



Associazione Italiana di Oncologia Medica  
SEZIONE NEURONI LADO

**POST ESMO**

*from*  
**BARCELONA**

*to*  
**REAL WORLD**

— ROMA —

NH Collection Vittorio Veneto - C.so d'Italia, 1

2 - 3 Dicembre 2019

# I TUMORI DELLA TESTA E COLLO: IL PARERE DELL'ESPERTO

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*Oncologia Medica e Ricerca Translazionale*

*A.O. S. Croce e Carle - Cuneo*

*e*

*Consultant - Oncologia Medica*

*Candiolo Cancer Center FPO - IRCCS*

*Candiolo (Torino)*

# DISCLOSURE INFORMATION

Marco Merlano

## ***Personal financial interests:***

- Consultancy, speaker, advisory role: Merck KGaA;
- Consultancy, advisory role: Merck Sharp & Dohme, Bristol-Myers Squibb;
- Speaker: AstraZeneca;
- Stocks: Glaxo Smith Kline;

## ***Institutional financial interests:***

- Funding research project: Merck KGaA

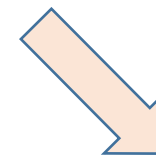
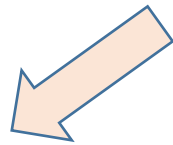
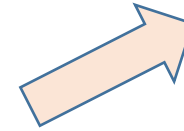
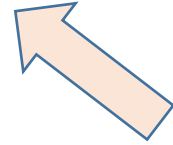
## ***Leadership roles:***

- Vice President: Gruppo Oncologico Nord-Ovest (GONO)

**STARTING FROM OLD  
APPROACH**

**SELECTING BETTER  
PATIENTS**

**HOW TO INCREASE  
OUTCOME ???**

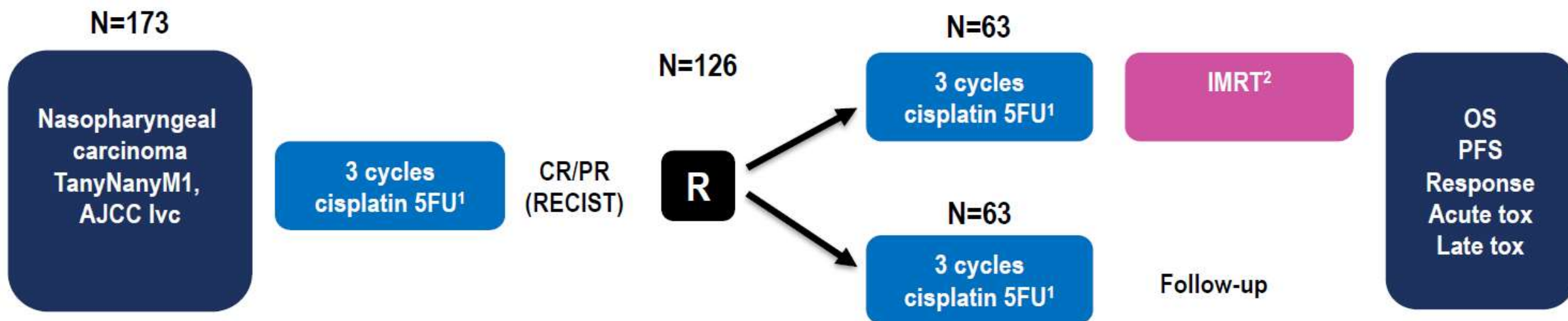


**WITH NOVEL  
COMBINATIONS**

**WITH NOVEL TARGET**

# CHEMOTHERAPY COMBINED WITH RADIOTHERAPY VS CHEMOTHERAPY ALONE FOR DISTANT METASTATIC NASOPHARYNGEAL CARCINOMA (11080)

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.

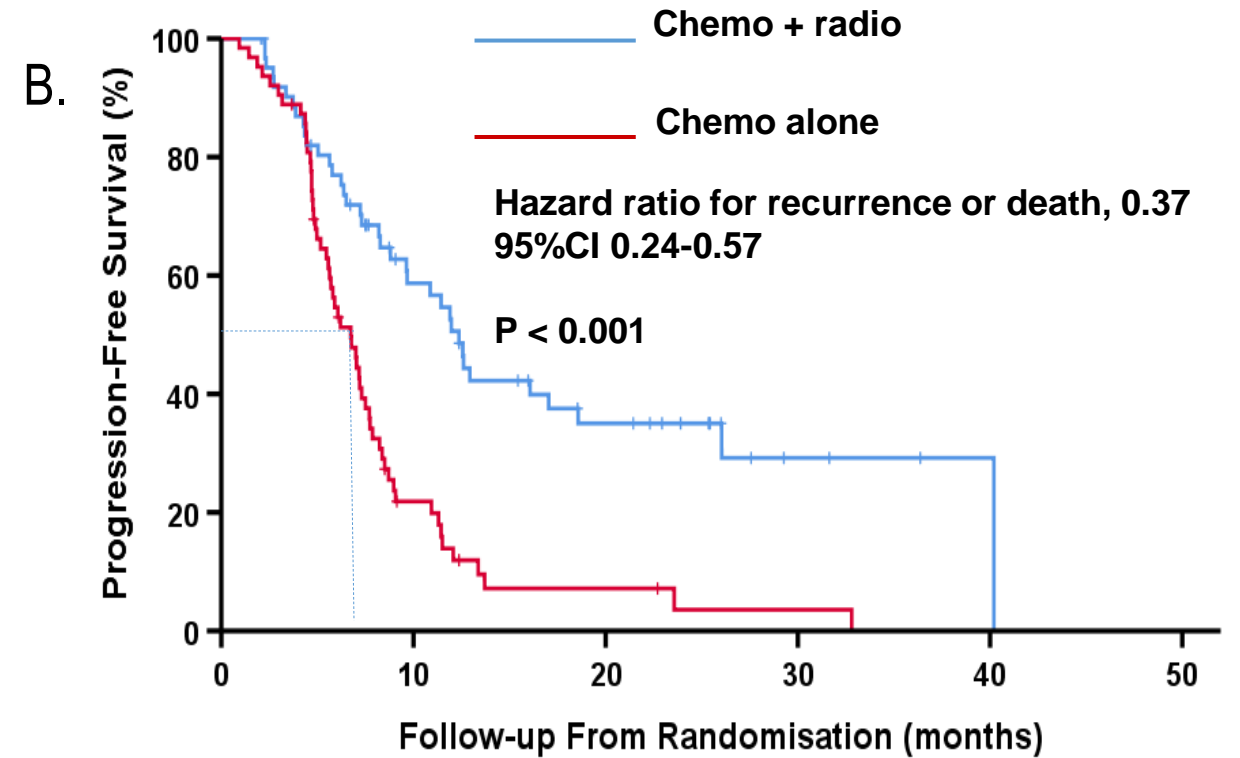
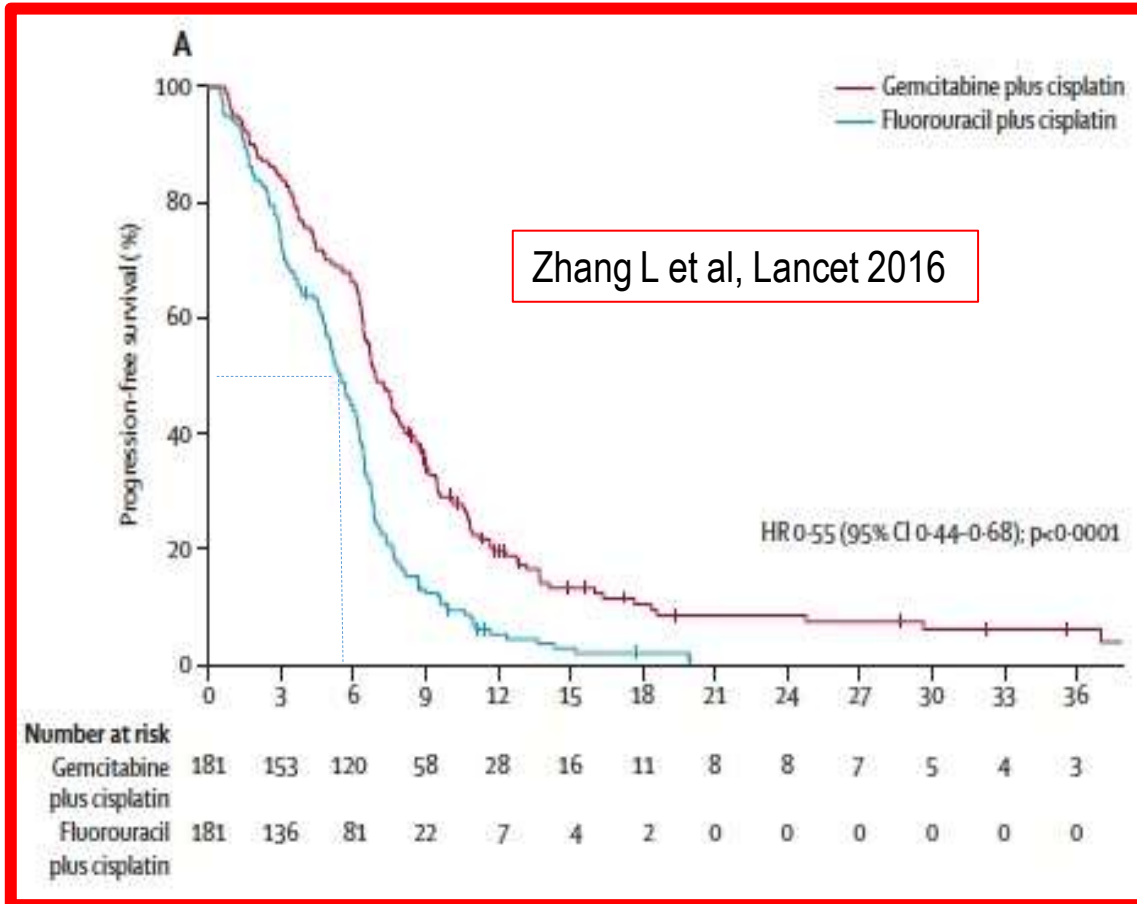


