BACK TO THE FUTURE: OLD AND NEW DRUGS IN HEAD AND NECK CANCER

Comprehensive Cancer Center

- ***Alessandra Cassano, MD, PhD***
- ***Oncologia Medica***
- ***Università Cattolica del S. Cuore***
- ***Fondazione Universitaria Policlinico Gemelli, IRCCS***

The EGFR overexpression in head and neck cancer

Comprehensive Cancer Center

› Cancer Res. 1993 Aug 1;53(15):3579-84.

Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer

J R Grandis [1], D J Tweardy

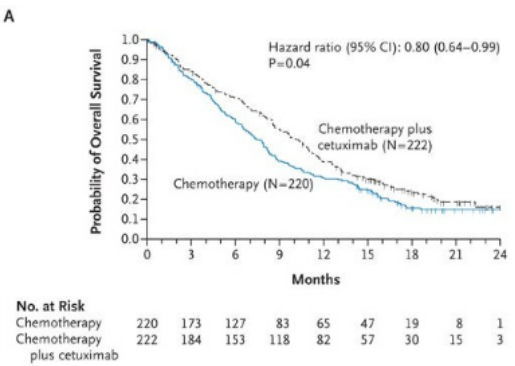
In 10 SCCHN cell lines, TGF-alpha mRNA was increased by a mean of 16-fold and EGFR mRNA levels were increased by a mean of 77-fold

The NEW ENGLAND JOURNAL of MEDICINE

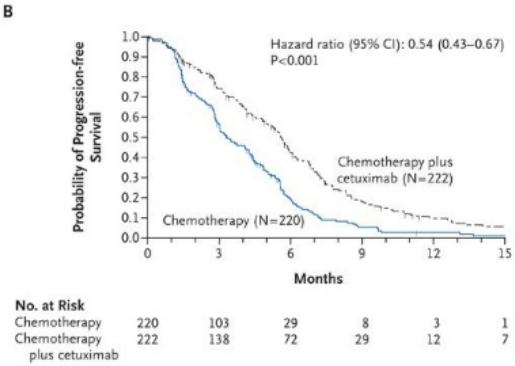
September 11, 2008
N Engl J Med 2008; 359:1116-1127
DOI: 10.1056/NEJMoa0802656

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., Dmytro Zabolotnyy, M.D., Ph.D., Heinz-Roland Kienzer, M.D., Didier Cupissol, M.D., Frederic Peyrade, M.D., Marco Benasso, M.D., et al.



The median OS was 10.1 months in the cetuximab group and 7.4 months in the chemotherapy-alone group (hazard ratio for death, 0.80; P=0.04)



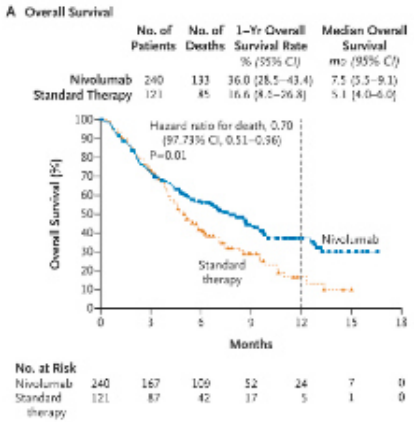
Median PFS was 5.6 months in the cetuximab group and 3.3 months in the chemotherapy-alone group (hazard ratio for progression, 0.54; P<0.001)

Immunotherapy in head and neck checkmate 141

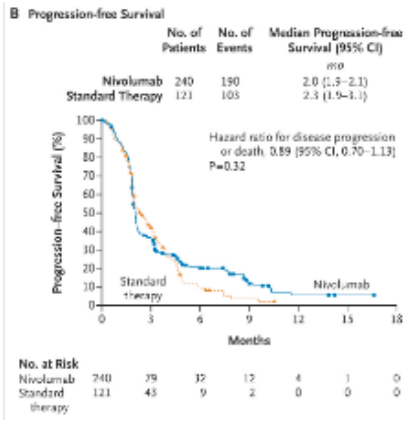
The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

Robert L. Ferris, M.D., Ph.D., George Blumenschein, Jr., M.D., Jerome Fayette, M.D., Ph.D., Joel Guigay, M.D., A. Dimitrios Colevas, M.D., Lisa Licitra, M.D., Kevin Harrington, Ph.D., F.R.C.P., F.R.C.R., Stefan Kasper, M.D., Everett E. Vokes, M.D., Caroline Even, M.D., Francis Worden, M.D., Nabil F. Saba, M.D., et al.



The median OS was 7.5 months in the nivolumab group versus 5.1 months HR 0.7 (p_0.01)



The median PFS was 2.0 months in the nivolumab group versus 2.3 months in the standard-therapy group

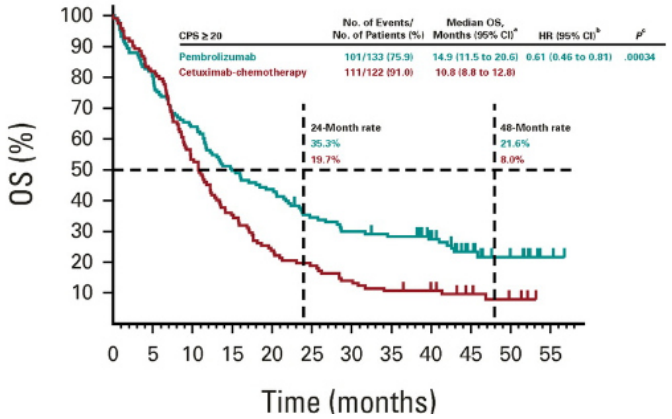
Immunotherapy in head and neck keynote 048

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

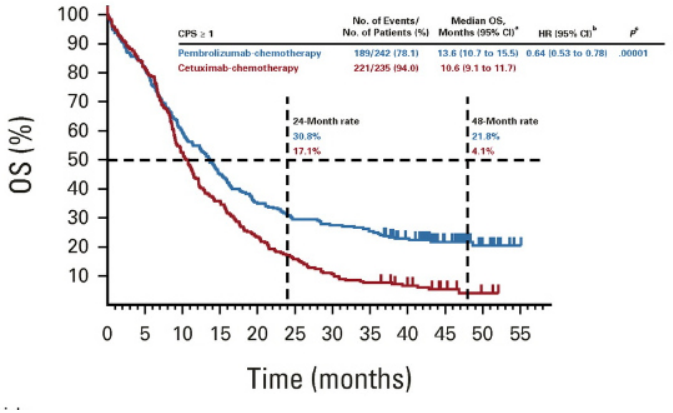
Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study

Kevin J. Harrington, PhD[1]; Barbara Burtness, MD[2]; Richard Greil, MD[3,4]; Denis Soulières, MD[5]; Makoto Tahara, MD[6]; Gilberto de Castro Jr, MD[7]; ...

Show More



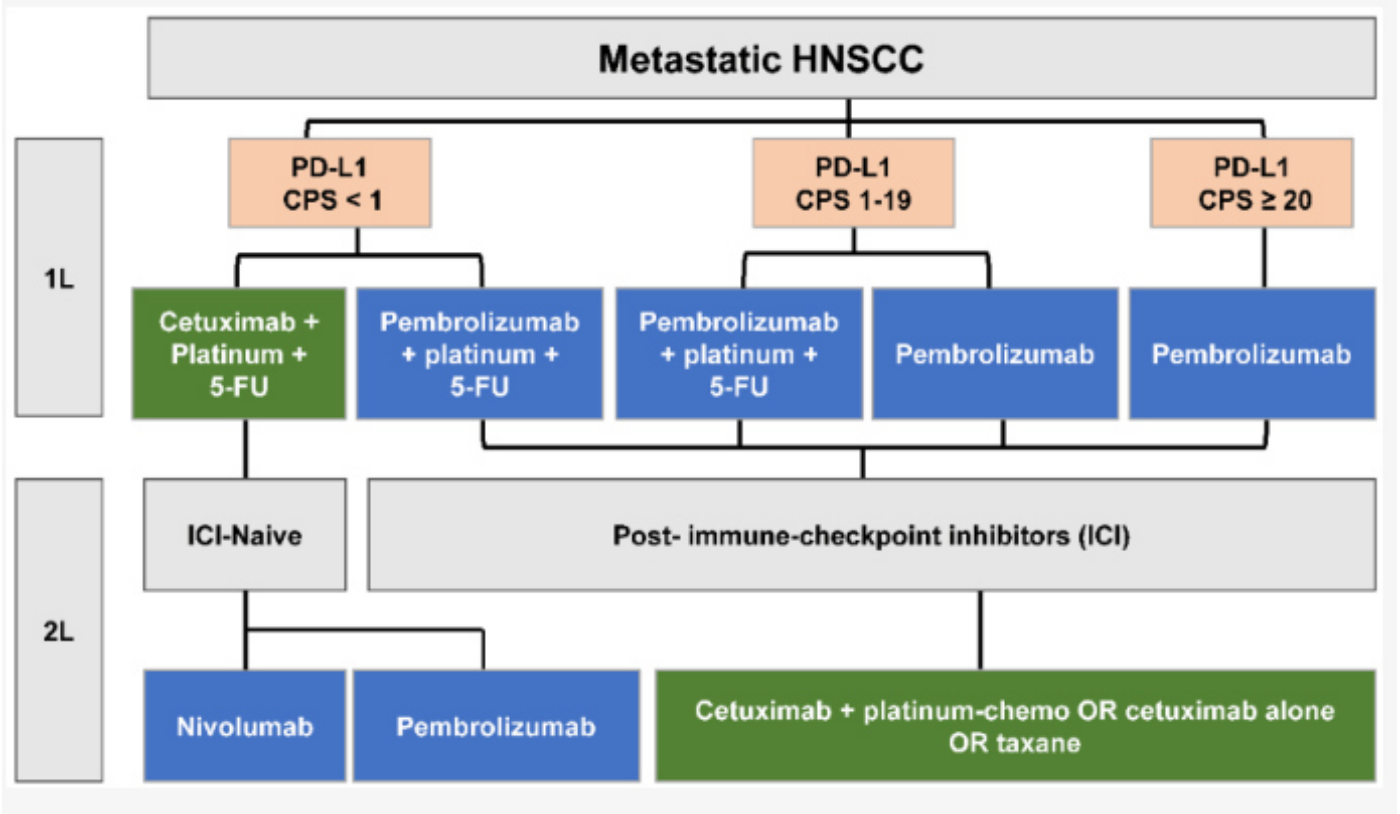
The median OS was 14.9 months for pembrolizumab alone versus 10.8 months for cetuximab-chemotherapy in the PD-L1 CPS ≥ 20 population (HR, 0.61)



mOS for pembrolizumab+chemotherapy was 13.6 months versus 10.6 months for EXTREME in the CPS ≥ 1 population (HR, 0.64)

