
SAPIENZA
UNIVERSITÀ DI ROMA

# I TUMORI DEL TESTA COLLO : NUOVE PROSPETTIVE

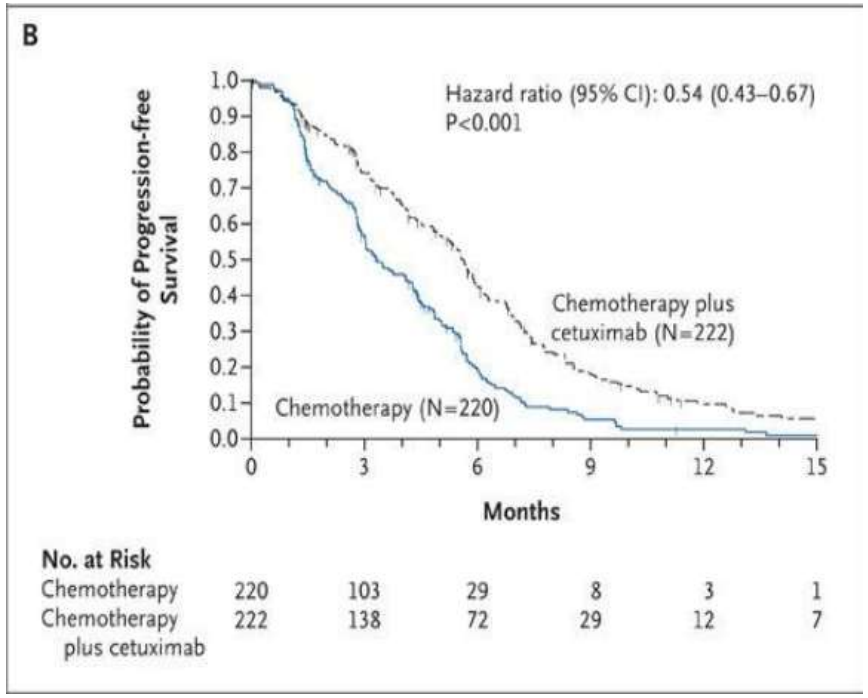
ANDREA BOTTICELLI

SAPIENZA UNIVERSITA' DI ROMA

Roma, 2.12.2019

# DA DOVE PARTIAMO …

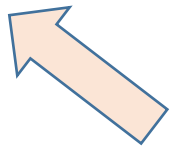
- Head and Neck cancers represent the **sixth most common type of cancer** worldwide, with a prevalence of 6% that translate into **650,000** new cases for year.
- The Head and Neck cancer annual **specific mortality is 1-2%** with **330,000** deaths occurred for year

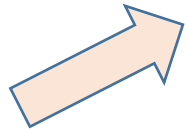



**OS : 10 MESI !!!**

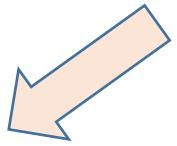
STARTING FROM OLD APPROACH

SELECTING BETTER PATIENTS





**HOW TO INCREASE OUTCOME ???**

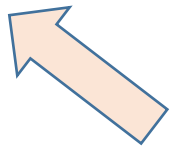


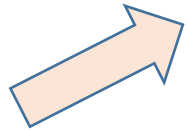
WITH NOVEL COMBINATIONS

WITH NOVEL TARGET

STARTING FROM OLD APPROACH

SELECTING PATIENTS BETTER





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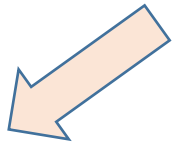

WITH NOVEL COMBINATIONS

WITH NOVEL TARGET

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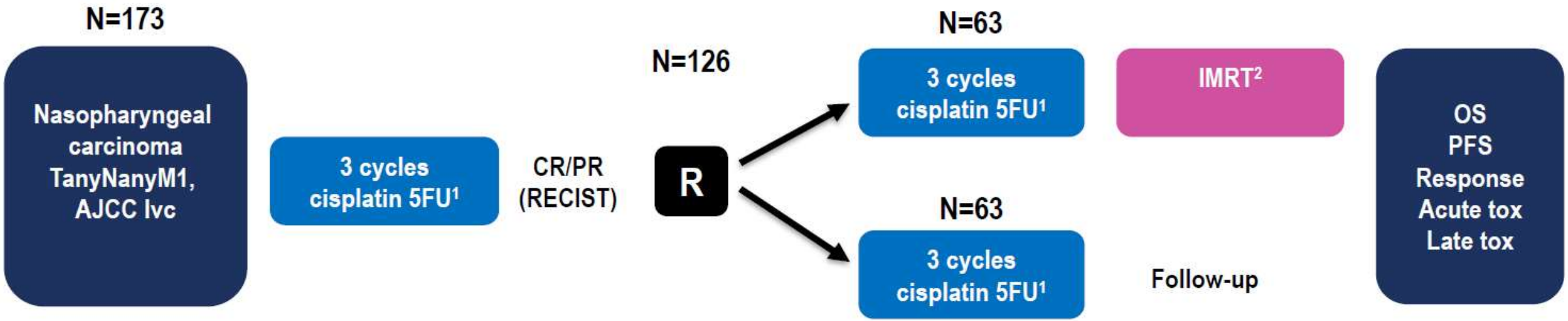
# CHEMOTHERAPY COMBINED WITH RADIOTHERAPY VS CHEMOTHERAPY ALONE FOR DISTANT METASTATIC NASOPHARYNGEAL CARCINOMA (1108O)

**Prof. Ming-Yuan Chen, Principal Investigator** (Sun Yat-sen University, Guangzhou/CHINA), R. You, L. You-Ping, P.Y. Huang, X. Zou, G.P. Shen, H.D. Zhang.

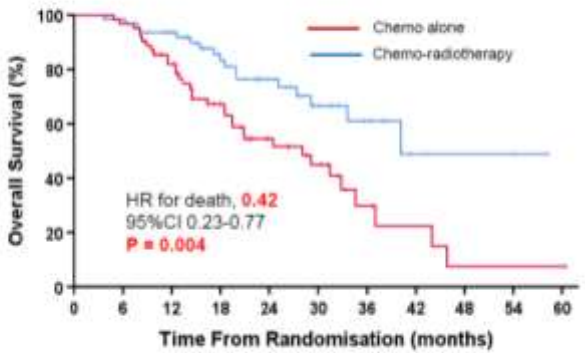



[1] cisplatin 100 mg/m$^2$, iv, day 1, fluorouracil 5 g/m$^2$ continuously iv 120 h
[2] 66-70 Gy in 28-33 fr on primary tumor, 60-66 Gy in 28-33 fr on lymph nodes

**Closed at interim analysis**

## OVERALL SURVIVAL

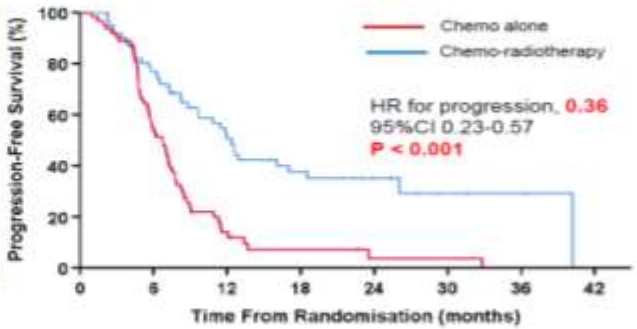
| | Chemo + radiotherapy N = 63 | Chemo alone N = 63 |
|---|---|---|
| Overall survival | | |
| Deaths | 17 (27.0%) | 34 (54.0%) |
| OS 6 mo | 98.4% (95.2-100.0) | 96.8% (92.5-100.0) |
| OS 12 mo | 93.6% (87.5-99.7) | 81.9% (72.3-91.5) |
| OS 24 mo | 76.4% (64.4-88.4) | 54.5% (41.0-68.0) |




The date of last follow-up: August 2019,
the median follow-up: 26.7 months

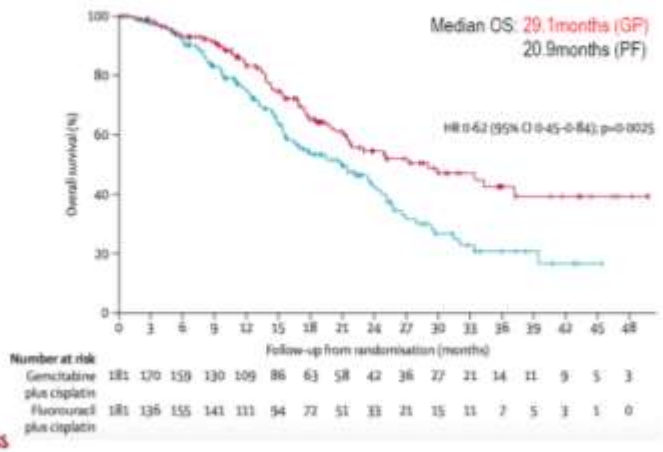
## PROGRESSION FREE SURVIVAL

| | Chemo + radiotherapy N = 63 | Chemo alone N = 63 |
|---|---|---|
| PFS | | |
| Failures | 37 (58.7%) | 56 (88.9%) |
| Median PFS, mo | 12.4 (10.5-14.2) | 6.7 (5.4-8.0) |
| PFS 6 mo | 76.9% (66.3-87.5) | 54.6% (42.1-67.1) |
| PFS 12 mo | 50.6% (37.3-63.9) | 13.9% (4.7-23.1) |
| PFS 24 mo | 35.0% (21.7-48.3) | 3.6% (0-9.7) |




The date of last follow-up: August 2019
the median follow-up: 26.7 months

## GEMCITABINE + CISPLATIN SUPERIOR TO CISPLATIN + 5FU




PFS 7 vs 5,6 months

Zhang et al. Lancet 2016

## CONCLUSIONS

- Radiotherapy to the primary tumor and LN added to chemotherapy significantly improves OS in chemotherapy-sensitive metastatic NPC patients.