<sup>1</sup> cisplatin 100 mg/m<sup>2</sup>, iv, day 1, fluorouracil 5 g/m<sup>2</sup> continuously iv 120 h

<sup>2</sup> 66-70 Gy in 28-33 fr on primary tumor, 60-66 Gy in 28-33 fr on lymph nodes

**Closed at interim analysis**

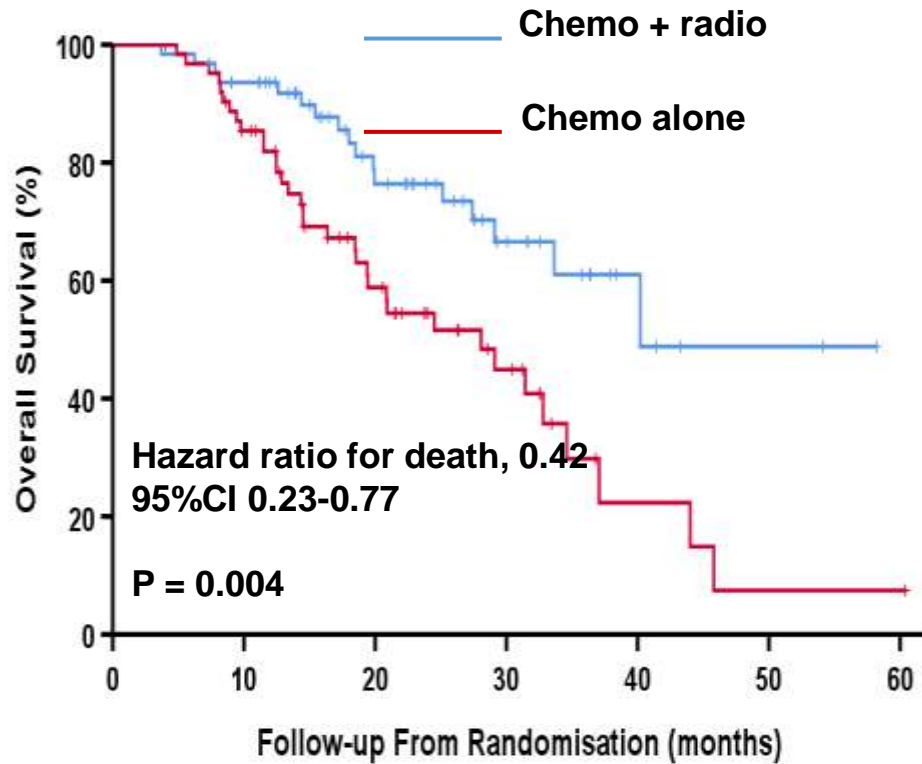
# RESULTS ② : Efficacy



Number at Risk	0	10	20	30	40	50
Chemo + radio	63	29	14	3	1	0
Chemo alone	63	11	3	1	0	0

# RESULTS (2) : Efficacy

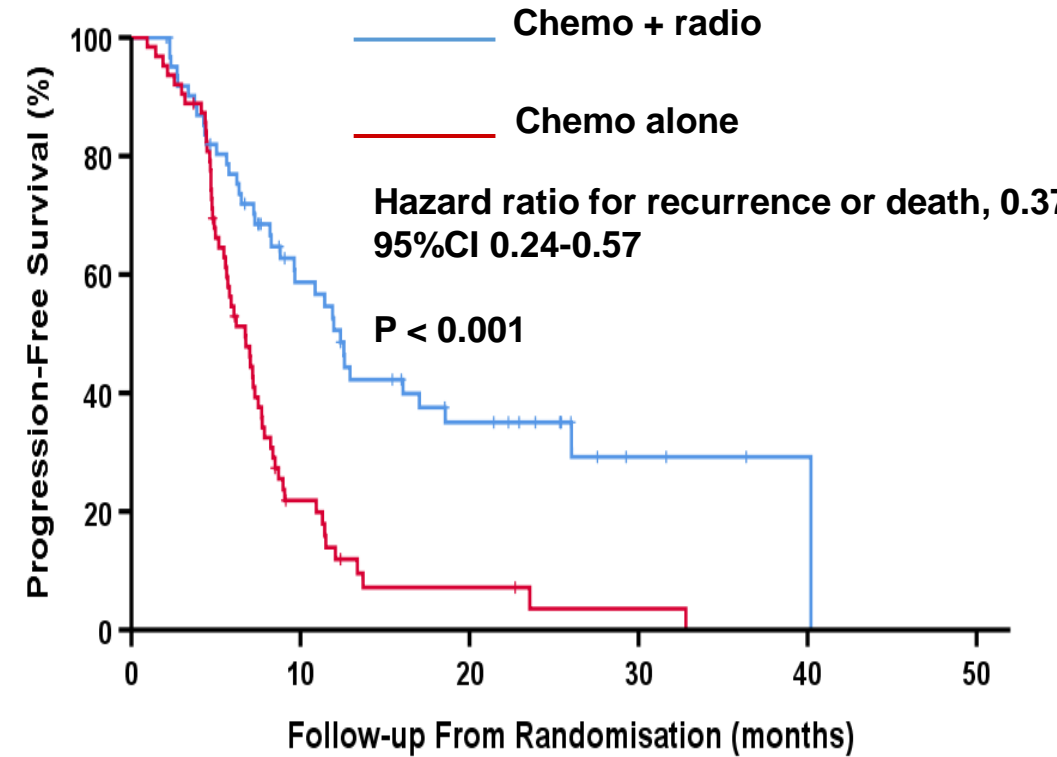
A.



Number at Risk

Chemo + radio	63	56	33	16	5	2	0
Chemo alone	63	51	28	13	3	1	0

B.



Number at Risk

Chemo + radio	63	29	14	3	1	0
Chemo alone	63	11	3	1	0	0

# RESULTS (2) Efficacy

	Chemo + radiotherapy N = 63	Chemo alone N = 63
Overall survival		
Deaths	17 (27.0%)	34 (54.0%)
OS rate at 6 months	98.4% (95.2%-100.0%)	96.8% (92.5%-100.0%)
<b>OS rate at 12 months</b>	<b>93.6% (87.5%-99.7%)</b>	<b>81.9% (72.3%-91.5%)</b>
OS rate at 24 months	76.4% (64.4%-88.4%)	54.5% (41.0%-68.0%)
Progression-free survival		
Failures	37 (58.7%)	56 (88.9%)
Median PFS, months	12.4 (10.5-14.2)	6.7 (5.4-8.0)
PFS rate at 6 months	76.9% (66.3%-87.5%)	54.6% (42.1%-67.1%)
<b>PFS rate at 12 months</b>	<b>50.6% (37.3%-63.9%)</b>	<b>13.9% (4.7%-23.1%)</b>
PFS rate at 24 months	35.0% (21.7%-48.3%)	3.6% (0%-9.7%)

	Chemoradiotherapy N = 63	Chemo alone N = 63
Response to treatment (at the end of chemotherapy)		
Complete response	5 (7.9%)	4 (6.3%)
Partial response	46 (73.0%)	48 (76.2%)
Stable disease	5 (7.9%)	2 (3.2%)
Progressive disease	7 (11.1%)	9 (14.3%)
<b>Overall response</b>	<b>51 (80.9%)</b>	<b>52 (82.5%)</b>
<b>Disease control</b>	<b>56 (88.9%)</b>	<b>55 (85.7%)</b>
Response to treatment (at the end of radiotherapy)¶		
Complete response	10 (16.4%)	-----
Partial response	36 (59.0%)	-----
Stable disease	5 (8.2%)	-----
Progressive disease	8 (13.1%)	-----
Not assessable	2 (3.3%)	-----
<b>Overall response</b>	<b>46 (75.4%)</b>	-----
<b>Disease control</b>	<b>51 (83.6%)</b>	-----

# CONCLUSIONS

- In line with other retrospective analysis, in this prospective randomized study radiotherapy added to chemotherapy significantly improved OS in chemotherapy-sensitive metastatic NPC patients.
- Are patients with limited (or just one) residual sites of disease (induced oligometastases<sup>1</sup>) those who benefit?