Comprehensive Cancer Center

Current treatment of R/M head and neck squamous cell carcinoma

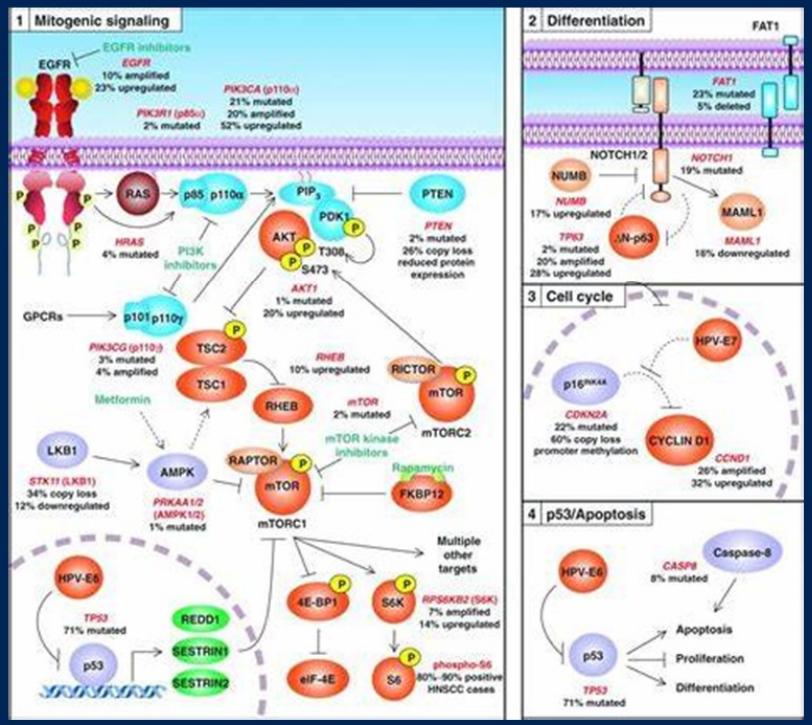


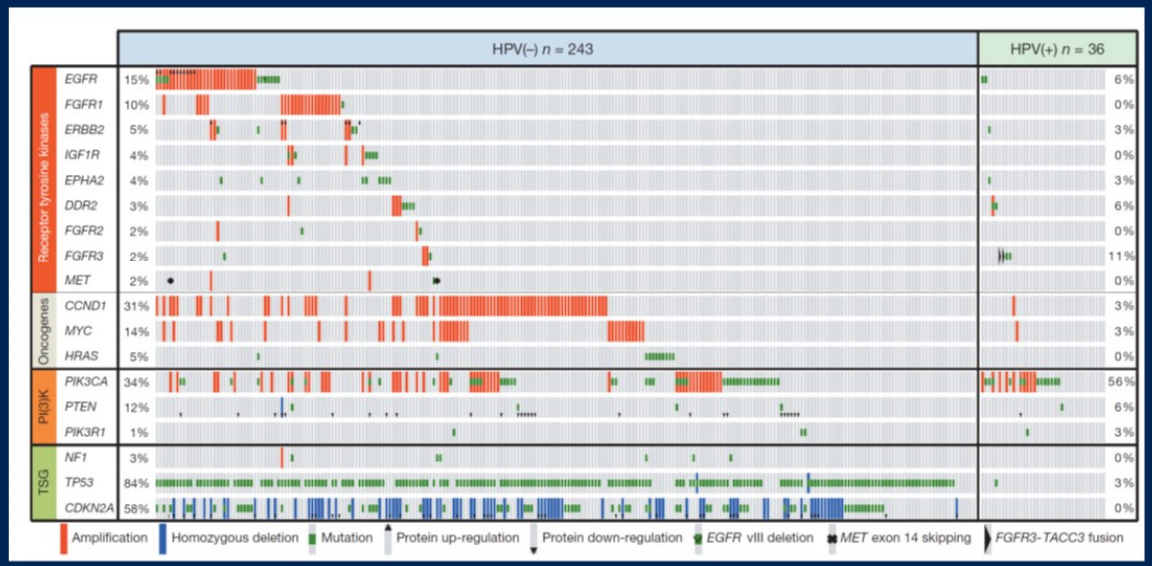
Recurrent/Metastatic HNSCC Treatment

- Single agent chemotherapeutic options after failure of first line therapy result in poor response rates (3-13% historically)
- HNSCC tumors often have high levels of mutations/alterations (especially HPV neg)
  - Response to novel targeted agents?
- HNSCC patients often have impaired immune functions but tumors with high T cell infiltration have superior survival outcomes
  - Can immune dysfunction be reversed?

Denaro et al, Oncology 2014, Patel et al., Clin Med Insights Ear Nose Throat, 2012

Mutations and other Alterations in HNSCC

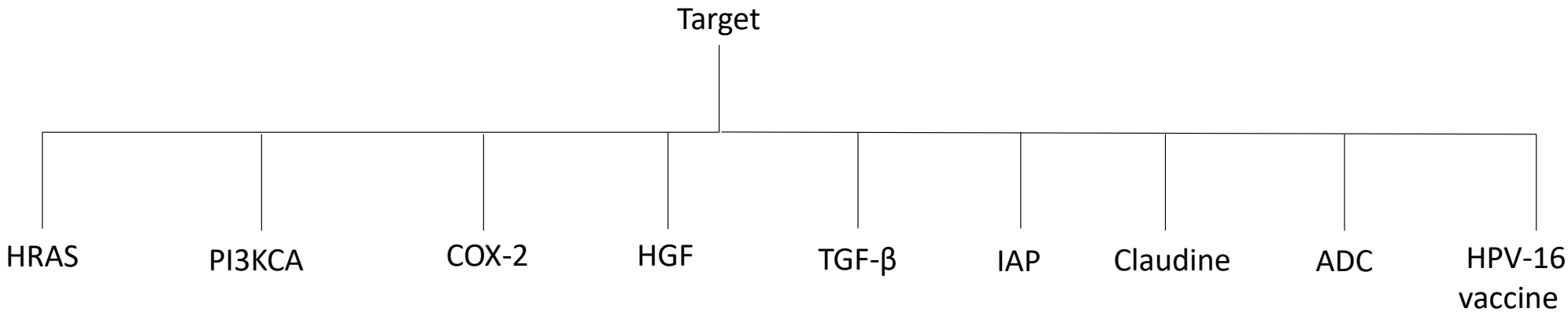




Iglesias-Bartolome et al, Cancer Discovery, 2013; The Cancer Genome Atlas network, Nature, 2015

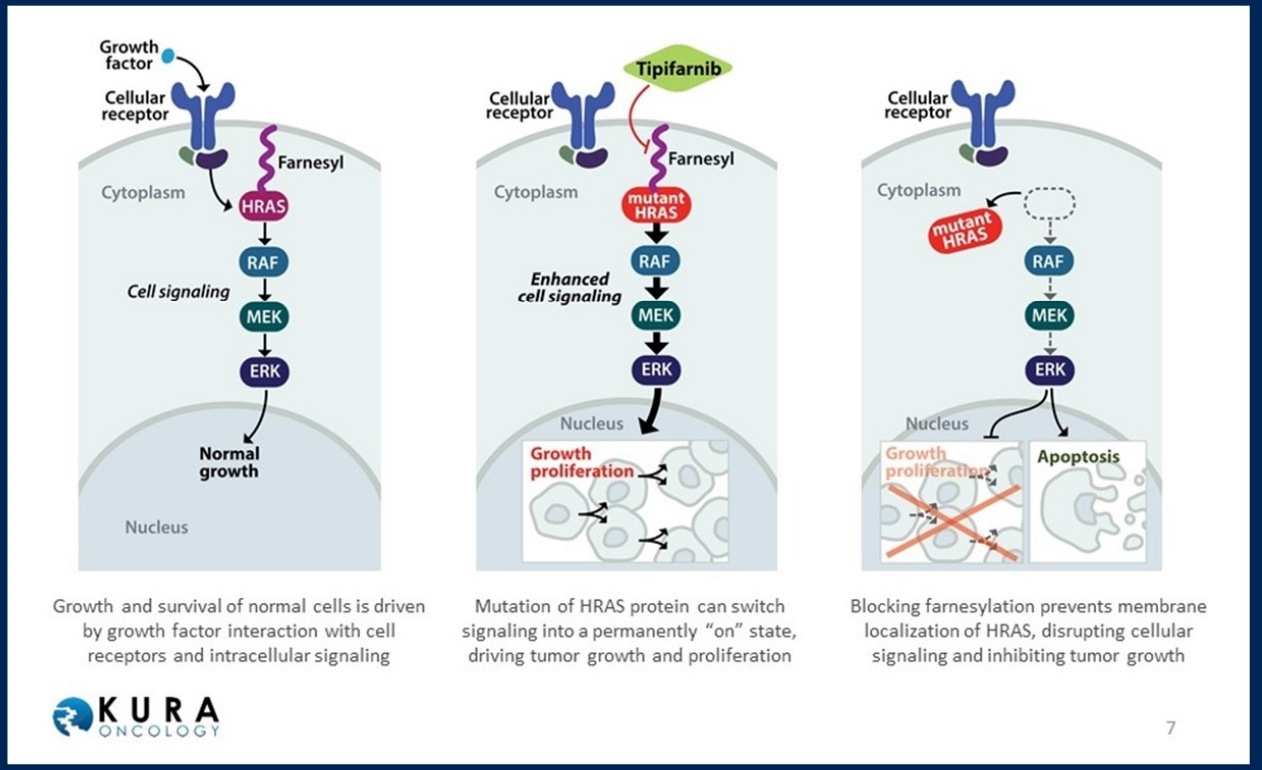
Comprehensive Cancer Center

Personalized medicine in R/M head and neck squamous cell carcinoma
THE GREAT CHALLENGE



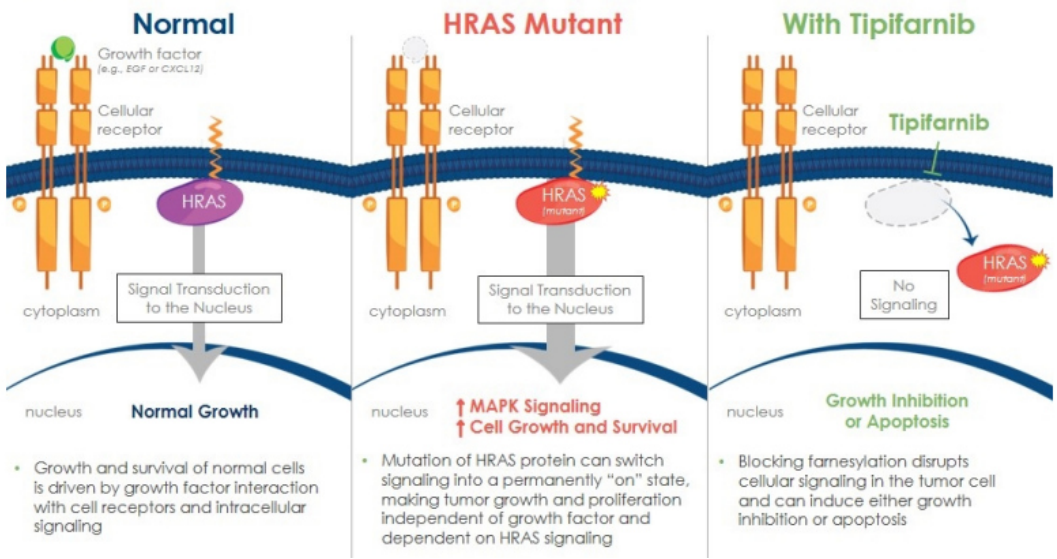
Tipifarnib (hRAS inhibitor)

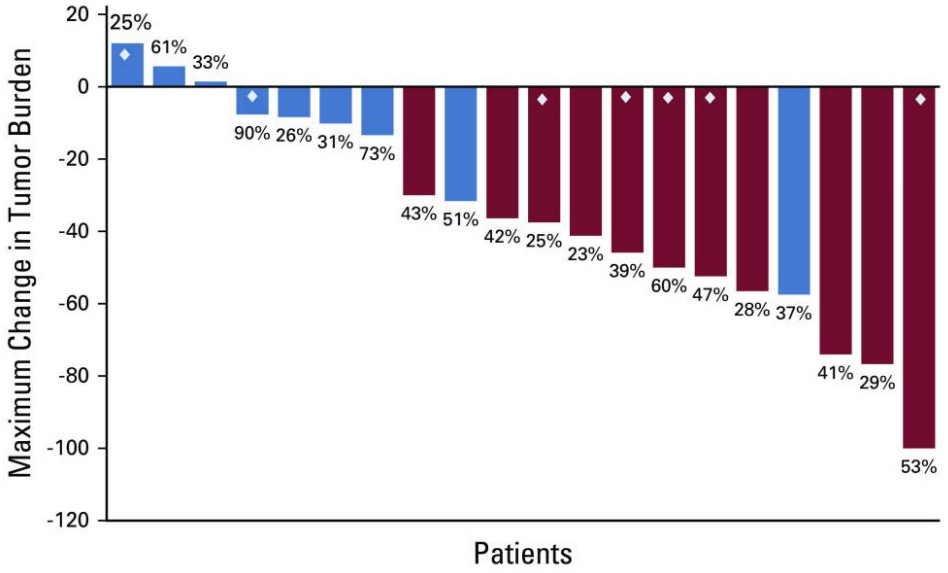
4-8% hRAS mutations in HNSCC



Farnesil-transferase inhibitor: old drug for a new target in head and neck

Comprehensive Cancer Center

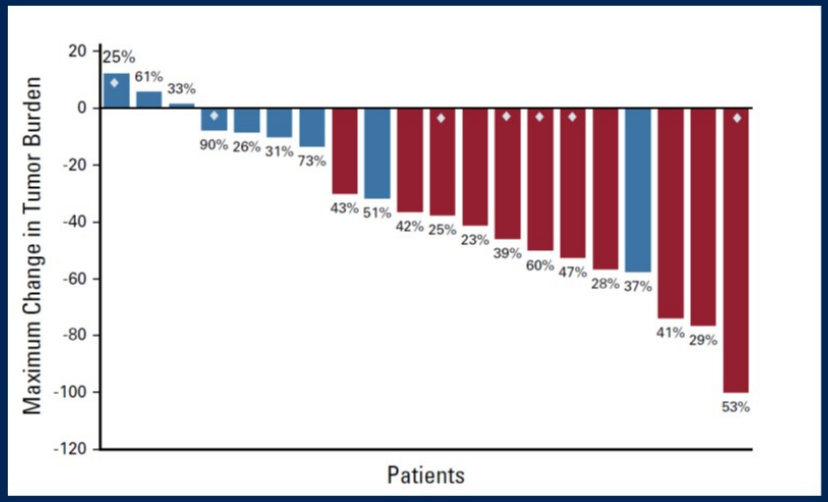


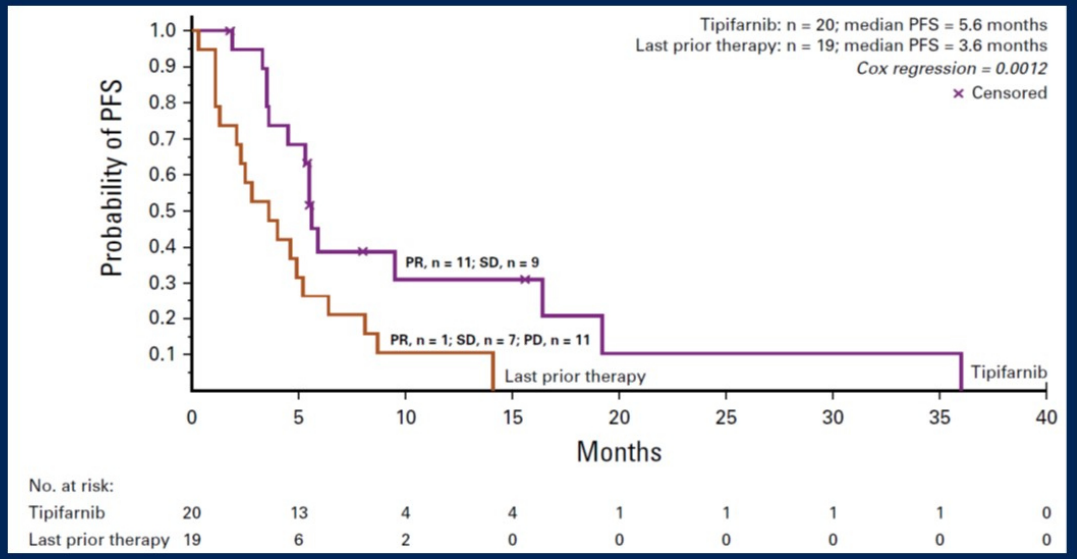


Outcome	Median (months), % (95% CI), n = 20[a]
Objective response rate	55.0 (31.5 to 76.9)
PFS	5.6 (3.6 to 16.4)
PFS - on last prior cancer therapy	3.6 (1.3 to 5.2)
Overall survival	15.4 (7.0 to 29.7)