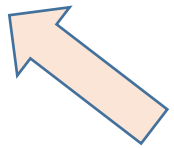
➢ **This treatment paradigm represents the new standard of care**

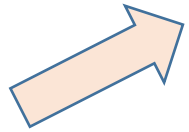
**Remaining questions:**

- Can we safely replace 5FU by gemcitabine?
- Do all patients benefit or just the patients with low metastatic burden?
- Could patients with oligometastatic disease benefit from a more aggressive approach?

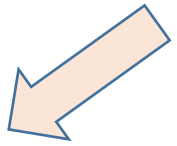
STARTING FROM OLD APPROACH

SELECTING BETTER PATIENTS





**HOW TO INCREASE OUTCOME ???**



WITH NOVEL COMBINATIONS

WITH NOVEL TARGET

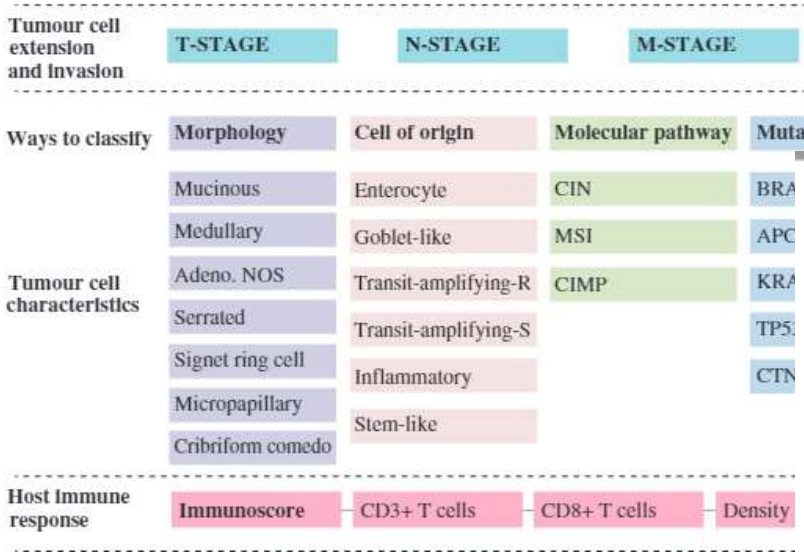
PD1114

# High Immunoscore® is associated with good response to neo-adjuvant chemotherapy and prolonged survival in advanced Head and Neck cancer patients

Haitham Mirghani, Clémence Mure, Bernhard Mlecnik, Fabienne Hermitte, Elise Martel, Odile Casiraghi, Mariana Iacob, Caroline Even, Jérôme Galon.

# FROM CRC TO HN CANCER…






**IMMUNOSCORE® METHODOLOGY**

- Digital method for the quantification of the densities of CD3+ and CD8+ T cells in the center of the tumour (CT) and the invasive margin (IM);
- Stratifies patients into 3 Immunoscore® categories (Low, Intermediate and High) and as a continuous variable
- Prognostic and predictive value of Immunoscore® validated in localized colon cancer

**COHORT**

130 patients involved in the study (62 Hypopharynx, 68 Larynx):

- 110 patients with a valid Immunoscore® results (53 hypopharynx, 57 larynx).
- 103 patients with valid Immunoscore® results and complete clinical data (47 Hypopharynx, 56 larynx).
- 108 patients with valid Immunoscore® and response assessment data

**IMMUNOSCORE® DISTRIBUTION**

Immunoscore® distribution in the total cohort (N=110)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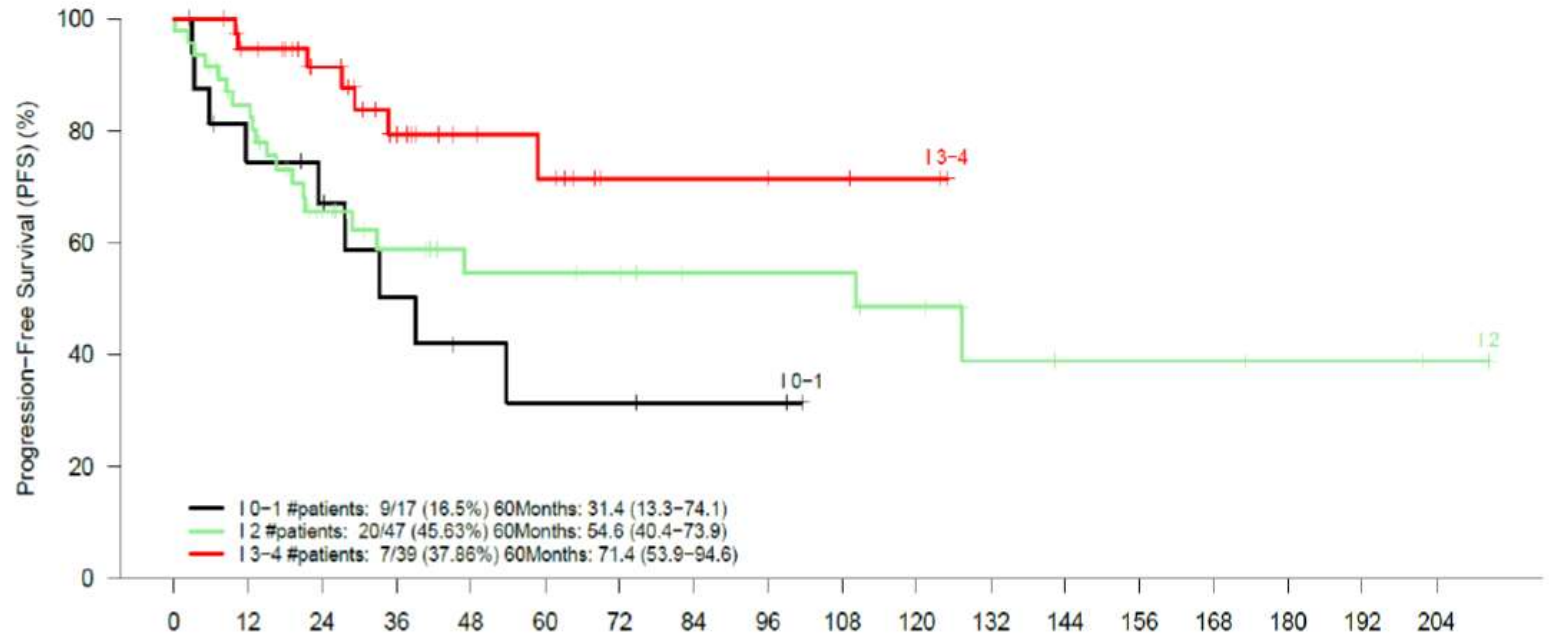
# A High Immunoscore® is associated with better prognostic (5-year PFS)




**In the global cohort (n=103), 5-years PFS rate was:**

**- 71.4% (CI 53.9–94.6) for IS high (3-4) patients**

**- 54.6%, CI 95% (40.4–73.9) for IS Intermediate (2) patients**

**- 31.4%, CI 95% (13.3–74.1) for IS Low (0-1) patients**

**High vs Low HR = 0.27 CI 95% (0.10–0.74), P corrected= 0.0214.**

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# PD-L1 : NEVERENDING STORY…

## PD-L1 STAINING

**TPS** (Tumor Proportion Score)

$$TPS = \frac{\text{Number of PD-L1 stained } \textbf{tumor cells}}{\text{Total number of viable tumor cells}} \times 100$$

*Reported as a* ***percentage***

**CPS** (Combined Positive Score)

$$CPS = \frac{\text{Number of PD-L1 stained } \textbf{cells} \text{ (tumor cells, lymphocytes, macrophages)}}{\text{Total number of viable tumor cells}} \times 100$$

*Reported as a* ***number*** *(capped at 100)*

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## KEYNOTE 040 STUDY DESIGN

**Key Eligibility Criteria**

- SCC of the oral cavity, pharynx, or larynx
- PD after platinum-containing regimen
- ECOG PS 0 or 1