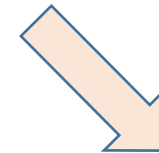
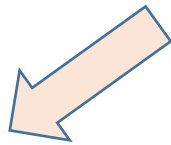
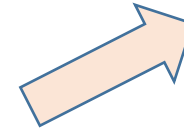
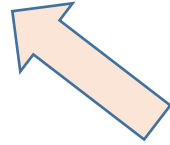
1. Reys DK, Pienta KJ, Oncotarget 2015



**STARTING FROM OLD  
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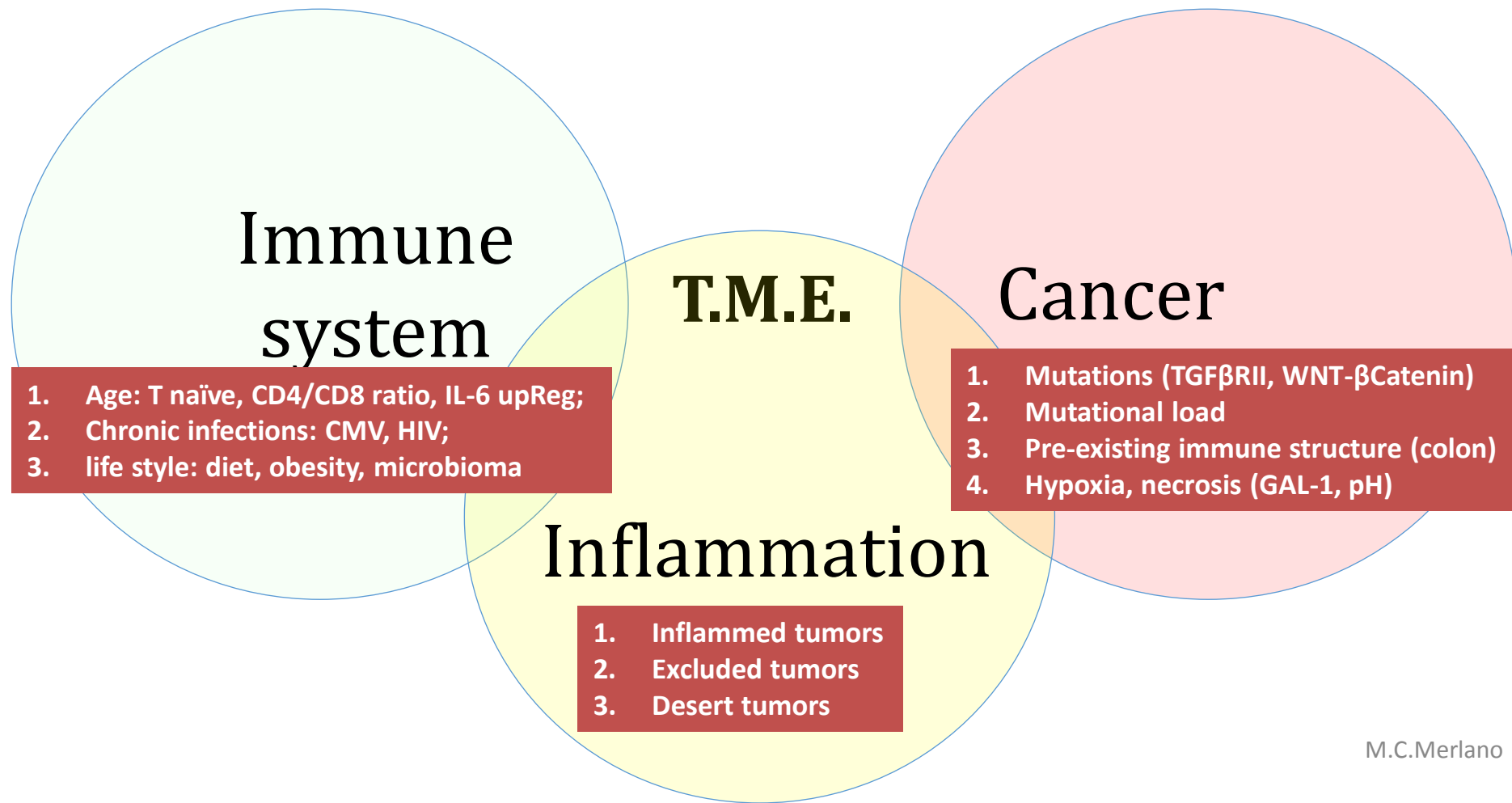
**HOW TO INCREASE  
OUTCOME ???**



