
# Role of immunotherapy in virus related head and neck cancer

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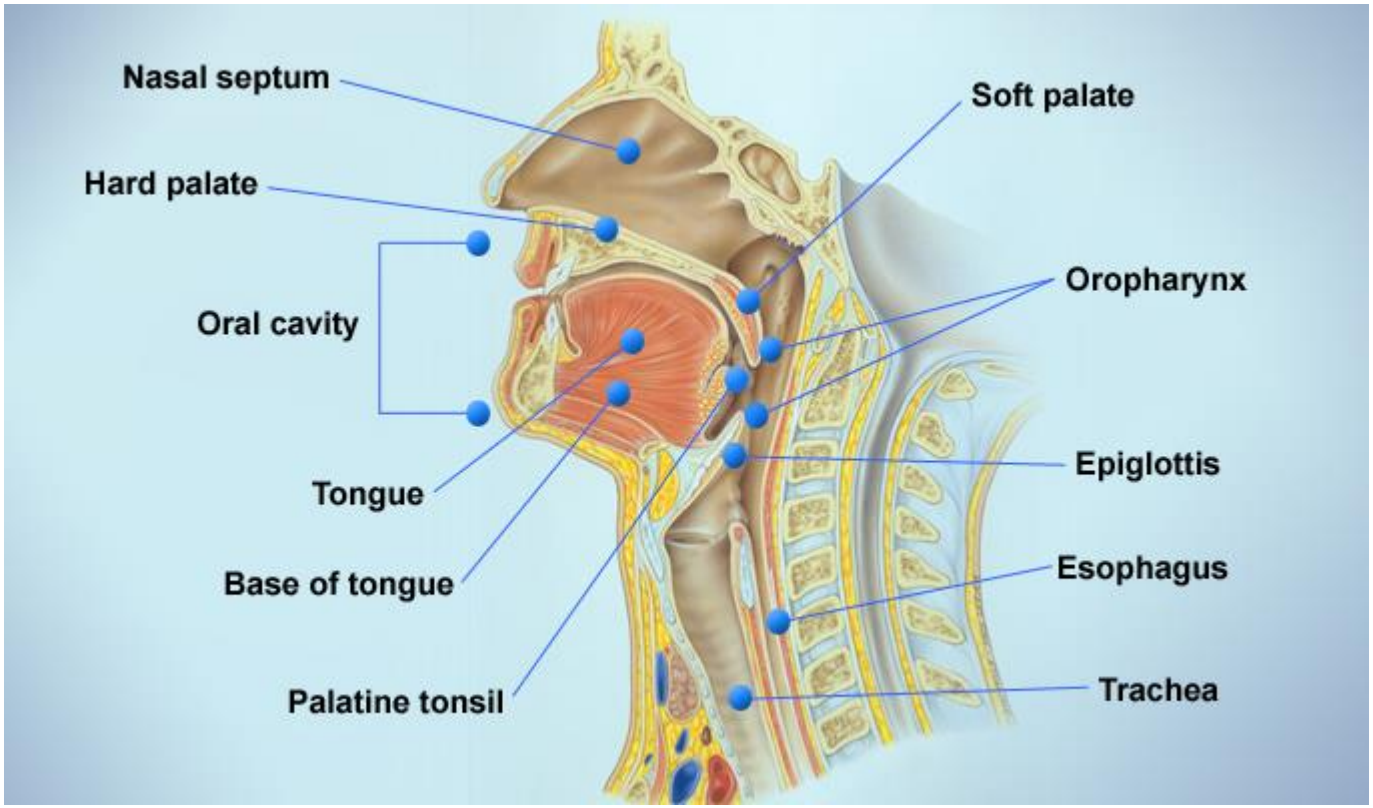
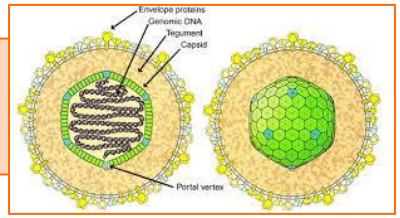
Oncologia ASO S. Croce e Carle Cuneo

# Virus-related HNC

- HNSCC (oropharynx) →HPV
- Nasopharyngeal Cancer (NPC)→EBV



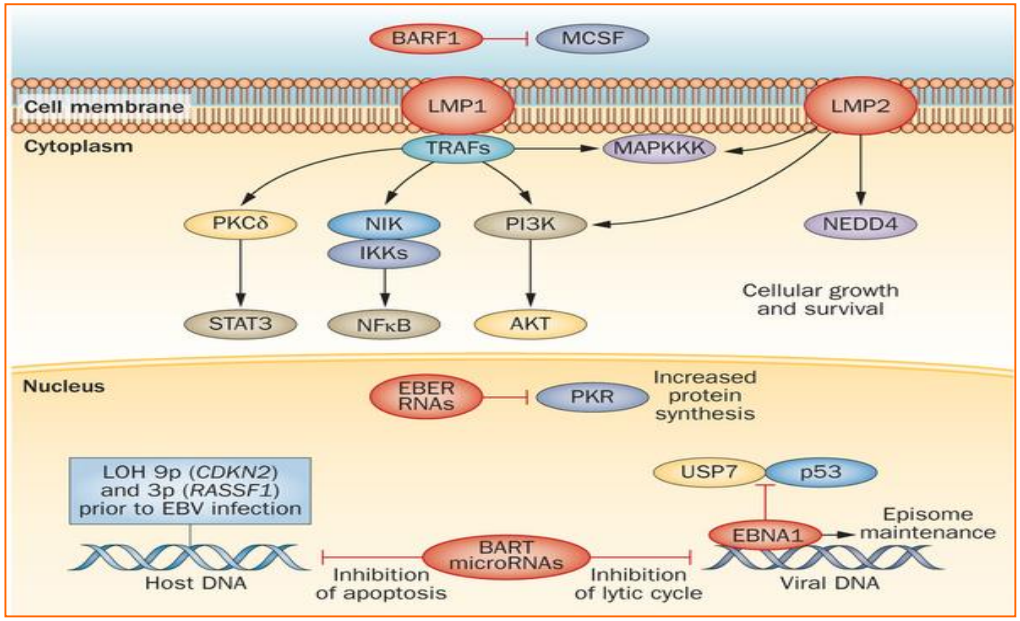
# EBV



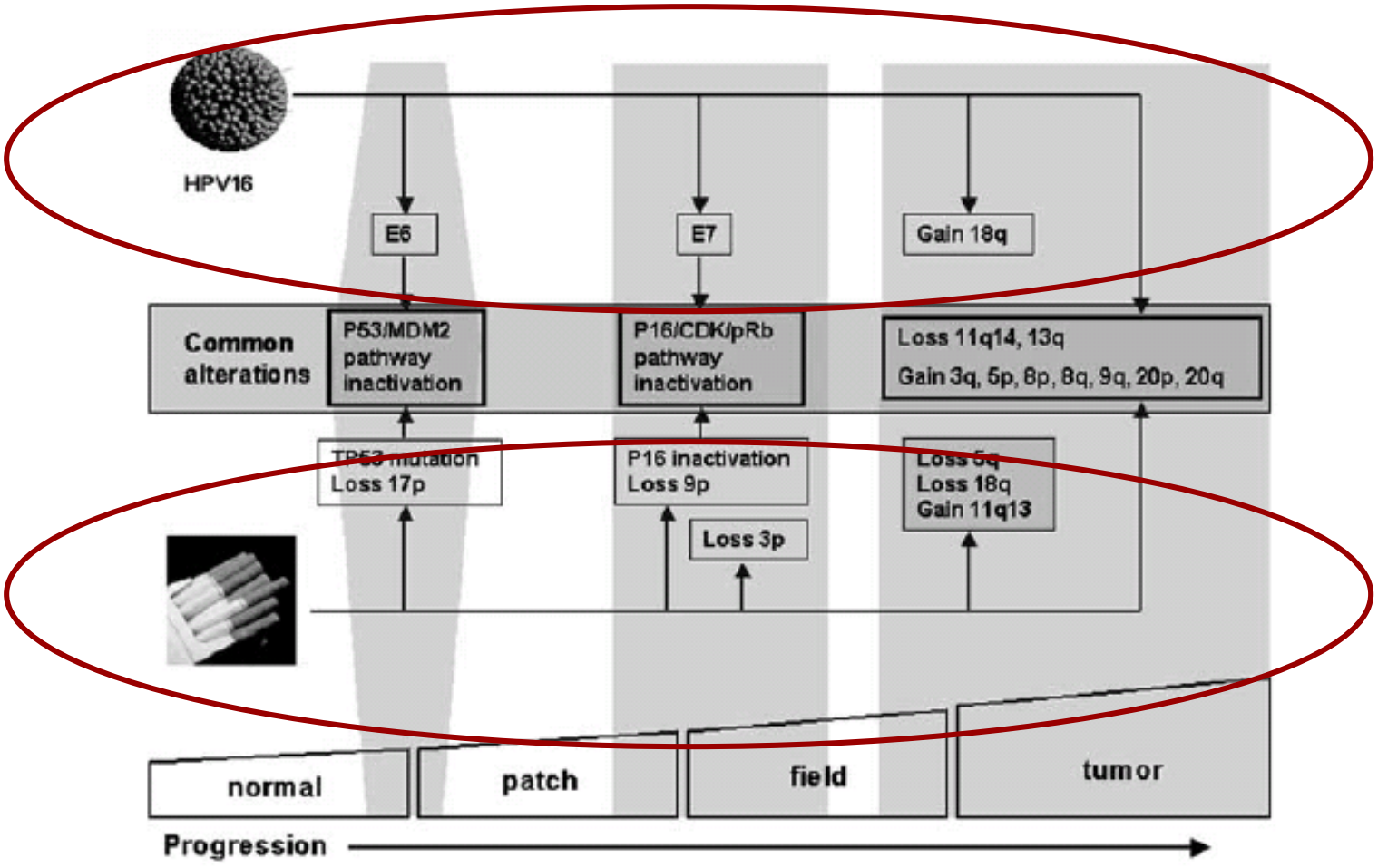

- 1st human virus to be directly implicated in carcinogenesis
- EBV associated NPC is characterized by peritumoral immune infiltrate.
- EBV-related NPC expresses a type II latency program
- Immunotherapy directed against EBV antigen targets has been previously explored in clinical trials, and is likely to be validated as an important target in NPC as randomized data emerges in the near future.

# EBV immunoescape

- < HLA I and HLA II to escape CD4/CD8 T-cell recognition
- < expression of the most immunogenic LMP and EBNA3 family



# 2 HNSCC

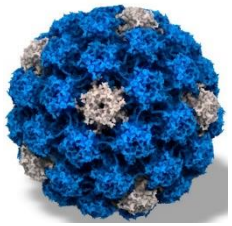



Smeets SJ Oncogene 2006

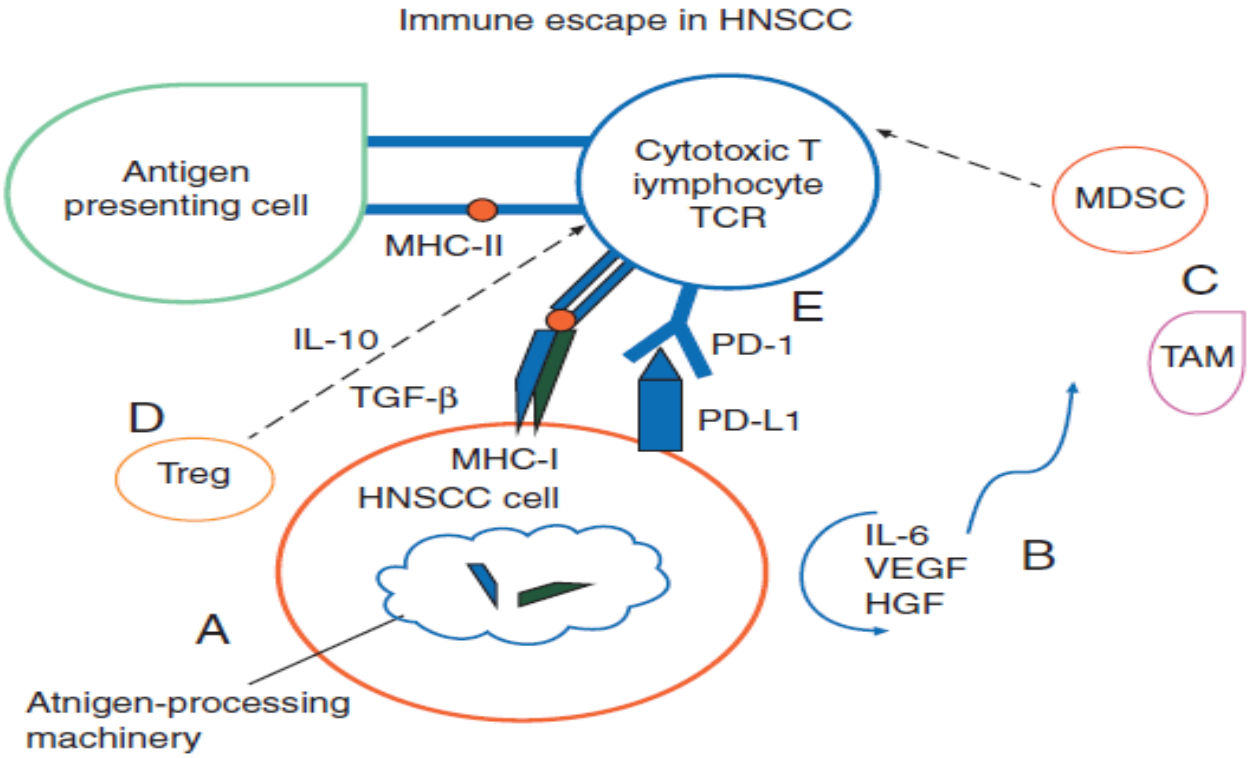
# Immunogenicity

HNSCC has been intensely studied as an immunosuppressive disease

HPVneg HNSCC =  +  + deficit in immunosurveillance

HPVpos HNSCC=  + deficient Th1 response (reduced responses to early antigens-E5, E6, E7 as compared to late antigens L1)

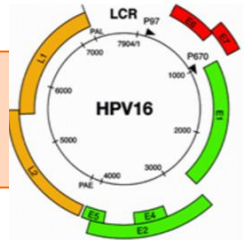
# Immunoescape in HNSCC




From Economopoulou et al Annals Oncology 2016

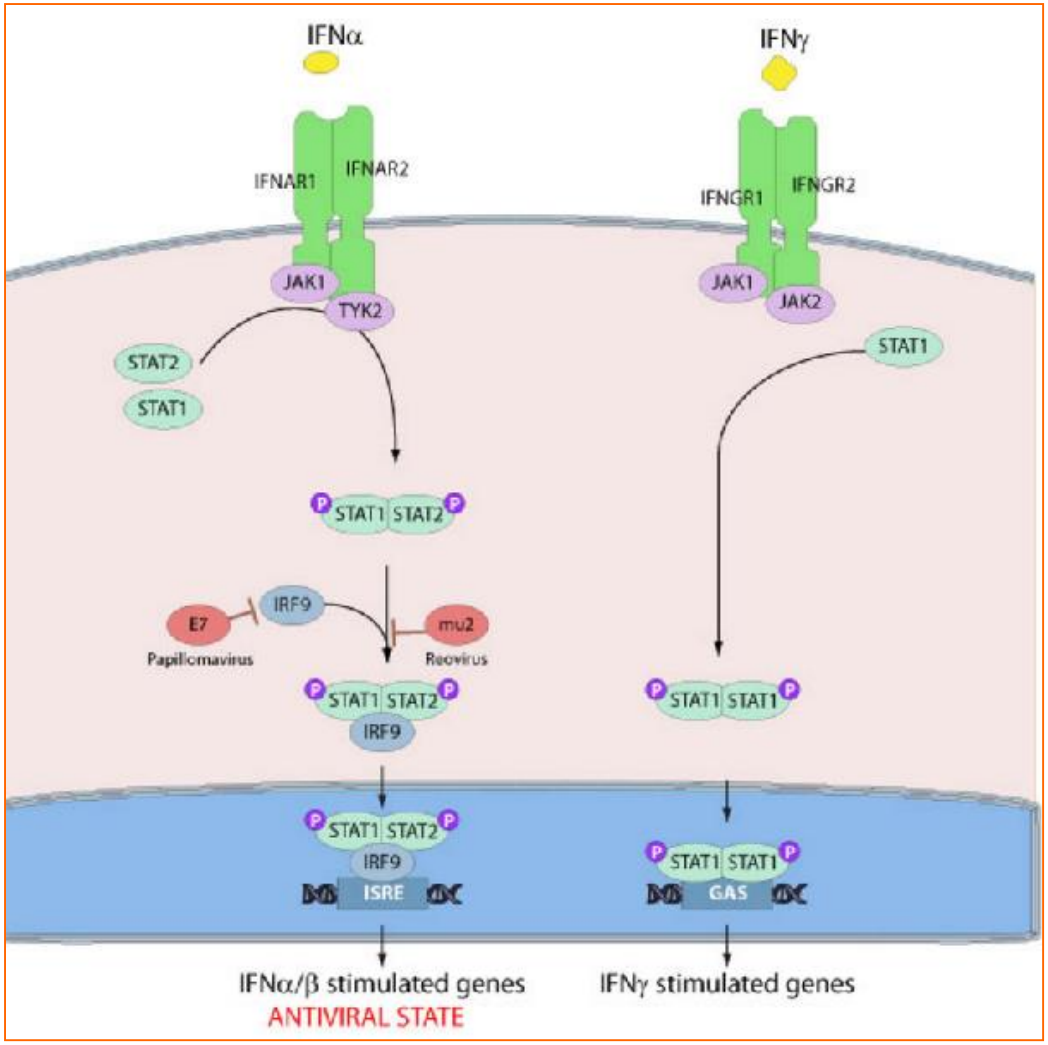
(A) Reduction of HLA class I expression and impairing of APM.
(B) High levels of IL-6, VEGF and HGF,PDL1,IL10,TGF-β
(C) Recruitment of suppressive myeloid cells,such as MDSC and TAMs.
(D) Induction of Tregs.
(E) Downregulation of co-stimulatory signals.

