Tumor Antigen Specific mAb Immunotherapy and Combinations for Head and Neck Cancer

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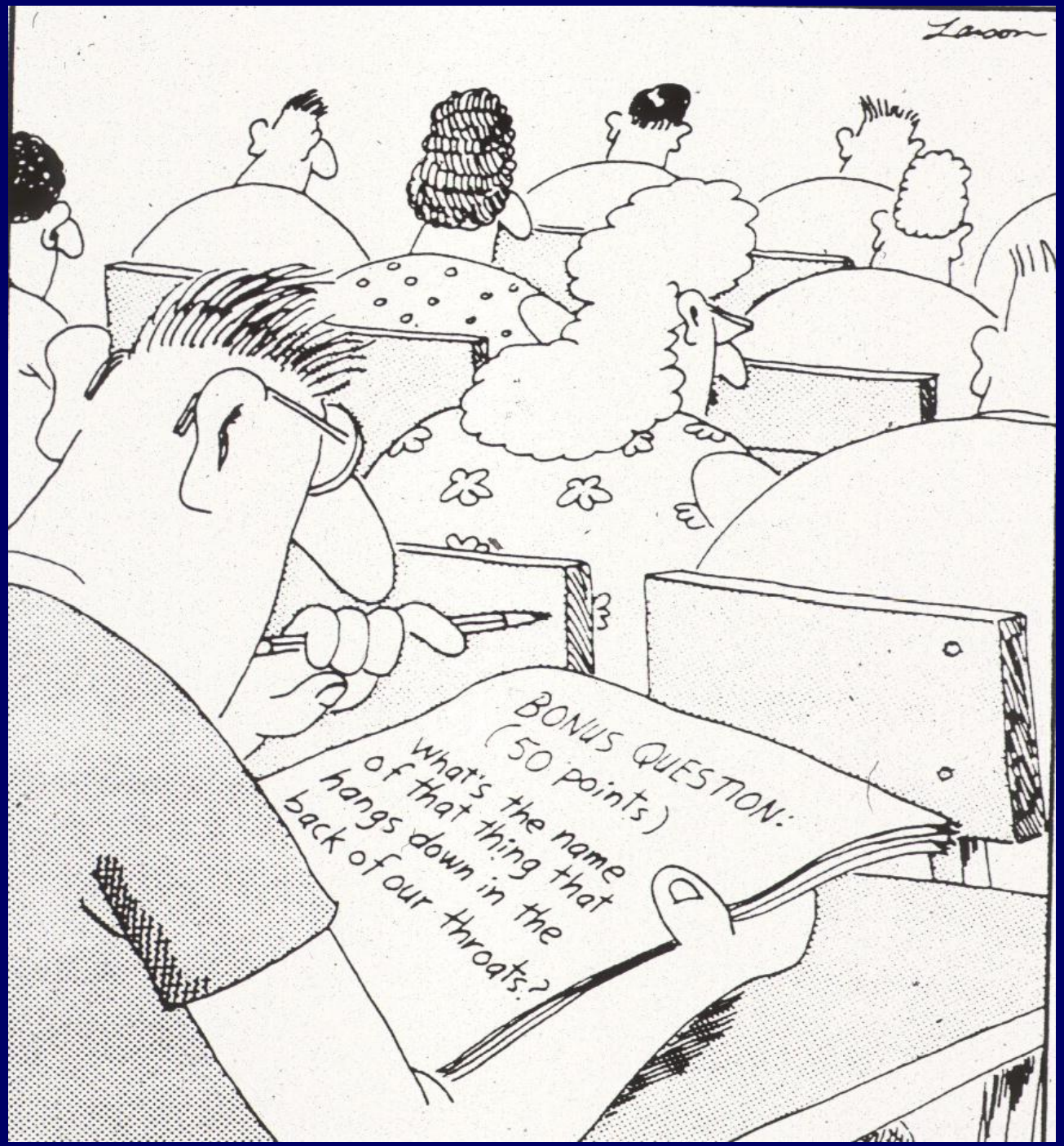
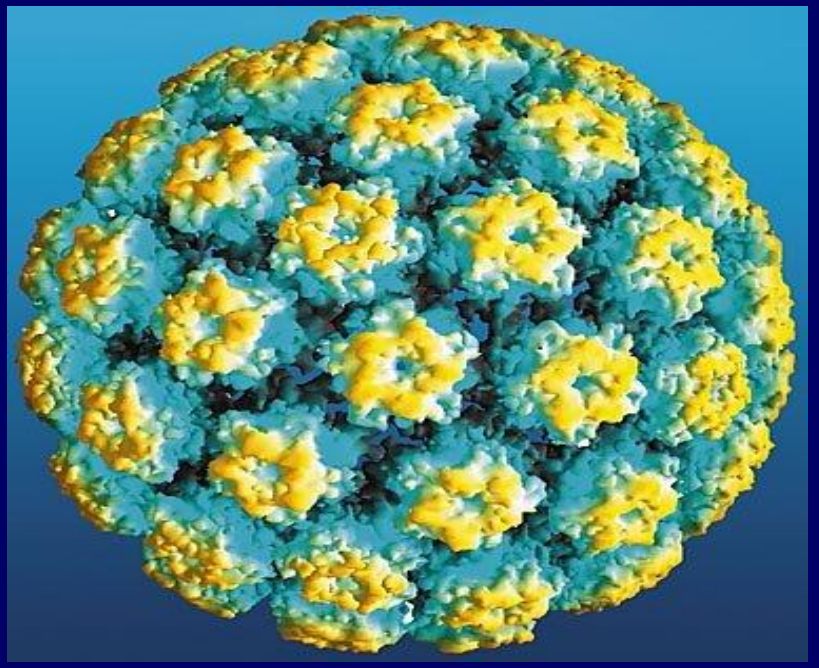
Disclosures

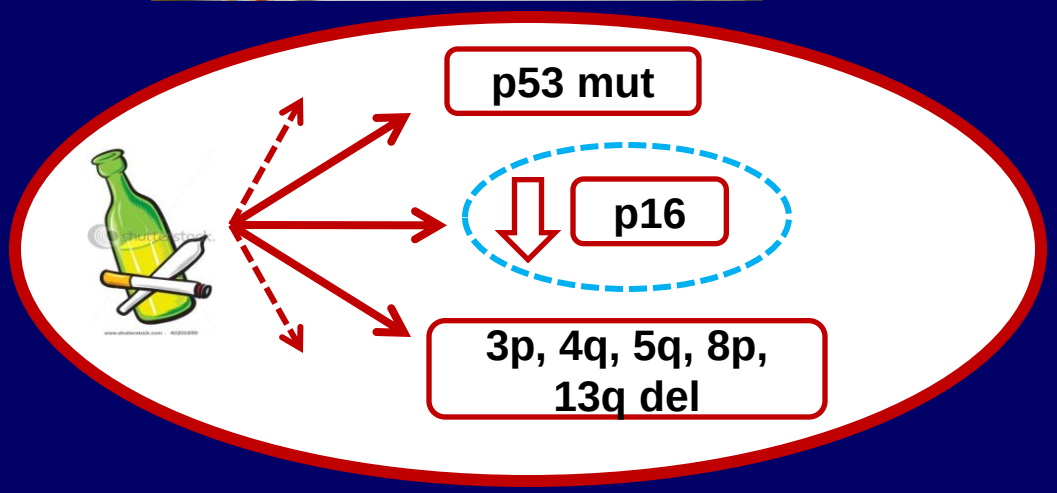
"Heal with Steel"

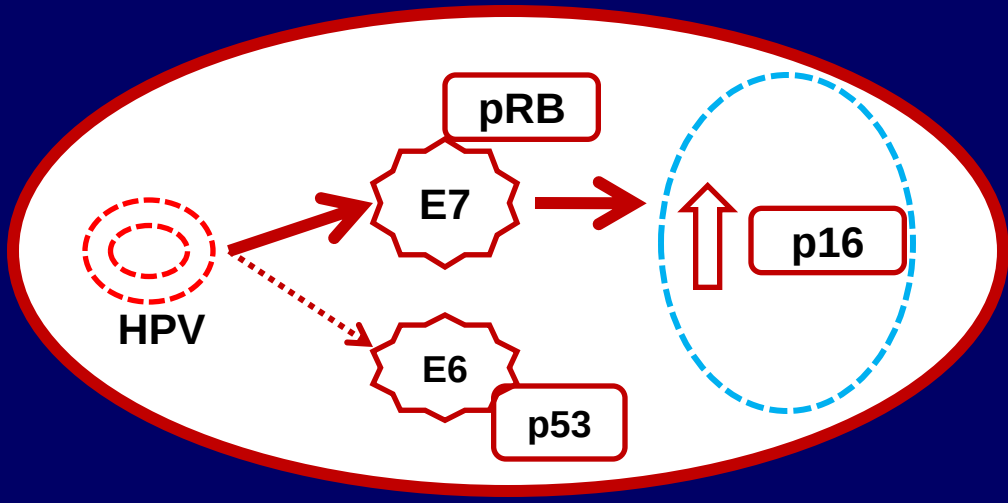
Amgen: Clinical trial/research funding
Bristol-Myers Squibb: Advisory board, Clinical trial/research funding VentiRx Pharmaceuticals: research funding


Larson
BONUS QUESTION:
(50 points)
What's the name
of that thing that
hangs down in the
back of our throats?

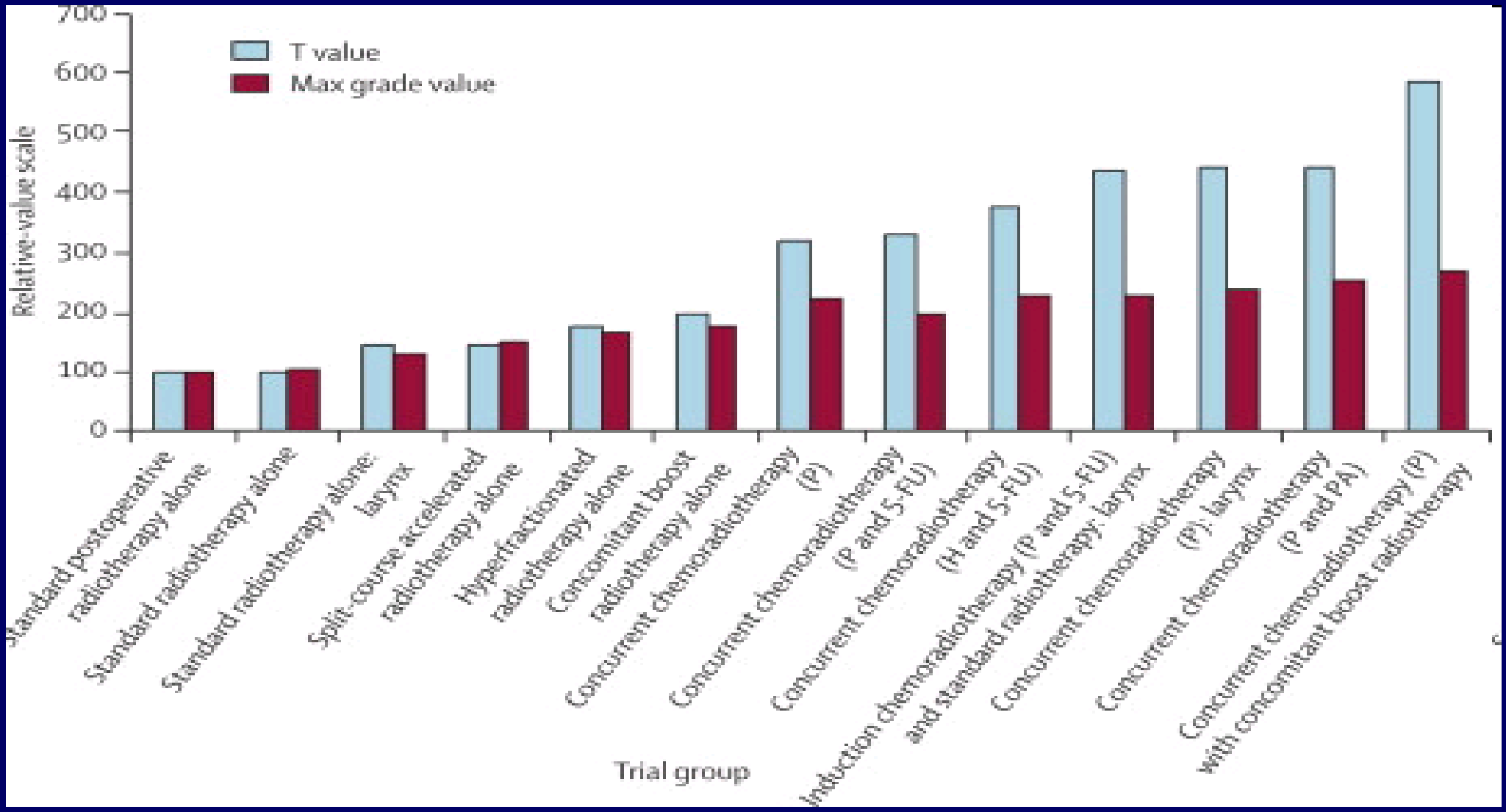
Two distinct diseases comprise HNC







Escalating Chemoradiation Morbidity

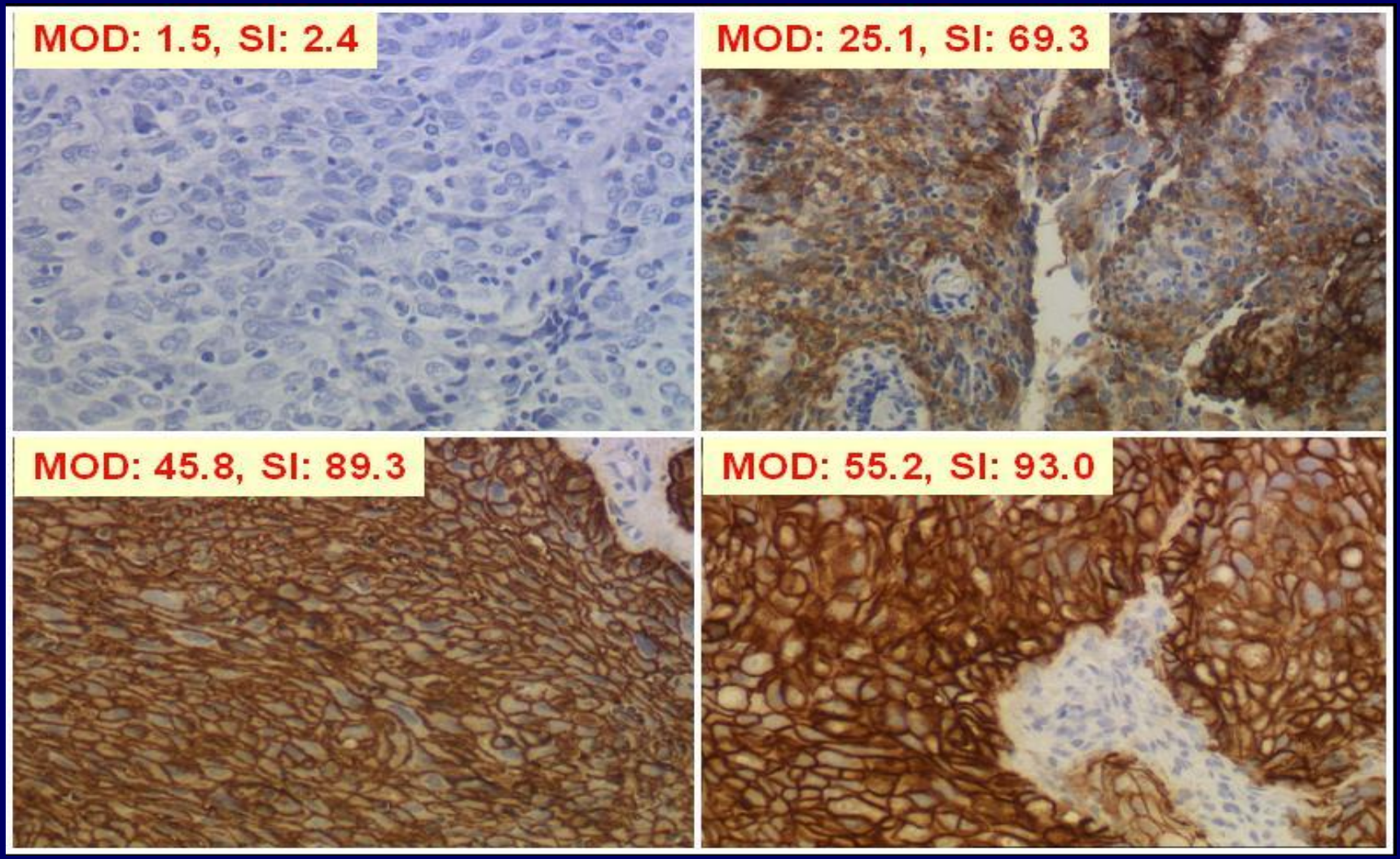


Trotti A et al. Lancet Oncol 2007;8:6713-24.

Convergence of "targeted therapy" with "immunotherapy"
The promise of tumor-targeted biological agents

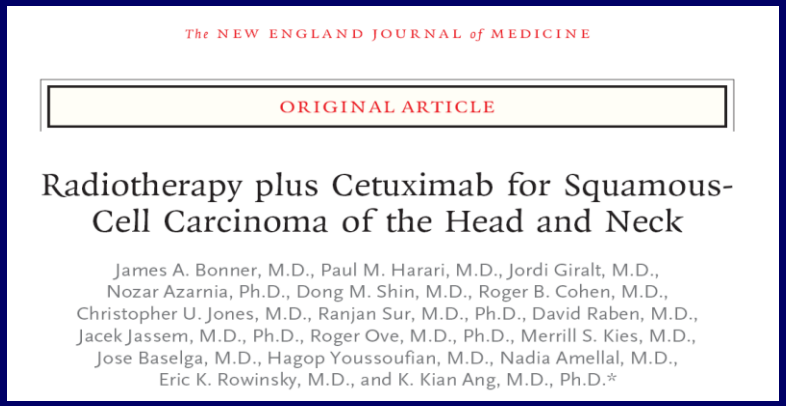
- Agents that do not directly attack DNA
- Directed against important biological/molecular targets – sparing the normal cells (bone marrow)
- Well-tolerated drugs that can be combined safely with cytotoxics

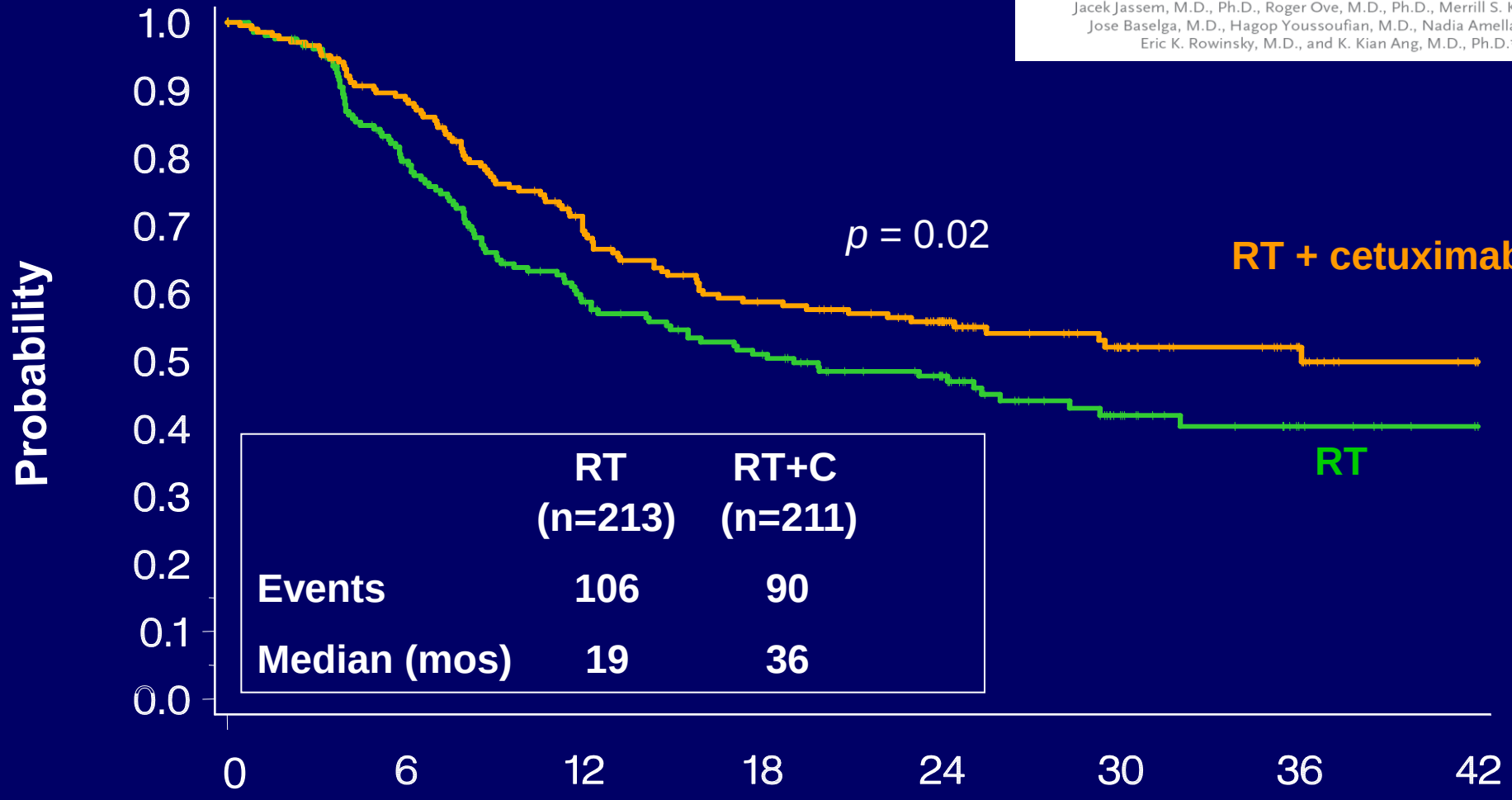
EGFR - Human SCCHN (+ in 80-100%)



