500 fold

30y

28.3m

Tumori della testa e collo nei pazienti con anemia di Fanconi

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AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA
CONGRESSO NAZIONALE AIEOP
ROMA, 22-24 Settembre 2025
CENTRO CONGRESSI
UNIVERSITÀ CATTOLICA
DEL SACRO CUORE

Disclosures of Luigi Lorini

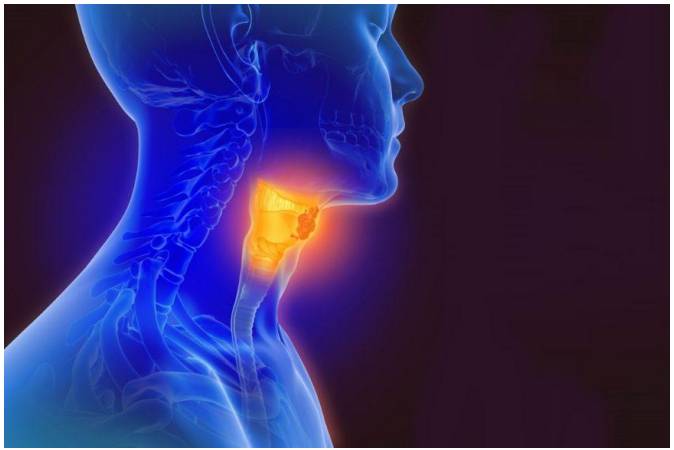
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
None							

Outline

1. Differences with common HNSCC - epidemiology
2. Differences with common HNSCC - treatment
3. Future perspectives
4. Conclusions and THM

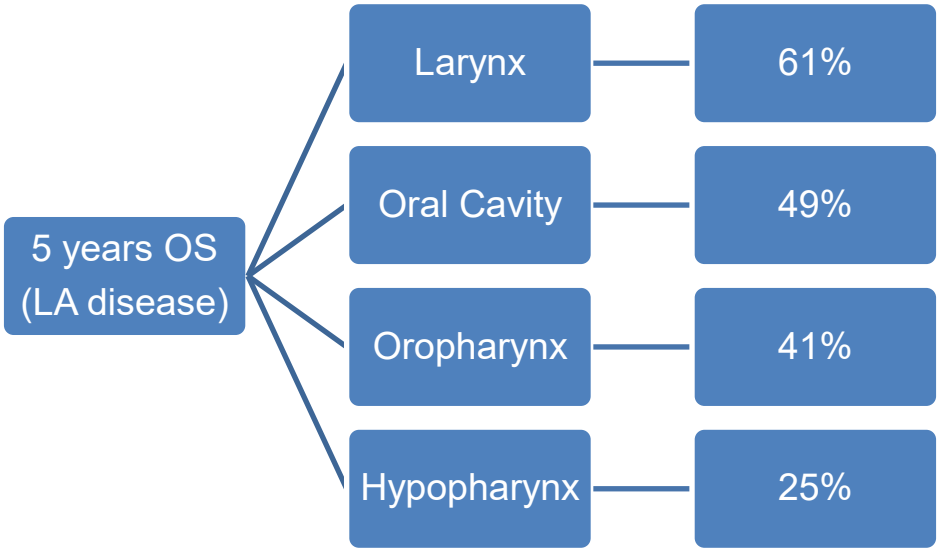
Background on head and neck tumor

- Mostly represented by Squamous Cell Carcinoma (HNSCC) (90%)
- 7° most common cancer worldwide (annual incidence 700000; annual mortality 350000)
- Incidence increase of 30% by 2030
- Higly impacting on patients QoL
- Median age 60y