# HPV Immunoescape




| L1 | Major capsid protein |
|---|---|
| L2 | Minor capsid protein |
| E1/2 | Viral replication |
| E4 | Assembly and release viral particle |
| E5 | interacts with HLA-I heavy chain, resulting in reduced cell surface HLA-I [van der Burg SH 2012,Ashrafi GH, 2010].<br>Interaction with EGF |
| E7 | down-regulates cell expression both of HLA class I, and transporter associated with antigen processing (TAP) [Li W, 2010]. The mechanism of has been proposed to occur by E7 interacting with IRF-1 and disrupting its control of these key target genes for antigen expression [Um SJ 2002].<br>Inactivation rb |
| E6 | inhibits the STAT-1 pathway. Using multiple mechanisms the early viral genes preferentially alter the infected epithelial cell as a means to prevent immune detection and recognition by antiviral T cells .<br>Destruction of p53 |

# HPV and IFN


IFNα
IFNγ
IFNAR1
IFNAR2
IFNGR1
IFNGR2
JAK1
TYK2
JAK1
JAK2
STAT2
STAT1
STAT1
STAT1 STAT2
E7
Papillomavirus
IRF9
mu2
Reovirus
STAT1 STAT2
IRF9
STAT1 STAT1
STAT1 STAT2
IRF9
ISRE
STAT1 STAT1
GAS
IFNα/β stimulated genes
ANTIVIRAL STATE
IFNγ stimulated genes

# Strong Association Of Immune-Related Gene Expression Signatures and Best Overall Response and Progression Free Survival in Patients with Head and Neck Cancer

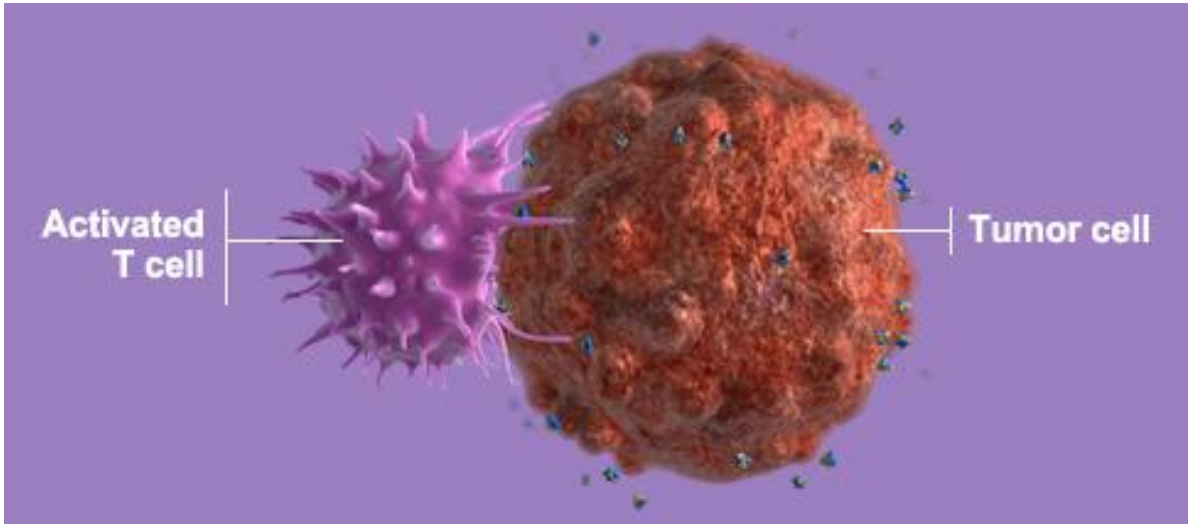
| Signature | Nominal 1-sided P value* | |
|---|---|---|
| | Best Overall Response<br>N = 40 | Progression Free Survival<br>N = 43 |
| IFNγ (6-gene) | 0.005 | < 0.001 |
| TCR signaling (13-gene) | 0.071 | 0.002 |
| Expanded-immune (18-gene) | 0.015 | < 0.001 |
| De novo (33-gene) | 0.018 | < 0.001 |

*From logistic or Cox regression for overall response and progression-free survival, respectively BOR and PFS as assessed by investigator

Selvert TS, et al. ASCO 2015. Abstract# 6017

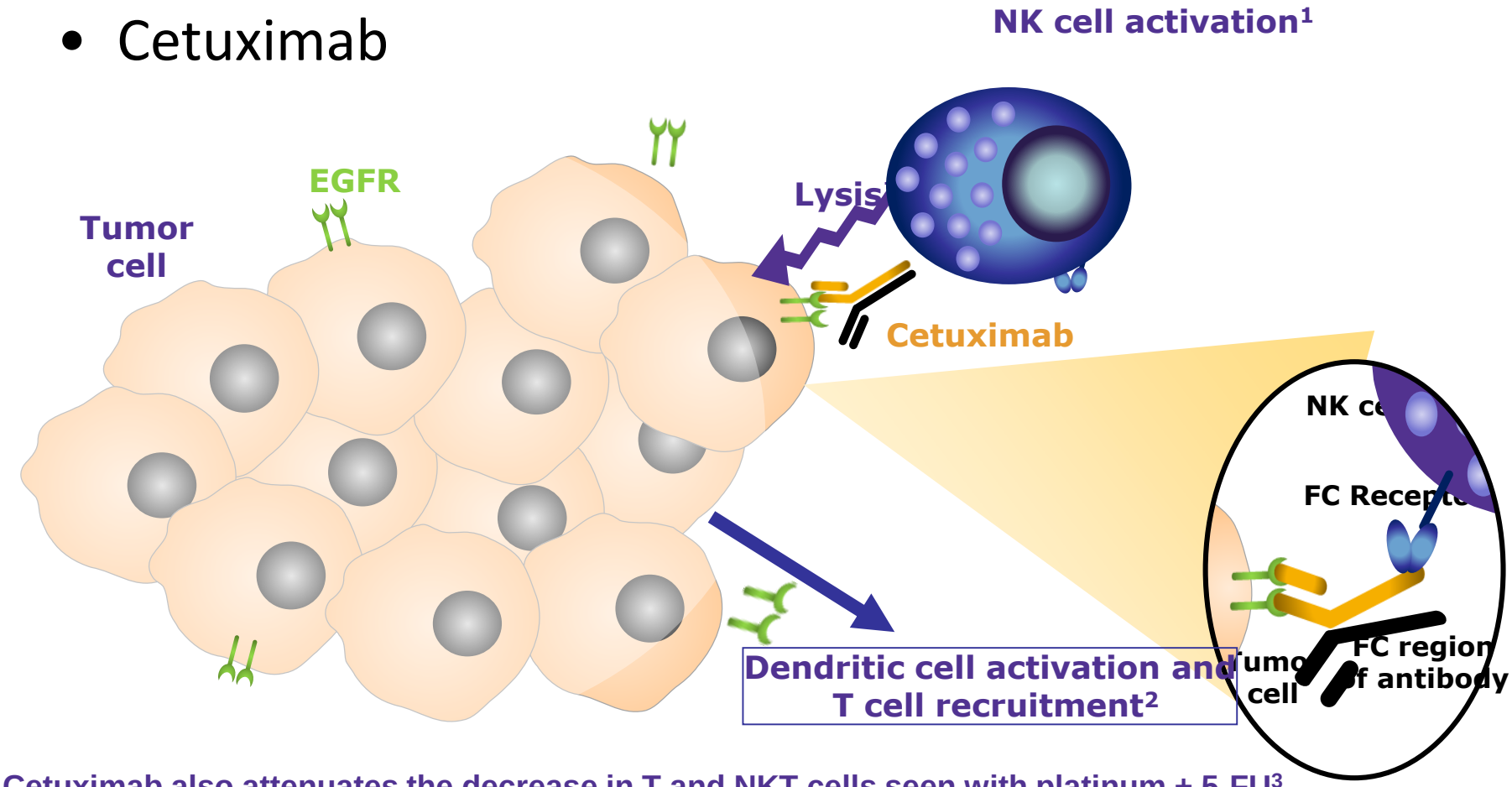
# Immunotherapy in HNC

1. Monoclonal Antibodies
2. Checkpoint Inhibitors
3. Vaccination
4. Adoptive therapy/CAR/TILs



# First immunotherapy

- Cetuximab




Cetuximab also attenuates the decrease in T and NKT cells seen with platinum + 5-FU[3]

1. Trivedi S, et al. Ann Oncol 2015;26:40–47;
2. Belluci R, et al. OncoImmunol 2015;4:6,e1008824;
3. Lo Nigro C, et al. Cancer Res 2015;75:1327.

# BioRT

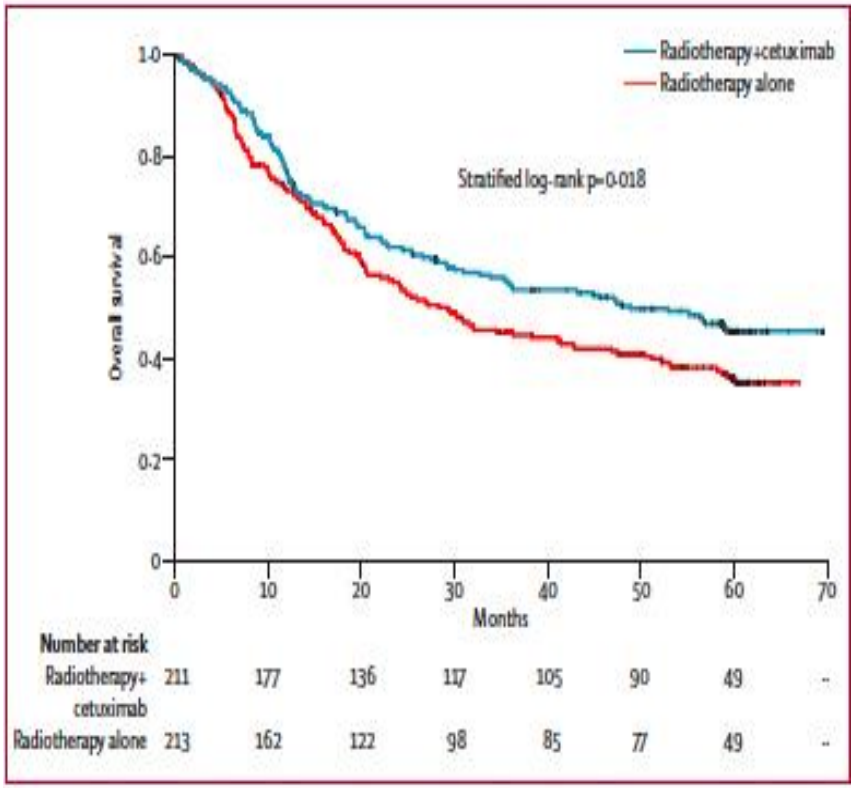
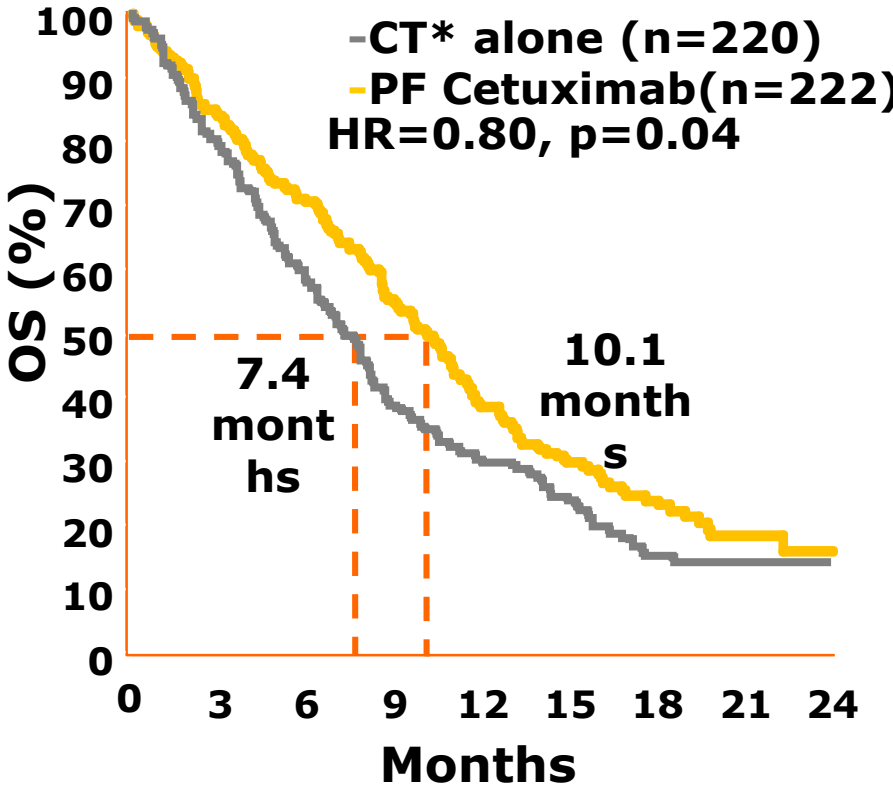



Figure 2: Overall survival by treatment: 5-year update (median follow-up 60 months)

5 y OS 46% vs 36%
27% reduction in death risk (HR=0.73)
Rash intensity correlates with > OS
>OS in all primary sites

Bonner et al Lancet Oncol 2010

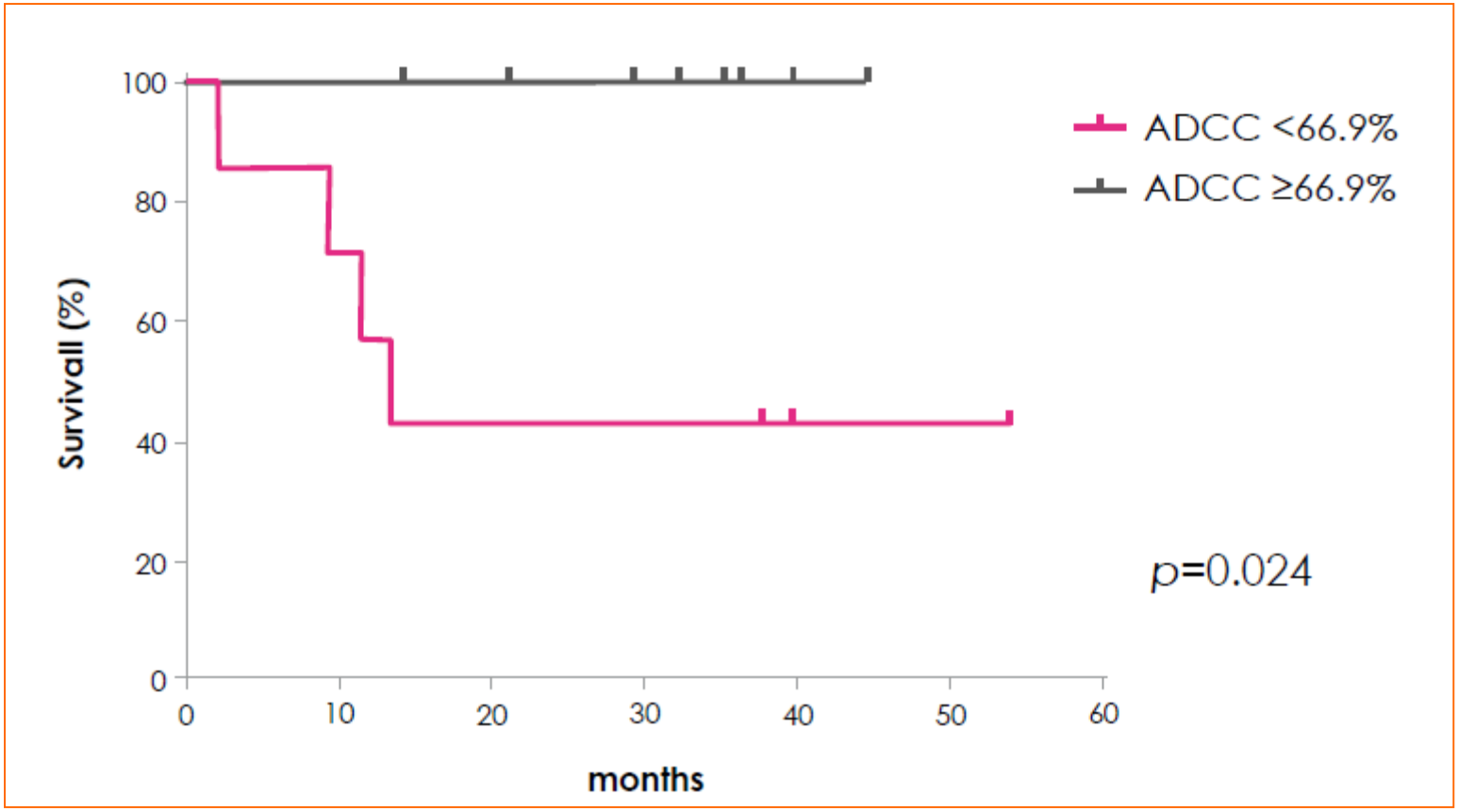
# R/M HNSCC




81% DCR in the cet arm

Vermorken JB, et al. N Engl J Med 2008;359:1116–1127.

