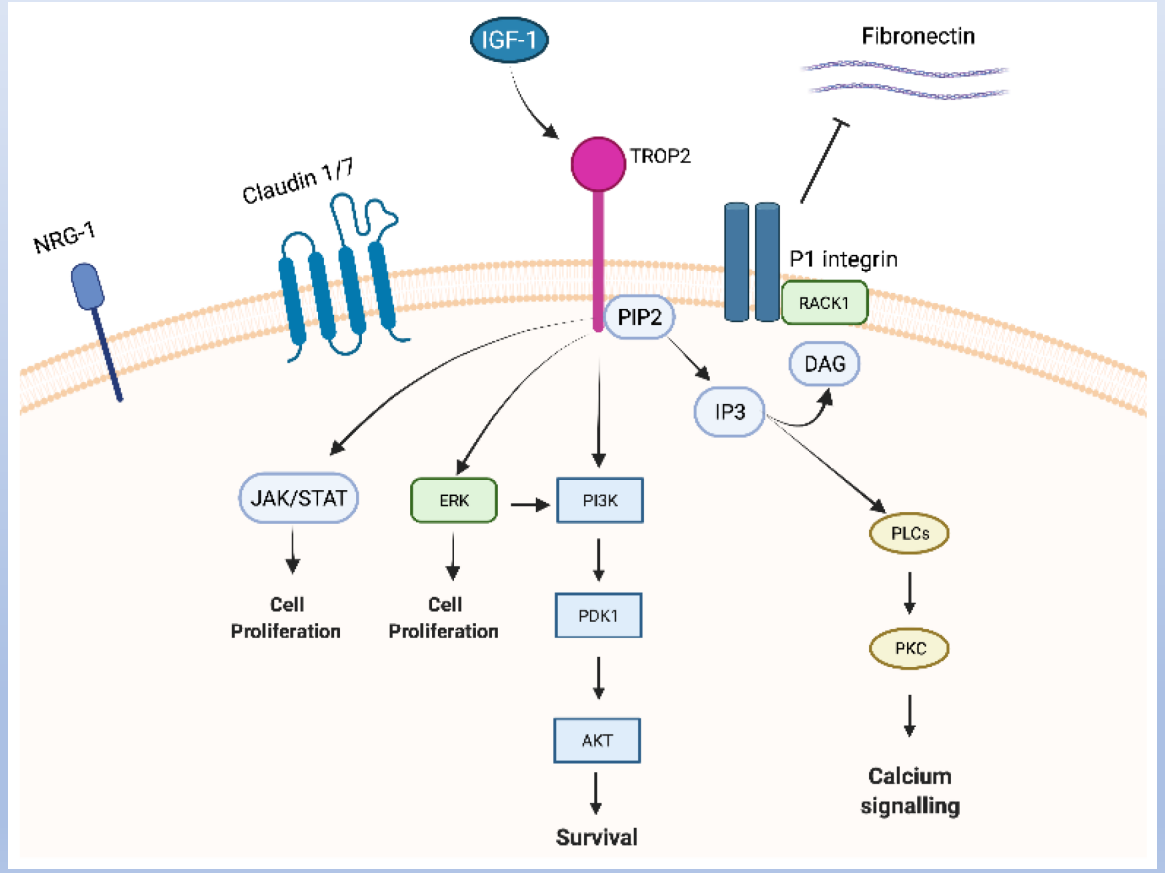
- HRD phenotype common in HNSCC
- Mutation and promoter hypermethylation of DNA repair genes (BRCA1, BRCA2, ATR, ATM, and FANC) and PTEN
- Olaparib - PARP inhibitor – additive to platinums, upregulates PD-L1
- Single arm phase II
  - First line RM-HNSCC
  - Olaparib + Pembrolizumab + Carboplatin x 6 cycles then maintenance Olaparib + Pembro
  - First stage – 12 patients enrolled
  - ORR – 67%