Ho AL Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations. J Clin Oncol. 2021

Tipifarnib (hRAS inhibitor)



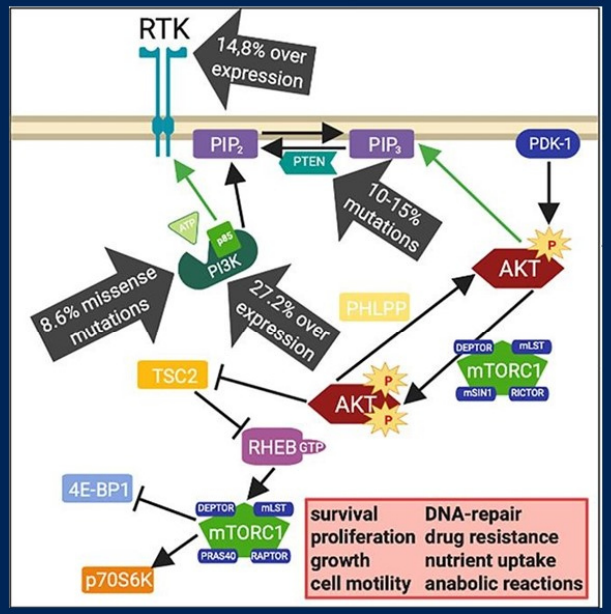


- Open label phase II
- Limited to ≥ 20% hRAS variant allele frequency
- 55% ORR
- PFS of 5.6mo

- FDA Breakthrough Designation

Ho, et al, JCO, 2021

PI3K Inhibitors

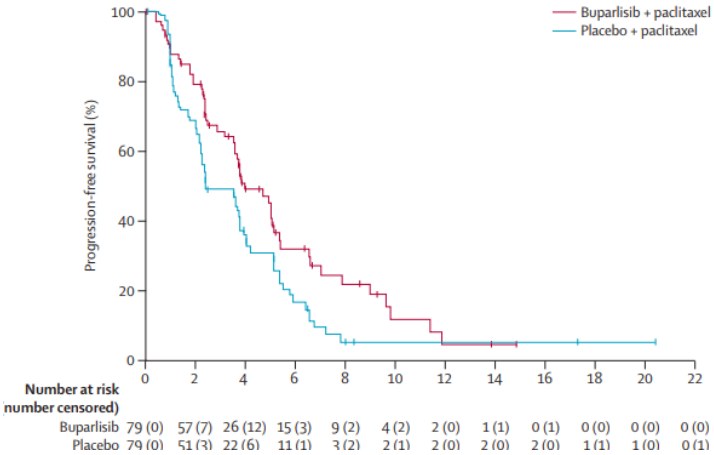


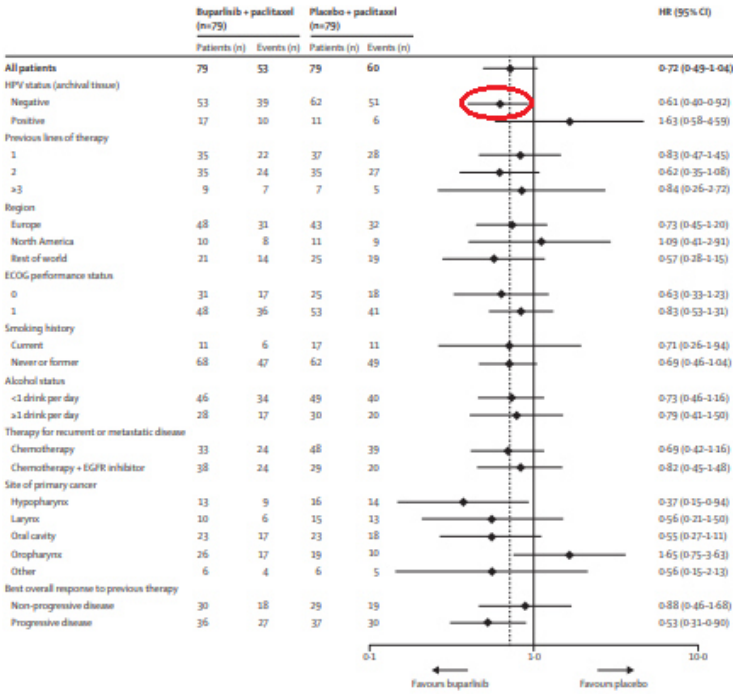
- High rate of PI3K mutations
  - 56% in HPV+
  - 39% in HPV-
- BERIL-1 Phase II randomized (158 pts) with paclitaxel and placebo vs paclitaxel and buparlisib (PI3Ki)
  - PFS of 4.6 vs 3.5 mo in buparlisib group vs placebo
  - Phase III ongoing

Marquard et al., Biochemical Pharmacology, 2020

PI3KCa inhibitor: Buparlisib

- BERIL-1 is a randomized phase II study. Evalueted buparlisib in combination with paclitaxel in patients with platinum pre-treated R/M HNSCC
- ORR of 31% in the buparlisib group with a median PFS and OS of 4.5 and 10.4 months, respectively compared with 3.5 and 6.5 months in the placebo group, regardless of PI3KCa mutations



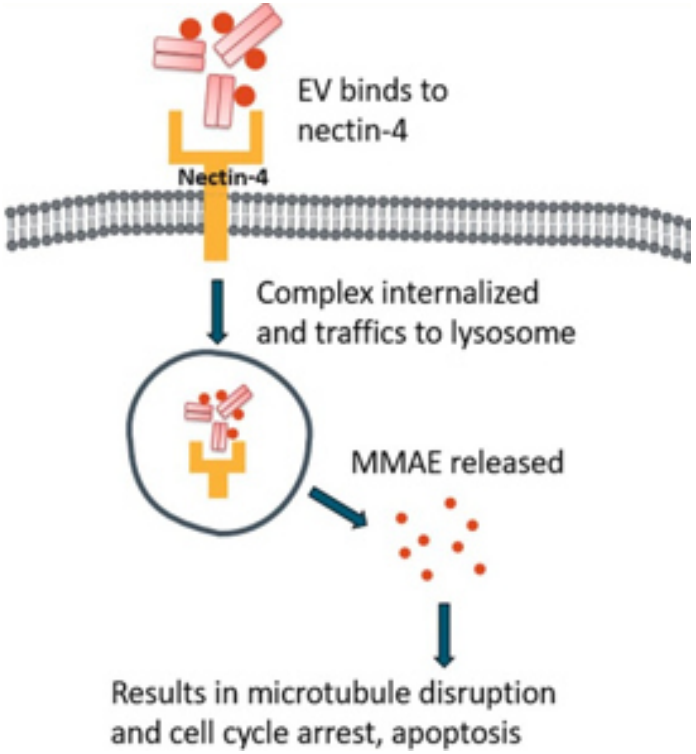


- Results of the phase III BURAN trial are awaited…

Soulières D,. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Oncol. 2017

EV-202 The role of enfortumab vedotin in head and neck cancer

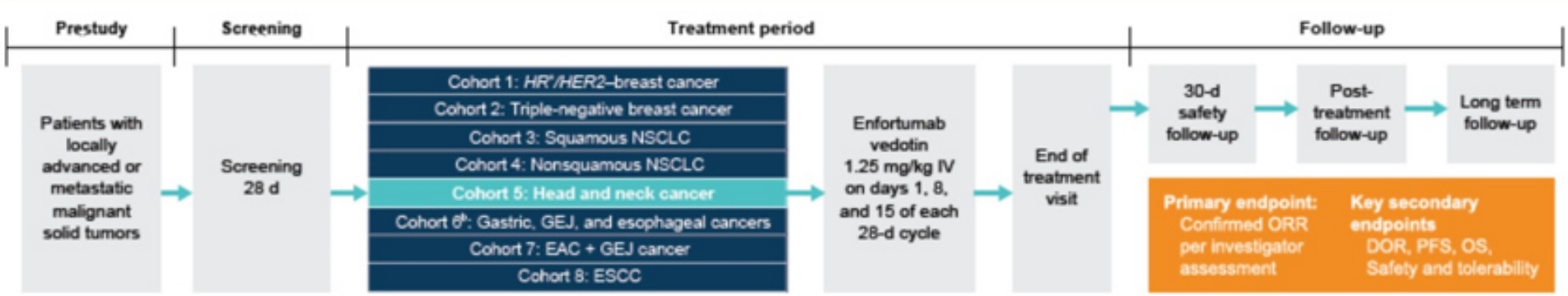
- Nectin-4 is a cell-adhesion molecule, and is expressed in 86.2% in head and neck cancers
- Enfortumab vedotin is an antibody-drug conjugated directed against Nectin-4 attached to Auristatine E, a microtubule disrupted agent.
- Enfortumab vedotin is already approved in the urotelial cancinoma



Sanders et al Oncotarget 2022

Comprehensive Cancer Center

EV-202 Study design



Key Eligibility

- Histologically or cytologically confirmed HNC except nasopharynx and salivary gland
- Progression/relapse on platinum for locally advanced or metastatic disease
- ≤2 lines cytotoxic systemic therapy
- Progressed/relapsed on PD-1/L1 inhibitor therapy
- Nectin-4 expression not required

Comprehensive Cancer Center

EV-202 Study design

Parameter/Variable	Patients (N=46)
Confirmed ORR[a]	11 (23.9)
95% CI,[b] %	12.6–38.8
Confirmed DCR[c]	26 (56.5)
95% CI,[b] %	41.1–71.1
BOR	
Confirmed CR	1 (2.2)
Confirmed PR	10 (21.7)
SD	15 (32.6)
Progressive disease	10 (21.7)
Not evaluable[d]	10 (21.7)