# Cetuximab and ADCC




OS prediction when ADCC basal activity is correlated with EGFR: our experience on 16 pts with LAHNSCC with EGFR3+ and ADCC basal level >66.9%

Lattanzio L (Denaro N) Cancer Immunol Immunother 2016 Subm.

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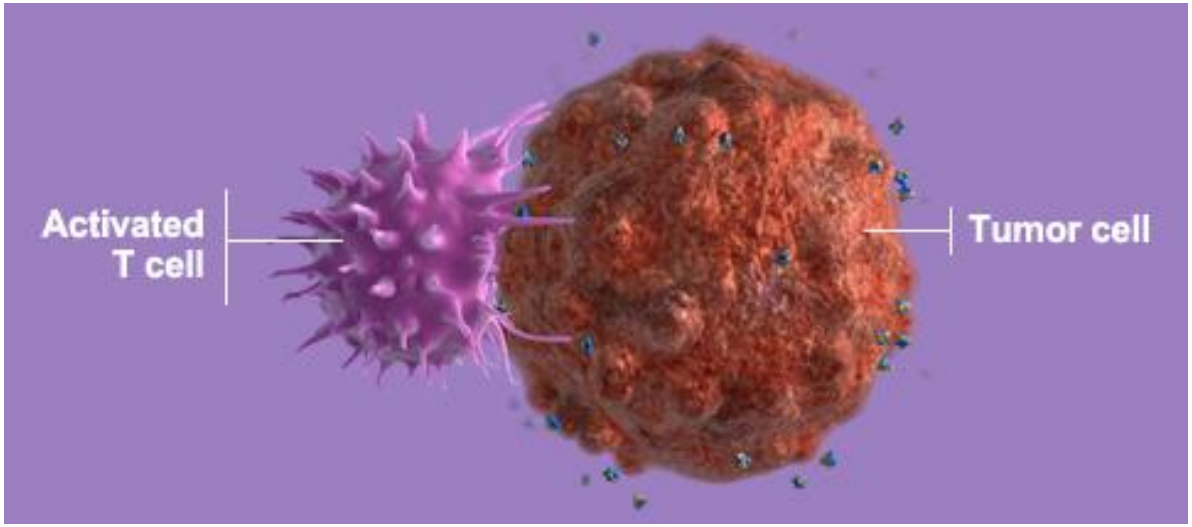
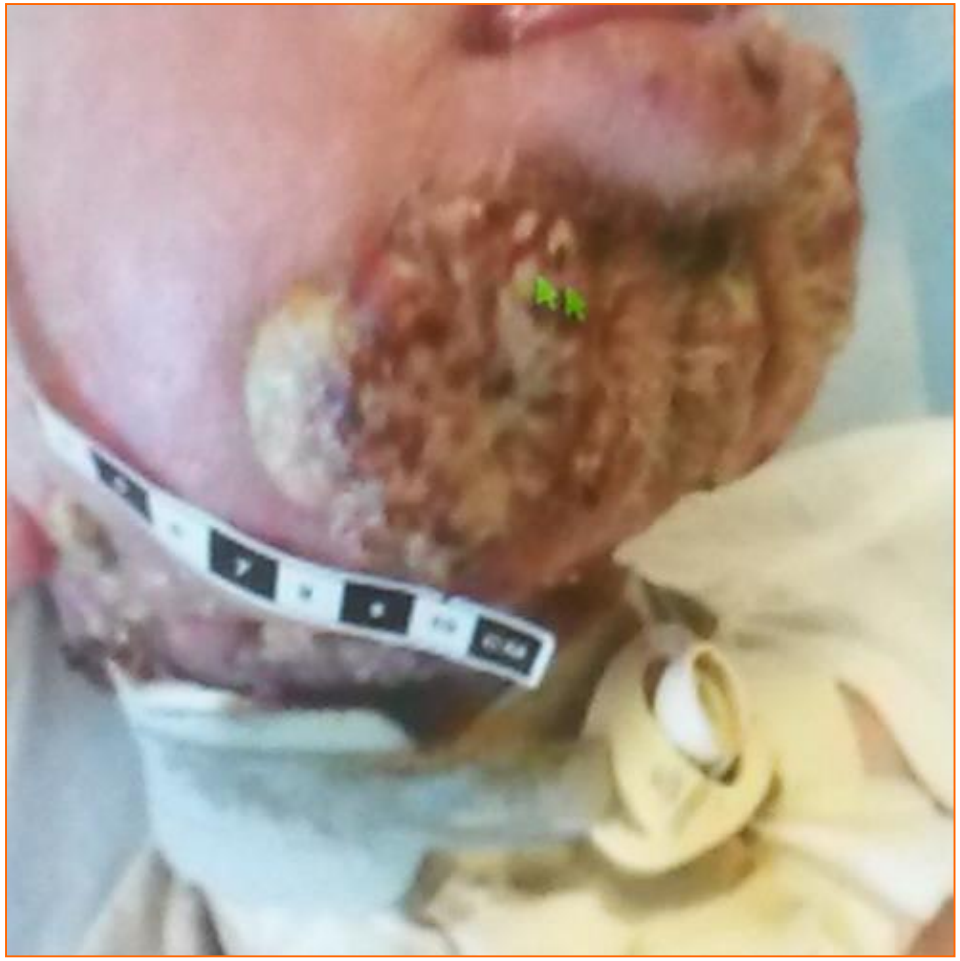
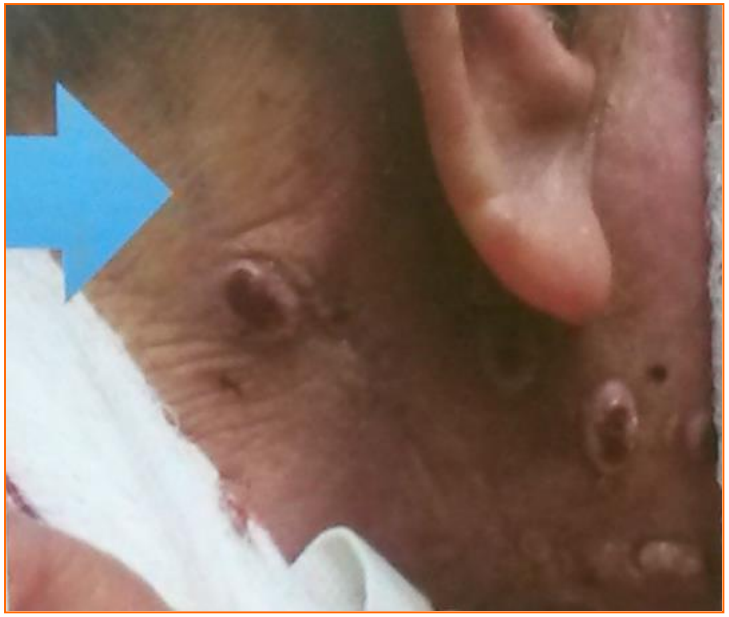


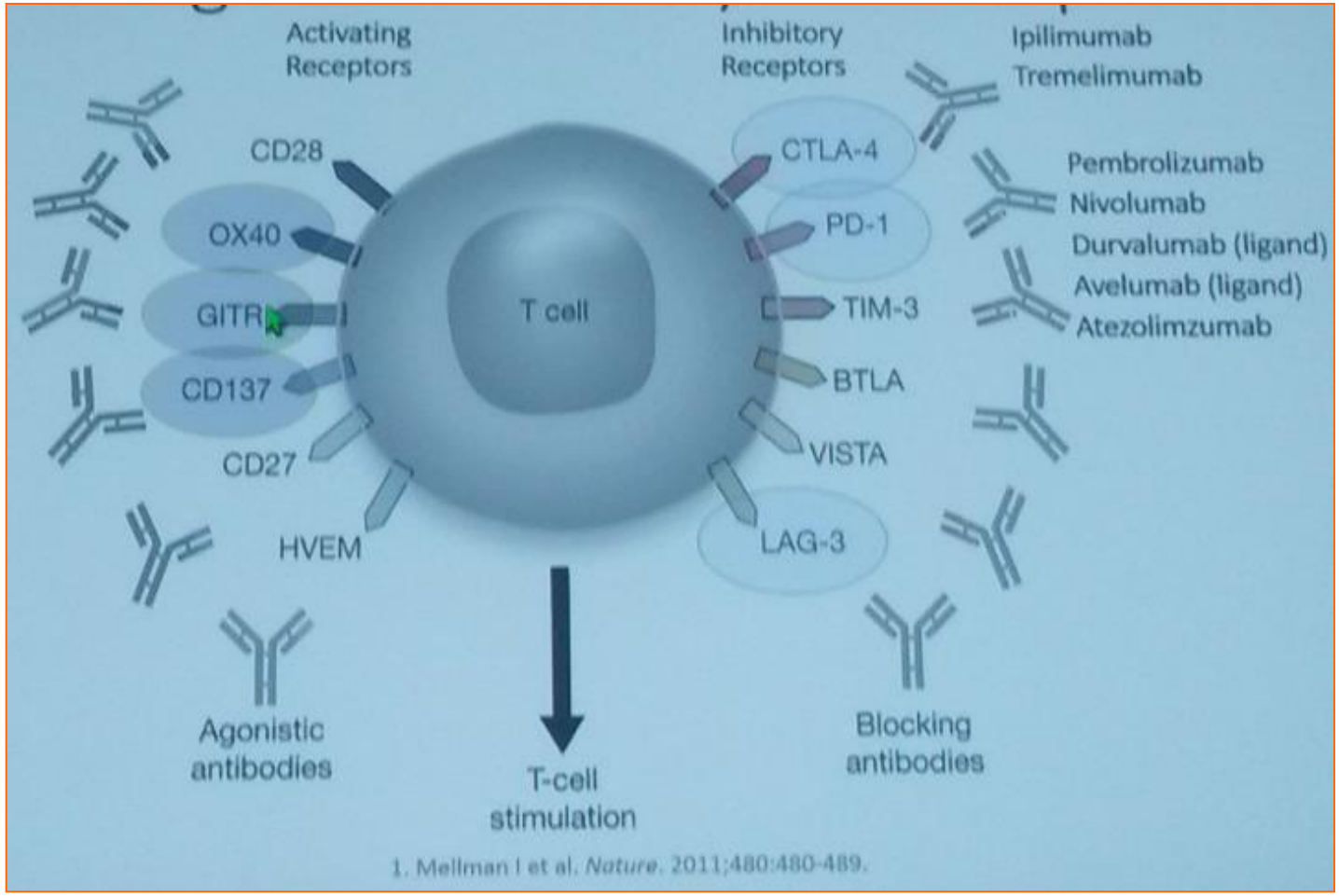
# Checkpoints inhibitors may work





Unpubblished data
University of Chicago
presented at ESMO2016

# Checkpoint Inhibitors/stimulators



# antiCTLA4

- Ipilimumab +Rt+cet (wCDDP)

(NCT01860430;NCT01935921)

- Ipi + Pembrolizumab
- Ipi+Enoblituzumab

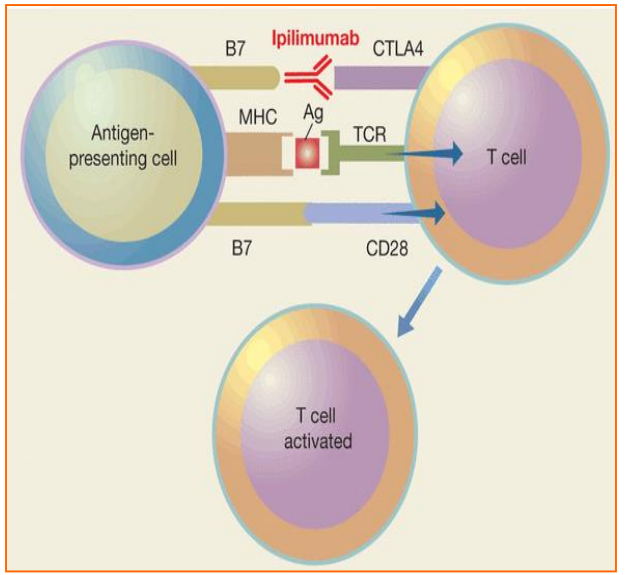
(NCT02381314)

- Ipi+ KIR(killer cell IG like receptors)

(NCT01750580)