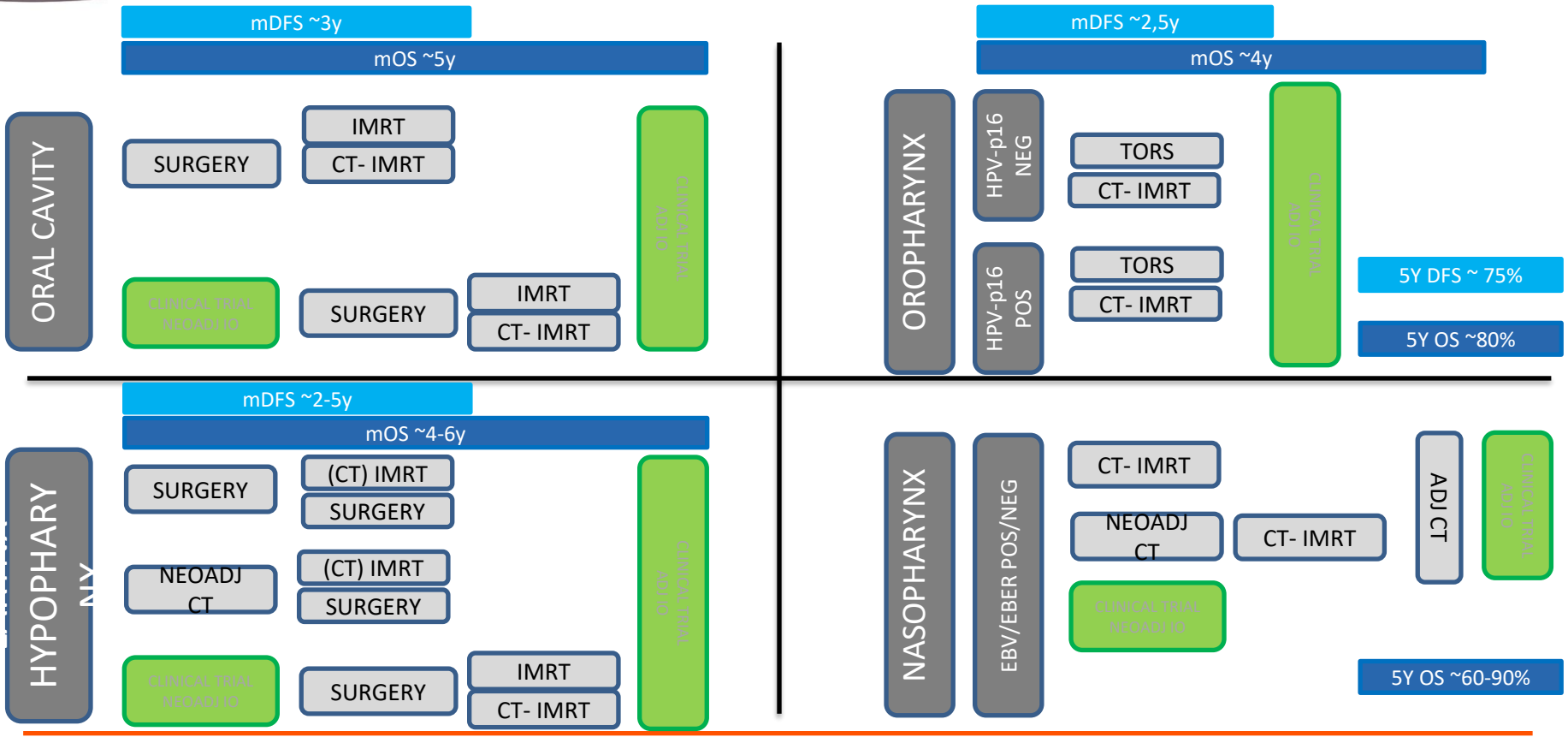
Sung, 2020 Ca Cancer J

Background on head and neck tumor - Prognosis



- 80% classified as advanced disease (LA) (stage III-IV AJCC VIII ed) at diagnosis
- 50% relapse in 5 years
- Once disease relapse, the 1 year OS is 15%

LA HNSCC standard of care ECOG 0-1



Importance of adherence and treatment intensity….

TABLE 3. Cumulative cisplatin dose in retrospective studies.

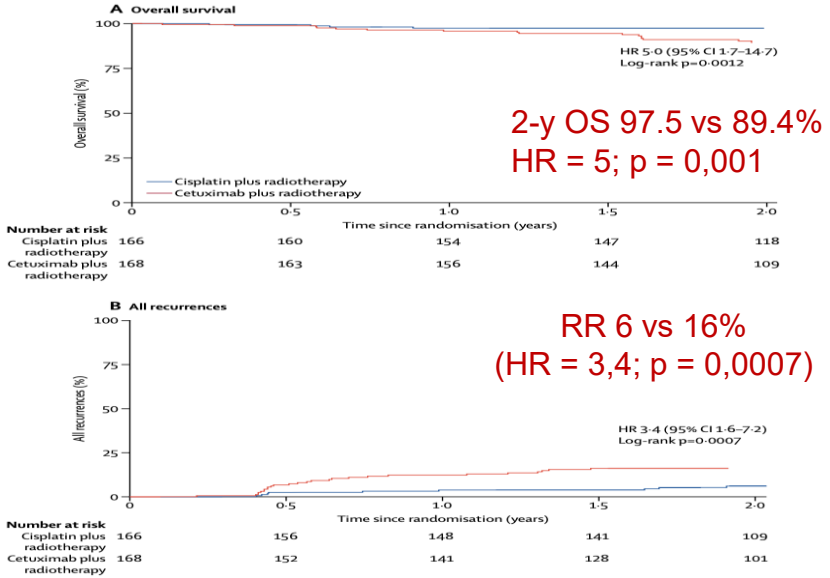
Author	TH type	Period	Sites/stage	No. of patients	Treatment	Cumulative CP dose, median, mg/m^2	Median follow-up, y	Survival at 2 y		
								LRC	EFS	OS
Fountzilas et al[25]	D	1991–1992	OC, OP, HP, L, NP, CUP III, IV	48	RT: 70 Gy, 1.8 Gy/d CP: 100 mg/m^2/3 wk	300 G1: 200 ($N=6$) G2: 300 ($N=42$)	2.2	 N.R. N.R.	N.S. G1: 50% G2: 55%	$p<.001$ G1: 17% G2: 75%
Gupta et al[26]	D	1996–2004	OC, OP, HP, L III, IV	264	RT: 66–70 Gy, 2–2.1 Gy/d CP: 30 mg/m^2/wk	180 G1: ≤150 ($N=96$) G2: ≥180 ($N=168$)	1.6	$p=.009$ G1: 40% G2: 57%	$p=.011$ G1: 39% G2: 67%	 N.R. N.R.
Lau et al[27]	D	2000–2002	OC, OP, HP, L, CUP II–IV	56	RT: 70 Gy, 2 Gy/d CP: 20 mg/m^2/d 1–4, wk 1 and 5	 G1: ≤80 ($N=21$) G2: 160 ($N=35$)	1.3	N.S. N.R. N.R.	 N.R. N.R.	$p=.044$ G1: 50.8% G2: 69.6%
Steinmann et al[28]	D, PO	2001–2006	OC, OP, HP, L, NP I–IV	78	RT: 50.4–70 Gy, 2 Gy/d CP: 40 mg/m^2/wk	160 G1: <200 ($N=43$) G2: ≥200 ($N=35$) G1: <160 ($N=14$) G2: ≥160 ($N=64$)	3	N.S. G1: 69%* G2: 81%* N.S. G1: 73%* G2: 86%*	 N.R. N.R. N.R. N.R.	N.S. G1: 69%* G2: 70%* N.S. G1: 66%* G2: 86%*
Rades et al[29]	D, PO	2000–2008	OC, OP, HP, L III, IV	160	RT: 60–72 Gy/2 Gy/d CP: G1: 100 mg/m^2/3 wk G2: 20 mg/m^2/d 1–5, wk 1 and 5	 G1: 300 ($N=74$)† G2: 200 ($N=86$)†	2	N.S. G1: 79% G2: 69%	 N.R. N.R.	N.S. G1: 72% G2: 73%
Espeli et al[30]	D, PO	2002–2009	OC, OP, HP, L, NP I–IV	94	RT: 66–70 Gy, 2 Gy/d CP: G1: 100 mg/m^2/3 wk G2: 40 mg/m^2/wk	 G1: 232 ($N=54$) G2: 186 ($N=40$)	2.8	 N.R. N.R.	N.S. G1: 52% G2: 46%	$p=.041$ G1: 78% G2: 51%
Geiger et al[31]	PO	2004–2010	OC, OP, HP, L, CUP, PNS III–IV	104	RT: 60–70 Gy, −2.2 Gy/d CP: G1: 100 mg/m^2/3 wk G2: 25–30 mg/m^2/wk	 G1: 200 ($N=51$) G2: 150 ($N=53$)	5	 N.R. N.R.	N.S. G1: 73% G2: 74%	N.S. G1: 88% G2: 78%