**WITH NOVEL  
COMBINATIONS**

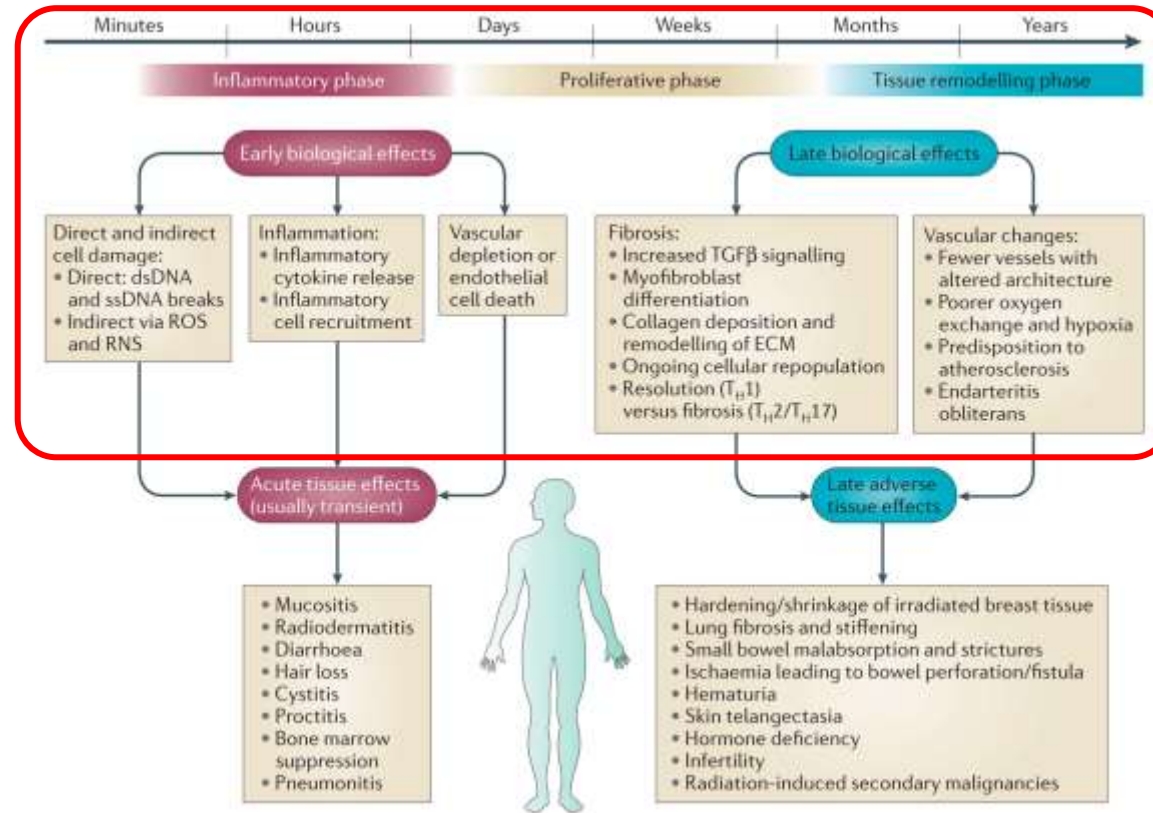
**WITH NOVEL TARGET**

# Factors affecting the TME (and response to immunotherapy)



# TREATMENT EFFECTS

## Effects of RT (at curative dose) over time



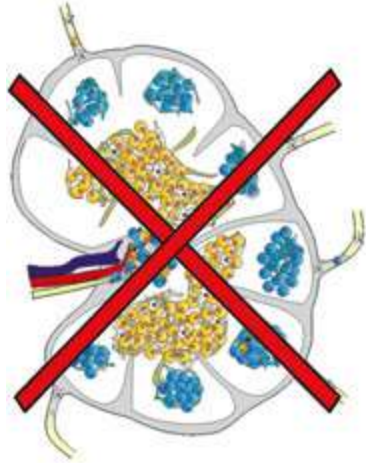
# TREATMENT EFFECTS

Clinical and Experimental Immunology

REVIEW ARTICLE

doi:10.1111/j.1365-2249.2012.04602.x

## Lymph node dissection – understanding the immunological function of lymph nodes



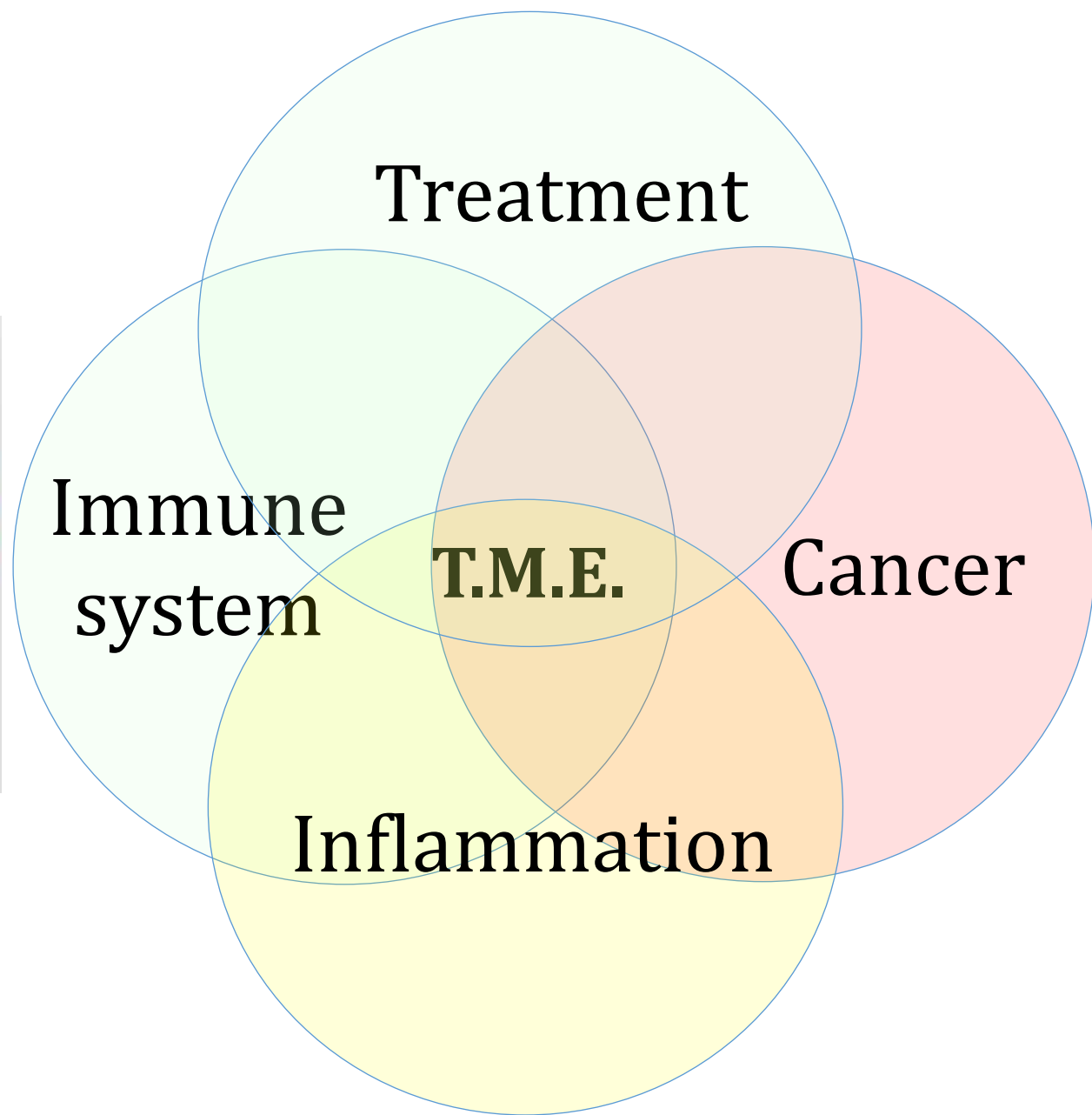
Immune response in the H&N region



Immune response in the Gut

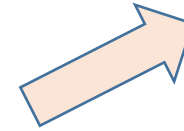
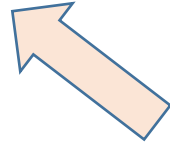


Mucosal tolerance (infections)

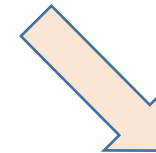
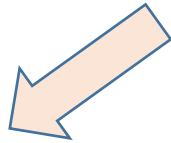


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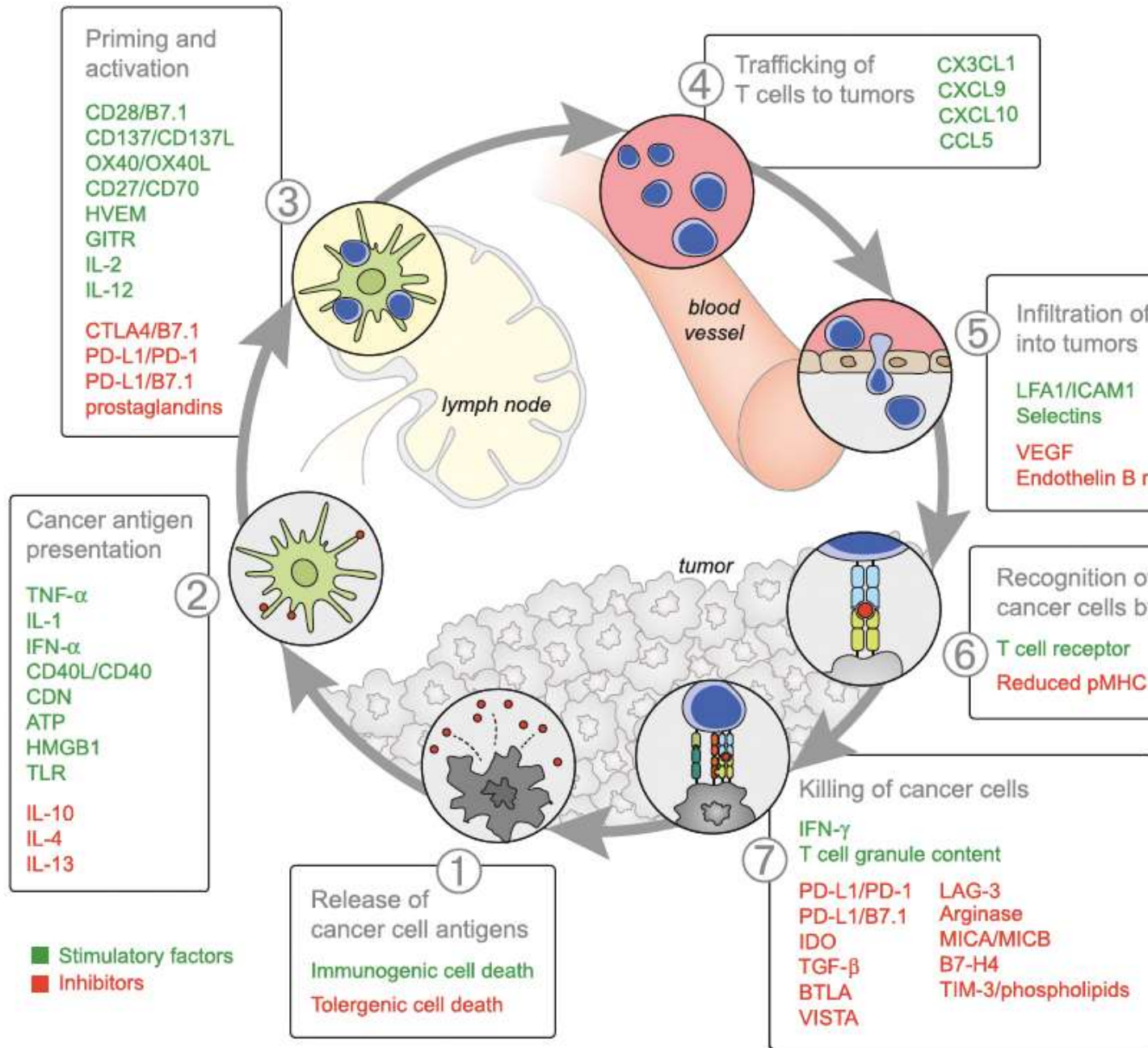


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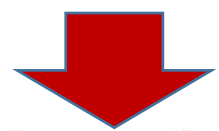
**WITH NOVEL TARGET**