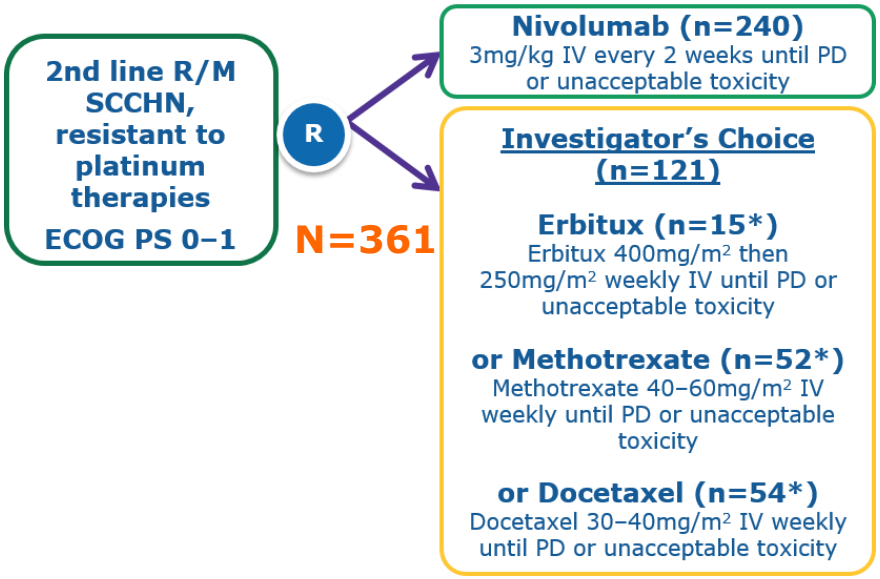
- Tremelimumab ±

Durvalumab

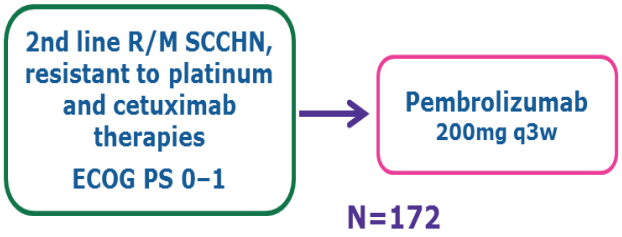


# CheckMate 141, KEYNOTE-55 & KEYNOTE-012 Study designs

## CheckMate 141[1]

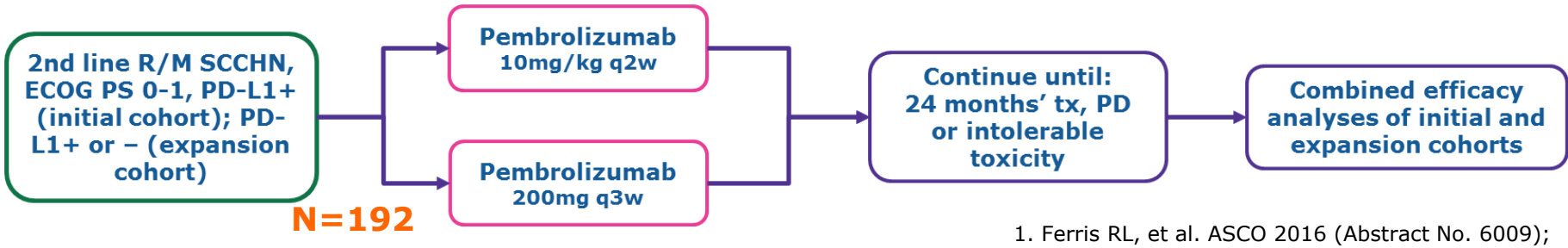



## KEYNOTE-055[2,3]




- 84% had ≥2 prior lines of therapy for metastatic disease

## KEYNOTE-012[4]

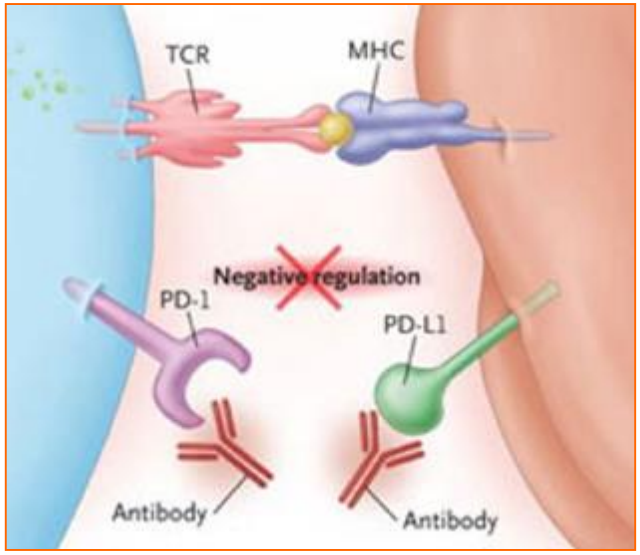



*ITT population (Note: 13 patients actually received cetuximab);
†ASCO 2016 data cover analysis of the first 50 patients

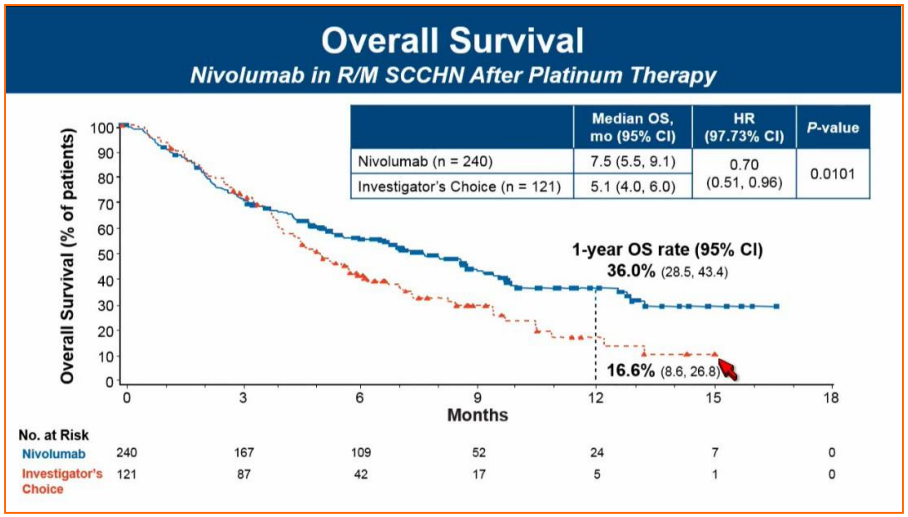

1. Ferris RL, et al. ASCO 2016 (Abstract No. 6009);
2. Bauml J, et al. ASCO 2016 (Abstract No. 6011);
3. https://clinicaltrials.gov/ct2/show/NCT02255097 (Accessed May 29, 2016);
4. Chow LQ, et al. ASCO 2016 (Abstract No. 6010)

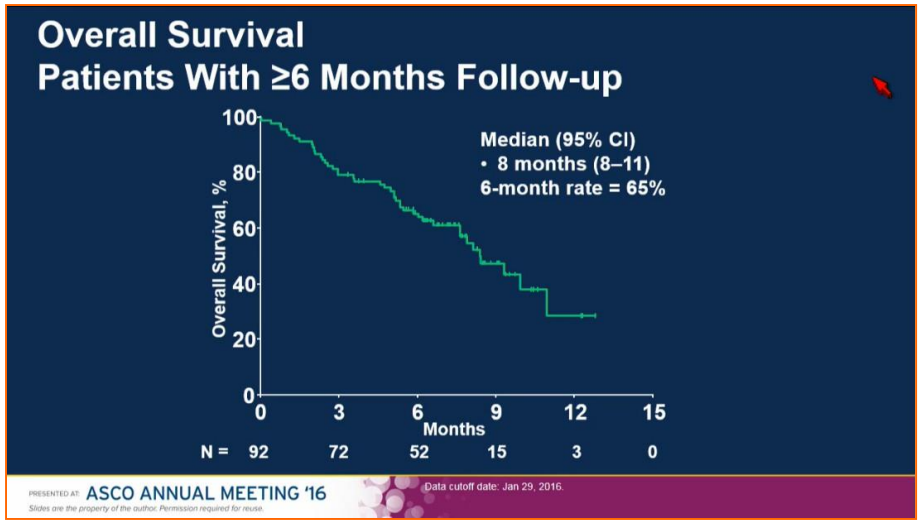
# antiPD1

| | |
|---|---|
| Checkmate 651 | Nivo +Ipi vs+Extreme |
| NCT02426892 | Nivo+HPV16 vaccine ISA101 |
| NCT02684253 | Nivo+SRT |
| NCT02327078 | Nivo+epacadostat (IDO inhibitor) |
| NCT02335918 | Nivo +varlilumab (anti CD27) |
| NCT02526017 | Nivo+FPA008 (CSF-1R TAM inhibitor) |
| NCT01714739 | Nivo + anti KIR |
| NCT0198109 | Nivo + anti Lag3 |
| Checkmate 741 | 2° line Ipi+nivo vs Nivo |
| Keynote 048 | Pembro vs EXTREME vs Pembro+EXTREME |
| NCT02858310 | E7 TCR ± Pembrolizumab |
| NCT02626000 | Pembro+Talimogene laherparepvec |
| NCT02538510 | Pembro+vorinostat |
| NCT02636036 | Pembro+enadenotucirev |
| NCT02452424 | Pembro+PLX3397 |
| NCT 02475213 | Pembro+MGA271(anti B7-H3) |

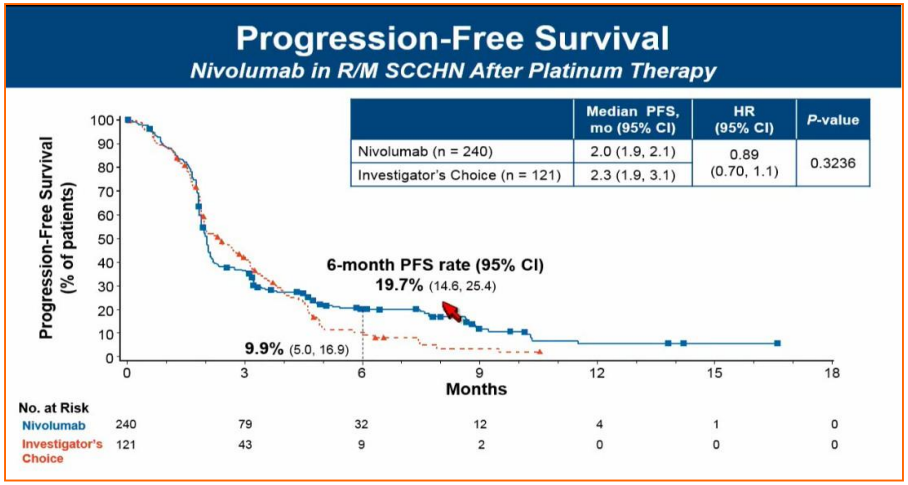


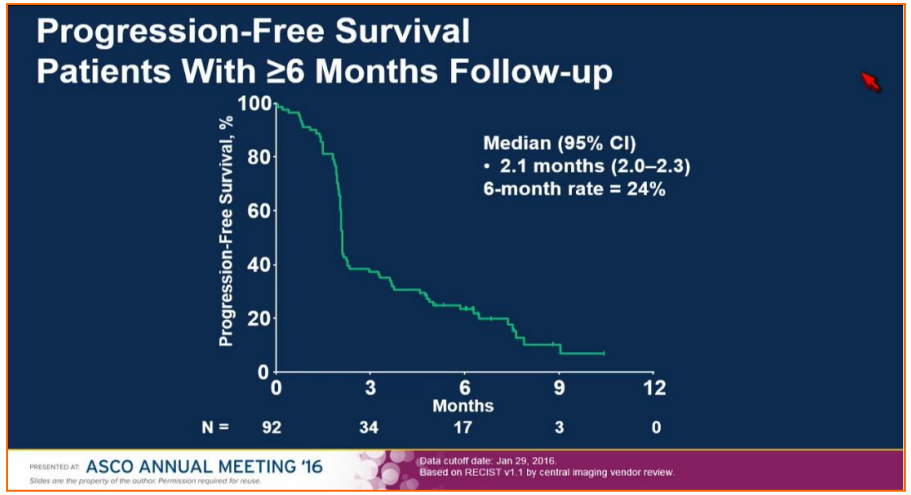
# CHECKMATE 141: OS




# CHECKMATE 141: PFS

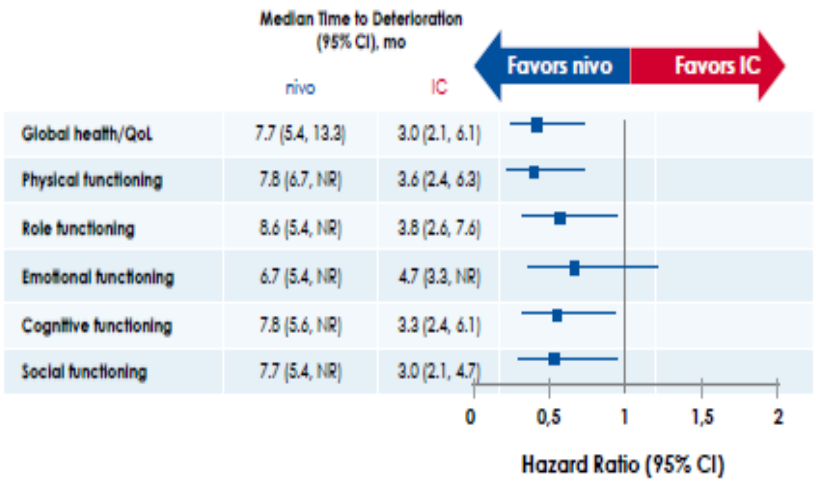


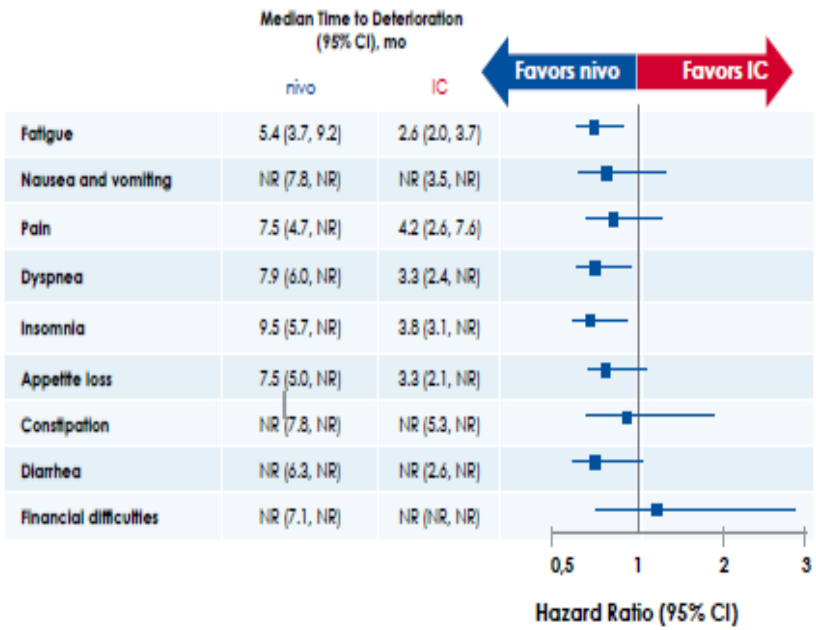

1. Ferris RL, et al. ASCO 2016 (Abstract No. 6009);
2. Bauml J, et al. ASCO 2016 (Abstract No. 6011).

# Checkmate 141

## EORTC QLQ-C30 Time to Deterioration (Functioning) CheckMate 141: nivolumab vs IC in R/M SCCHN After Platinum Therapy



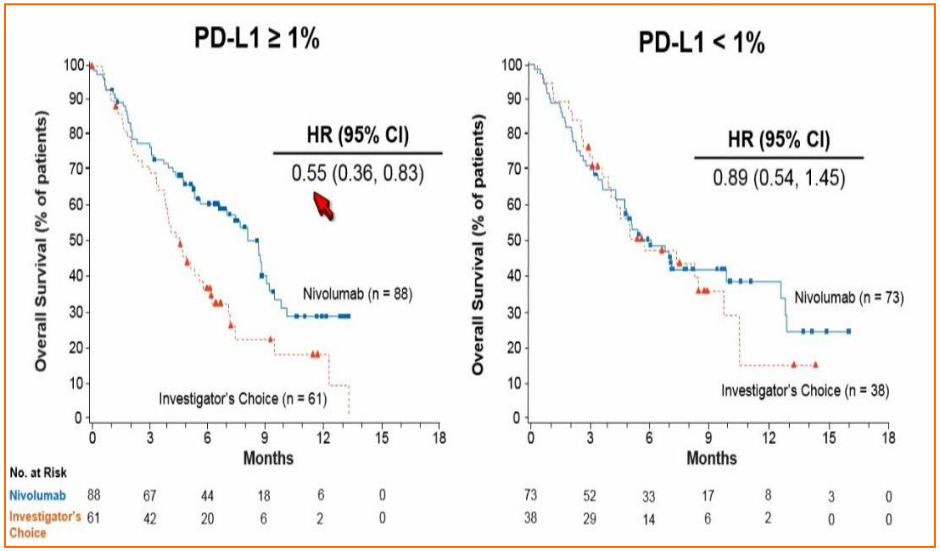

## EORTC QLQ-C30 Time to Deterioration (Symptoms) CheckMate 141: nivolumab vs IC in R/M SCCHN After Platinum Therapy

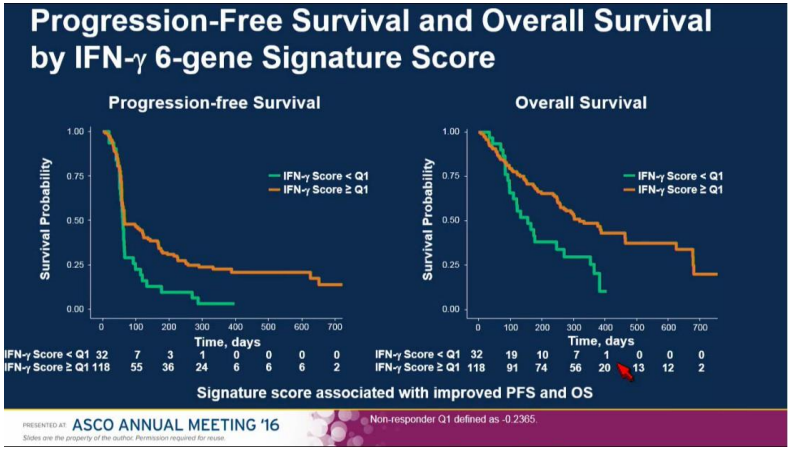


# Biomarkers

| | CheckMate 141[1] (nivolumab arm only) n=240 | | | KEYNOTE-055[2,3] n=92 | KEYNOTE-012[4]* |
|---|---|---|---|---|---|
| | PD-L1 | | | PD-L1 | PD-L1 |
| **CUT-OFF** | **≥1%** | **≥5%** | **≥10%** | **+** | |
| **ORR, %** | 18 | 26 | 33 | 17 | |
| **Median OS, months** | 8.7 | 8.8 | 8.7 | NR | |
| **Median PFS, months** | 2.1 | 3.2 | 2.1 | | |