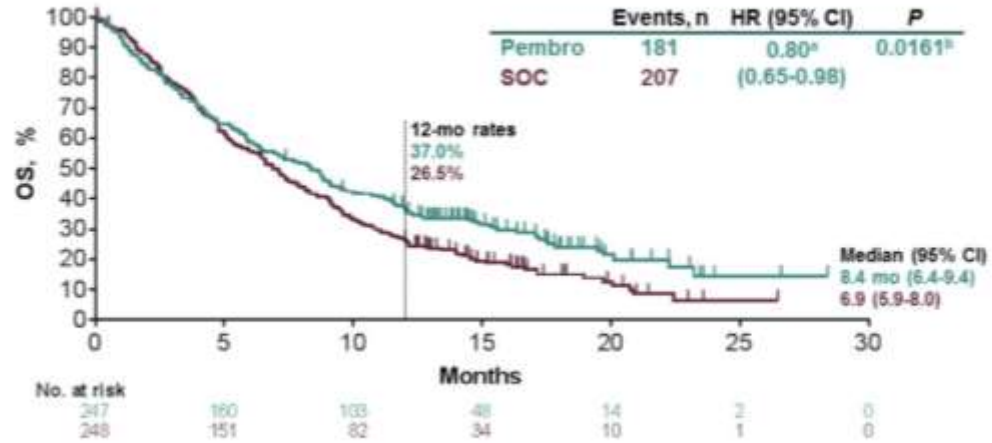
N=495

R 1:1

- Pembrolizumab 200 mg IV Q3W for 2 y
- Methotrexate 40 mg/m² QW[d] OR Docetaxel 75 mg/m² Q3W OR Cetuximab 250 mg/m² QW[e]

Cohen et al. Lancet 2019

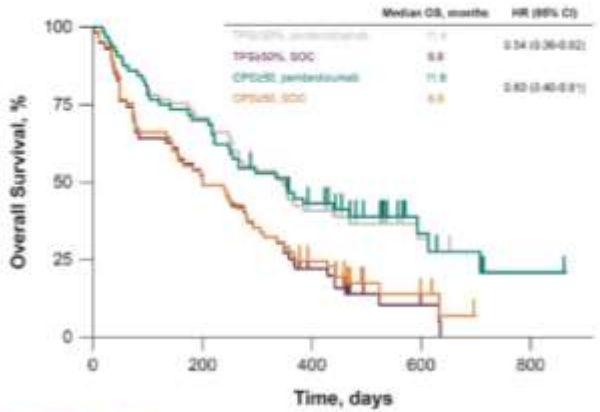
## OVERALL SURVIVAL



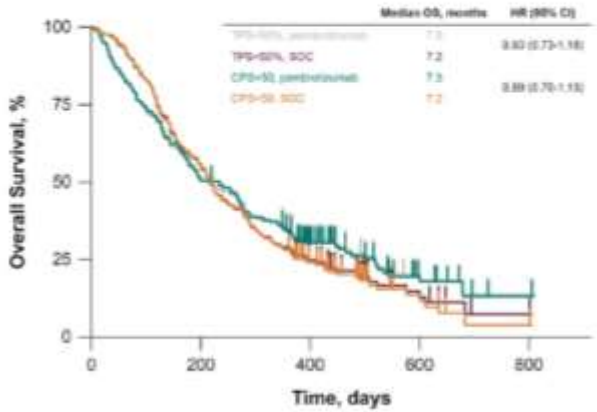

Cohen et al. Lancet 2019

## OVERALL SURVIVAL OF PATIENTS WITH SCORES ≥ 50 OR < 50

### TPS or CPS ≥50



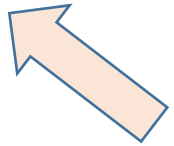

### TPS or CPS <50

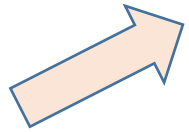



Cohen et al. ESMO 2019.

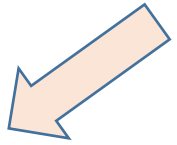
STARTING FROM OLD APPROACH

BETTER SELECTING PATIENTS





**HOW TO INCREASE OUTCOME ???**



**WITH NOVEL COMBINATIONS**

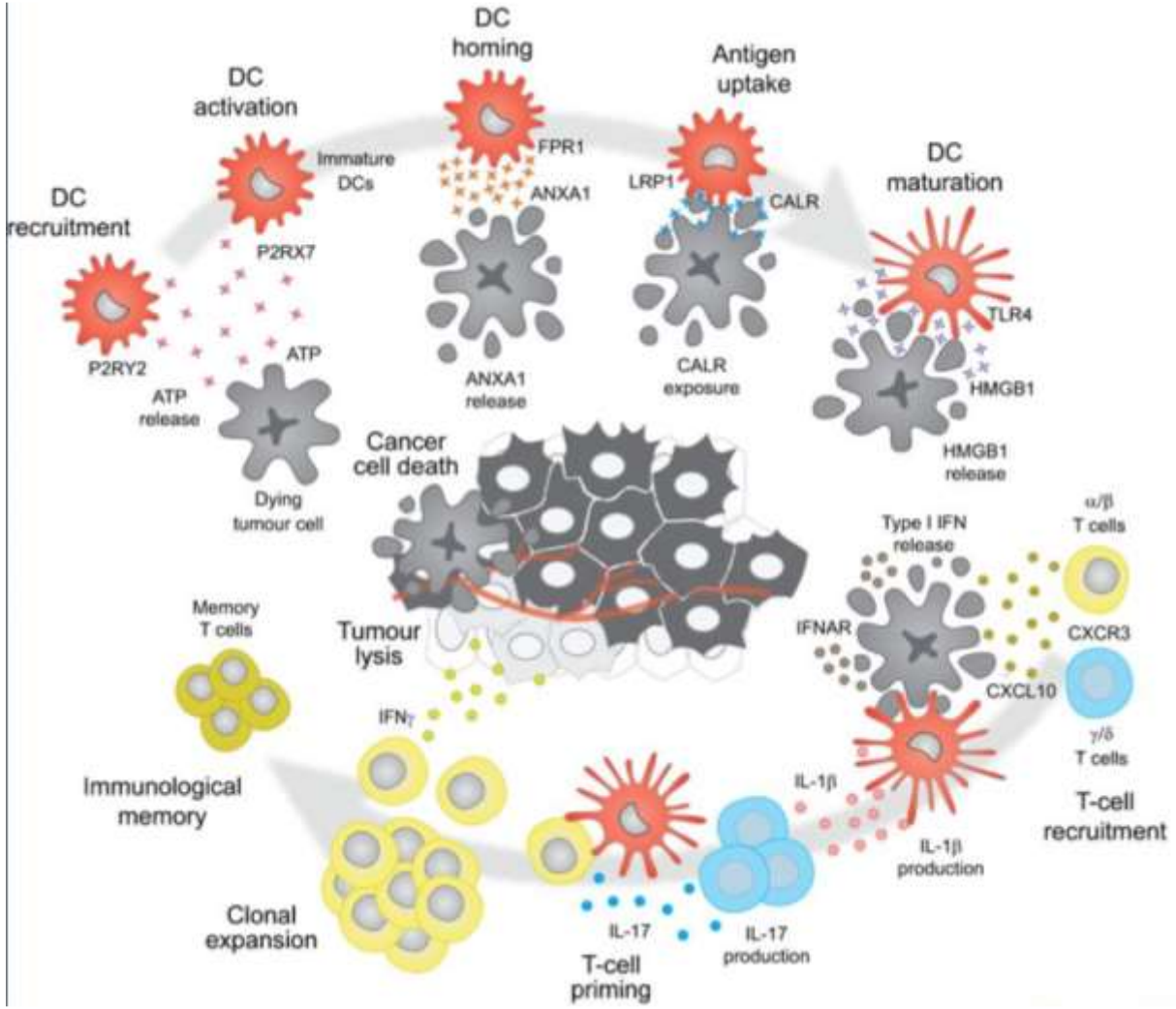
**WITH NOVEL TARGET**

# Protocol-Specified Final Results of the KEYNOTE-048 Trial of Pembrolizumab as First-Line Therapy for Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Danny Rischin[1], Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté,[8] Prakash Neupane,[9] Åse Bratland,[10] Thorsten Fuereder,[11] Brett GM Hughes,[12] Ricard Mesia,[13] Nuttapong Ngamphaiboon,[14] Tamara Rordorf,[15] Wan Zamaniah Wan Ishak,[16] Yayan Zhang,[17] Fan Jin,[17] Burak Gumuscu,[17] Barbara Burtness[18]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK; [3]Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; [4]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Barcelona, Spain; [9]University of Kansas Medical Center, Kansas City, KS, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna, Vienna, Austria; [12]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, QLD, Australia; [13]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Malaysia; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA

# CHT + IMMUNO



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# DOUBLE-BLIND RANDOMIZED PHASE II RESULTS COMPARING CONCURRENT HIGH-DOSE CISPLATIN CHEMORADIATION PLUS DEBIO 1143 OR PLACEBO IN HIGH-RISK PATIENTS WITH LOCALLY-ADVANCED SCCHN (LBA65)

**Prof. Jean Bourhis, Principal Investigator** (CHUV Lausanne – Suisse) on behalf of the GORTEC Investigators:
XS. Sun, Y. Pointreau, C. Sire, C. Le Tourneau, A. Coutte, MC. Kaminsky-Forret, M. Alfonsi, P. Boisselier, L. Martin, JP. Delord, F. Clatot, J. Miroir, F. Rolland, P. Crompton, S. Brienza, S. Szyldergemajn, C. Even and Y. Tao.

