CÁNCER DE CABEZA Y CUELLO LOCO - REGIONAL

INMUNOTERAPIA NEOADYUVANTE, CONCOMITANTE Y ADYUVANTE

Aldo B. Fiorini Talavera
Complejo Asistencial de Segovia

Clinical & Translational Oncology

SEOM clinical guidelines for the treatment of head and neck cancer (2017)

L. C. Iglesias Docampo[1] · V. Arrazubi Arrula[2] · N. Baste Rotllan[3] · A. Carral Maseda[4] · B. Cirauqui Cirauqui[5] · Y. Escobar[6] · J. J. Lambea Sorrosal[7] · M. Pastor Borgoñón[8] · A. Rueda[9] · J. J. Cruz Hernández[10]

Fig. 1 Treatment algorithm for resectable locally advanced disease (III–IVA)

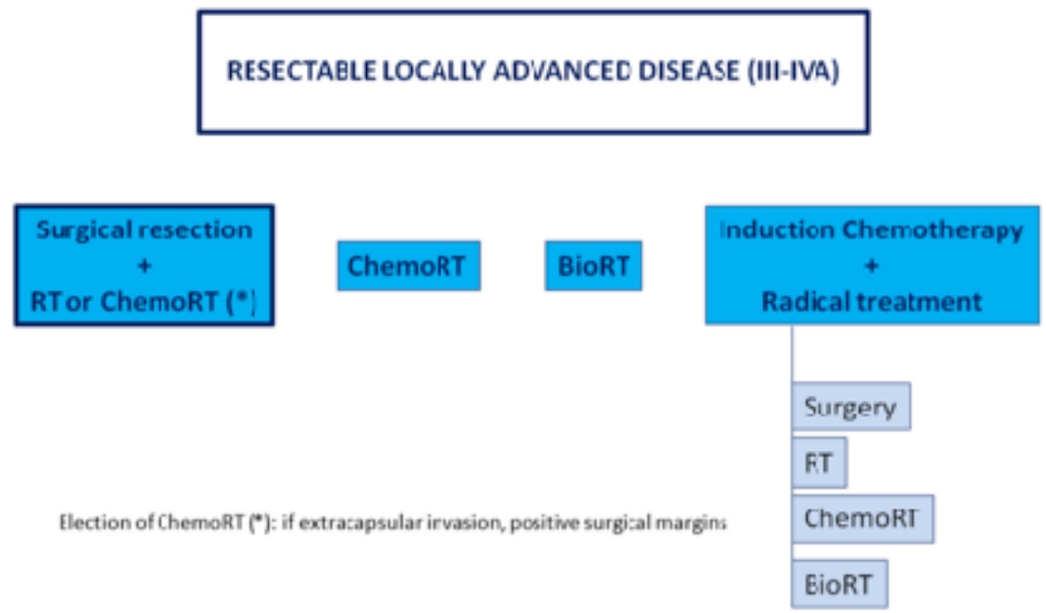
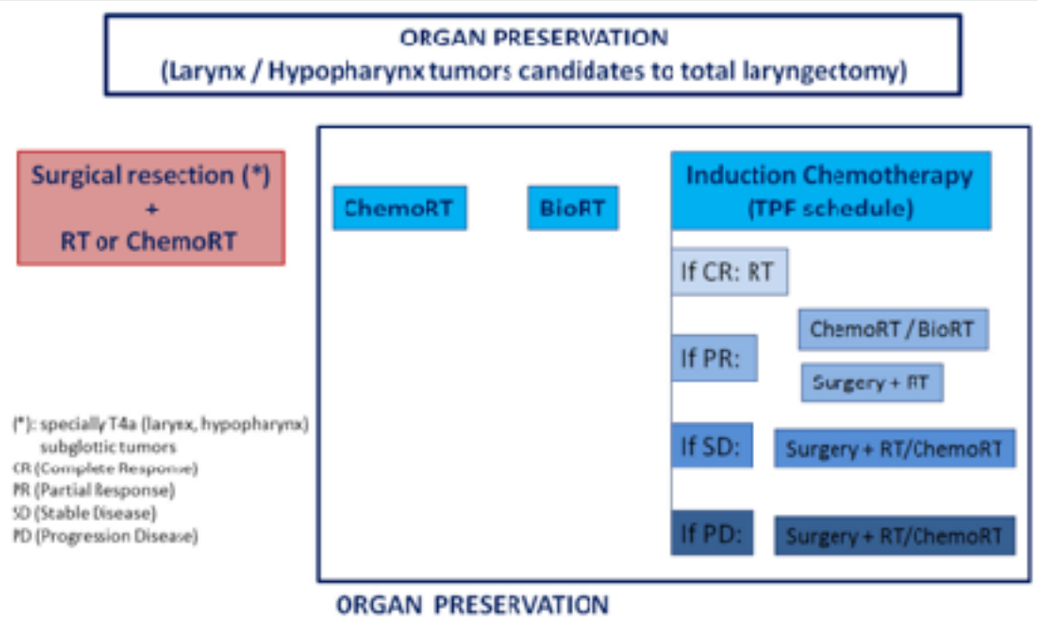


Fig. 2 Larynx preservation algorithm (resectable locally advanced disease)



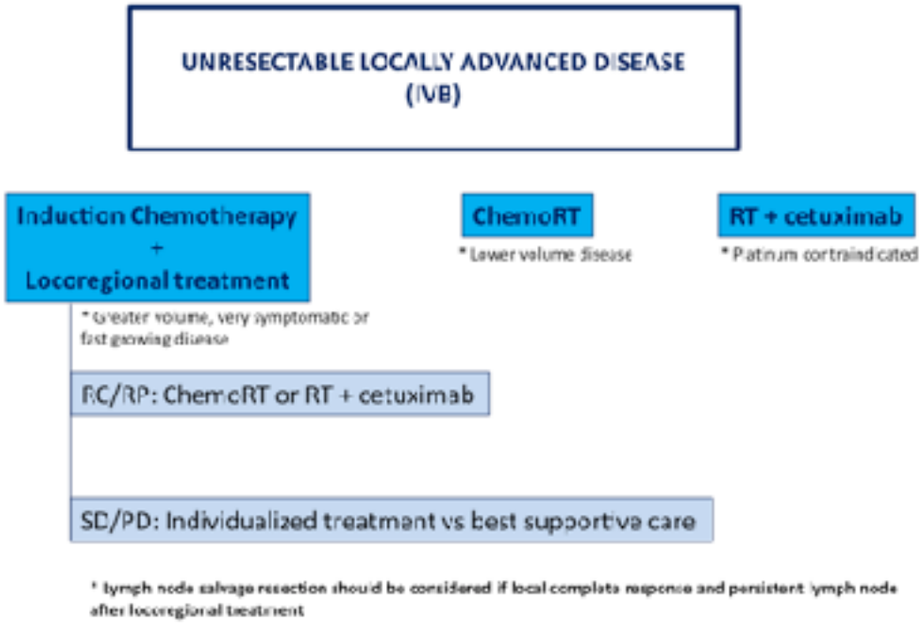


Fig. 3 Treatment algorithm for unresectable locally advanced disease (IV-B)

Clin Transl Oncol (2018) 20:75–83

NCCN 2018
H&N Cancers

Printed by Aviv Ronen on 12/9/2018 7:01:30 AM. For personal use only. Not approved for distribution. Copyright © 2018 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Head and Neck Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).

- The preferred chemoradiotherapy approach for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy.
- Cisplatin-based induction chemotherapy can be used, followed by radiation-based loco-regional treatment (ie, sequential chemoRT). However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state-of-the-art concurrent chemoRT (cisplatin preferred, category 1) has not been established in randomized studies.
- Cisplatin-based induction chemotherapy followed by high-dose, every-3-week cisplatin chemoradiotherapy is not recommended due to toxicity concerns.[1,2]
- After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone versus radiotherapy plus weekly carboplatin or cetuximab are among the options.

Squamous Cell Cancers
Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary
- Primary systemic therapy + concurrent RT
  - High-dose cisplatin[3,4] (preferred) (category 1)
  - Cetuximab[5] (category 1 for oropharynx, hypopharynx, or larynx; category 2B for lip, oral cavity, ethmoid sinus, maxillary sinus, occult primary)
  - Carboplatin/infusional 5-FU (category 1)[6,7]
  - 5-FU/hydroxyurea[8]
  - Cisplatin/paclitaxel[9]
  - Cisplatin/infusional 5-FU[9]
  - Carboplatin/paclitaxel[10] (category 2B)
  - Weekly cisplatin 40 mg/m² (category 2B)[11,12]
- Postoperative chemoradiation
  - Cisplatin[13-18] (category 1 for high-risk** non-oropharyngeal cancers)

Nasopharynx:
- Chemoradiation followed by adjuvant chemotherapy
  - Cisplatin + RT followed by cisplatin/5-FU[19-20] or carboplatin/5-FU[21] (category 2B for carboplatin/5-FU)
- Cisplatin + RT without adjuvant chemotherapy (category 2B)[22]

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary
- Induction*/Sequential chemotherapy
  - Docetaxel/cisplatin/5-FU[23-25] (category 1 if induction is chosen)
  - Paclitaxel/cisplatin/infusional 5-FU[26]
  - Following induction, agents used with concurrent chemoradiation typically include weekly carboplatin, weekly cisplatin (category 2B), or weekly cetuximab[3,27,28]

Nasopharynx:
- Induction/Sequential chemotherapy
  - Docetaxel/cisplatin/5-FU[29]
  - Docetaxel/cisplatin (category 2B)[30]
  - Cisplatin/5-FU[31]
  - Cisplatin/epirubicin/paclitaxel
  - Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[20] or carboplatin[27]

*The categories of evidence and consensus for induction therapy vary depending on site. (See disease-specific site in the Head and Neck Table of Co
**Adverse features: extranodal extension and/or positive margins.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 2.2018, 08/20/18 © National Comprehensive Cancer Network, Inc. 2018, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Aviv Ronen on 12/9/2018 7:01:30 AM. For personal use only. Not approved for distribution. Copyright © 2018 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Head and Neck Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

- The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).
- Unless otherwise specified, regimens listed below can be used for either nasopharyngeal or non-nasopharyngeal cancer.

Recurrent, Unresectable, or Metastatic (with no surgery or RT option)
- First-Line Combination Therapy Options:
  - Cisplatin or carboplatin/5-FU/cetuximab[30] (non-nasopharyngeal) (category 1)
  - Cisplatin or carboplatin/docetaxel[31] or paclitaxel[32]
  - Cisplatin/cetuximab[33] (non-nasopharyngeal)
  - Cisplatin/5-FU[32,34]
  - Cisplatin or carboplatin/docetaxel/cetuximab[35] (non-nasopharyngeal)
  - Cisplatin or carboplatin/paclitaxel/cetuximab[36,37] (non-nasopharyngeal)
  - Cisplatin/gemcitabine[38,39] (category 1) (nasopharyngeal)
  - Carboplatin/cetuximab[41] (nasopharyngeal)
- First-Line Single-Agent Options:
  - Cisplatin[33,42]
  - Carboplatin[43]
  - Paclitaxel[44]
  - Docetaxel[45,46]
  - 5-FU[42]
  - Methotrexate[47,48]
  - Cetuximab[49] (non-nasopharyngeal)
  - Gemcitabine[50] (nasopharyngeal)
  - Capecitabine[51]
- Second-Line Therapy or Subsequent Therapy Options:
  - Combination therapy options listed above
  - Single-agent options listed above
  - Nivolumab[52] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 1)
  - Pembrolizumab[53-55]
    - Non-nasopharyngeal: if disease progression on or after platinum-containing chemotherapy
    - Nasopharyngeal: if previously treated, PD-L1-positive recurrent or metastatic disease (category 2B)
  - Afatinib[56] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 2B)

See References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 2.2018, 08/20/18 © National Comprehensive Cancer Network, Inc. 2018, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

¿Inmunoterapia en enfermedad localmente avanzada?

¿Inmunoterapia en enfermedad localmente avanzada?

NCBI
PubMed.gov
US National Library of Medicine
National Institutes of Health

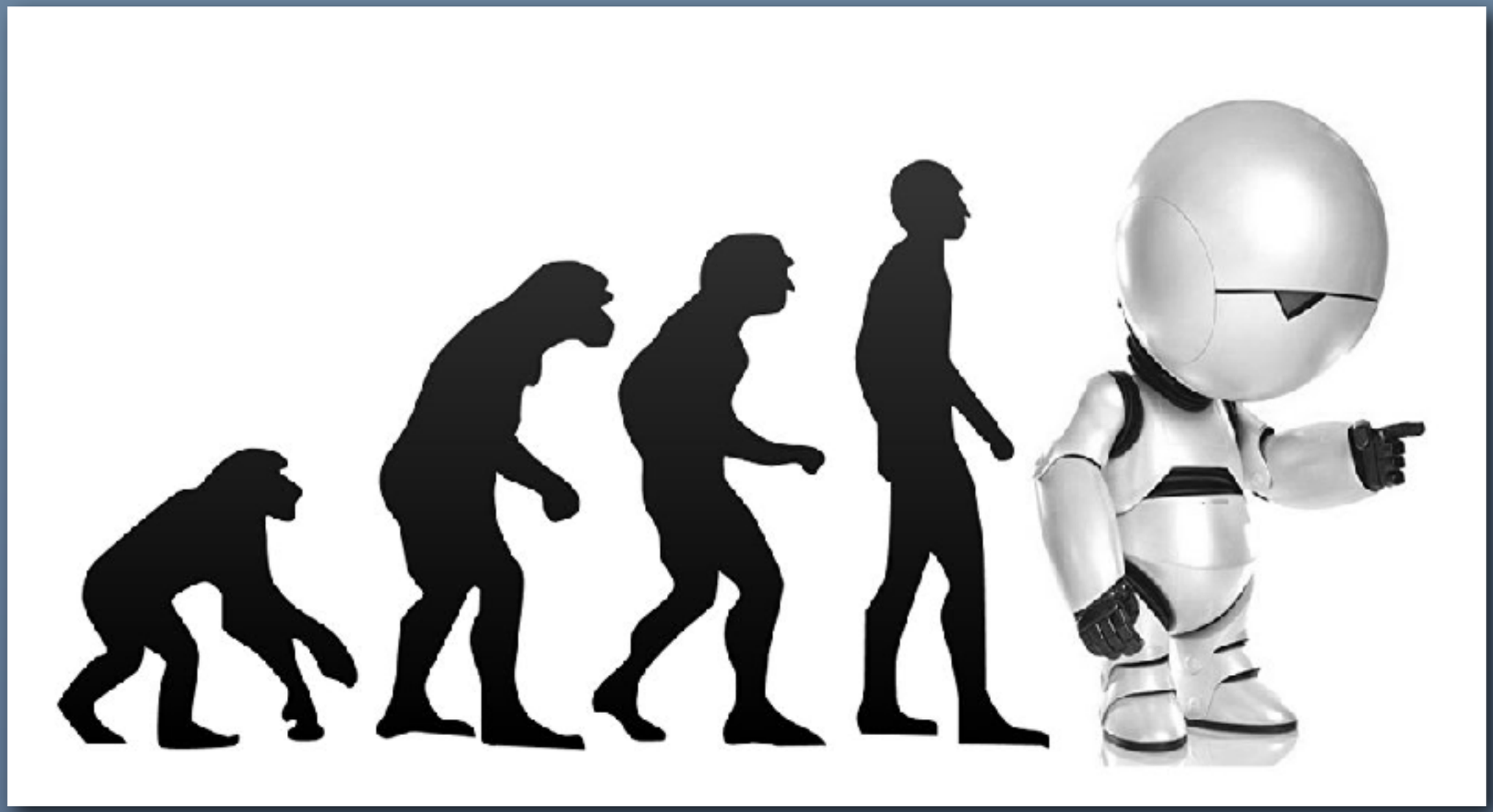
UpToDate

NIH U.S. National Library of Medicine
ClinicalTrials.gov

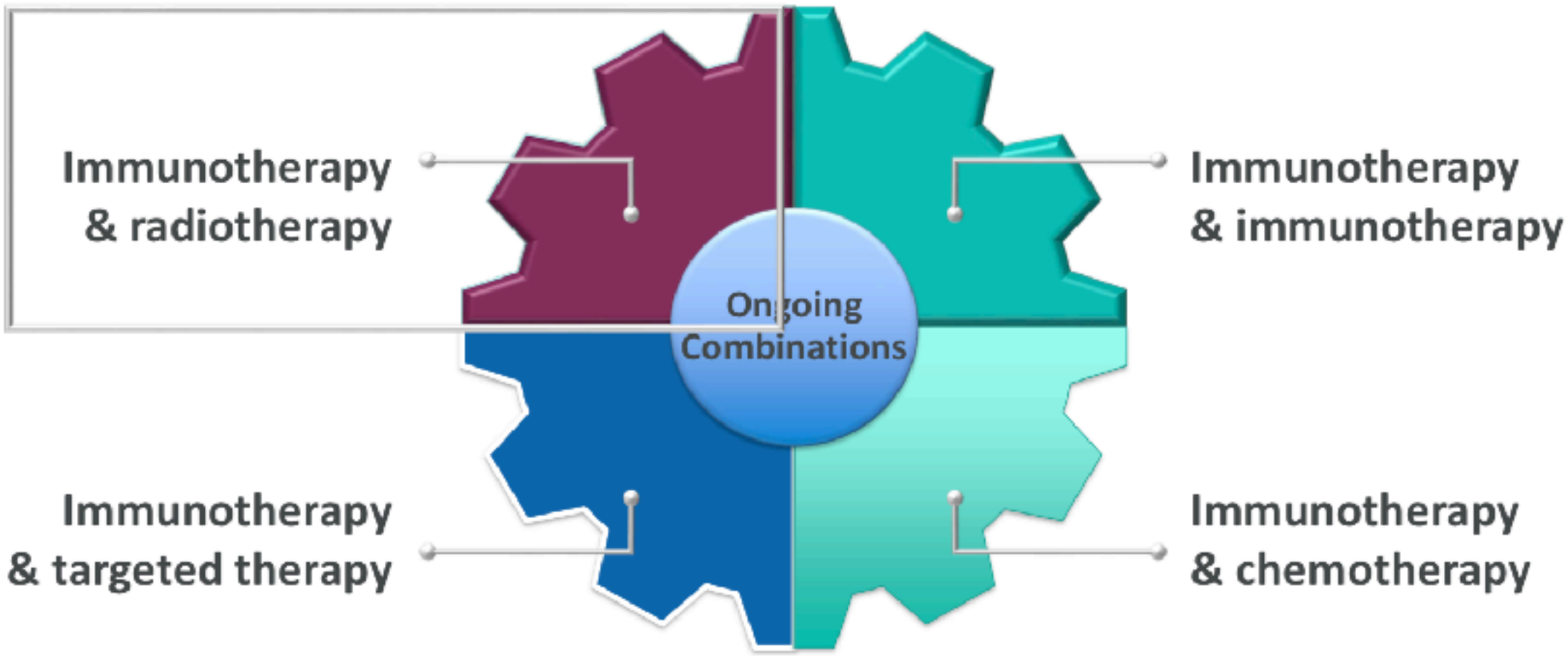
2018 ASCO
ANNUAL MEETING
#ASCO18

MUNICH 2018 ESMO congress

Más de 90 estudios de cáncer de cabeza y cuello e inmunoterapia

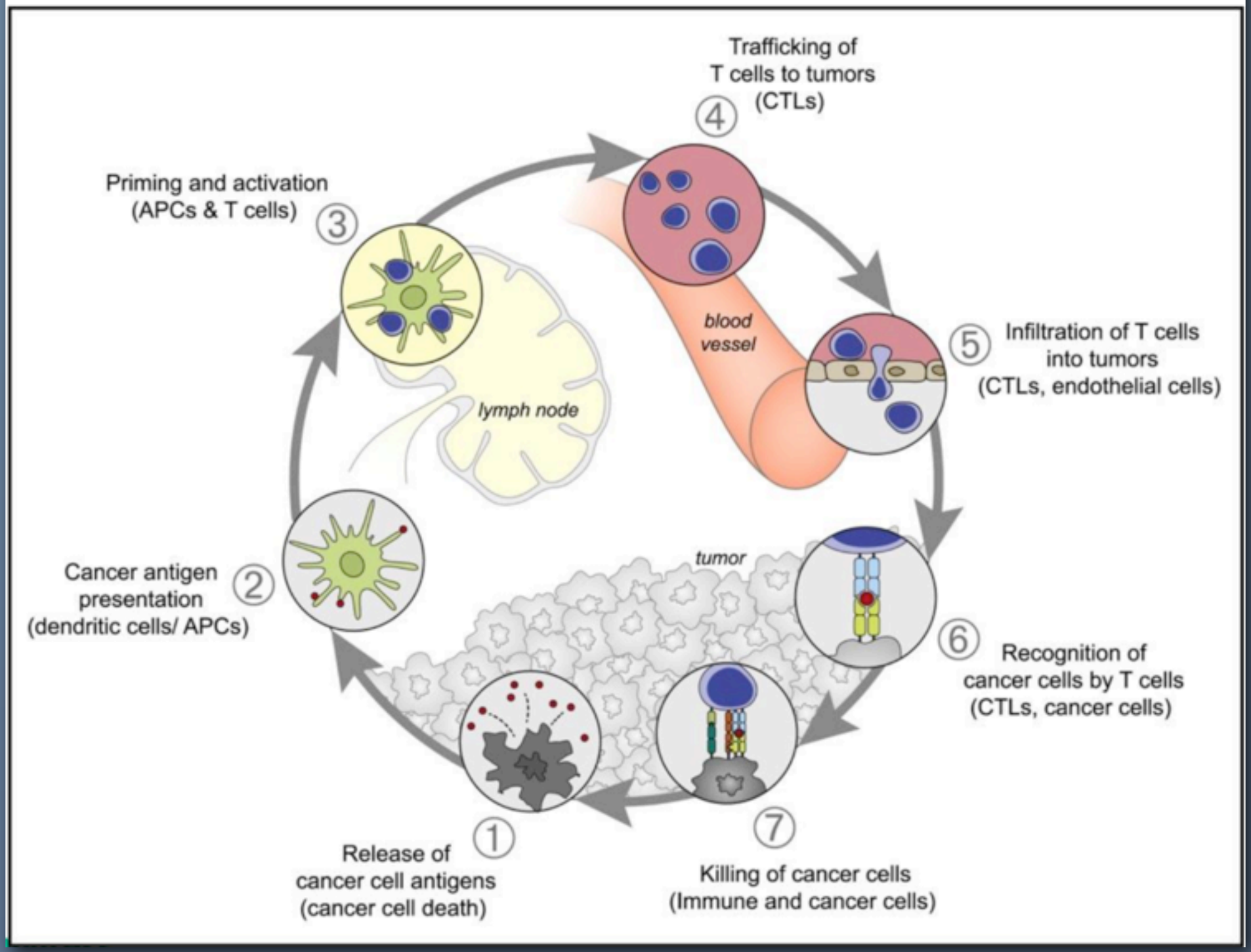


Potential Immunotherapy Combinations



Cohen E, ESMO 2018

The Cancer-Immunity Cycle



INMUNOTERAPIA NEOADYUVANTE

MADRID 2017 ESMO congress

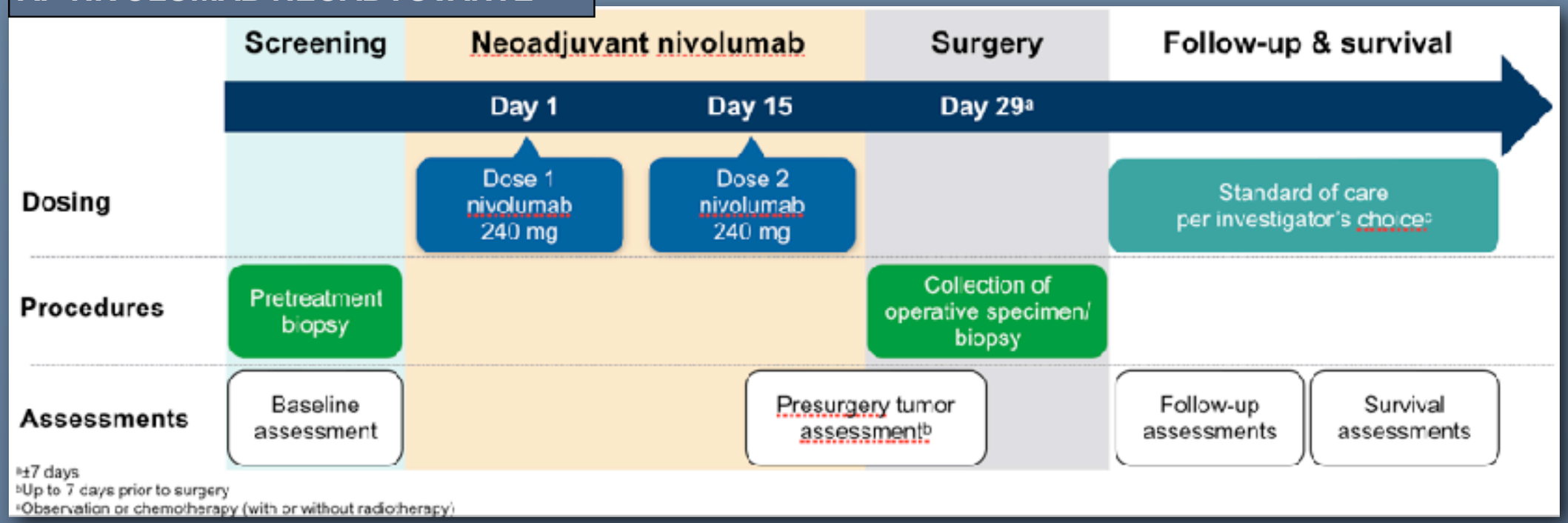
LBA46 An open-label, multicohort, phase 1/2 study in patients with virus-associated cancers (CheckMate 358): Safety and efficacy of neoadjuvant nivolumab in squamous cell carcinoma of the head and neck (SCCHN)

ClinicalTrials.gov Identifier: NCT02488759

Recruitment Status : Recruiting
First Posted : July 2, 2015
Last Update Posted : October 19, 2015
See Contacts and Locations

Estudio multicorte para evaluar seguridad y eficacia de nivolumab en 5 brazos: nivo neoadyuvante, nivo enf avanzada, nivo+ipi novo+relatlinib, nivo+daratumumab en pacientes con tumores asociados a virus.