*Data for tumor and inflammatory cells




Chow LQ, et al. ASCO 2016 (Abstract No. 6010)

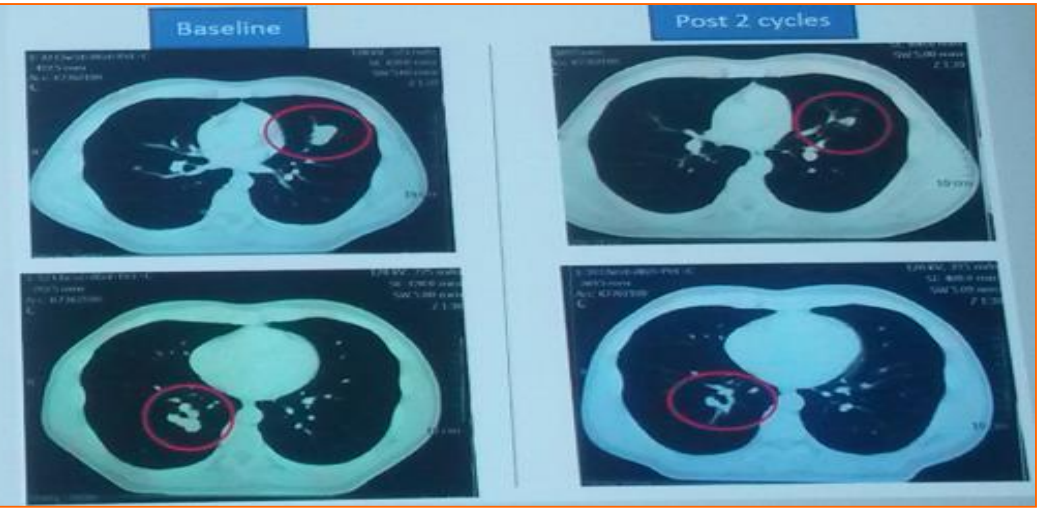
# Nivolumab in NPC

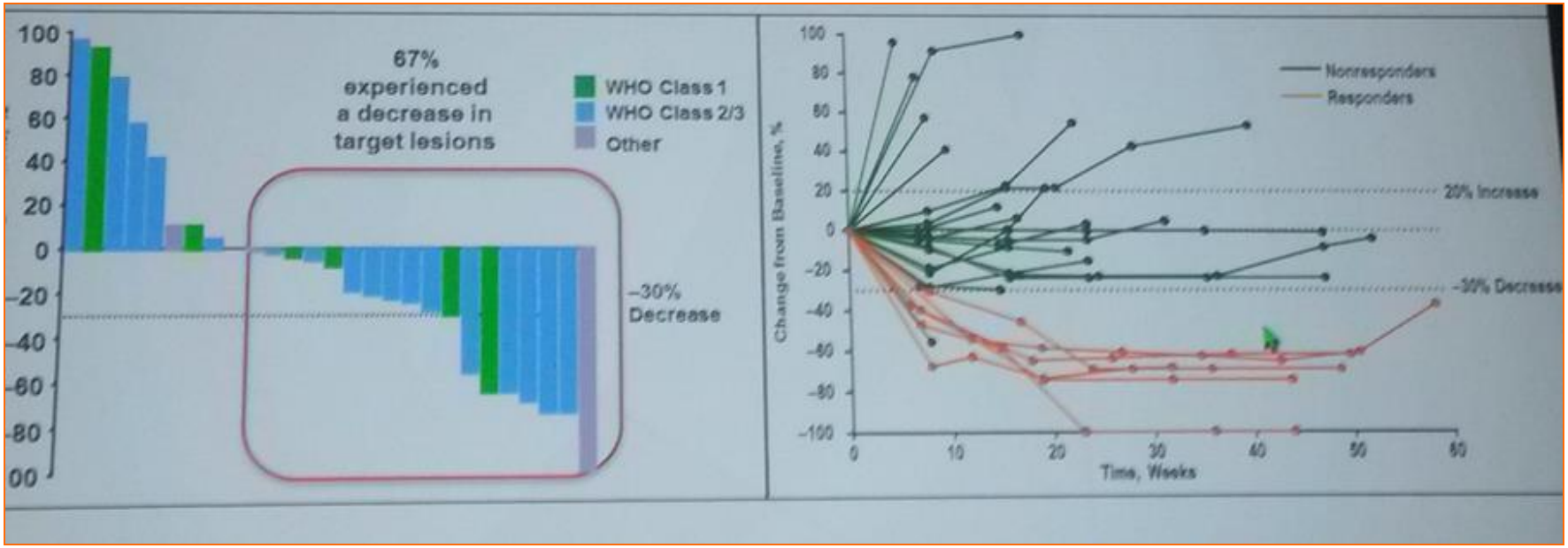
**CTEP-NCI, Mayo Clinic Phase II Consortium study** (PI: B Ma. Hong Kong, Singapore, Mayo Clinic P2C sites) NCT02339558

Recurrent/ Metastatic NPC – any prior line.

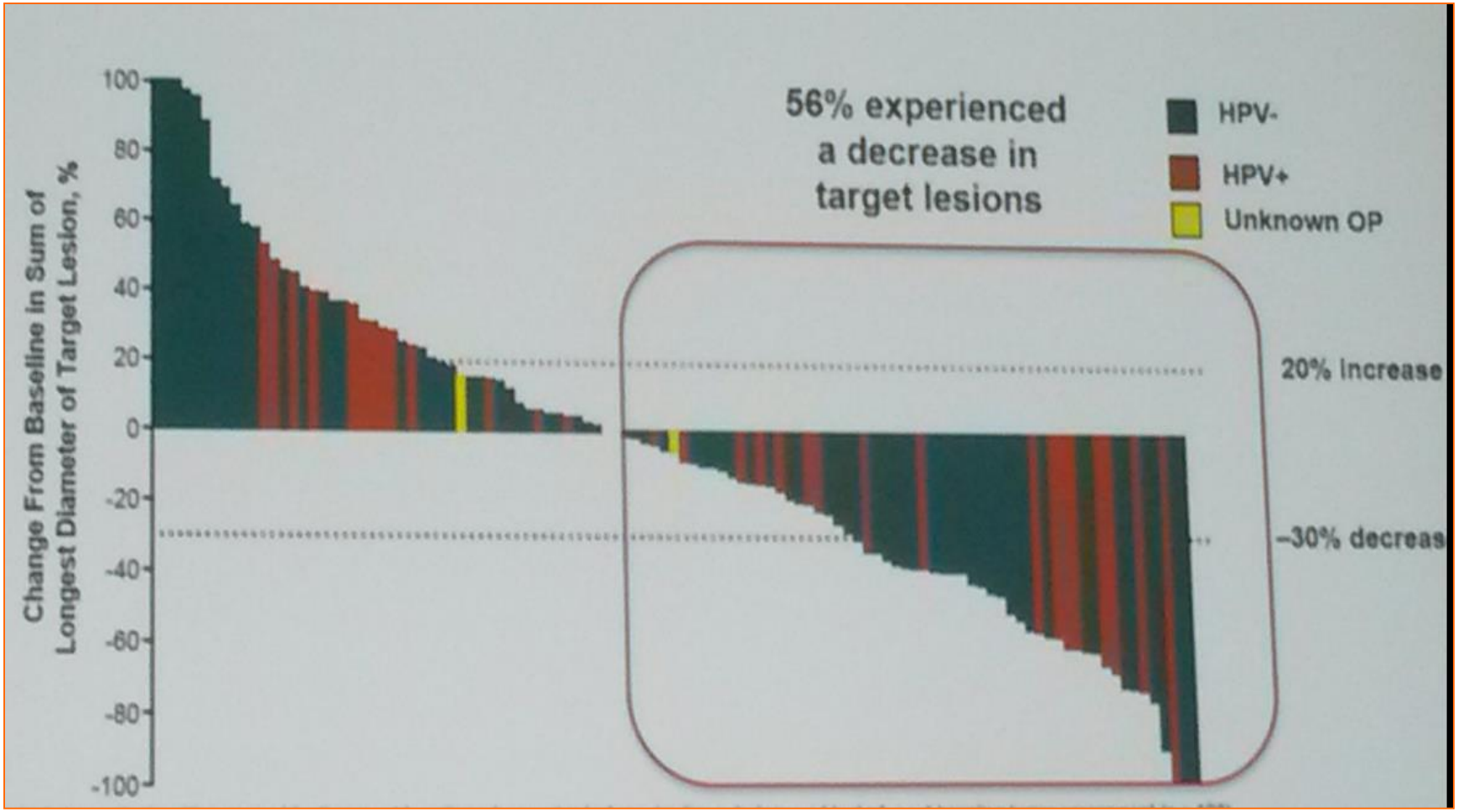
Correlative: EBV DNA, cytokines, functional MRI

Enrolling since November 2015.



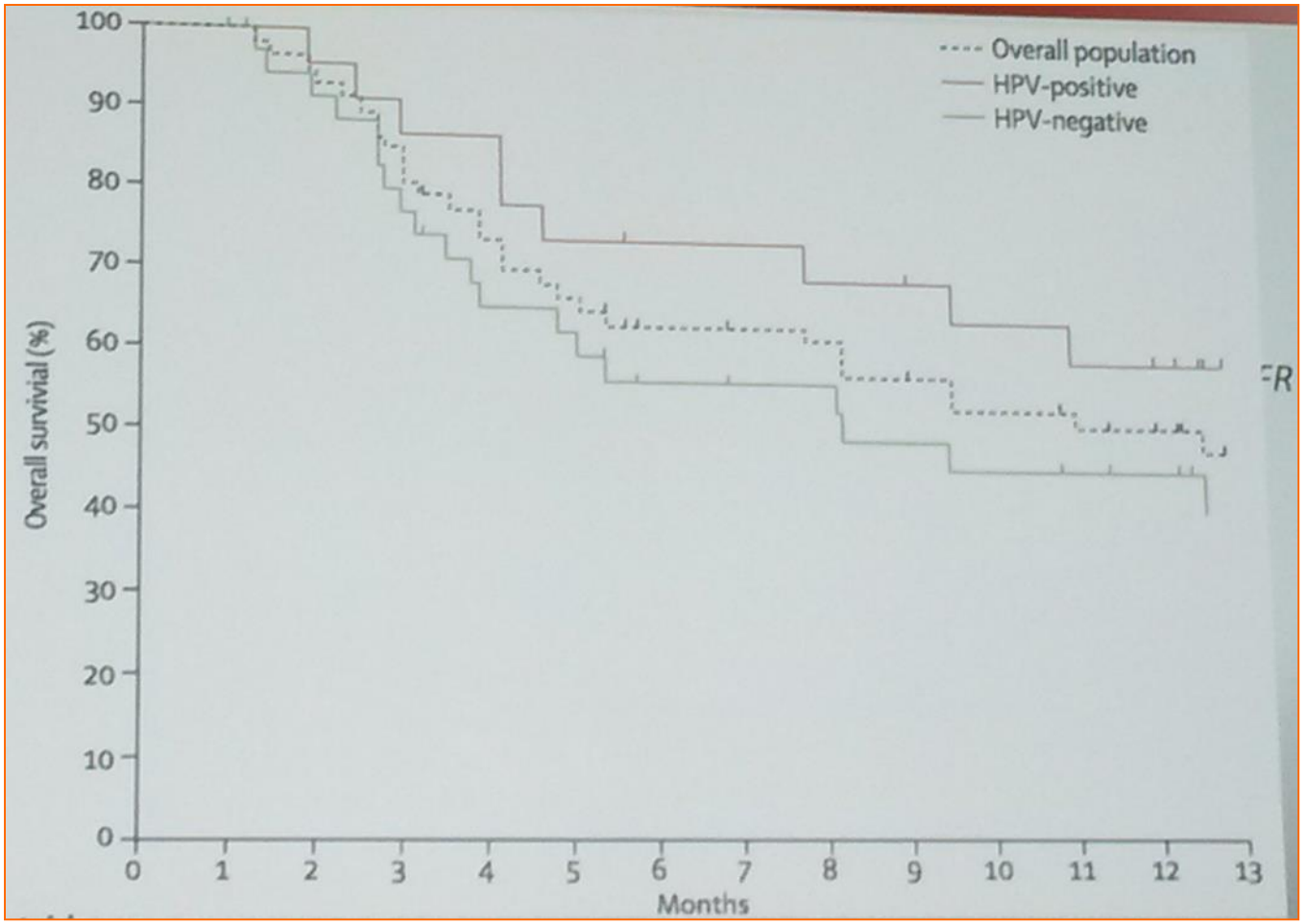



# Tumor shrinkage in Keynote 012




ORR 18.2%SD 31.3%

# No differences in HPVpos/neg




1. Selwert T, et al. Lancet Oncol, 2016; 17(7):956-6
2. Ferris RL, et al. J Clin Oncol 2016;34(suppl):6009

# Keynote 055

| Response Evaluation | All Patients† (N = 171) | | | HPV-Positive‡ (n = 37) | | | HPV-Negative‡ (n = 131) | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | 95% CI | n | % | 95% CI | n | % | 95% CI |
| **Overall Response Rate** | **28** | **16** | **11-23** | **6** | **16** | **6-32** | **20** | **15** | **10-23** |
| Complete Response | 1 | 1 | 0-3 | 0 | 0 | 0-10 | 1 | 1 | 0-4 |
| Partial Response | 27 | 16 | 11-22 | 6 | 16 | 6-32 | 19 | 15 | 9-22 |
| Stable Disease | 33 | 19 | 14-26 | 6 | 16 | 6-32 | 26 | 20 | 13-28 |
| Progressive Disease | 87 | 51 | 43-59 | 21 | 57 | 40-73 | 66 | 50 | 42-59 |
| Non evaluable¶ | 4 | 2 | 1-6 | 0 | 0 | 0-10 | 4 | 3 | 1-8 |
| Not available§ | 19 | 11 | 7-17 | 4 | 11 | 3-25 | 15 | 12 | 7-18 |

*†Patients who received ≥1 dose of pembrolizumab. ‡HPV status determined using p16 immunohistochemistry for tumors of the oropharynx. Nonoropharyngeal tumors were considered HPV negative. ¶Images were not available §Data were unavailable because of death or withdrawal from the study prior to the first scheduled scan.*

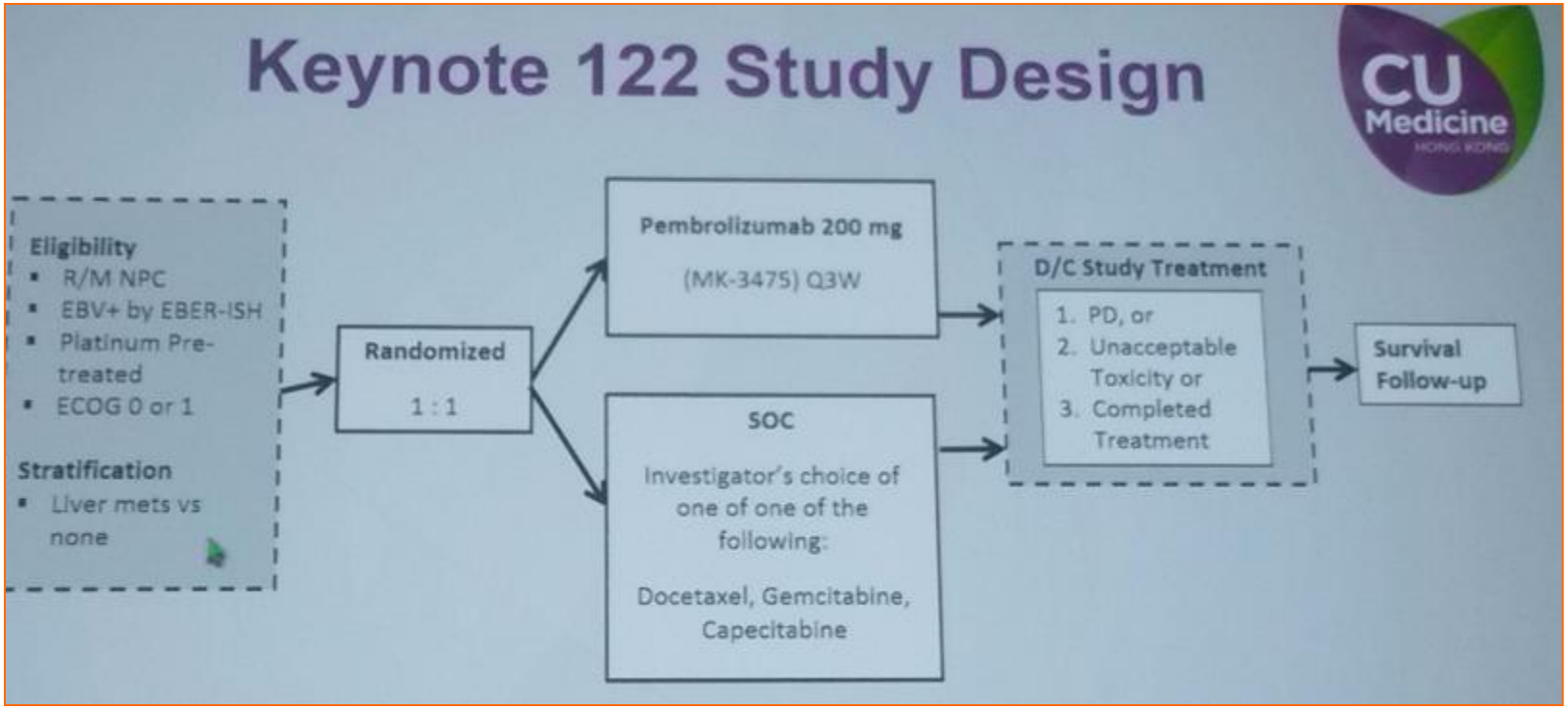
# New potential options in 2nd line R/M

| | CheckMate 141[1] (Niv vs IC) | Pembrolizumab[2] |
|---|---|---|
| ORR, % | 13.3 vs 5.8 | 17 |
| CR, % | 2.5 vs 0.8 | - |
| PR, % | 10.8 vs 5.0 | 17 |
| SD, % | 22.9vs 35.5 | 55 |
| PD, % | 41.7vs 34.7 | 19 |
| NA | 22.1vs 24.0 | 9 |

ORR, overall response rate; CR complete response; PD, progressive disease; PR, partial response; SD, stable disease; NA not applicable.