**ASCO 2023 - 10.1200/JCO.2023.41.16_suppl.6016 Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 6016-6016*

4. TROP2

- Sacituzumab govitecan (SG) - Trop-2-directed antibody-drug conjugate





*Overview of Trop-2 in Cancer: From Pre-Clinical Studies to Future Directions in Clinical Settings. Cancers (Basel). 2023 Mar 13;15(6):1744

OncologyPRO > Meeting Resources > ESMO Congress 2023

Mini oral session - Head and neck cancer

859MO - Sacituzumab govitecan (SG) in patients (pts) with relapsed/refractory (R/R) advanced head and neck squamous cell carcinoma (HNSCC): Results from the phase II TROPiCS-03 basket trial

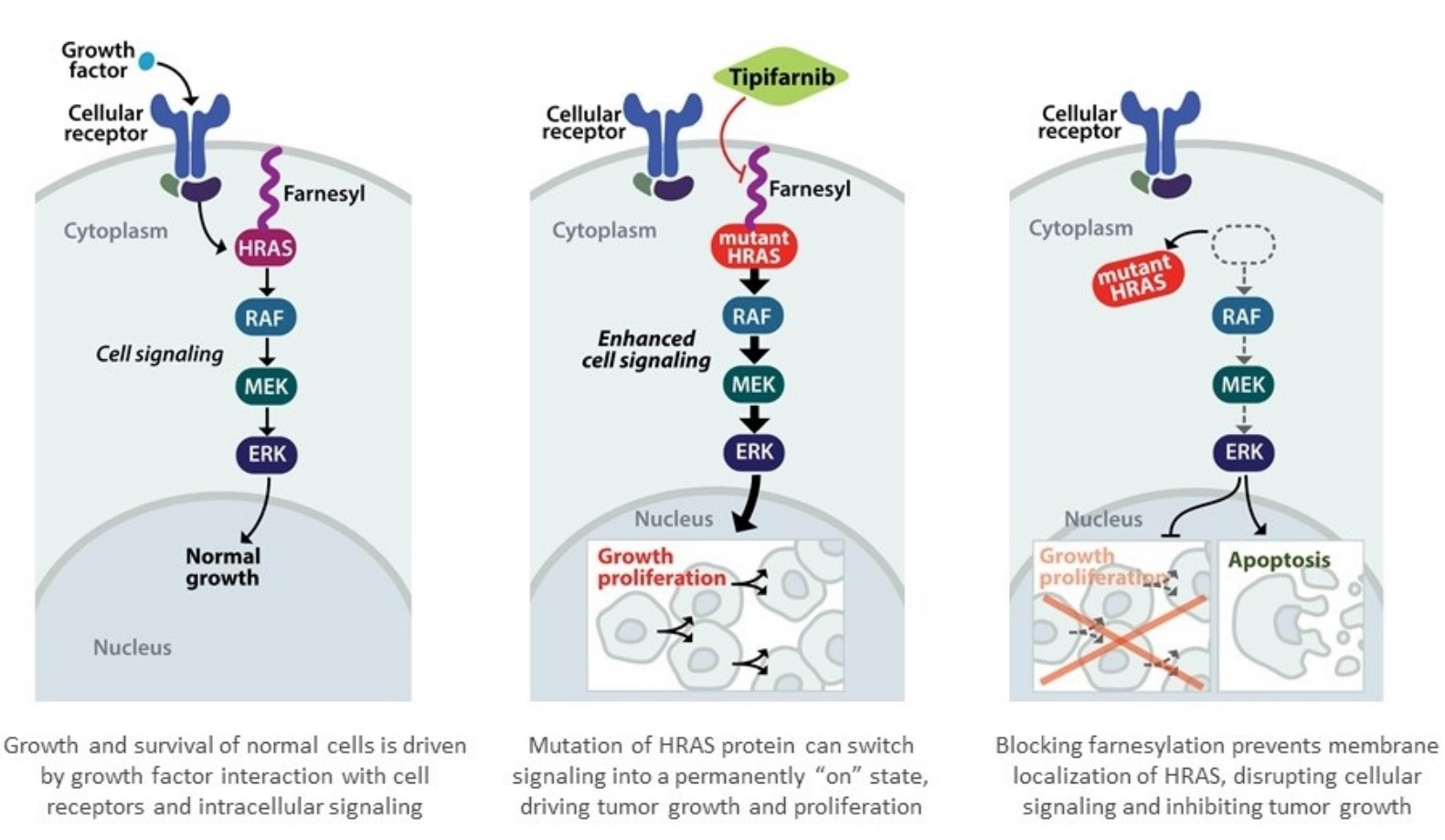
- 43 patients
- RM HNSCC 2nd line
  - progressed after prior platinum-based chemo and anti-PD-(L)1 therapy
  - Median number of prior therapies = 3
- no TRAEs leading to discontinuation