A.- NIVOLUMAB NEOADYUVANTE

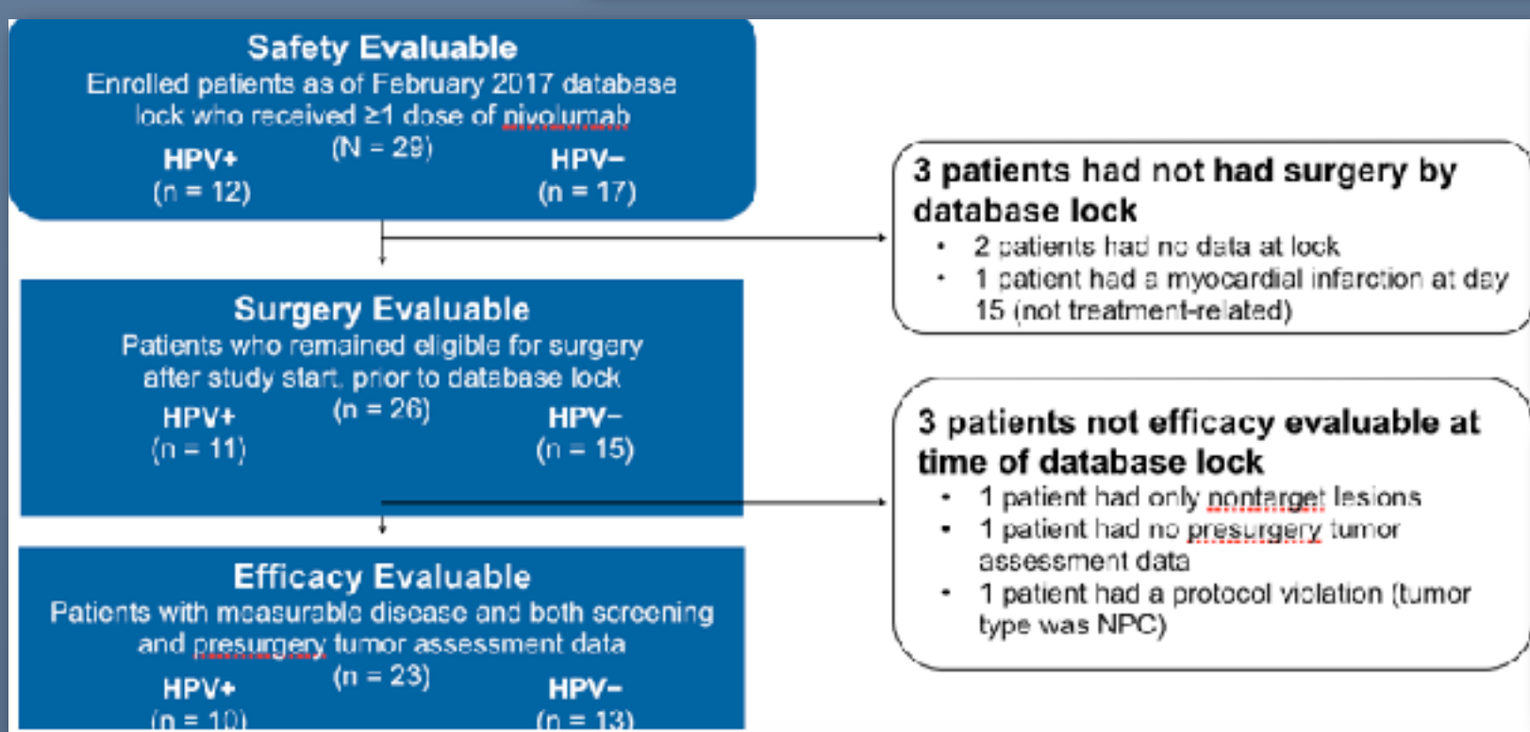


Inclusión:
-SCCHN cavidad oral, faringe o laringe, ≥T1 y ≥N1.
-Resecable con bx previa.
-ECOG 0-1
-VPH (p16)

-Objetivo primario: seguridad y tolerabilidad (TRAEs, TRAEs graves, retraso a cirugía > 4 semanas)
-Objetivos secundarios: cambio en volumen tumor al tras 2 dosis de nivolumab, PFS (ongoing), PCR (ongoing), cambios en microambiente (ongoing)

Ferris R, ESMO 2017

	HPV+ (n = 12)	HPV− (n = 17)
Age, median (range), y	59.5 (34–82)	56.0 (42–76)
Male, n (%)	10 (83.3)	14 (82.4)
Region, n (%)		
North America	4 (33.3)	10 (58.8)
Europe	8 (66.7)	7 (41.2)
ECOG PS, n (%)		
0	9 (75.0)	12 (70.6)
1	3 (25.0)	5 (29.4)
Tumor site, n (%)		
Oral cavity	7 (58.3)	8 (47.1)
Oropharynx	4 (33.3)	2 (11.8)
Hypopharynx	0	3 (17.6)
Larynx	0	2 (11.8)
Unknown	1 (8.3)	2 (11.8)
Tumor PD-L1 expression, n (%)[a]		
≥1%	8 (66.7)	11 (64.7)
<1%	1 (8.3)	4 (23.5)
Not quantifiable	3 (25.0)	2 (11.8)



	HPV+ (n = 12)	HPV− (n = 17)
Follow-up, median (range), weeks	21.8 (2.1–41.0)	11.6 (3.7–56.3)
Received both doses of nivolumab, n (%)	12 (100.0)	17 (100.0)

	HPV+ (n = 11)	HPV− (n = 15)
Rate of surgery/biopsy delay due to TRAEs, n (%) [95% CI]	0 [0, 28.5]	0 [0, 21.8]

Ferris R, ESMO 2017

Toxicidad

TRAEs en >1 paciente

	HPV+ (n = 12)		HPV− (n = 17)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)	**9 (75.0)**	**2 (16.7)**	**10 (58.8)**	**2 (11.8)**
Amylase increased	2 (16.7)	0	2 (11.8)	0
Lipase increased	1 (8.3)	1 (8.3)	2 (11.8)	2 (11.8)
Fatigue	1 (8.3)	0	2 (11.8)	0
Chills	1 (8.3)	0	1 (5.9)	0
Pyrexia	1 (8.3)	0	1 (5.9)	0
Mouth hemorrhage	1 (8.3)	0	1 (5.9)	0

TRAEs graves

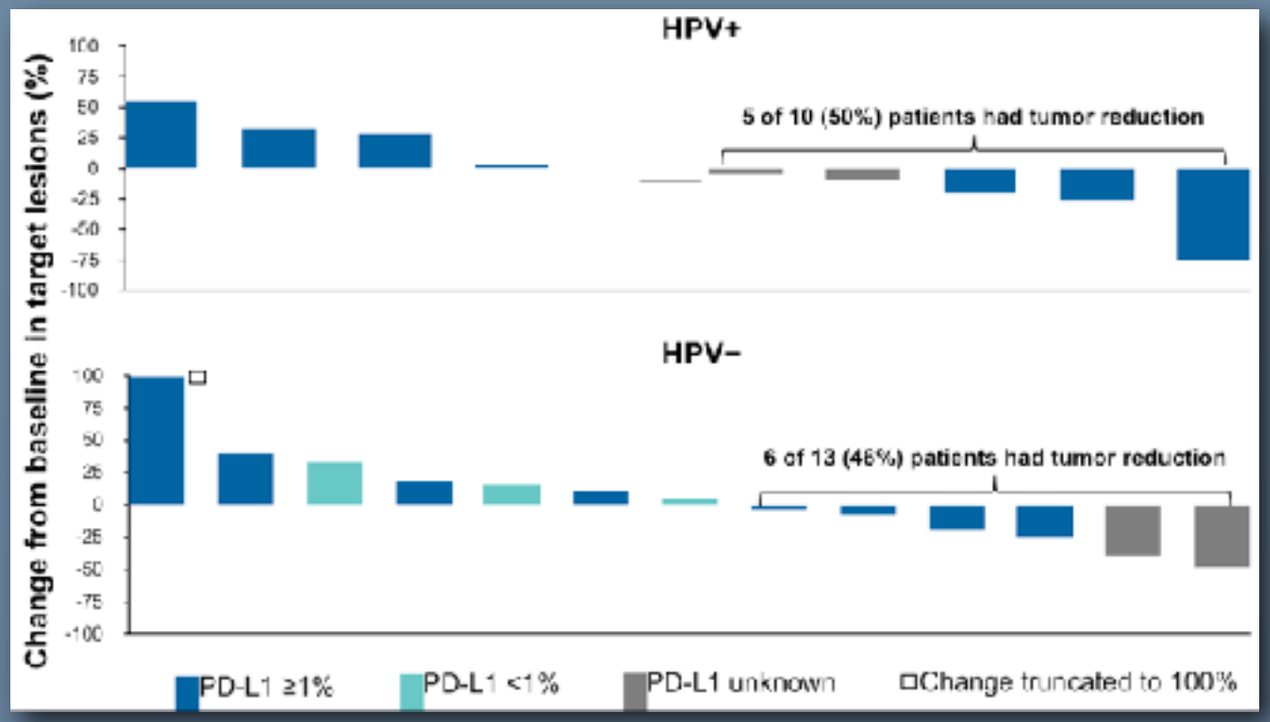
	HPV+ (n = 12)		HPV− (n = 17)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any serious TRAE, n (%)	**1 (8.3)**	**1 (8.3)**	**3 (17.6)**	**0**
Glossodynia	1 (8.3)	1 (8.3)	0	0
Mouth hemorrhage	1 (8.3)	0	1 (5.9)	0
Chills	0	0	1 (5.9)	0
Fatigue	0	0	1 (5.9)	0
Hyperhidrosis	0	0	1 (5.9)	0
Pancreatitis	0	0	1 (5.9)	0
Pyrexia	0	0	1 (5.9)	0

TRAEs de clase

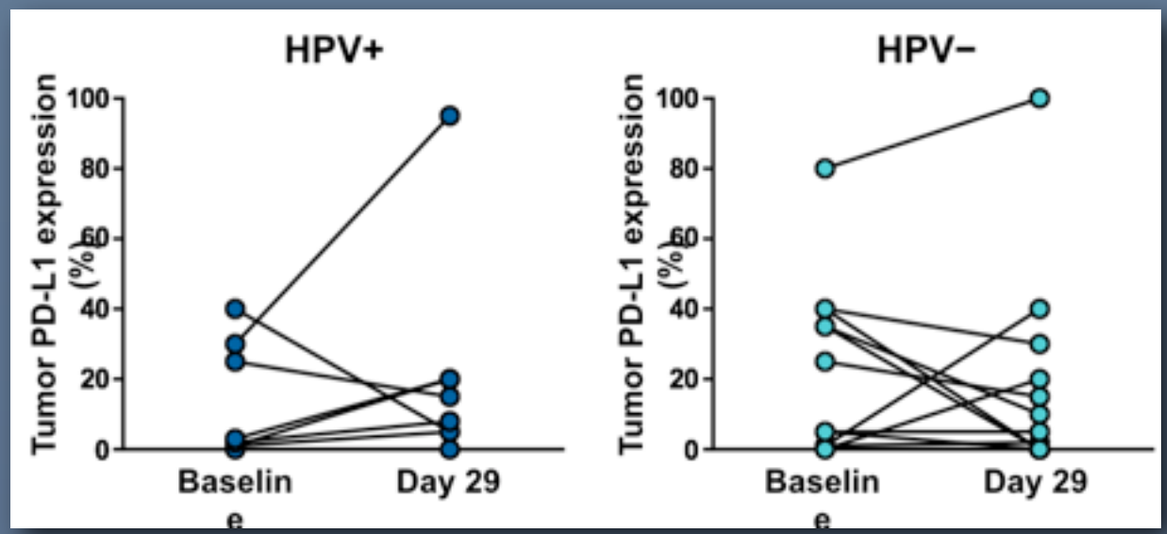
	HPV+ (n = 12)		HPV− (n = 17)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Gastrointestinal	1 (8.3)	0	0	0
Skin	1 (8.3)	0	0	0
Hypersensitivity/ infusion reaction	0	0	1 (5.9)	0
Endocrine	0	0	0	0
Hepatic	0	0	0	0
Pulmonary	0	0	0	0
Renal	0	0	0	0

Ferris R, ESMO 2017

Respuesta tumoral con 2 dosis de Nivolumab



Cambio en la expresión de PDL-1



CONCLUSIONES:

- Primeros datos publicados de en estudio con anti-PD1 en neoadyuvancia en pacientes HPV+/- SCCHN.
- Nivolumab neoadyuvante:
  - Tratamiento factible
  - Puede reducir el tamaño tumoral (rpta. 50% independiente de PVH, 3 rpta>40%).
  - Bien tolerado, sin demora quirúrgica por TRAE.
- Los análisis de los cambios en microambiente, PFS y PCR están pendientes.

Ferris R, ESMO 2017

2018 ASCO ANNUAL MEETING

Phase II Multi-site Investigation of Neoadjuvant Pembrolizumab and Adjuvant Concurrent Radiation and Pembrolizumab with or without Cisplatin in Resected Head and Neck Squamous Cell Carcinoma

University of CINCINNATI

Trisha M. Wise-Draper[1], Matthew O. Old[2], Francis P. Worden[3], Paul E. O'Brien[4], Ezra E.W. Cohen[5], Neal Dunlap[6], Michelle L. Mierzwa[3], Keith Casper[3], Sarah Palackdharry[1], Benjamin Hinrichs[1], Alfredo Molinolo[5], Vinita Takiar[1], Jonathan Mark[1], Alice Tang[1], Muhammad Kashif Riaz[1], John C. Morris[1], Nooshin Hashemi[1], Changchun Xie[1], Maura L. Gillison[8]

University of Cincinnati Cancer Institute, Cincinnati, OH[1]; The Ohio State University, Columbus, OH[2]; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI[3]; Medical University of South Carolina, Charleston, SC[4]; University of California, San Diego, La Jolla, CA[5]; University of Louisville, James Graham Brown Cancer Center, Louisville, KY[6]; University of Michigan, Ann Arbor, MI[7]; The University of Texas MD Anderson Cancer Center, Houston, TX[8]

Background

Methods

Results

Patient Characteristics

Pembrolizumab Induces Pathological Treatment Effect

Pembrolizumab induces anti-tumor immune signature in those with TE

All Adverse Events

Pembrolizumab Related Adverse Events

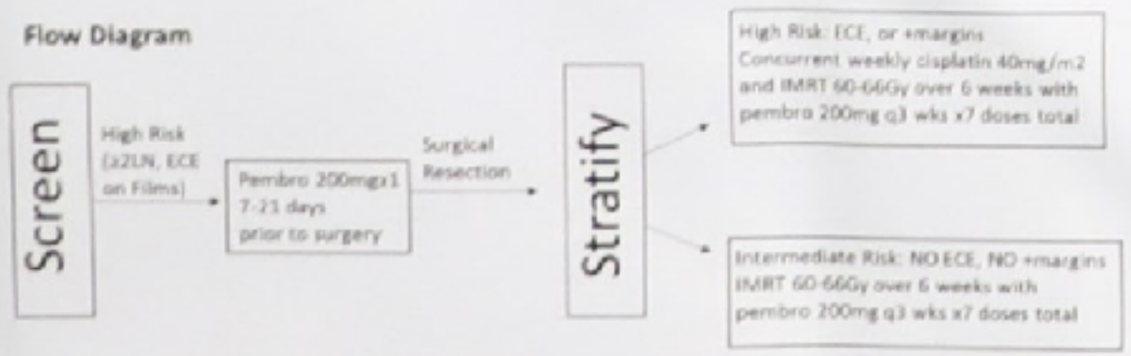
Conclusions

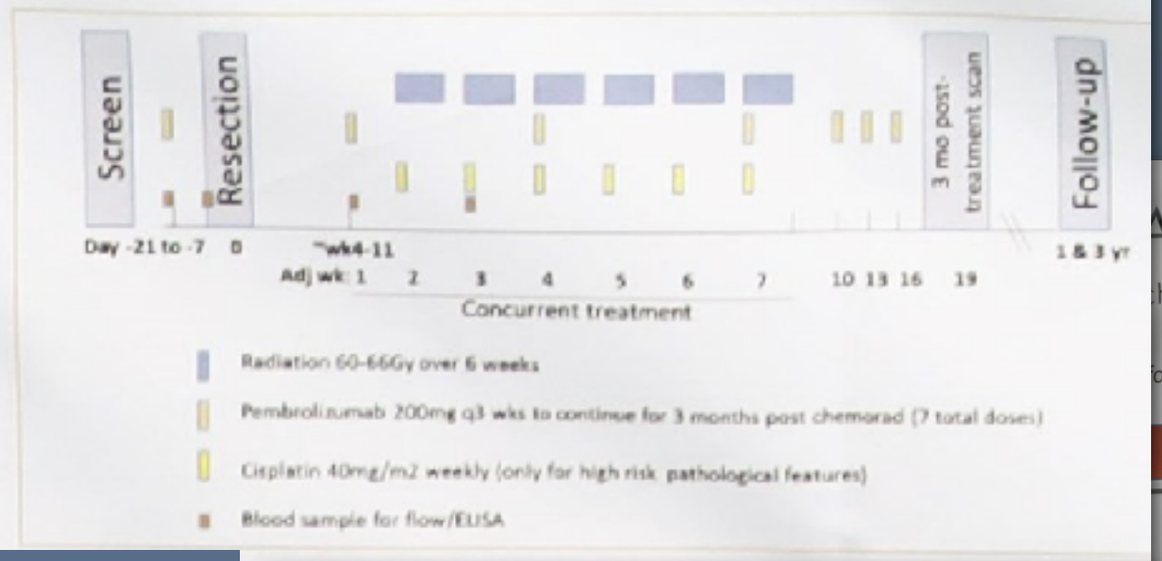
- Pembrolizumab induces a pathological response in >50% tumors after just 1 administration
- Neoadjuvant and adjuvant pembrolizumab is safe with minimal related Adverse Events and no unexpected events
- Pembrolizumab results in increased anti-tumor inflammatory response in patients with pathological response

Acknowledgements

The phase II study was supported by Merck. Correlative analysis was supported by a KL2 awarded to Dr. Wise-Draper as part of a CTSA grant at the University of Cincinnati as well as a grant from the CoD. We would like to thank the University of Cincinnati Cancer Institute Clinical Trials Coordinators and our pathology tissue core for the success of this study.

Estudio fase 2 de ventana quirúrgica con Pembrolizumab NeoAd y adyuvante +RT +- CDDP tras IQx.





Pacientes de alto riesgo (T3-4 y/o N≥2)
Neoadyuvancia: Pembrolizumab 200mg x 1d, 1 a 3 semanas antes de la cirugía.
Adyuvancia (estratificado según riesgo): Pembrolizumab c/3 sem x 6 dosis + RT 60-66Gy +/- CDDP 40mg/m2 sem. Se obtuvieron tejidos antes y después de cirugía.

- Primary Objectives: 1. Determine the frequency and severity of side effects of pembrolizumab when administered in combination with radiation alone or cisplatin and radiation therapy (CRT) in patients undergoing adjuvant treatment for resected HNSCC. 2. To estimate the 1 and 3 year disease free survival (DFS) combining pembrolizumab with adjuvant CRT in patients with resected high risk HNSCC. 3. To estimate the 1 and 3 year disease free survival (DFS) combining pembrolizumab with adjuvant radiation in patients with resected intermediate risk HNSCC.
- Statistical analysis was based upon RTOG 9501 historical controls with DFS at 1 year and 3 years being 66% and 47% respectively for patients with high risk features undergoing CRT. We expected that at least 50% of patients (~40 patients) based on defined inclusion criteria will have high risk disease confirmed at resection (+ECE or + margins). With an expected sample size of at least N=40 in the CRT arm, and adding pembrolizumab to cisplatin and radiation, we expect to reach over 80% power to detect an increase of 21% in RFS at year 1 (87% RFS compared to 66% at 1 year) using exact test at significance level, alpha=0.025 (one-sided). In comparison, assuming that we will reach a similar 1 year DFS of 58% in the radiation alone arm, by adding pembrolizumab, and assuming N=40, we expect to reach over 80% power to detect an increase of 22% in RFS at 1 year (80% RFS compared to 58% at 1 year).
- Safety analysis includes all patients receiving at least 1 dose of treatment and adverse events are graded using CTCAE v4.03.

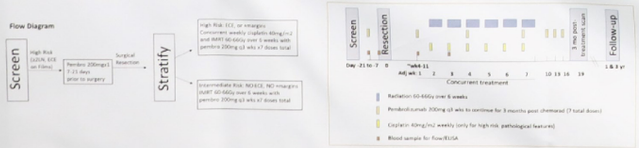


Figure 2. Clinical Trial Schema. Eligible patients with high-risk (Stage III/IV) locally advanced HNSCC were consented to receive pembrolizumab 200 mg I.V. 1-3 weeks before planned surgical resection. Pretreatment biopsies and resection specimens were archived for H&E and immunohistochemistry. Peripheral blood (red boxes) was collected for functional analysis pre-pembrolizumab, post-pembrolizumab prior to surgery, and post surgery prior to adjuvant week 1 and 3 (see schema). Patients are followed for disease-free and overall survival. Safety was determined by delays in SOC treatment.

between patients with high vs. intermediate risk pathological features (left) and patients with TE
allocation to date of relapse or last date known alive. Kaplan Meier Curves are displayed and survival

All Adverse Events

CTCAE Category	Adverse Event	RT (n=15) Any Grade no. %	Grade 1	Grade 2	Grade 3	Grade 4	CRT (n=19) Any Grade no. %	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders	Anemia	3 20%	3	0	0	0	8 42%	1	7	0	0
	Febrile neutropenia	0 0%	0	0	0	0	2 11%	0	0	2	0
Cardiac Disorders	Heart failure	0 0%	0	0	0	0	1 5%	0	0	1	0
	Myocardial infarction	0 0%	0	0	0	0	1 5%	0	0	1	0
Ear and labyrinth disorders	Venous injury	0 0%	0	0	0	0	1 5%	0	0	1	0
	Tinnitus	0 0%	0	0	0	0	6 32%	6	0	0	0
Endocrine disorders	Hyperthyroidism	2 13%	2	0	0	0	2 11%	2	0	0	0
	Autoimmune Colitis	0 0%	0	0	0	0	1 5%	0	1	0	0
Gastrointestinal disorders	Constipation	5 33%	3	2	0	0	1 5%	1	0	0	0
	Diarrhea	1 7%	1	0	0	0	5 26%	3	2	0	0
	Duodenal hemorrhage	1 7%	0	0	1	0	0 0%	0	0	0	0
	Dysphagia	3 20%	1	2	0	0	6 32%	0	2	4	0
	Oral pain	3 20%	2	1	0	0	3 16%	0	1	0	0
	Mucositis	3 20%	0	1	2	0	10 53%	4	6	0	0
	Nausea	4 27%	3	1	0	0	9 47%	5	2	2	0
	Vomiting	2 13%	2	0	0	0	8 42%	5	1	2	0
General disorders and administration site conditions	Edema Face	2 13%	2	0	0	0	3 16%	2	1	0	0
	Fatigue	4 27%	2	1	1	0	7 37%	4	3	0	0
	Pain	6 40%	4	1	1	0	7 37%	2	5	0	0
Infections and infestations	Mucosal infection	2 13%	1	1	0	0	5 26%	1	3	1	0
Injury, poisoning and procedural complications	Dermatitis radiation	5 33%	3	1	1	0	5 26%	2	3	0	0
Investigations	AST increased	0 0%	0	0	0	0	3 16%	2	0	1	0
	Lymphocyte count decreased	3 20%	1	1	0	1	2 11%	0	0	2	0
	Platelet count decreased	0 0%	0	0	0	0	5 26%	3	1	1	0
	Weight loss	6 40%	5	1	0	0	4 21%	2	1	1	0
	White blood cell count decreased	1 7%	1	0	0	0	4 21%	0	2	2	0
Metabolism and nutrition disorders	Anorexia	2 13%	1	1	0	0	3 16%	1	1	1	0
	Dehydration	2 13%	0	2	0	0	2 11%	0	1	1	0
	Hyperglycemia	1 7%	1	0	0	0	3 16%	2	0	1	0
Musculoskeletal and connective tissue disorders	Arthralgia	1 7%	0	1	0	0	0 0%	0	0	0	0
Nervous system disorders	Dysgeusia	4 27%	3	1	0	0	1 5%	1	0	0	0
Psychiatric disorders	Insomnia	2 13%	1	1	0	0	5 26%	3	2	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2 13%	2	0	0	0	2 11%	1	1	0	0
	Sore Throat	4 27%	3	1	0	0	4 21%	1	3	0	0
Skin and subcutaneous tissue disorders	Rash	5 33%	4	1	0	0	3 16%	2	1	0	0
	Hypertension	2 13%	0	1	1	0	3 16%	1	1	1	0
Vascular disorders	Lymphedema	5 33%	5	0	0	0	2 11%	2	0	0	0

Pembrolizuma

CTCAE Category
Endocrine disorders
Gastrointestinal disorders
General disorders and administration site condition
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Nervous System Disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Vascular Disorders

Table 3. Adverse Events. The left table i
common AEs were anemia, mucositis,
vomiting were more common in those t
were nausea and fatigue.