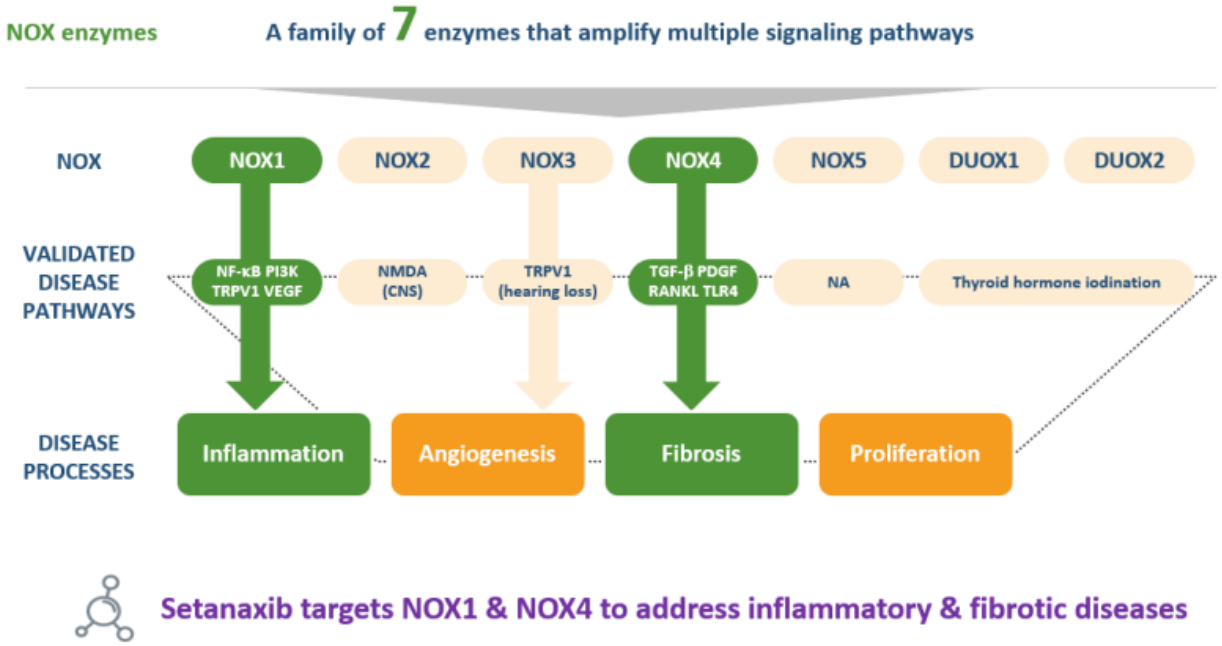
Median PFS 3.9 mo and median OS 5.98

Comprehensive Cancer Center

NOX-1/4 inhibition setanaxib: mechanism of action

- Setanaxib is the first-in-class inhibitors of NOX and NAPPH protein

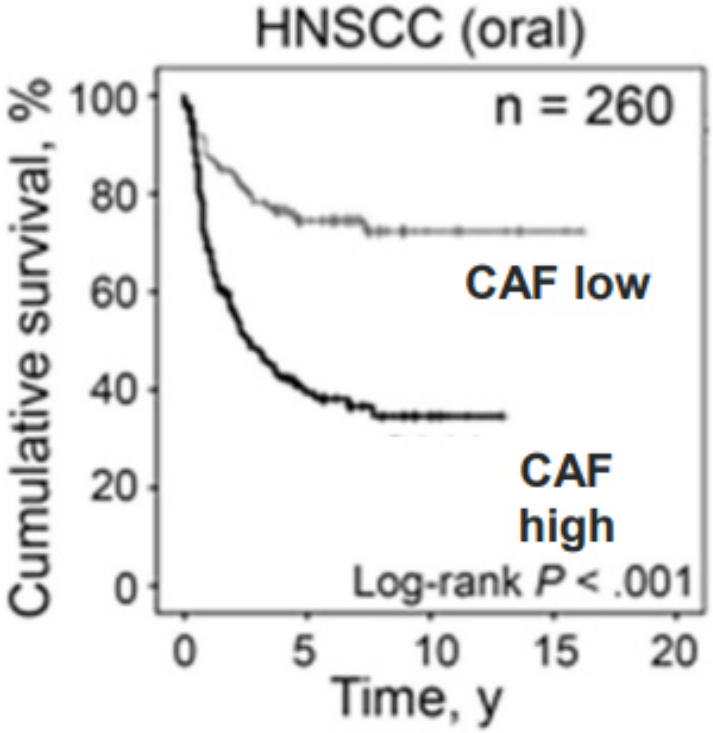
- NOX protein are extremely important for the differenzion of fibroblast into cancer assciated fibroblast (CAF)



Comprehensive Cancer Center

NOX-1/4 inhibition setanaxib: CAF levels are associated with prognosis

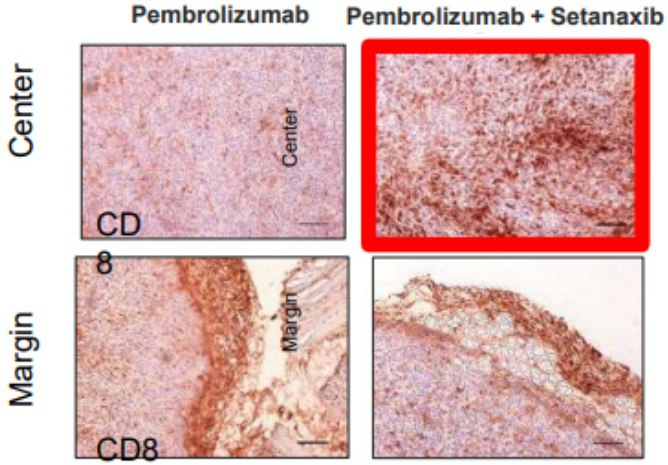
- High CAF numbers in a tumour results in exclusion of TILs from the tumour and result in a poor prognosis
- Cancer-associated fibroblast (CAFs) can be found in many solid tumours, and are essentially the same as activated myofibroblasts
- A relationship between the number of CAFs in the tumour and prognosis in SCCHN has been established

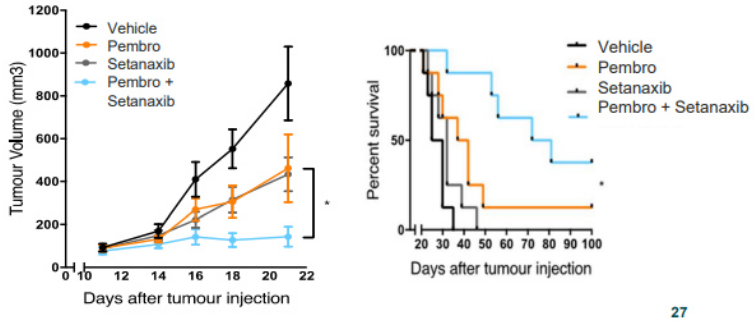


Comprehensive Cancer Center

NOX-1/4 inhibition setanaxib: interaction of CAF and immune response

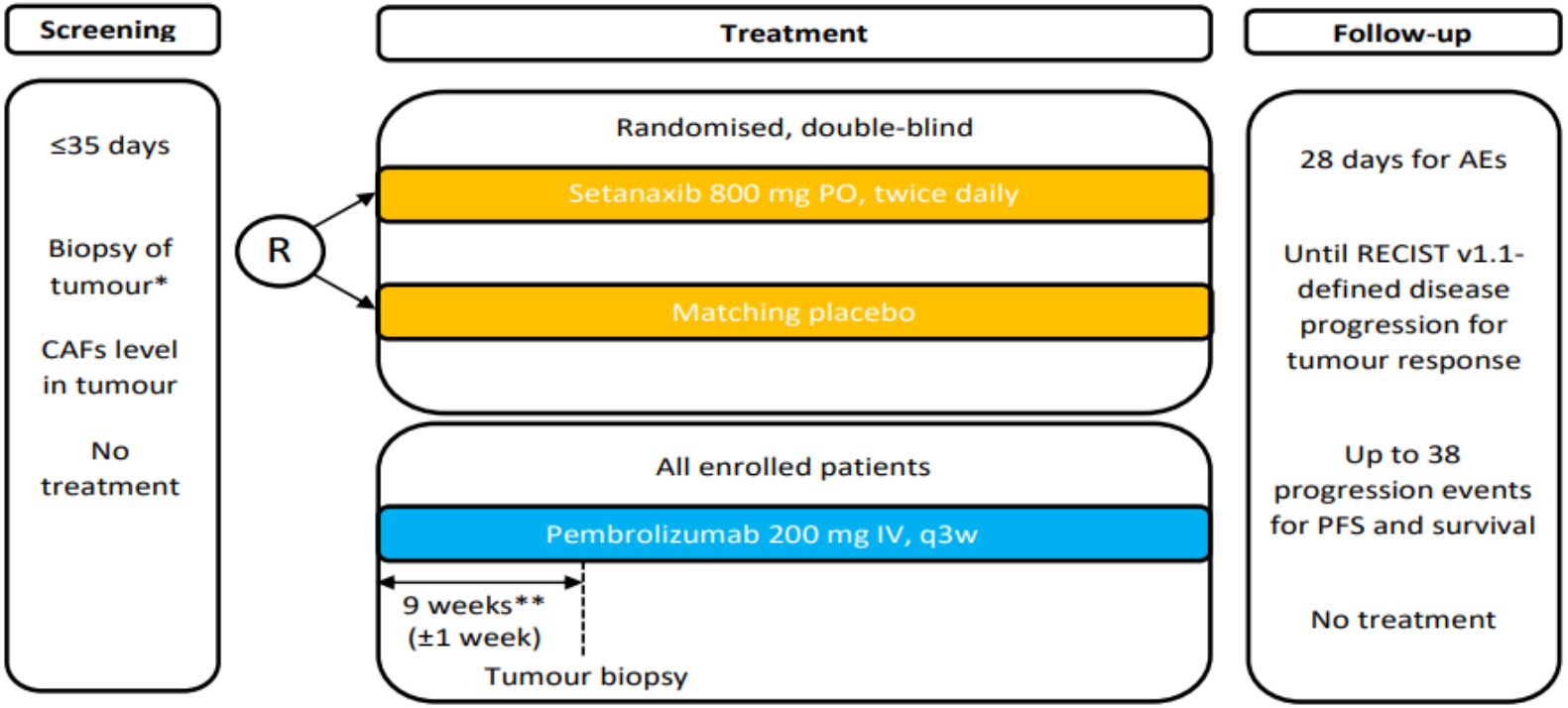
- Immunotherapy is not effective in highly fibrotic tumors
- CAF oppose immunotherapy by shielding tumors from T-cells
- Targeting CAF with setanaxib may restore response to immunotherapy
- Pre-clinical evidence suggest that treatment with Setanaxib + pembrolizumab results in an impovement in **Overall survival** and penetretion of **TILs in the tumor**





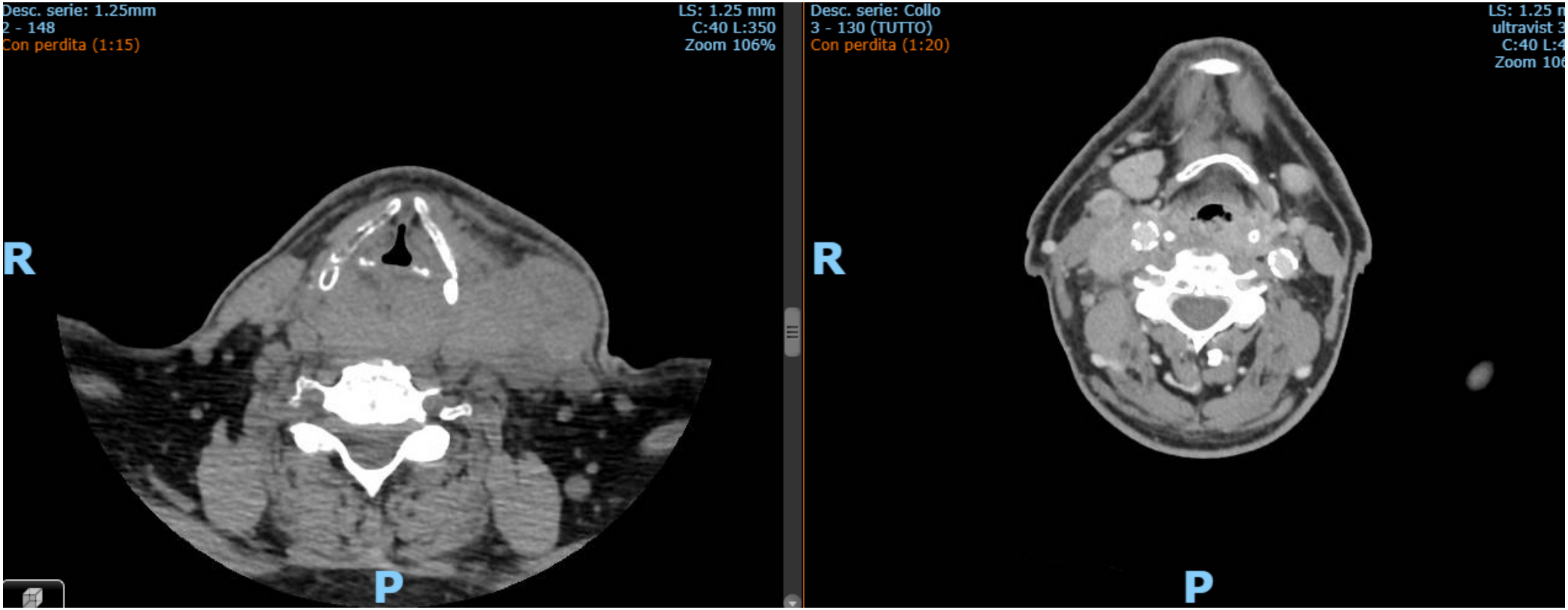
Comprehensive Cancer Center

Phase II trial CALLIDITAS



Comprehensive Cancer Center

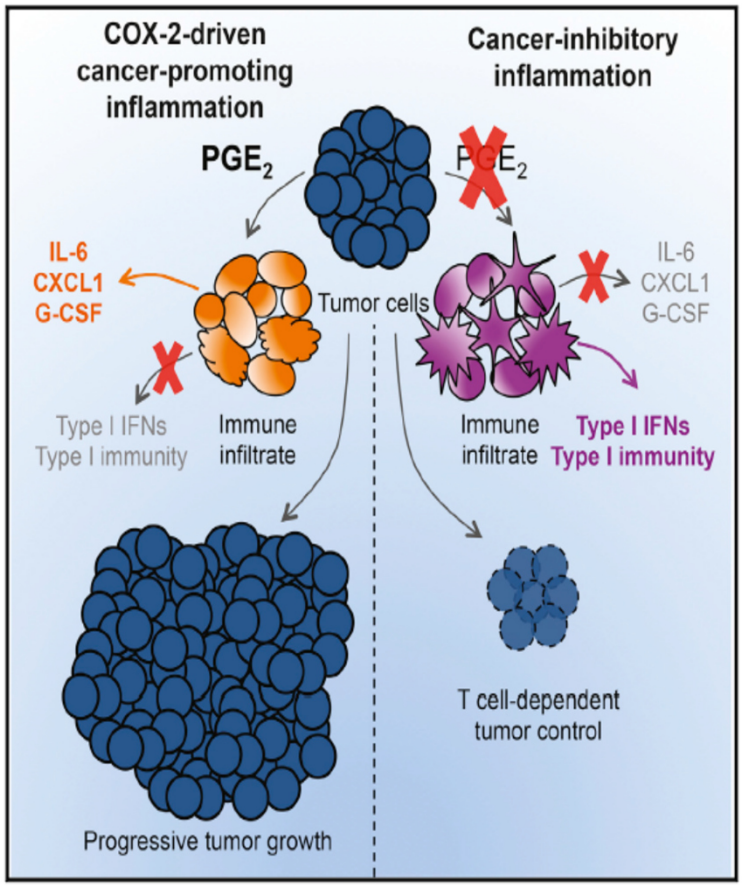
Example in a patient for just TWO CYCLE!