1. Ferris RL, et al. ASCO 2016 (Abstract No. 6009);
2. Bauml J, et al. ASCO 2016 (Abstract No. 6011).

# Pembrolizumab in NPC



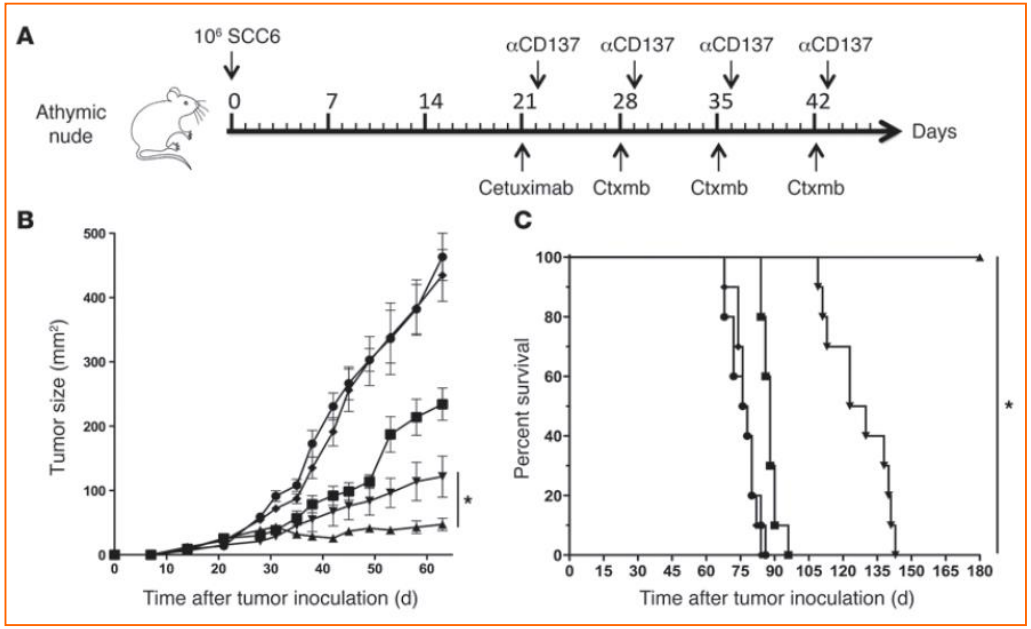

Enrolling since may 2016

# Anti PDL1

- Durvalumab 14%ORR
- Durvalumab +ADXS11-001 (NCT02291055)
- KESTREL study: Durvalumab±Tremelimumab vs EXTREME
- EAGLE study Durvalumab±Tremelimumab in platinum resistant
- Avelumab +PF05092566(Anti CD137)
- Avelumab vs IC in NPC

# costimulatory

- CD40 agonist
- OX40 agonist
- CD137 agonist
- TLR agonist




*Kohrt HE et al, The journal of clinical investigation 2014;124;2668-82*

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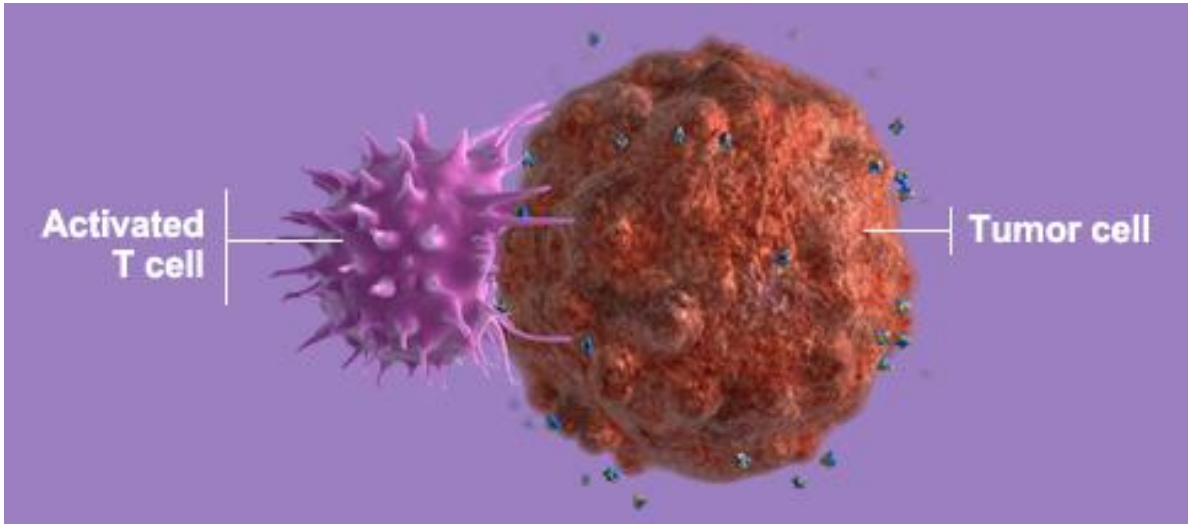
3. Vaccination
4. Adoptive therapy/CAR/TILs



# Vaccination

- Protein vaccines (ex. HLAI-II restricted MAGE and HPV16 peptides; E6-7long peptides)
- DNA vaccines (stable and easy to product but inadeguate antigenicity)
- Tumor cellular vaccine (tumor cell modified ex vivo modified to produce IL12)
- Dendritic cell vaccine (DC exposed to HPV Ags)
- Live Vectors(Listeria Monocytogenes,oncolytic viral vaccine)

# HPV Vaccination

- E6 and E7 are most frequently targeted
- PROPHILATYC goal: high-titers of HPV neutralizing Ab (capable of preventing initial infections) Gardasyl® Cervarix®
- THERAPEUTIC goal: induce CD8+ HPV-specific T cell immune response.

# Peptide/DNA Vaccine

- Hespecta (HPV +six peptide conjugated to amplivant)
- Rationale is to stimulate CD8+ response conjugating two of the HPV16 E6 SLP to Amplivant® a synthetic Toll-like receptor (TLR) 2 ligand
- pNGVL4a-CRT/E7 DNA vaccine using an electroporation device;phase I on32pts

# ADXS 11

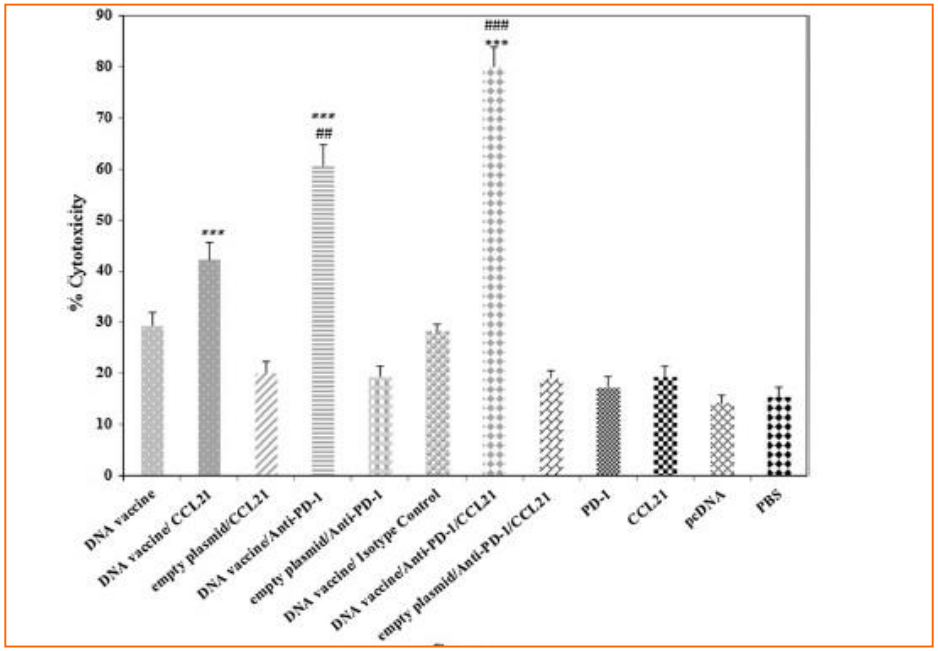
- Live attenuated Listeria monocytogenes (genetically modified) to induce HPV E6/7 specific CD8+ CTL response
- Ongoing trials:

  -**ADXS11-001** Vaccination Prior to Robotic Surgery, HPV-Pos Oropharynx

  -**ADXS11-001** or Durvalumab Alone or Combination In Previously Treated LA/RM Cervical or HPV+ HNC

# DNA vaccine strategy

- DNA vaccine + CCL21 adiuvant (blocks PDL1 and secondary lymphoid tissue chemokine)
- > CD8+ >regression. <VEGF, IL-10 and splenic IL-4 >IFN-γ




Moeini S Arch Vir 2016

# VGX3100 /INO3112

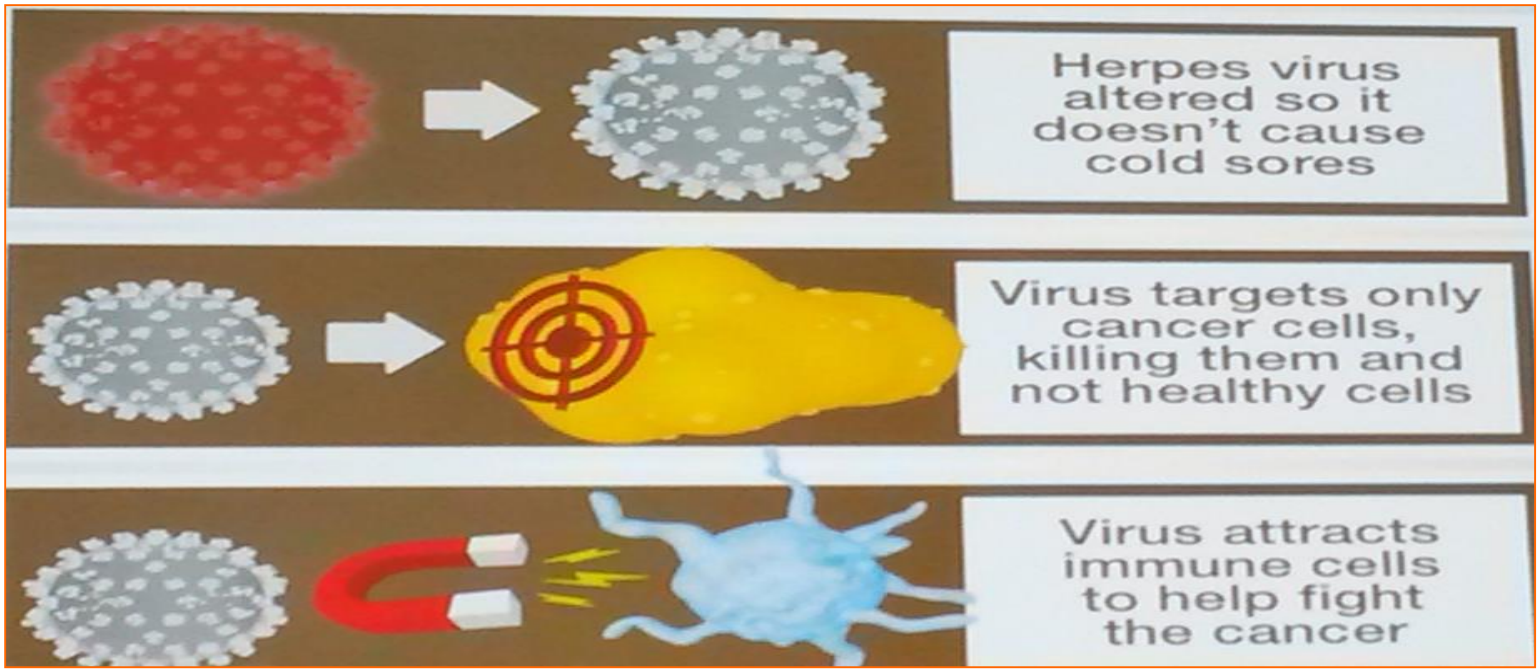
- **INO-3112** [1] is a combination of 6 mg VGX-3100, and immune activator expressing 1 mg of DNA-based IL-12 (INO-9012) delivered by electroporation

- **VGX-3100** [2], is a DNA vaccine with plasmids targeting E6 and E7 proteins of both HPV subtypes 16 and 18.
- Several trials reported vaccine to be safe, results are awaited

[1] Yang Z Ann Onc (2015) 26
[2] Trimble CL Lancet Onc Vol386 2015

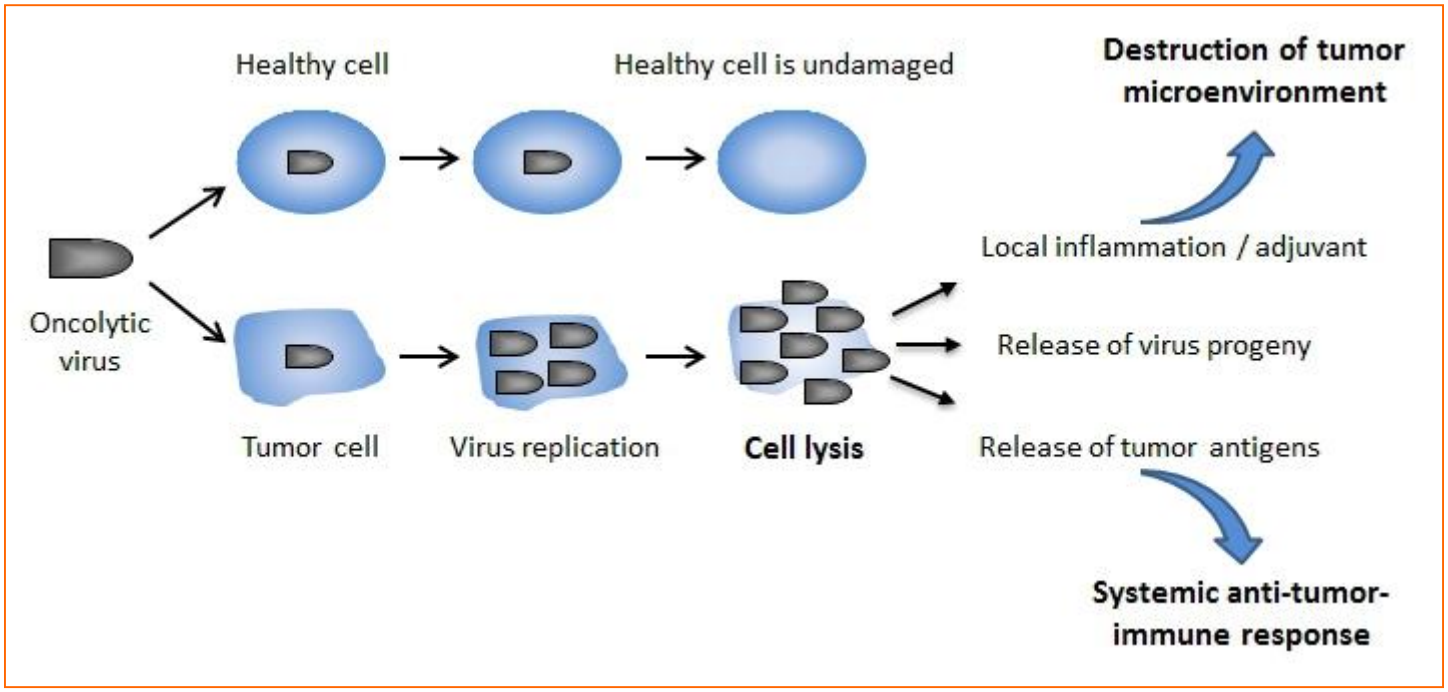
# Oncolytic viral therapy

- HSV/GMCSF
- TG4001 (HPV16 E6/7+IL2)
- TVEC (talimogene-laherparepvec) (ongoing in combination with Pembro Phase I/II)