Patient Characteristics

Characteristic	(N= 34)
Age	
Median -yr	55
Range - yr	27-76
Sex- no. (%)	
Male	23 (68)
Female	11 (32)
Racial or Ethnic Group - no. (%)	
White	33 (97)
Hispanic	1 (3)
Black	0 (0)
Other	0 (0)
Smoker >10 pk year (%)	
Yes	17 (50)
No	17 (50)
Alcohol use >5 drinks/wk (%)	
Yes	12 (35)
No	22 (65)
ECOG performance score- no. (%)	
Zero	25 (74)
One	9 (26)
Site of Tumor - no. (%)	
Oral Cavity	30 (88)
Larynx	4 (12)
Clinical Stage - no. (%)	
T Stage	
Tx	1 (3)
T1	2 (6)
T2	4 (12)
T3	6 (18)
T4	21 (62)
N Stage	
N0	6 (18)
N1	3 (9)
N2a	1 (3)
N2b	13 (35)
N2c	11 (32)

- 34/80 patients have been enrolled
- Four patients have withdrawn (2 due to decision to receive treatment closer to home and 2 due to secondary thyroid cancer)
- 16/16 patients completed safety lead-in without Dose Limiting Toxicity which was defined as delay in standard of care (> 7 days delay in surgery, >3 days for radiation, and/or >7 days for cisplatin dose)

Patient #	Clinical Stage	Tumor Site	HPV Status (RNA in Situ)	% Treatment Response	% Remaining Viable Tumor*	Path stage	Pathological Risk	Clinical Response
HN1S01-01	T4aN0M0	Oral Cavity	Negative	< 10%	90%	T4aN1	Intermediate	Recurrence
HN1S01-02	T3N2bM0	Oral Cavity	Negative	80-90%	10-20%	T3N2b	High	NED
HN1S01-04	T3N2bM0	Oral Cavity	Negative	70-80%	20-30%	T2N2c	High	NED
HN1S01-05	T3N1M0	Oral Cavity	Negative	< 10%	90%	T3N1	Intermediate	NA- thyroid ca
HN1S01-06	T3N0M0	Oral Cavity	Negative	80-90%	10-20%	T1N0	Intermediate	NED
HN1S01-07	T4aN2bM0	Oral Cavity	Positive	< 10%	90%	T3N2b	High	Progressive Disease
HN1S01-08	T2N2bM0	Oral Cavity	Positive	< 10%	90%	T1N0	Intermediate	NA- withdrew
HN1S01-10	T4aN1M0	Oral Cavity	Negative	20-30%	70-80%	T4aN0	Intermediate	NED
HN1S01-11	TxN2bM0	Oral Cavity	Negative	70-80%	20-30%	TxN2b	High	NED
HN1S01-12	T1N2cM0	Oral Cavity	Negative	20-30%	only 2mm tumor remaining	T4aN2c	High	NED
HN1S01-13	T2N2bM0	Oral Cavity	Negative	< 10%	90%	T4aN2c	High	Recurrence
HN1S01-14	T2N2bM0	Oral Cavity	Positive	90-100%	0%	T0N0	CR- Intermediate	NED
HN1S01-15	T1N2cM0	Oral Cavity	Pending	100%	0%	T0N1	Intermediate	NA- thyroid ca
HN1S01-16	T3N2cM0	Oral Cavity	Pending	< 10%	90%	T3N2b	High	Too Early
HN1S01-17	T4aN2bM0	Oral Cavity	Pending	40-50%	50-60%	T3N2b	High	Too Early
HN1S01-18	T4aN0M0	Oral Cavity	Pending	< 10%	90%	T4aN0	High	Too Early**
HN1S01-19	T4aN0M0	Oral Cavity	Pending	40-50%	50-60%	T2N2c	High	Too Early
HN1S01-21	T2N2bM0	Oral Cavity	Pending	< 10%	90%	T2N0	Intermediate	Too Early
HN1S01-22	T4aN2bM0	Oral Cavity	Pending	< 10%	90%	T4aN2b	High	Too Early
HN1S01-23	T4aN2bM0	Oral Cavity	Pending	< 10%	90%	T4aN2b	High	Too Early
HN1S01-24	T4aN2cM0	Oral Cavity	Pending	Pending	Pending	T4aN2b	High	Too Early
HN1S02-01	T4N2bM0	Oral Cavity	Negative	<10%	90%	T4aN2c	High	Recurrence
HN1S02-02	T4aN2cM0	Oral Cavity	Positive	<10%	Only 1mm microinvasive tumor remaining	T4bN2c	High	NED
HN1S02-03	T4N2cM0	Oral Cavity	Positive	95-100%	5%	T4aN2b	Intermediate	NED
HN1S02-04	T4N2aMx	Oral Cavity	Negative	10-15%	85-90%	T4aN2a	Intermediate	NED
HN1S02-05	T4aN2cM0	Oral Cavity	Negative	<10%	90%	T4aN2c	High	NED
HN1S03-01	T4aN2bM0	Oral Cavity	Pending	Pending	Pending	T4aN2b	High	NED
HN1S03-02	T4aN2cM0	Larynx	Pending	NA	NA	T4aN2b	High	NA- Withdrew
HN1S04-01	T4N2cM0	Larynx	Positive	<10%	90%	T4N2cM0	Intermediate	NED
HN1S04-02	T4aN0M0	Larynx	Positive	10-15%	85-90%	T4aN0M0	Intermediate	NED
HN1S04-04	T4aN0M0	Larynx	Pending	Pending	Pending	T4aN0M0	Intermediate	NED
HN1S04-05	T3N1M0	Oral Cavity	Pending	Pending	Pending	T3N2cM0	High	NED
HN1S04-06	T4aN2cM0	Oral Cavity	Pending	Pending	Pending	T4aN2cM0	Intermediate	Progressive Disease
HN1S04-07	T4N2cM0	Oral Cavity	Pending	Pending	Pending	T4N2cM0	Intermediate	NED

- 19/34 (56%) High risk
- **14/27 (52%) Respuesta Patológica (>10% de respuesta tumoral)**
- 6/19 (32%) Respuesta Patológica Mayor (>70%), de los cuales 1 (5%) rpta. completa (*análisis previo)
- La rpta. clínica se valoró a los 3 meses tras RT/recaída: **Recaía 5 (23%) vs. NED 17 (77%)**

Phase II Multi-site Investigation of Neoadjuvant Pembrolizumab and Adjuvant Concurrent Radiation and Pembrolizumab with or without Cisplatin in Resected Head and Neck Squamous Cell Carcinoma

University of CINCINNATI

Trisha M. Wise-Draper[1], Matthew O. Old[2], Francis P. Worden[3], Paul E. O'Brien[4], Ezra E.W. Cohen[5], Neal Dunlap[6], Michelle L. Mierzwa[3], Keith Casper[3], Sarah Palackdharry[1], Benjamin Hinrichs[1], Alfredo Molinolo[5], Vinita Takiar[1], Jonathan Mark[1], Alice Tang[1], Muhammad Kashif Riaz[1], John C. Morris[1], Nooshin Hashemi[1], Changchun Xie[1], Maura L. Gillison[8]

University of Cincinnati Cancer Institute, Cincinnati, OH[1]; The Ohio State University, Columbus, OH[2]; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI[3]; Medical University of South Carolina, Charleston, SC[4]; University of California,

All Adverse Events

CTCAE Category	Adverse Event	RT (n=15) Any Grade no.	%	Grade 1	Grade 2	Grade 3	Grade 4	CRT (n=19) Any Grade no.	%	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders	Anemia	3	20%	3	0	0	0	8	42%	1	7	0	0
	Febrile neutropenia	0	0%	0	0	0	0	2	11%	0	0	2	0
Cardiac Disorders	Heart failure	0	0%	0	0	0	0	1	5%	0	0	1	0
	Myocardial Infarction	0	0%	0	0	0	0	1	5%	0	0	1	0
	Venous injury	0	0%	0	0	0	0	1	5%	0	0	1	0
Ear and labyrinth disorders	Tinnitus	0	0%	0	0	0	0	6	32%	6	0	0	0
Endocrine disorders	Hyperthyroidism	2	13%	2	0	0	0	2	11%	2	0	0	0
	Autoimmune Colitis	0	0%	0	0	0	0	1	5%	0	1	0	0
Gastrointestinal disorders	Constipation	5	33%	3	2	0	0	1	5%	1	0	0	0
	Diarrhea	1	7%	1	0	0	0	5	26%	3	2	0	0
	Duodenal hemorrhage	1	7%	0	0	1	0	0	0%	0	0	0	0
	Dysphagia	3	20%	1	2	0	0	6	32%	0	2	4	0
	Oral pain	3	20%	2	1	0	0	3	16%	0	3	0	0
	Mucositis	3	20%	0	1	2	0	10	53%	4	6	0	0
	Nausea	4	27%	3	1	0	0	9	47%	5	2	2	0
	Vomiting	2	13%	2	0	0	0	8	42%	5	1	2	0
General disorders and administration site conditions	Edema Face	2	13%	2	0	0	0	3	16%	2	1	0	0
	Fatigue	4	27%	2	1	1	0	7	37%	4	3	0	0
	Pain	6	40%	4	1	1	0	7	37%	2	5	0	0
Infections and infestations	Mucosal infection	2	13%	1	1	0	0	5	26%	1	3	1	0
Injury, poisoning and procedural complications	Dermatitis radiation	5	33%	3	1	1	0	5	26%	2	3	0	0
Investigations	AST increased	0	0%	0	0	0	0	3	16%	2	0	1	0
	Lymphocyte count decreased	3	20%	1	1	0	1	2	11%	0	0	2	0
	Platelet count decreased	0	0%	0	0	0	0	5	26%	3	1	1	0
	Weight loss	6	40%	5	1	0	0	4	21%	2	1	1	0
	White blood cell count decreased	1	7%	1	0	0	0	4	21%	0	2	2	0
Metabolism and nutrition disorders	Anorexia	2	13%	1	1	0	0	3	16%	1	1	1	0
	Dehydration	2	13%	0	2	0	0	2	11%	0	1	1	0
	Hyperglycemia	1	7%	1	0	0	0	3	16%	2	0	1	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	7%	0	1	0	0	0	0%	0	0	0	0
Nervous system disorders	Dysgeusia	4	27%	3	1	0	0	1	5%	1	0	0	0
Psychiatric disorders	Insomnia	2	13%	1	1	0	0	5	26%	3	2	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	13%	2	0	0	0	2	11%	1	1	0	0
	Sore Throat	4	27%	3	1	0	0	4	21%	1	3	0	0
Skin and subcutaneous tissue disorders	Rash	5	33%	4	1	0	0	3	16%	2	1	0	0
Vascular disorders	Hypertension	2	13%	0	1	1	0	3	16%	1	1	1	0
	Lymphedema	5	33%	5	0	0	0	2	11%	2	0	0	0

Pembrolizumab Related Adverse Events

CTCAE Category	Adverse Event	Any Grade no.	%	Grade 1	Grade 2	Grade 3	Grade
Endocrine disorders	Hyperthyroidism	1	3%	1	0	0	
	Hypothryoidism	1	3%	0	1	0	
	Autoimmune Colitis	1	3%	0	0	1	
Gastrointestinal disorders	Diarrhea	1	3%	0	1	0	
	Duodenal hemorrhage	1	3%	0	0	1	0
	Mucositis	1	3%	0	0	1	0
	Nausea	3	9%	2	0	1	0
	Vomiting	1	3%	0	0	1	0
General disorders and administration site conditions	Fatigue	3	9%	2	1	0	0
	Pain	1	3%	1	0	0	0
Investigations	ALT increased	1	3%	0	1	0	0
Metabolism and nutrition disorders	Anorexia	1	3%	1	0	0	0
	Hypomagnesemia	1	3%	1	0	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	3%	0	1	0	0
Nervous System Disorders	Headache	1	3%	1	0	0	0
	Syncope	1	3%	0	0	1	0
Respiratory, thoracic and mediastinal disorders	Cough	1	3%	0	1	0	0
Skin and subcutaneous tissue disorders	Dry skin	1	3%	1	0	0	0
	Pruritis	1	3%	1	0	0	0
	Rash	1	3%	1	0	0	0
Vascular Disorders	Lymphedema	1	3%	1	0	0	0

Table 3. Adverse Events. The left table indicates all reported adverse events in the first 34 patients. The most common AEs were anemia, mucositis, fatigue and nausea. Decrease in cellular counts and nausea and vomiting were more common in those that received cisplatin. The most common pembrolizumab related AEs were nausea and fatigue.

- Pembrolizumab induces a pathological response in >50% tumors after just 1 administration
- Neoadjuvant and adjuvant pembrolizumab is safe with minimal related Adverse Events and no unexpected events
- Pembrolizumab results in increased anti-tumor inflammatory response in patients with pathological response

2018 ASCO ANNUAL MEETING

University of CINCINNATI

Gene Expression Signature after One Dose of Neoadjuvant Pembrolizumab Associated with Tumor Response in Head and Neck Squamous Cell Carcinoma

Eejung Kim, Sarah Palackdharry, Benyamin Yaniv, Jonathan Mark, Alice Tang, Keith Wilson, Yash Patil, Edith Janssen, Laura Conforti, Vinita Takiar, Benjamin Hinrichs, and Trisha Wise-Draper
University of Cincinnati, College of Medicine

BACKGROUND & PURPOSE

Immune checkpoint inhibitors have been shown to induce durable tumor responses in a subset of recurrent and/or metastatic HNSCC. Higher expression of PD-L1, INF-γ, and composite signatures such as 'T cell-inflamed' profiles have been reported as biomarkers of response. However, prospective analysis of gene expression profiles after a single dose of Pembrolizumab compared to pre-treatment biopsy have not been reported. As a part of clinical trial "Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02841033), we have investigated gene expression changes associated with Pembrolizumab pathological response in HNSCC.

METHODS

Total RNA was extracted from 11 paired FFPE tissue samples of pre- and post- one dose of Pembrolizumab. Total RNA was subjected to a hybridization-based digital counting assay (NanoString), which measures mRNAs of 770 immune-related genes and controls. RNA counts were normalized and log-transformed. Gene expression comparison analysis was performed between pre- and post- Pembrolizumab treatment and between five responders and six non-responders. Response was defined as more than 10% of pathologic treatment effect (Figure 1).

Figure 1. Phase I Investigation of Adjuvant Cisplatin and Radiation with Pembrolizumab in Resected HNSCC (NCT02841033) Trial design

Statistical analysis: Log 2 transformed raw read counts of mRNA was used for analysis. Welch's t-test was performed to calculate t-statistics and p-value in all comparisons. Non-parametric method (permutation test with 1000 permutations) was used to further validate results in Figure 4.

RESULTS

RNA from non-responder samples (Patient 1,5,8,7,13) showed high correlation between biopsy and resection sample, implying that perturbation (one dose of pembrolizumab) did not cause significant gene expression change. Responder samples (Patient 2,4,6,10,11,14) had disparate gene expression between biopsy and resection samples (Figure 2, 3).

Figure 2. Responders show more gene expression changes after pembrolizumab

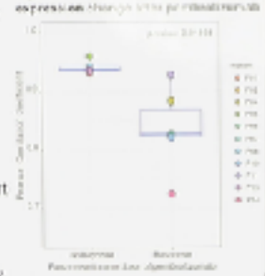


Figure 3. Pearson correlation of gene expression of 770 genes

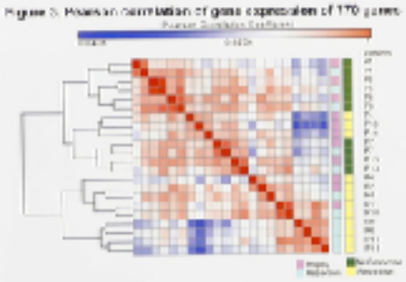
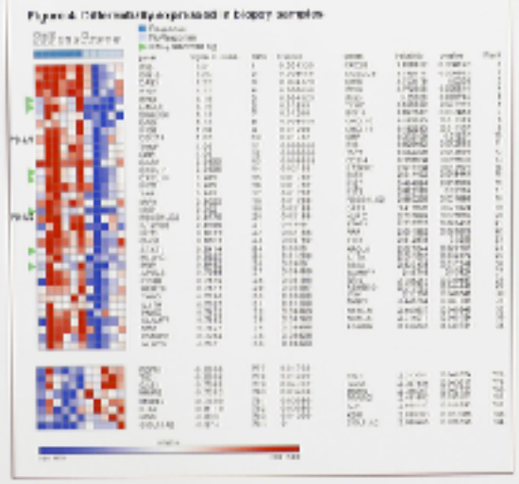


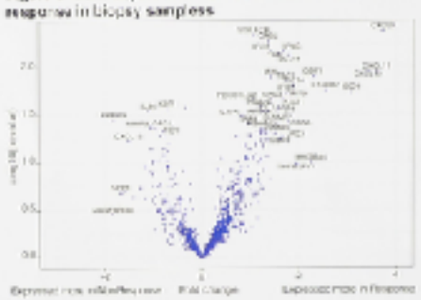
Figure 4. Differentially expressed in biopsy samples



RESULTS

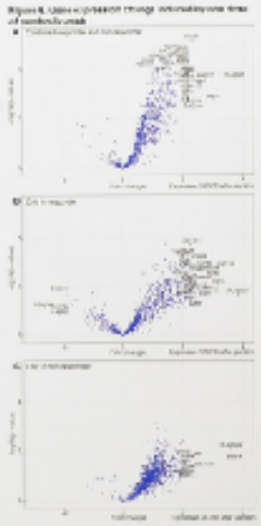
Higher expression of PD-L1, PD-L2, and INF-γ induced genes in pre-treatment samples (biopsy samples) were associated with tumor response after one dose of Pembrolizumab. Figure 4 shows similar list of genes two different statistic test (permutation test and Welch's t-test). INF-γ induced genes including CXCL9, CXCL10, CXCL11, STAT1, CASL, IFI35, and IDO1 showed higher expression in samples with response (Figure 4, 5).

Figure 5. Gene expression difference associated with response in biopsy samples



As the genes whose expressions were measured in our study were highly enriched in immune related genes, majority of genes' expression increased after one dose of pembrolizumab (Figure 6A). This effect was more pronounced in response samples (Patient 1,5,8,7,13, Figure 6B). Only a few genes were significantly differentially expressed in non-response samples as expected (Figure 6C).

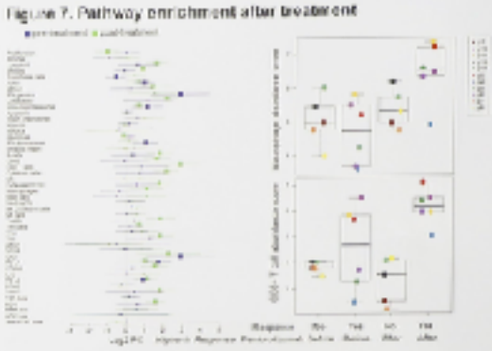
Figure 6. Gene expression change associated with time of pembrolizumab



RESULTS

Existence of T cells, B cells, NK cells, macrophages, neutrophils in pre-treatment samples were not predictive of response. However, macrophages, T and B lymphocytes were increased in post-treatment samples of responders, implying that these were recruited effectors. There was no such difference in NK cells and neutrophils. (Figure 7)

Figure 7. Pathway enrichment after treatment



CONCLUSIONS

Pathologic response after one dose of pembrolizumab in HNSCC is strongly correlated with PD-L1, PD-L2, and interferon-γ induced genes. These observations are concordant with previous studies. Non-responding tumors show much less gene expression change after one dose of pembrolizumab, probably because of blunted, or no recruitment of immune effector cells. CD8+ T cells, Macrophages, and B cells are more abundant after one dose of pembrolizumab in samples with response.

ACKNOWLEDGEMENT

The authors thank Merck &Co. Inc. for funding clinical trial "Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02841033). We also thank KL2 grant for supporting gene expression experiments.

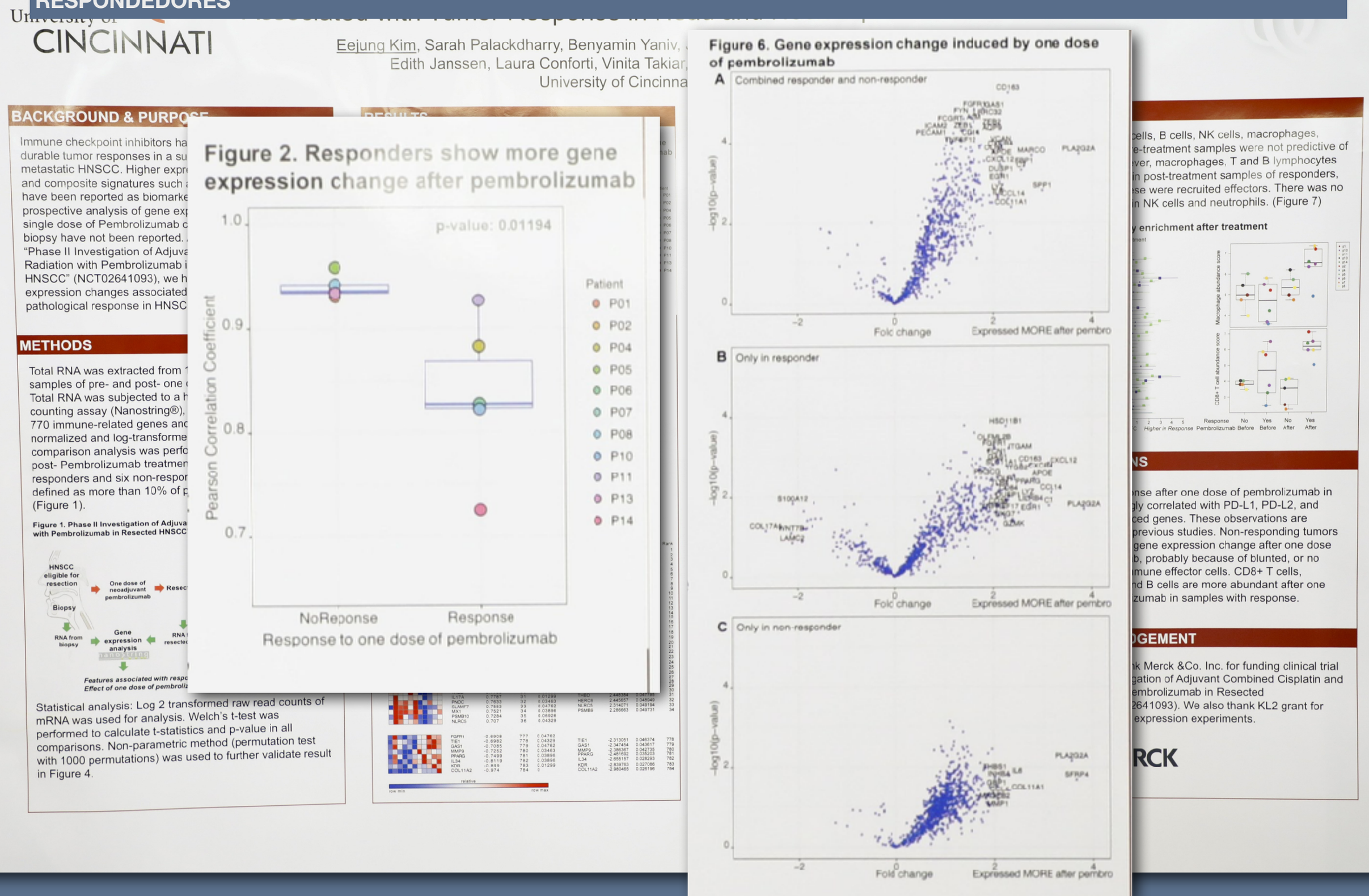
MERCK

11 pacientes: biopsias pre y post - pembrolizumab 200mg x 1 dosis.

5 pcts respuesta (>10% de RP) vs 6 NO respuesta

Kim E, abs #6059, ASCO 2018

Analizan el RNA y determinan que hay una ALTA CORRELACIÓN en la expresión genética pre y post Pembrolizumab en los "NO RESPONDEDORES"



Kim E, abs #6059, ASCO 2018

Gene Expression Signature after One Dose of Neoadjuvant Pembrolizumab Associated with Tumor Response in Head and Neck Squamous Cell Carcinoma

University of Cincinnati

Eejung Kim, Sarah Palackdharry, Benyamin Yaniv, Jonathan Mark, Alice Tang, Keith Wilson, Yash Patil, Edith Janssen, Laura Conforti, Vinita Takiar, Benjamin Hinrichs, and Trisha Wise-Draper

University of Cincinnati, College of Medicine

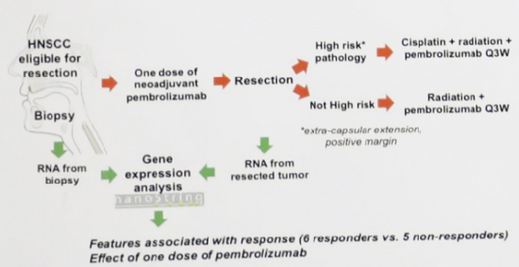
BACKGROUND & PURPOSE

Immune checkpoint inhibitors have been shown to induce durable tumor responses in a subset of recurrent and/or metastatic HNSCC. Higher expression of PD-L1, INF-γ, and composite signatures such as "T cell-inflamed" profiles have been reported as biomarkers of response. However, prospective analysis of gene expression profiles after a single dose of Pembrolizumab compared to pre-treatment biopsy have not been reported. As a part of clinical trial "Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02641093), we have investigated gene expression changes associated with Pembrolizumab pathological response in HNSCC.

METHODS

Total RNA was extracted from 11 paired FFPE tissue samples of pre- and post- one dose of Pembrolizumab. Total RNA was subjected to a hybridization-based digital counting assay (Nanostring®), which measures mRNAs of 770 immune-related genes and controls. RNA counts were normalized and log-transformed. Gene expression comparison analysis was performed between pre- and post- Pembrolizumab treatment and between five responders and six non-responders. Response was defined as more than 10% of pathologic treatment effect (Figure 1).

Figure 1. Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02641093) Trial design



Statistical analysis: Log 2 transformed raw read counts of mRNA was used for analysis. Welch's t-test was performed to calculate t-statistics and p-value in all comparisons. Non-parametric method (permutation test with 1000 permutations) was used to further validate result in Figure 4.