Ang et al. Cancer Research 2002
Grandis, et al. JNCI 1998

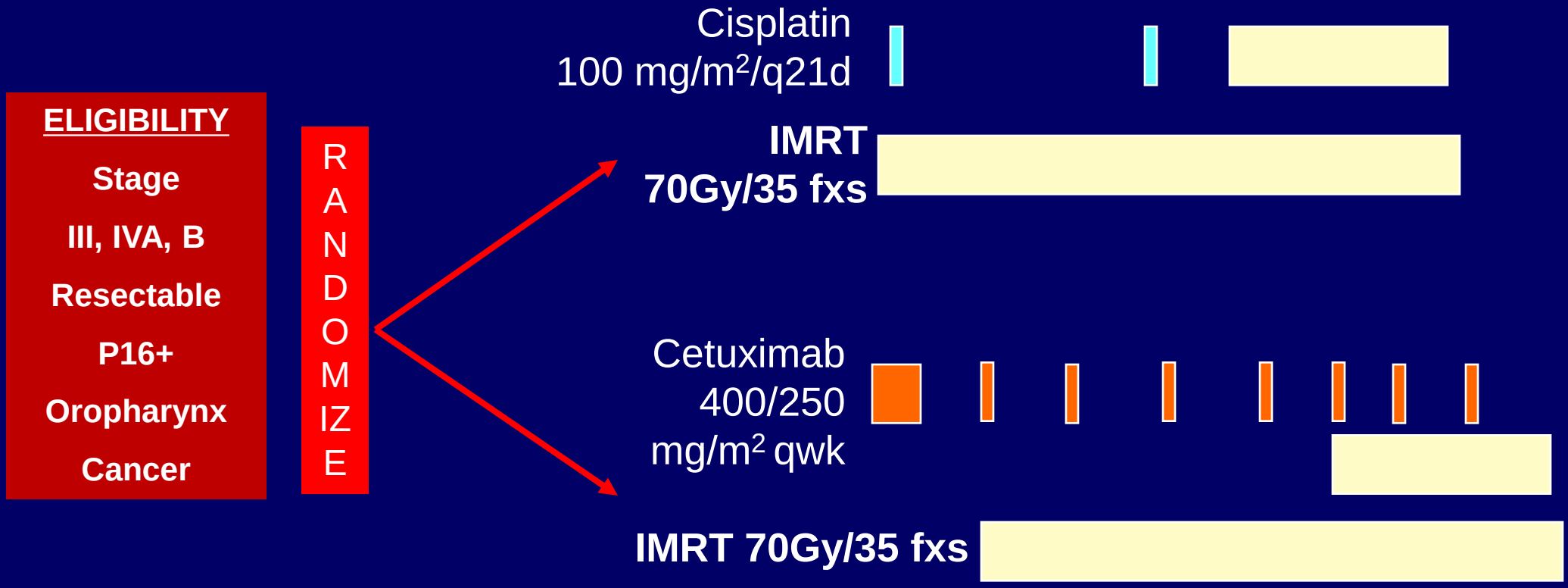
Cetuximab + RT in Locally Advanced SCCHN: Locoregional Control





Bonner, NEJM, 2006

RTOG 1016: A Randomized Phase III Trial of Chemoradiotherapy With Cisplatinum or Cetuximab in P16+ Oropharynx Cancer

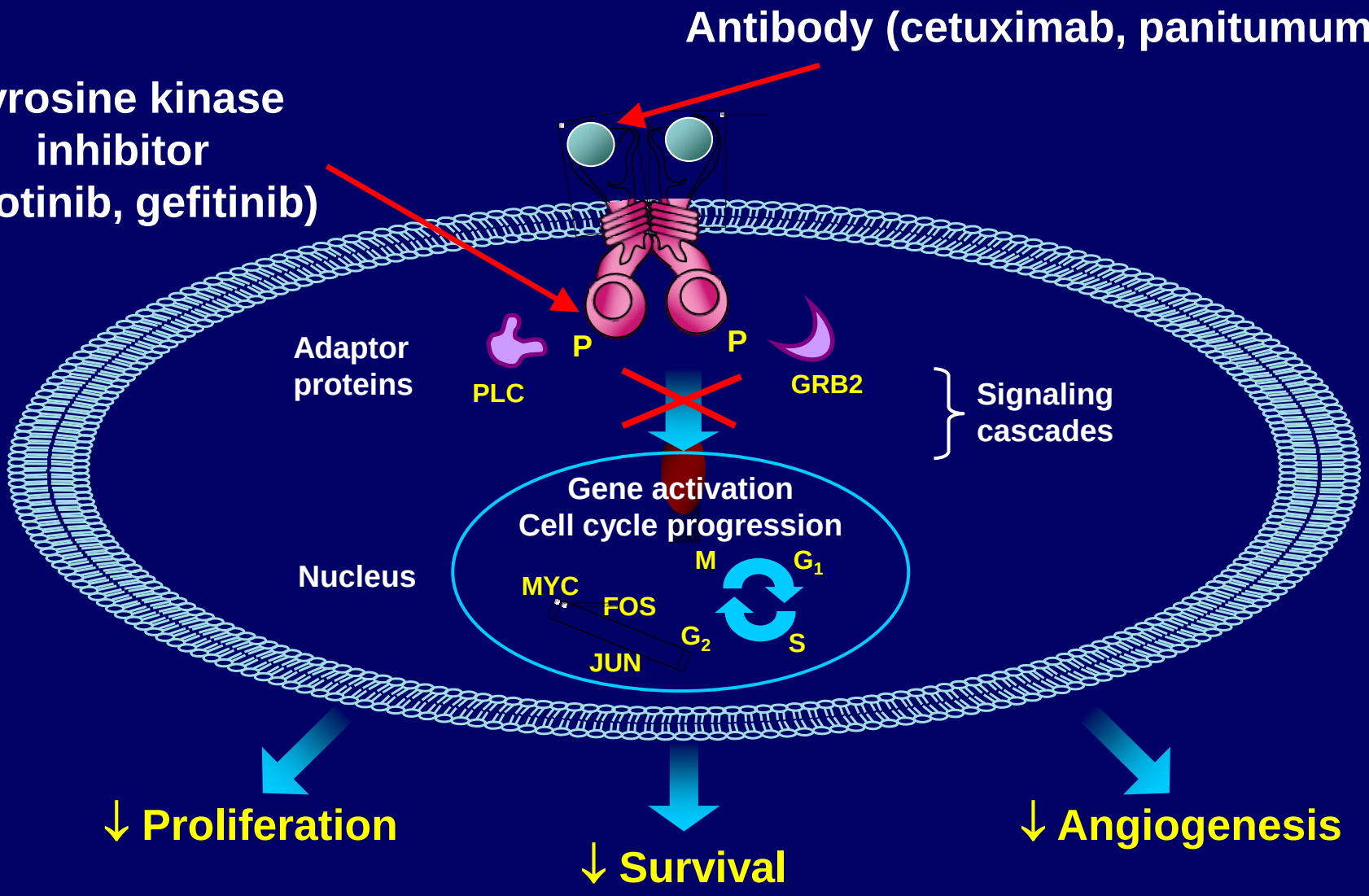


Stratify: HPV, smoking, stage

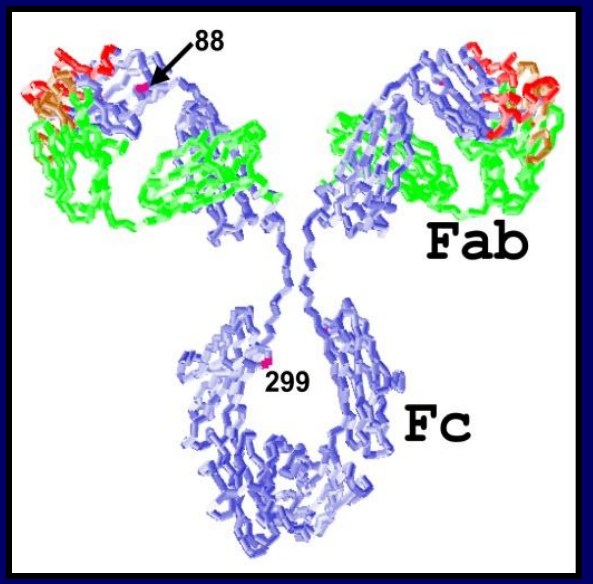
Cetuximab loading dose = 400 mg/m^2 on Day 1 of Cycle1 with induction

IMRT = intensity-modulated radiation therapy.
ClinicalTrials.gov.

EGFR Inhibition – immune mechanism of action?



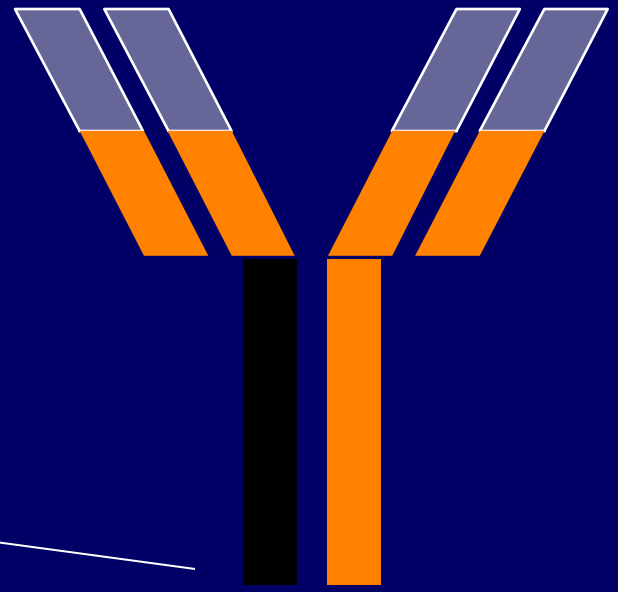
Cetuximab
anti-EGFR monoclonal Ab



- IgG1 (chimeric mAb)
- High-affinity and prevents ligand binding to EGFR
- ↑ apoptosis ↓ angiogenesis
- Clinical anti-tumor activity in ≈20% (Bonner, Vermorken), *not* correlated with level of EGFR expression or gene copy number

Structure of a mAb

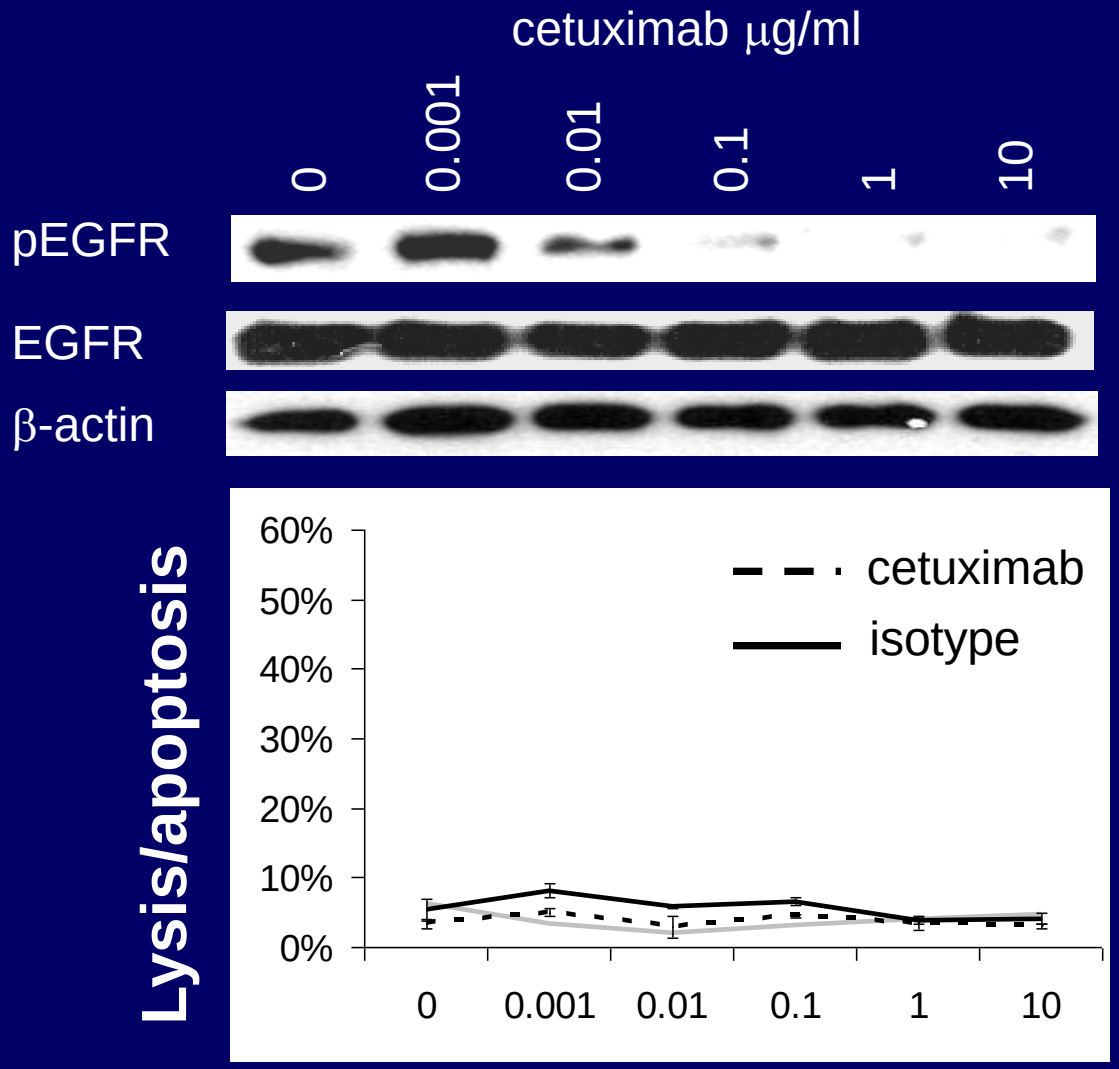
Variable Portion
F(ab): epitope specific
In chimeric mAb this portion is murine



Fc Portion
Constant portion
(changes depending on the isotype)

EGFR mAb therapy in SCCHN: inhibition of phosphorylation or immunotherapy?

Cetuximab blocks EGFR activation but does not kill HNC cells

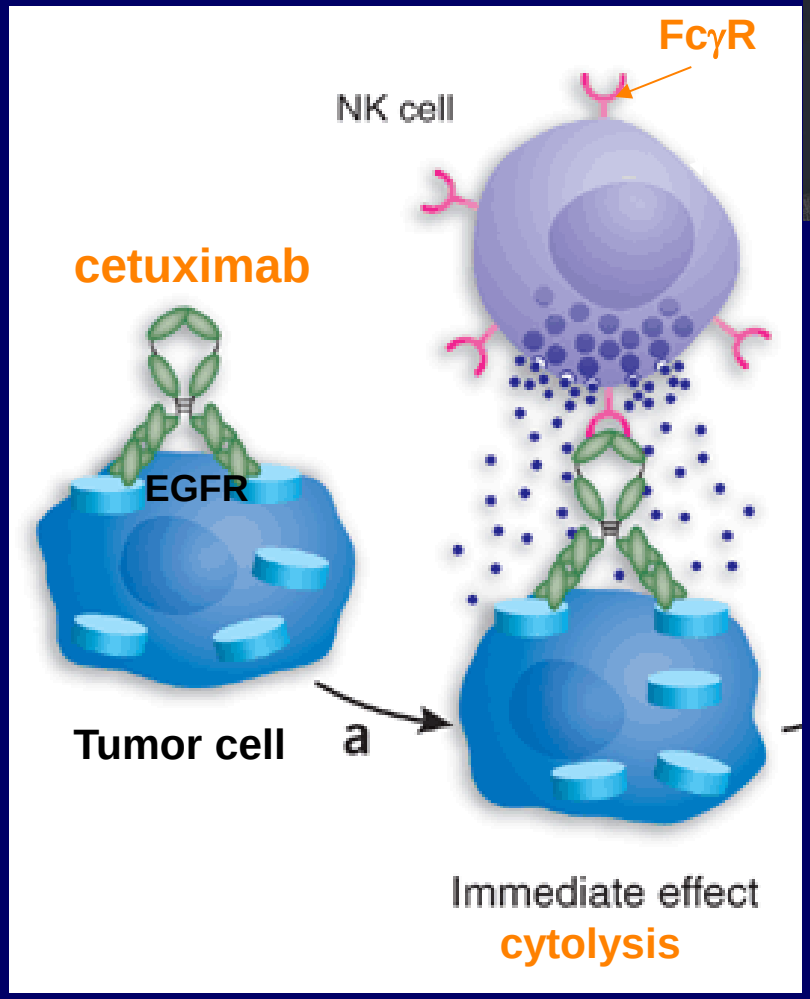


Lopez-Albaitero 2007

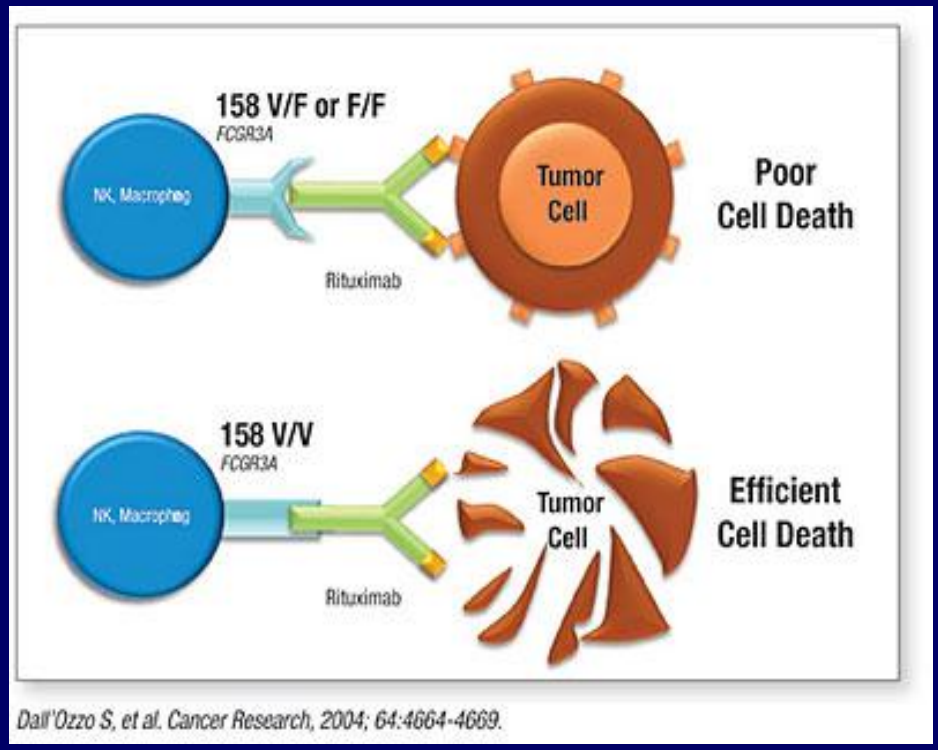
Antibody dependent cell cytotoxicity (ADCC)

- Polymerized mAb complexes trigger responses in macrophages and NK cells through the FcγR receptors
- There are several types of FcγR on *effector* cells, these variations influence the response against a mAb depending on its isotype.