**Perché così tante molecole non hanno dato i risultati sperati? ONE DOES NOT FIT ALL!**

IMMUNE DESERT	IMMUNE EXCLUDED	INFLAMED
DIFFERENCES OF IMMUNE ACTIVITY		
T cells are absent from the tumor and the tumoral microenvironment	T cells have accumulated, but are not efficiently infiltrating the tumoral microenvironment	T cells have infiltrated, but are not functioning properly
ESSENTIAL CELL ACTIVITY REQUIRED		
GENERATE <small>activate, tumour-infiltrated T cells</small>	INFILTRATE <small>tumour</small>	KILL <small>tumour</small>

**...AND REDUNDANT MECHANISMS IN EACH ONE**



*Review Article*  
**Combinatorial Approach to Improve Cancer Immunotherapy: Rational Drug Design Strategy to Simultaneously Hit Multiple Targets to Kill Tumor Cells and to Activate the Immune System**

Shweta Joshi<sup>1</sup> and Donald L. Durden<sup>1,2</sup>

<sup>1</sup>Division of Pediatric Hematology-Oncology, Department of Pediatrics, Moores Cancer Center, University of California, San Diego, CA, USA

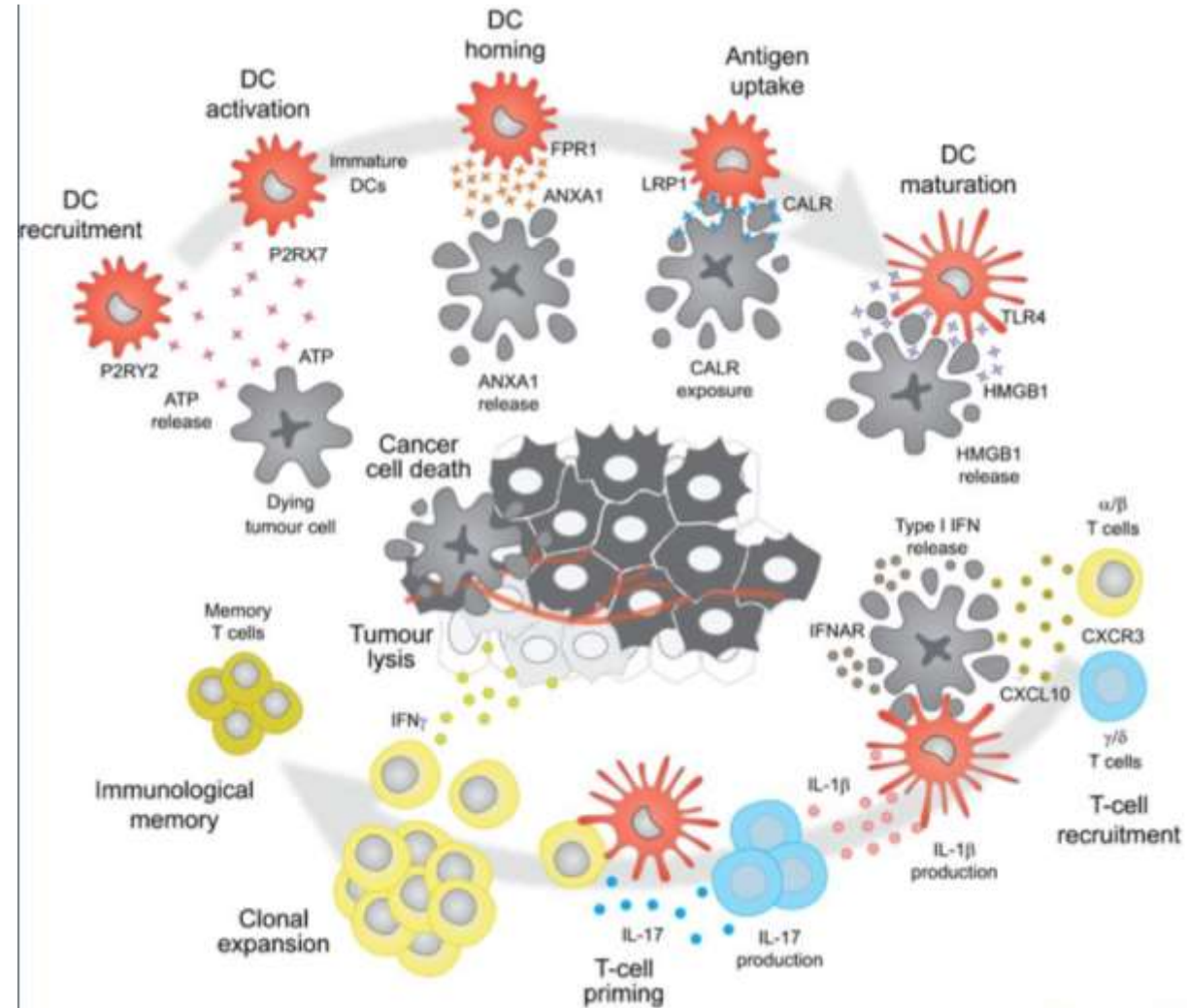
<sup>2</sup>SignalRx Pharmaceuticals, Inc., San Diego, CA, USA

# 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)

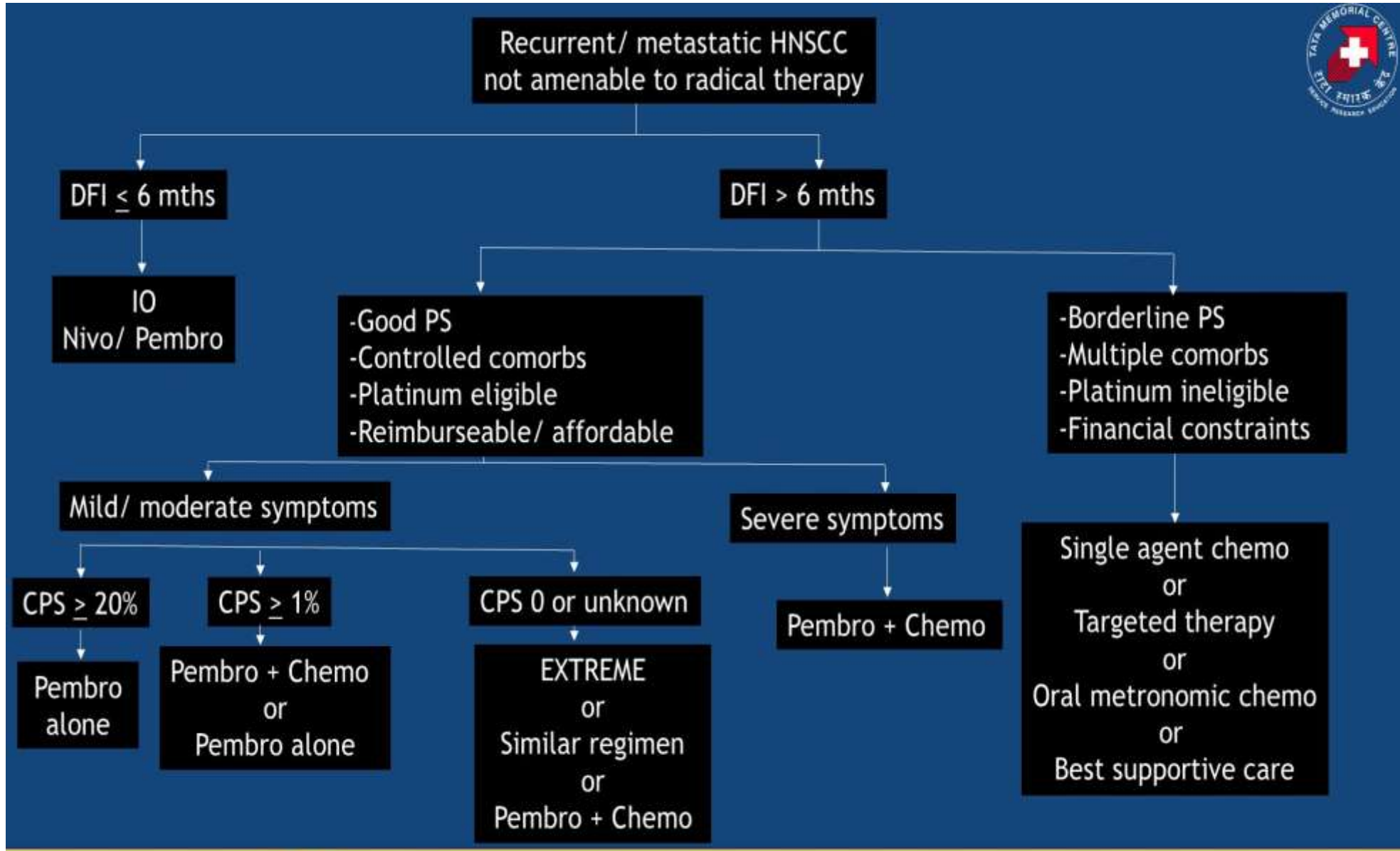
Danny Rischin<sup>1</sup>, Kevin Harrington,<sup>2</sup> Richard Greil,<sup>3</sup> Denis Soulières,<sup>4</sup> Makoto Tahara,<sup>5</sup> Gilberto de Castro,<sup>6</sup> Amanda Psyrris,<sup>7</sup> Neus Basté,<sup>8</sup> Prakash Neupane,<sup>9</sup> Ase Bratland,<sup>10</sup> Thorsten Fuereeder,<sup>11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