RESULTS

RNA from non-responder samples(Patient 1,5,8,7,13) showed high correlation between biopsy and resection sample, implying that perturbation (one dose of pembrolizumab) did not cause significant gene expression change. Responder samples (Patient 2,4,6,10,11,14) had disparate gene expression between biopsy and resection samples (Figure 2, 3).

Figure 2. Responders show more gene expression change after pembrolizumab

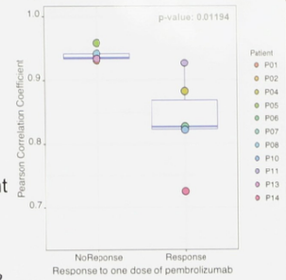


Figure 3. Pearson correlation of gene expression of 770 genes

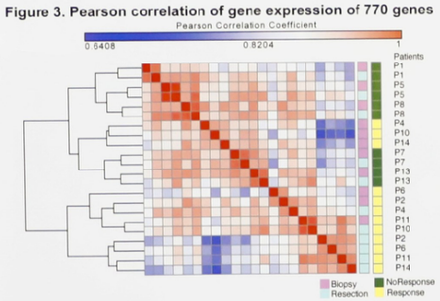


Figure 4. Differentially expressed in biopsy samples

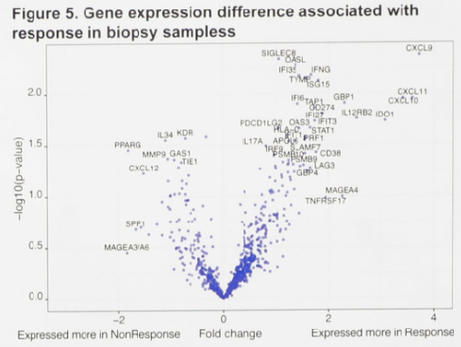
genes	Signal to noise	Rank	p-value
IFI6	1.31	1	0.004329
ISG15	1.25	2	0.008658
OAS3	1.22	3	0.004329
IFI27	1.22	4	0.008658
IFNG	1.18	5	0.004329
CXCL9	1.16	6	0.01299
SIGLEC8	1.13	7	0.01299
OASL	1.12	8	0.008658
IFI35	1.08	9	0.01299
CD274	1.07	10	0.01732
TYMP	1.06	11	0.008658
GBP1	1.06	12	0.008658
OAS2	0.9839	13	0.008658
CXCL11	0.9636	14	0.02165
CXCL10	0.961	15	0.01732
IFIT1	0.955	16	0.01732
TAP1	0.925	17	0.01732
IRF9	0.9025	18	0.01299
IDO1	0.902	19	0.02165
PDCD1LG2	0.8775	20	0.02165
IL12RB2	0.8756	21	0.0303
IFIT3	0.8731	22	0.02165
OAS1	0.8503	23	0.04762
STAT1	0.8414	24	0.0303
HLA-C	0.8225	25	0.01299
PRF1	0.8152	26	0.0303
APOL6	0.7988	27	0.03463
CD38	0.7839	28	0.05195
HERC6	0.7831	29	0.02597
THBD	0.7796	30	0.03896
IL17A	0.7787	31	0.01299
PNOC	0.7633	32	0.03463
SLAMF7	0.7583	33	0.04762
MX1	0.7521	34	0.03896
PSMB10	0.7284	35	0.06926
NLRC5	0.707	36	0.04329
FGFR1	-0.6908	777	0.04762
TIE1	-0.6982	778	0.04329
GAS1	-0.7085	779	0.04762
MMP9	-0.7252	780	0.03463
PPARG	-0.7499	781	0.03896
IL34	-0.8119	782	0.03896
KDR	-0.899	783	0.01299
COL11A2	-0.974	784	0

genes	t-statistic	p-value	Rank
CXCL9	3.828812	0.004192	1
SIGLEC8	3.749171	0.004562	2
OASL	3.703179	0.0053	3
IFNG	3.772356	0.006619	4
IFI35	3.55828	0.006745	5
TYMP	3.506523	0.007119	6
ISG15	3.897587	0.007483	7
CXCL10	3.185233	0.011129	8
CXCL11	3.192293	0.011157	9
GBP1	3.375109	0.01237	10
IFI6	3.825462	0.012562	11
TAP1	3.062008	0.013695	12
CD274	3.318604	0.015601	13
IL12RB2	2.903074	0.017527	14
IDO1	2.941102	0.018441	15
IFI27	3.494924	0.018542	16
IFIT3	2.852155	0.02159	17
PDCD1LG2	2.860235	0.021688	18
OAS3	3.411626	0.021924	19
HLA-C	2.701699	0.025662	20
STAT1	2.737737	0.026413	21
PRF1	2.661992	0.028202	22
IFIT1	2.912878	0.0289	23
APOL6	2.627644	0.029197	24
IL17A	2.561885	0.032372	25
CD38	2.523438	0.037245	26
SLAMF7	2.48716	0.03824	27
IRF9	2.708261	0.039497	28
PSMB10	2.375723	0.044446	29
IFIH1	2.32356	0.046548	30
THBD	2.448384	0.047795	31
HERC6	2.445657	0.048949	32
NLRC5	2.314071	0.049194	33
PSMB9	2.266663	0.049731	34
TIE1	-2.313051	0.046374	778
GAS1	-2.347464	0.043617	779
MMP9	-2.386367	0.042735	780
PPARG	-2.481692	0.035203	781
IL34	-2.655157	0.028293	782
KDR	-2.839763	0.027086	783
COL11A2	-2.980465	0.026196	784

RESULTS

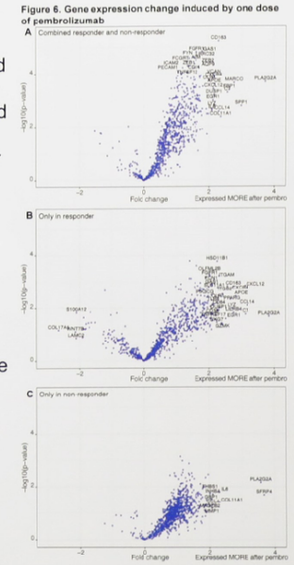
Higher expression of PD-L1, PD-L2, and INF-γ induced genes in pre-treatment samples (biopsy samples) were associated with tumor response after one dose of Pembrolizumab. Figure 4 shows similar list of genes two different statistic test (permutation test and Welch's t-test). INF-γ induced genes including CXCL9, CXCL10, CXCL11, STAT1, OASL, IFI35, and IDO1 showed higher expression in samples with response (Figure 4, 5).

Figure 5. Gene expression difference associated with response in biopsy samples



As the genes whose expression were measured in our study were highly enriched in immune related genes, majority of genes' expression increased after one dose of pembrolizumab (Figure 6A). This effect was more pronounced in response samples (Patient 1,5,8,7,13, Figure 6B). Only a few genes were significantly differentially expressed in non-response samples as expected (Figure 6C).

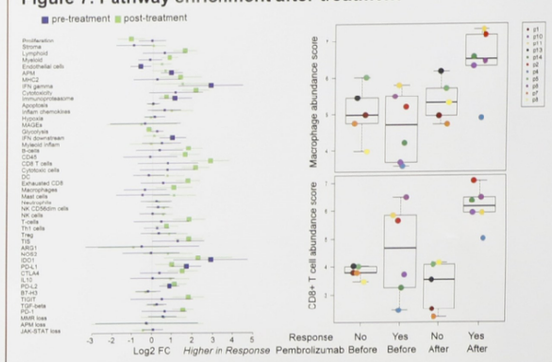
Figure 6. Gene expression change induced by one dose of pembrolizumab



RESULTS

Existence of T cells, B cells, NK cells, macrophages, neutrophils in pre-treatment samples were not predictive of response. However, macrophages, T and B lymphocytes were increased in post-treatment samples of responders, implying that these were recruited effectors. There was no such difference in NK cells and neutrophils. (Figure 7)

Figure 7. Pathway enrichment after treatment



CONCLUSIONS

Pathologic response after one dose of pembrolizumab in HNSCC is strongly correlated with PD-L1, PD-L2, and interferon-γ induced genes. These observations are concordant with previous studies. Non-responding tumors show much less gene expression change after one dose of pembrolizumab, probably because of blunted, or no recruitment of immune effector cells. CD8+ T cells, Macrophages, and B cells are more abundant after one dose of pembrolizumab in samples with response.

ACKNOWLEDGEMENT

The authors thank Merck &Co. Inc. for funding clinical trial "Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02641093). We also thank KL2 grant for supporting gene expression experiments.

MERCK

Kim E, abs #6059, ASCO 2018

2018 ASCO ANNUAL MEETING

EARLE A. CHILES RESEARCH INSTITUTE

PROVIDENCE Cancer Institute

Neoadjuvant anti-OX40 (MEDI6469) prior to surgery in head and neck squamous cell carcinoma

R. Bryan Bell, MD, DDS, FACS

Co-Director, Providence Head and Neck Cancer Program

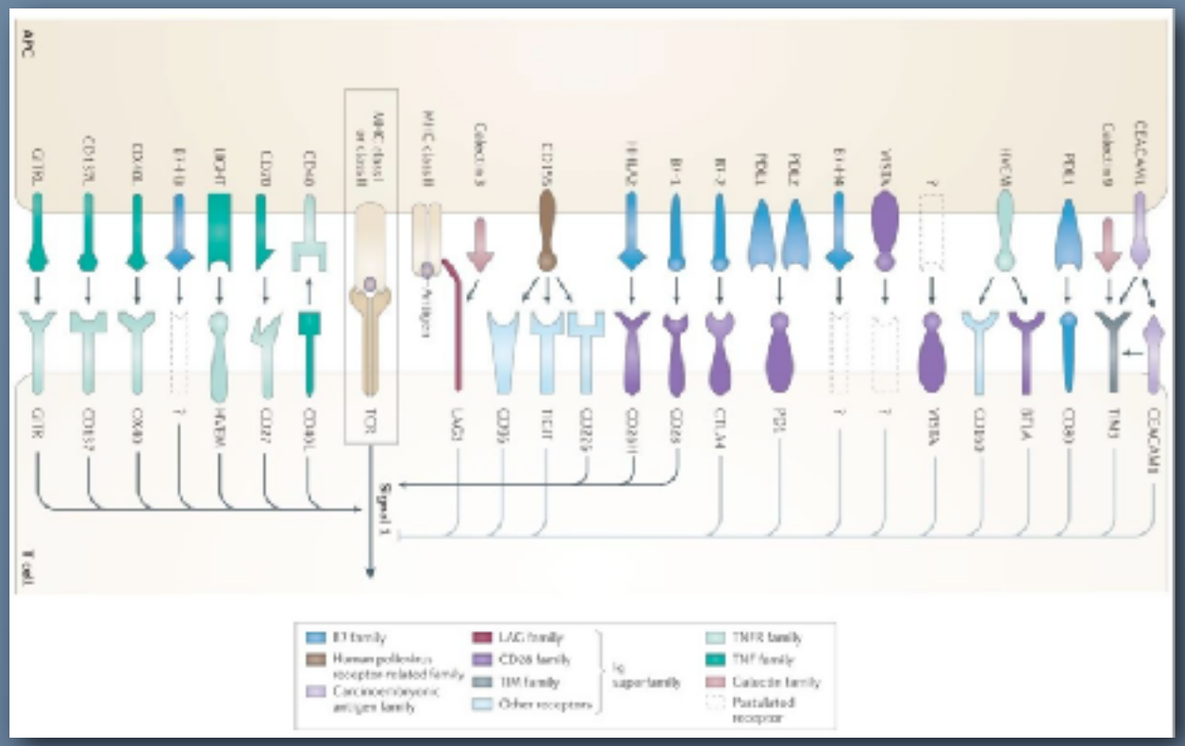
Rom Leidner, MD

Co-Director, Providence Head and Neck Cancer Program

Brendan Curti, MD

Director, Providence Melanoma Program

Presented By Richard Bell at 2018 ASCO Annual Meeting



OX40 es una glicoproteína transmembrana miembro de la superfamilia de Receptores de TNF y una **potente molécula coestimuladora** que, cuando se activa, **puede aumentar la proliferación celular.**

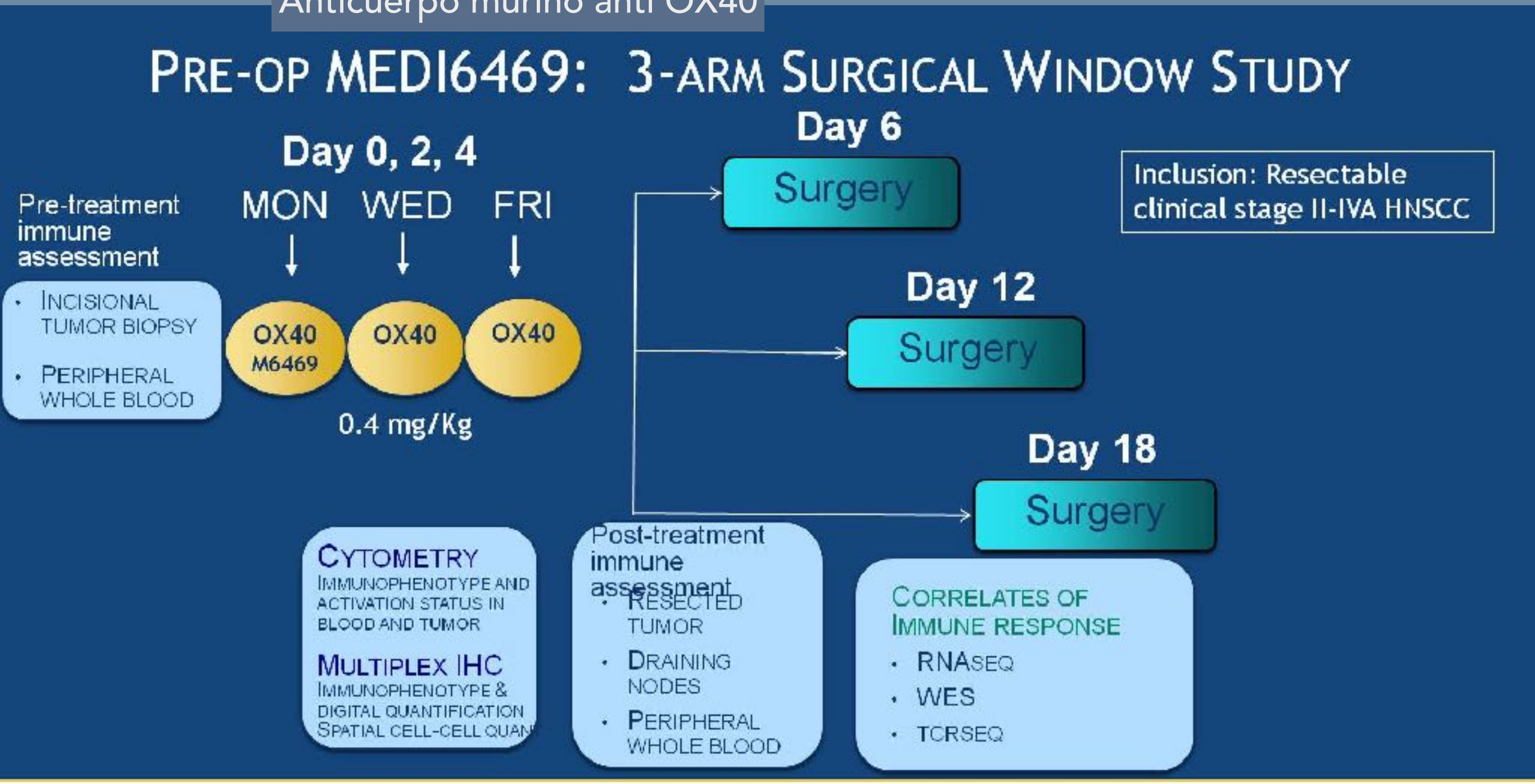
OX40, PD-1 and CTLA-4 are selectively expressed on tumor-infiltrating T cells in head and neck cancer

Ryan Montler[1], R Bryan Bell[2,3], Colin Thalhofer[1], Rom Leidner[2,3], Zipei Feng[2,4], Bernard A Fox[2], Allen C Cheng[3], Tuan G Bui[3], Christopher Tucker[1,2], Helena Hoen[2] and Andrew Weinberg[1,2]

Clinical & Translational Immunology (2016) **5**, e70;

En una serie de muestras de resección quirúrgica definitiva de TTCC se observó que **OX40**, así como otras proteínas moduladoras, como PD1 y CTLA-4 se **expresaron en los linfocitos infiltrantes de tumores (TILS),** pero no en la sangre, independiente del estado PVH.

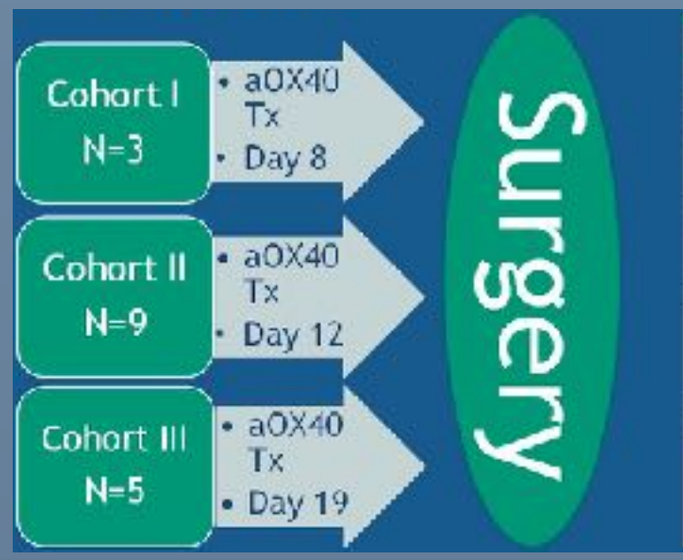
Anticuerpo murino anti OX40



Bell R, 2018 ASCO Annual Meeting

Objetivo Primario: seguridad y factibilidad (retraso de la cirugía, efectos adversos y relacionados con complicaciones quirúrgicas).

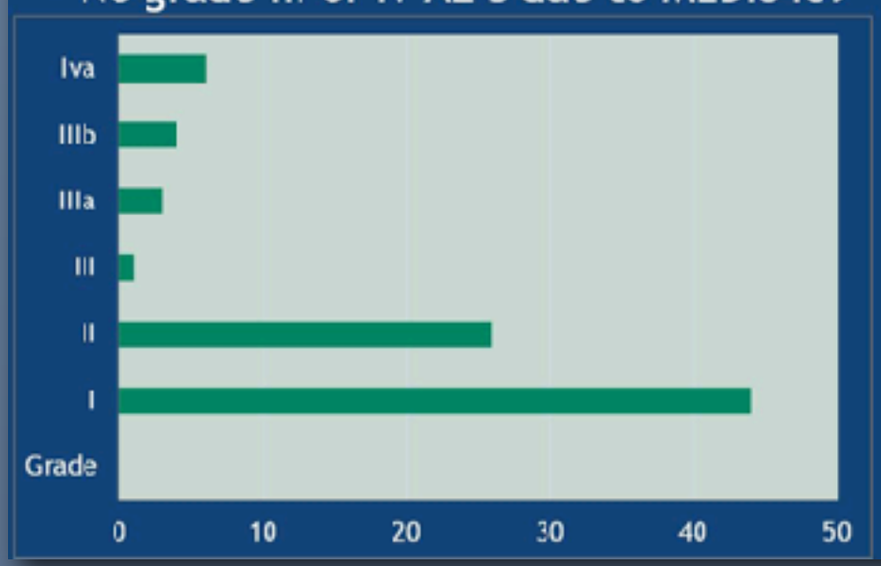
Estudios exploratorios: "pico" de respuesta inmunológica, correlación clínica-inmunológica, OS, DFS.



Characteristics		N=17	%
Age		59.71	
Gender	Male	13	76
	Female	4	24
HPV status	Pos (+)	6	35
	Neg (-)	11	65
Stage (AJCC 7th Ed).	II	2	12
	III	5	29
	IV/IVA	10	59
Site	Oral	7	41
	Oropharynx	7	41
	Hypopharynx	1	6
	Larynx	2	12

Primary Endpoints

- MEDI6469 did not delay or interfere with surgery in any patients
- No grade III or IV AE's due to MEDI6469



Clavien-Dindo for >Grade III

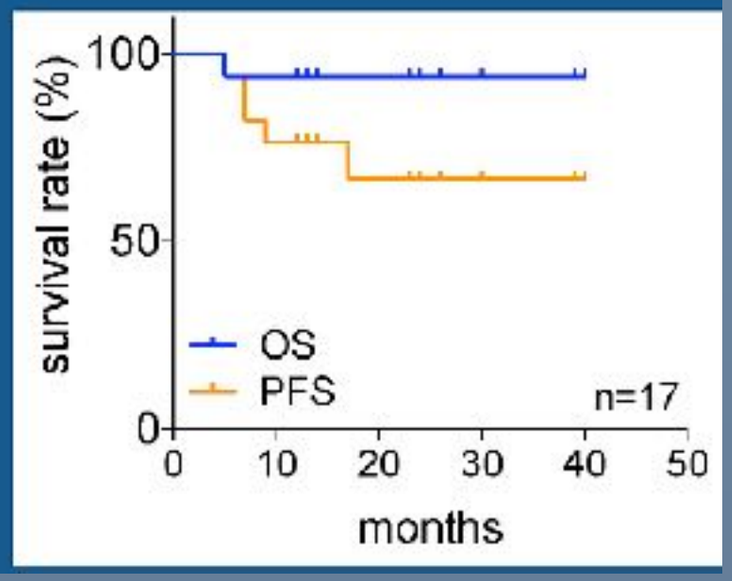
Subject	Event	Grade
003-DMS	Post-Op Respiratory Failure	IIIb
004-KAC	Hypoxia	IIIa
005-CTS	Acute Respiratory Failure	IVa
	Hypertension	IVa
	Non-ST Elevated Myocardial Infarction	IVa
	Stent Placement	IIIb
	Visual Changes	IIIa
006-SWH	Acute Respiratory Failure	IVa
	Hypoxia	IIIa
	Gastrointestinal Access for Support	IIIb
	Sepsis	IVa
	Cellulitis	III
	Beta Streptococcus	IVa
009-BCG	Hemoptysis	IIIb
	Hyponatremia	III

CLASIFICACIÓN DE CLAVIEN DINDO, HERRAMIENTA VALIDADA PARA EVALUAR LAS COMPLICACIONES QUIRÚRGICAS: NINGUNA ESTUVO RELACIONADA CON EL TRATAMIENTO DE INMUNOTERAPIA.

Bell R, 2018 ASCO Annual Meeting

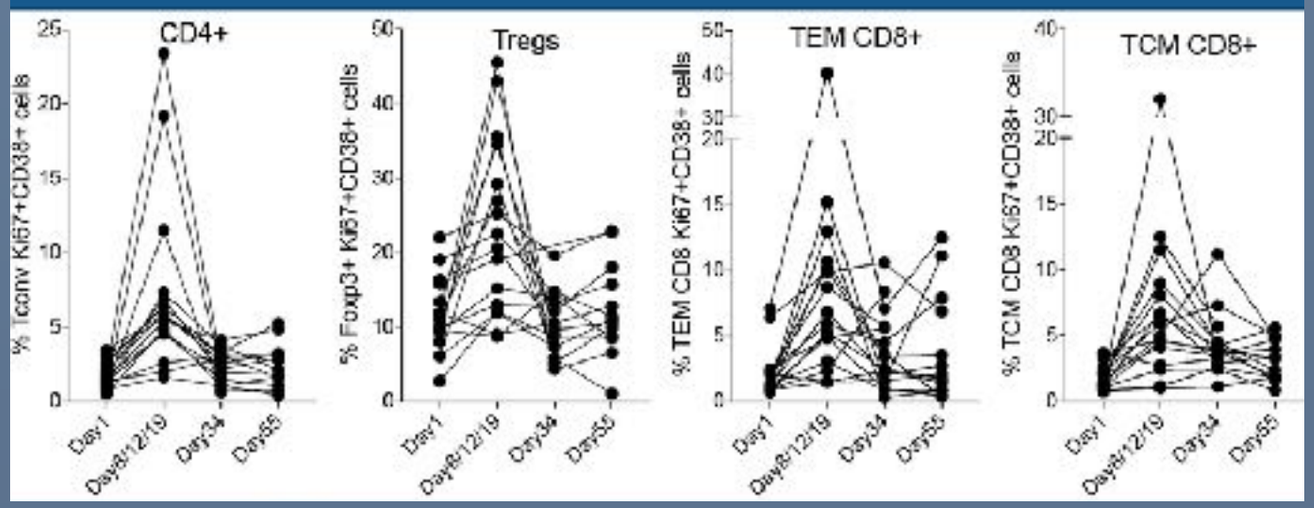
Clinical Outcome

- Median post-op follow up=24 mo
- 5/17 (29%) recurred (1 local (HPV-), 4 distant (HPV+=1; HPV-=3)
- 1 death: HNOX10, Recurrence 3 mo s/p adjuvant RT, germline mutation (POLE), somatic mutations (TP53, CDKN2A)



Immunological Response: Flow Cytometry

- Phenotypic changes in PBMC over time after MEDI6469



Conclusiones:

- MEDI6469 neoadyuvante: seguro, no retrasó la cirugía, no complicaciones qx relacionadas.
- Pico de activación de células t a las 2 semanas.
- Pendiente análisis NGS: TMB y correlación con IR. OS y DFS.
-

Bell R, 2018 ASCO Annual Meeting

2018 ASCO ANNUAL MEETING

A Cancer Research UK (CRUK) randomised, double-blind, placebo-controlled Phase IIa trial of AMG 319 given orally as a neoadjuvant therapy in patients with *human papillomavirus* (HPV) positive and negative head and neck squamous cell carcinoma (HNSCC)

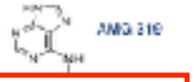
CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT

ecmc AMGEN

We thank participating patients, supporting staff & Institutions, Cancer Research UK as Sponsor and funder of the trial, Amgen for supply of IMP & the CRUK Formulation Unit for trial supply management.