**PART A**
Dose escalation Phase I*
**Primary endpoint**
Definition of MTD/RP2D with CRT

Debio 1143 RP2D: 200mg QD

**PART B** Randomized Phase II

N=96 (ITT)
R
1:1

**Debio 1143 + CRT n=48**
- Debio 1143 at RP2D/Placebo D1- D14 every 21 days
- CDDP 100mg/m² every 21 days, both up to 3 cycles
- Radiation 2Gy 5d/week for up to 70Gy/50Gy to GTV/elective lymph nodes

**Placebo + CRT n=47**

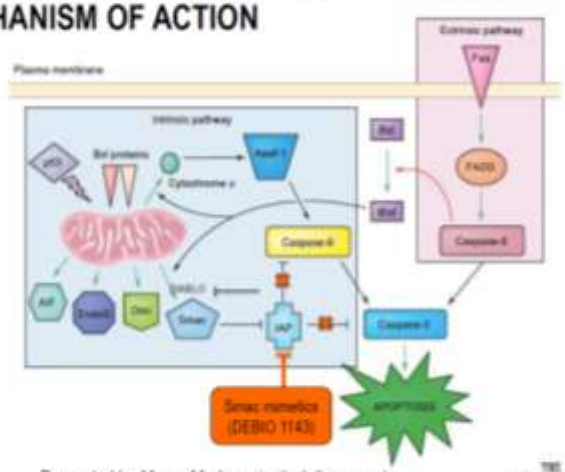
Stratified by
- N2-N1 vs N2-N3
- Primary tumor site (OPC vs non-OPC)
  - If, OPC by HPV/p16 status

**Primary endpoint**
- Locoregional control rate at 18 months after CRT (Δ>20% between arms with 0.8 power at 0.2 significance level)

**Key secondary endpoints**
- PFS
- Duration of LRC
- Overall survival
- OR and CR at 3 and 6 months after CRT completion

# CHT + TARGET

## TARGETING INHIBITOR OF APOPTOSIS PROTEINS (IAP): MECHANISM OF ACTION



IAP antagonists:

1. Promote tumor cell apoptosis
2. Regulate multiple steps in antitumor immunity

Presented by Marco Merlano, invited discussant

From: Shuzaki EN et al. TRENDS Biochem Sience 2004 - modified

# PRIMARY ENDPOINT

## LRC-rate at 18 months (as per investigator) - ITT

| | Debio 1143 + CRT N=48 | Placebo + CRT N=48 | Debio 1143 vs. Placebo + CRT |
|---|---|---|---|
| **Event-Free at 18 Months** | 26 (54.2%) | 16 (33.3%) | |
| **Event or Censored before 18 Months** | 22 (45.8%) | 32 (66.7%) | |
| Events | 9 (18.8%) | 11 (22.9%) | |
| Censored | 13 (27.1%) | 21 (43.8%) | |
| | | | |
| **Locoregional Control Rate (%)** (95% CI) | **54.2** (39.2 ; 68.6) | **33.3** (20.4 ; 48.4) | **Δ:20.8** **(1.4 ; 40.2)** |
| Odds Ratio (95% CI) (Debio 1143 vs. Placebo) | | | 2.69 (1.13 ; 6.42) |
| **p-value** | | | **0.026** |

**Primary endpoint met: LRC-rate improve by >20% at 18 months after CRT**

**Safety with Debio 1143 was predictable and manageable without increases in life-threatening toxicities nor late toxicities**

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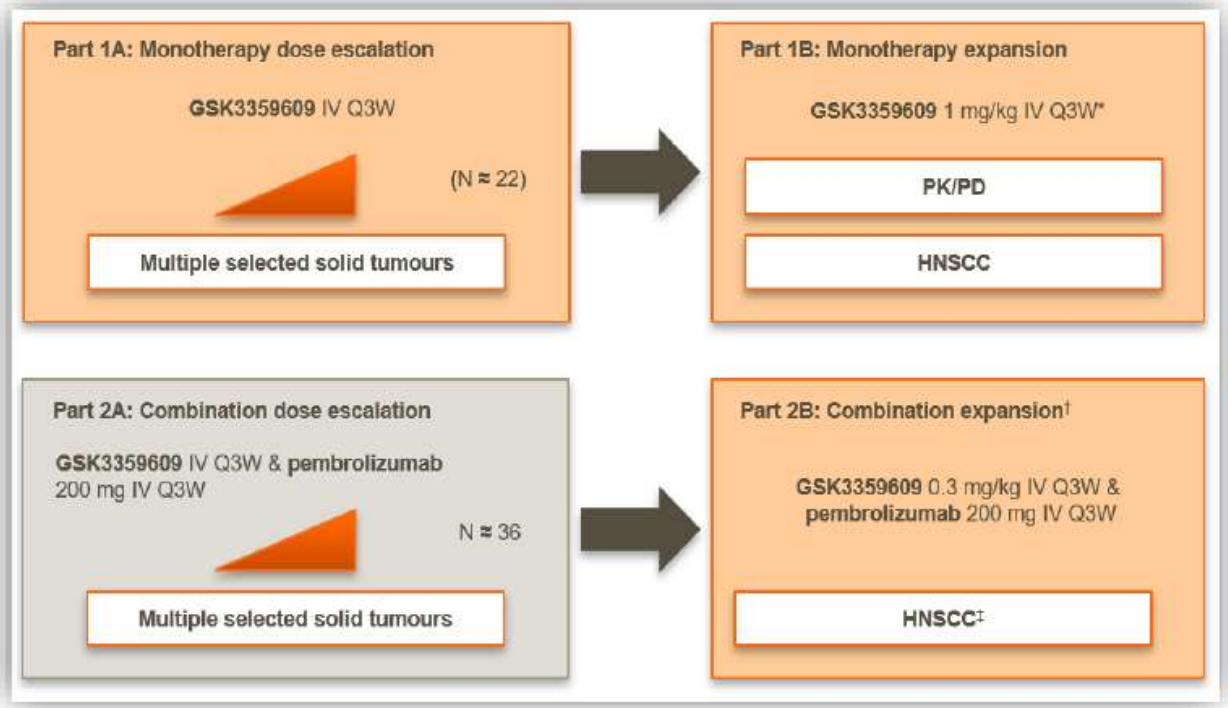
# Inducible T-cell co-stimulatory (ICOS) receptor agonist, GSK3359609 alone and in combination with pembrolizumab: preliminary results from INDUCE-1 expansion cohorts in head and neck squamous cell carcinoma (HNSCC)

## INDUCE-1: Study Design




**COMBO IMMUNO**

**ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28**

Andreas Hutloff*, Anna M. Dittrich*†, Katja C. Beier*†, Barbara Eljaschewitsch*, Regine Kraft‡, Ionnis Anagnostopoulos§ & Richard A. Kroczek*

*Hutloff et al Nature 1999*

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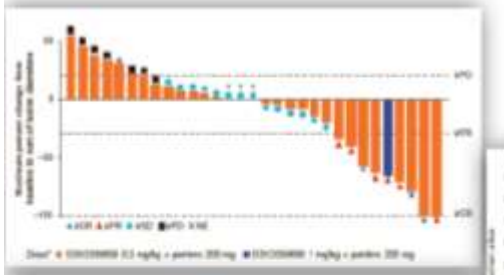
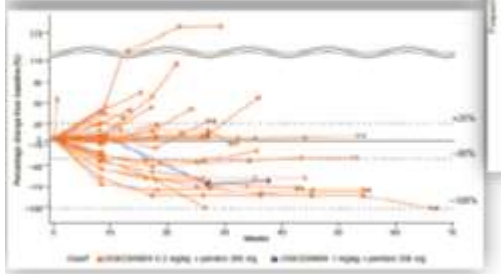
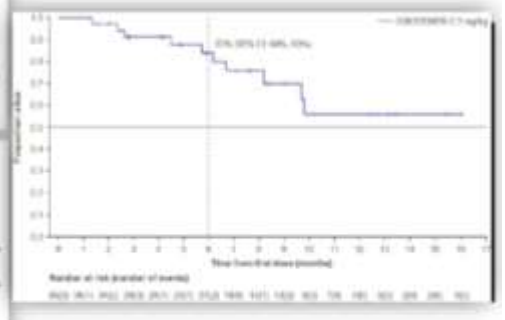
*Rischin D, Groenland S, Lim AM, Martin-Liberal J, Moreno V, Trigo J, Le Tourneau C, Mathew M, Cho D, Hansen A, Vicente Baz D, Maio M, Italiano A, Bauman J, Chisamore M, Zhou H, Ellis C, Ballas M, Hoos A, Angevin E*

# RESULTS:

## Combo cohort: Efficacy







- In the combination cohort:
  - ORR was 24% (n=8; 95% CI: 10.7, 41.2) and DCR was 65% (n=22; 95% CI: 46.5, 80.3) from 34 evaluable patients
  - Responses were durable with all responding patients maintaining benefit for ≥6 months
  - Median OS was not reached at time of analysis (95% CI: 8.2, NR); further analyses of OS are ongoing
  - Median PFS was 5.6 months (95% CI: 2.4, 7.4)