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

## CHT + IMMUNO

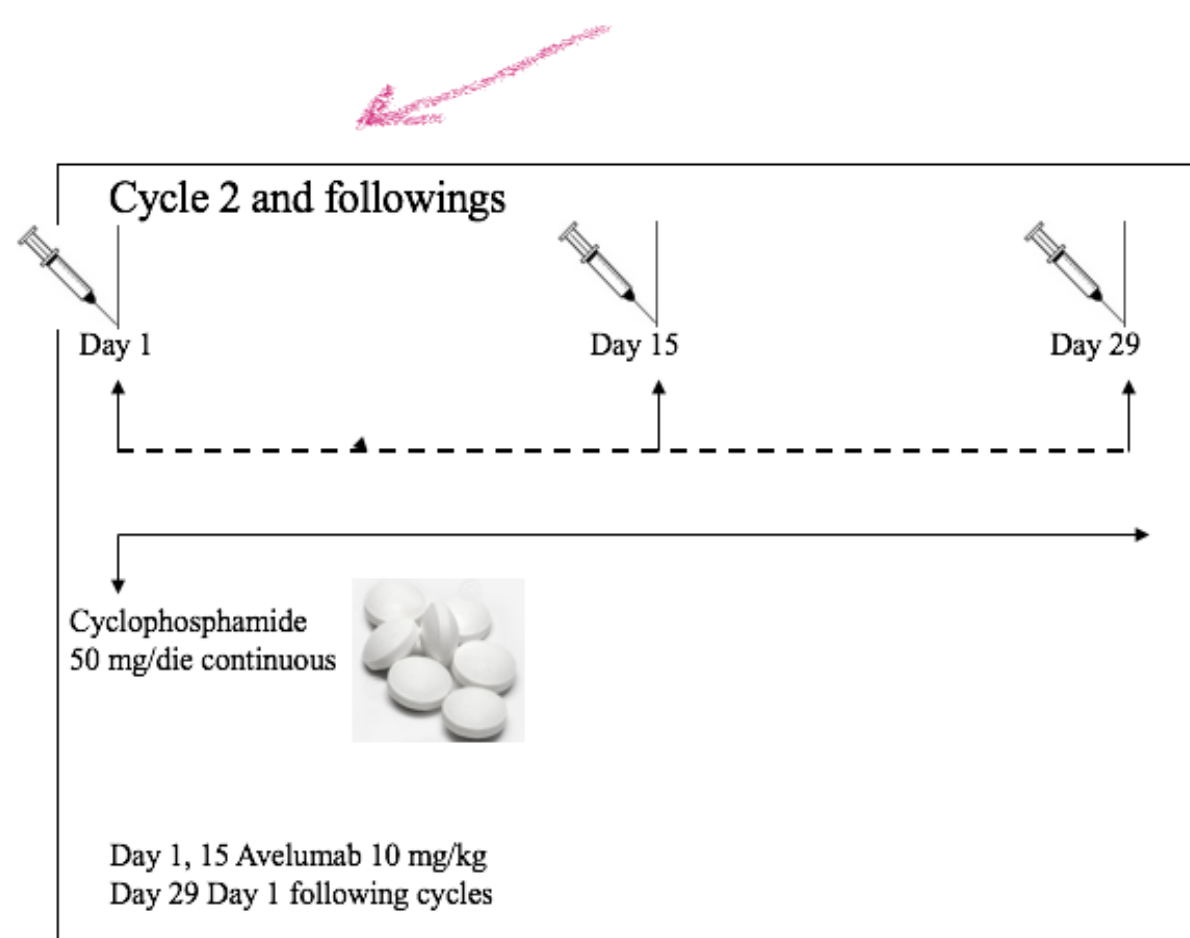
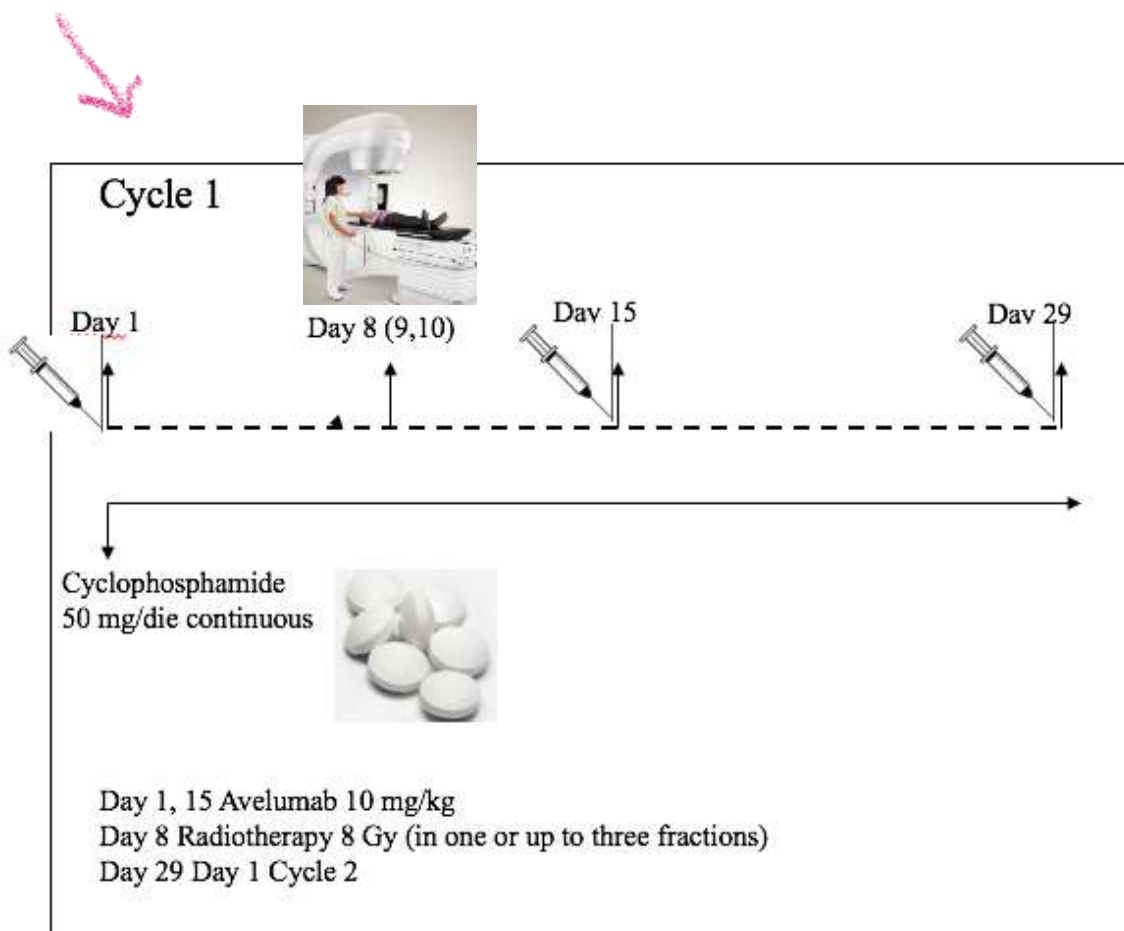






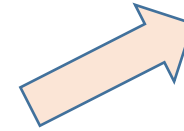
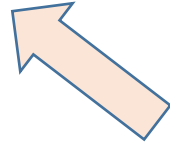
## Activation of immune responses in patients with relapsed-metastatic head and neck cancer (CONFRONT phase I-II trial): Multimodality immunotherapy with avelumab, short-course radiotherapy, and cyclophosphamide.

Merlano MC<sup>1</sup>, Merlotti AM<sup>2</sup>, Licitra L<sup>3</sup>, Denaro N<sup>1</sup>, Fea E<sup>1</sup>, Galizia D<sup>4</sup>, Di Maio M<sup>5</sup>, Fruttero C<sup>6</sup>, Curcio P<sup>7</sup>, Vecchio S<sup>8</sup>, Russi EG<sup>2</sup>, Corvò R<sup>9</sup>.