[1]Christian H.H Ottensmeier, [2]Terry Jones, [3]Joseph J Sacco, [4]James Anthony McCaul, [5]Peter Brennan, [6]Claire Paterson, [3]Andrew Graeme Schache, [3]Richard Shaw, [7]Rabindra P Singh, [8]Joseph H. Davies, [9]Lindsey Chudley, [9]Danielle Jeffrey, [10]Gareth Thomas, [11]Paul Loadman, [12]Nicola A Dobbs, [12]Louisa Essame, [12]Gary Acton, [12]Sidath Katugampola, [13]Khalid Ali, [14]Bart Vanhaesebroeck, [1]Emma King; [1]University of Southampton, United Kingdom (UK); [2]University of Liverpool, UK; [3]Clatterbridge Cancer Centre, Liverpool, UK; [4]Queen Elizabeth University Hospital, Glasgow, UK; [5]Queen Alexandra Hospital, Portsmouth, UK; [6]Beatson West of Scotland Cancer Centre, Glasgow, UK; [7]University Hospital Southampton, UK; [8]Dorset Cancer Centre Poole, Hampshire, UK; [9]MSH lab, ECMC, University of Southampton, UK; [10]Cancer Sciences Unit, University of Southampton, UK; [11]Institute of Cancer Therapeutics, Bradford, UK; [12]Centre for Drug Development (CDD), Cancer Research UK, London, UK; [13]Amgen, US; [14]UCL Cancer Institute, London, UK.

Introduction



AMG319 es un inhibidor Pi3kinasa. Pi3kinasa relacionada con la señalización, diferenciación y supervivencia de las células B, teniendo también un efecto modulador sobre las células T. Su inhibición podría alterar la supresión del sistema inmune mediada por células T y causar la liberación de células CD8 al tumor.

- Phase I dose escalation trial in CLL
- 28 patients: RP2D 400mg once daily

Primary Objectives

- To assess changes in immune infiltration in tumour before and after treatment with AMG 319
- To assess the safety and toxicity profile of AMG 319 in HNSCC

Methods

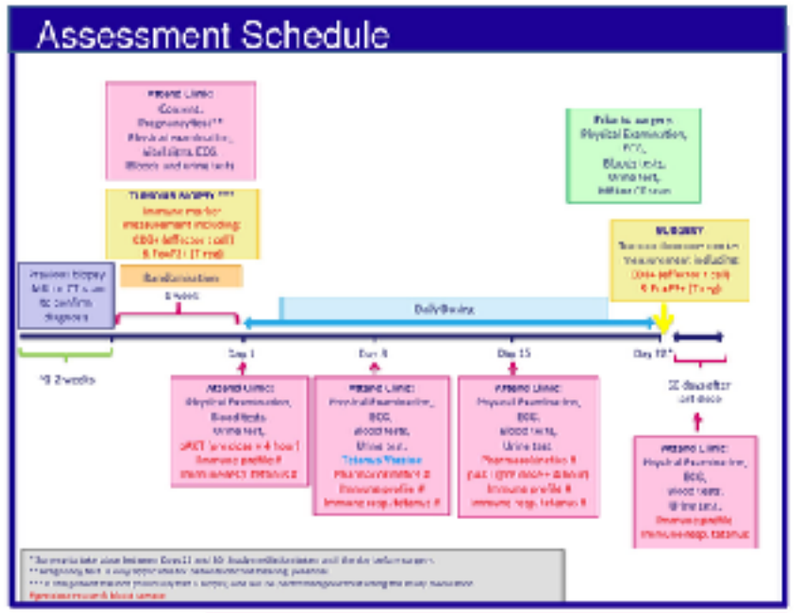
Patient Population

- HNSCC of the hypopharynx, oropharynx, oral cavity, supraglottis or larynx (except T1 glottic tumours) for whom surgery with curative intent ± post-operative radiotherapy or chemoradiotherapy as the treatment of choice
- ECOG 0/1, adequate organ function and no active autoimmune disease

Treatment Schedule

- Two arms: either AMG 319 once daily or matching placebo (2:1) once daily, administered orally for 20-29 days.

Assessment Schedule



Preliminary Results (Blinded data)

- 30 patients (pts) enrolled & treated:
  - 22 pts: 400 mg
  - 8 pts: 300 mg

Analysis of immune markers (CD8+, FoxP3) pending.

Treatment delivery

< 80% of planned treatment due to adverse events:

- 400 mg - 0/22 pts (30-64%)
- 300 mg - 3/8 pts (31-43%)

Toxicity presented from Days 8-11; resulting in withdrawal from the trial in 12 pts.

Safety & tolerability (AMG 319 & placebo)

Drug Related Adverse Event	400 mg (n=22) Results worst CTCAE Grade		300mg (n=8) Results worst CTCAE Grade	
	3 / 4	2	3 / 4	2
Skin rash	7	4	2	2
Diarrhoea	3	1	1	
Colitis	1		1	1
Nausea/vomiting		4		2
Fever		1	1	
Immune reaction	1			
Nausea				2
Vomiting	1		1	1
Headache	1	3		
Decreased lymphocytes	1	3	1	
Raised ALT/AST	2	4		1

None. All data are subject to quality control/assurance processes.

Efficacy:

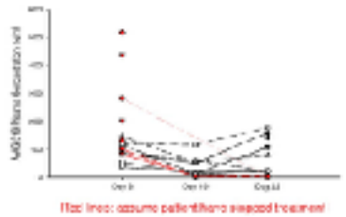
One patient (400 mg) with T1 oral cavity carcinoma had a pathological CR.

Other responses (to be reviewed):

ir PR (2 pts), ir SD (16 pts), ir PD (6 pts)

Steady State Pharmacokinetics:

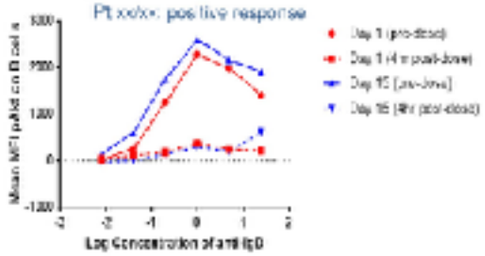
All treated patients (300 & 400 mg) with measurable levels of AMG 319 in blood.



Post hoc: assume patients have stopped treatment

pAKT:

6/8 pts: > 50% reduction in AUC pre vs 4 hr post-dose on D1 and/or D15. 1 pt also showed > 50% reduction pre dose Day 15



Immune response to tetanus vaccine:

7/10 pts made a significant response to vaccine (antibodies ≥ 1.5 fold increase over baseline p<0.05)

Conclusions

Cutaneous and GI toxicities are consistent with T reg depletion suggesting that efficacy and toxicity may be mechanistically inter-related at the doses and schedule tested. The toxicities experienced were not significantly different in intensity/incidence in the doses tested.

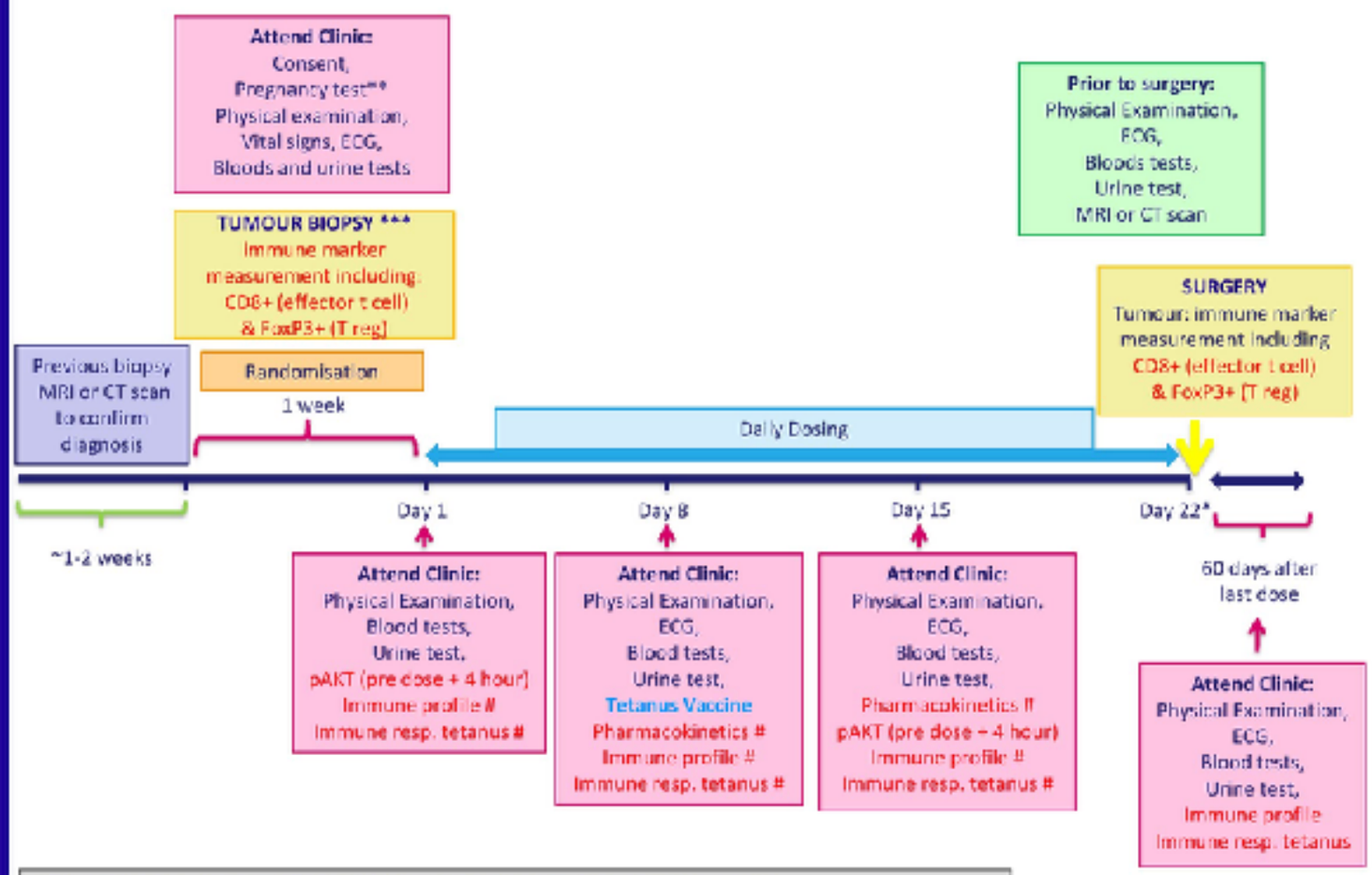
The percentage inhibition demonstrated in the pAkt assay is similar in magnitude to that seen previously with AMG 319 in patients with advanced B cell malignancies, supporting target inhibition.

Despite the encouraging clinical response and demonstration of target engagement, the risk benefit profile of AMG 319 with the doses, schedule of administration and patient population tested is not favourable. The trial has been closed to recruitment but clinical evaluation of additional schedules is under consideration.

C.H.Ottensmeier@soton.ac.uk

Ottensmeier C, abs #6068, ASCO 2018

Assessment Schedule



CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT

ecmc AMGEN

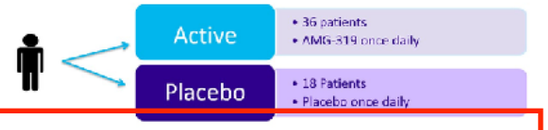
We thank participating patients, supporting staff & Institutions, Cancer Research UK as Sponsor and funder of the trial, Amgen for supply of IMP & the CRUK Formulation Unit for trial supply management.

Andrew Graeme Schache, [3]Richard Shaw, [7]Rabindra P Singh, [8]Joseph H. Davies, [12]Sidath Katugampola, [13]Khalid Ali, [14]Bart Vanhaesebroeck, [1]Emma King; [1]University of ... Alexandra Hospital, Portsmouth, UK; [6]Beatson West of Scotland Cancer Centre, Glasgow, UK; [7]University Hospital ... UK; [11]Institute of Cancer Therapeutics, Bradford, UK; [12]Centre for Drug Development (CDD), Cancer Research UK,

Primary Objectives

- To assess changes in immune infiltration in tumour before and after treatment with AMG 319
- To assess the safety and toxicity profile of AMG 319 in HNSCC

Methods



Patient Population

- HNSCC of the hypopharynx, oropharynx, oral cavity, supraglottis or larynx (except T1 glottic tumours) for whom surgery with curative intent ± post-operative radiotherapy or chemoradiotherapy as the treatment of choice.
- ECOG 0/1, adequate organ function and no active autoimmune disease

Treatment Schedule

- Two arms: either AMG 319 once daily or matching placebo (2:1) once daily, administered orally for 20-29 days.

Preliminary Results (Blinded data)

- 30 patients (pts) enrolled & treated:
  - 22 pts: 400 mg
  - 8 pts: 300 mg

Analysis of immune markers (CD8+, FoxP3) pending.

Treatment delivery

< 80% of planned treatment due to adverse events:

- 400 mg - 8/22 pts (30-64%)
- 300 mg - 3/8 pts (31-43%)

Toxicity presented from Days 8-11; resulting in withdrawal from the trial in 12 pts.

...afety & tolerability (AMG 319 & placebo)

Drug Related Adverse Event	400 mg (n=22) No. pts worst CTCAE Grade		300 mg (n=8) No. pts worst CTCAE Grade	
	3 / 4	2	3 / 4	2
...in rash	7	4	2	2
...iarrhoea	4	3	1	
...olitis	1		1	1
...u-like symptoms		4		2
...ever		3	1	
...mmune reaction	1			
...ausea				2
...omiting	1		1	1
...eadache	1	3		
...ecreased Lymphocytes	1	3	1	
...aised AST/ALT	2	4		1

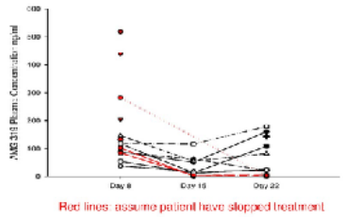
Note: All data are subject to quality control/assurance processes.

Efficacy:

One patient (400 mg) with T1 oral cavity carcinoma had a pathological CR.
Other responses (to be reviewed):
ir PR (2 pts), ir SD (16 pts), ir PD (6 pts)

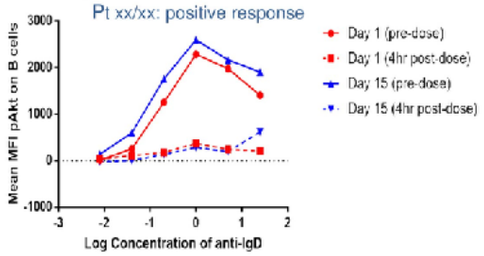
Steady State Pharmacokinetics:

All treated patients (300 & 400 mg) with measurable levels of AMG 319 in blood.



pAkt:

6/8 pts: > 50% reduction in AUC pre vs 4 hr post-dose on D1 and/or D15. 1 pt also showed > 50% reduction pre dose Day 15



Immune response to tetanus vaccine:

7/10 pts made a significant response to vaccine (antibodies ≥ 1.5 fold increase over baseline $p<0.05$).

Conclusions

Cutaneous and GI toxicities are consistent with T reg depletion suggesting that efficacy and toxicity may be mechanistically inter-related at the doses and schedule tested. The toxicities experienced were not significantly different in intensity/incidence in the doses tested.

The percentage inhibition demonstrated in the pAkt assay is similar in magnitude to that seen previously with AMG 319 in patients with advanced B cell malignancies, supporting target inhibition.

Despite the encouraging clinical response and demonstration of target engagement, the risk benefit profile of AMG 319 with the doses, schedule of administration and patient population tested is not favourable. The trial has been closed to recruitment but clinical evaluation of additional schedules is under consideration.

C.H.Ottensmeier@soton.ac.uk

Ottensmeier C, abs #6068, ASCO 2018

Safety & tolerability (AMG 319 & placebo)

Drug Related Adverse Event	400 mg (n=22) No. pts worst CTCAE Grade		300 mg (n=8) No. pts worst CTCAE Grade	
	3 / 4	2	3 / 4	2
Skin rash	7	4	2	2
Diarrhoea	4	3	1	
Colitis	1		1	1
Flu-like symptoms		4		2
Fever		3	1	
Immune reaction	1			
Nausea				2
Vomiting	1		1	1
Headache	1	3		
Decreased Lymphocytes	1	3	1	
Raised AST/ALT	2	4		1

A Cancer Rese
Phase IIa trial
with *human*

controlled
patients
d neck

CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT

ecmc AMGEN

We thank participating patients, supporting staff & Institutions. Cancer Research UK as Sponsor and funder of the trial, Amgen for supply of IMP & the CRUK Formulation Unit for trial supply management.

[1]Christian H.H Ottensmei
[9]Lindsey Chudley, [9]Danie
Southampton, United Kingdom (UK
Southampton, UK; [8]Dorset Cancer
London, UK; [13]Amgen, US, [14]UCL C

Paterson, [3]Andrew Graeme Schache, [3]Richard Shaw, [7]Rabindra P Singh, [8]Joseph H. Davies,
Gary Acton, [12]Sidath Katugampola, [13]Khalid Ali, [14]Bart Vanhaesebroeck, [1]Emma King; [1]University of
gow, UK; [5]Queen Alexandra Hospital, Portsmouth, UK; [6]Beatson West of Scotland Cancer Centre, Glasgow, UK; [7]University Hospital
Southampton, UK; [11]Institute of Cancer Therapeutics, Bradford, UK; [12]Centre for Drug Development (CDD), Cancer Research UK,

Introduction

Background

- AMG 319 is a PI3Kinase
- PI3Kinase delta isoform i
  cell signalling, differentiat
  additional effect on modu
- Inhibition is expected to b
  suppression of the immu
  CD8+ T cells into the tum
  [Khaild A et al, Nature 20

Previous Clinical Experienc

- Phase I dose escalation t
- 28 patients: RP2D 400m

Primary Objectives

- To assess changes in immune infiltration in tumour before and after treatment with AMG 319
- To assess the safety and toxicity profile of AMG 319 in HNSCC

Methods

Patient Population

- HNSCC of the hypopharynx, oropharynx, oral cavity, supraglottis or larynx (except T1 glottic tumours) for whom surgery with curative intent ± post-operative radiotherapy or chemoradiotherapy as the treatment of choice.
- ECOG 0/1, adequate organ function and no active autoimmune disease

Treatment Schedule

- Two arms: either AMG 319 once daily or matching placebo (2:1) once daily, administered orally for 20-29 days.

Preliminary Results (Blinded data)

- 30 patients (pts) enrolled & treated:
  - 22 pts: 400 mg
  - 8 pts: 300 mg

Analysis of immune markers (CD8+, FoxP3) pending.

Treatment delivery

< 80% of planned treatment due to adverse events:

- 400 mg - 8/22 pts (30-64%)
- 300 mg - 3/8 pts (31-43%)

Toxicity presented from Days 8-11; resulting in withdrawal from the trial in 12 pts.

Safety & tolerability (AMG 319 & placebo)

Drug Related Adverse Event	400 mg (n=22) No. pts worst CTCAE Grade		300 mg (n=8) No. pts worst CTCAE Grade	
	3 / 4	2	3 / 4	2
Skin rash	7	4	2	2
Diarrhoea	4	3	1	
Colitis	1		1	1
Flu-like symptoms		4		2
Fever		3	1	
Immune reaction	1			
Nausea				2
Vomiting	1		1	1
Headache	1	3		
Decreased Lymphocytes	1	3	1	
Raised AST/ALT	2	4		1

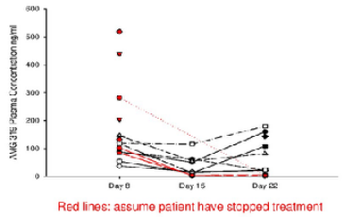
Note: All data are subject to quality control/assurance processes.

Efficacy:

One patient (400 mg) with T1 oral cavity carcinoma had a pathological CR.
Other responses (to be reviewed):
ir PR (2 pts), ir SD (16 pts), ir PD (6 pts)

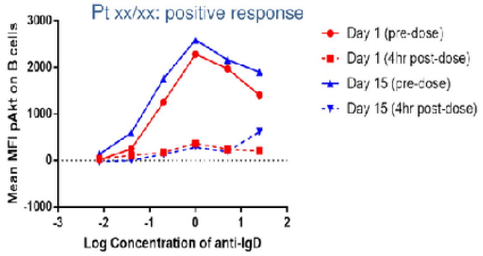
Steady State Pharmacokinetics:

All treated patients (300 & 400 mg) with measurable levels of AMG 319 in blood.



pAkt:

6/8 pts: > 50% reduction in AUC pre vs 4 hr post-dose on D1 and/or D15. 1 pt also showed > 50% reduction pre dose Day 15



Immune response to tetanus vaccine:

7/10 pts made a significant response to vaccine (antibodies ≥ 1.5 fold increase over baseline $p<0.05$).

Conclusions

Cutaneous and GI toxicities are consistent with T reg depletion suggesting that efficacy and toxicity may be mechanistically inter-related at the doses and schedule tested. The toxicities experienced were not significantly different in intensity/incidence in the doses tested.

The percentage inhibition demonstrated in the pAkt assay is similar in magnitude to that seen previously with AMG 319 in patients with advanced B cell malignancies, supporting target inhibition.

Despite the encouraging clinical response and demonstration of target engagement, the risk benefit profile of AMG 319 with the doses, schedule of administration and patient population tested is not favourable. The trial has been closed to recruitment but clinical evaluation of additional schedules is under consideration.

C.H.Ottensmeier@soton.ac.uk

Ottensmeier C, abs #6068, ASCO 2018

MUNICH 2018 ESMO congress

A Phase II Window of Opportunity Study of Preoperative Olaparib with Cisplatin or Durvalumab or Olaparib alone in Patients with Operable SCCHN (OPHELIA)

NIH U.S. National Library of Medicine

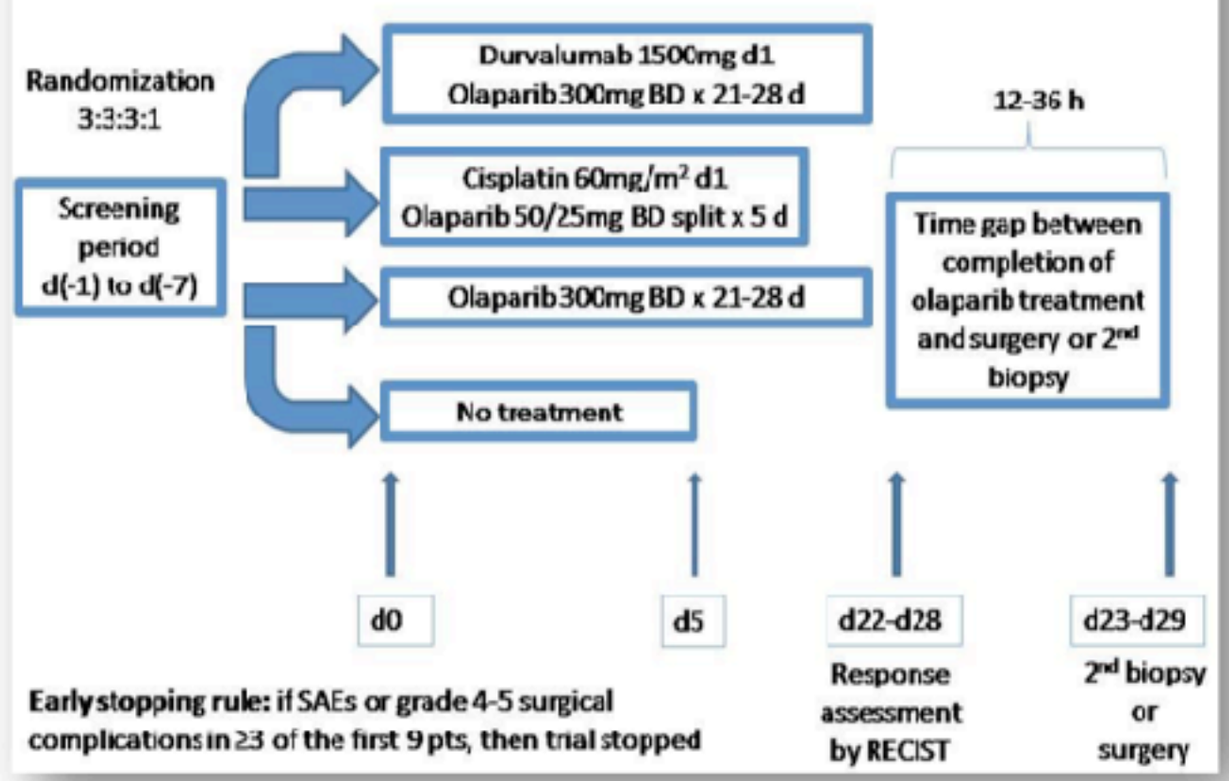
ClinicalTrials.gov

Preoperative Administration of Olaparib With Cisplatin or With Durvalumab or Alone or no Tratment in Patients Who Are Candidates for Surgery of Carcinoma of the Head and Neck. (OPHELIA)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02882308

Recruitment Status : Recruiting
First Posted : August 29, 2016
Last Update Posted : November 27, 2018
See Contacts and Locations