Potential immune effect of mAb for cancer therapy – explanation for variability in responses



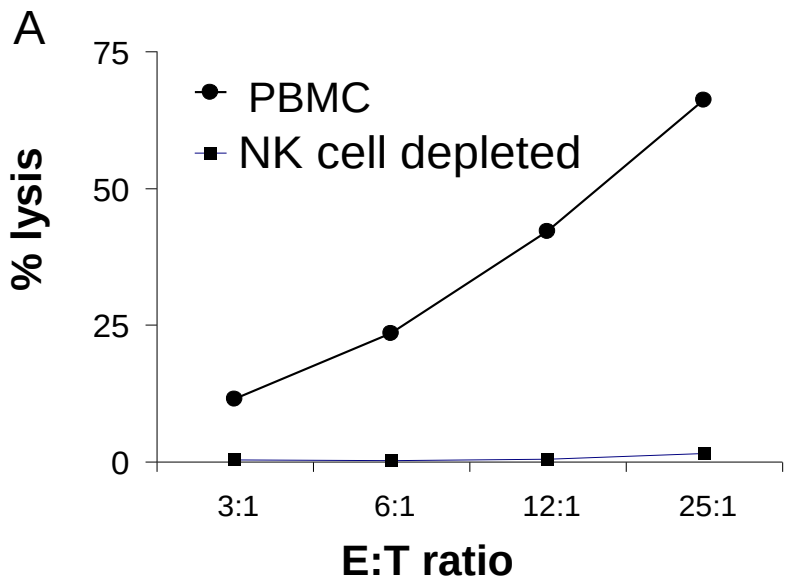
lysis

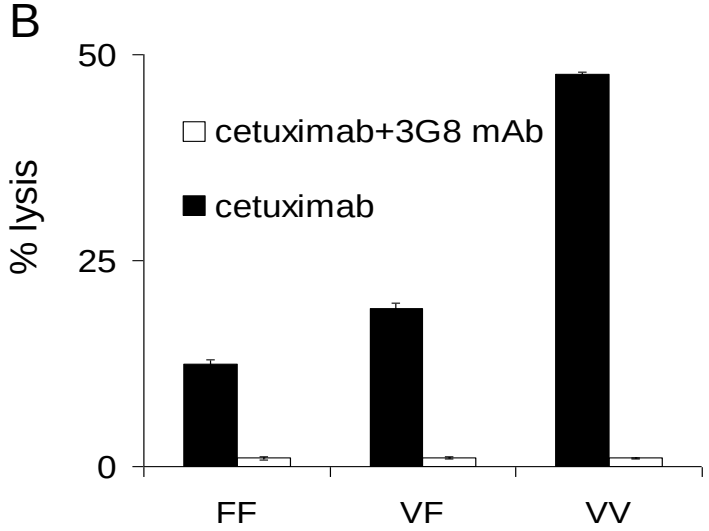


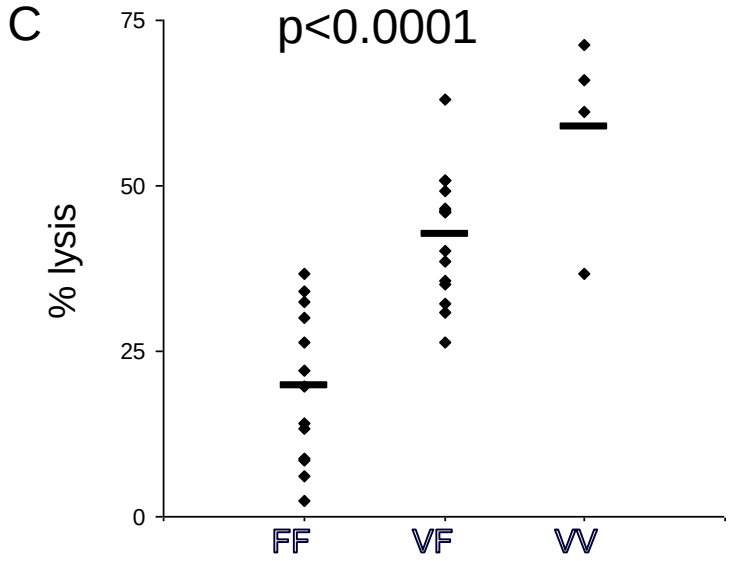
Dall'Ozzo S, et al. Cancer Research, 2004; 64:4664-4669.

Modified from Adams et al *Nature Biotechnology* **23**, 1147 - 1157 (2005)

Cetuximab mediated ADCC correlates with FcγR genotype



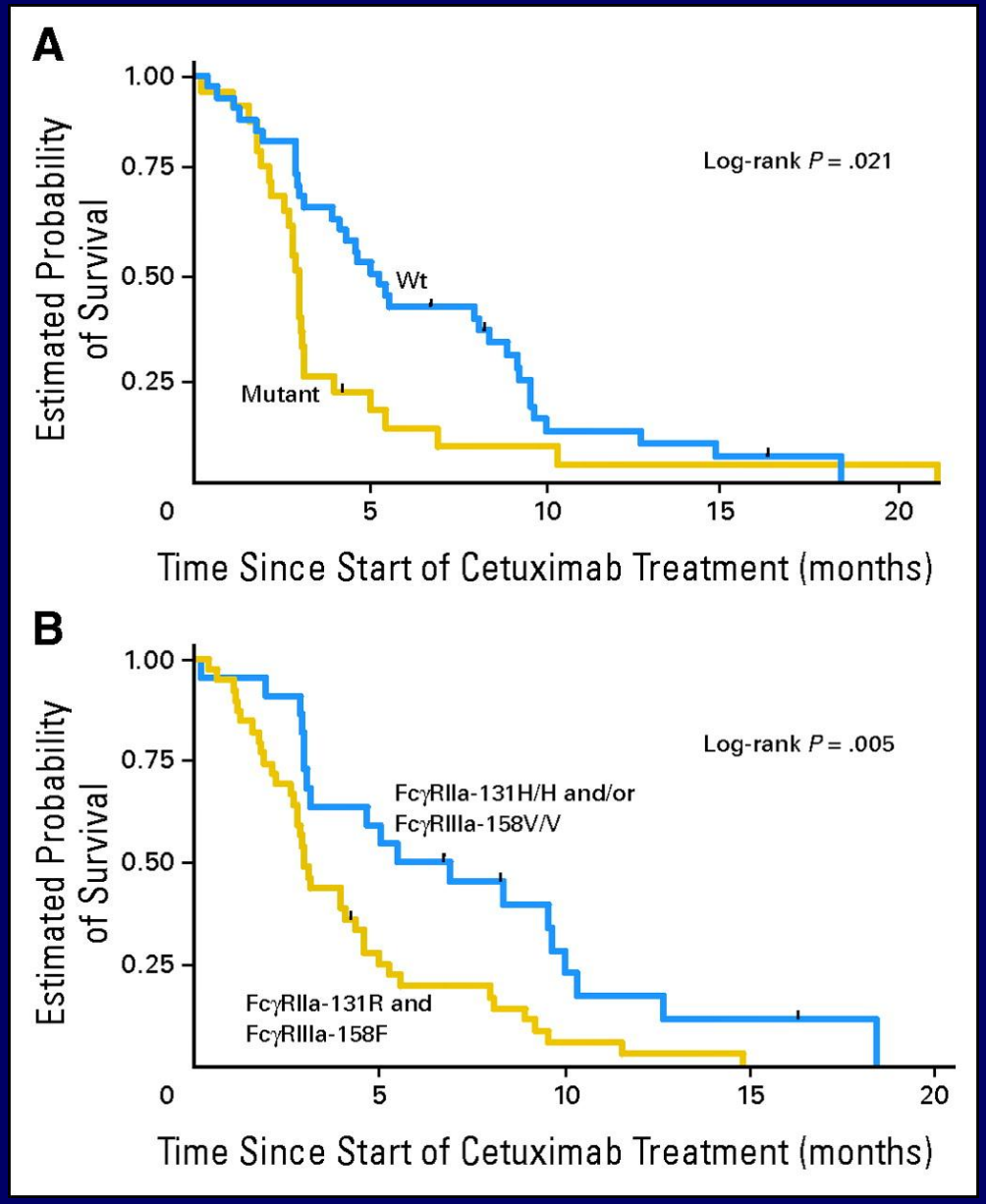




Lopez-Albaitero *CII* 2009

Progression-free survival for patients with metastatic colorectal cancer (mCRC) according to the presence or absence of (A) KRAS mutation and to the (B) Fc{gamma}R polymorphisms combination

Is cetuximab activity immune mediated?



Bibeau, F. et al. J Clin Oncol; 27:1122-1129 2009

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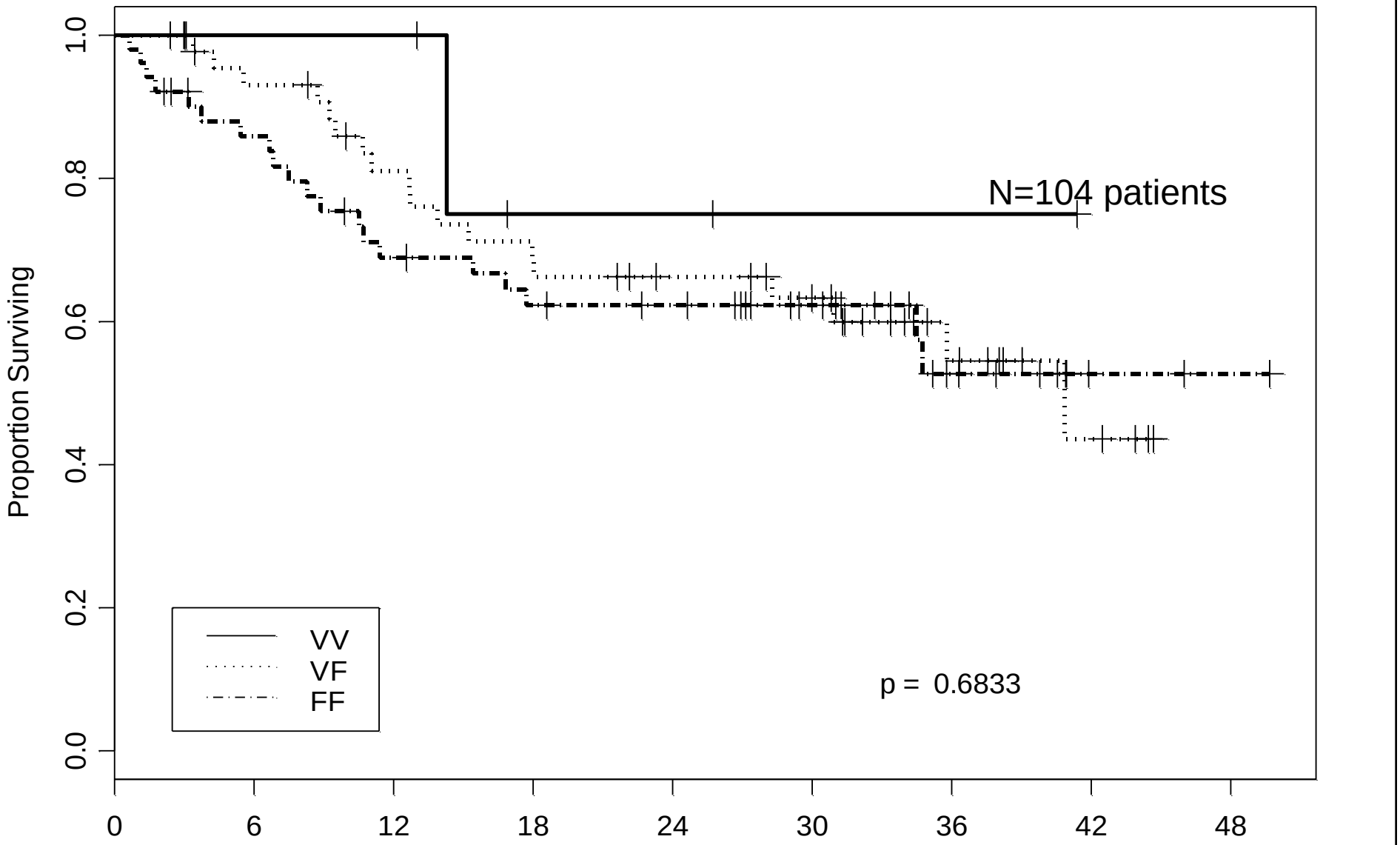
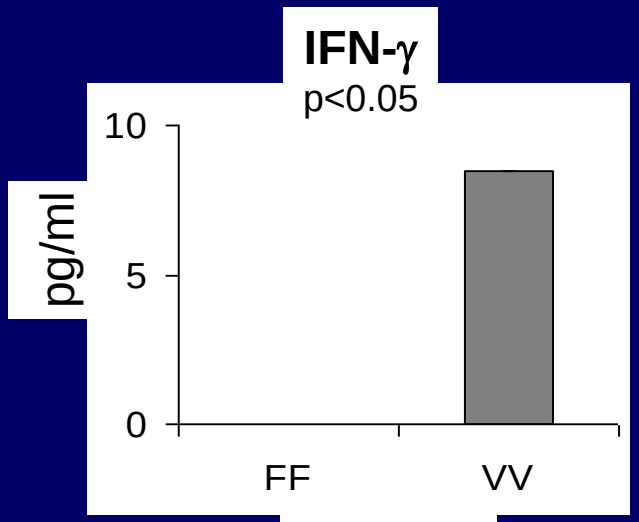
Disease-Specific Survival by FCgamma RIIIa

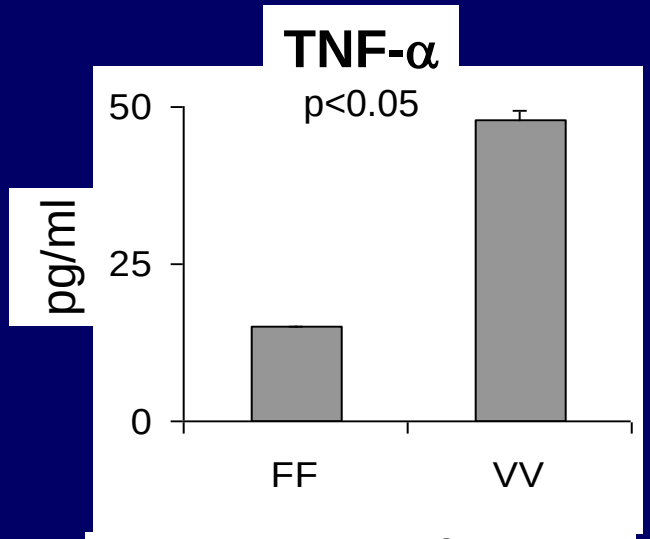


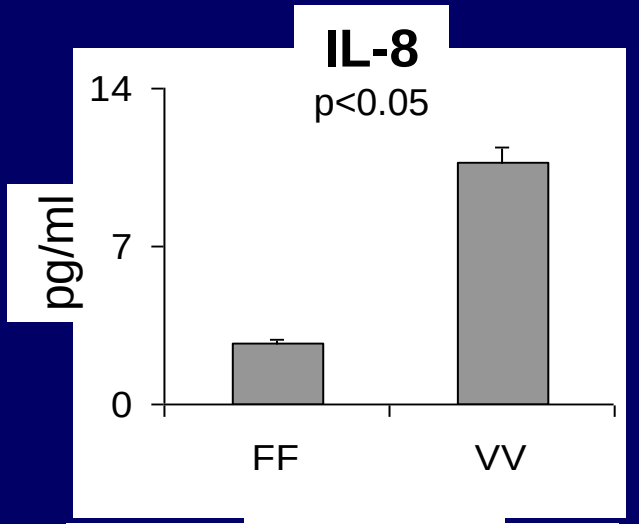
Srivastava, *Clin Can Res* 2013

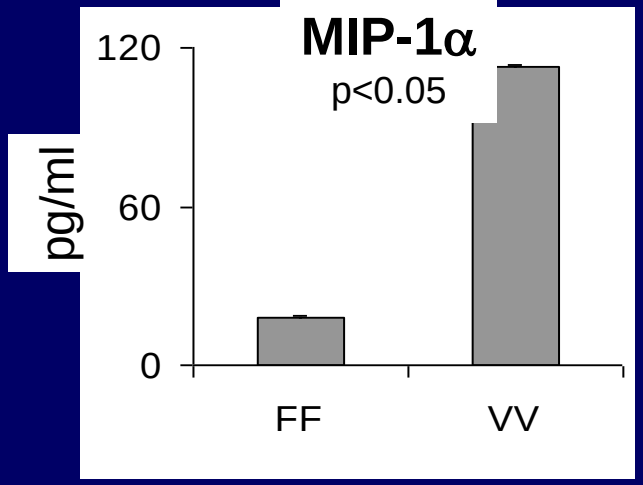
Results confirmed with RTOG 0522 trial

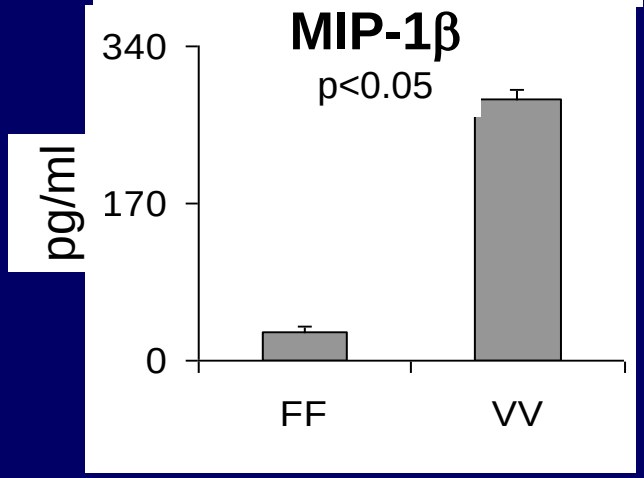
Cetuximab activated NK cells secrete cytokines and chemokines associated with recruitment of T cells and dendritic cells – bridging a network of antitumor lymphocyte activation?