Abbreviations: TH, treatment; CP, cisplatin; LRC, locoregional control; EFS, event-free survival; OS, overall survival; D, definitive; OC, oral cavity; OP, oropharynx; HP, hypopharynx; L, larynx; NP, nasopharynx; CUP, cancer of unknown primary; RT, radiotherapy; G1, group 1; G2, group 2; N.R., not reported; N.S., not statistically significant; PO, postoperative; PNS, Paranasal sinuses.
* At 18 months.
† Planned cumulative dose.

Strojan A. et al. Head and Neck 2016

Can we spare cisplatin?

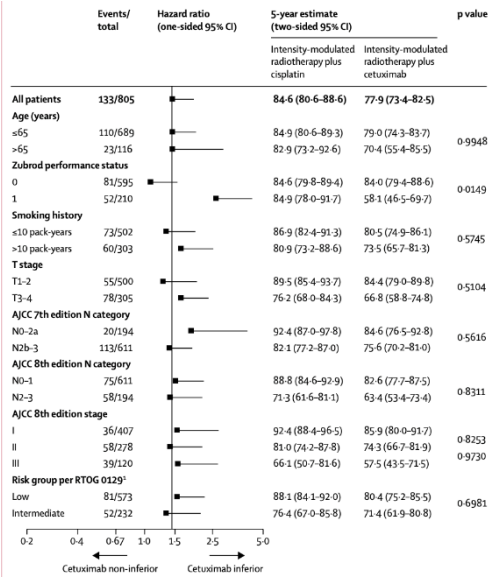
De-Escalate



2-y OS 97.5 vs 89.4%
HR = 5; p = 0,001

RR 6 vs 16%
(HR = 3,4; p = 0,0007)

RTOG1016



Inferior 5y OS in all subgroups

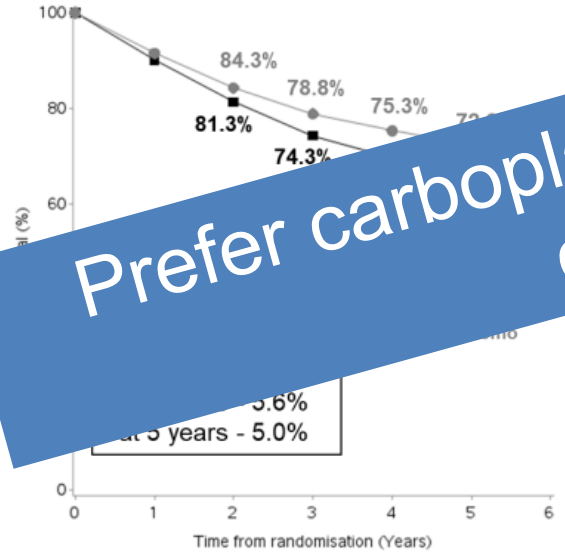
HUMANITAS CANCER CENTER

Mehanna H. et al, Lancet 2018
Gillison M et al, Lancet 2019

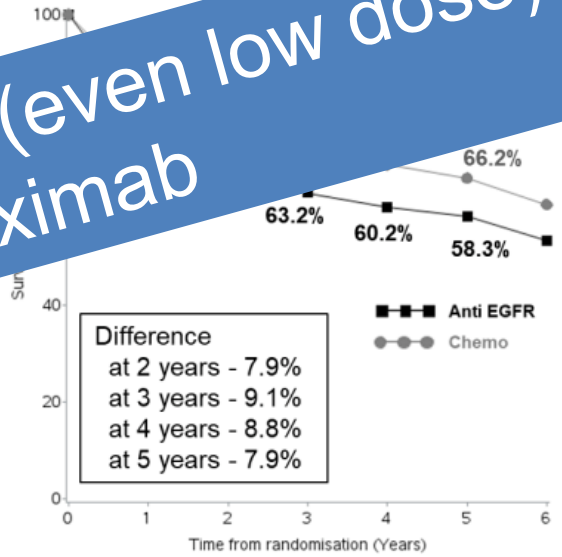
What about platinum unfit patients?