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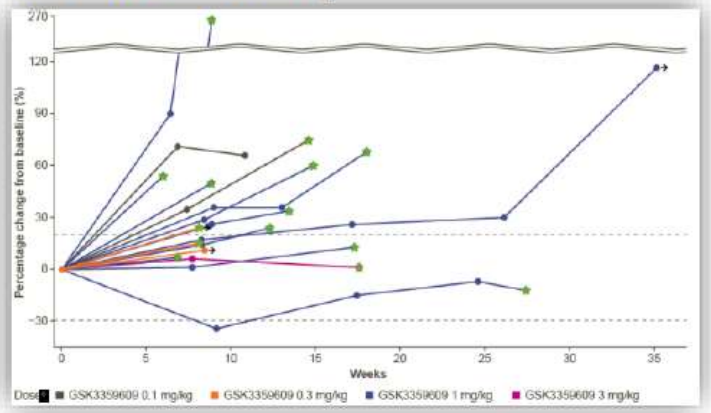
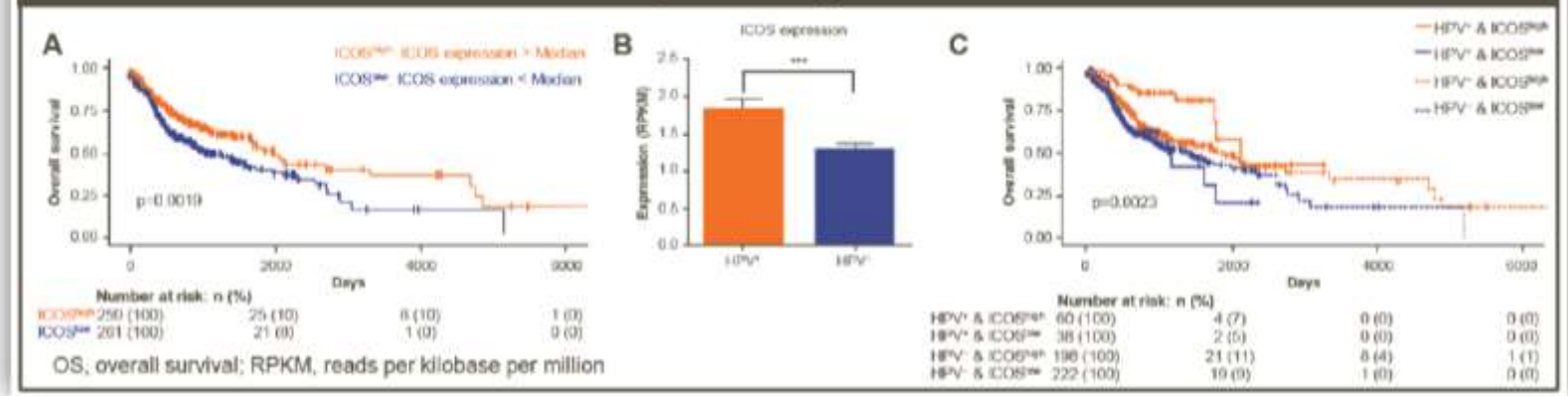
## Mono cohort: Efficacy




- Of the 16 evaluable patients in the monotherapy cohort, ORR was 6% (n=1; 95% CI: 0.2, 30.2) and DCR was 31% (n=5; 95% CI: 11.0, 58.7)

**Figure 2. A) OS rates are higher in patients with high ICOS-expressing ($ICOS^{high}$) HNSCC tumours when compared with patients with low ICOS expressing ($ICOS^{low}$) HNSCC tumours; B) ICOS expression is higher in $HPV^{+}$ H&N tumours than those that are $HPV^{-}$; and C) OS rates are higher in patients with $HPV^{+}/ICOS^{high}$ HNSCC tumours, when compared with patients with $HPV^{+}ICOS^{low}$ HNSCC tumours**




OS, overall survival; RPKM, reads per kilobase per million

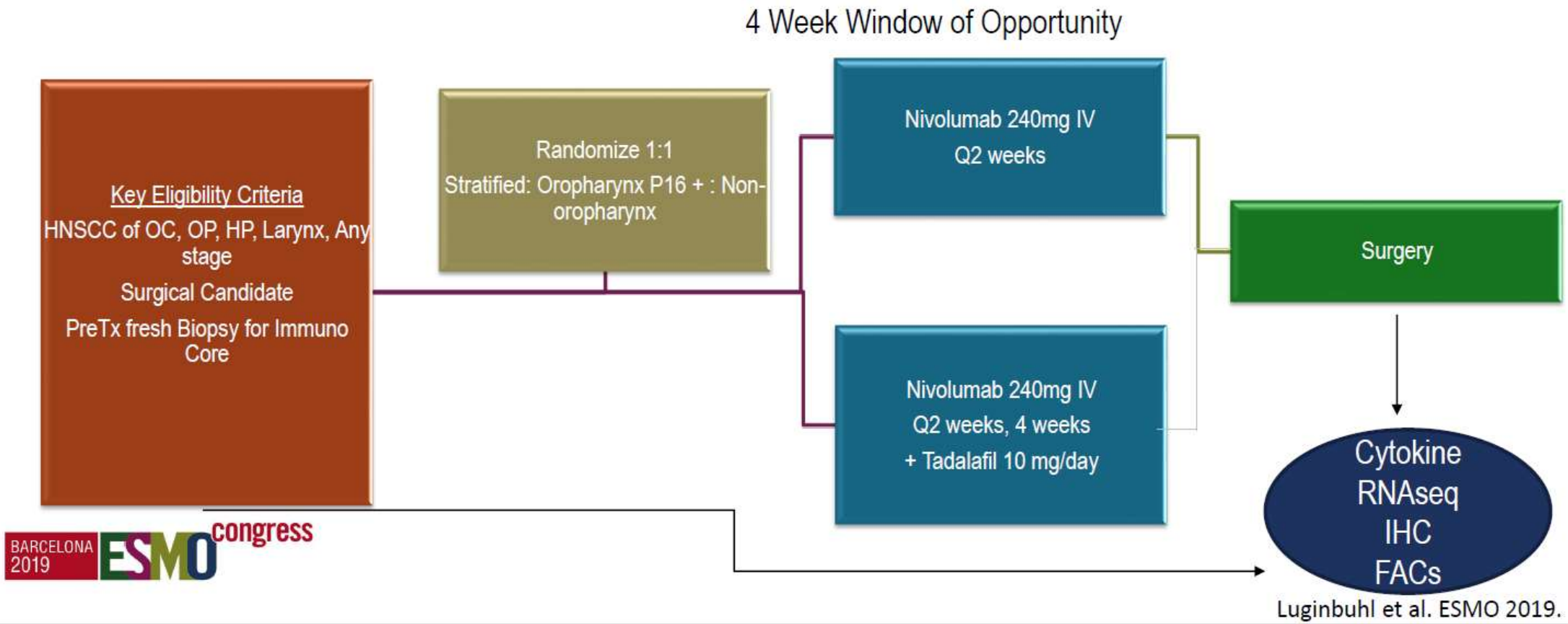
# IMMUNO + MODULATORI

## NIVOLUMAB + TADALAFIL (ABSTR. 1116)

Background: Tadalafil alters immune microenvironment

↑ $CD8^+$ effector cells with boost in IL-2 production

↓ Myeloid Derived Suppressor Cells (MDSCs), Tregs, Arginase

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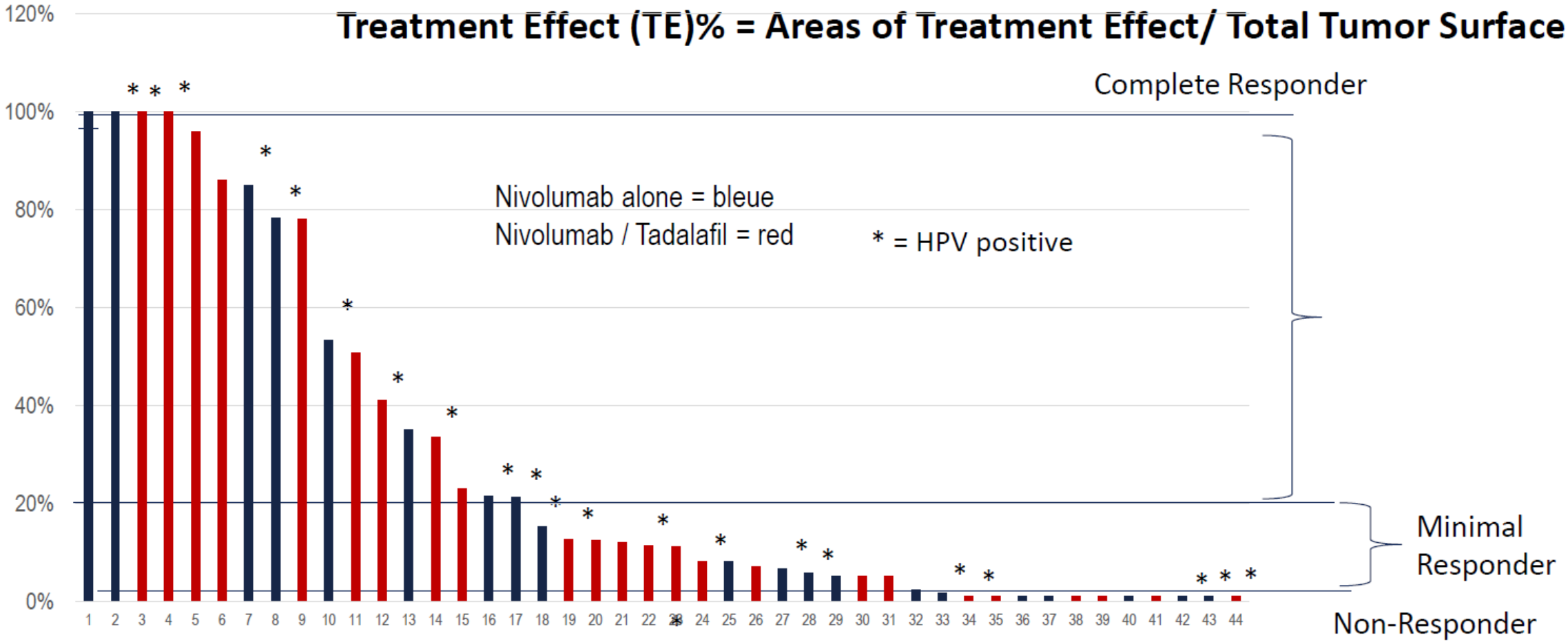
Luginbuhl et al. ESMO 2019.