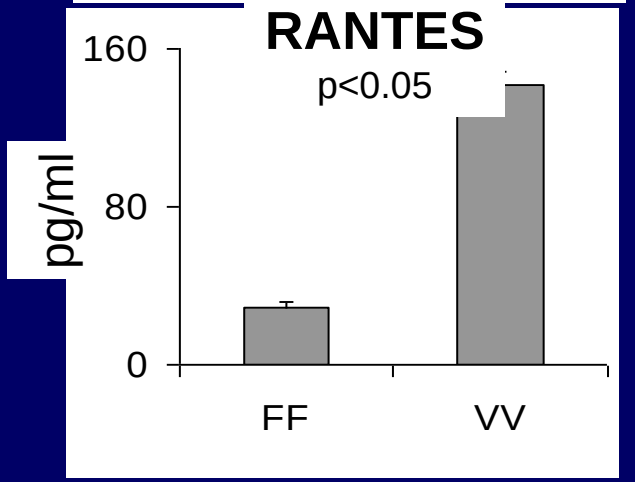




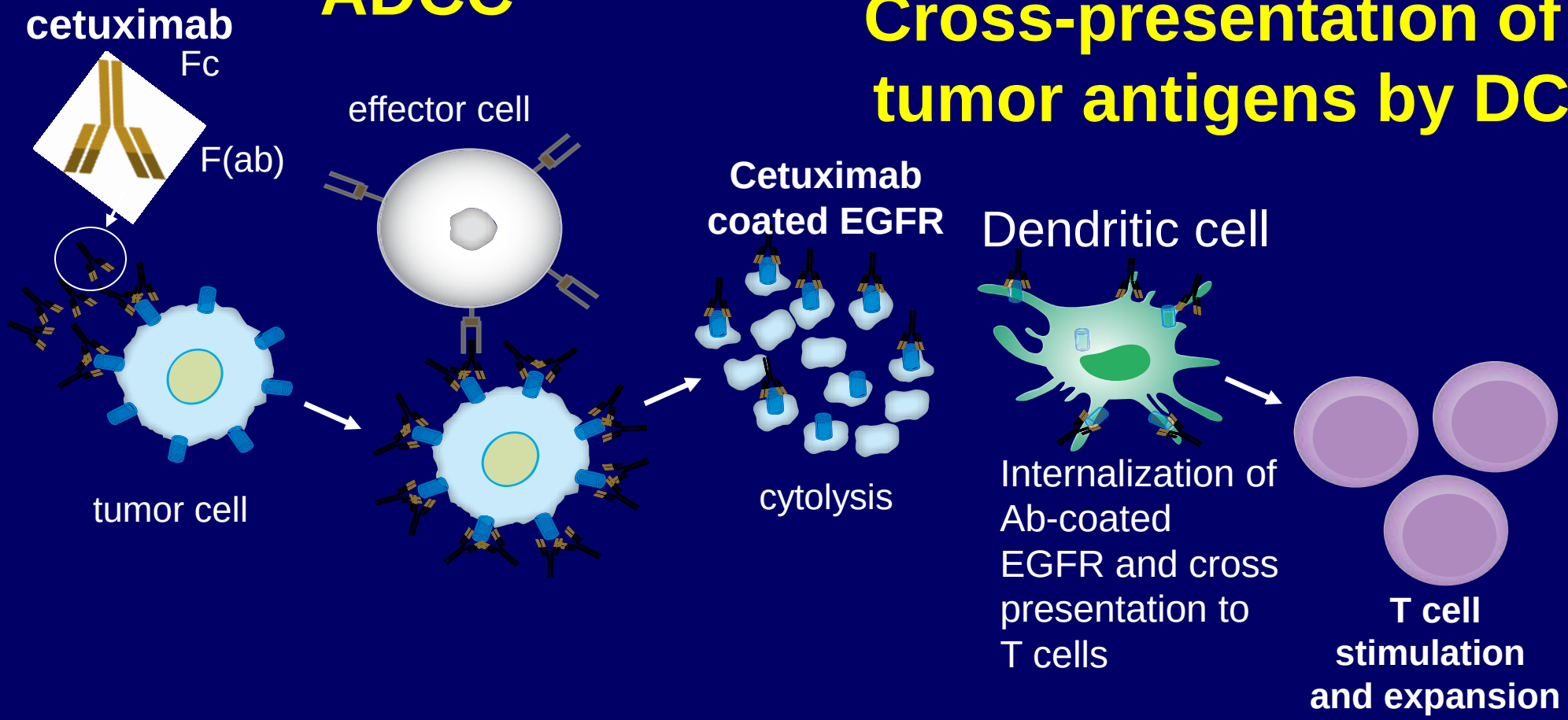






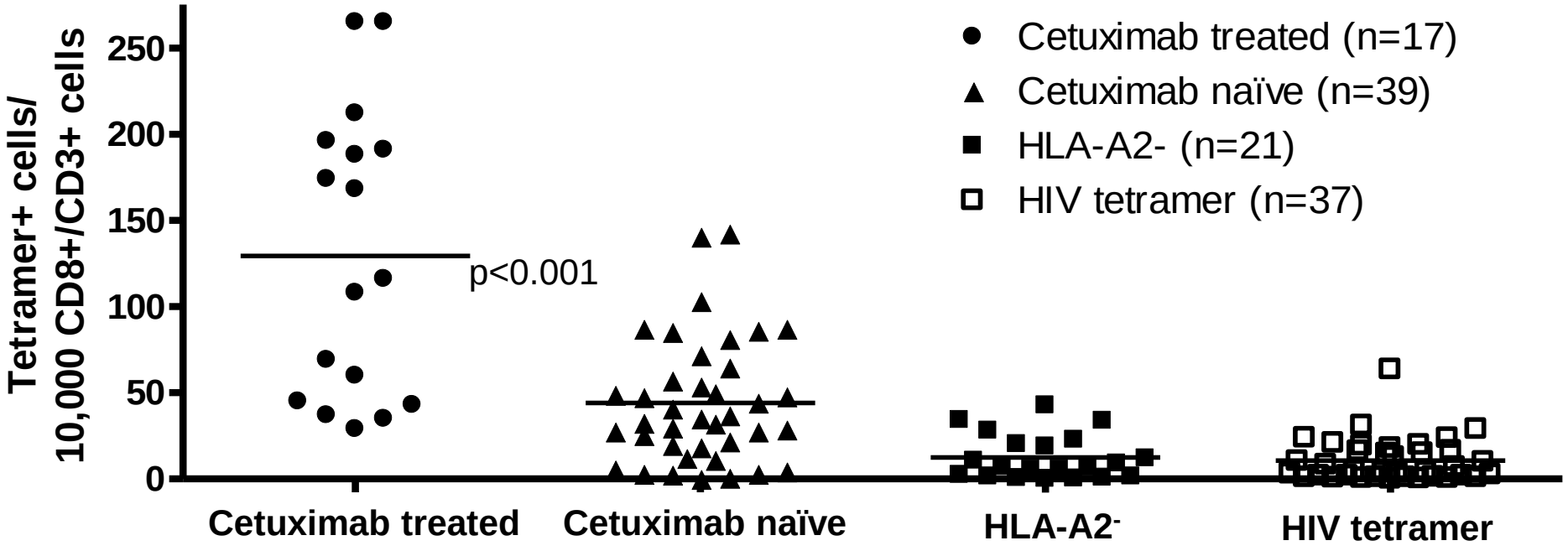


ADCC



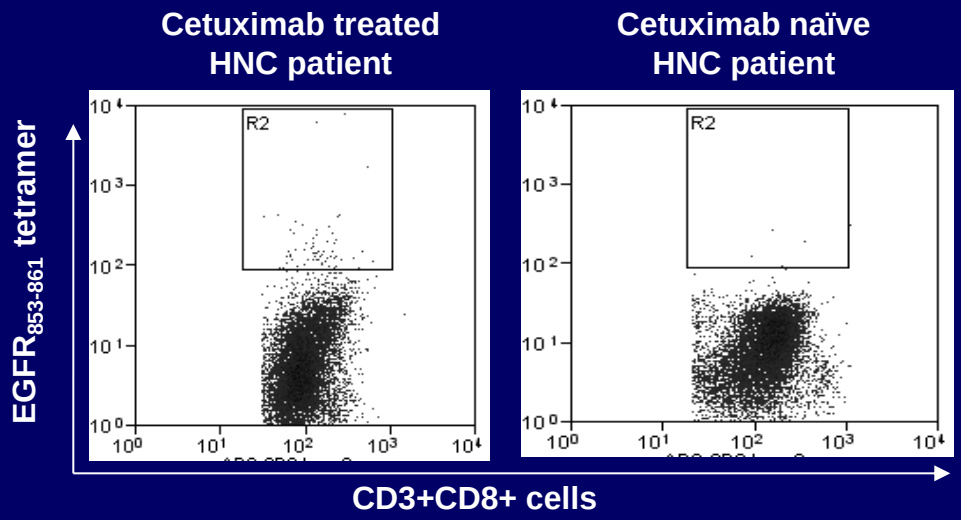
Cross-presentation of tumor antigens by DC

EGFR-specific tetramer+ T cell frequencies are elevated in cetuximab treated HNC patients compared cetuximab naïve HNC patients



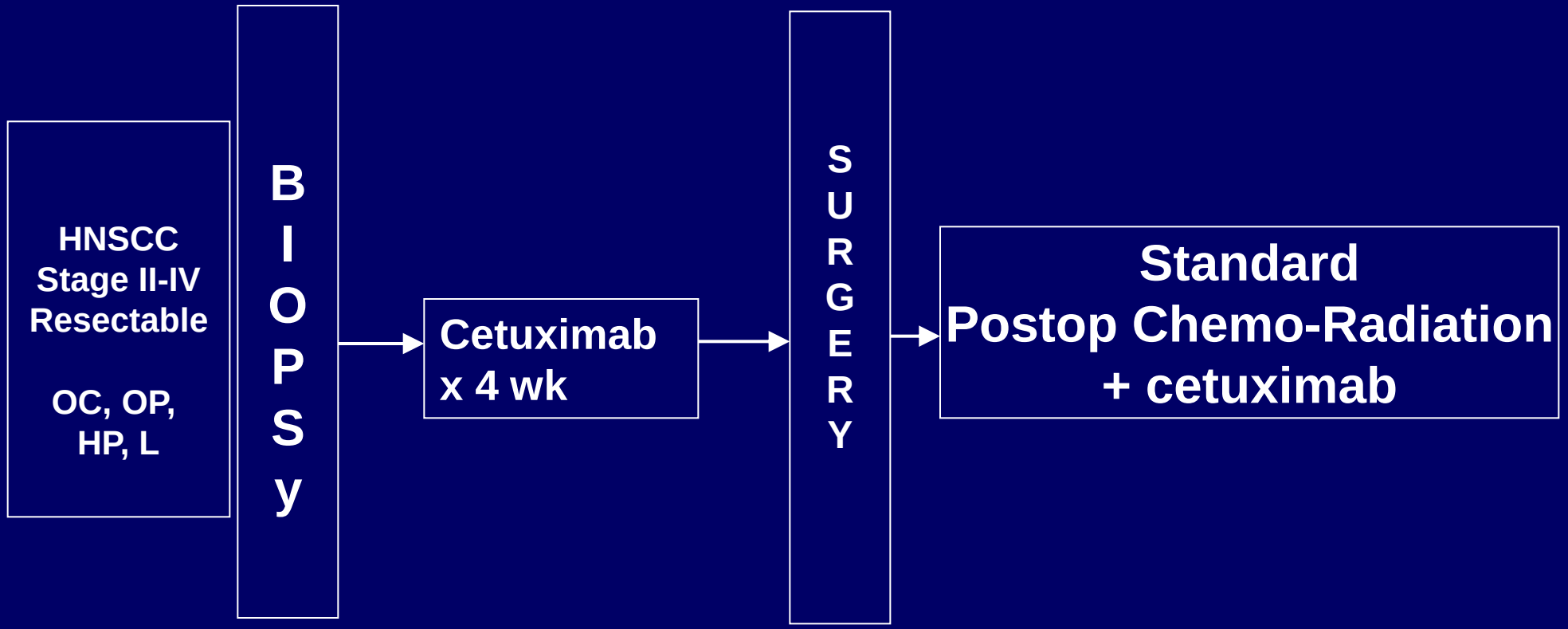
Athanassios Argiris, MD
Michael Gibson, MD
James Ohr, MD

Pedro Andrade, MD



Srivastava,
Clin Cancer Res, 2013

Neoadjuvant Cetuximab Followed by Surgery/CRT and adjuvant Cetuximab (UPCI Protocol #08-013)



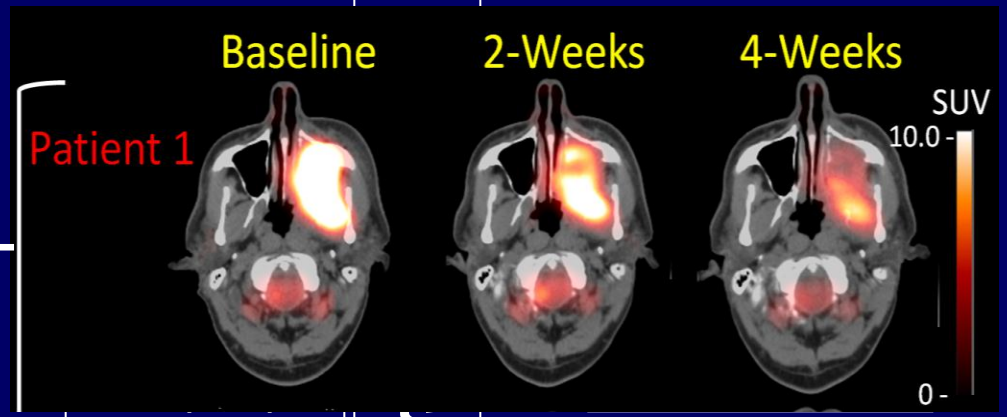
Endpoints:
Modulation of biomarkers, 2-yr DFS
Sample size N=33/40

R01 DE 19727
P50 CA097190

PI - Ferris

Neoadjuvant Cetuximab
Followed by Surgery and adjuvant Cetuximab
(UPCI Protocol #08-013)

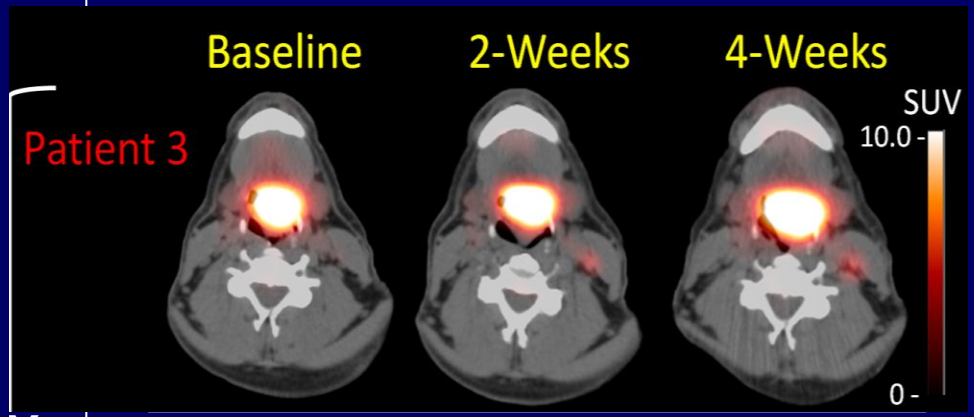
Responder



HP, L

S
y

Nonresponder

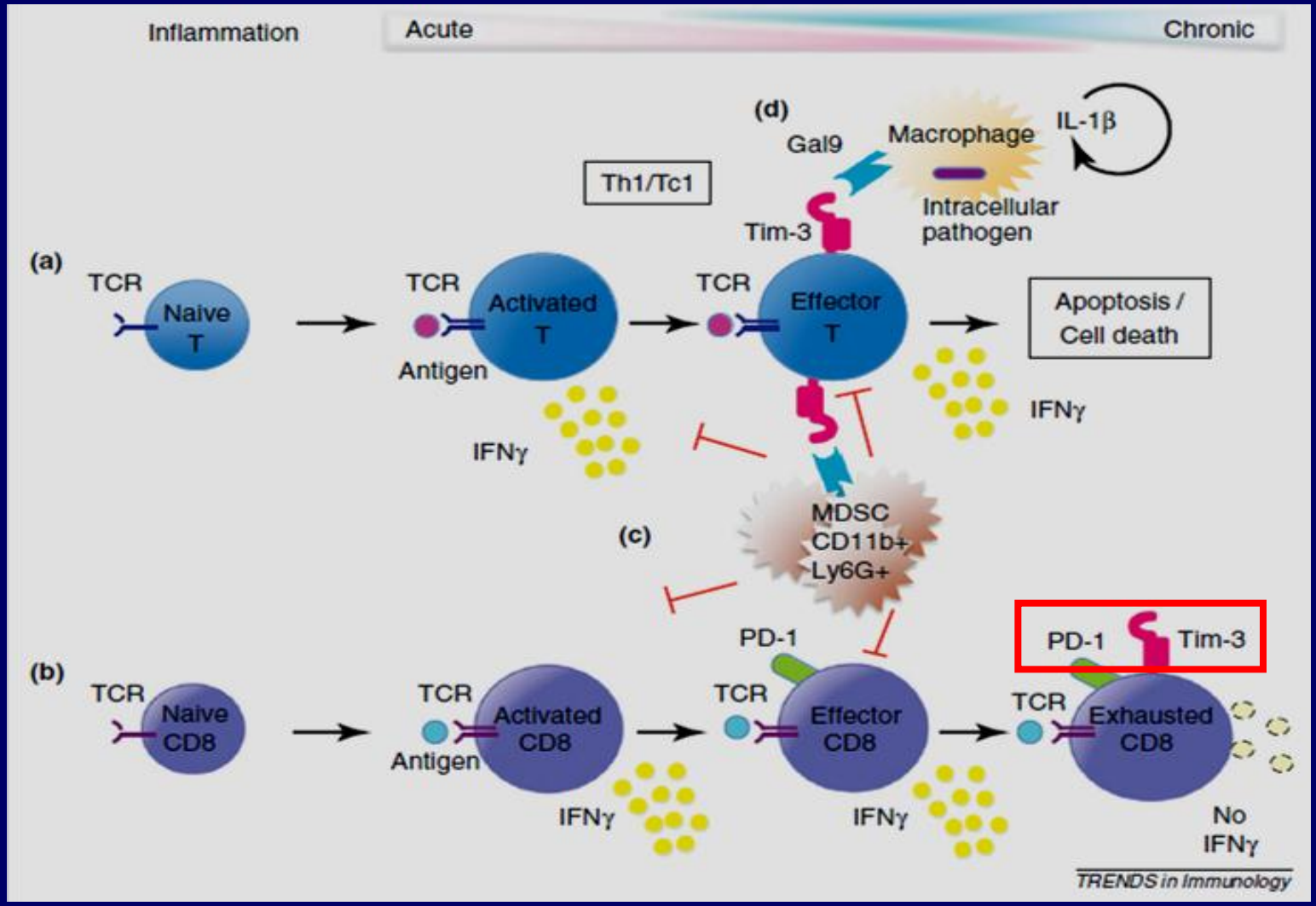


Y

Endpoints:
Modulation of immune biomarkers, 2-yr PFS
ACCRUAL 33/40

James Mountz, MD, PhD

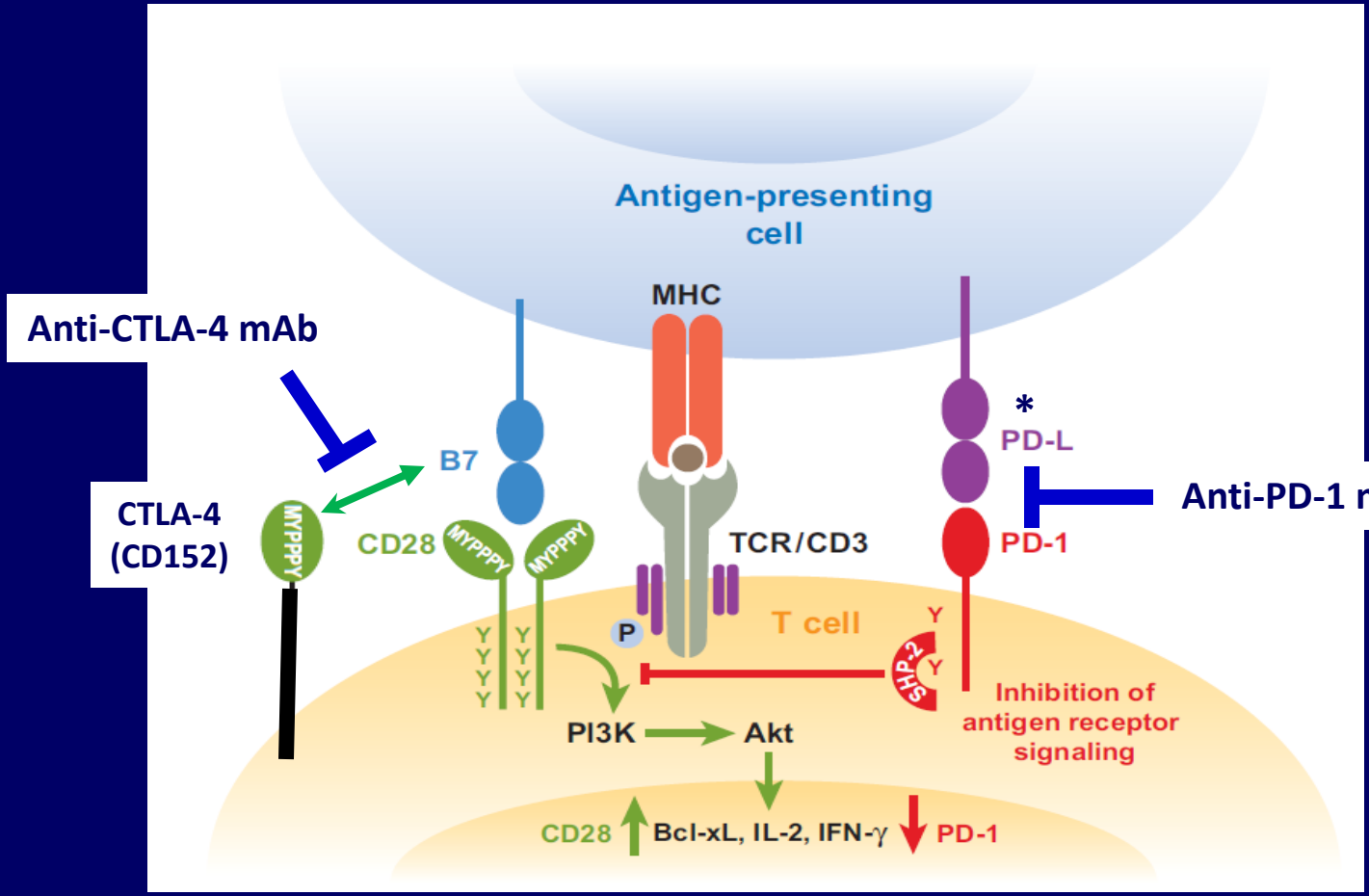
Exhausted CD8$^+$ T cells express PD-1 and Tim-3 during chronic antigen stimulation