Efficacy	Advanced HNSCC SG n = 43
ORR (95% CI), [a] %	16 (7-31)
BOR, [a] n (%)	
CR	0
PR	7 (16)
SD	21 (49)
PD	9 (21)

**ESMO 2023* - Annals of Oncology (2023) 34 (suppl_2): S554-S593. 10.1016/annonc/annonc1326

5. mHRAS

- mHRAS 4-8% HNSCC
- HRAS dependent on farnesyl transferase (FT)
- Tipifarnib - a FT inhibitor (FTI)



Growth and survival of normal cells is driven by growth factor interaction with cell receptors and intracellular signaling

Mutation of HRAS protein can switch signaling into a permanently "on" state, driving tumor growth and proliferation

Blocking farnesylation prevents membrane localization of HRAS, disrupting cellular signaling and inhibiting tumor growth

**https://www.sec.gov/Archives/edgar/data/1422143/000156459016020613/kura-ex991_17.htm – Accessed Jan 4, 2024*

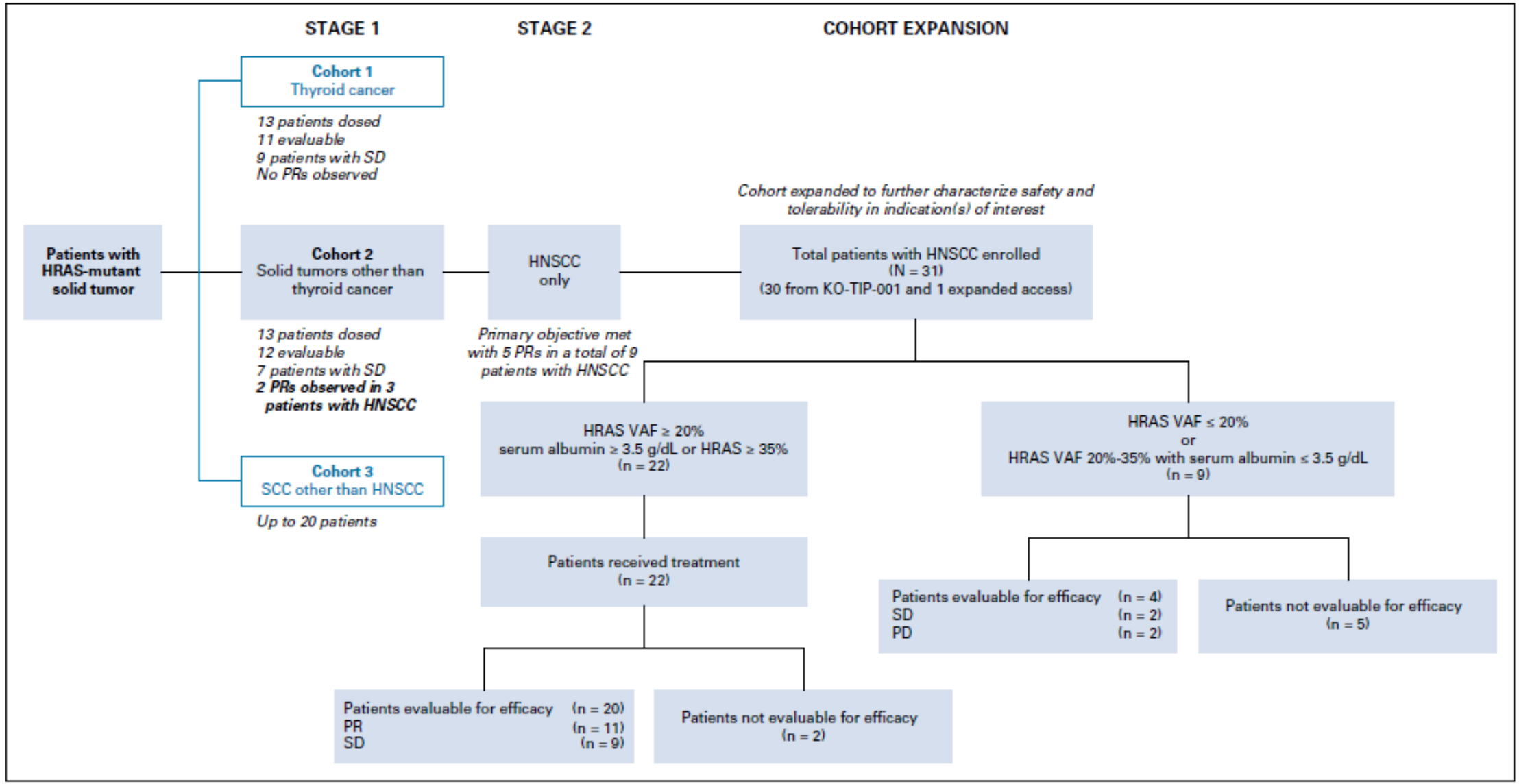


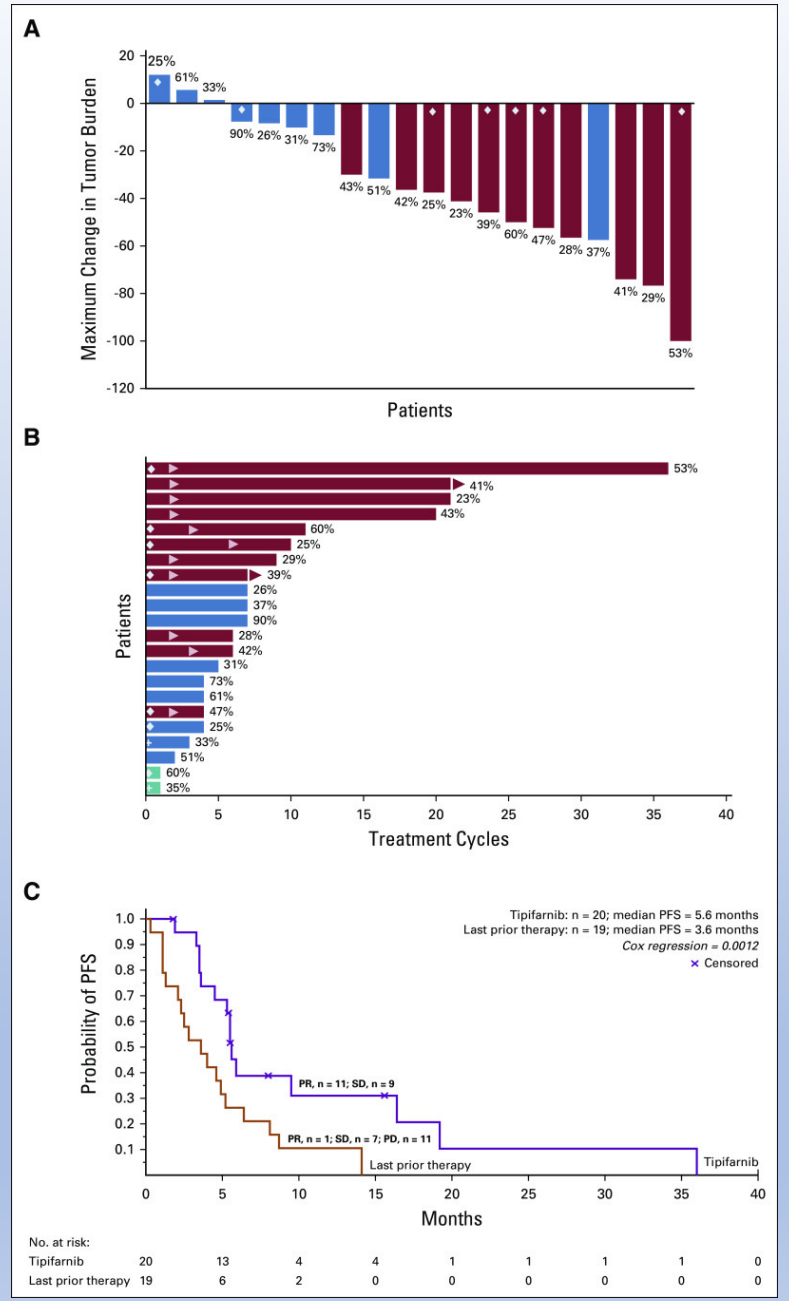
FIG 1. Study overview. HNSCC, head and neck squamous cell carcinoma; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease; VAF, variant allele frequency.