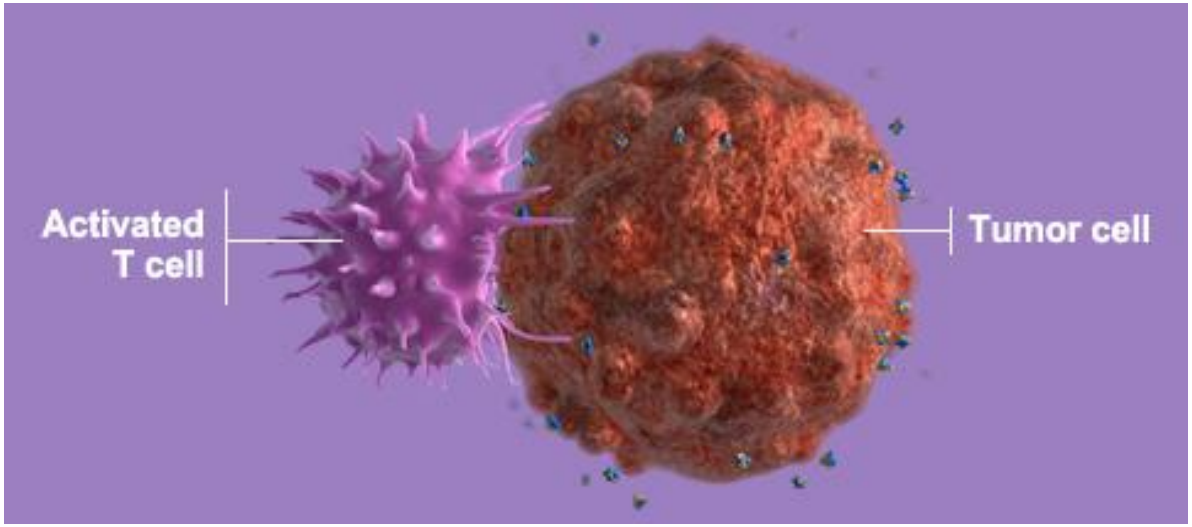
# Oncolytic viral therapy

- Engineered to express EBV epitopes, co-express immunostimulatory
- expanded autologous T cells against EBV using a ADE1-LMPpoly adenoviral vector was unsatisfatory



# Immunotherapy in HNC

1. Monoclonal Antibodies
2. Checkpoint Inhibitors
3. Vaccination
4. Adoptive therapy/CAR/TILs

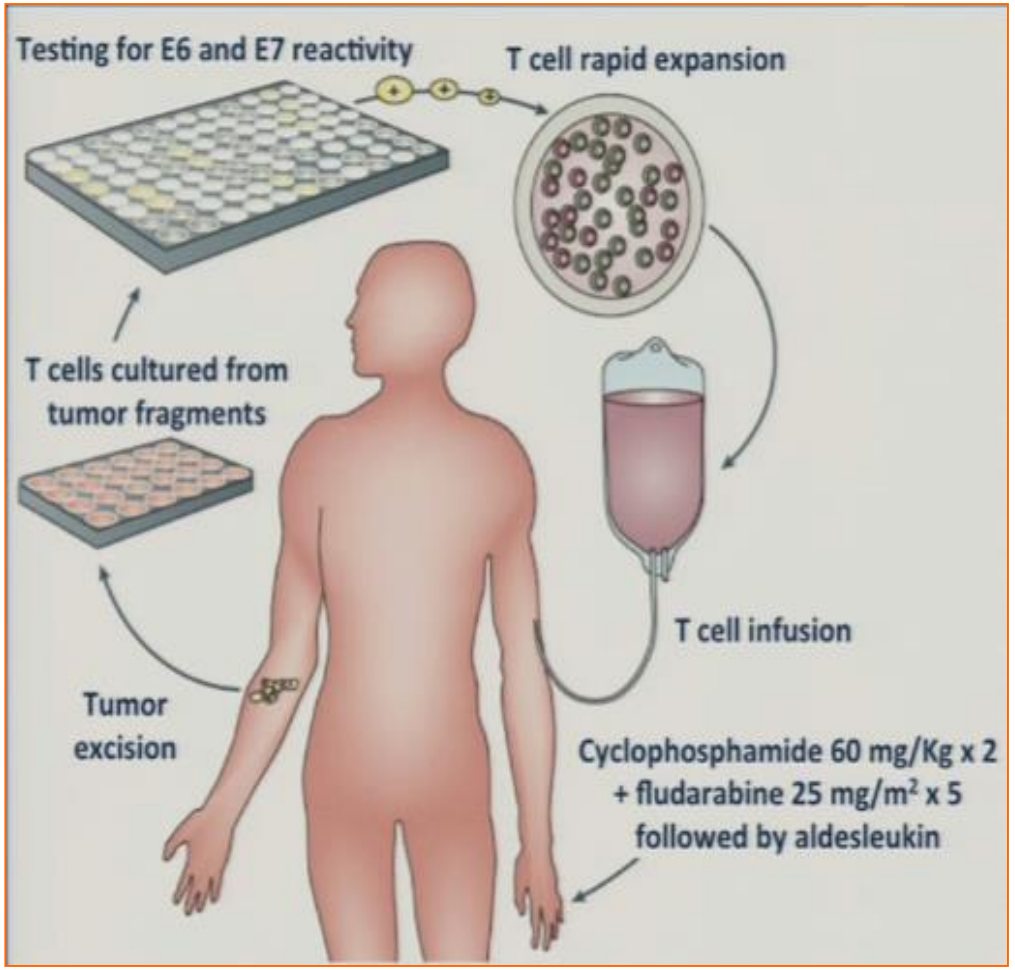


# TIL

TIL from resected tumors → expanded with IL-2 in culture→ reinfusion into patients following lymphodepleting CT.

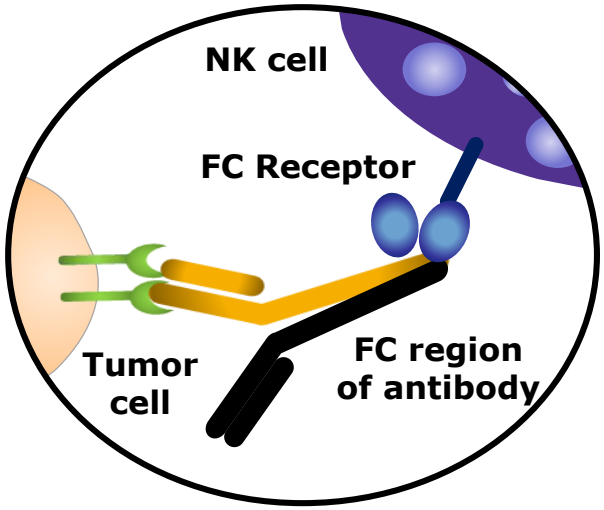
Leukapheresis→

Conditioning CT →reinfusion (NCT01585428)

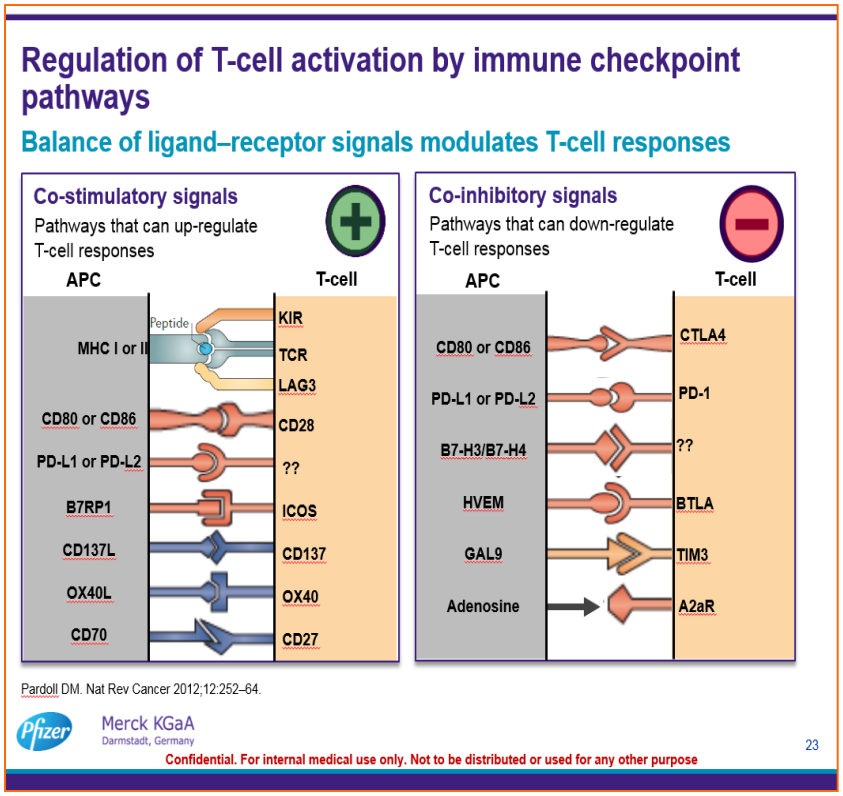


# Future directions

## ADCC

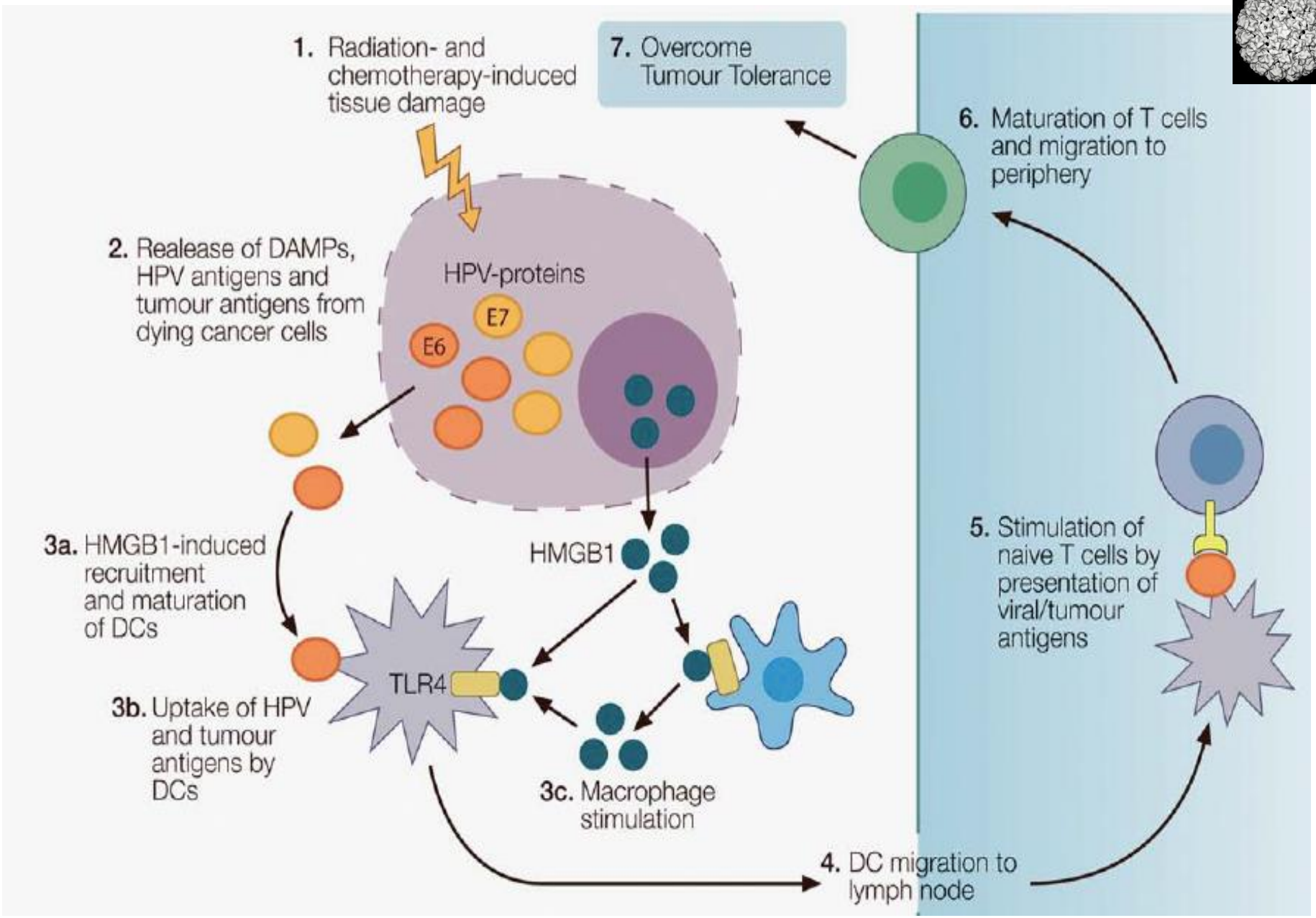



## T cell receptor regulation



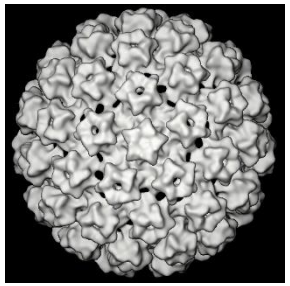

## Microbioma


1. Janeway CA Jr, et al. Immunobiology; The immune system in health and disease; 5th Ed. 2001
2. 2. Pardoil DM. Nat Rev Cancer 2012; 12: 252–62



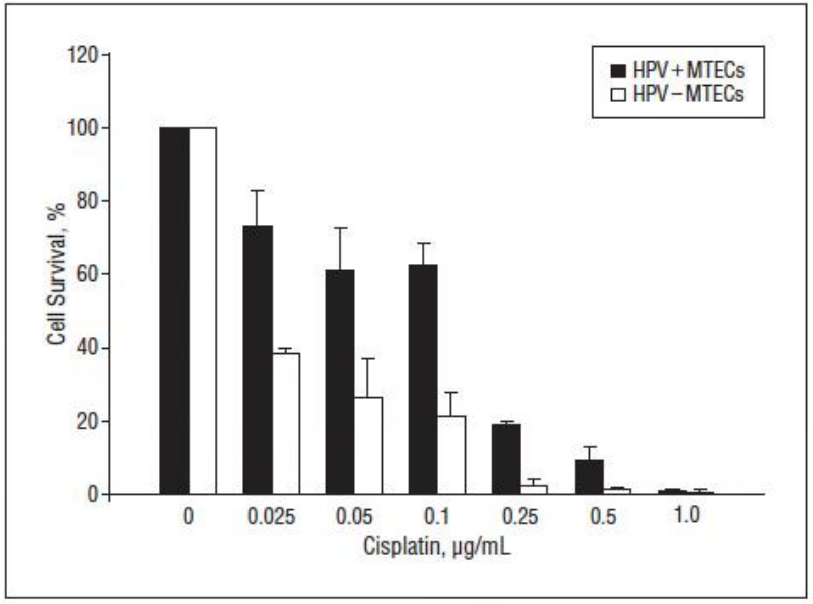

***Andersen AS et al Int.l J Cancer 2013:134,2755-2763***

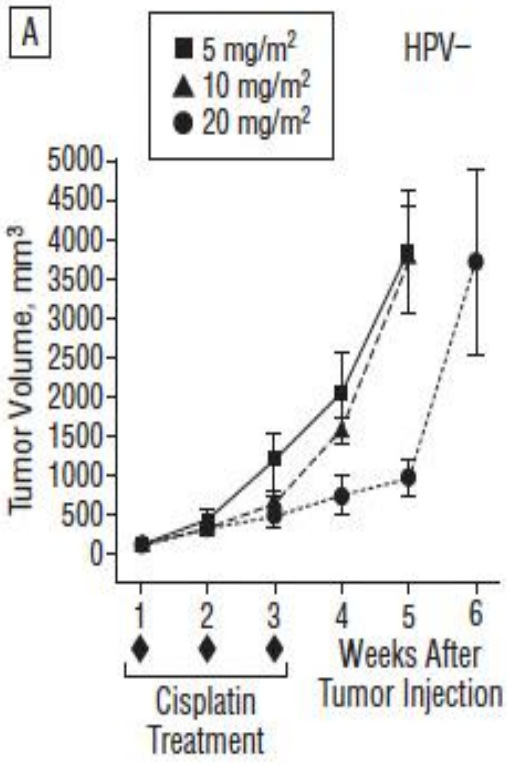
# Immune Response During Therapy With Cisplatin or Radiation for Human Papillomavirus–Related Head and Neck Cancer