Trends in Immunology August 2011, Vol. 32, No. 8

Blocking inhibitory receptors to reactivate exhausted T cells

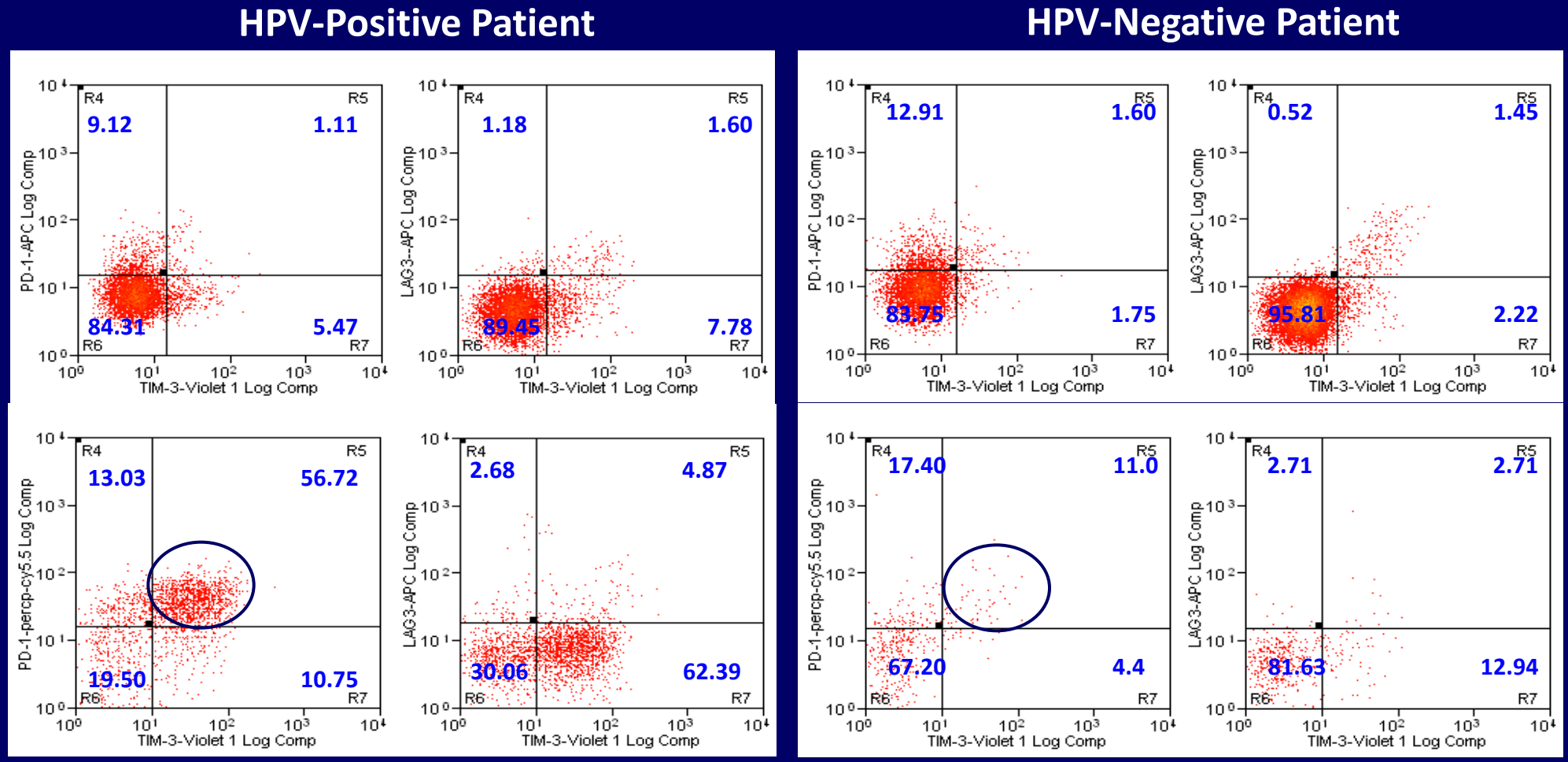
New immunotherapeutic targets: CTLA-4 and PD-1 (Programmed death 1)



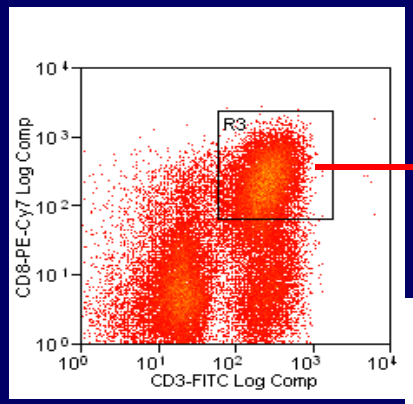
(* PD-Ligand expressed on cancer cells)

Modified from Annu. Rev. Immunol. 2008. 26:677–704

TIM-3, PD-1, and LAG-3 Expression by CD8+ TIL and PBL (HPV+ vs HPV-)



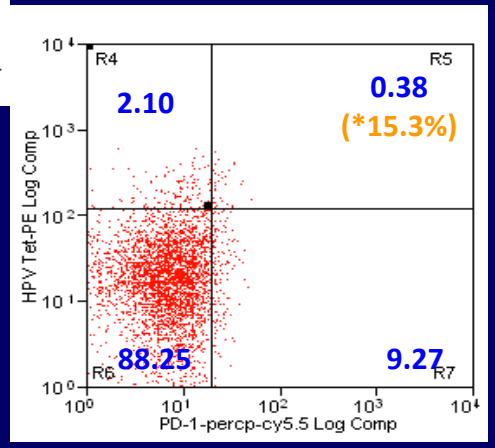
Checkpoint Receptors on HPV E7-Tetramer+ TIL (HPV+ Patient 11-6369)

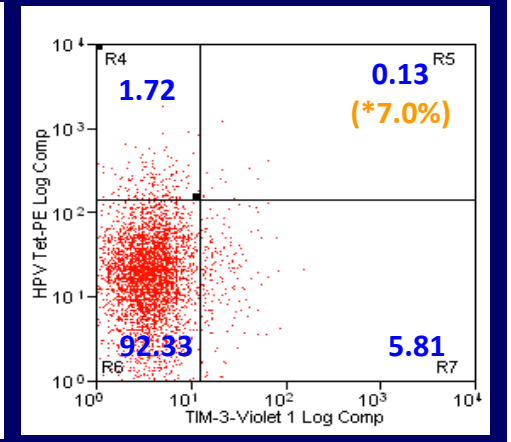


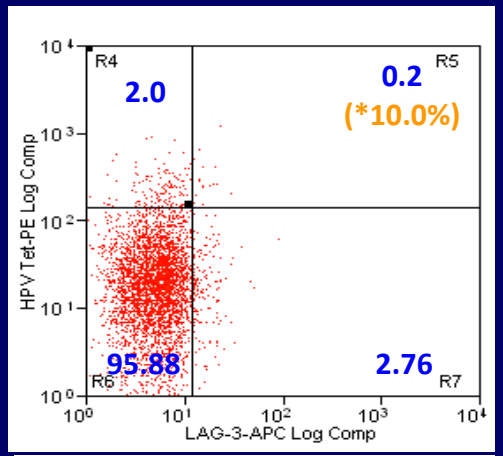
analysis

* % in tetramer + Cells

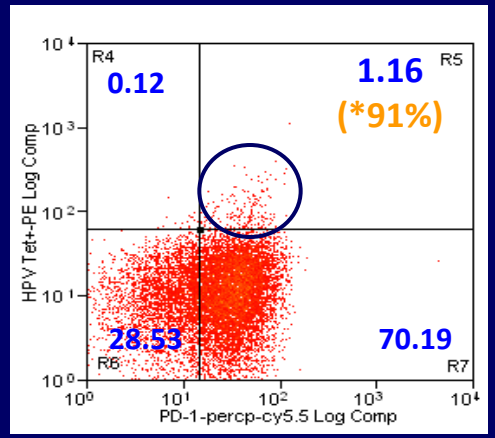
PBL

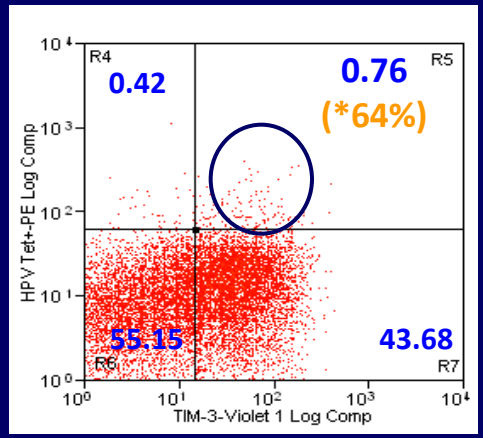


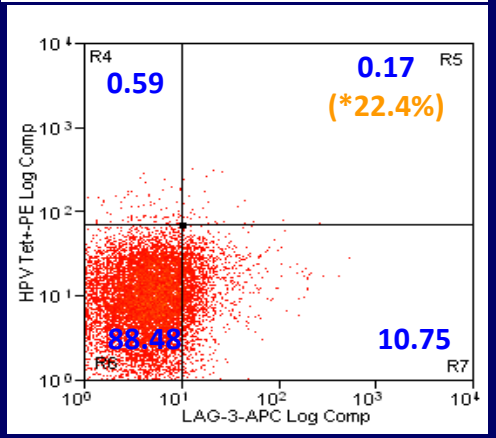




TIL

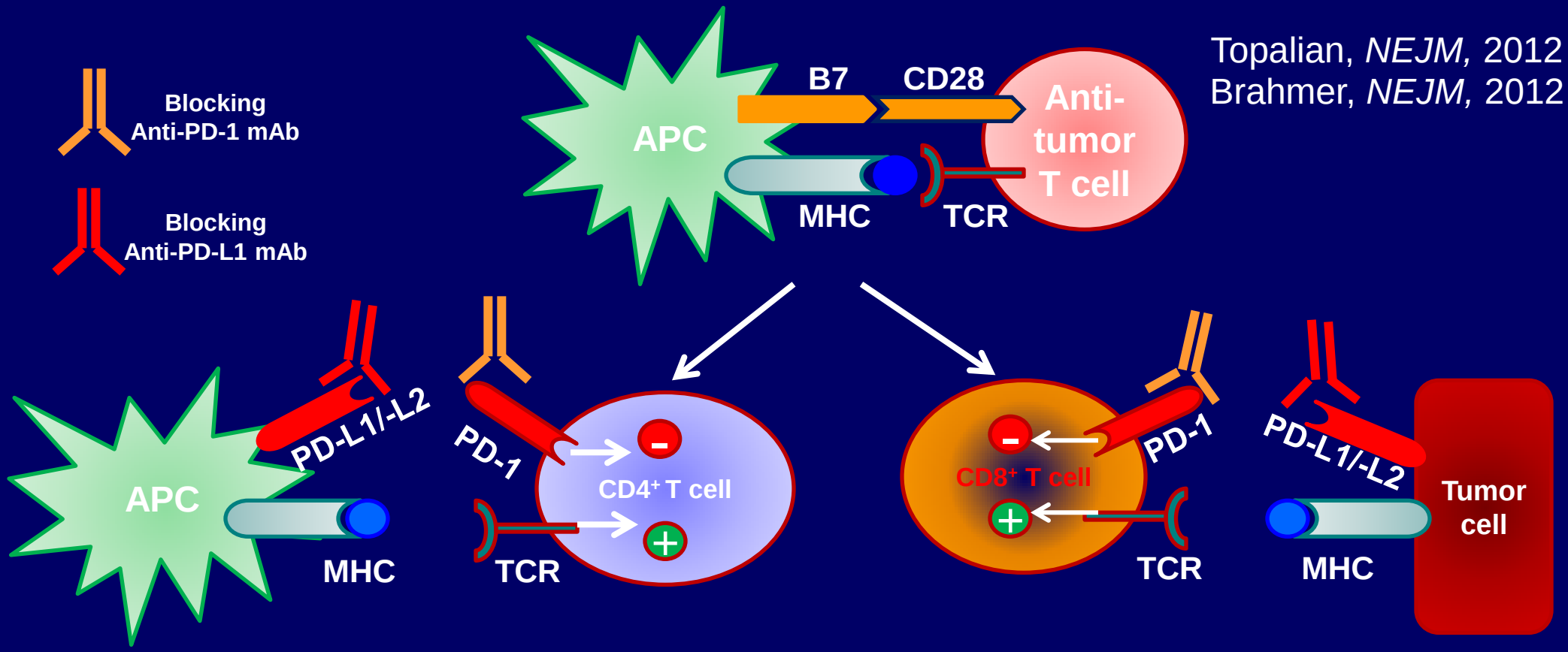






HPV+ sample contains higher proportion of PD-1+/TIM-3+ cells on HPV E7-tetramer+ TIL than PBL

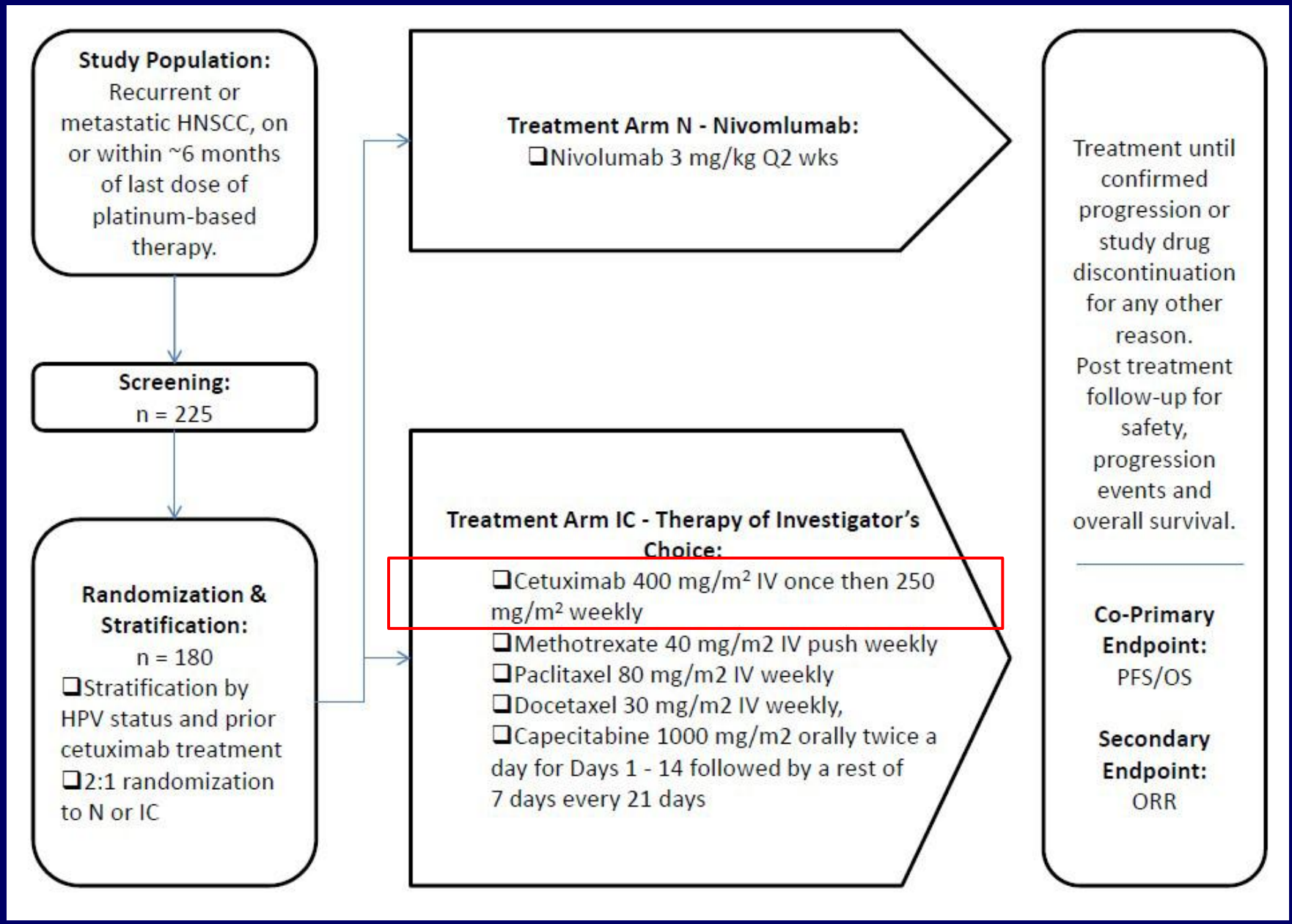
Targeting the PD-1/PD-L1 pathway



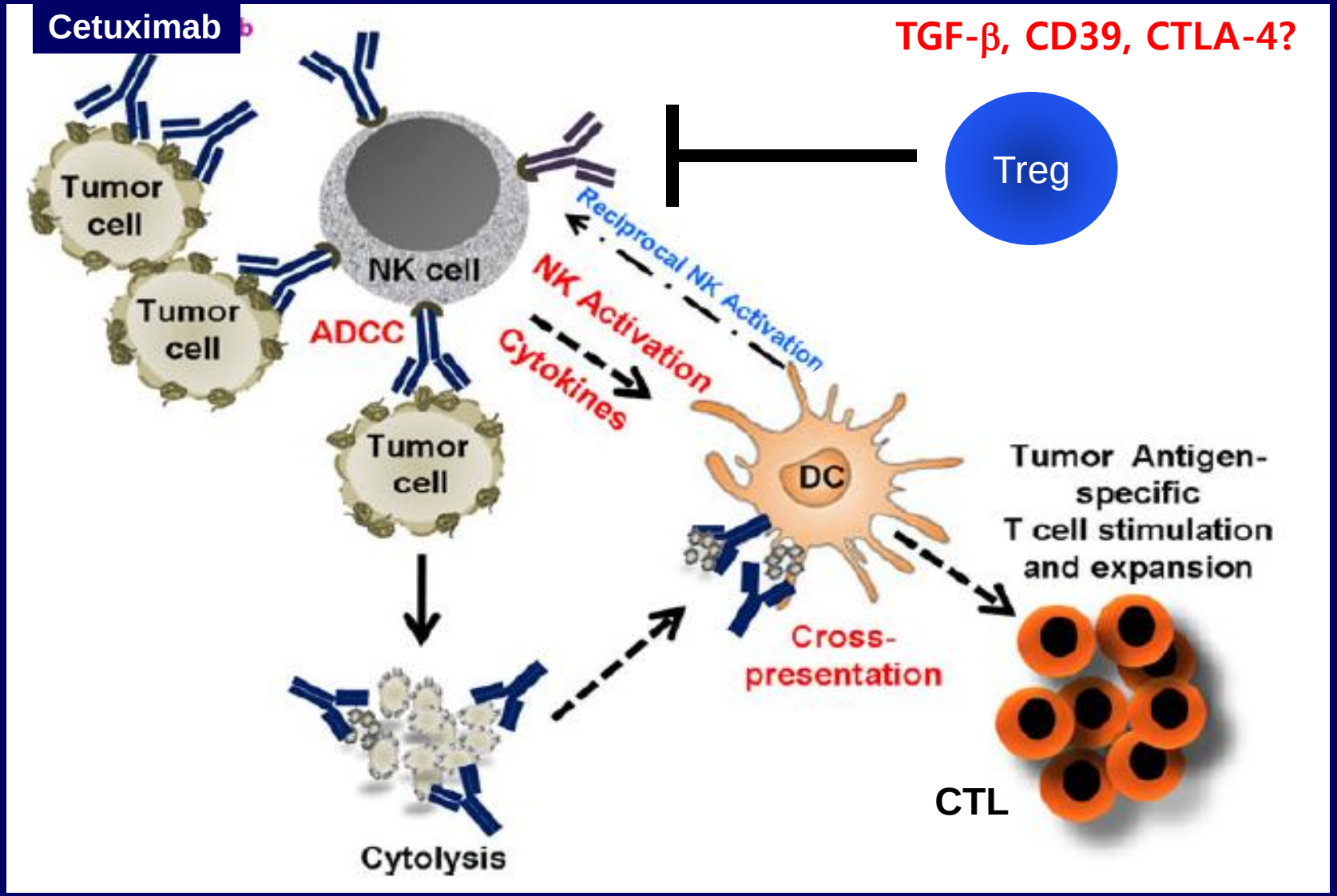
Topalian, *NEJM,* 2012
Brahmer, *NEJM,* 2012