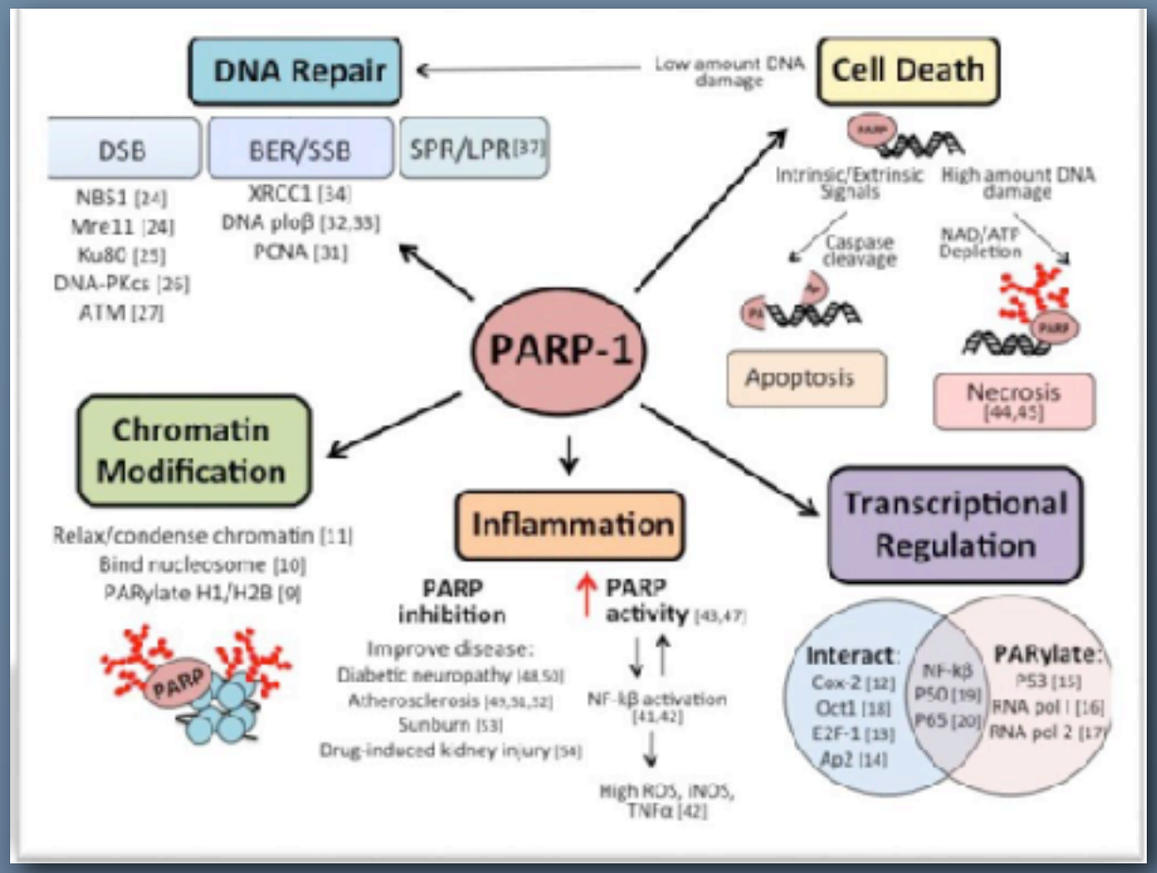
A: Cis-Olaparib
B: Olaparib
C: Olaparib-Durva
D: No treatment

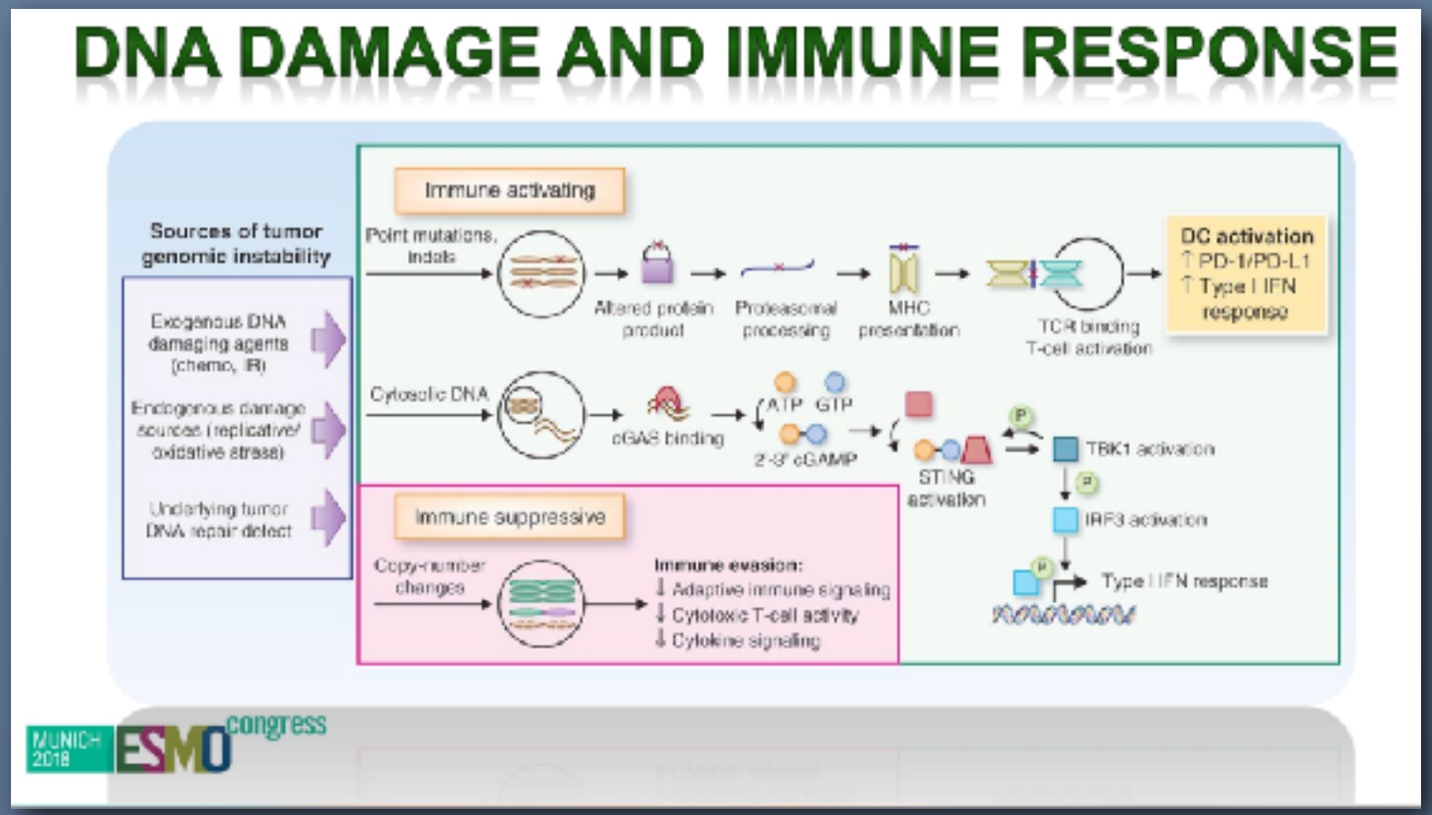
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Figure 1. Treatment diagram of Ophelia trial NCT 02882308

Psyrri A, ESMO 2018

La citotoxicidad inducida por olaparib provoca la inhibición de la actividad enzimática de la PARP y aumenta la formación de complejos de PARP-DNA, provocando daños al DNA y la muerte de la célula tumoral.
Se postula que aumentando el daño en el DNA se puede inducir la actividad inmune y aumentar los niveles de PD-L1.





Endpoints:

-Primary:

Change in Ki67 proliferation index (ΔKi67 reduction 25% in post-treatment biopsy)

-Secondary:

Response rate (RR), rate of complete pathologic response (pCR)

Correlative biomarker & genomic assessment in the pre-/post-treatment blood & tumor

Accrual Goal:

41 patients will be randomized 3:3:3:1 to olaparib-cis (A): olaparib (B): durvalumab-olaparib (C): no treatment (D)

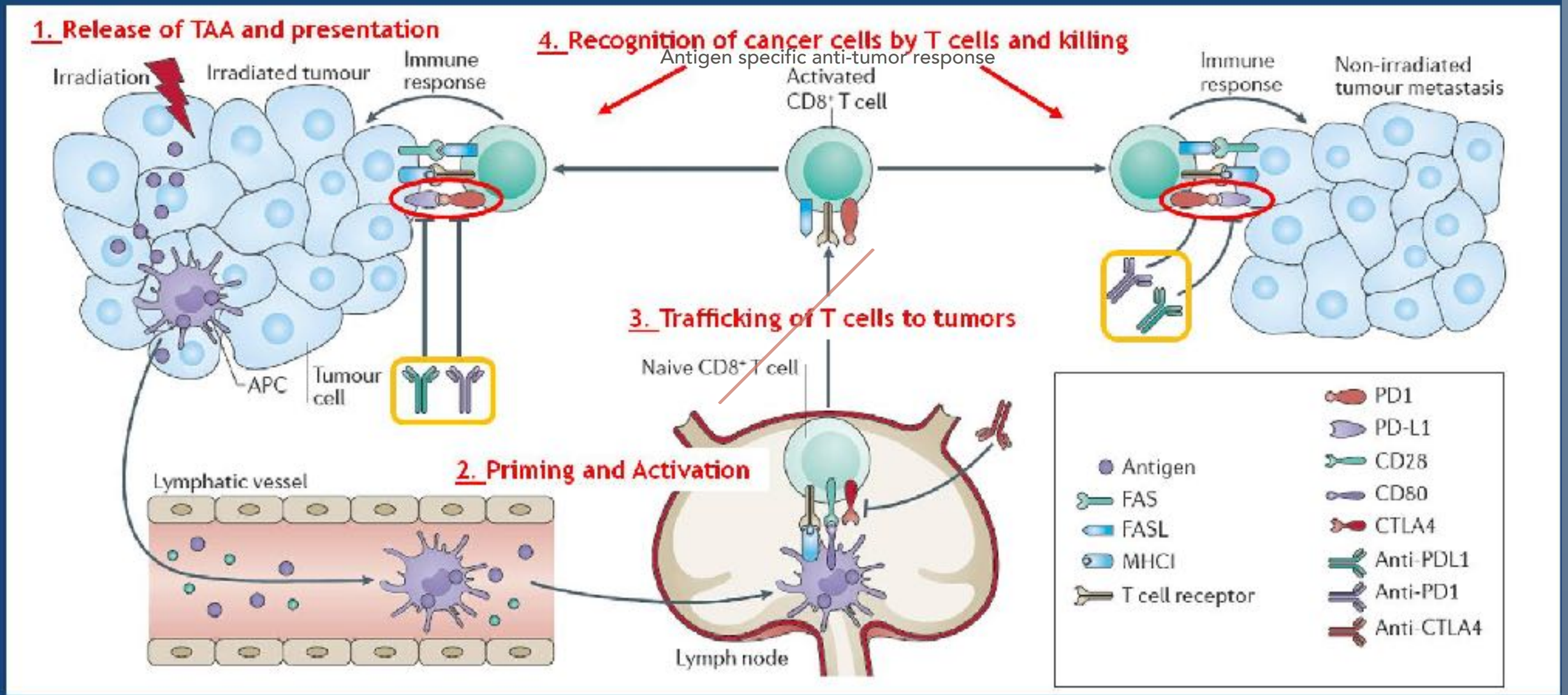
Estado actual: Desde agosto/2016 29 pacientes reclutados; **todavía no abierta la rama con durvalumab (oct/18).**

Age	47-85
Sex	23M:5F
Tobacco	89% (>10 pk yr)
Alcohol	57% (16/28)
Subsite -Oral cavity -Oropharynx -Larynx/Hypopharynx	 22 3 3
Stage I	3
Stage II	1
Stage III	8
Stage IV	16
cT4	12
cN +	15

INMUNOTERAPIA CONCOMITANTE

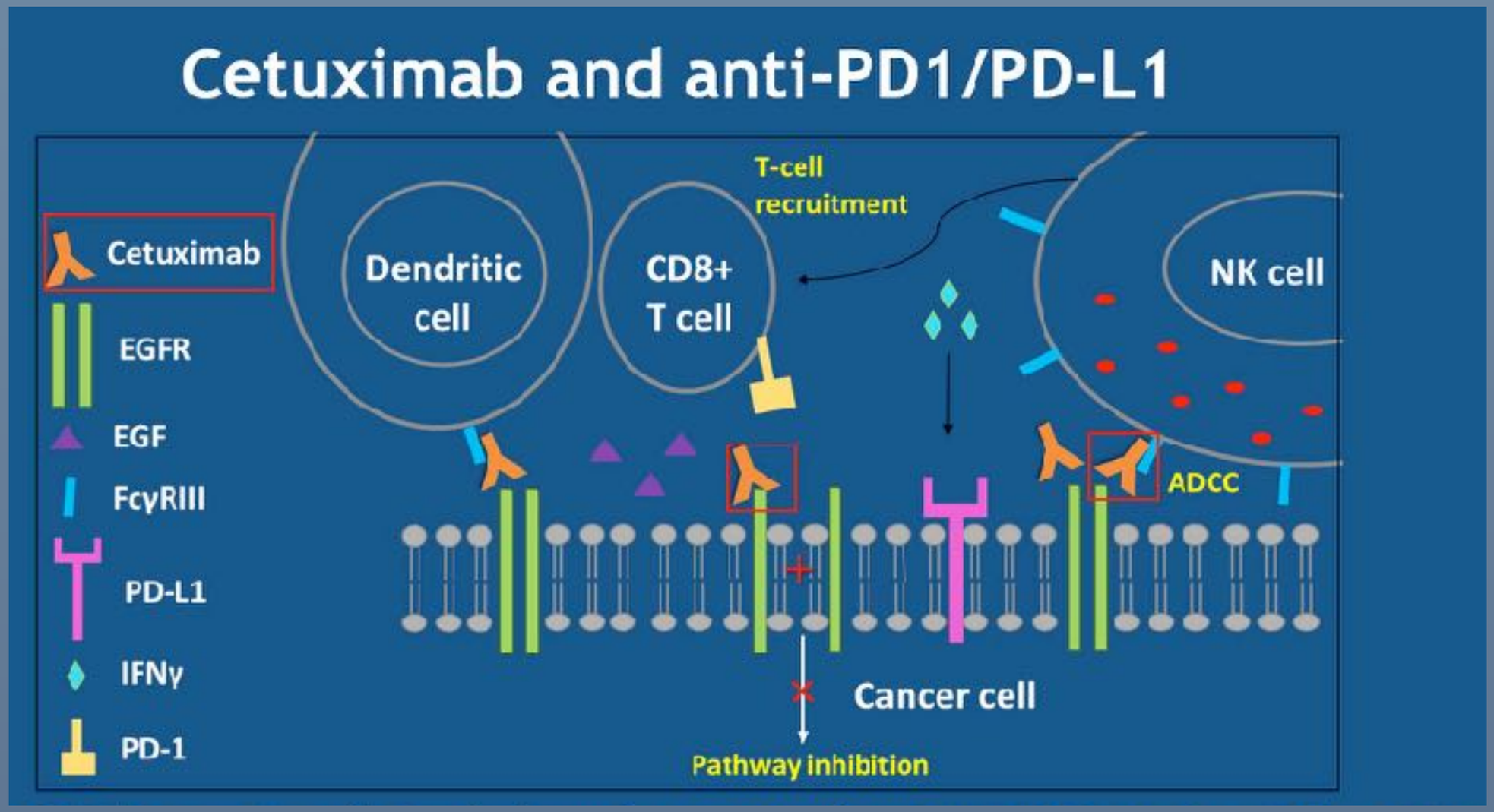
2018 ASCO ANNUAL MEETING

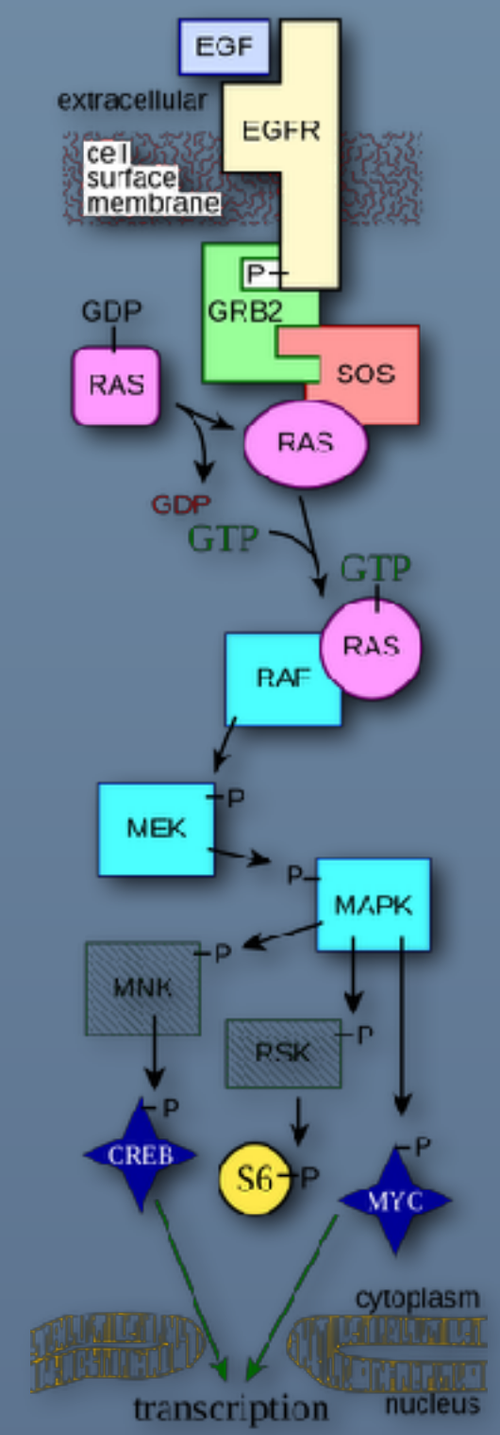
Radiotherapy (XRT) and immune response



*TAA: tumour associated antigens

Ferrarroto R, ASCO 2018; adapted from Ngwa W. Nature Reviews Cancer, 2018





CTX SE UNE A EGFR BLOQUEANDO ESTA VÍA. LAS CITOCINAS LIBERADAS CONDUCEN A UNA MAYOR EXPRESIÓN DE PD-L1 EN EL TUMOR, QUE PUEDE SER BLOQUEADA POR ANTICUERPOS, PRODUCIENDO UNA **ACTIVIDAD SINÉRGICA AL CTX**

2017 ASCO ANNUAL MEETING

Safety of Pembrolizumab with Chemoradiation (CRT) in Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-SCCHN).

- Steven F. Powell[1], Mark M. Gitau[2], Christopher J. Sumey[1], John T. Reynolds[3], Andrew M. Terrell[2], Michele M. Lohr[1], Steven C. McGraw[1], Ryan K. Nowak[1], Ashley W. Jensen[2], Miran J. Blanchard[2], Christie A. Ellison[1], Lora J. Black[1], Paul A. Thompson, PhD[1], Kathryn A. Gold[1], Ezra E.W. Cohen[4], John H. Lee[1,5], William C. Spanos[1]

(NCT02586207)

INCLUSION

Squamous cell carcinoma of the oral cavity (excluding lip), oropharynx, hypopharynx, or larynx

Stage III, IVA, or IVB

HPV + or HPV - (by p16 IHC)

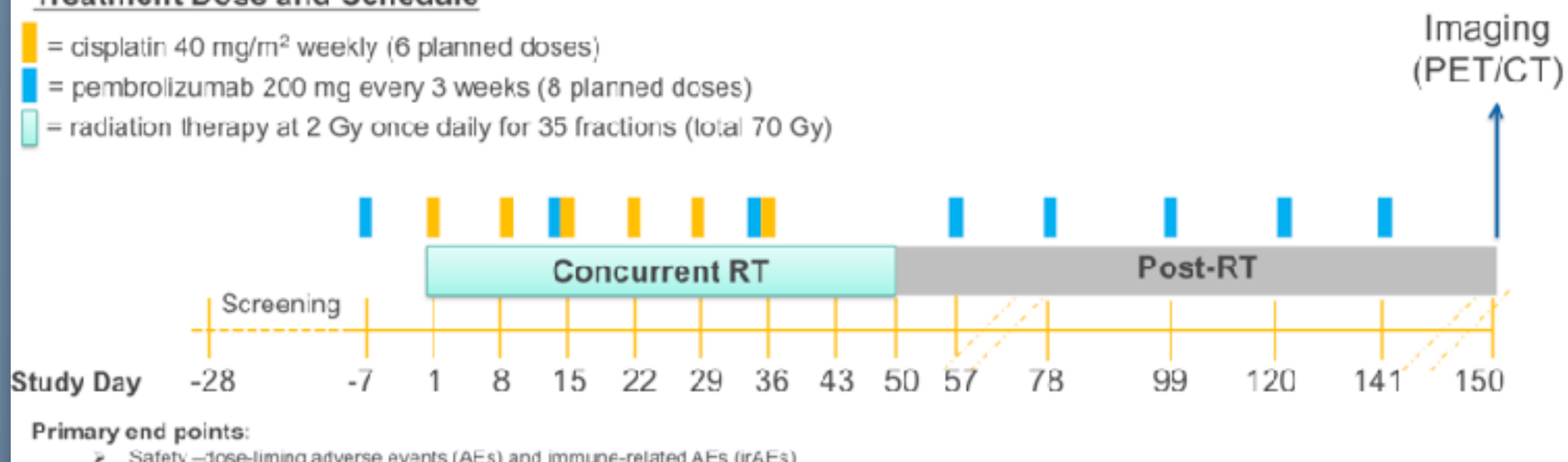
Age ≥18

ECOG PS 0-1

RECIST 1.1 measurable disease

cisplatin eligible

Treatment Dose and Schedule



Primary end points:
- Safety – dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

Secondary end points: PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)

27 pacientes HNSCC E III - IVB no operados: 20 orofaringe HPV+, 2 orofaringe HPV-, 1hipofaringe HPV- y 4 laringe HPV-) de nov/15 a ago/16:

- 21 (78%) dosis completa de pembrolizumab.
- 3 (11%) interrupciones por irAES (neuropatia periférica motora G2, elevación GOT G3, Sd. Lhermite-like G1).
- 3 (11%) interrupciones por causas relacionadas con protocolo.
- 100% 70Gy RT sin retrasos >5d
- 23 (80%) >200mg/m2 CDDP
- 1 muerte no tóxica.
- cohortes de expansión de 34 pts HPV + y 23 pus HPV- para evaluar la eficacia.

AE	All Grades	Grade 3	Grade 4
Dysphagia	26 (96%)	12 (44%)	None
Mucositis (oral/pharyngeal)	26 (96%)	8 (30%)	
Dermatitis radiation	22 (81%)	4 (15%)	
Weight loss	22 (81%)	4 (15%)	
Neutropenia	17 (63%)	9 (33%)	1(4%)
Anemia	25 (93%)	4 (15%)	None
Thrombocytopenia	11 9(41%)	2 (7%)	
Hyponatremia	20 (74%)	5 (19%)	None
Hypomagnesemia	17 (63%)	1 (4%)	
Hypophosphatemia	12 (44%)	4 (15%)	1 (4%

Powell SF, et al. ASCO. 2017 Abstract 601

Pembrolizumab Plus Chemoradiation vs Chemoradiation Alone for Locally Advanced Head and Neck Squamous Cell Carcinoma: The Phase 3 KEYNOTE-412 Study

J. P. Machiels[1]; L. Licitra[2]; Y. G. Tao[3]; C.-J. Y...; D. Burtness[7]; V. Gregoire[1]; S. Agarwala[8]; J. Y...; S. Ikeda[12]; R.-L. Hong[13]; J. Y. Ge[14]; H. Brown...

[1]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [2]Fondazione ... University of Milan, Milan, Italy; [3]Gustave Roussy, Villejuif, France; ... [illegible]; Peter MacCallum Cancer Centre, East Melbourne, VIC, A... Toronto, ON, Canada; [7]Yale University School of Medicine, New Ha... Bethlehem, PA, USA; [illegible] Oncology–Austin Central, Austin, TX; [11]Hacettepe University, Ankara, Turkey; [12]...Medical Hospital, Tokyo...; [13]National Taiwan University Hospital, Taipei, Taiwan; [14]Merck & Co...

NIH U.S. National Library of Medicine
ClinicalTrials.gov
Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾
Home > Search Results > Study Record Detail
Save this study

Trial record **1 of 1** for: keynote 412

Previous Study | Return to List | Next Study

Study of Pembrolizumab (MK-3475) or Placebo With Chemoradiation in Participants With Locally Advanced Head and Neck Squamous Cell Carcinoma (MK-3475-412/KEYNOTE-412)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03040999

Recruitment Status : Recruiting
First Posted : February 2, 2017
Last Update Posted : November 26, 2018

See **Contacts and Locations**

Sponsor:
Merck Sharp & Dohme Corp.

BACKGROUND

- Head and neck squamous cell carcinoma (HNSCC) is a common cancer that affects the oral cavity, the pharynx, and the larynx[1]
- Approximately 60% of patients have locally or regionally advanced disease at the time of diagnosis[2]
  - Chemoradiation or surgery followed by radiotherapy with or without chemotherapy is considered the standard of care for patients with locally advanced HNSCC[2]
  - Between 40% and 60% of patients with locally advanced HNSCC will experience relapse despite multimodal therapy[3]
- Programmed death 1 (PD-1) is an immune checkpoint receptor known to play a role in tumor immune evasion (**Figure 1**); the PD-1 ligand PD-L1 is also highly expressed in HNSCC tumors[4-7]
- Pembrolizumab is a humanized monoclonal antibody that binds to PD-1, preventing interaction with its ligands PD-L1 and PD-L2[8]
  - Pembrolizumab is currently approved in more than 80 countries for the treatment of ≥1 advanced malignancies
  - It is approved in the United States for recurrent or metastatic HNSCC in patients exhibiting disease progression on or after platinum-containing chemotherapy[8]
- Evidence is mounting that radiotherapy might act as an immunologic stimulus, potentially counteracting the immunosuppressive tumor microenvironment; this has resulted in significant interest in the combination of radiotherapy and immunotherapeutic agents[9]
- KEYNOTE-412 (ClinicalTrials.gov, NCT03040999) is a phase 3 randomized, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of pembrolizumab given in combination with chemoradiation therapy (CRT) compared with the efficacy and safety of placebo in combination with CRT in patients with locally advanced HNSCC

Figure 1. Pembrolizumab and the PD-1 Pathway

MHC-1, major histocompatibility complex 1; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2.