# PATHOLOGIC TREATMENT EFFECT: PRIMARY SITE (ABSTR. 1116)

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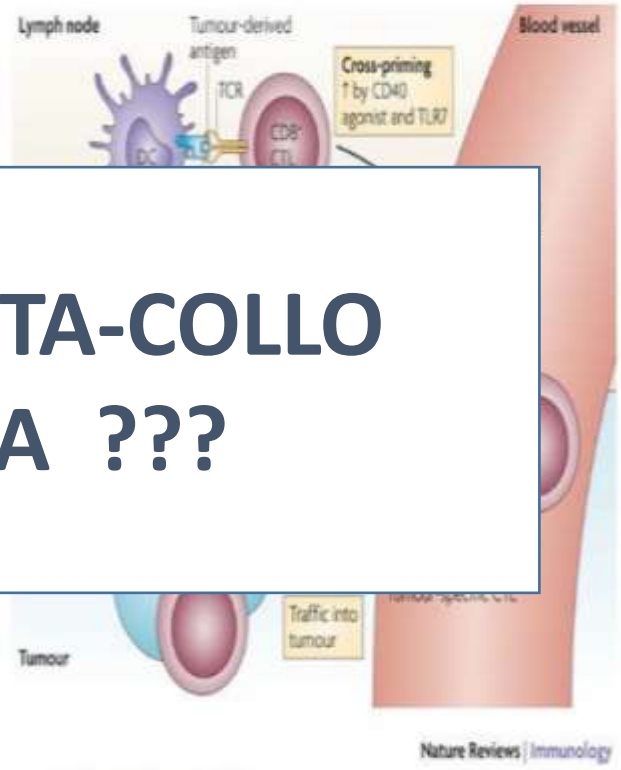
Luginbuhl et al. ESMO 2019.

# IL SETTING …CONTA!

- Neoadjuvant
  - Chemotherapy cross-priming
  - Opportunity for novel combinations




**E NEL TESTA-COLLO CONTA ???**



## Immunotherapy with pembrolizumab in HPV-negative locally advanced, surgically resectable HNSCC

Pre-treatment biopsy and PBMCs → Neoadjuvant Pembrolizumab (1 dose) → 2-3 weeks → Surgery (original margins) with biopsy and PBMCs

- -ECE/margins →standard of care
- +ECE/margins →PO-ACRT → Maintenance pembrolizumab

NCT02296684

ASCO ANNUAL MEETING '17 | #ASCO17 Presented by: R. Uppaluri

## Tumor Response

| Patient ID | cTNM | pTNM | ECE/ +Margin | LRR/DM | Time from pembro to surgery (days) | Response | Method |
|---|---|---|---|---|---|---|---|
| 1 | T4N2c | T4N2c | + | None | 15 | + | Exam/CT |
| 2 | T4N2b | T4N2b | + | None* | 15 | | |
| 3 | T4N0 | T2N0 | | None | 18 | | |
| 4 | T4N0 | T3N0 | | None | 17 | + | Exam/CT/Path |
| 5 | T4N2c | T4N2c | + | None | 15 | | |
| 6 | T4N0 | T4N0 | | None | 19 | | |
| 7 | T4N1 | T3N0 | | None | 18 | | |
| 8 | T4N0 | T4NX | | None | 15 | | |
| 9 | T4N2b | T4N1 | | None | 18 | | |
| 10 | T4N2b | T4N1 | | None | 14 | + | Path |
| 11 | T4N0 | T4N1 | | None | 21 | | |
| 12 | T4N2a | T4N0 | | None | 16 | | |
| 13 | T2N1 | T1N1 | | None | 14 | + | Exam/path |
| 14 | T4N2b | T3N0 | + | None | 18 | + | Exam |
| 15 | T4N2c | T4N2c | + | None | 13+34 | + | Path |
| 16 | T4N2 | T4N2b | + | None** | 15 | | |
| 17 | T4N2c | T4N1 | + | None | 16 | + | Path |
| 18 | T4N2B | T4N2b | | None | 22 | + | Path |
| 19 | T4N2b | T4N2b | | None | 14 | + | Exam/Path |
| 20 | T2N2B | T1N0 | | None | 15 | + | Exam/CT/Path |
| 21 | T4N1 | T4N1 | + | None | 19 | + | Path |
| 22 | T2N2b | T2N2b | + | None | 16 | | |
| 23 | T4N2b | T4N2b | + | Surgery 5/15 | 20 | + | Path |
| 24 | T4N0 | T4N0 | | Surgery 5/12 | 18 | | |
| 25 | T4N2c | | | Surgery on 6/13 | | | |

Response= change in tumor noted on exam, CT or pathology

50% (12/24) with evidence of response

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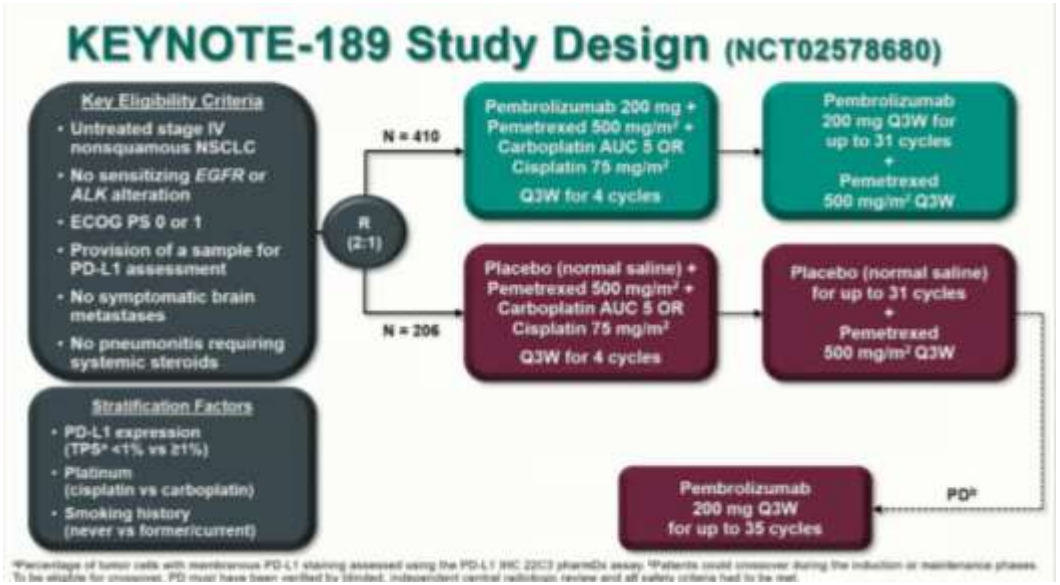
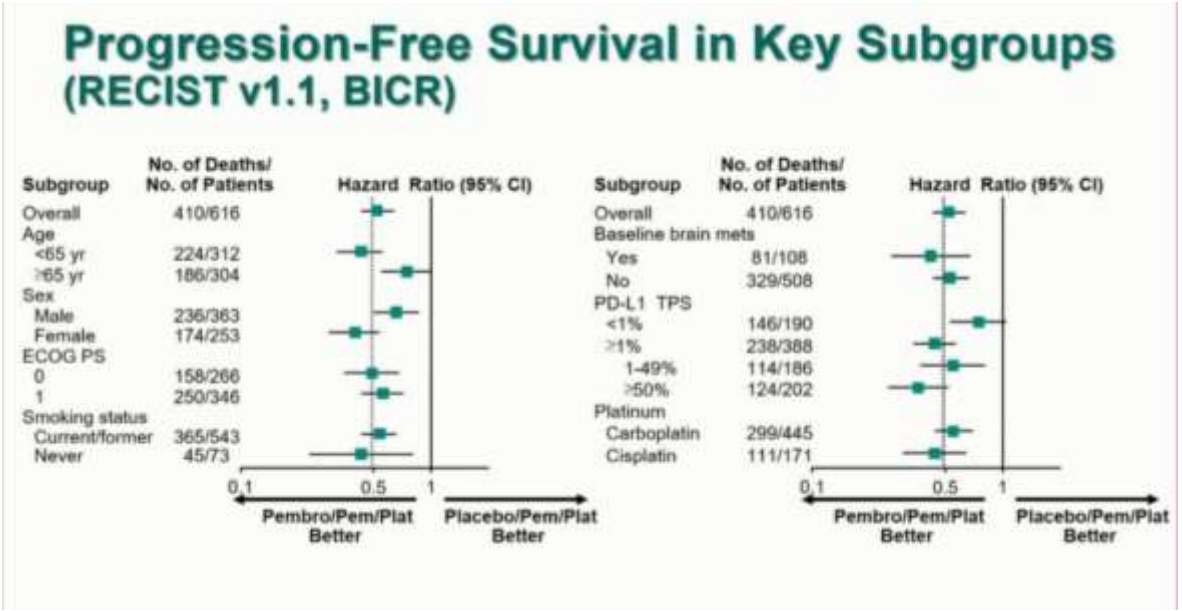
# NEED TRIAL
# 53 PAZIENTI HN 2L

| | Univariate analysis |
|---|---|
| | P value |
| Age (≥ 69 years) | ns |
| Sex | ns |
| linfoadenectomia | ns |
| N linfonodi | ns |
| Sedi metastatiche | ns |
| PS | ns |
| CBDCA vs CDDP | 0,03 |