*William C. Spanos, MD; Paul Nowicki, MD; Dong Wook Lee, MD; Andrew Hoover, BS; Bruce Hostager, PhD; Anjali Gupta, MD; Mary E. Anderson, MS; John H. Lee, MD*

*Arch Otolaryngol Head Neck Surg. 2009;135(11):1137-1146*



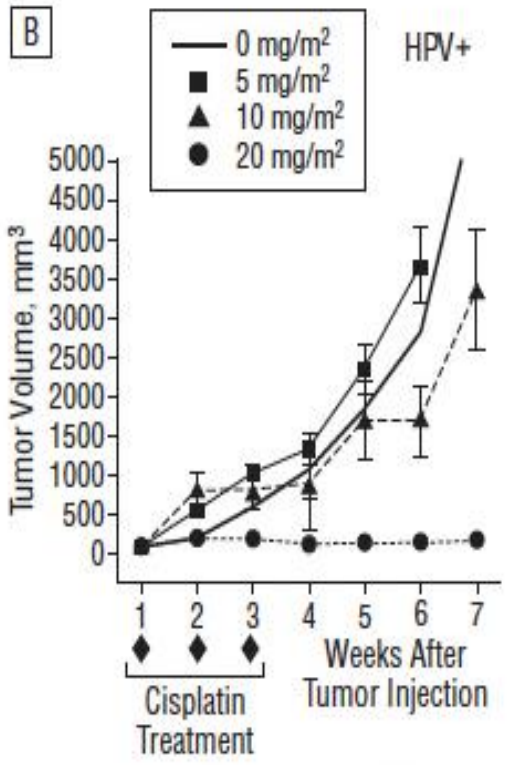
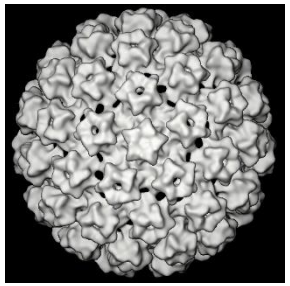




**Figure 4.** Human papillomavirus–positive (HPV+) mouse tonsil epithelial cells (MTECs) are more resistant to cisplatin than are HPV-negative (HPV–) HPV– MTECs. The MTECs were plated, were allowed to attach, and were treated with cisplatin for 24 hours; colony formation was then assessed. The HPV+ and HPV– MTECs were incubated with escalating doses of cisplatin and were allowed to grow until a 15-cell colony size was achieved. Three plates were used per condition, and the results were averaged across 2 experiments. The percentage of surviving cells that formed colonies were quantified. The HPV+ MTECs are more resistant (approximately 63%) to cisplatin than are the HPV– cells ($P<.02$, Mann-Whitney test). Error bars represent SE.

ORIGINAL ARTICLE

# Immune Response During Therapy With Cisplatin or Radiation for Human Papillomavirus–Related Head and Neck Cancer



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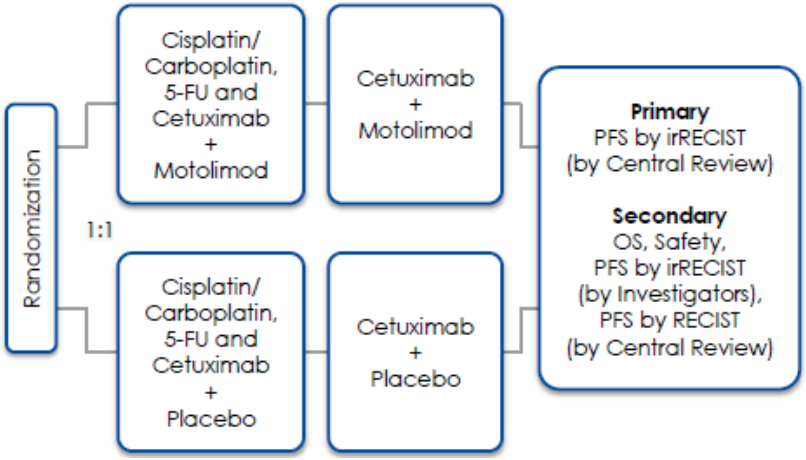
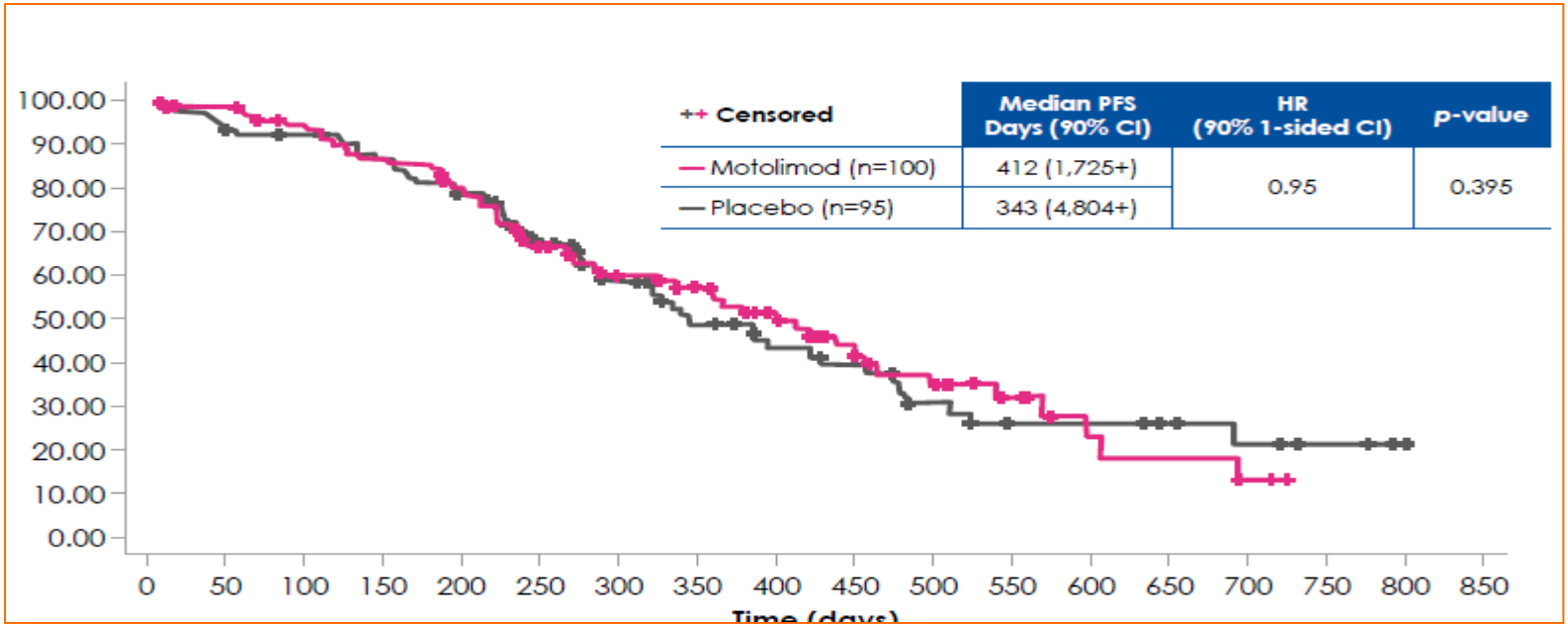
*Arch Otolaryngol Head Neck Surg. 2009;135(11):1137-1146*

| Model | | HPV status | Tumour clearance | | |
|---|---|---|---|---|---|
| | | | RT | CT | CRT |
| Human cell lines | | Pos | No | No | No |
| | | Neg | No | No | No |
| Mouse model | Immunocompetent mice | Pos | Yes | Yes | Yes |
| | | Neg | No | No | No |
| | Immunodeficient mice | Pos | No | No | No |
| | | Neg | No | No | No |

# Active 8


Randomization
1:1
Cisplatin/ Carboplatin, 5-FU and Cetuximab + Motolimod
Cetuximab + Motolimod
Cisplatin/ Carboplatin, 5-FU and Cetuximab + Placebo
Cetuximab + Placebo
Primary
PFS by irRECIST (by Central Review)
Secondary
OS, Safety, PFS by irRECIST (by Investigators), PFS by RECIST (by Central Review)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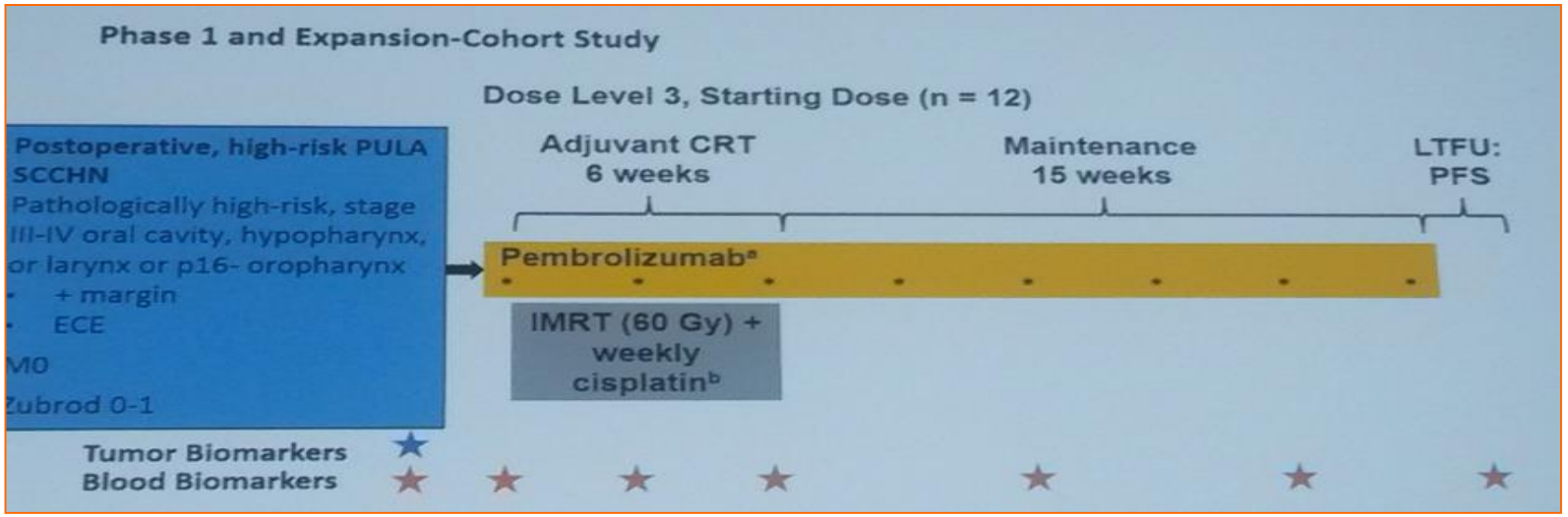
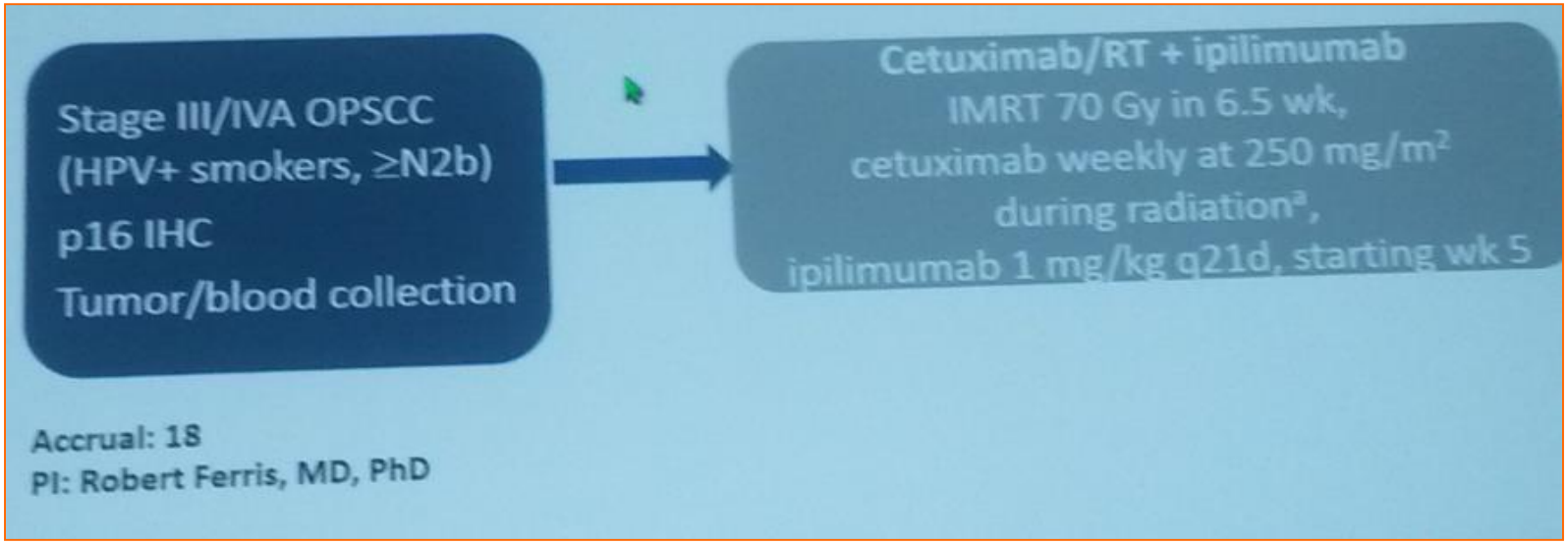
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
Time (days)
++ Censored
Median PFS Days (90% CI)
HR (90% 1-sided CI)
p-value
Motolimod (n=100)
412 (1,725+)
0.95
0.395
Placebo (n=95)
343 (4,804+)

# Immunotherapy+RT



# PULA HNSCC

| Protocol Therapy | Week of Treatment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 11 | 14 |
| **IMRT**<br>70-74 Gy, standard fractionation | | X | X | X | X | X | X | X | | |
| **Cetuximab**<br>400 mg/m² load then 250 mg | X | X | X | X | X | X | X | X | | |
| **Ipilimumab**<br>Cohort -1: 1 mg/kg<br>Cohort 1 (start): 3 mg/kg<br>Cohort 2: 10 mg/kg | | | | | X | | | X | X | X |

| | NCI CTCAE GRADE | |
|---|---|---|
| **IMMUNE-RELATED** | **Grade 1-2** | **Grade 3-4** |
| **Dermatologic** | | |
| Rash | 13 (72%) | 5 (28%) |
| **Gastrointestinal** | | |
| Diarrhea | 0 | 1 (6%) |
| Colitis | 0 | 1 (6%) |
| Transaminitis | 1 (6%) | 0 |
| **Endocrine** | | |
| Acute thyroiditis | 1 (6%) | 0 |
| **REGIMEN-RELATED** | **Grade 1-2** | **Grade 3-4** |
| **Mucositis** | 6 (33%) | 12 (67%) |
| **Radiation Dermatitis** | 14 (78%) | 4 (22%) |
| **Hypothyroidism** | 6 (33%) | 0 |

# Conclusions

- Immunotherapy is active both in HPV pos and neg HNSCC and in EBV associated NPC

→ We NEED TO SELECT PATIENTS

- PDL1 (IHC) can enrich but still about 8 % PDL1 neg responds
- Basal ADCC could be a marker for mAbs activity
- Therapeutic Vaccination appears safe, but positive results from ongoing phase II/III trials are awaited

# Conclusions

- AntiPD1 therapy achieves OS 40% at 1 y in heavily pretreated patients,safety is good, some responses may be durable
- However RR =15-20%

→ We NEED TO IMPROVE RESPONSES

- Inducing inflammation in Tumor Microenviroment? stimulating STING?

# THANK YOU FOR YOUR ATTENTION