**Tipifarnib in Head and Neck Squamous Cell Carcinoma With HRAS Mutations. J Clin Oncol. 2021 Jun 10;39(17):1856-1864*

mHRAS

- 20 patients VAF >20%
  - ORR 55%
  - mPFS 5.6 months
  - mOS 15.4 months

- Adverse events
  - Anemia 37%
  - Lymphopenia 13%



*Tipifarnib in Head and Neck Squamous Cell Carcinoma With HRAS Mutations. J Clin Oncol. 2021 Jun 10;39(17):1856-1864

AIM-HN Study

- Global, open-label single-arm study
- Efficacy and tolerability of tipifarnib in second line plus R/M m*HRAS* HNSCC patients
- ORR in patients with m*HRAS* VAF ≥ 20% (High VAF population)
- Tipifarnib 600 mg orally twice a day for 7 days in alternating weeks (Days 1-7 and 15-21) of 28-day cycles

**10.1200/JCO.2021.39.15_suppl.TPS6087 Journal of Clinical Oncology 39, no. 15_suppl*

AIM-HN Results

- 59 pts
  - 50 (85%) ha
  - Investigator
  - IRF, ORR w
  - Median PFS
  - Median OS

	Investigator Assessment (n=50)	Independent Review Facility (n=50)
Best Overall Response, n (%)		
Confirmed Complete Response (CR)	1 (2)	1 (2)
Confirmed Partial Response (PR)	14 (28)	9 (18)
Stable Disease (SD)	17 (34)	14 (28)
Progressive Disease (PD)	6 (12)	14 (28)
Not Evaluable (NE)	12 (24)	12 (24)
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]