OBJECTIVES

Primary

- Compare event-free survival per RECIST v1.1 by blinded independent central review in patients treated with pembrolizumab combined with CRT and patients treated with placebo combined with CRT

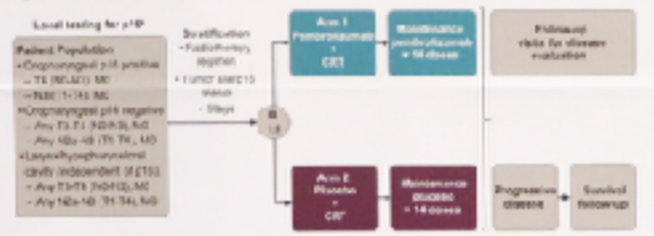
Secondary

- Compare the following in patients treated with pembrolizumab combined with CRT and patients treated with placebo combined with CRT:
  - Overall survival
  - Safety and tolerability
  - Change from baseline in global health status/quality of life using the EORTC Quality of Life Core 30 questionnaire (QLQ-C30) and in swallowing, speech, and pain symptoms using the EORTC supplementary module QLQ-H&N35

DESIGN

- Approximately 780 patients will be enrolled in the trial (**Figure 2**)
- Patients will be randomly assigned (1:1) to receive either pembrolizumab 200 mg every 3 weeks plus CRT or placebo (normal saline solution) every 3 weeks plus CRT
  - The CRT regimen is outlined in **Table 1**
- The trial will be split into 3 phases:
  - Pembrolizumab/placebo priming dose, CRT, and 2 additional pembrolizumab/placebo doses (8 weeks)
  - Pembrolizumab/placebo maintenance dosing (14 doses) and post-CRT follow-up (up to 1 year)
  - Posttreatment follow-up (years 2-5+)
- Patients will continue treatment until they receive 17 doses of pembrolizumab or placebo, or until they experience disease progression (as determined by a central imaging vendor) or unacceptable toxicity, or until investigator/patient decision to withdraw the patient from the study
- Study will be stratified by radiotherapy regimen, tumor site/p16 status, and stage

Figure 2. Study Design



CRT, chemoradiation therapy; R, randomization.
[a]Expression of p16 is highly correlated with human papillomavirus (HPV) in oropharyngeal cancer. [illegible]

Table 1. CRT Treatment Regimens[a]

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Chemotherapy regimen[b]				
Cisplatin	100 mg/m²	Q3W	IV infusion	Cycle 1 day 5, cycle 2 day 8, and cycle 3 day 8 of the first treatment phase[c]
Radiotherapy regimen				
AFX	70 Gy	6 fractions per week (example: 3 doses over 5 days, 2 days off, or 6 doses over 5 days, 1 day off)	AFX	6 weeks (35 fractions [6 fractions in final week]); study weeks 2-7
or				
SFX	70 Gy	5 fractions per week (example: 5 doses over 5 days, 2 days off)	SFX	7 weeks (35 fractions); study weeks 2-8

AFX, accelerated fractionation; CRT, chemoradiation therapy; IV, intravenous; Q3W, every 3 weeks; SFX, standard fractionation.
[a]A pembrolizumab or placebo priming dose will be administered 1 week before the start of CRT, followed by 2 pembrolizumab or placebo infusions during CRT, which are then continued for an additional 14 doses of pembrolizumab or placebo after CRT for a total number of pembrolizumab or placebo infusions of 17 (total duration of pembrolizumab/placebo is 1 year).
[b]It is recommended that cisplatin be started on the first day of radiation therapy (RT) [illegible]. Cisplatin should be infused before RT delivery. Follow local product label and institutional guidelines. Cisplatin will not be administered after completion of RT (AFX or SFX regimen). If excessive toxicity with cisplatin is detected, the cisplatin dose will be changed to 40 mg/m² weekly [illegible] for any new patients enrolled in the study only after formal notification by the sponsor.
[c]Cycle 3 day 8 applies only to the SFX RT regimen.

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Pathologically proven new diagnosis of squamous cell carcinoma of: – Oropharyngeal p16 positive · T4 (N0-N3), M0 · N3 (T1-T4), M0 – Oropharyngeal p16 negative · Any T3-T4 (N0-N3), M0 · Any N2a-N3 (T1-T4), M0 – Larynx/hypopharynx/oral cavity[a] (independent of p16) · Any T3-T4 (N0-N3), M0 · Any N2a-N3 (T1-T4), M0 • Results available from local testing of HPV status for oropharyngeal cancer[b] • Provision of tissue from a core or excisional biopsy for PD-L1 biomarker analysis • Evaluable tumor burden assessed by CT or MRI based on RECIST v1.1 • Eligible for definitive CRT and not considered for primary surgery based on investigator decision • ECOG performance status 0 or 1 • Adequate organ function	• Cancer outside the oropharynx, larynx, hypopharynx, or oral cavity • Prior systemic therapy, targeted therapy, RT, or radical surgery for head and neck cancer under study • Grade ≥2 audiometric hearing loss or neuropathy • Grade 3/4 bleeding owing to underlying malignancy • Diagnosis of immunodeficiency or having undergone systemic steroid therapy or any other form of immunosuppressive therapy during the 7 days before the first dose of trial treatment • Current pneumonitis or history of noninfectious pneumonitis that necessitated use of steroids • Active autoimmune disease that necessitated systemic treatment within the preceding 2 years • Active CNS metastases or carcinomatous meningitis

CNS, central nervous system; CRT, chemoradiation therapy; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; MRI, magnetic resonance imaging; PD-L1, programmed death ligand 1; RT, radiation therapy.
[a]Patients with oral cavity tumors must have unresectable disease.
[b]Tumor p16 expression must be evaluated by assessment of immunohistochemistry analysis by CINtec p16 histology assay (Ventana Medical Systems Inc., Mountain View, CA) using the Benchmark Ultra autostainer (Ventana Medical Systems Inc.) and standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in ≥70% of tumor cells.

Assessments and Follow-Up

- Tumors will be evaluated by computed tomography (CT) or magnetic resonance imaging at baseline, 12 weeks after the end of CRT, every 3 months for 3 years after randomization, then every 6 months for years 4 through 5
- During screening, a fluorodeoxyglucose–positron emission tomography (FDG-PET) or FDG-PET/CT scan should be acquired within 28 days of randomization. At 12 weeks after CRT, a FDG-PET or FDG-PET/CT scan will be acquired as part of neck management
- Patients will be evaluated to determine the necessity of neck dissection 12 weeks after completion of CRT; neck dissection will be recommended in cases of persistent disease
- If a patient experiences disease progression or starts a new anticancer therapy, the patient will begin the survival follow-up phase; patients will be contacted every 3 months during years 1 through 3 and every 6 months during years 4 and 5 until death, withdrawal of consent, or the end of the study, whichever occurs first
- Patient-reported outcomes (PROs) will be assessed at weeks 1 and 7 during treatment phase 1, every 3 months up to year 2, and every 12 months up to year 5
- Adverse events will be monitored throughout the study and during the follow-up period and will be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
  - Treatment-related late-occurring toxicities will be recorded up to year 5 after end of treatment

Analyses

Efficacy

- Efficacy will be assessed in the intent-to-treat population, which will include all randomly assigned patients
- The nonparametric Kaplan-Meier method will be used to estimate the survival curves; treatment differences will be tested using the stratified log-rank test, and a stratified Cox proportional hazards model with the Efron method of tie handling will be used to estimate the magnitude of treatment differences

Safety

- Safety will be assessed in all patients in the as-treated population, which will include all randomly assigned patients who received ≥1 doses of study treatment
- Safety will be analyzed using a tiered approach

PROs

- PROs will be assessed in the full-analysis-set population, which will include all patients for whom ≥1 PRO assessment is available and who have received ≥1 doses of study treatment
- A constrained longitudinal data analysis model will be used to assess treatment differences in PROs

STATUS

- Enrollment in KEYNOTE-412 is ongoing in 21 countries in North America, South America, Europe, and Asia-Pacific (**Figure 3**)

Figure 3. Countries With Currently Open Sites of Enrollment for KEYNOTE-412 (in green)

References

1. Vigneswaran N, Williams MD. Oral Maxillofac Surg Clin North Am. 2014;26:123-141.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): head and neck cancers (Version 1.2016). [illegible] Accessed April 30, 2016.
3. Machiels JP et al. [illegible] 2016 [illegible]
4. Iwai Y et al. Proc Natl Acad Sci U S A. 2002;99:12293-12297.
5. Dong H et al. Nat Med. 2002;8:793-800.
6. Lyford-Pike S et al. Cancer Res. 2013;73:1733-1741.
7. [illegible] et al. [illegible]
8. Merck Sharp & Dohme Corp. KEYTRUDA® (pembrolizumab) injection, for intravenous use. Whitehouse Station, NJ, USA; 03/2017.
9. Kang J et al. J Immunother Cancer. 2016;4:51.

Acknowledgments

The authors thank the patients and their families and caregivers for participating in this trial and all investigators and site personnel. Medical writing and/or editorial assistance was provided by Jemimah Walker, PhD, and Matthew Grzywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA.

Contact Information

Contact the author at jean-pascal.machiels@uclouvain.be for questions and comments

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® and the author of this poster.

https://tinyurl.com/y8g3guth

Pembrolizumab Plus Chemoradiation vs Chemoradiation Alone for Locally Advanced Head and Neck Squamous Cell Carcinoma: The Phase 3 KEYNOTE-412 Study

J.-P. Machiels[1]; L. Licitra[2]; Y. G. Tao[3]; C.-J. Yen[4]; D. Rischin
B. Burtness[7]; V. Gregoire[1]; S. Agarwala[8]; J. Yorio[9]; J.-P. Del
S. Ikeda[12]; R.-L. Hong[13]; J. Y. Ge[14]; H. Brown[14]; B. Bidadi[14];

[1]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [2]Fondazione IRCCS Istituto Nazio
University of Milan, Milan, Italy; [3]Gustave Roussy, Villejuif, France; [4]National Cheng Kung
Taiwan; [5]Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia; [6]Princess Mar
Toronto, ON, Canada; [7]Yale University School of Medicine, New Haven, CT, USA; [8]St. Lu
Bethlehem, PA, USA; [9]Texas Oncology–Austin Central, Austin, TX, USA; [10]Institut Claudi
[11]Hacettepe Universitesi, Ankara, Turkey; [12]Medical Hospital, Tokyo Medical and Dental U
[13]National Taiwan University Hospital, Taipei, Taiwan; [14]Merck & Co., Inc., Kenilworth, NJ,

U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

Home > Search Results > Study Record Detail

Save this study

Trial record 1 of 1 for: keynote 412

Previous Study | Return to List | Next Study

Study of Pembrolizumab (MK-3475) or Placebo With Chemoradiation in Participants With Locally Advanced Head and Neck Squamous Cell Carcinoma (MK-3475-412/KEYNOTE-412)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

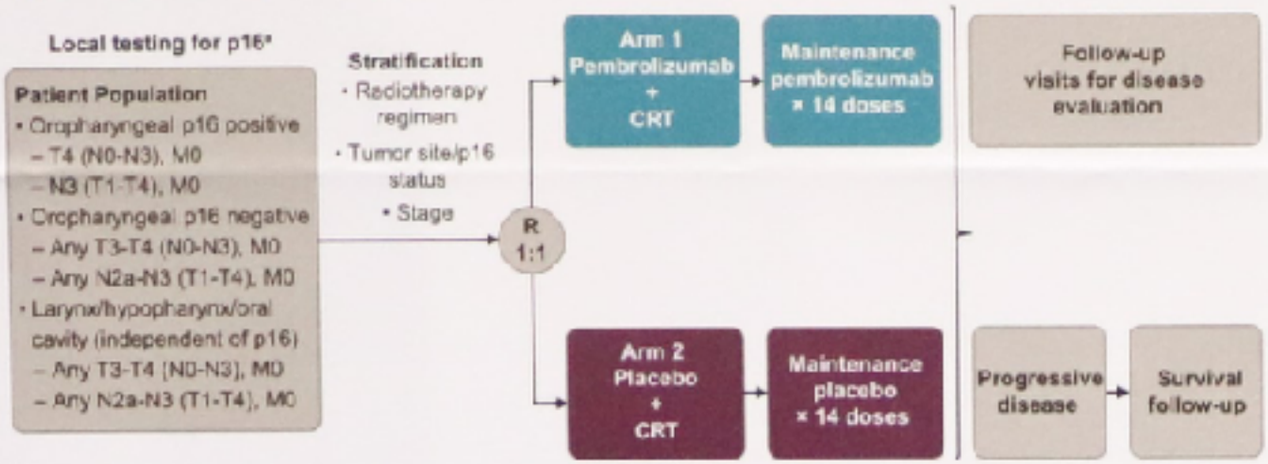
ClinicalTrials.gov Identifier: NCT03040999

Recruitment Status : Recruiting
First Posted : February 2, 2017
Last Update Posted : November 26, 2018

See Contacts and Locations

Sponsor:
Merck Sharp & Dohme Corp.

Figure 2. Study Design



CRT, chemoradiation therapy; R, randomization.
[a]Expression of p16 is highly correlated with human papillomavirus (HPV) in oropharyngeal cancer. Tumors outside the oropharynx will be considered HPV negative regardless of results of p16 staining.

Table 1. CRT Treatment Regimens[a]

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Chemotherapy regimen[b]				
Cisplatin	100 mg/m^2	Q3W	IV infusion	Cycle 1 day 8, cycle 2 day 8; and cycle 3 day 8 of the first treatment phase[c]
Radiotherapy regimen				
AFX	70 Gy	6 fractions per week (example: 6 doses over 5 days, 2 days off, or 6 doses over 6 days, 1 day off)	AFX	6 weeks (35 fractions [5 fractions in final week]) study weeks 2-7
or				
SFX	70 Gy	5 fractions per week (example: 5 doses over 5 days, 2 days off)	SFX	7 weeks (35 fractions) study weeks 2-8

AFX, accelerated fractionation; CRT, chemoradiation therapy; IV, intravenous; Q3W, every 3 weeks; SFX, standard fractionation.
[a]A pembrolizumab or placebo priming dose will be administered 1 week before the start of CRT, followed by 2 pembrolizumab or placebo infusions during CRT, which are then continued for an additional 14 doses of pembrolizumab or placebo after CRT for a total number of pembrolizumab or placebo infusions of 17 (total duration of pembrolizumab/placebo is 1 year).
[b]It is recommended that cisplatin be started on the first day of radiation therapy (RT) (±2 days). Cisplatin should be infused before RT delivery. Follow local product label and institutional guidelines. Cisplatin will not be administered after completion of RT (AFX or SFX regimen). If excessive toxicity with cisplatin is detected, the cisplatin dose will be changed to 40 mg/m^2 weekly (weeks 2-6) for any new patients enrolled in the study only after formal notification by the sponsor.
[c]Cycle 3 day 8 applies only to the SFX RT regimen.

- If a patient experiences disease progression or starts a new anticancer therapy, the patient will begin the survival follow-up phase; patients will be contacted every 3 months during years 1 through 3 and every 6 months during years 4 and 5 until death, withdrawal of consent, or the end of the study, whichever occurs first
- Patient-reported outcomes (PROs) will be assessed at weeks 1 and 7 during treatment phase 1, every 3 months up to year 2, and every 12 months up to year 5
- Adverse events will be monitored throughout the study and during the follow-up period and will be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Pathologically proven new diagnosis of squamous cell carcinoma of – Oropharyngeal p16 positive • T4 (N0-N3), M0 • N3 (T1-T4), M0 – Oropharyngeal p16 negative • Any T3-T4 (N0-N3), M0 • Any N2a-N3 (T1-T4), M0 – Larynx/hypopharynx/oral cavity[a] (independent of p16) • Any T3-T4 (N0-N3), M0 • Any N2a-N3 (T1-T4), M0 • Results available from local testing of HPV status for oropharyngeal cancer[b] • Provision of tissue from a core or excisional biopsy for PD-L1 biomarker analysis • Evaluable tumor burden assessed by CT or MRI based on RECIST v1.1 • Eligible for definitive CRT and not considered for primary surgery based on investigator decision • ECOG performance status 0 or 1 • Adequate organ function	• Cancer outside the oropharynx, larynx, hypopharynx, or oral cavity • Prior systemic therapy, targeted therapy, RT, or radical surgery for head and neck cancer under study • Grade ≥2 audiometric hearing loss or neuropathy • Grade 3/4 bleeding owing to underlying malignancy • Diagnosis of immunodeficiency or having undergone systemic steroid therapy or any other form of immunosuppressive therapy during the 7 days before the first dose of trial treatment • Current pneumonitis or history of noninfectious pneumonitis that necessitated use of steroids • Active autoimmune disease that necessitated systemic treatment within the preceding 2 years • Active CNS metastases or carcinomatous meningitis

CNS, central nervous system; CRT, chemoradiation therapy; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; MRI, magnetic resonance imaging; PD-L1, programmed death ligand 1; RT, radiation therapy.
[a]Patients with oral cavity tumors must have unresectable disease.
[b]Tumor p16 expression must be evaluated by assessment of immunohistochemistry analysis by CINtec p16 histology assay (Ventana Medical Systems Inc., Mountain View, CA) using the Benchmark Ultra autostainer (Ventana Medical Systems Inc.) and standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in ≥70% of tumor cells.

and site personnel. Medical writing and/or editorial assistance was provided by Jemimah Walker, PhD, and Matthew Grzywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA.

Contact Information

Contact the author at jean-pascal.machiels@uclouvain.be for questions and comments

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® and the author of this poster.

https://tinyurl.com/y8g3gzfn

2018 ASCO ANNUAL MEETING

Safety and early efficacy of Nivolumab added to CDDP- or CTX-radiotherapy platforms for patients with intermediate and high-risk local-regionally advanced HNSCC

RTOG FOUNDATION INC

RTOG Foundation 3504

FASE 1

High-risk HNSCC
OC, larynx, hypopharynx, p16 neg OP, AJCC 7th Ed
T1-2 N2a-N3
T3-4 N0-3

Intermediate risk
P16 pos OP
>10 ppy
-T1-2N2b, T3-4 N0-3
≤ 10 ppy
-T4 N0-N3, T1-3 N3

Arm 1:
Nivolumab 240 mg Q2W x 10
Cisplatin 40 mg/m² Q1W x 7

Arm 2:
Nivolumab 240 mg Q2W x 1 then 360 mg Q3W x 6
Cisplatin 100 mg/m² Q3W x 3

Arm 3:
Nivolumab 240 mg Q2W x 10
Cetuximab 400 mg/m² x1 then 250 mg/m2 Q1W x 7

Arm 4:
Nivolumab 240 mg Q2W x 10

XRT: 70 Gy/35 Fx/7 wks
Adjuvant: Nivolumab 480 mg Q4W x 7

Objectives: To evaluate safety of each treatment arm, feasibility of adjuvant nivolumab, and early efficacy

DLT:
- toxicidad inmunorelacionada G-3 no resuelta en 28 días.
- > 2 semanas de retraso en RT x nivo.
- imposibilidad de completar RT por nivo.
- imposibilidad de recibir 70% CDDP o CTX x nivo.

Statistical Design

Safety evaluation (within arm)
- > 2 DLT out of 8 evaluable patients, regimen too toxic
- ≤ 2 DLT out of 8 evaluable patients, regimen safe
- If true DLT rate ≥ 45%, 78% probability declared too toxic
- If true DLT rate ≤ 20%, 80% probability declared safe

Feasibility of adjuvant (across all arms)
- ≥ 4 of 8 receive 7 doses, adjuvant feasible
- If true rate 7 doses is ≥ 60%, 83% probability declared feasible
- If true rate 7 doses is ≤ 30%, 81% probability declared infeasible

Robert Ferris at 2018 ASCO Annual Meeting

2018 ASCO ANNUAL MEETING

RTOG FOUNDATION INC

	Arm 1: RT + cis q7 + nivo (n=10)	Arm 2: RT + cis q21 + nivo (n=9)	Arm 3: RT + cetux + nivo (n=10)
Median (min-max) follow-up, months	11.5 (0.9-16.1)	10.4 (8.3-11.2)	8.0 (1.5-17.4)
Deaths	0	1 (COD unknown)	0
Disease progression	0	0	1 (lung mets at 6mo)

Event	Arm 1: RT + cis q7 + nivo (n = 10)		Arm 2: RT + cis q21 + nivo (n = 9)		Arm 3: RT + cetux + nivo (n = 10)	
	Grade 1-2 (n)	Grade 3–4 (n)	Grade 1-2 (n)	Grade 3–4 (n)	Grade 1-2 (n)	Grade 3–4 (n)
Endocrine						
Hypothyroidism	3	0	3	0	2	0
Hyperthyroidism	2	0	2	0	1	0
Gastrointestinal						
Colitis	1	0	0	0	1	0
Diarrhea	4	1	0	2	4	0
Hepatic						
Transaminitis	3	0	2	0	2	0
Pancreatic						
Lipase	0	2	2	1	1	1
Amylase	3	1	1	1	0	0
Renal	0	0	1	0	0	0

Event	Arms 1,2,3: Nivo + cis or cetuximab + XRT (n=29)[a]		CHECKMATE 141 Nivo (n=236)	
	G1-2 (n)	G3-4 (n)	G1-2 (n)	G3-4 (n)
Endocrine				
Hypothyroidism	8 (27.6%)	0 (0%)	9 (3.8%)	0 (0%)
Hyperthyroidism	5 (17.3%)	0 (0%)	2 (0.8%)	0 (0%)
Gastrointestinal				
Colitis	2 (6.9%)	0 (0%)	16 (6.8%)	0 (0%)
Diarrhea	8 (27.6%)	3 (10.4%)	16 (6.8%)	0 (0%)
Hepatic				
Transaminitis	7 (24.1%)	0 (0%)	3 (1.2%)	1 (0.4%)
Pancreatic				
Lipase	3 (10.4%)	4 (13.8%)	NR (<5%)	4 (1.7%)
Amylase	4 (13.8%)	2 (6.9%)	NR (<5%)	3 (1.3%)
Renal	1 (3.4%)	0 (0%)	1 (0.4%)	0 (0%)

CONCLUSIONES:

- La toxicidad limitante de dosis para el brazo 3 (cetuximab-RT-nivolumab) fue aceptable (1/10 DLT). Previamente se había reportado DLT aceptable para los brazos 1 y 2.
- No se han reportado nuevas alarma de seguridad al combinar nivolumab con CTX RT.
- Nivolumab no afecta la administración de cetuximab y RT (tampoco con CDDP + RT en brazo 2).
- Es factible completar 7 dosis de nivolumab adyuvante 480mg c/4sem (2/8 pcts interrumpieron el tratamiento por IRAE.
- Los datos preliminares parecen ser prometedores.
- Estudios Fase 3 en desarrollo.

Robert Ferris at 2018 ASCO Annual Meeting

GORTEC
Groupe Oncologie Radiothérapie Tête Et Cou
Radiotherapy oncology group for head & neck

A randomized trial of pembrolizumab versus cetuximab, concomitant with radiotherapy (RT) in locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN): safety results of the GORTEC 2015-01 PembroRad randomized trial

UNICANCER HEAD & NECK Group

Clinicaltrial.gov: NCT 02707588

Xu Shan Sun[1], Christian Sire[2], Yungan Tao[3], Laurent Martin[4], Marc Alfonsi[5], Jean Brisc Prevost[6], Michel Rives[7], Cedrik Lafond[8], Jean-Marc Touran[9], Julien Blou[10], Lionnel Geoffrois[11], Alexandre Coulie[12], Xavier Liem[13], Elodie Vauleon[14], Franck Drouet[15], Jean-François Romes[16], Gabriel Wekst[17], Laura Sinigaglia[17], Joel Guigay[18], Anne Auperin[3], Jean Bourhis[19]

[1]Rosington & Muffleford [2]Lorient [3]Villejuif [4]Le Mans [5]Avignon [6]Rouen [7]Toulouse [8]Le Mans [9]Poitiers [10]Clermont-Ferrand [11]Nancy [12]Amiens [13]Dijon [14]Rennes [15]Saint Nazaire [16]La Roche Sur Yon [17]Trier [18]Nice, France; [19]Lausanne, Switzerland

Corresponding author: jean.bourhis@gortec.fr

BACKGROUND

Based on the hypothesis of a potential synergistic effect of the anti-PD1 pembrolizumab when combined with RT, this new combination was tested in a randomized trial against the well established standards of care (ScC) cetuximab-RT in LA-SCCHN.

PATIENTS & METHODS

Randomization

R 1:1

- **Arm A:** cetuximab 400 mg/m² loading dose and 250 mg/m² weekly
- **Arm B:** Pembrolizumab 200 mg Q3W during RT

Stratification

- **N stage:** *N0-1 vs N2-3*
- **P16 status and tumor site**
  OPC positive vs negative or Non OPC

In both arms: IMRT (69-98 Gy in 33 fractions)

Main Inclusion criteria

- Patients unfit for receiving high dose cisplatin
- Non operated stage III-IVa-b
- SCC of oral cavity, oro/hypopharynx and larynx
- Non metastatic

Hypothesis

To detect a difference between arms of 60% to 80% in loco-regional control at 15 months (primary endpoint), inclusion of 66 patients per arm was required to achieve a power of at least 0.85 at 2-sided significance level of 0.20, with less than 15% unevaluable patients.

ACCRUAL

133 patients were randomized from May 2016 to October 2017 by 27 centers.