Ferris, RL, *Cancer* , 2012

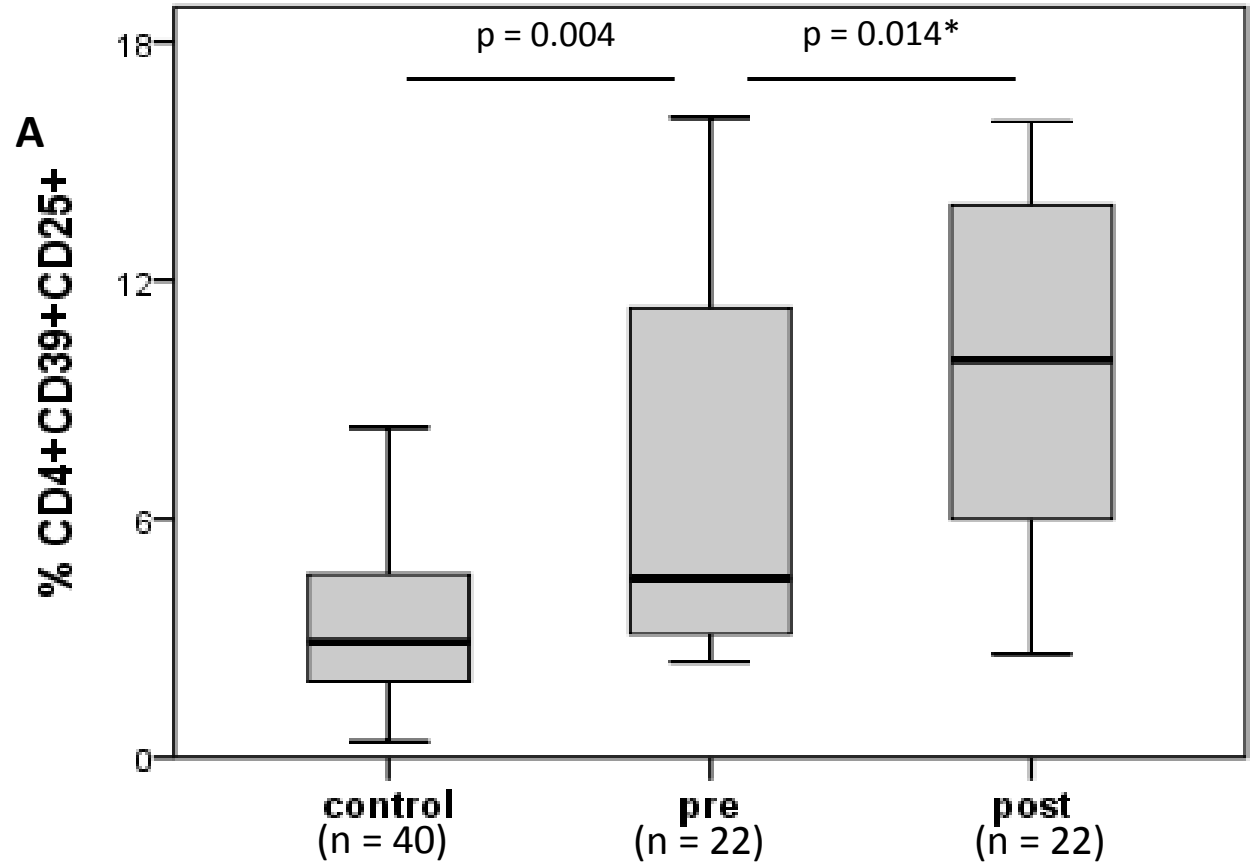
CA209-141: *Randomized Phase II/III Trial of Nivolumab vs Cetuximab in Recurrent or Metastatic Platinum-refractory HNSCC*



Immune Responses induced by cetuximab treatment

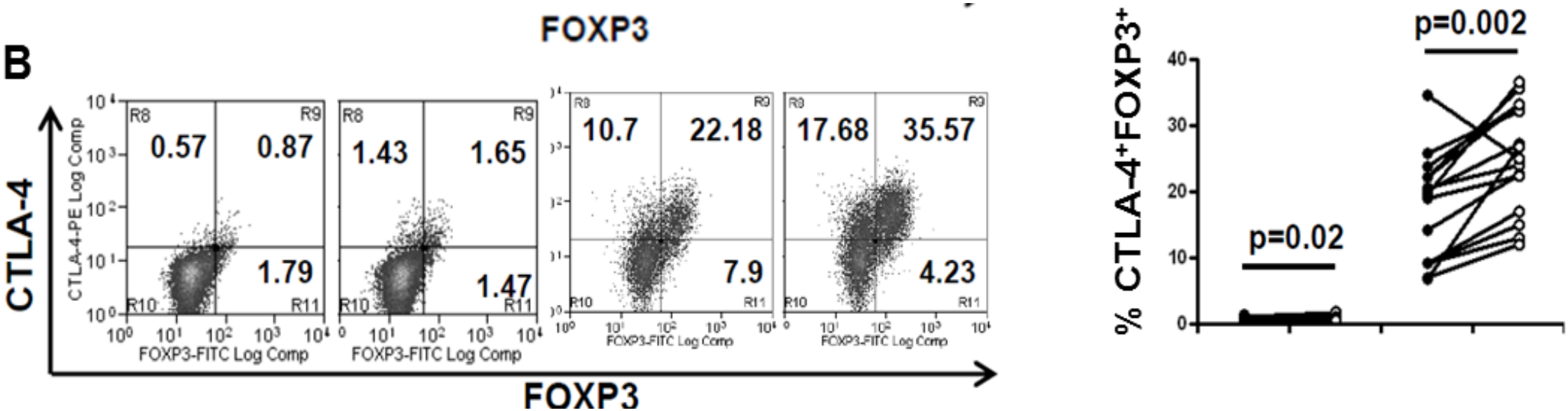


Cetuximab induces suppressor/regulatory T cells in treated HNSCC patients

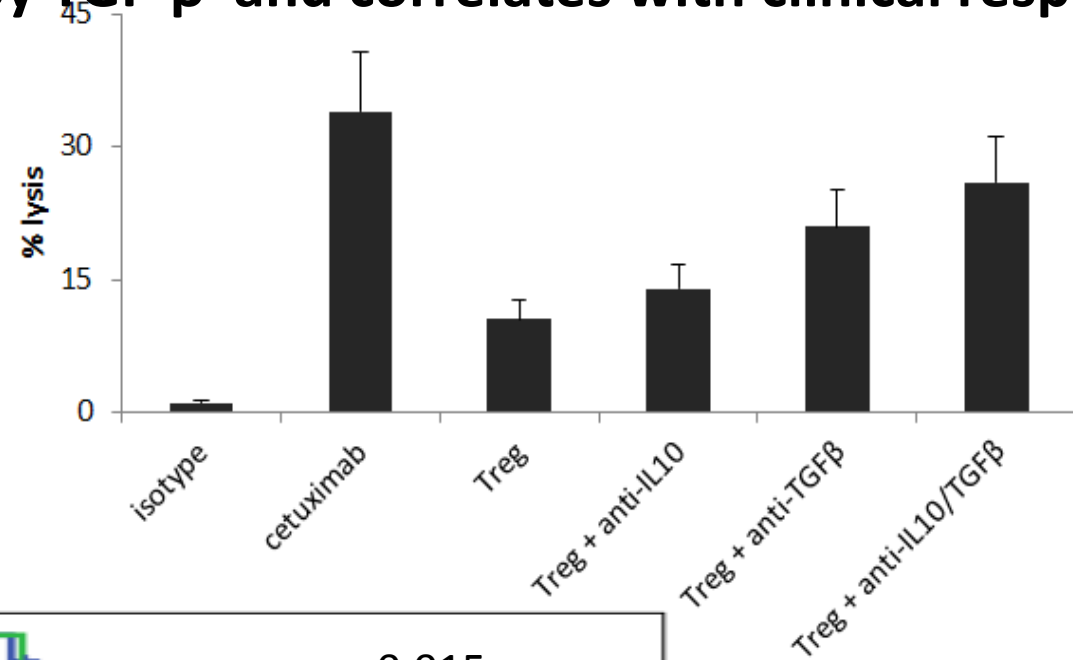


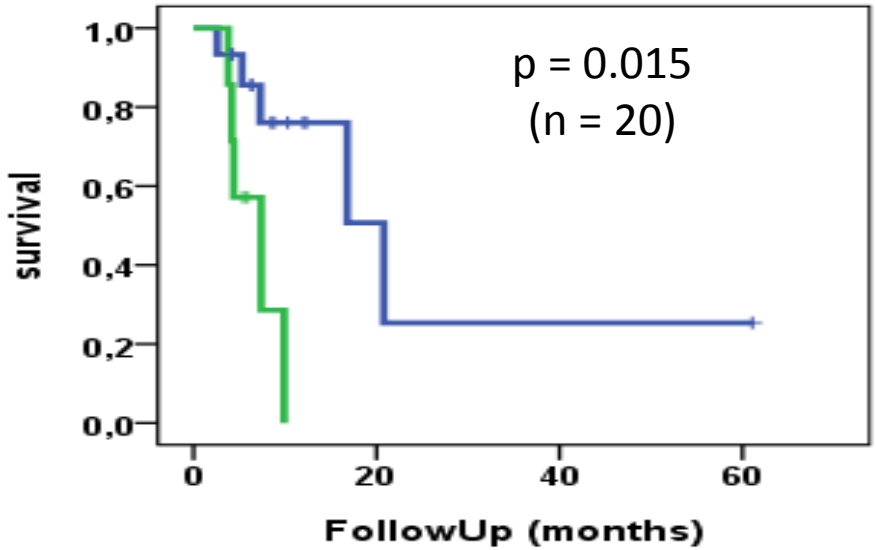
* paired Wilcoxon Sign test

Cetuximab induces CTLA-4+ Treg cells in treated HNSCC patients



Treg suppression of cetuximab mediated antitumor activity Is mediated by TGF-β and correlates with clinical response





$CD4^+CD39^+CD25^+$ Treg before cetuximab treatment:

> 6% < 6%

Phase Ib Trial of Concurrent Cetuximab/IMRT with Ipilimumab, Plus Biomarker Correlatives, in Locally Advanced, High Risk Oropharynx Cancer

SCHEMA

Stage III-IVA OPSCC (HPV- HPV+ smokers, ≥N2b) p16 IHC Tumor/ Blood collection

→

Cetuximab/Radiotherapy Plus Ipilimumab

RT 66 Gy with 200 cGy daily fractions in 6.5 weeks

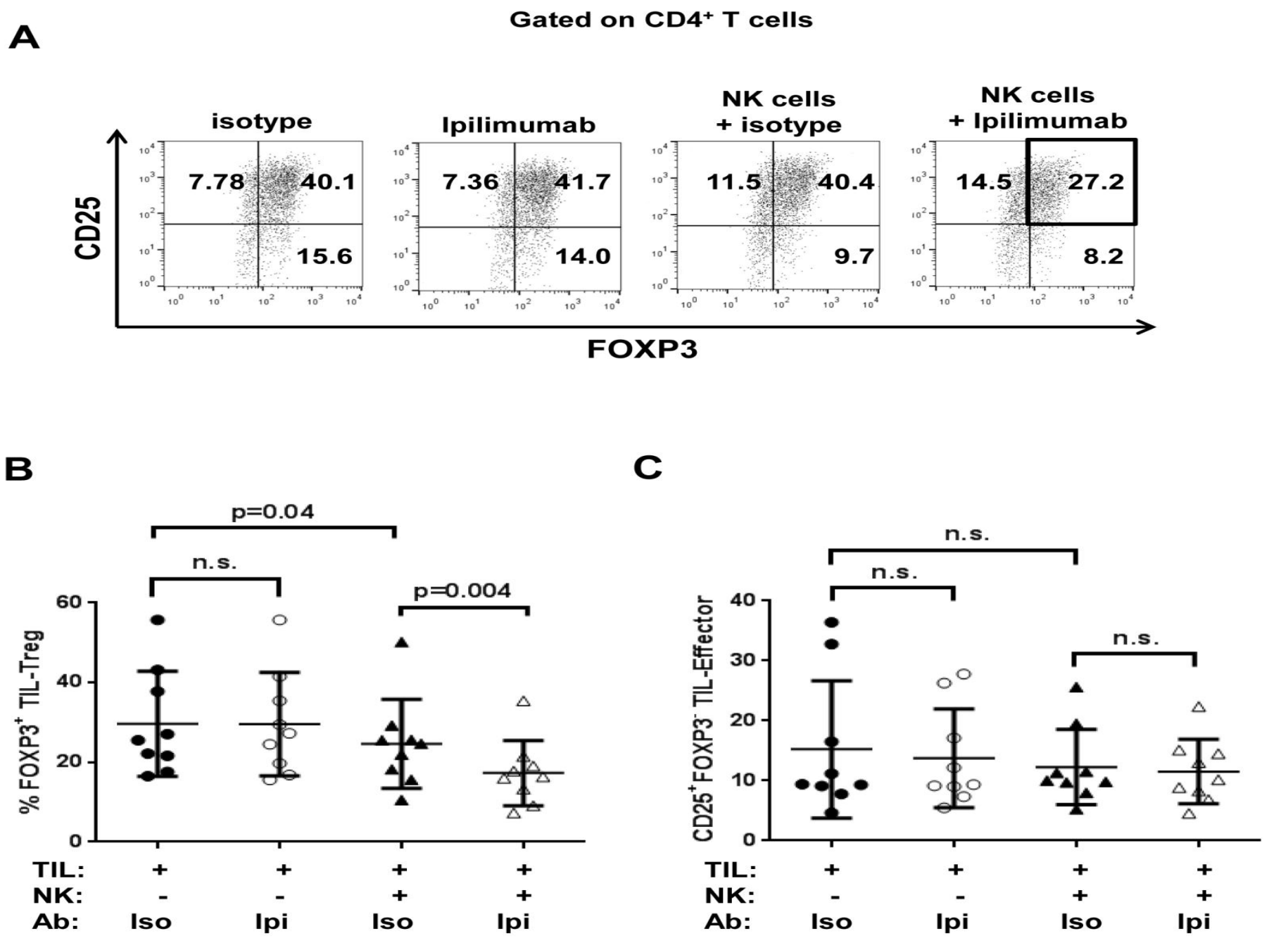
Cetuximab weekly at 250 mg/m^2 during radiation*

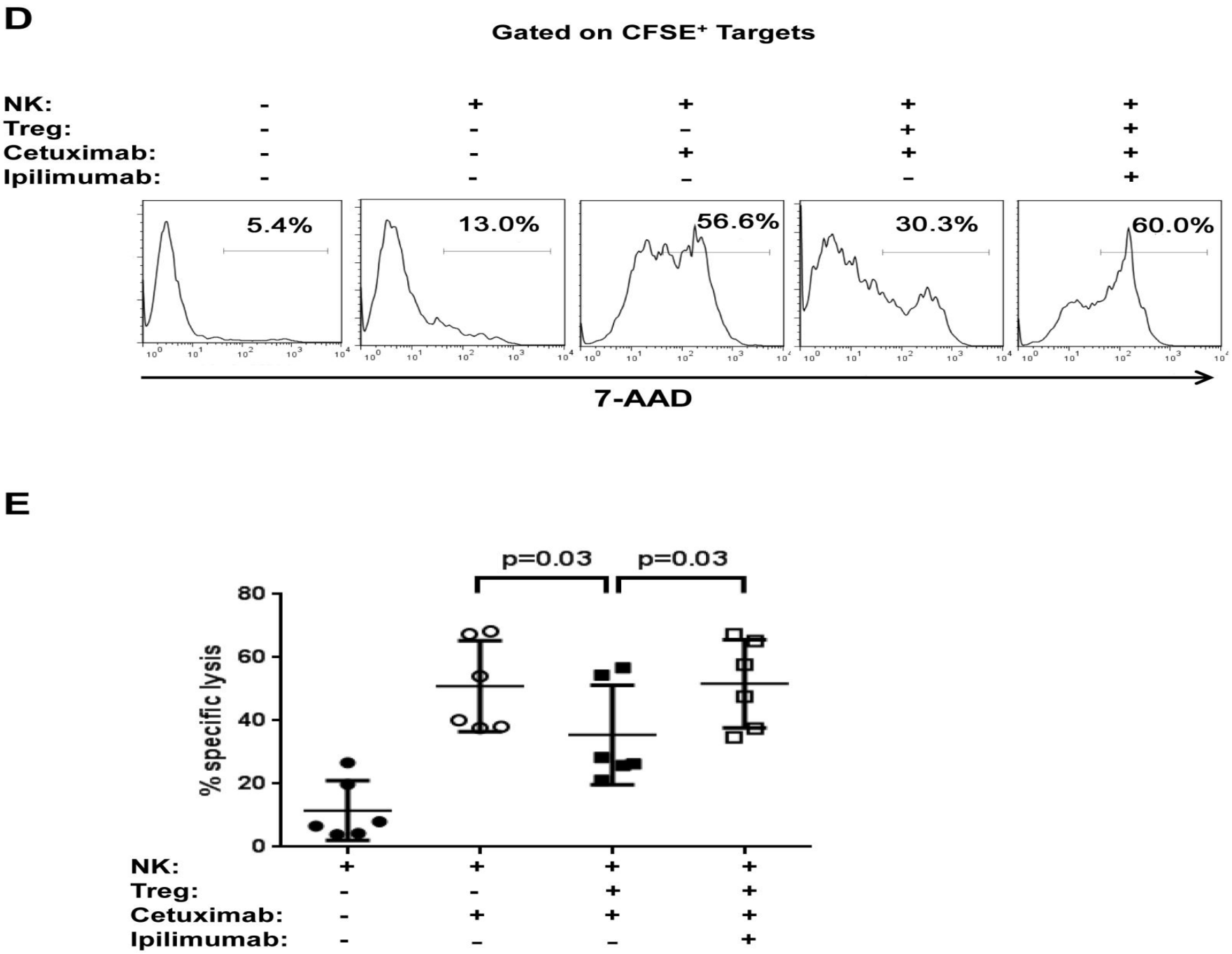
Ipilimumab 3, 10 mg/kg q21 days, starting week 4

*after loading dose of 400 mg/m^2 on cycle 1, day 1

Ipilimumab will be continued at indicated dose for additional 2 cycles.