07/2023

09/2023

COX-2



Zelenay S et al, Cell 2015

In Brief

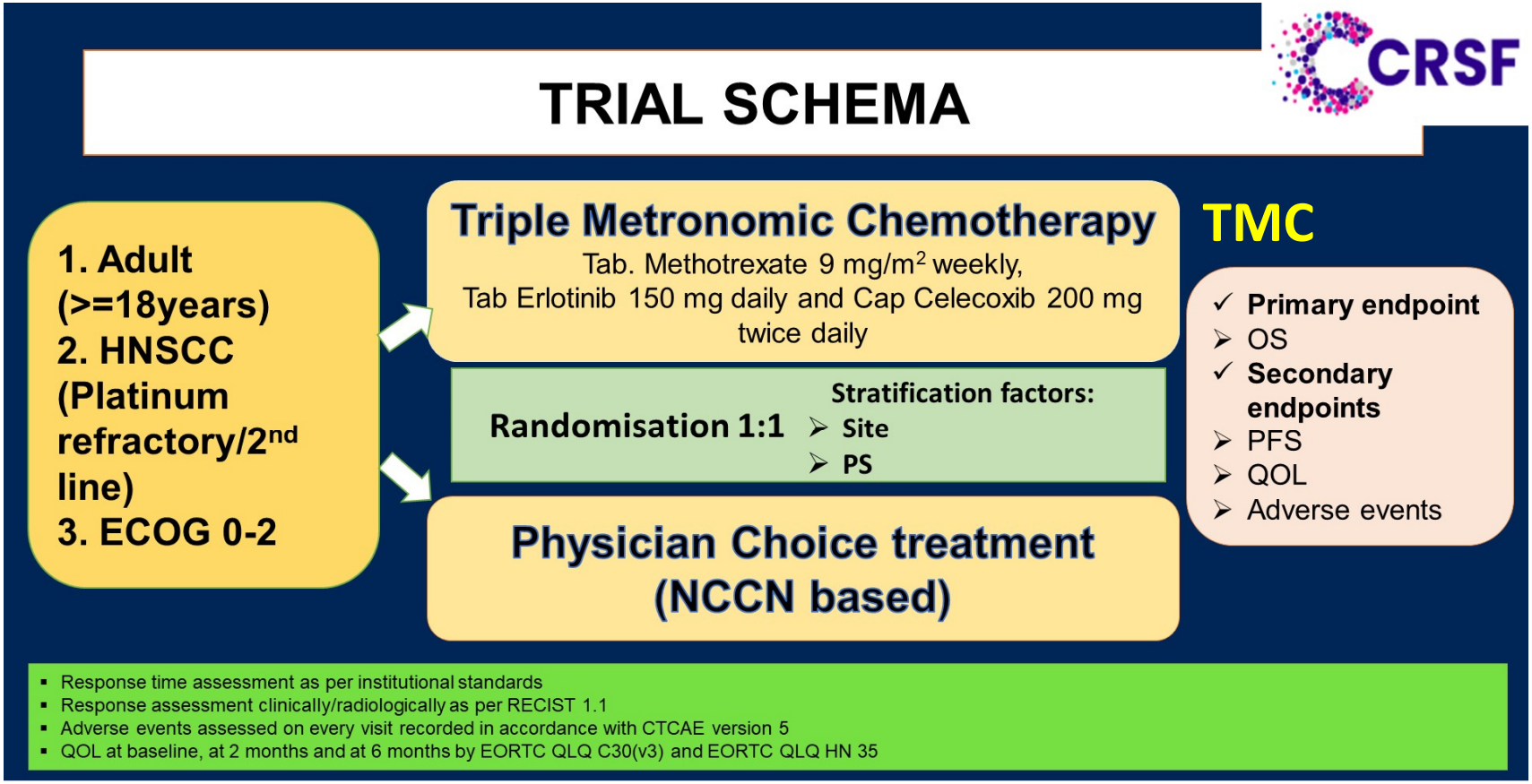
Cyclooxygenase-driven prostaglandin E2, produced by a variety of tumors, drives malignant growth through successful evasion of type I interferon and/or T-cell-dependent tumor elimination. A remarkable synergy between cyclooxygenase inhibitors and checkpoint blockade immunotherapy results in tumor eradication.

CANCER RESEARCH COMMUNICATIONS
AACR American Association for Cancer Research
RESEARCH ARTICLE https://doi.org/10.1158/2767-9764.CRC-23-0210 OPEN ACCESS

Inhibition of Microsomal Prostaglandin E2 Synthase Reduces Collagen Deposition in Melanoma Tumors and May Improve Immunotherapy Efficacy by Reducing T-cell Exhaustion

Fukuda Y, Cancer Res Commun, 2023

COX



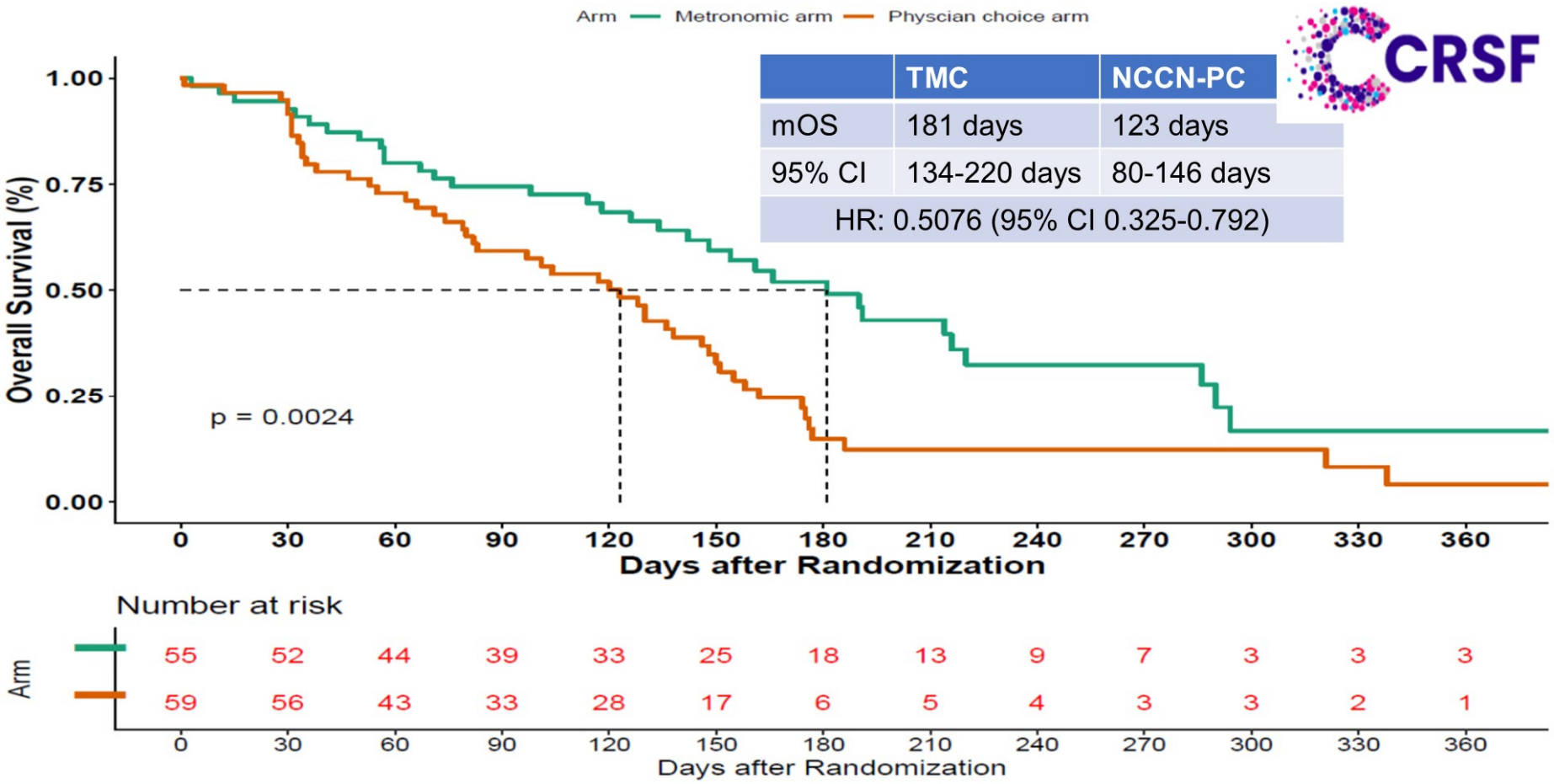
TMC benefits

- Oral intake
- ↓ AEs
- ↑QoL
- ↓ Costs

Physician Choice:

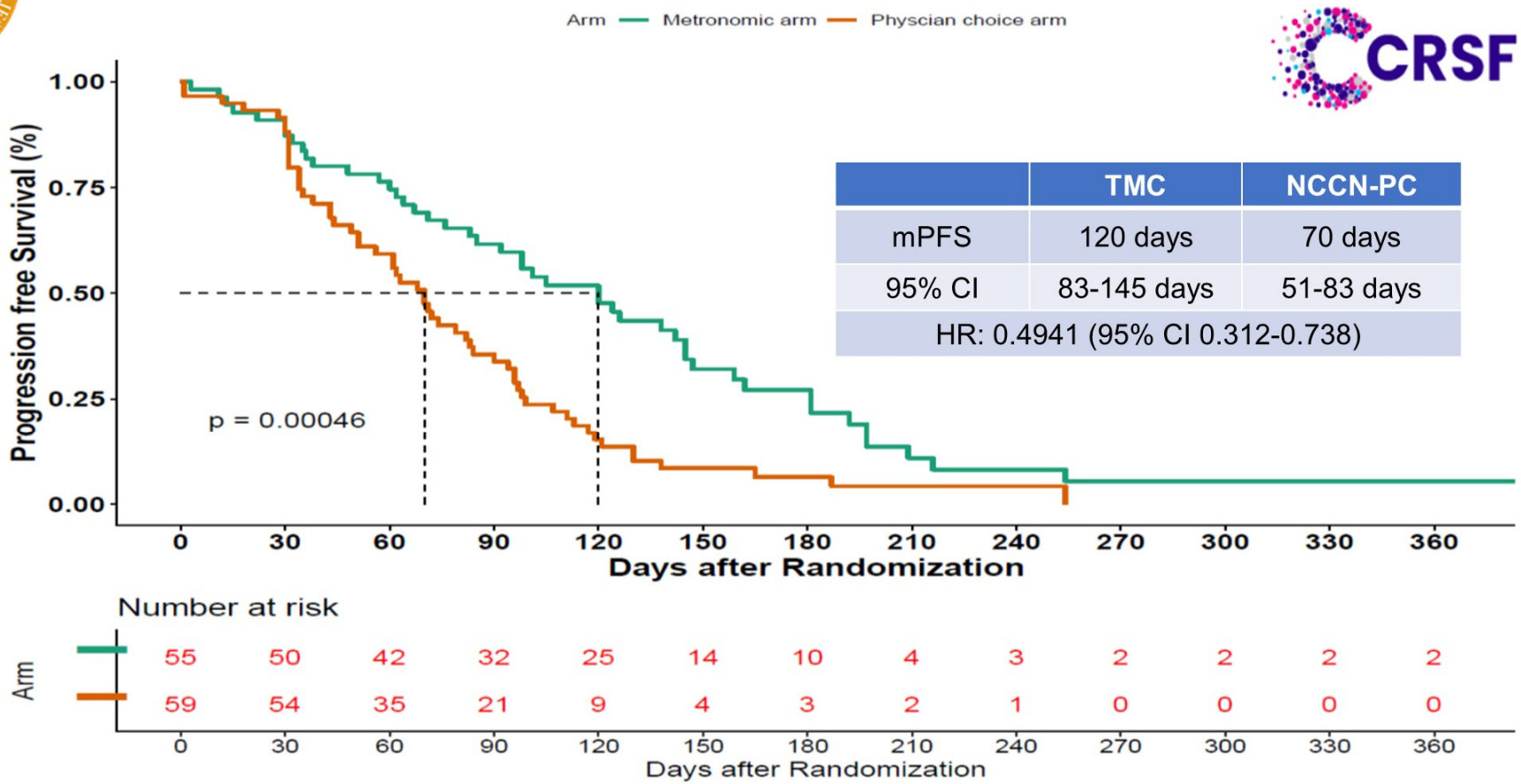
- Nivo/Pembro
- 5FU/Cape
- Taxane
- Cetuximab/Afatinib