MACH-EGFR – REPLACING with anti-EGFR (comparison 2)

Results: Overall survival



Progression-free su



Prefer carboplatin (even low dose) to cetuximab

MADRID 2023 ESMO congress

Standard-of-Care in R/M HNSCC: ECOG0-1

1L R/M HNSCC

PD-L1 CPS≥1

Platinum-sensitive

PD-L1 CPS<1

Platinum-refractory

OS 12-18 m

PFS 3-6 m

PEMBROLIZUMAB

PEMBROLIZUMAB + PF

EXTREME/TPEX

NIVOLUMAB

OS 8 m

PFS 2-3 m

NIVOLUMAB

Clinical Trials

Clinical Trials

Clinical Trials

Single Agents
Taxanes, MTX, Cetuximab, Capecitabine

ORR 10-20%
mOS 6-7 m
mPFS 2-3 m

Oliva M ESMO 2023; ; Machiels JP. et al. Ann Onc. 2020; Martinez-Trufero, BJC 2010; Peron J. Anticancer Drugs, 2012; Chevalier, Cancer Med. 2021; Cphen, E. Lancet 2019

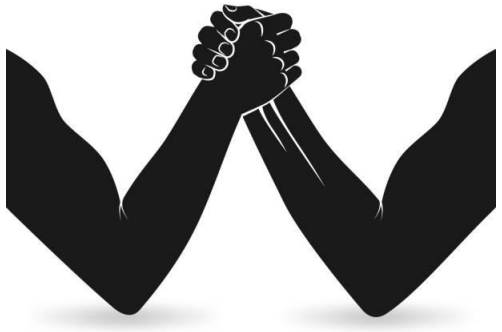
HNSCC in Fanconi Anemia - epidemiology

- 40 fold increase risk of developing any cancer, 75% after 40y
- 500 fold increase in the risk of developing HNSCC if compared with general pop
- Median age of onset 30 year, younger (18-20y) if patients undergone SCT
- Oral cavity most common site (60%)
- 43% at stage IV (AJCC VII ed)

Fanconi Anemia
RESEARCH FUND, INC.

HPV or not HPV related?

- Controversial data in different series
- Oral Cavity not usual site for HPV pos tumor
- Carcinogenesis drive by lack of repair of DNA than HPV
- Reccomended vaccination (patients immunodepressed)



Real World Data – IFAR Registry

Natural History and Management of Fanconi Anemia Patients with Head and Neck Cancer: A 10-year Follow-up

David I. Kutler, MD[1], Krupa R. Patel, BA[2], Arleen D. Auerbach, PhD[3], Jennifer Kennedy, MS[4], Francis P. Lach, BS[4], Erica Sanborn, MS[4], Marc A. Cohen, MD[1], William I. Kuhel, MD[1], and Agata Smogorzewska, MD PhD[4]

- 35 pts, mean age 32 y, no history of tobacco or alcol
- 74% Oral cavity; 75% HPV (p16) pos
- 30 surgery: 23% complication (2 wound infection, 1 sepsi, 1 pneumonia, 1 free flap..)
- 16 RT: High grade mucositis: 56%; Hematologic abnormalities 50%; dysphagia 50%;
- CT: cetuximab well tollerated, cisplatin bad tollerated (tot 6 patients)
- 48% second cancer
- 5 Y OS rate 39%;
- 57 cause specific survival rate 47%

Treatment of Fanconi Anemia-Associated Head and Neck Cancer: Opportunities to Improve Outcomes

Rex H. Lee[1], Hyunseok Kang[2], Sue S. Yom[3], Agata Smogorzewska[4], Daniel E. Johnson[1], Jennifer R. Grandis[1,*]

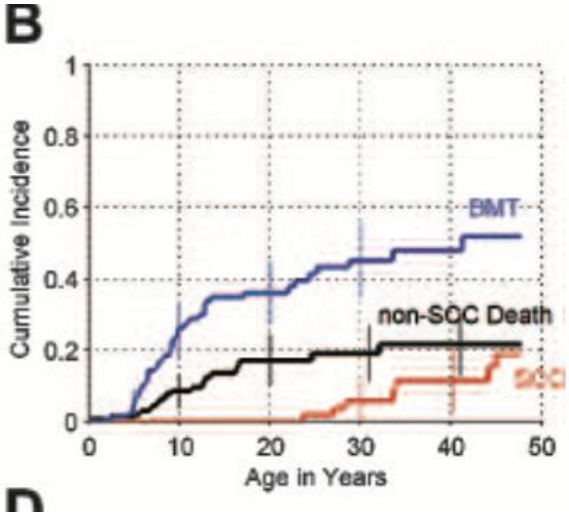
[1]Department of Otolaryngology – Head and Neck Surgery, University of California San Francisco, San Francisco, CA, USA