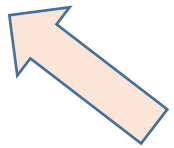
Botticelli, Mezi, Pomati, Cassano, Ronzino, Pizzuti, Vici, Cortellini, Salati, Nuti, Marchetti. unsubmitted

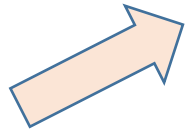


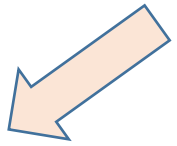
STARTING FROM OLD APPROACH

BETTER SELECTING PATIENTS





**HOW TO INCREASE OUTCOME ???**



WITH NOVEL COMBINATIONS

**WITH NOVEL TARGET**

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UCLouvain
Institut de recherche expérimentale et clinique

INSTITUT ROI ALBERT II

EORTC
The future of cancer therapy

# A PHASE II STUDY OF MONALIZUMAB IN PATIENTS WITH RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

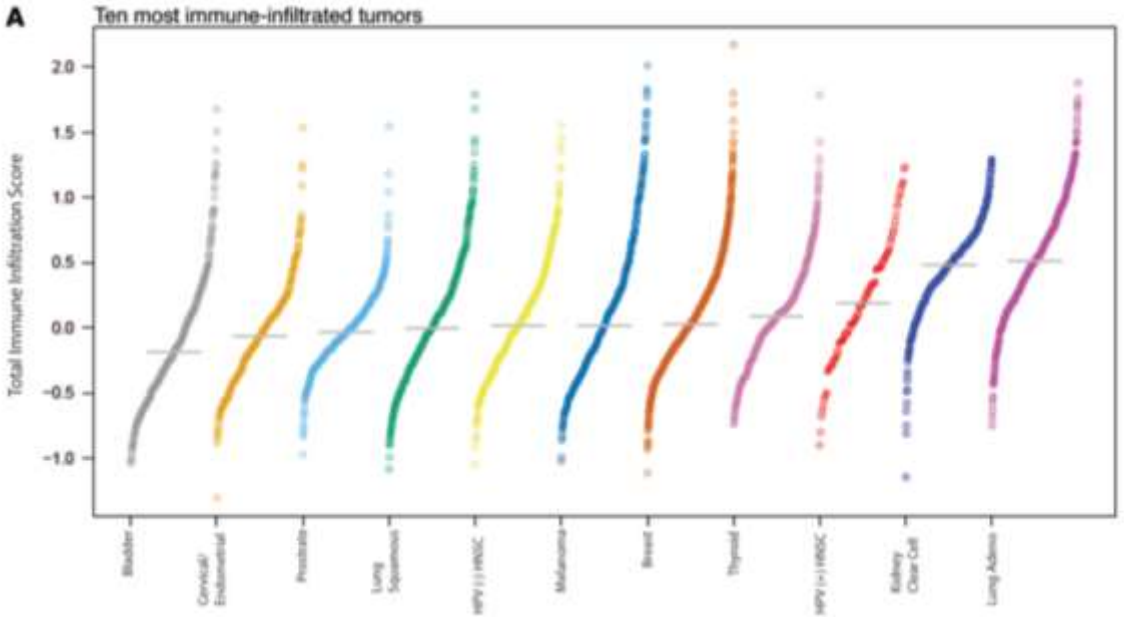
## RESULTS OF THE I1 COHORT OF THE EORTC-HNCG-1559 TRIAL (UPSTREAM)

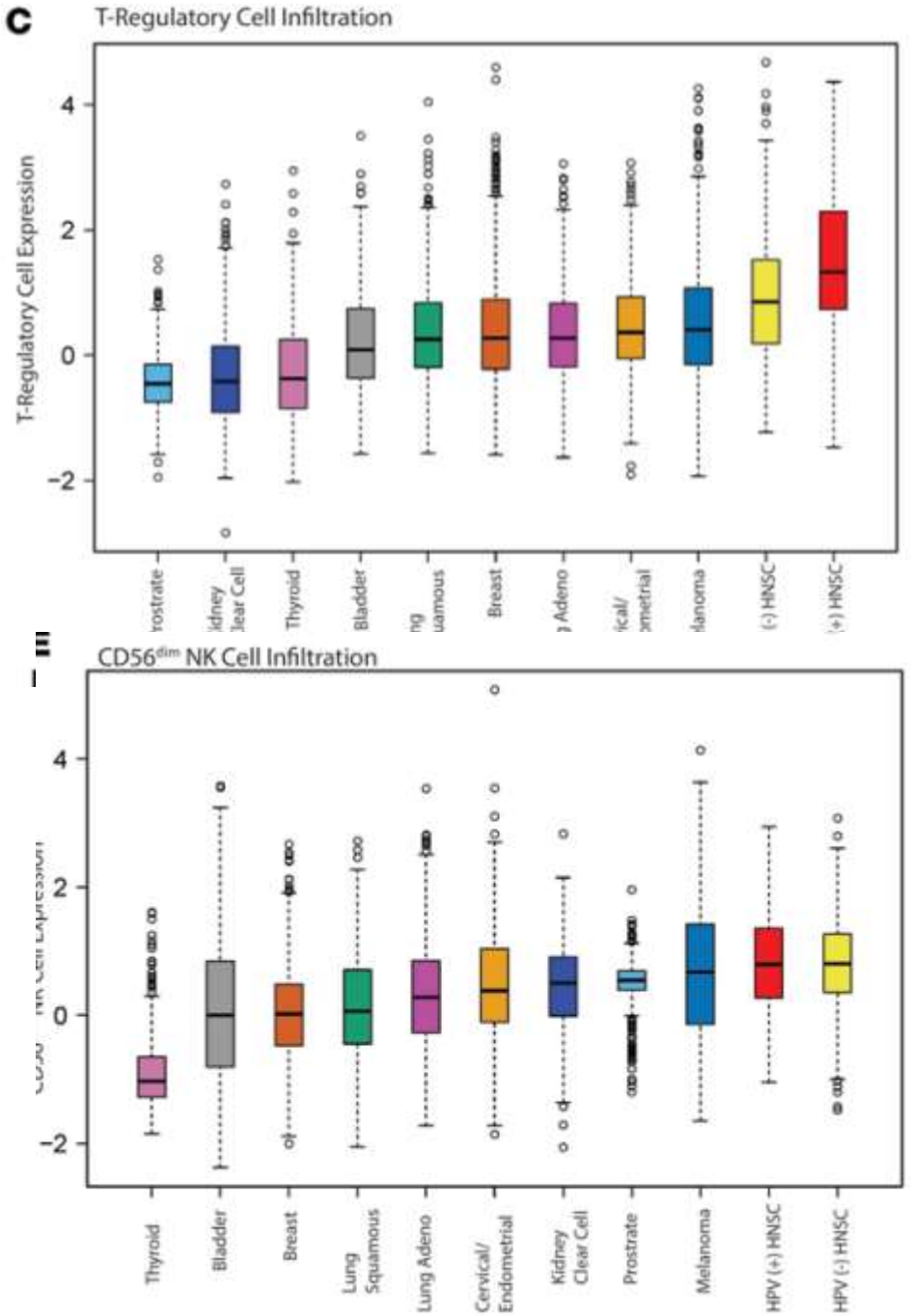
R Galot, C Le Tourneau, E Saada-Bouzid, A Daste, C Even, P Debruyne, S Henry, S Zanetta, A Rutten, L Licitra, JL Canon, MC Kaminsky, P Specenier, S Rottey, L Dirix, T Raveloarivahy, C Fortpied, M Vanlancker, AS Govaerts, JP Machiels