COX



	TMC	NCCN-PC
mOS	181 days	123 days
95% CI	134-220 days	80-146 days
HR: 0.5076 (95% CI 0.325-0.792)		

COX



	TMC	NCCN-PC
mPFS	120 days	70 days
95% CI	83-145 days	51-83 days
HR: 0.4941 (95% CI 0.312-0.738)		

PRESENTED BY: DR. RUSHABH KOTHARI, MBBS, MD Medicine, DM Medical Oncology

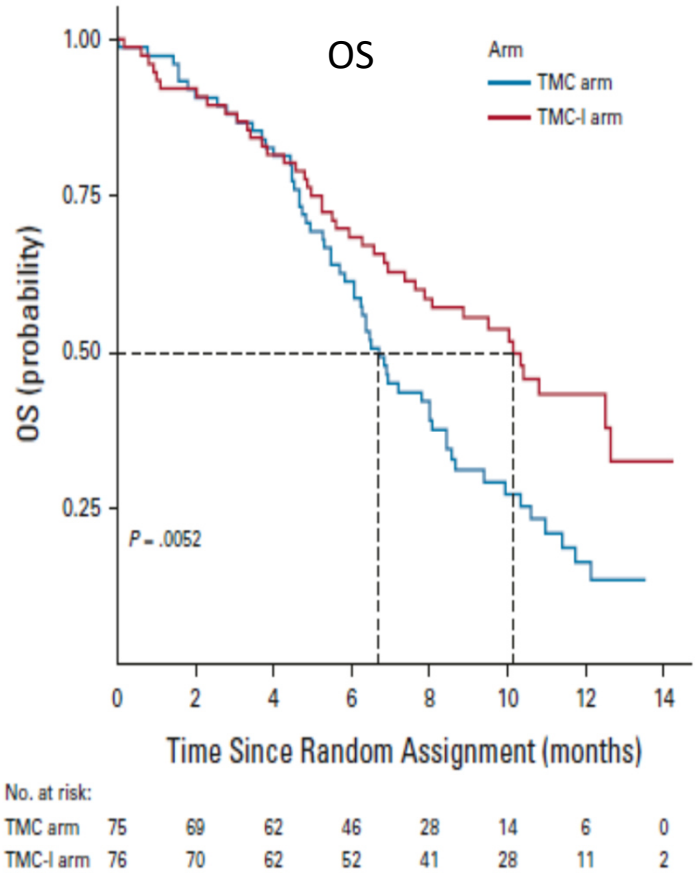
COX

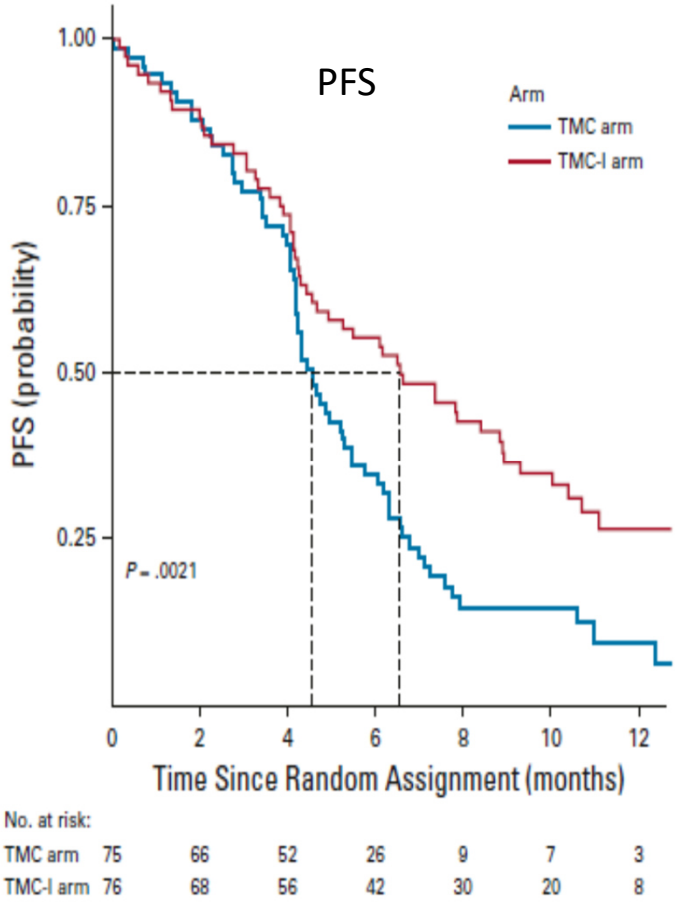
Low-Dose Immunotherapy in Head and Neck Cancer: A Randomized Study

Vijay Maruti Patil, MBBS, MD, DM[1]; Vanita Noronha, MBBS, MD, DM[1]; Nandini Menon, MBBS, MD, DNB[1]; Rahul Rai, MBBS, MD[1]; Atanu Bhattacharjee, PhD[2]; Ajay Singh, MBBS, MD, DM[1]; Kavita Nawale, PDCR[1]; Shweta Jogdhankar, MSc[1]; Rupali Tambe, BCom[1]; Sachin Dhumal, BHMS[1]; Riddhi Sawant, PDCR[1]; Mitali Alone, MSc[1]; Devanshi Karla, MSc[1]; Zoya Peelay, MSc[1]; Shruti Pathak, MSc[1]; Arun Balaji, MASLP[3]; Suman Kumar, MBBS, DNB[4]; Nilendu Purandare, MBBS, DNB[5]; Archi Agarwal, MBBS, DNB[5]; Ameya Puranik, MBBS, DNB[5]; Abhishek Mahajan, MBBS, DNB[4]; Amit Janu, MBBS, DNB[4]; Gunjesh Kumar Singh, MBBS, MD, DM[1]; Neha Mittal, MBBS, MD[6]; Subhash Yadav, MBBS, MD[6]; Shripad Banavali, MBBS, MD[1]; and Kumar Prabhash, MBBS, MD, DM[1]

Patil V et al, J Clin Oncol 2022

COX





Nivolumab
20 mg flat dose once every 3 weeks

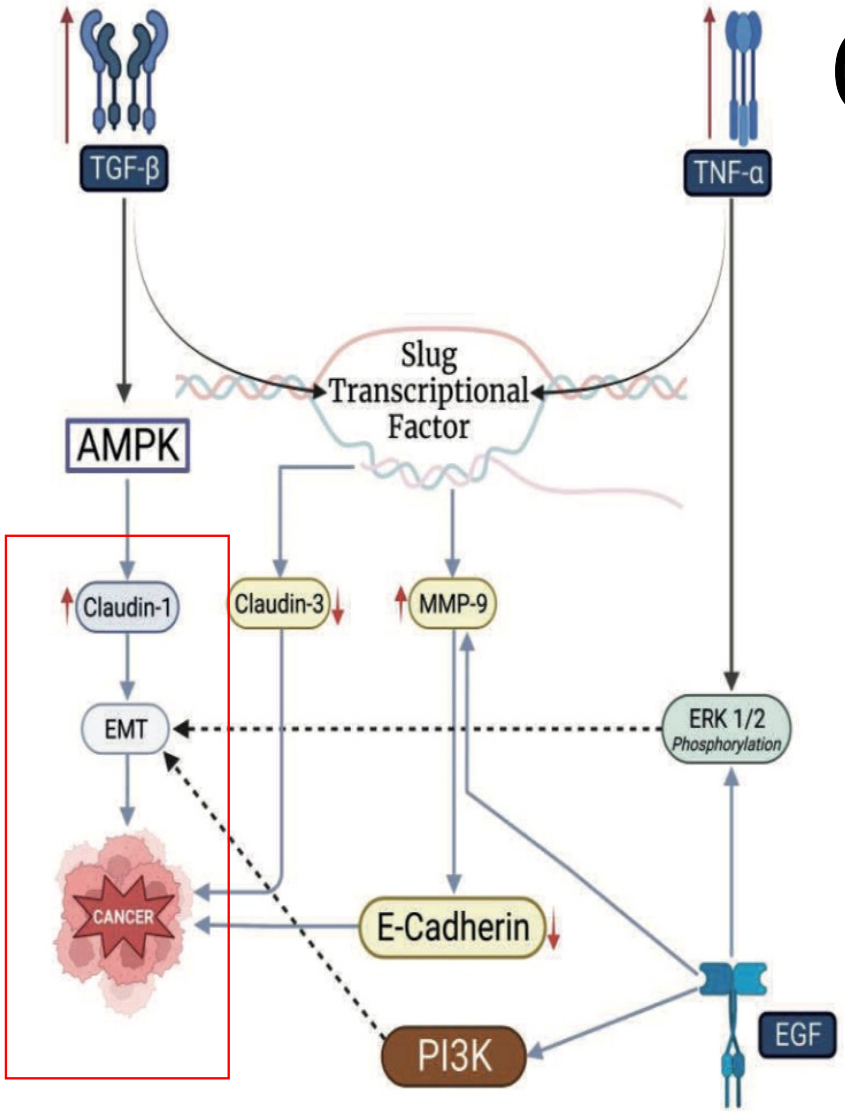
Primary Endpoint 1y-OS

1y-OS TMC = 16.3% (95% CI 8% - 27.4%)
1 y OS TMC-I = 43.4% (95% CI 30.8% – 55.3%)
p=0.0036

mOS TMC = 6.7 months (95% CI 5.8 – 8.1)
mOS TMC-I = 10.1 months (95% CI 7.4 – 12.6)
p = 0.0052

Patil V et al, J Clin Oncol 2022

Claudin



Review

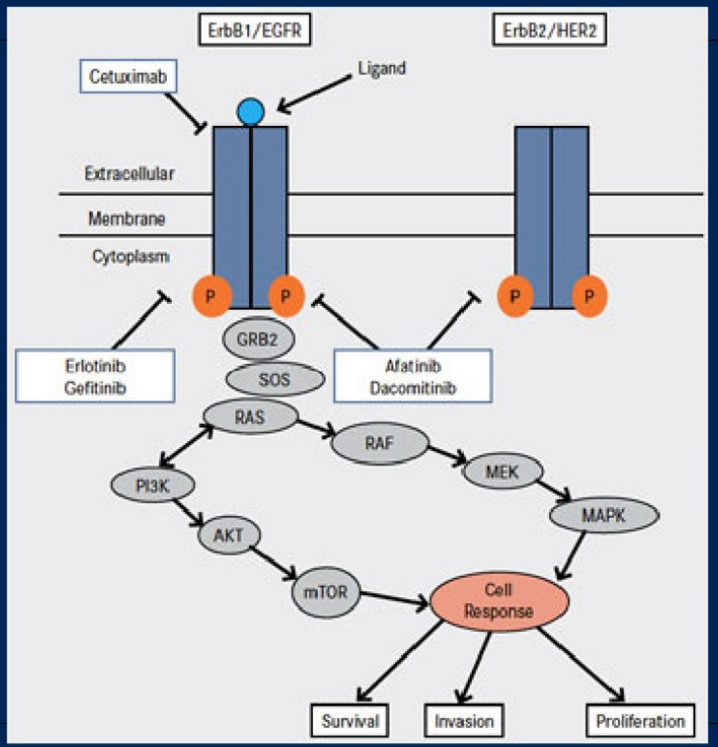
Aberrant Expression of Claudins in Head and Neck Carcinomas and Their Prognostic and Therapeutic Value: A Narrative Review

Tarek Ziad Arabi [1], Linah Abdulmohsen Algheryafi [1], Nora A. Alodah [1], Hamza M. Kossai Enabi [1], Amjad Abdullah Alshehry [1] and Abderrahman Ouban [1,2,*]

Cancers, 2023

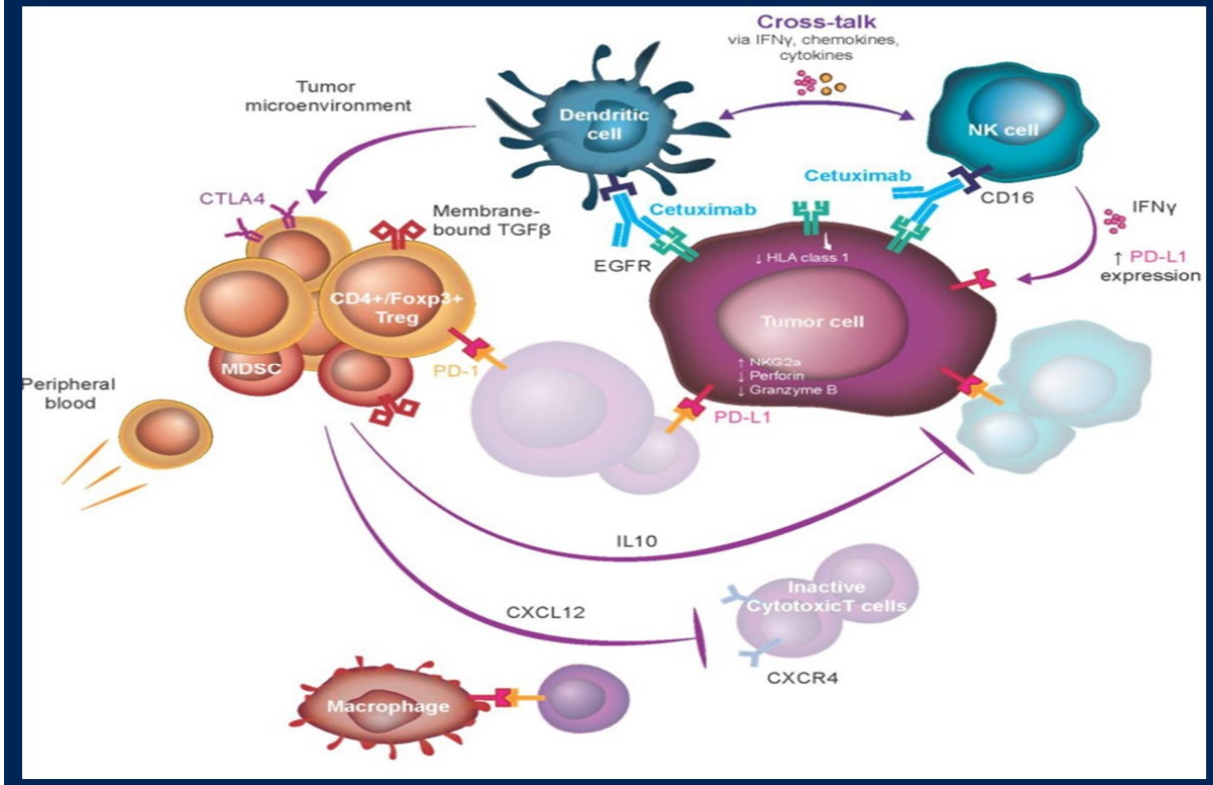
EGFR inhibitors

- Afatinib
  - Small molecule inhibitor (pan-ERB)
  - ~10% ORR
- Cetuximab
  - Recombinant Chimeric Antibody
  - 14% ORR as single agent
  - Chemotherapy combinations