- 119 pts
- FANCA (68%) and FANCB (17%), 60% data not available
- 70% oral cavity; 40% stage IV; 59% HPV pos;
- 106/119 surgical resected (22 adj RT e 9 adj CRT)
- Adj RT: 6/22 interrupted
- 9 definitive RT; 9 def CRT (50% completed RT and 30% CT); prior HSCT did not change outcomes
- 6 palliative CT all interrupted due to tox
- EGFRi well tollerated (with RT or alone)

Problems: Previous HSCT

Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants

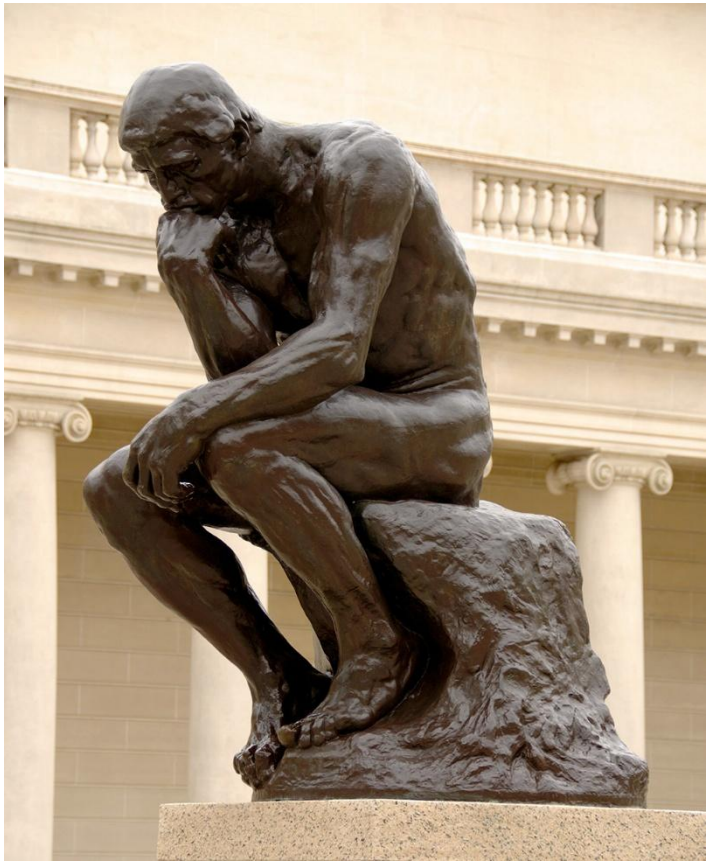
Philip S. Rosenberg, Gerard Socié, Blanche P. Alter, and Eliane Gluckman



- 4.4 fold increase risk
- 15 years after transplant 10.1% developed SCC
- Younger age (18 vs 33)
- High grade GVHD at higher risk
- No difference in outcomes after RT
- Due to RT and CT conditioning regimen: may we avoid RT?

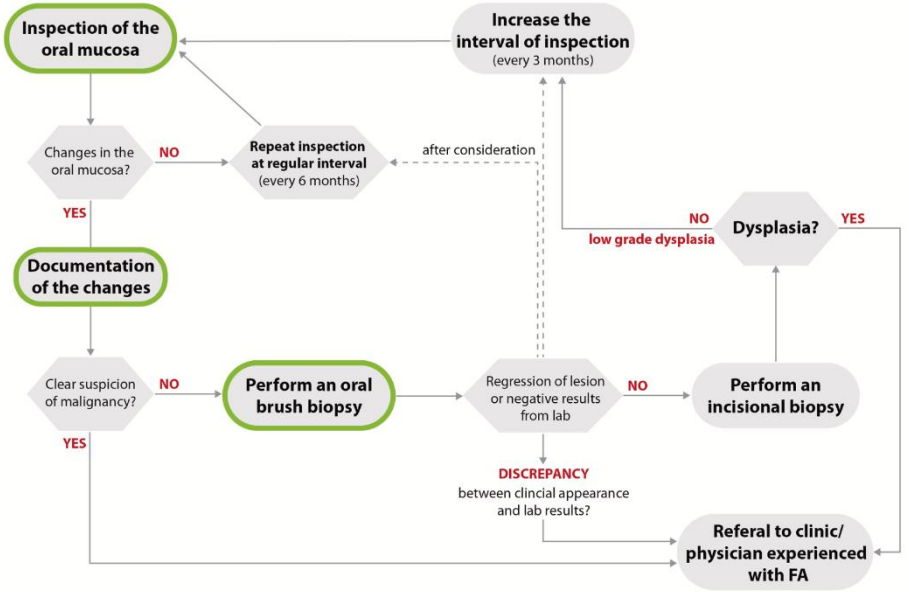
Problems:

- High risk of RT toxicities (bleeding, pancytopenia) and consequent high risk of treatment interruption
- High risk of CT «conventional» toxicities (even life threatening)
- High risk of secondary malignancies
- Tumor from young age (median 30 y, but even 13 y)