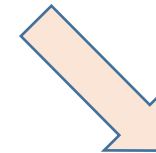
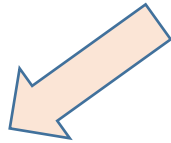


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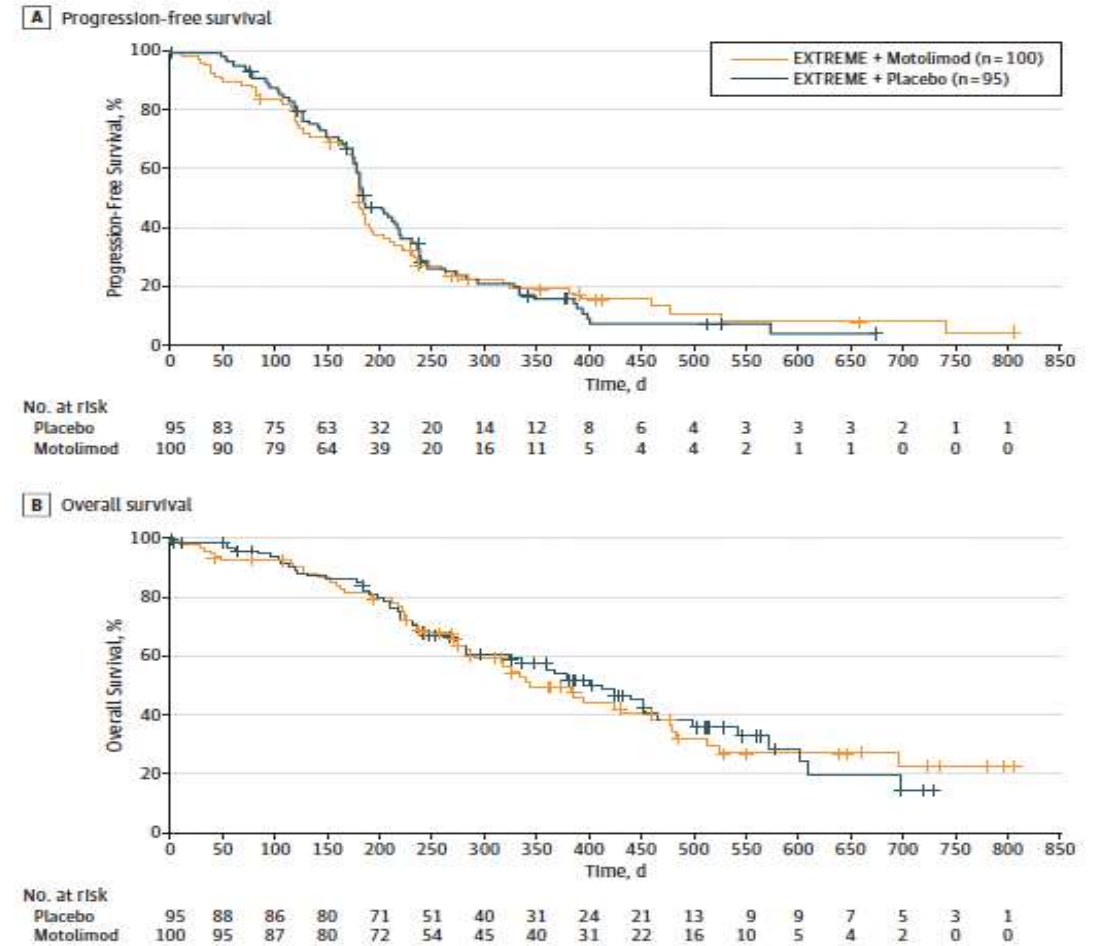
JAMA Oncology | Brief Report

## Effect of Adding Motolimod to Standard Combination Chemotherapy and Cetuximab Treatment of Patients With Squamous Cell Carcinoma of the Head and Neck The Active8 Randomized Clinical Trial

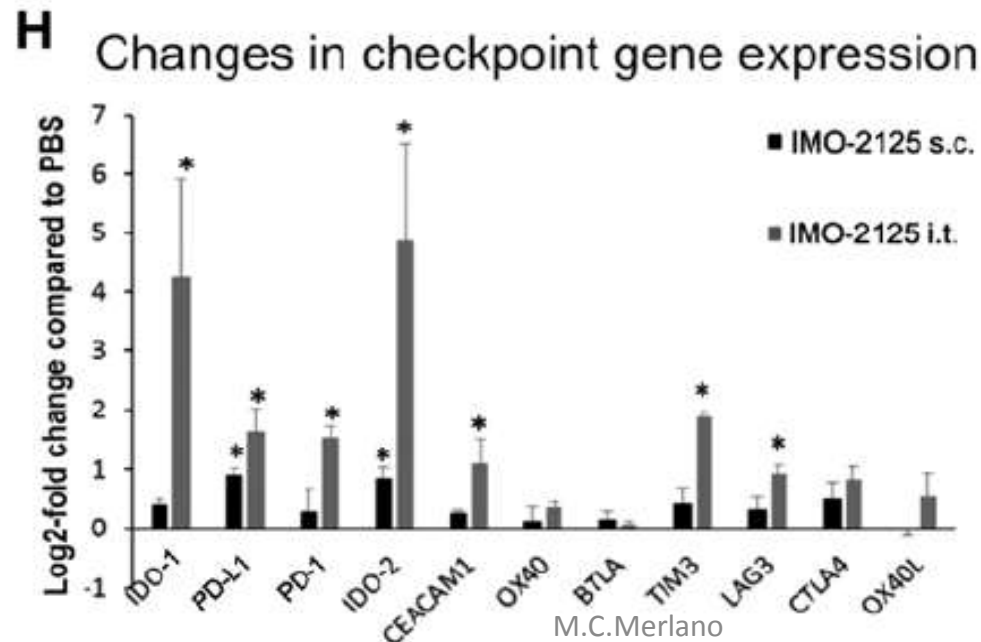
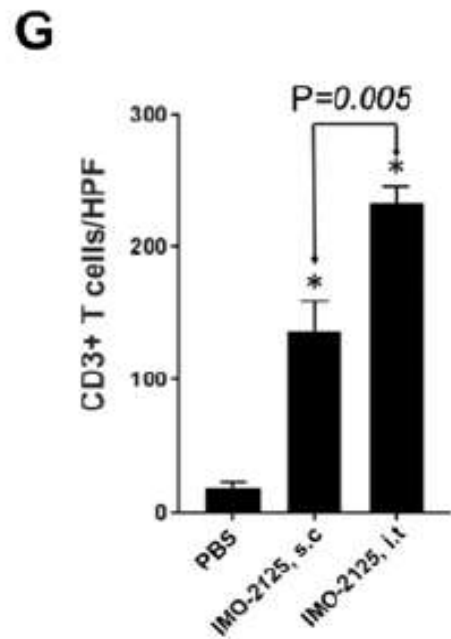
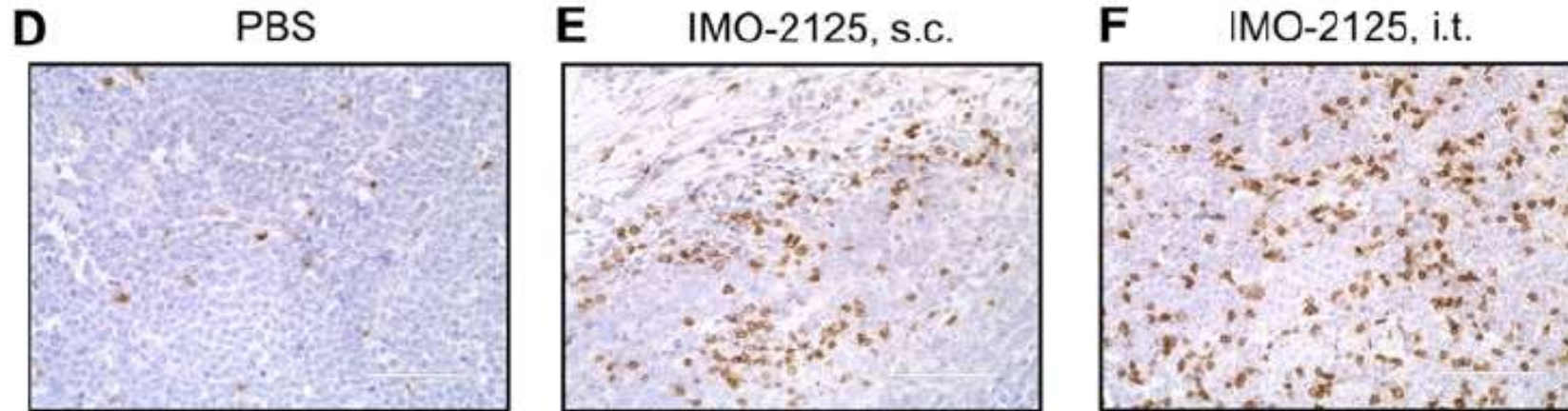
Robert L. Ferris, MD, PhD; Nabil F. Saba, MD; Barbara J. Gitlitz, MD; Robert Haddad, MD; Ammar Sukari, MD; Prakash Neupane, MD; John C. Morris, MD; Krzysztof Misiukiewicz, MD; Julie E. Bauman, MD, MPH; Moon Fenton, MD, PhD; Antonio Jimeno, MD; Douglas R. Adkins, MD; Charles J. Schneider, MD; Assuntina G. Sacco, MD; Keisuke Shirai, MD; Daniel W. Bowles, MD; Michael Gibson, MD, PhD; Tobenna Nwizu, MD; Raphael Gottardo, PhD; Kristi L. Manjarrez, BS; Gregory N. Dietsch, PhD; James Kyle Bryan, MD; Robert M. Hershberg, MD, PhD; Ezra E. W. Cohen, MD