Denaro et al, Journal of Oncology Translational Research, 2015

EGFR and PD-1 inhibitor Combinations

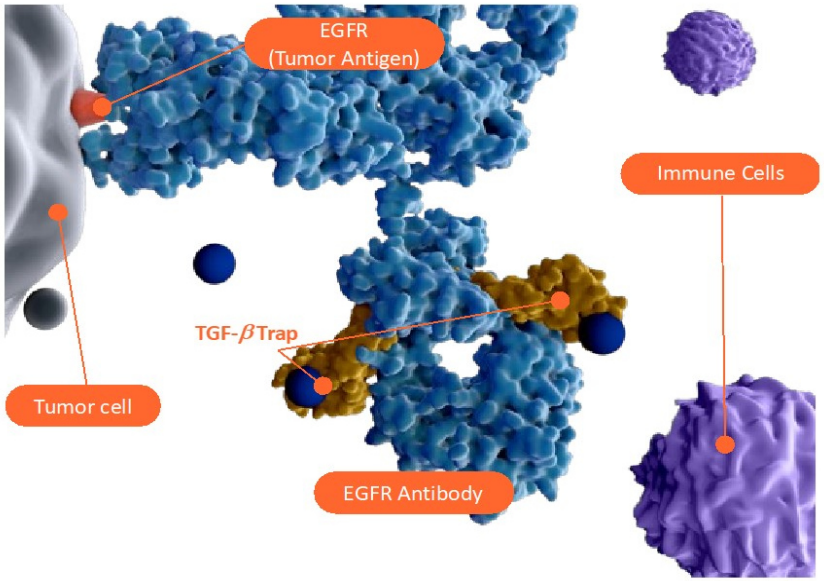


- Phase II pembrolizumab and cetuximab
  - 45% ORR
- Phase II afatinib and pembrolizumab
  - 41% ORR
- Phase II avelumab and cetuximab
  - 50% ORR

Ferris, R. L. *et al. Cancer Treatment Reviews* **63**, 48–60 (2018)
Sacco et al, Lancet Oncology, 2021; Kao et al., CCR, 2022; Forster et al, Annals of Oncology, 2020

Bispecific Antibodies

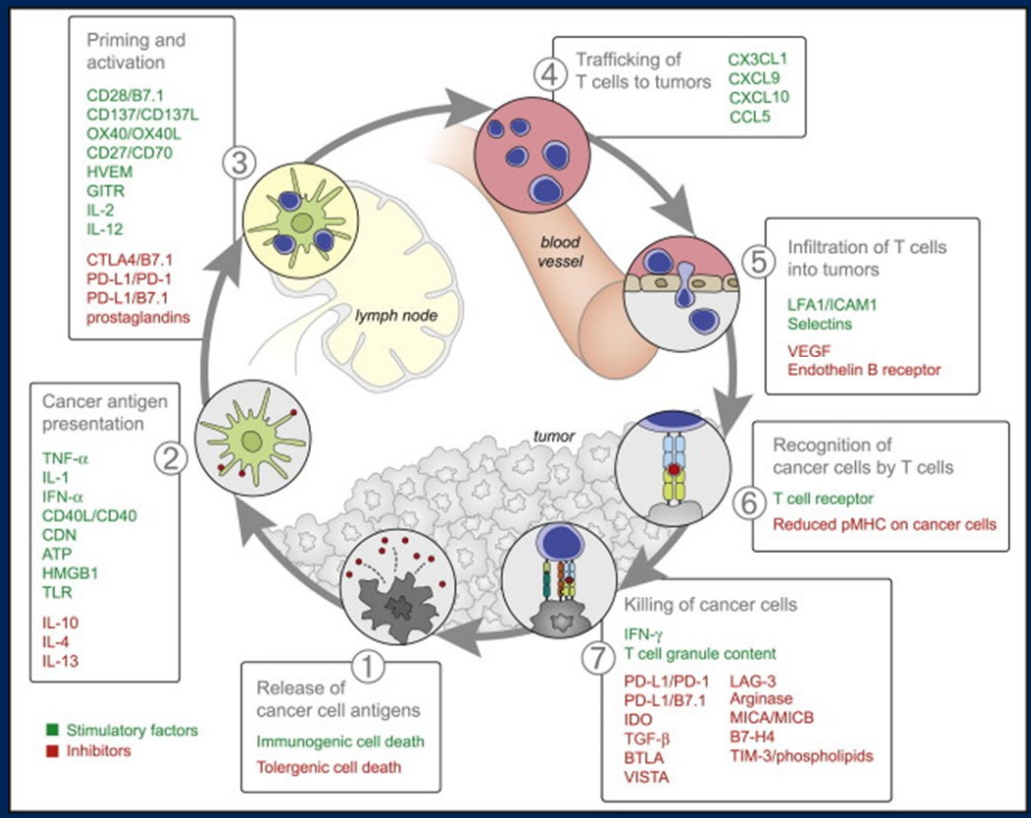
BCA101: Targeting a TGF-β trap to EGFR expressing tumors



Proposed mechanisms of action

1. Localizes TGF-β inhibition to the TME through an EGFR-directed approach
2. Aims to increase anti-tumor activity via enhanced ADCC and increased NK cell activation
3. Dual inhibition of EGFR and TGF-β prevents epithelial-mesenchymal transition (EMT) and metastasis

Immune Activators/Inhibitors



Chen and Mellman, Immunity 2013

VEGF inhibition in combination with αPD-1

TABLE 4. Efficacy Outcomes (investigator review, immune-related RECIST)

Parameter	RCC (n = 30)	Endometrial (n = 23)	SCCHN (n = 22)	Melanoma (n = 21)	NSCLC (n = 21)	Urothelial (n = 20)
Best overall response						
Complete response	0 (0)	2 (9)	1 (5)	1 (5)	1 (5)	1 (5)
Partial response	21 (70)	10 (44)	9 (41)	9 (43)	6 (29)	4 (20)
Stable disease	8 (27)	10 (44)	10 (46)	7 (33)	10 (48)	9 (45)
Progressive disease	1 (3)	1 (4)	0 (0)	3 (14)	2 (10)	2 (10)
Unknown	0 (0)	0 (0)	2 (9)	1 (5)	2 (10)	4 (20)
ORR[a]	21 (70)	12 (52)	10 (46)	10 (48)	7 (33)[b]	5 (25)
(95% CI)	(50.6 to 85.3)	(30.6 to 73.2)	(24.4 to 67.8)	(25.7 to 70.2)	(14.6 to 57.0)	(8.7 to 49.1)
ORR_{Week24}	19 (63)	12 (52)	8 (36)	10 (48)	7 (33)	5 (25)
(95% CI)	(43.9 to 80.1)	(30.6 to 73.2)	(17.2 to 59.3)	(25.7 to 70.2)	(14.6 to 57.0)	(8.7 to 49.1)
Median DOR, months (95% CI)	20.0 (9.0 to 22.9)	NE (2.6 to NE)	2 (2.2 to 12.6	12.5 (2.7 to NE)	10.9 (2.4 to NE)	NE (6.5 to NE)
Median PFS, months (95% CI)	19.8 (9.9 to 24.1)	9.7 (4.2 to NE)	7 (4.0 to 9.8	5.5 (2.6 to 15.8)	5.9 (2.3 to 13.8)	5.4 (1.3 to NE)

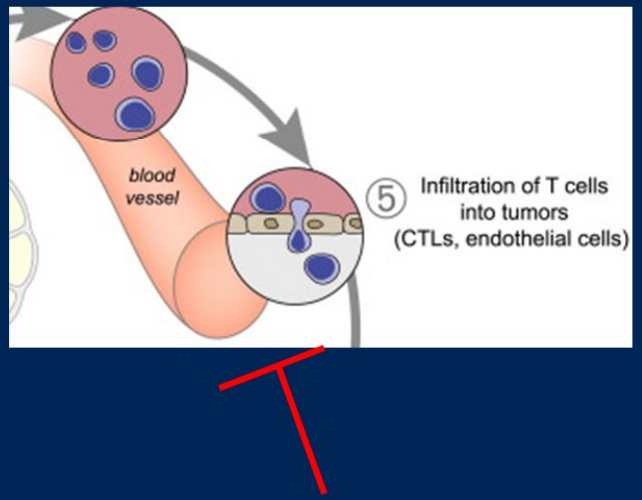
NOTE. Values are presented as No. (%) unless otherwise indicated.

Abbreviations: DOR, duration of response; NE, not evaluable; NSCLC, non–small-cell lung cancer; ORR, objective response rate; ORR_{week24}, objective response rate at week 24; PFS, progression-free survival; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.

[a]ORR is defined as the proportion of patients who had a confirmed complete or partial response per independent review by immune-related RECIST at the time of data cutoff. Four patients achieved a response after week 24 (2 patients in the RCC cohort and 2 patients in the SCCHN cohort).

[b]Two patients in the NSCLC cohort with a response (1 complete response and 1 partial response) had received prior programmed cell death-1/programmed cell death-ligand 1 therapy (both nivolumab).