Importance of follow up

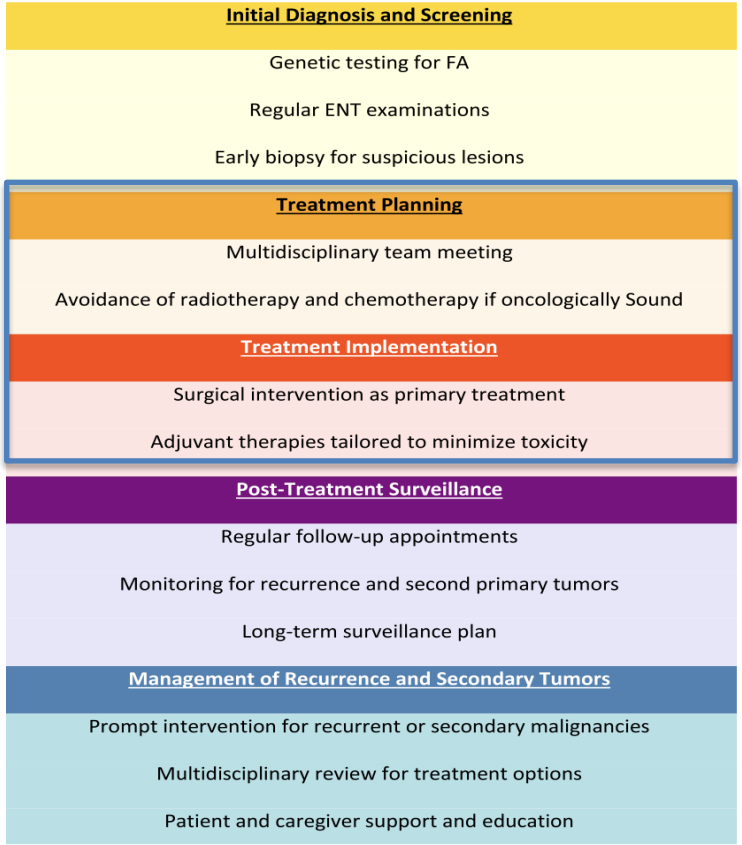
- ENT follow up since 15 years old (3-4 months)
- If history of OPMD, every 2 months
- High volume centers
- NBI imaging
- OPMD detection



Beddok et al. 2025

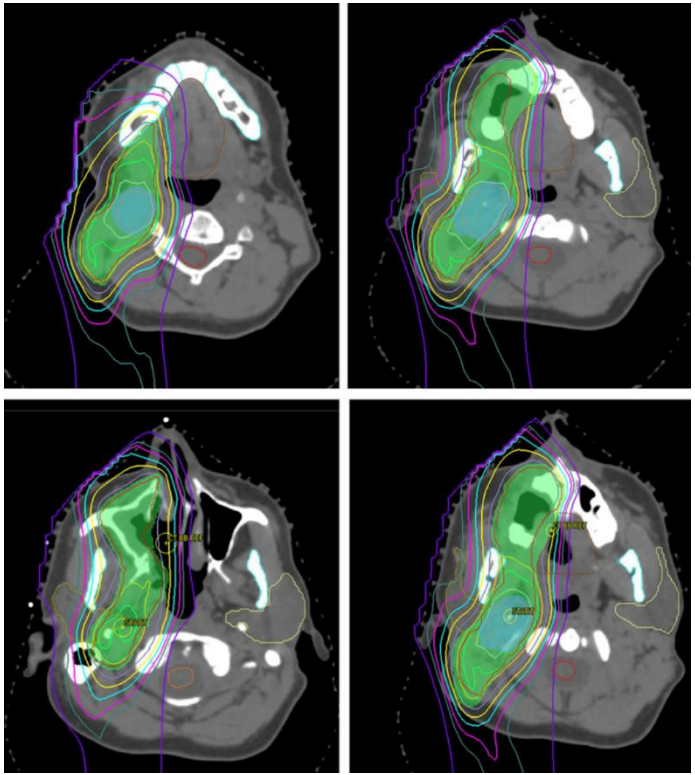
Aggressive surgery

- Surgery well tollerated, outocomes similar to non FA patients
- Even with clear margins, high risk of relapse
- High attention on preoperative preparation, and post operative bone marrow activity
- Higher lost of flap risk
- To avoid RT and/or CT when possible



Beckham et al. 2019; Tsur et al. 2025

RT in high volume centers



- High risk of complication
- Risk of bleeding and pancytopenia
- Mandatory for clinical outcome
- Importance of pretreatment abilitation
- Aware of complication
- Advantages with IMRT (proton for the future?)

Beckham et al. 2019

How to avoid cisplatin? ICIs

Treatment of Fanconi Anemia-Associated Head and Neck Cancer: Opportunities to Improve Outcomes

Rex H. Lee[1], **Hyunseok Kang**[2], **Sue S. Yom**[3], **Agata Smogorzewska**[4], **Daniel E. Johnson**[1], **Jennifer R. Grandis**[1,*]

[1]Department of Otolaryngology – Head and Neck Surgery, University of California San Francisco, San Francisco, CA, USA

- In non FA patients, in patients receiving SCT, 13% acute GVHD and 11% chronic GVHD (possible prevention with low dose steroid and mTORi)
- 3 pts reported: 1 died after 3 doses fro nivolumab induce encephalopaties, 1 died after 10 days of administration; 1 still alive after pembrolizumab in curative setting
- Need more data
- PDL1 expression in FA agents?
- Intratumoral ICIs?