esmo.org

**NUOVA IMMUNO**

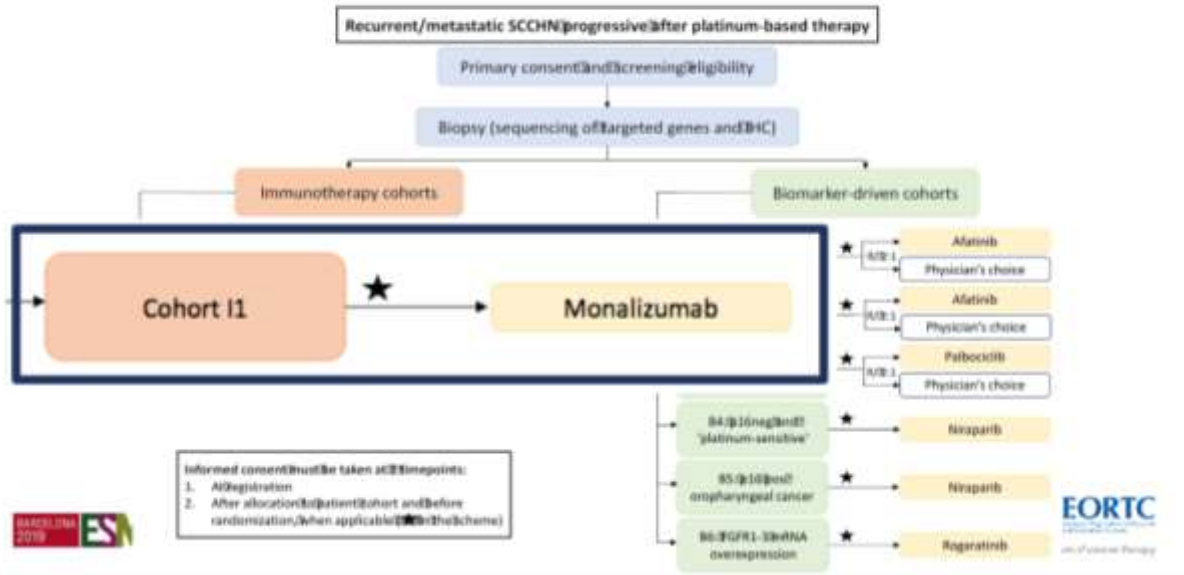
# SONO TUMORI «IMMUNO-INFILTRATI»



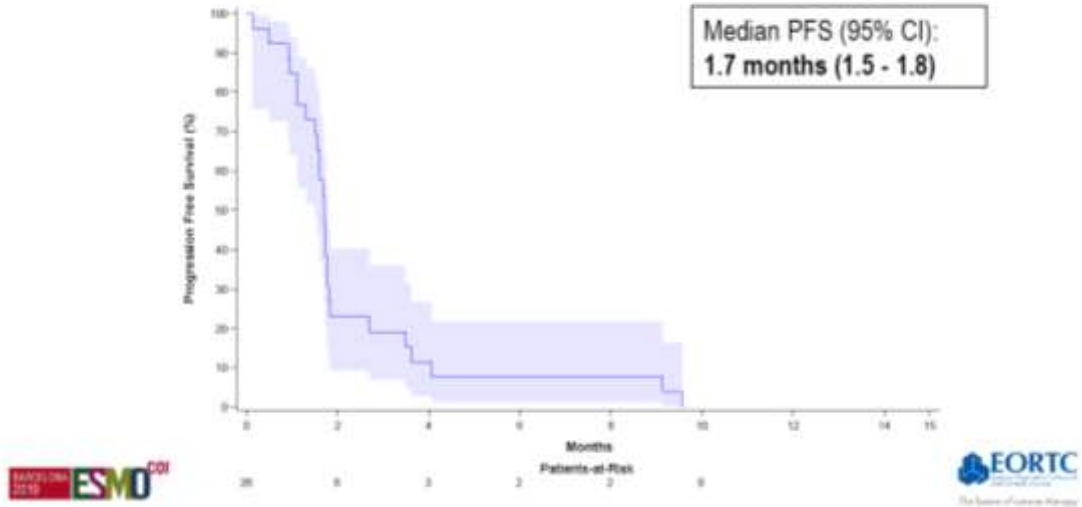




MandalR et al, JCI insight 2016

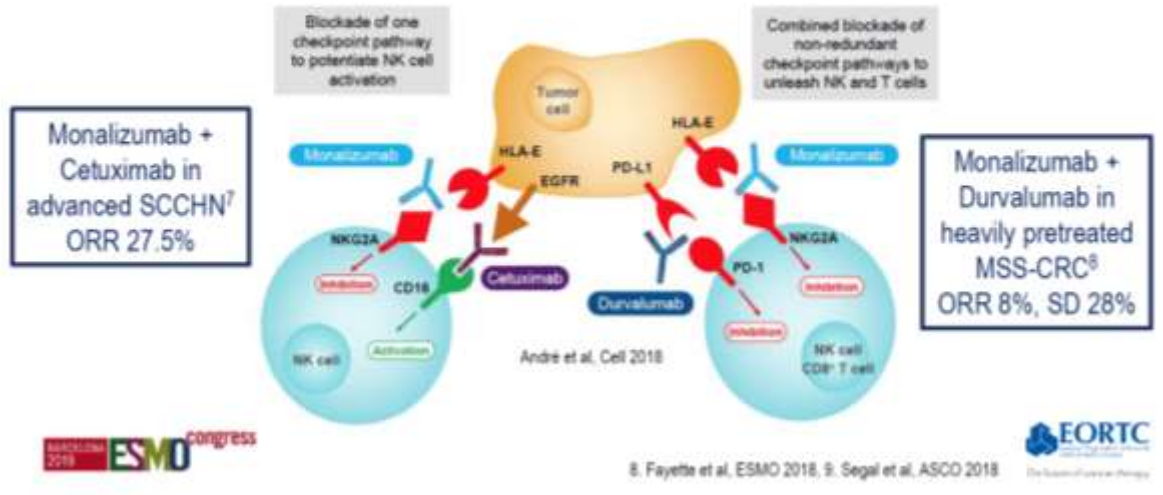
## EORTC-HNCG-1559 TRIAL (UPSTREAM)




## PROGRESSION-FREE SURVIVAL




## MONALIZUMAB




8. Fayette et al. ESMO 2018. 9. Segal et al. ASCO 2018

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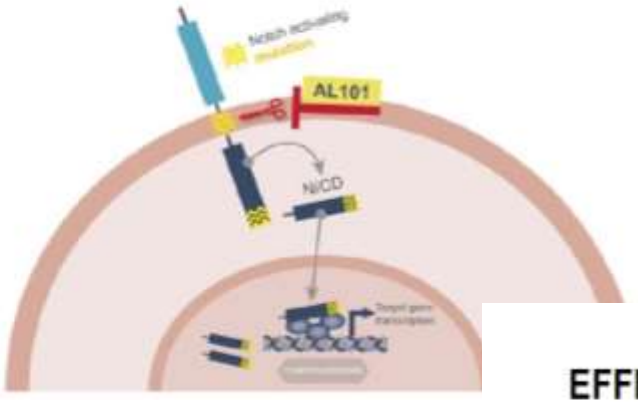
# ACCURACY: A PHASE 2 TRIAL OF AL101, A PAN-NOTCH INHIBITOR, IN PATIENTS WITH RECURRENT/METASTASTIC ADENOID CYCTIC CARCINOMA WITH *NOTCH* ACTIVATING MUTATIONS: PRELIMINARY SAFETY AND EFFICACY DATA (1148P)

**R. Ferrarotto,** (MDAndersen), I.J. Wirth, J. Muzaffar, C. Rodriguez, E. Dekel, R.M. Walker, C. Nadri-Shay, G.S. Gordon, G. Gordon, A.L Ho

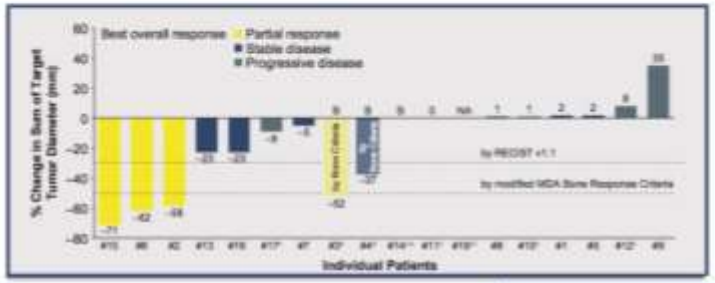
## NUOVA TARGET

- Activating *NOTCH* mutations in 34% of ACCs
- Distinct pattern of metastasis, poor prognosis

Treatment: AL101: 4 mg IV weekly

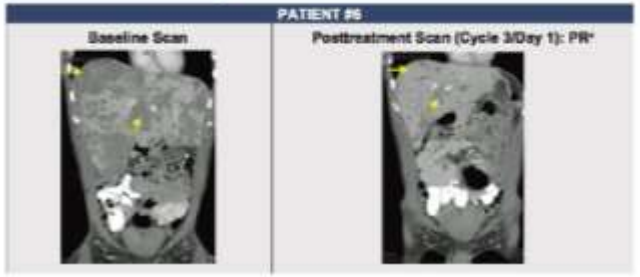



### EFFICACY




Well tolerated
PR 22%
SD 39%
PD 39%

Promising results, stage 2 ongoing

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# COME CAMBIERÀ LA NOSTRA PRATICA CLINICA ?

## IL PUNTO DI VISTA DELL'ESPERTO…