Ferris and Bauman


A
Gated on CD4+ T cells
isotype
Ipilimumab
NK cells + isotype
NK cells + Ipilimumab
CD25
FOXP3
7.78
40.1
15.6
7.36
41.7
14.0
11.5
40.4
9.7
14.5
27.2
8.2
B
p=0.04
n.s.
p=0.004
% FOXP3+ TIL-Treg
60
40
20
0
TIL: + + + +
NK: - - + +
Ab: Iso Ipi Iso Ipi
C
n.s.
n.s.
n.s.
CD25+FOXP3- TIL-Effector
40
30
20
10
0
TIL: + + + +
NK: - - + +
Ab: Iso Ipi Iso Ipi


D
Gated on CFSE+ Targets
NK: - + + + +
Treg: - - - + +
Cetuximab: - - + + +
Ipilimumab: - - - - +
5.4%
13.0%
56.6%
30.3%
60.0%
7-AAD
E
p=0.03
p=0.03
% specific lysis
80
60
40
20
0
NK: + + + +
Treg: - - + +
Cetuximab: - + + +
Ipilimumab: - - - +

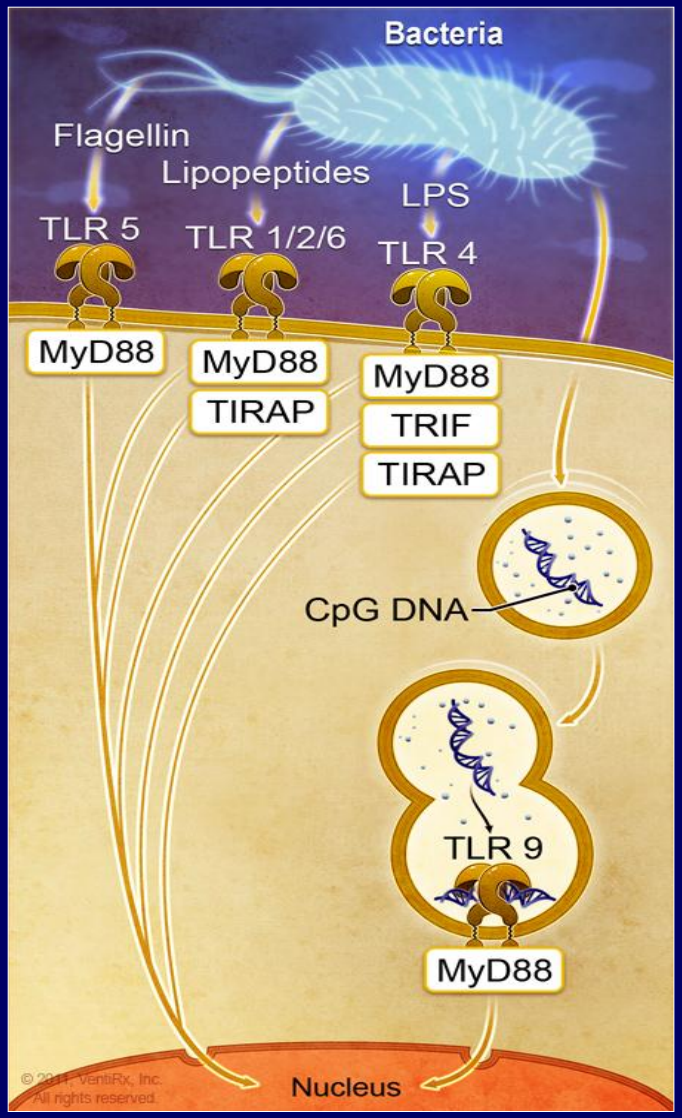
Summary

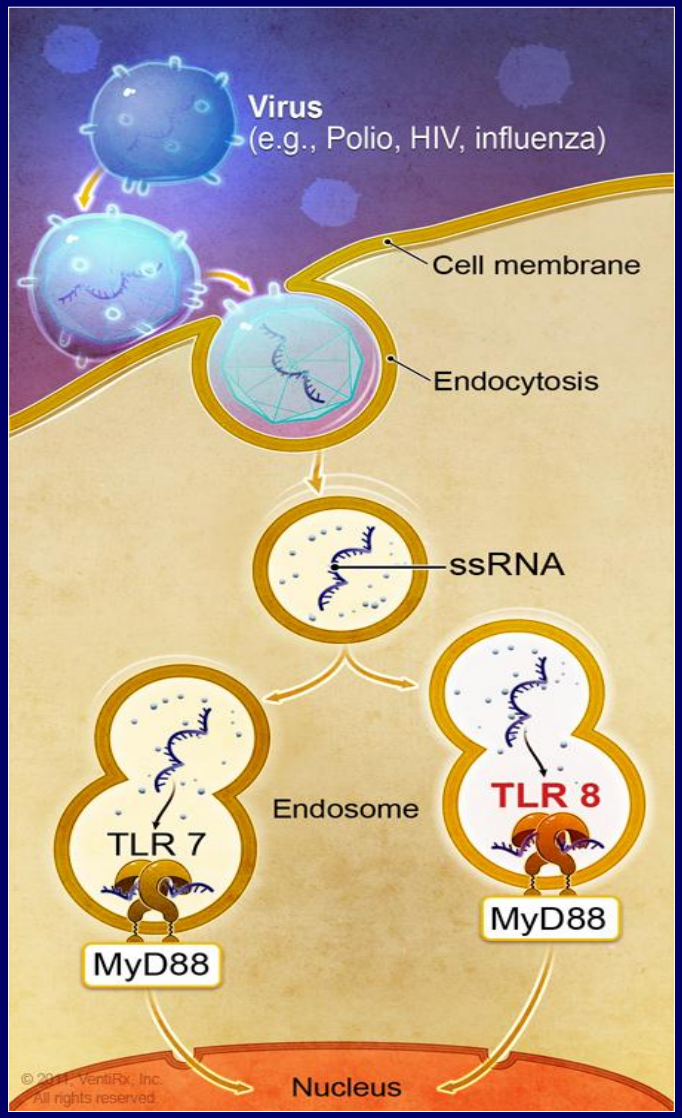
- Cellular immunity (antitumor NK and T cells) are induced by cetuximab

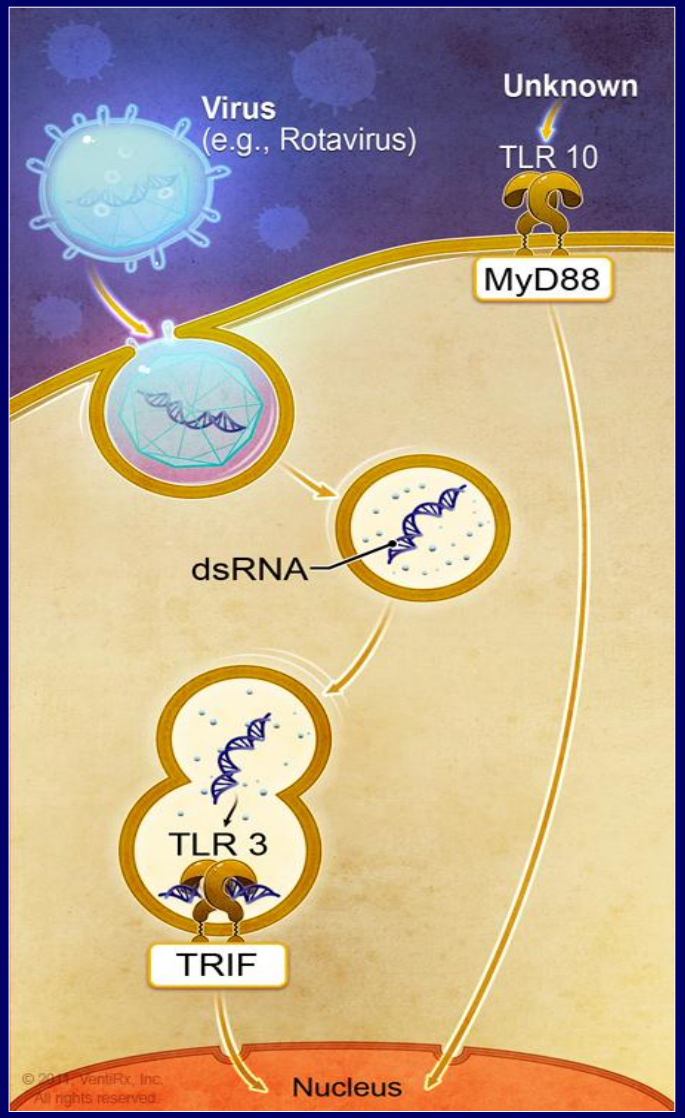
- Suppressive mechanisms include regulatory T cells (Treg) and checkpoint receptors (CTLA-4, PD-1, etc)

- But what else is clinically available for immuno-therapy of HNC? -> Toll Like Receptor Adjuvants
- TLR3 – poly IC:LC – plans for clinical trial
- Active8: EXTREME +/- TLR8 agonist trial

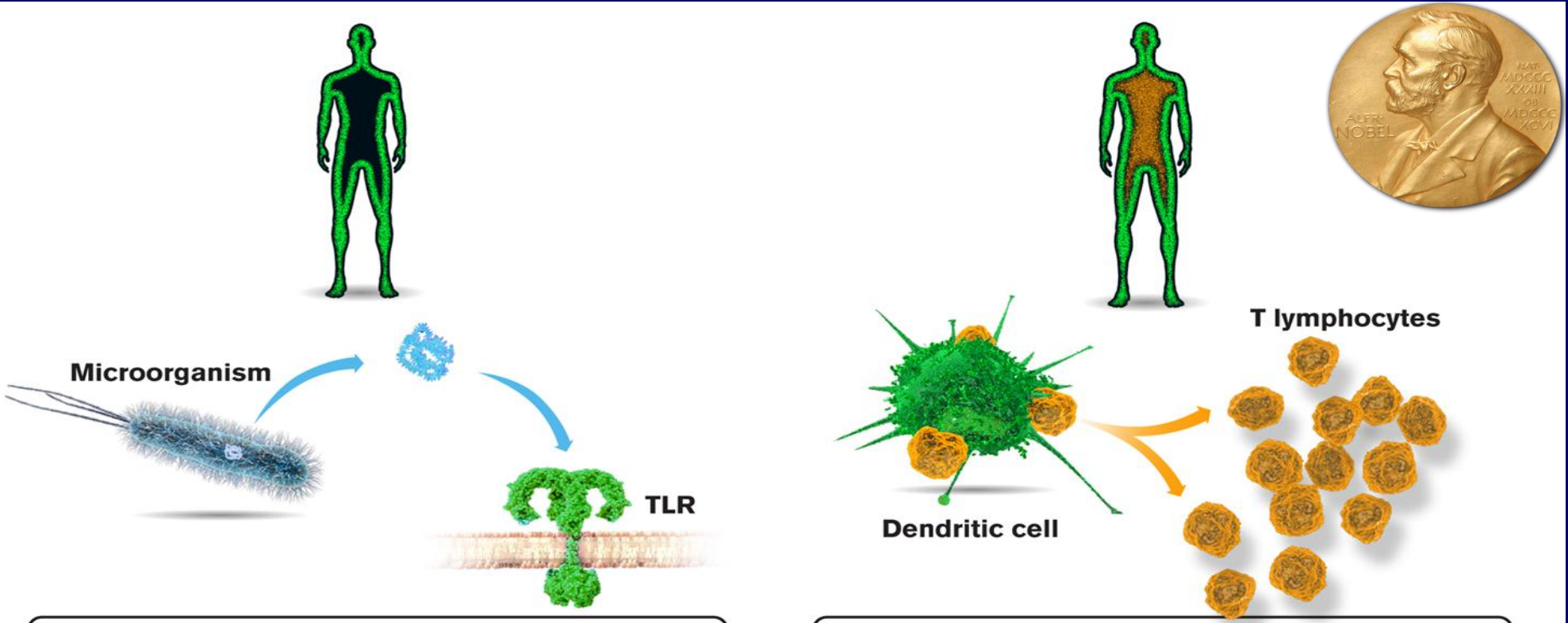
Human TLR Family and Known Ligands







The Nobel Prize in Physiology or Medicine 2011



1 Innate immunity

Components of microorganisms bind to Toll-like receptors located on many cells in the body. This activates innate immunity, which leads to inflammation and to the destruction of invading microorganisms.

2 Adaptive immunity

Dendritic cells activate T lymphocytes, which initiates adaptive immunity. A cascade of immune reactions follows, with formation of antibodies and killer cells.

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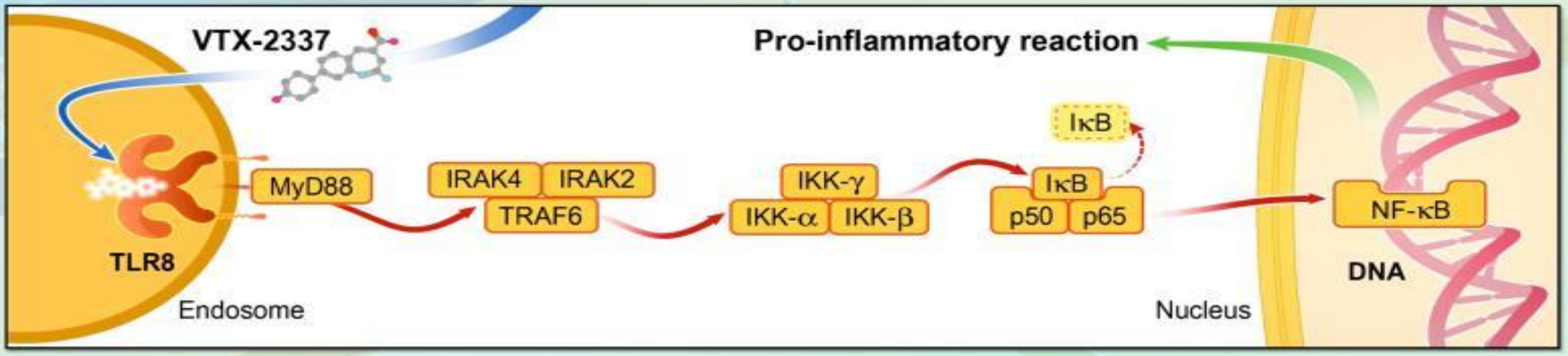
The 2011 Nobel Prize in Physiology or Medicine - Press Release". *Nobelprize.org. 11 Oct 2011 http://www.nobelprize.org/nobel_prizes/medicine/laureates/2011/press.html*

Toll-like Receptor 8 (TLR8) Pathway is Important in Human Immune Responses



- Activation induces potent Th1 immune response
- Expressed on myeloid dendritic cells ($CD11c^+$), monocytes ($CD14^+$), and natural killer cells ($CD56^+$) in humans
- Induces significant IL-12 production in humans
- Can be activated by small molecule agonists

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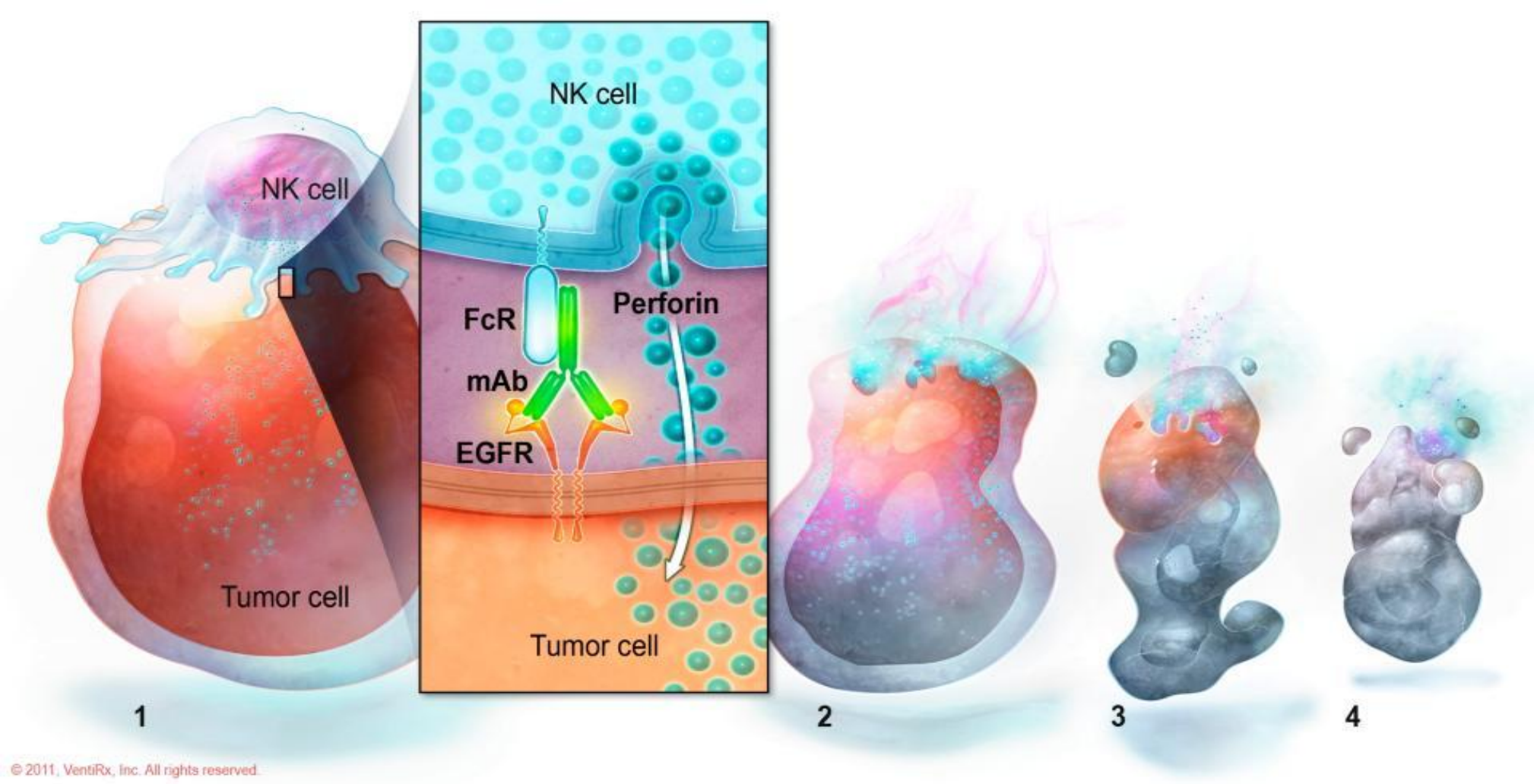
TLR8 – expression and function

	TLR8		
Expression	Myeloid DC, Monocytes	Plasmacytoid DC	Plasmacytoid DC, B-cells
Natural Ligand	ssRNA	ssRNA	Bacterial DNA
Small Molecule Agonist	Yes	Yes	No
IL-12 induction	Yes	No	No
TNFα induction	Yes	No	No
IFNα induction	No	Yes	Yes

Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Can Augment Tumor Cell Killing



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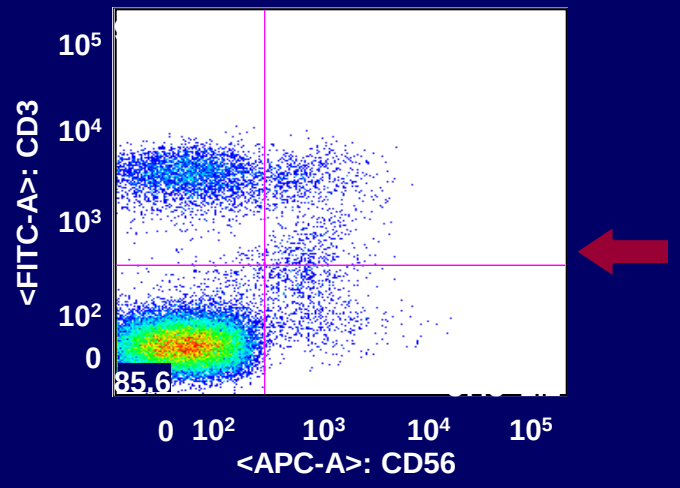
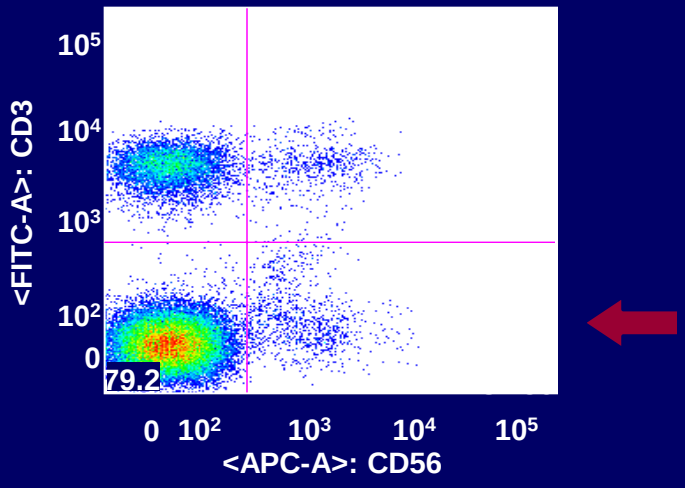
Phase 1b Head & Neck Trial: VTX-2337 + cetuximab

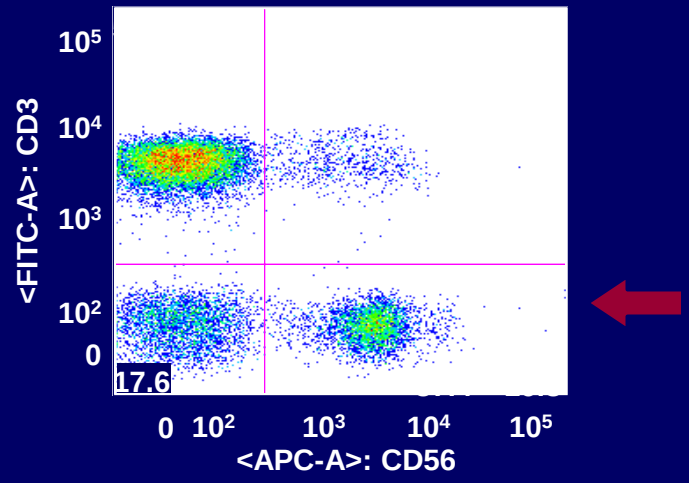
Representative Flow Cytometry Data

t=0 hr

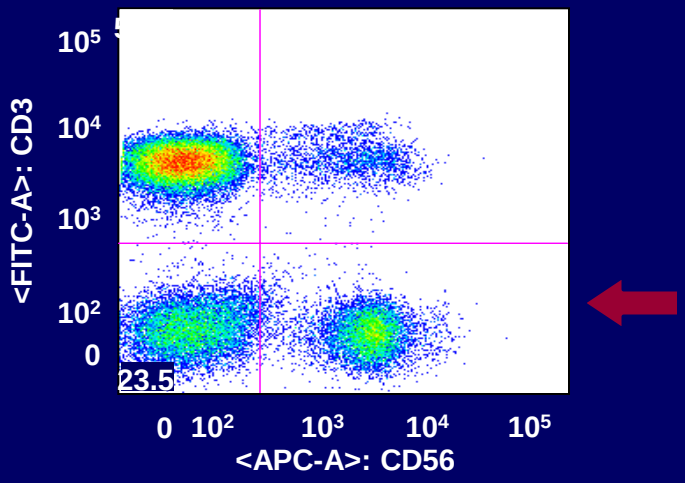




t=24 hr



Day 1



Day 15

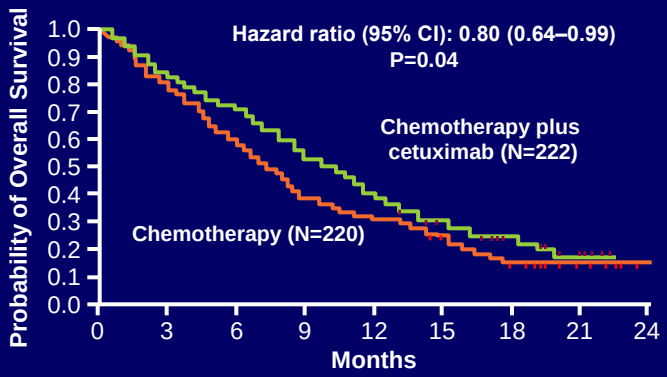
Targeting EXTREME Patient Population

- First-line therapy in locally advanced and metastatic head and neck cancer
- SOC: platinum, 5-FU, cetuximab
- 477 patients cisplatin (approx 60%) or carboplatin
- Primary Tumor sites:
  - oropharynx
  - hypopharynx
  - larynx