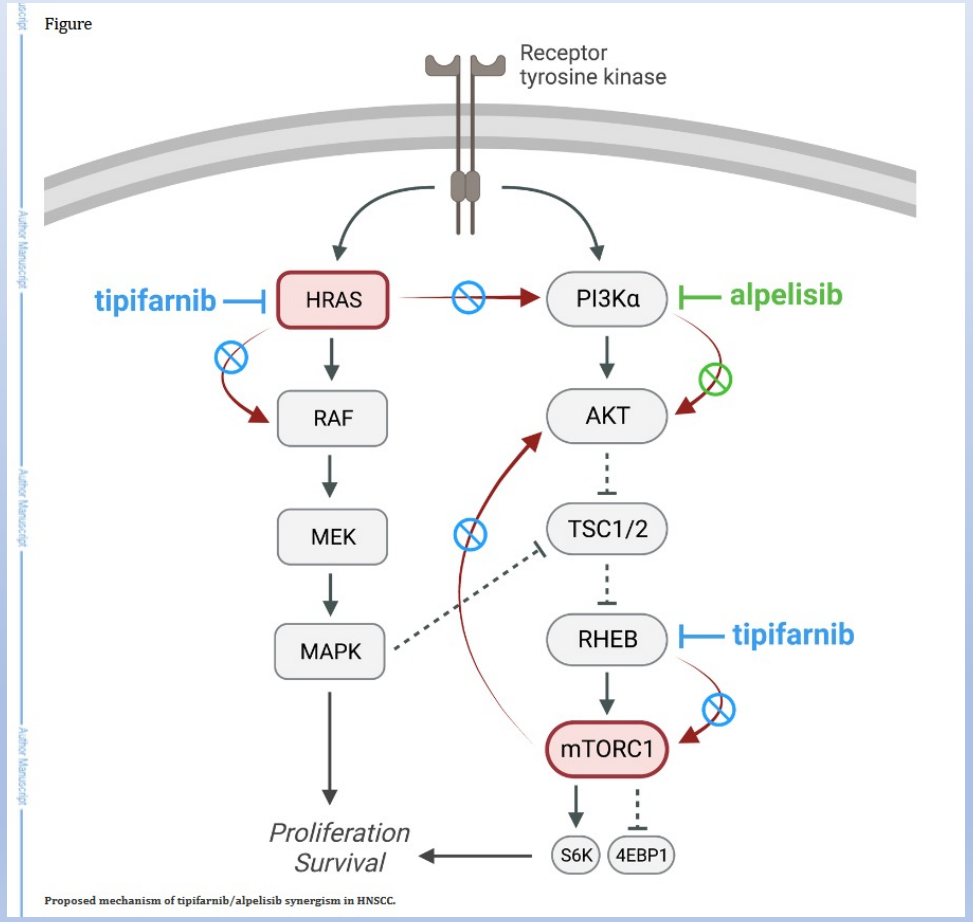
**ORR, objective response rate; -, not calculable; mDoR, median duration of response; mPFS, median progression free survival; CI, confidence interval.*

- Grade 3+ (TRAEs) in 33 pts (56%):
  - neutropenia (24%)
  - anemia (20%)
  - leukopenia (14%)
  - febrile neutropenia (7%)
  - 7% discontinued treatment due to TRAEs

ESMO 2023 Abstract LBA47 - Annals of Oncology (2023) 34 (suppl_2): S1254-S1335. 10.1016/annonc/annonc1358

Resistance mechanisms mHRAS

- HRAS + PI3K-mTOR inhibtors



*To Tip or Not to Tip: A New Combination for Precision Medicine in Head and Neck Cancer. Cancer Res. 2023 Oct 2;83(19):3162-3164. Smith AE, Chan S, *Tipifarnib Potentiates the Antitumor Effects of PI3Kα Inhibition in PIK3CA- and HRAS-Dysregulated HNSCC via Convergent Inhibition of mTOR Activity. Cancer Res. 2023 Oct 2;83(19):3252-3263