36% ORR



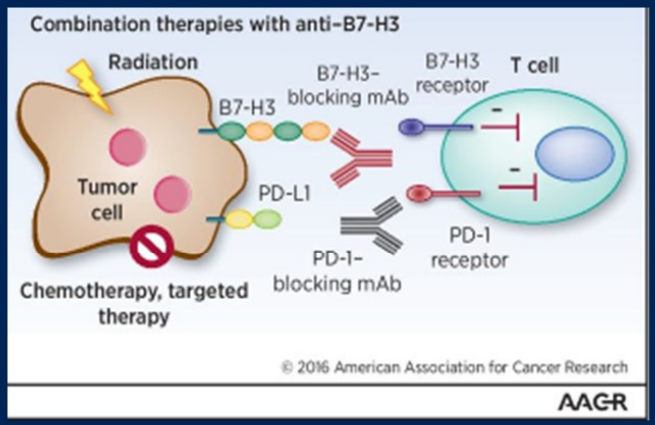
VEGF inhibition

LEAP 009 and 010 Studies Ongoing

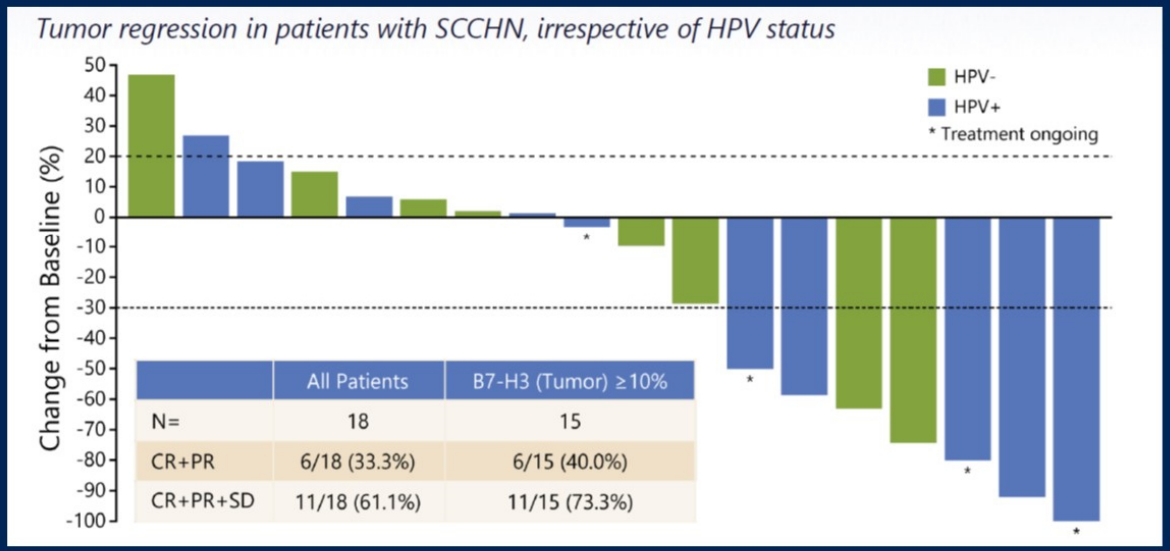
Taylor et al., JCO, 2020

Other Immune Checkpoint Inhibitors

B7-H3 Antibody Enoblituzumab with Pembrolizumab

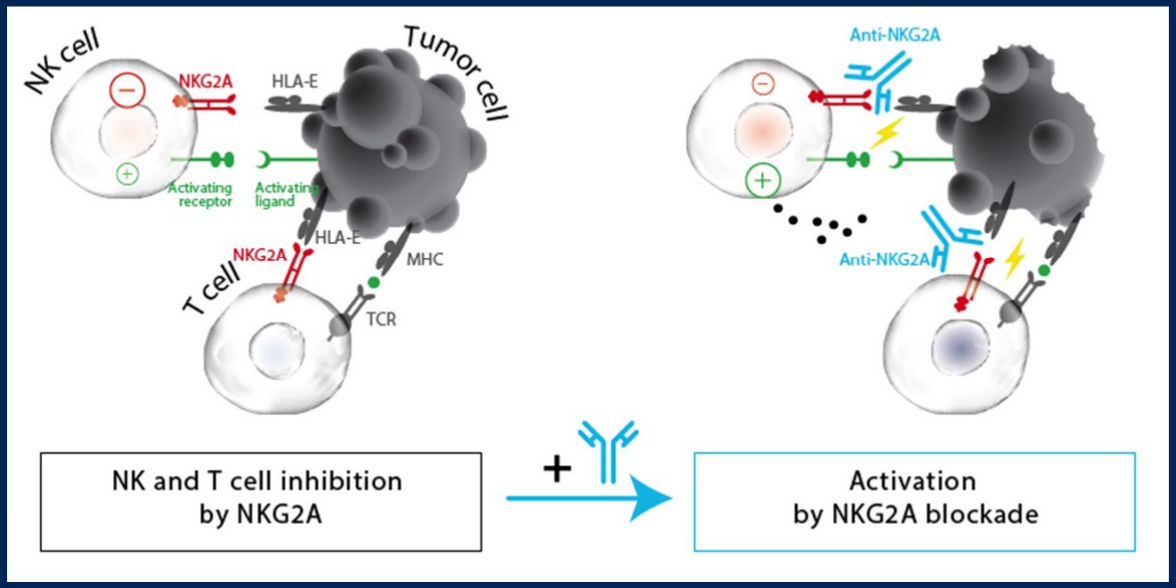


Induces ADCC



Aggarwal et al., SITC, 2018

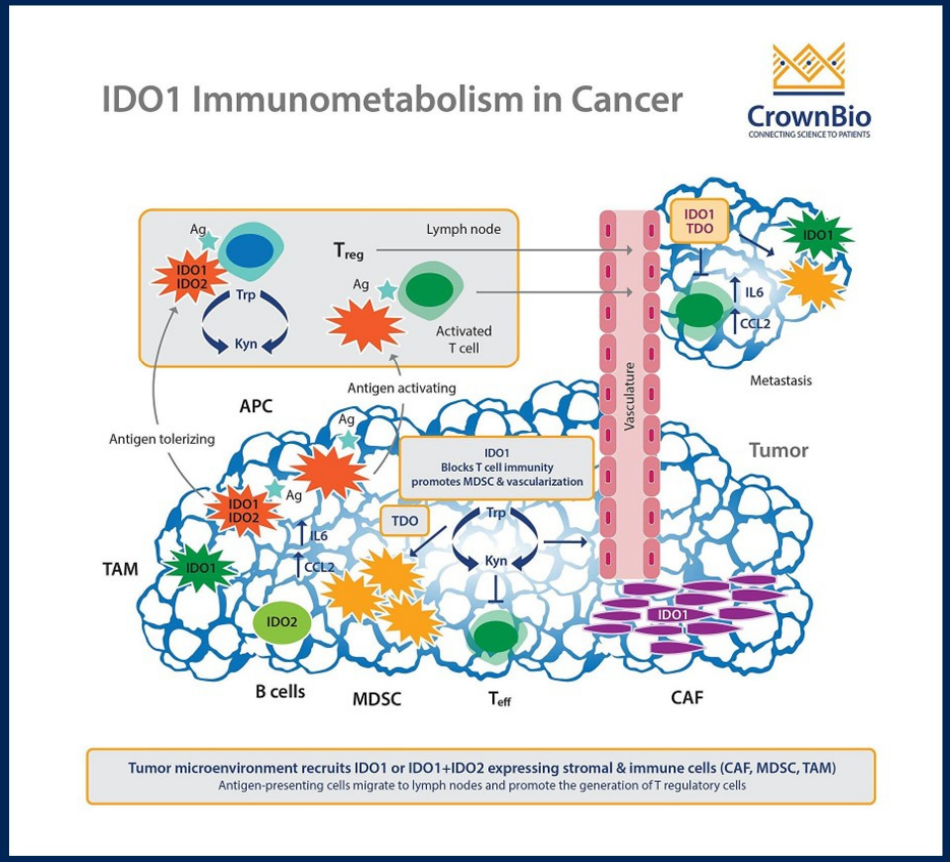
NKG2A Blockade- Monalizumab



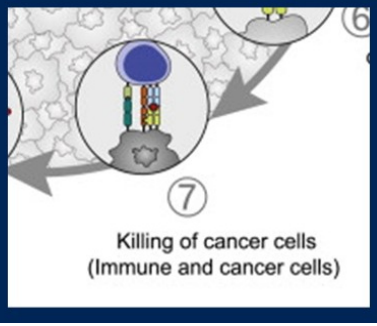
- Phase II study of monalizumab and cetuximab
  - ORR of 36% in IO naïve and 17% in IO pretreated patients
  - 12-month OS estimat of 44%
- Phase III and other combinations ongoing

Innate Pharma; Cohen et al, Annals of Oncology, 2019

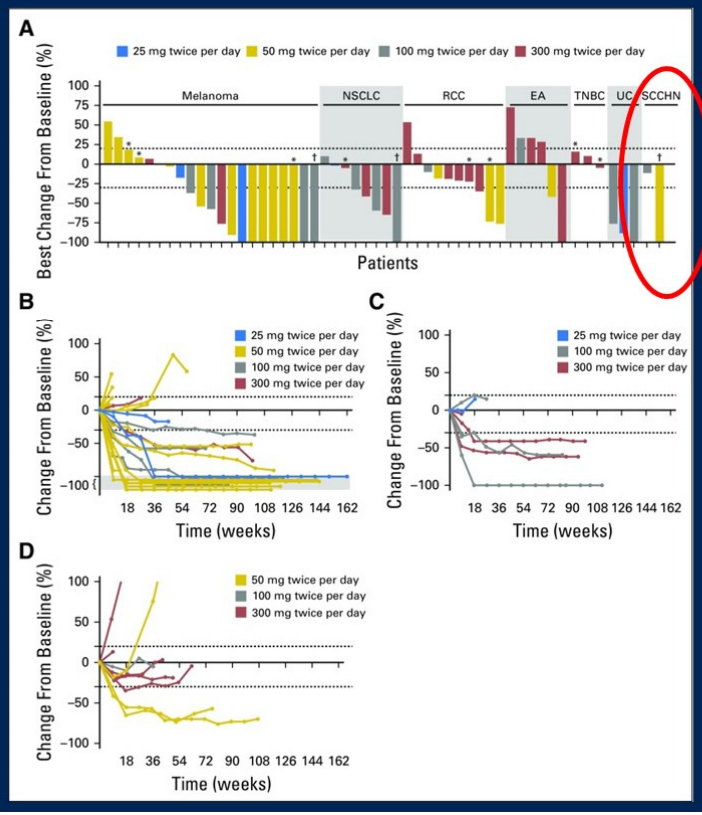
Tumor Microenvironment



- Upregulation of IDO1 is a potential mechanism to evade immunosurveillance
  - ↓ Tryptophan ↑ Kynurenine
  - ↓ T_{eff} and NK cells
  - ↑ T_{reg} cells, MDSCs, TAMs



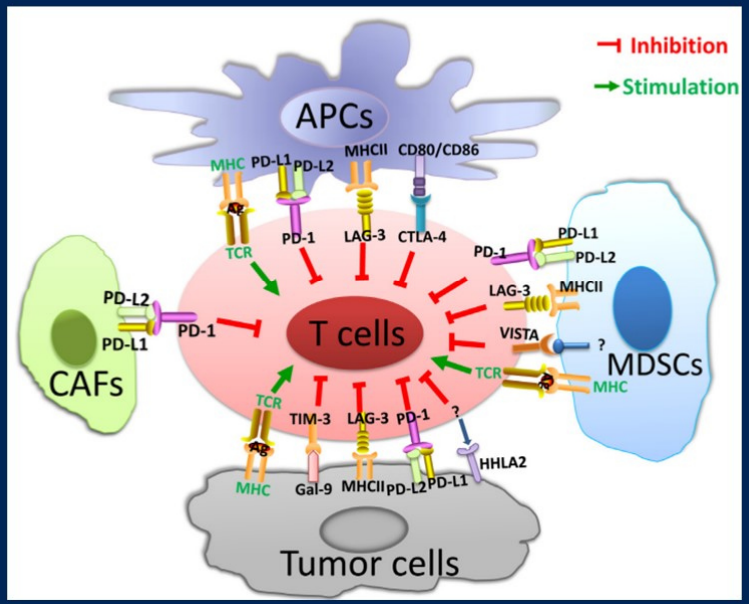
Epadacostat + Pembrolizumab in Solid Tumors



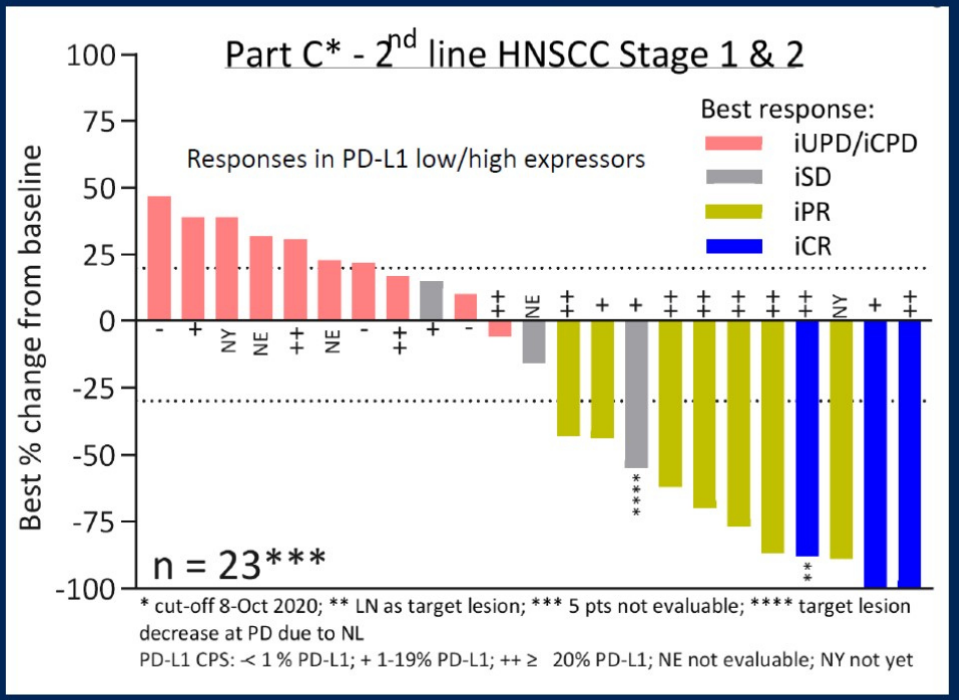
- Did not move forward due to failure to meet the primary endpoint in melanoma
- Novel inhibitors/ combinations in development

Mitchell et al., JCO 2018

TIM-3/LAG-3



TACTI-002



Pulido, Cancer Cell 2013; Long, Genes and Cancer, 2018; Krebs et al., SITC 2020

Other Promising Targets and Therapies in Clinical Trials

- Toll-like Receptors
- TGF-β
- SMAC inhibitors
- NOTCH1 loss- NOTCH1 inhibitor
  - (NCT03740100)
- ATMi, PARPi and other DNA damage modifiers
- Novel delivery systems
- Many others forthcoming

Conclusions

In Immuno-Oncology era, a chemo-free approach is still not realistic for most HNSCC!

Chemotherapy plus anti-EGFR (e.g. extreme-like regimens) still mantain a key role in R/M HNSCC (i.e. CPS PD-L1<1 or CPS PD-L1≥1 not eligible for I-line SOC and requiring tumor shrinkage)

To date, the comprehensive molecular profiling of HNSCC should be limited to clinical trials setting

The identification of new targets could be exploited to develop new drugs (i.e. ADC and bispecific antibodies as the most promising!)