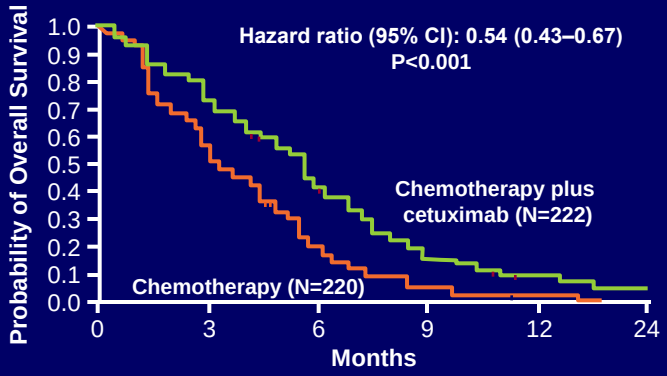
	PF + cetux	PF
OS	10.1 m	7.4 m
PFS	5.6 m	3.3 m
ORR	36%	20%
Disease Control	81%	60%

NEJM 2008:359:1116

Kaplan-Meier Estimates of Overall Survival and Progression-free Survival According to the Treatment Group

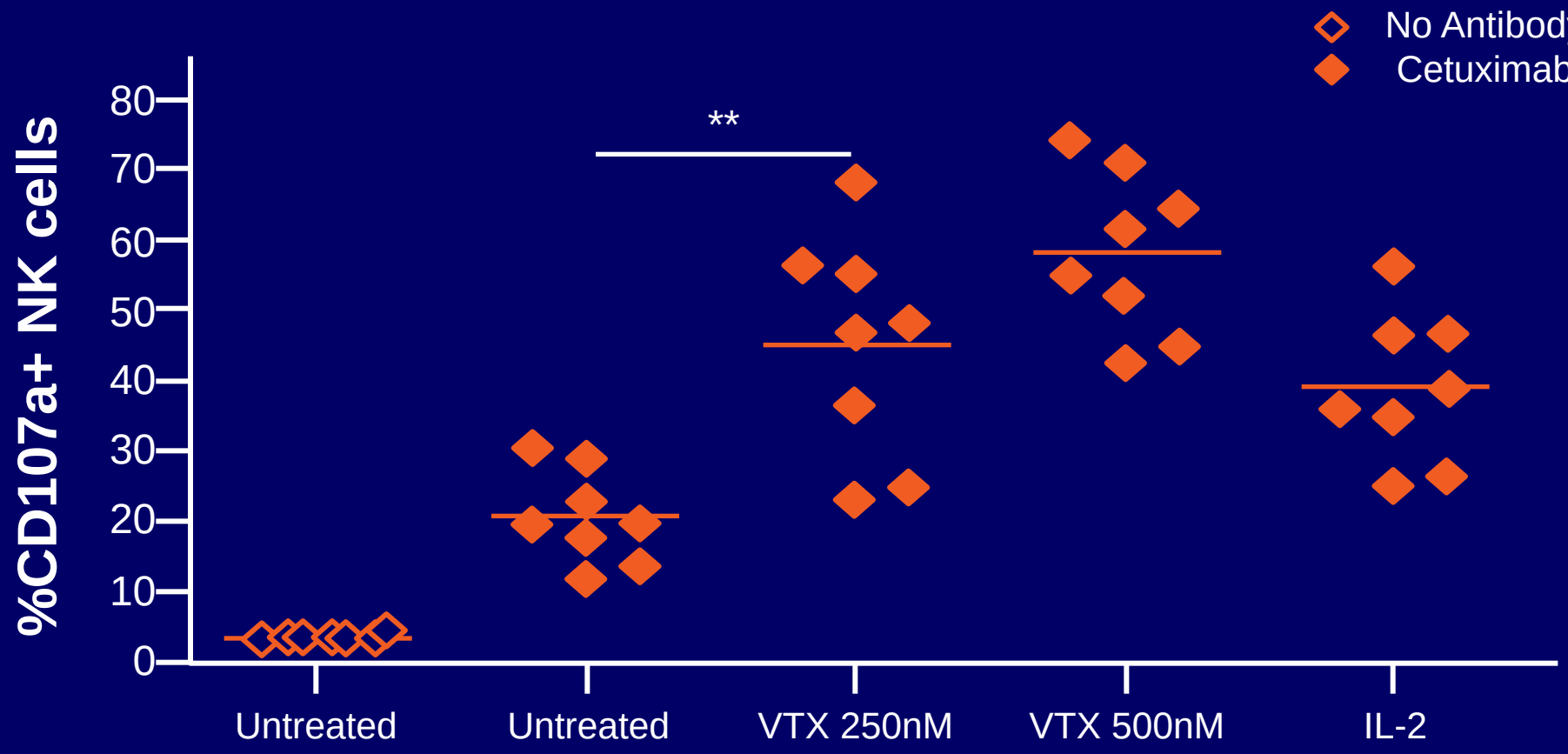


No. at Risk									
Chemotherapy	220	173	127	83	65	47	19	8	1
Chemotherapy plus cetuximab	222	184	153	118	82	57	30	15	3

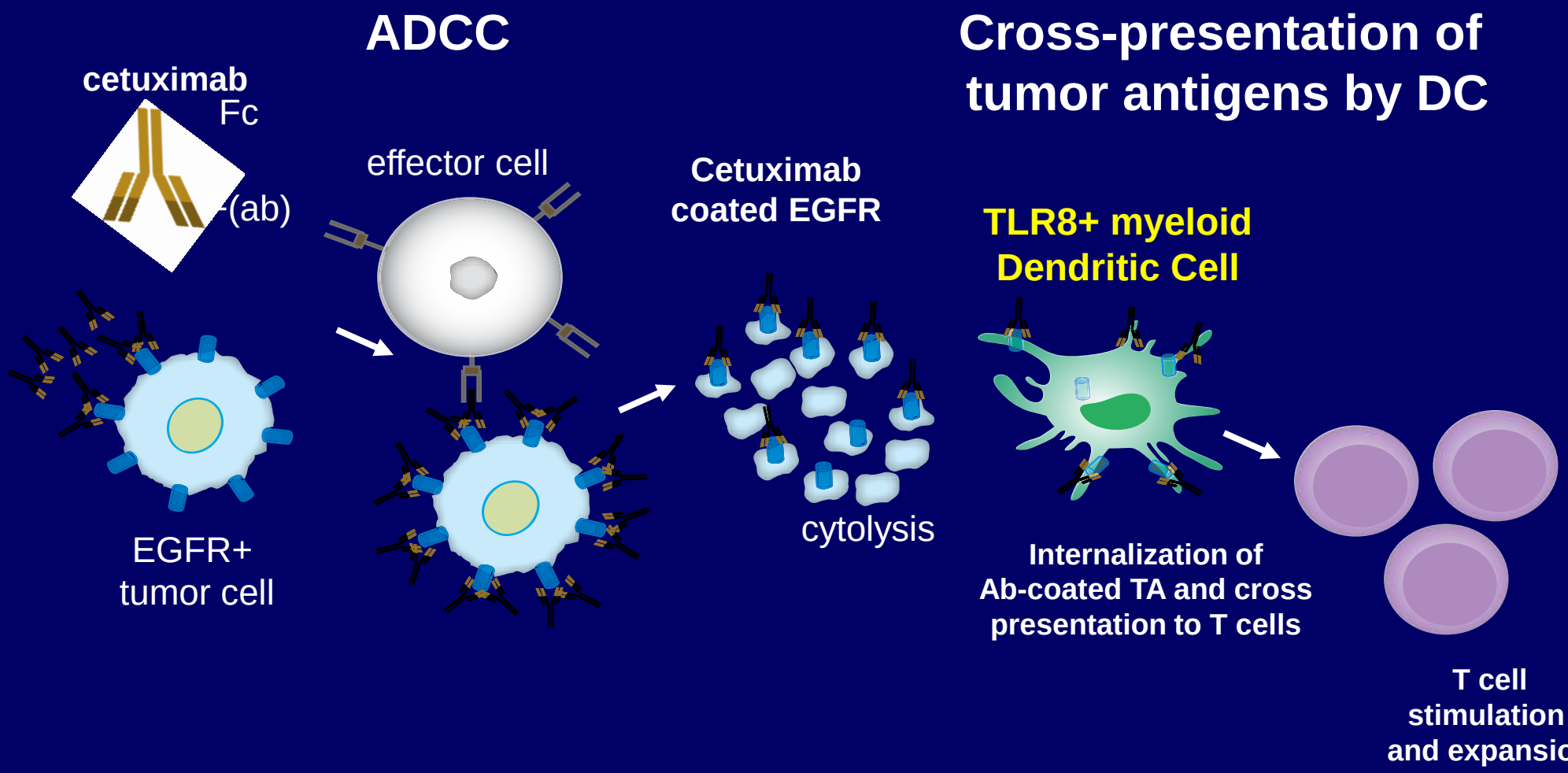


No. at Risk						
Chemotherapy	220	103	29	8	3	1
Chemotherapy plus cetuximab	222	138	72	29	12	7

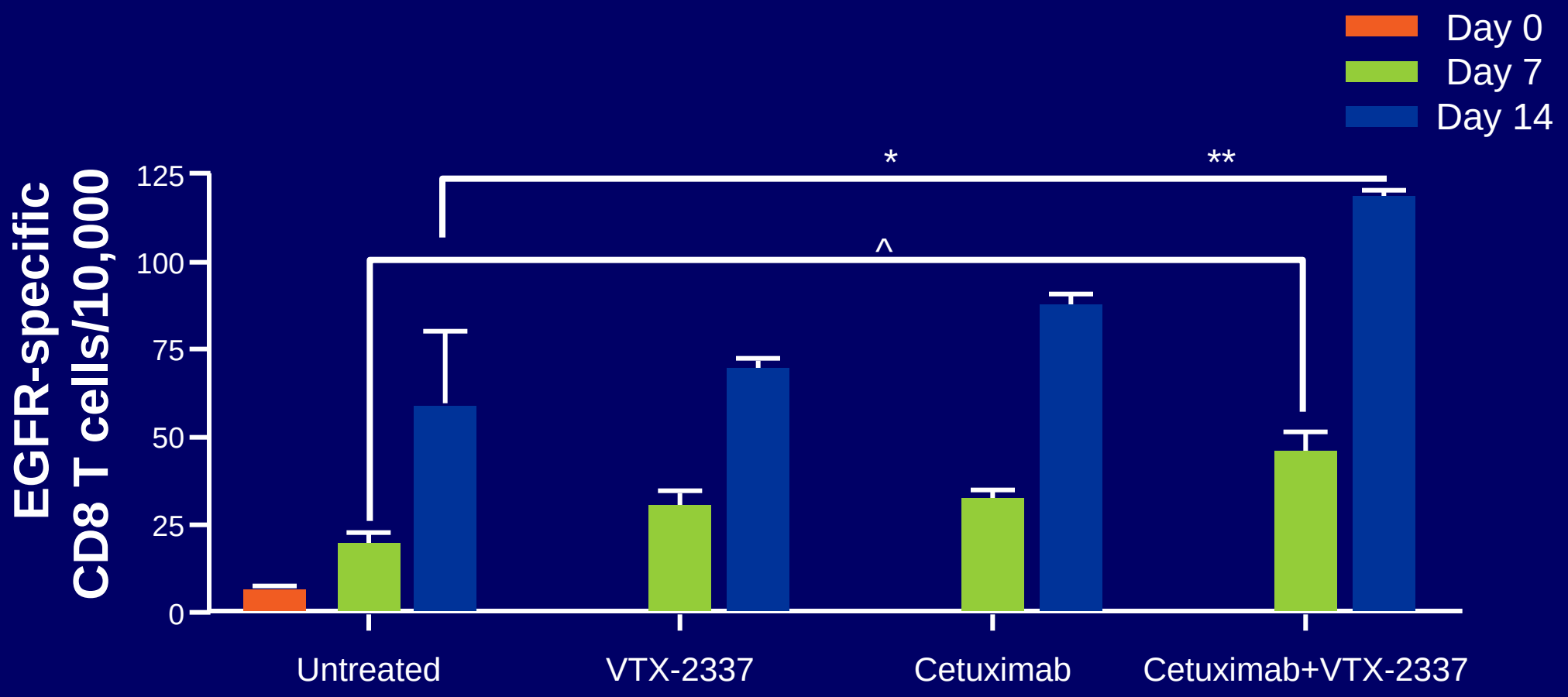
VTX-2337 enhanced cetuximab-dependent degranulation of NK cells



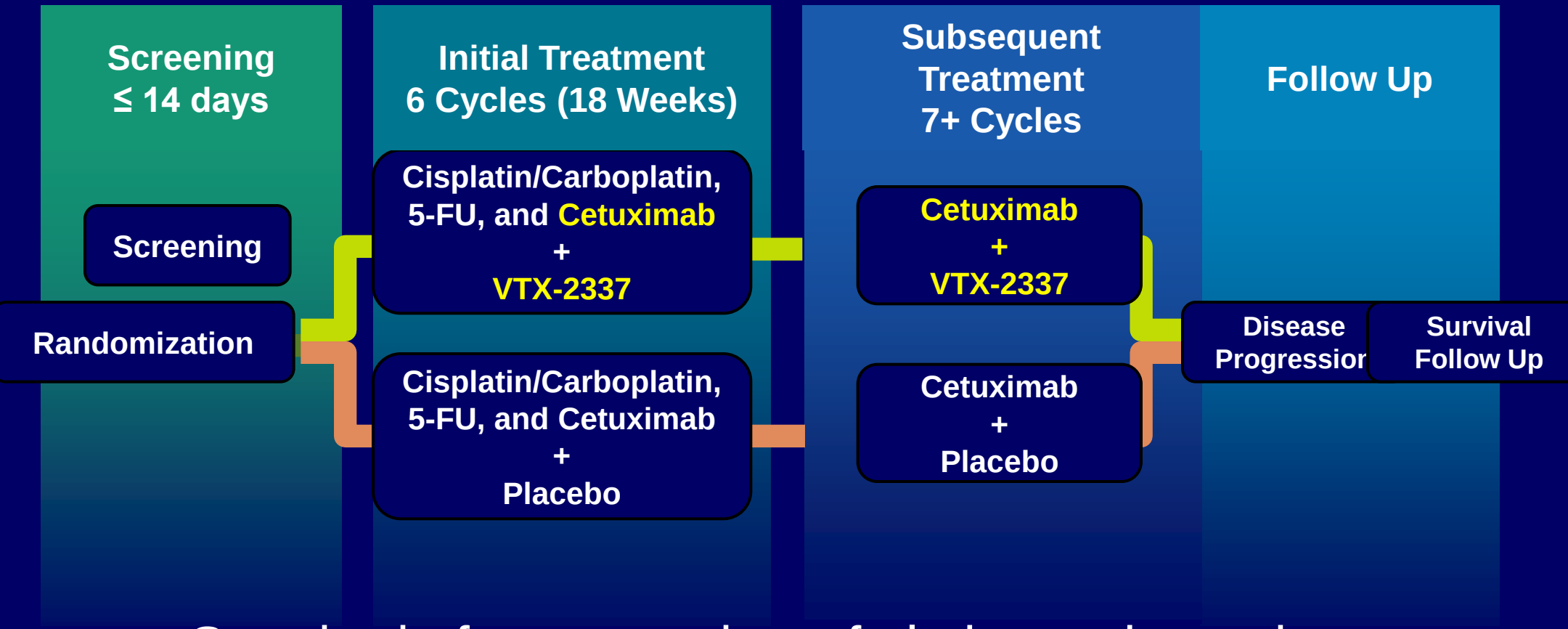
TLR8 stimulation (VTX-2337) May Enhance T cell priming Effects of mAb Response



In vitro stimulation of EGFR-specific T cells is enhanced by VTX-2337 stimulated, cetuximab-treated NK:DC



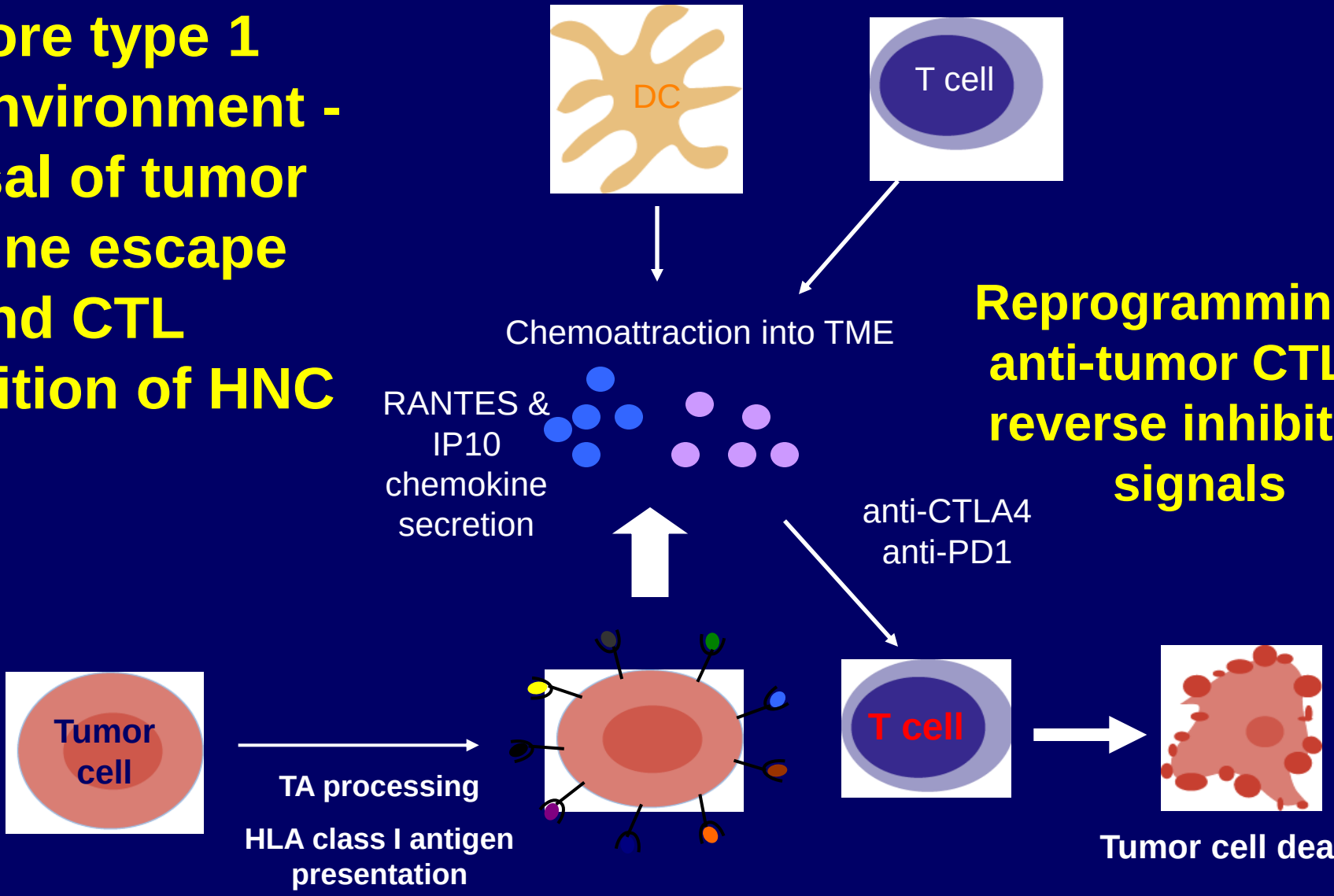
Active-8 trial: TLR8 adjuvant to enhance Cetuximab-based immunotherapy



Standard of care consists of platinum chemotherapy (cisplatin or carboplatin), 5-FU, and cetuximab

PI's- Cohen and Ferris

Targeting model to restore type 1 microenvironment - reversal of tumor immune escape and CTL recognition of HNC



Reprogramming of anti-tumor CTL to reverse inhibitory signals

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