KURRENT-HN Trial

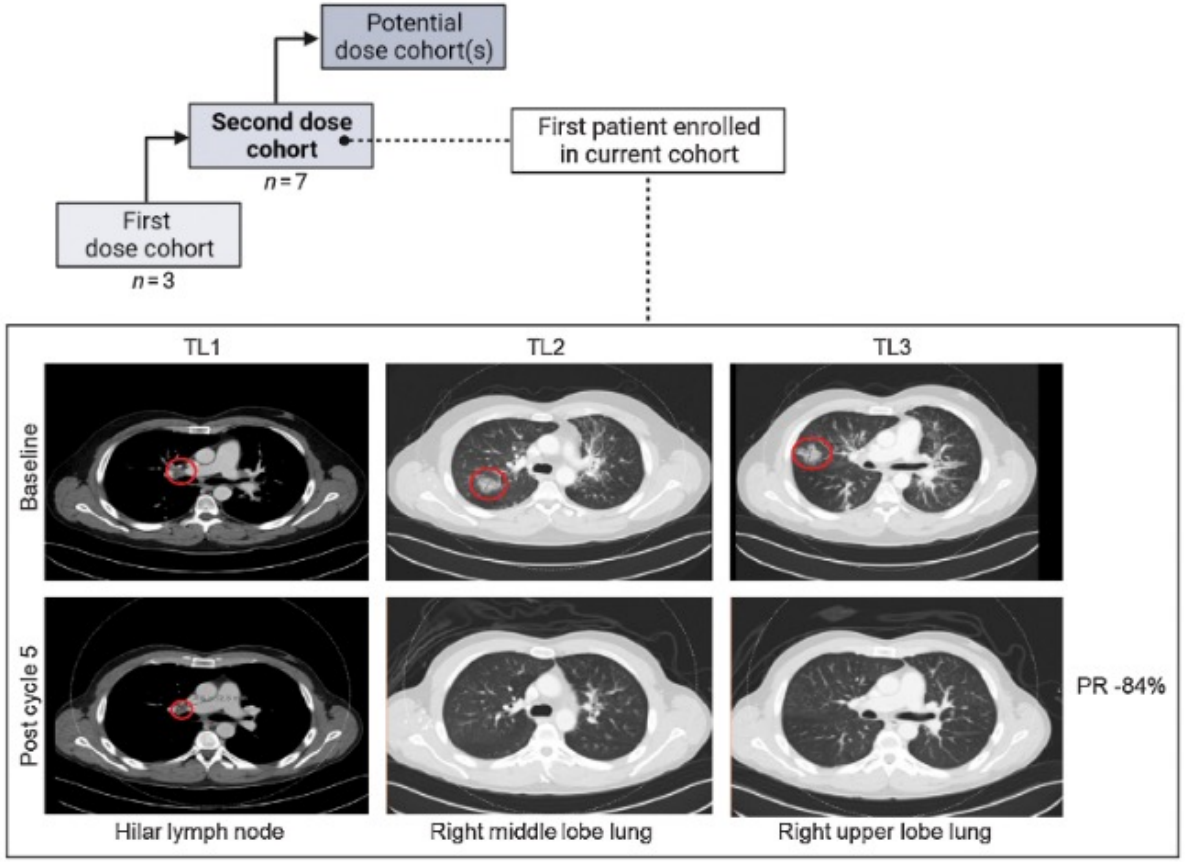


Figure 6.

Overview of ongoing KURRENT-HN tipifarnib–alpelisib dose escalation study and partial response (PR) of first patient enrolled in current dose cohort. CT of a patient with *PIK3CA*-mutant metastatic HNSCC at baseline and after five cycles of tipifarnib and alpelisib. Target lesions (red circles) are in the hilar lymph node and right upper lobe of the lungs. Patient experienced a partial response and remains on study at time of data cut (September 2022).

**Tipifarnib Potentiates the Antitumor Effects of PI3Kα Inhibition in PIK3CA- and HRAS-Dysregulated HNSCC via Convergent Inhibition of mTOR Activity. Cancer Res. 2023 Oct 2;83(19):3252-3263*

Take home points

- Most patients with HNSCC present with advanced disease
- Outcomes are poor
- Management of HNSCC is complex
  - Multidisciplinary team
  - Balance between treatment and morbidity
  - Lack of predictive biomarkers
- Several mutations are found in HNSCC however so far most have not been actionable
- Promising targets are:
  - HRAS
  - PI3K
  - TROP2