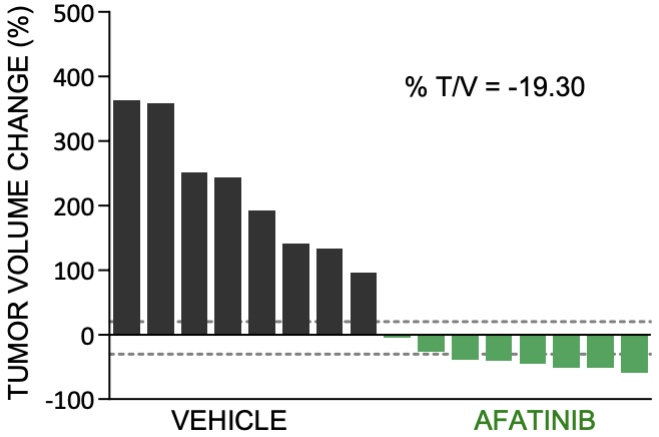
Beckam et al 2019; Kleber et al 2016; Lee et al 2021.

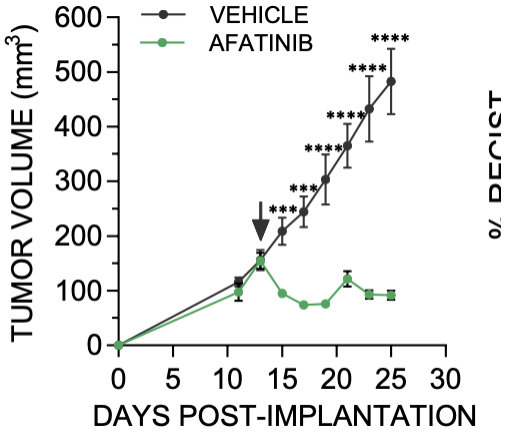
How to avoid cisplatin? EGFRi

AACR American Association for Cancer Research
Clinical Cancer Research

Gefitinib and afatinib show potential efficacy for Fanconi anemia-related head and neck cancer

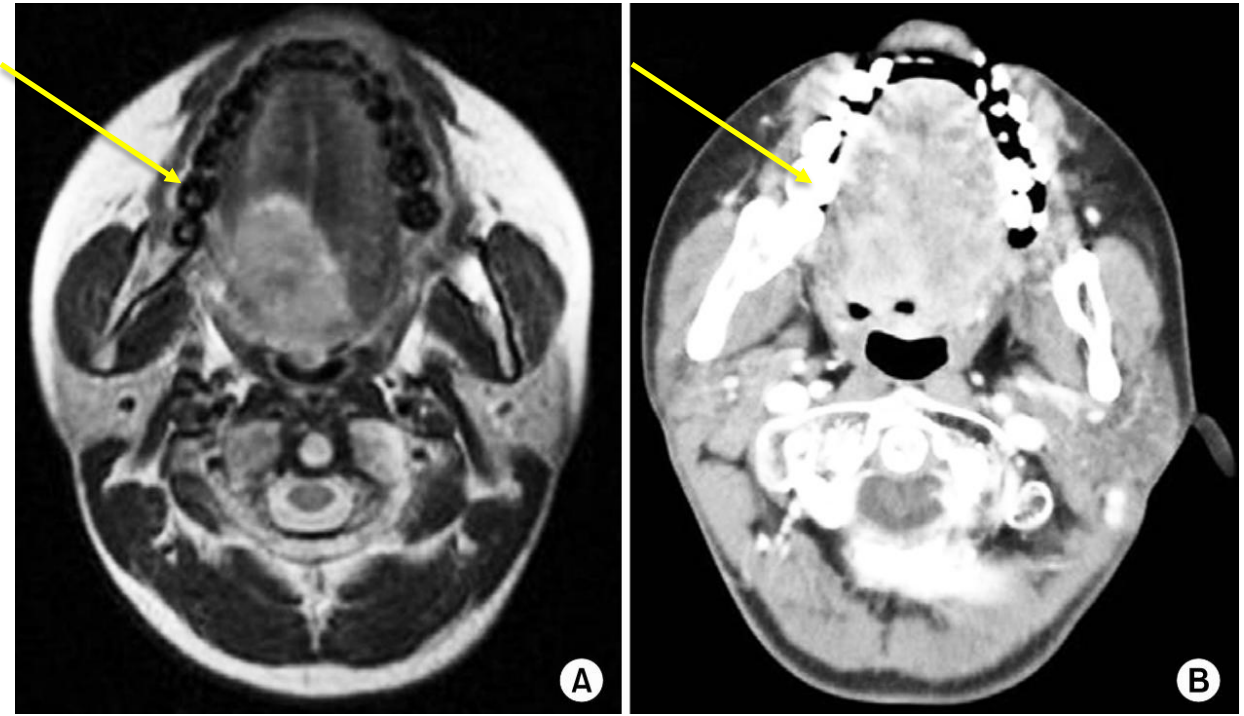
Helena Montanuy, Agueda Martínez-Barriocanal, José A. Casado, et al.