**Methods**  
**P-F-Cmab + six 21-day cycles**  
**of weekly subcutaneous**  
**motolimod (3 mg/m<sup>2</sup>) or**  
**placebo.**

Figure 2. Kaplan-Meier Analyses of Progression-Free Survival and Overall Survival in the Intent-to-Treat Population



# TLR9 Agonist IMO-2125. s.c. = sub-cutaneous; i.t. = intra-tumoral

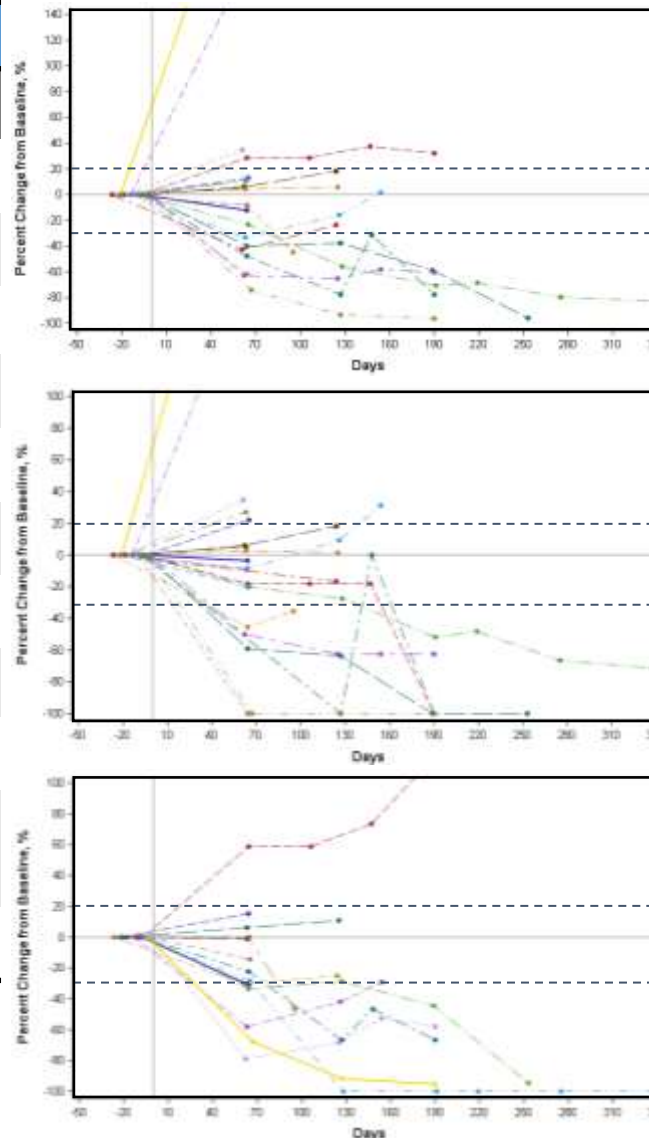


Intra-tumor delivery extends antitumor immune response to uninjected distal tumors resulting in a systemic efficacy

# EFFICACY

## Percent Change From Baseline for Target Lesions: SD-101 8 mg

	8 mg	2 mg
mITT patients, n*	22	2
<b>Objective response rate, n (%)</b>	6 (27.3)	
95% confidence interval	(16, 56)	
<b>Best overall response, n (%)</b>		
Complete response	0	
Partial response	6 (27.3)	
Stable disease	4 (18.2)	2 (100)
Progressive disease	10 (45.5)	
<b>Time to response (months)</b>		
Median (min, max)	2.1 (2.0, 4.2)	
<b>Duration of response (months)</b>		
Median (min, max)	3.6+ (0.0, 6.9)	



All Target Lesions

Injected Target Lesions

Non-Injected Target Lesions

\* mITT: patients on treatment but did not yet have their first CT scan and tumor assessment

# May be a problem of scheduling?

TLR9 Agonist SD 101 Intra Tumoral administration<sup>1,2</sup> ↑  
TLR7 Agonist Imiquinod Topic administration<sup>3</sup> ↑↓  
TLR8 Agonist Motolimod S.C. administration<sup>4</sup> ↓

**not: it's a problem  
of concentration!**

1. Cohen EE, ESMO 2018, Abstr 1050PD
2. Ribas A et al, Cancer Discovery 2018
3. Chi H et al, Frontiers in pharmacol 2017
4. Siu LL et al, JAMA 2018

## Lymphatic endothelial cells



- Tumor cells can invade existing lymphatics or stimulate lymphatic vessel sprouting with the production of factors, such as VEGFC or VEGFD.
- Lymphatic vessels are important in the dissemination of malignant cells, but they might also promote tumor development by mechanomodulation of the TME and altering the host immune response to the tumor.

## T lymphocytes



- Abundant in the majority of human and experimental cancers (up to 10% of all cells in the tumor).
- Found within and surrounding the tumor mass.
- Phenotypes of pro- and anti-tumor T cells can vary with disease type and stage. CD8<sup>+</sup> cytotoxic T cells, CD4<sup>+</sup> Th1 helper T cells and  $\gamma\delta$  T cells are usually associated with a good prognosis.
- FOXP3<sup>+</sup> T regulatory cells, CD4<sup>+</sup> Th2 helper T cells are usually associated with a poor prognosis.

## B lymphocytes



- Sometimes found at the margin of solid tumors.
- Often in secondary and tertiary structures adjacent to the TME.
- B cell infiltration is associated with good prognosis in some human cancers. However, deposition of B cells and immunoglobulin is tumor-promoting in some mouse cancer models.
- Immunosuppressive IL-10 producing subtypes of B cells, B10 or Breg cells also have tumor-promoting activity in mouse models.

## Myeloid cells



- Consist of several subtypes; probably the most abundant cell lineage in the TME.
- Tumor-associated macrophages (TAMs)**
- Typically tumor-promoting.
  - IL-10<sup>+</sup>, IL-12<sup>low</sup> phenotype and mannose-receptor-positive.
  - TAMs also produce angiogenic factors and accumulate in hypoxic or necrotic areas of the TME.
- Myeloid-derived suppressor cells (MDSCs)**
- Inhibitory immune cells producing large amounts of IL-10.
  - Inhibit cytotoxic T cells and polarize TAMs to a tumor-promoting phenotype.
- Tumor-associated neutrophils (TANs)**
- Can have both pro- and anti-tumor activity.
- Terminally-differentiated myeloid dendritic cells**
- Might be defective in the TME and cannot adequately stimulate an immune response to tumor-associated antigens.

## NK and NKT cells



- Innate cytotoxic lymphocytes, NK cells and NKT cells are usually found outside the tumor area.
- For some cancers they can predict a good prognosis.

## Cancer-associated fibroblasts



- Found in many human and experimental cancers, especially at the invasive margins.
- Produce tumor-promoting growth factors, chemokines, cytokines, ECM components and ECM remodeling enzymes.
- Can also have important immunosuppressive activity.

## Vascular endothelial cells



- Angiogenic factors produced by malignant cells, myeloid cells or CAFs in the TME stimulate sprouting of endothelial cells.
- The new blood vessels have chaotic branching and uneven vessel lumina. The vessels are also leaky, raising interstitial pressure, with uneven blood flow, oxygenation, nutrient and drug delivery in the TME.

## Mesenchymal stem cells



- Mesenchymal stem cells can be recruited from the bone marrow and give rise to CAFs, pericytes, adipocytes and smooth muscle cells in the TME.

## Adipocytes



- In some cancers, adipocytes actively aid recruitment of malignant cells through the secretion of adipokines.
- They also promote malignant cell growth by providing fatty acids as fuel for cancer cells.

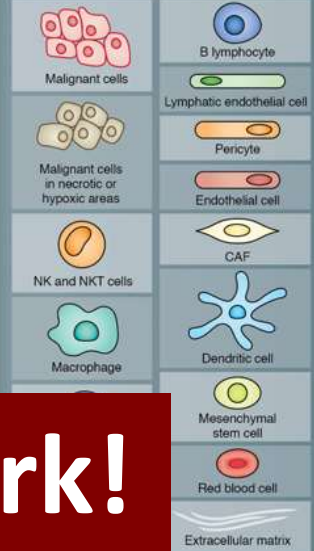
## Pericytes



- Perivascular stromal cells, pericytes, provide structural support for blood vessels in the TME.
- Low pericyte coverage of TME vessels correlates with poor prognosis and increased metastases.

# ...and the cytokines network!

## Key







**Thank You!**