Approved by EMA in 2018 for FA HNSCC

How to avoid cisplatin? EGFRi



- Active (case report/series)
- Safe, better tollerated than platinum based
- Rare treatent interruption

Beckam et al 2019; Kleber et al 2016; Lee et al 2021; Jung 2025

Opening of a phase Ib/II study to investigate the safety and efficacy of Afatinib in patients with Fanconi anemia and unresectable locally advanced or metastatic head and neck squamous cell carcinoma

Georgia Anguera[1], Oscar Gallego[1], Mireia Llobet[1], Núria Berga[2], Maria-Estela Moreno-Martinez[2], Xavier Leon[3], Christian Kratz[4], Ramon Garcia-Escudero[5,6,7], Jordi Minguillón[8,9] and Jordi Surrallés[10,11,12,13,14]*

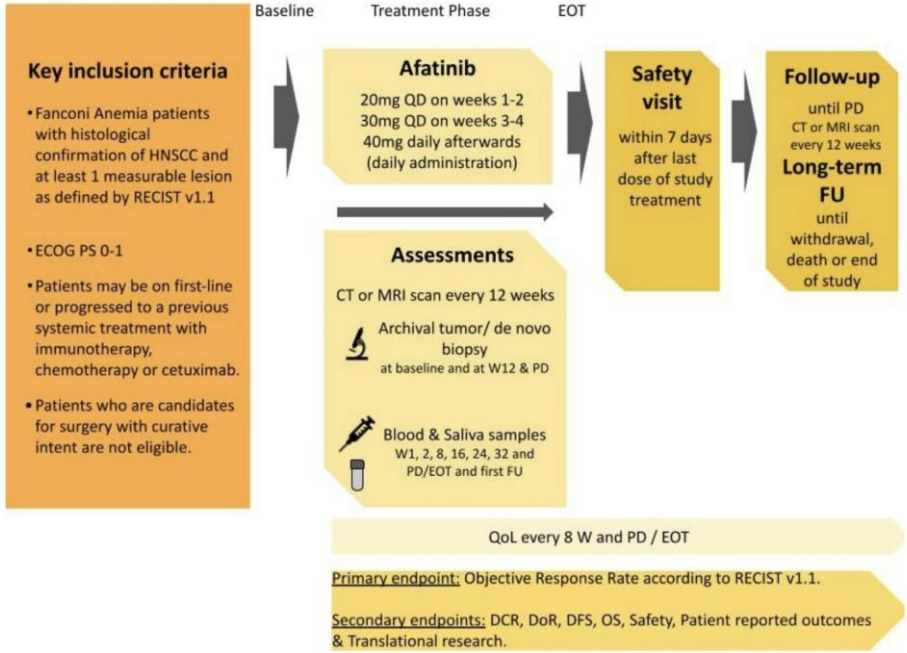
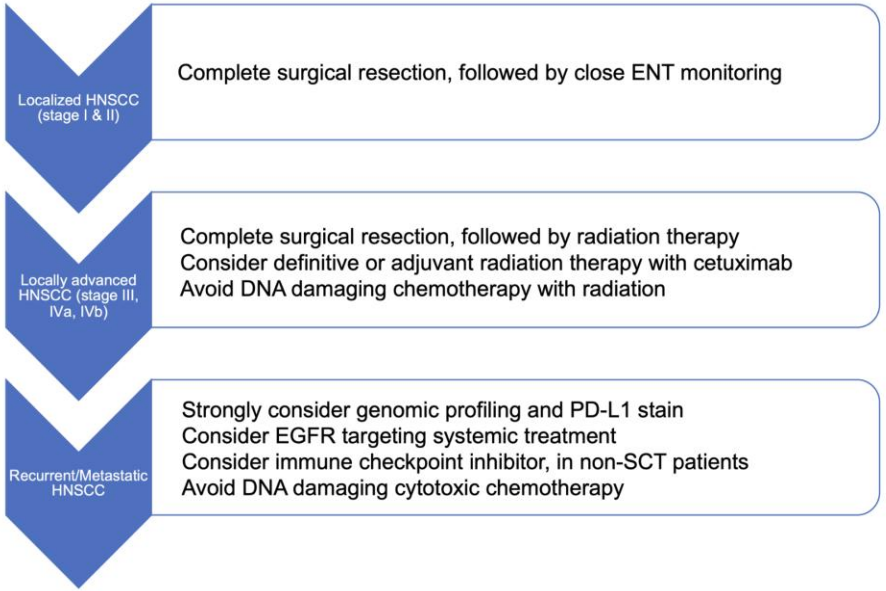


Fig. 1 The AFAN study protocol design


Localized HNSCC (stage I & II)
Complete surgical resection, followed by close ENT monitoring
Locally advanced HNSCC (stage III, IVa, IVb)
Complete surgical resection, followed by radiation therapy
Consider definitive or adjuvant radiation therapy with cetuximab
Avoid DNA damaging chemotherapy with radiation
Recurrent/Metastatic HNSCC
Strongly consider genomic profiling and PD-L1 stain
Consider EGFR targeting systemic treatment
Consider immune checkpoint inhibitor, in non-SCT patients
Avoid DNA damaging cytotoxic chemotherapy

Advantages

- Increase follow up may help in anticipate diagnosis, allowing for curative surgical treatment by sparing RT and CT tox
- RT in high volume center may help in anticipate RT toxicities, and to treat promptly
- EGFRi may be active and safer than CDDP
- By acknowledgment of risks, will be minimize the risk of fatal toxicities

Conclusion and THM

- FA pts have an high risk of HNSCC
- Early detection is essential for maximizing curative rate
- High risk of relapse
- Surgery and RT remains the gold standard → pretreatment assessment and close follow up for complications are essential
- CDDP and conventional CT must be spared
- ICIs need more data
- In case of need, EGFRi seems to be the best systemic option

Call to action

At the next young patients, with HNSCC, especially oral cavity, especially with a history of OPMDs, please, let's think and test for FA. In case let's centralize pts treatment

Thanks for your attention!