66 in the RT+ cetuximab (Arm A) and 67 in the RT-Pembrolizumab (Arm B)

RESULTS

Characteristics of the patients

N = 133 patients randomized, 85% males, Median age 65 years

Median pack years=40

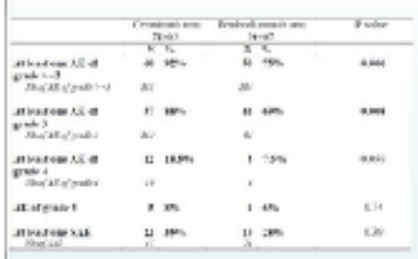
All characteristics well balanced between the two treatment arms

Treatment compliance

- 92% of pts received at least 33 fractions and 69.9 Gy in both arms
- 4 pts (3%) had anaphylactic reaction to cetuximab leading to definitive stop of cetuximab
- 74% pts received at least 7 administrations of cetuximab
- 87% pts received 3 administrations of pembrolizumab

SAFETY

The toxicity analysis was based on patients who received at least one administration of drug or underwent RT (N=133)



- The higher rate of AE grade >=3 in the cetuximab arm was mainly due to radiodermatitis, cutaneous rash and mucositis
- Dysthyroidism was more frequent in the Pembrolizumab arm than in the cetuximab arm (16% vs 6%, p=0.04)
- 4 pts had anaphylactic reaction to cetuximab
- 2 pts in the Pembrolizumab arm had unusual vascular adverse events:
  - *1 massive systemic arterial thrombosis*
  - *1 bilateral central retinal artery occlusion (leading to blindness)*
- 5 Deaths occured during treatment (2 in cetuximab arm, 3 in pembrolizumab arm) and 4 within 90 days after the end of treatment

CONCLUSION

- The toxicity profiles of *pembrolizumab + RT* & *cetuximab + RT* were different *(dysthyroidism vs mucosal & skin reactions)*
- Significantly more >= G3 in the cetuximab arm, essentially due to skin and mucosal reactions

2018 ASCO ANNUAL MEETING

Abs. #6018
Sun SX et al.
FASE 2
"PembroRAD"

PATIENTS & METHODS

Randomization

R 1:1

- **Arm A:** cetuximab 400 mg/m² loading dose and 250 mg/m² weekly
- **Arm B:** Pembrolizumab 200 mg Q3W during RT

Stratification

- **N stage:** *N0-1 vs N2-3*
- **P16 status and tumor site**

OPC positive vs negative or Non OPC

In both arms: IMRT (69.96 Gy in 33 fractions)

Main Inclusion criteria

- Patients unfit for receiving high dose cisplatin
- Non operated stage III-IVa-b
- SCC of oral cavity, oro/hypopharynx and larynx
- Non metastatic

Hypothesis

To detect a difference between arms of 60% to 80% in loco-regional control at 15 months (primary endpoint), inclusion of 66 patients per arm was required to achieve a power of at least 0.85 at 2-sided significance level of 0.20, with less than 15% unevaluable patients

ACCRUAL

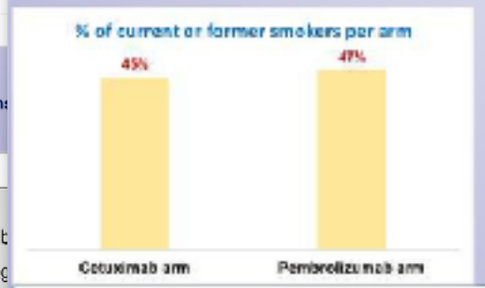
133 patients were randomized from May 2016 to October 2017 by 27 centers,

66 in the RT- cetuximab (Arm A) and 67 in the RT-Pembrolizumab (Arm B)

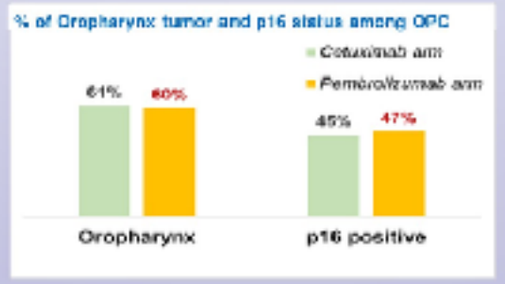
RESULTS

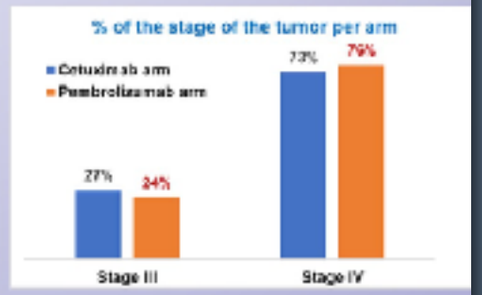
Characteristics of the patients

N = 133 patients randomized, 85% males, Median age 65 years



Median pack years=40





All characteristics well balanced between the two treatment arms

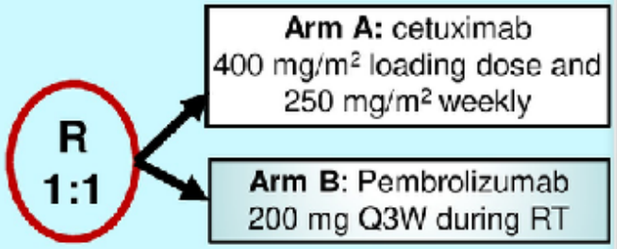
Treatment compliance

- **92% of pts** received at least 33 fractions and 69.9 Gy in both arms
- 4 pts (6%) had anaphylactic reaction to cetuximab leading to definitive stop of cetuximab
- **74% pts** received at least 7 administrations of cetuximab
- **87% pts** received 3 administrations of pembrolizumab

2018 ASCO ANNUAL MEETING

PATIENTS & METHODS

Randomization



Stratification

- **N stage:** *N0-1 vs N2-3*
- **P16 status and tumor site**
  OPC positive vs negative or Non OPC

In both arms: IMRT (69.96 Gy in 33 fractions)

Main Inclusion criteria

- Patients unfit for receiving high dose cisplatin
- Non operated stage III-IVa-b
- SCC of oral cavity, oro/hypopharynx and larynx
- Non metastatic

Hypothesis

To detect a difference between arms of 60% to 80% in loco-regional control at 15 months (primary endpoint), inclusion of 66 patients per arm was required to achieve a power of at least 0.85 at 2-sided significance level of 0.20, with less than 15% unevaluable patients

ACCRUAL

133 patients were randomized from May 2016 to October 2017 by 27 centers,

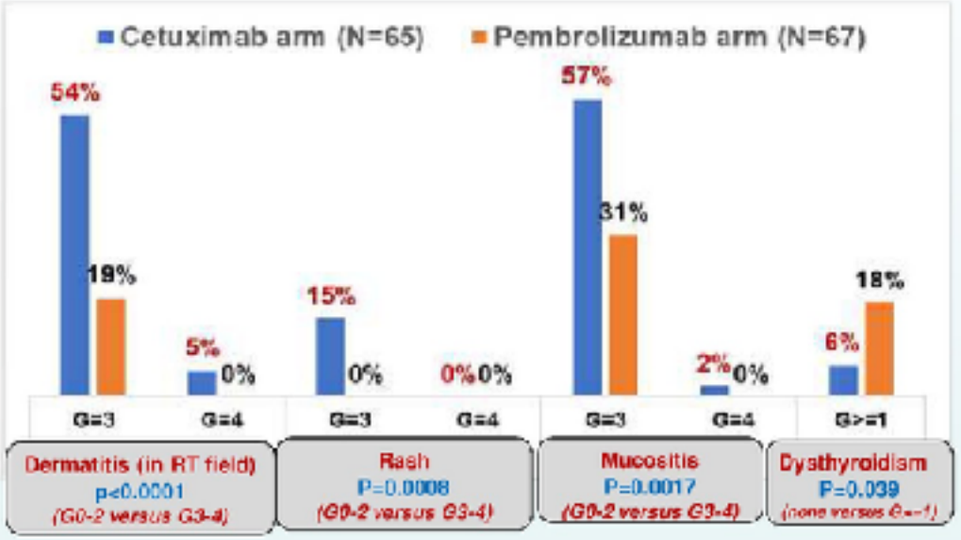
66 in the RT- cetuximab (Arm A) and 67 in the RT-Pembrolizumab (Arm B)

SAFETY

The toxicity analyses are based on pts who received at least one administration of drug or one fraction of RT (N=132)

	Cetuximab arm N=65		Pembrolizumab arm N=67		P value
	N	%	N	%	
At least one AE of grade >=3	**60**	**92%**	**50**	**75%**	**0.006**
Nb of AE of grade >=3	*185*		*104*		
At least one AE of grade 3	**57**	**88%**	**46**	**69%**	**0.008**
Nb of AE of grade 3	*164*		*94*		
At least one AE of grade 4	**12**	**18.5%**	**5**	**7.5%**	0.059
Nb of AE of grade 4	*19*		*6*		
AE of grade 5	**5**	**8%**	**4**	**6%**	0.74
At least one SAE	**23**	**35%**	**19**	**28%**	0.39
Nb of SAE	*47*		*24*		

Most frequent adverse events



- **The higher rate of AE grade >=3 in the cetuximab arm was mainly due to radiodermatitis, cutaneous rash and mucositis**
- **Dysthyroidism was more frequent in the Pembrolizumab arm than in the cetuximab arm (18% vs 6%, p=0.04)**
- **4 pts had anaphylactic reaction to cetuximab**
- **2 pts in the Pembrolizumab arm had unusual vascular adverse events:**
  - ***1 massive systemic arterial thrombosis***
  - ***1 bilateral central retinal artery occlusion (leading to blindness)***
- **5 Deaths occured during treatment** *(2 in cetuximab arm, 3 in pembrolizumab arm)* **and 4 within 90 days after the end of treatment**

umab arm had unusual vascular adverse events:
mic arterial thrombosis

mucosal & skin reactions)

>= G3 in the cetuximab arm, essentially due to skin and

2018 ASCO ANNUAL MEETING

DIFERENTE PERFIL DE TOXICIDAD (ALT. TIROIDEAS VS TOX. DE PIEL Y MUCOSAS
MAYOR TOXICIDAD G3 EN CTX+RT, PARTICULARMENTE MUCOCUTANEA

2018 ASCO ANNUAL MEETING

U.S. National Library of Medicine
ClinicalTrials.gov

Trial record 1 of 2 for: gortec 2017-01

Randomized Trial of Avelumab-cetuximab-radiotherapy Versus SOCs in LA SCCHN (REACH) [REACH]

ClinicalTrials.gov Identifier: NCT02955087

REACH

GORTEC

Avelumab-cetuximab-radiotherapy *versus* standards of care in locally advanced squamous cell carcinoma of the Head and Neck: Safety phase of the randomized **phase III trial GORTEC 2017-01 REACH**

Y. Tao[1], A. Auperin[1], XS. Sun[2], C. Sire[3], L. Martin[4], G. Bera[5], A. Coutte[6], J. Miroir[6], C. Lafond[7], N. Colin-Batailhou[8], A. Maillard[7], L. Gibel[8], C. Michel[8], J. Guigay[9], J. Bourhis[10#]

[1]Gustave Roussy, France, [2]CHRU J. Minjoz, France, [3]CH Bretagne Sud, France, [4]Centre G. Le Conquérant, France, [5]CHU Amiens Sud, France, [6]Centre J. Perrin, France, [7]Clinique V. Hugo, France, [8]GORTEC, France, [9]Centre Antoine Lacassagne, France, [10]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

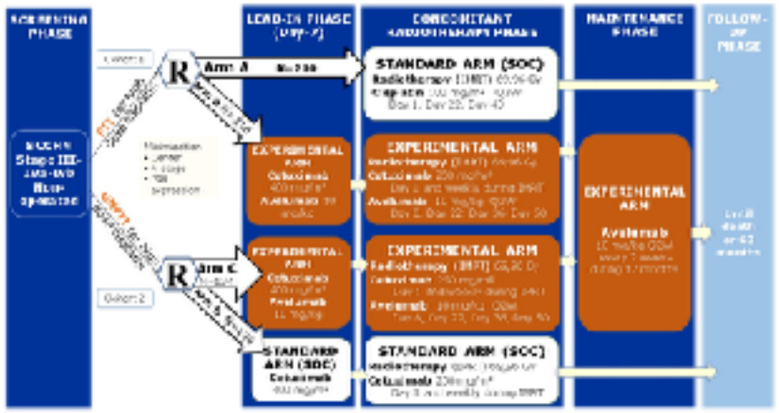
corresponding author: jean-bourhis@gortec.fr

BACKGROUND

Based on the hypothesis of a synergistic effect of the anti PD-L1 avelumab when combined with cetuximab and radiotherapy, this new combination is tested in a large scale randomized trial against 2 well established standards of care (SoC) in locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN).

DESIGN

This randomized multicenter phase III trial comprises 2 cohorts of patients deemed fit (Cohort 1, n=420) to receive high dose cisplatin (CDDP) or unfit to receive CDDP (Cohort 2, n=200). The SoC is IMRT (69.96 Gy, 33 fractions) combined with CDDP (100 mg/m², Q3W) in cohort 1 or with cetuximab in cohort 2 (400 mg/m² Day-7 and 250 mg/m² weekly). In both cohorts, experimental arms are IMRT concomitant with cetuximab and avelumab (10 mg/kg Day-7 and every 2 weeks) followed by avelumab 10 mg/kg bi-monthly for 12 months.



OBJECTIVE

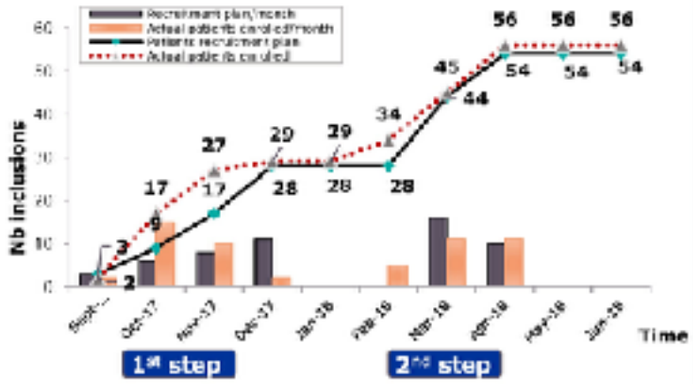
The primary objective is to test whether the combination avelumab-cetuximab-radiotherapy is superior to SoC for **progression-free survival** in each cohort.

METHODS

A run-in safety phase was performed to assess feasibility and tolerability/safety of the experimental combination. Monitoring of grade ≥ 4 acute adverse events in both experimental arms was planned with null and alternative hypotheses of 15 and 35%. Overall 1-sided α error of 0.10, Lan-DeMets alpha spending function, 95% power. **Safety phase data were reviewed by an Independent Data Safety Monitoring Committee (IDSMC).**

RESULTS

Safety Phase



This safety phase was approved by the IDSMC and planned to be run on the first 41 treated patients in the experimental arms after 8 weeks follow-up.

- **1st step** (14 patients): Stopping rule in case of ≥ 7 patients with grade ≥ 4 Adverse Event (AE)
- **2nd step** (27 patients): Stopping rule in case of ≥ 8 patients with grade ≥ 4 AE
- **3rd step** (41 patients): Stopping rule in case of ≥ 10 patients with grade ≥ 4 AE

Results of the 1st step

Between September and December 2017, 29 patients Stage III/IV SCCHN were randomized including 14 in the experimental arms. The 1st step safety analysis was presented to the IDSMC early in 2018.

All patients received the entire radiotherapy as planned. Eight out of the 14 patients received the full concomitant systemic regimen as planned: 3 patients received 7 cetuximab doses, 2 received 5 doses of cetuximab and 3 of avelumab, one received 3 doses of cetuximab and 2 of avelumab. Three patients in the 1st step (21.4%) developed grade 4 AE according to NCI CTCAE v4.03: one dermatitis, one lymphopenia, one oral mucositis.

Results of the 2nd step

Between February and April 2018, 27 additional patients w
28 in experimental arms).

CONCLUSION

- The safety stopping rule was not crossed
- The IDSMC gave approval to continue the trial
- Safety data of the 2nd step are currently collected and will soon be reviewed

Clinical Trial.gov ID: NCT02955087
Abstract # 6076

Abs. #6076
FASE 3
"REACH"

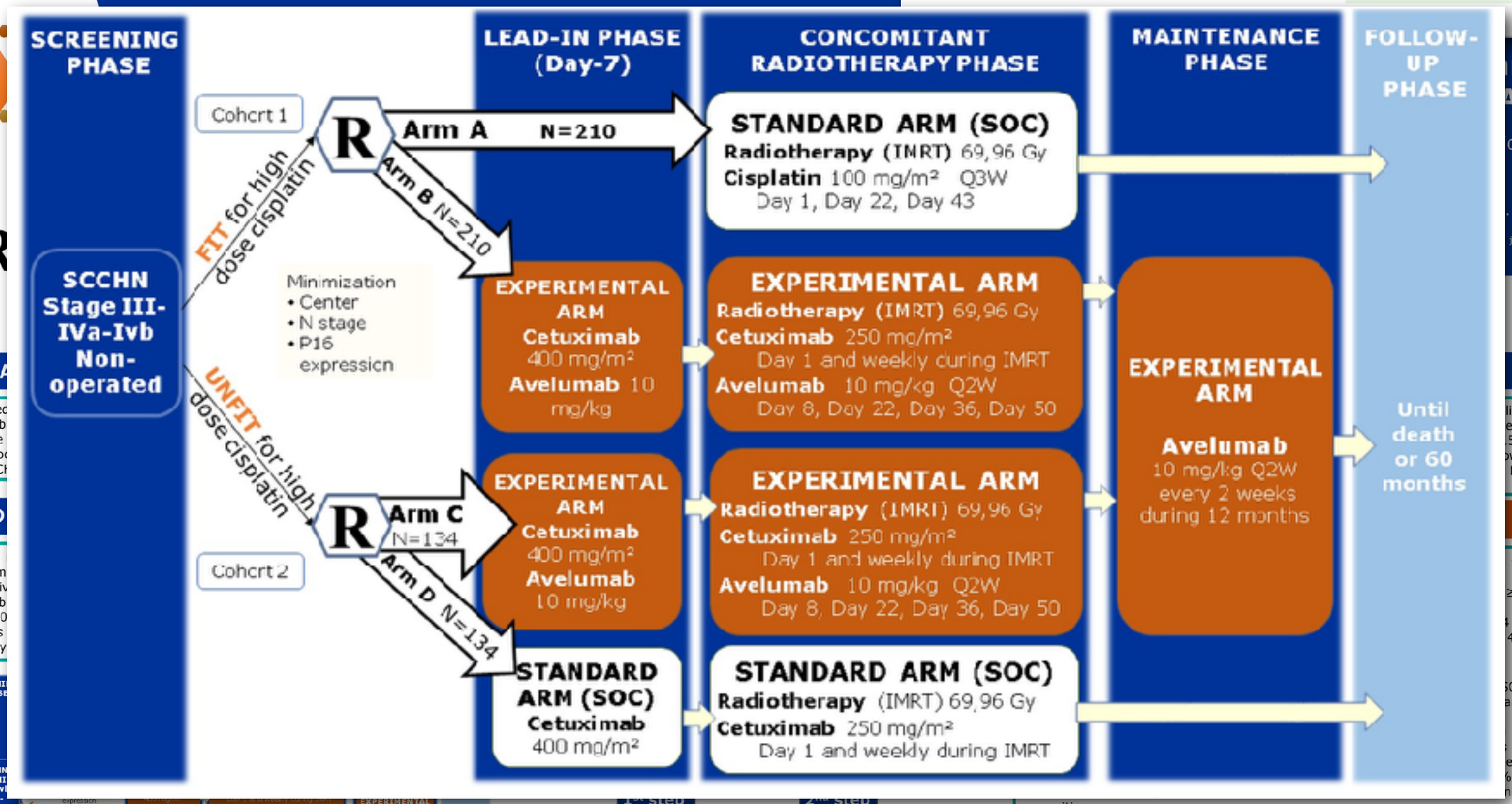
2018 ASCO ANNUAL MEETING

ClinicalTrials.gov

Randomized Trial of Avelumab-cetuximab-radiotherapy Versus SOCs in LA SCCHN (REACH) [REACH]

REACH

GORTEC



CONCLUSION

- The safety stopping rule was not crossed
- The IDSMC gave approval to continue the trial
- Safety data of the 2nd step are currently collected and will soon be reviewed

Results of the 2nd step

Between February and April 2018, 27 additional patients were enrolled (total 56 patients, 28 in experimental arms).

Clinical Trial.gov ID: NCT02999087
Abstract # 6076

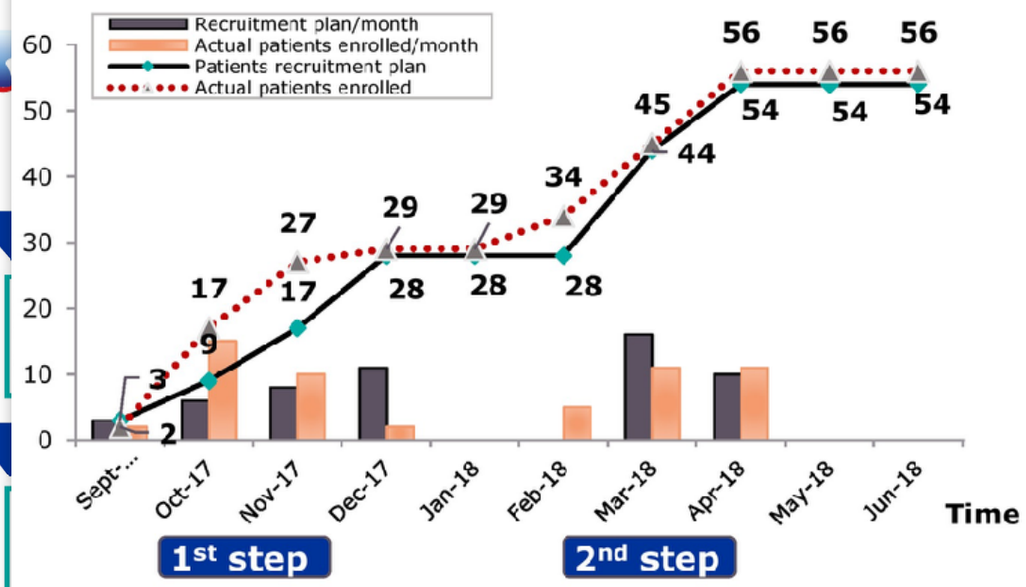
2018 ASCO ANNUAL MEETING

REACH

Avelumab-cetuximab-radiotherapy *versus* standards of care in locally advanced squamous cell carcinoma of the Head and Neck: Safety phase of the randomized **phase III trial GORTEC 2017-01 REACH**

RESULTS

Safety Phase



This safety phase was approved by the IDSMC and planned to be run on the first 41 treated patients in the experimental arms after 8 weeks follow-up.

- **1st step** (14 patients): Stopping rule in case of ≥ 7 patients with grade ≥ 4 Adverse Event (AE)
- **2nd step** (27 patients): Stopping rule in case of ≥ 8 patients with grade ≥ 4 AE
- **3rd step** (41 patients): Stopping rule in case of ≥ 10 patients with grade ≥ 4 AE

Results of the 1st step

Between September and December 2017, 29 patients Stage III/IV SCCHN were randomized including 14 in the experimental arms. The 1st step safety analysis was presented to the IDSMC early in 2018.

All patients received the entire radiotherapy as planned. Eight out of the 14 patients received the full concomitant systemic regimen as planned: 3 patients received 7 cetuximab doses, 2 received 5 doses of cetuximab and 3 of avelumab, one received 3 doses of cetuximab and 2 of avelumab. Three patients in the 1st step (21.4%) developed grade 4 AE according to NCI CTCAE v4.03: one dermatitis, one lymphopenia, one oral mucositis.

Results of the 2nd step

Between February and April 2018, 27 additional patients were enrolled (total 56 patients, 28 in experimental arms).

CONCLUSION

- The safety stopping rule was not crossed
- The IDSMC gave approval to continue the trial
- Safety data of the 2nd step are currently collected and will soon be reviewed

Clinical Trial.gov ID: NCT02999087
Abstract # 6076

CONCLUSION

- The safety stopping rule was not crossed
- The IDSMC gave approval to continue the trial
- Safety data of the 2nd step are currently collected and will soon be reviewed

Results of the 2nd step

Between February and April 2018, 27 additional patients were enrolled (total 56 patients, 28 in experimental arms).

Clinical Trial.gov ID: NCT02999087
Abstract # 6076

2018 ASCO ANNUAL MEETING

FASE 2

Preliminary Toxicity Data from the Combination of Pembrolizumab and Definitive-dose radiotherapy for locally advanced head and Neck Cancer with contraindication to cisplatin therapy

Jared Weiss, Jessica Bauman, Allison Mary Deal, Sid Sheth, Bhishamjit S. Chera, Collette Shen, Chris Hilliard, Tanguy Seiwert, Ranee Mehra, Juneko E. Grilley-Olson

Background

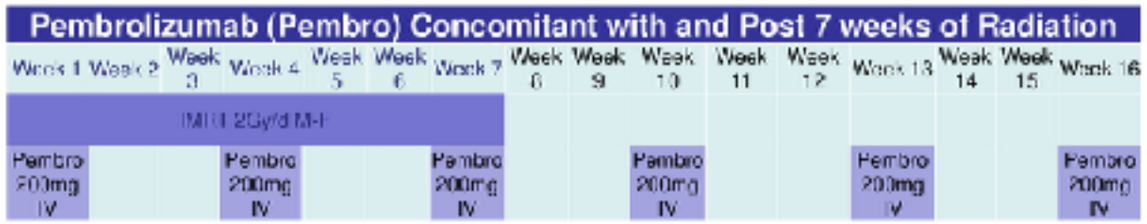
- Bolus cisplatin in combination with radiation therapy is a standard of care for the treatment of locally advanced SCCHN, but contraindications such as hearing loss, tinnitus, inadequate renal function or neuropathy are common.
- Pembrolizumab is a PD1 inhibitor with FDA approval for the treatment of platinum-refractory recurrent SCCHN.

Sample

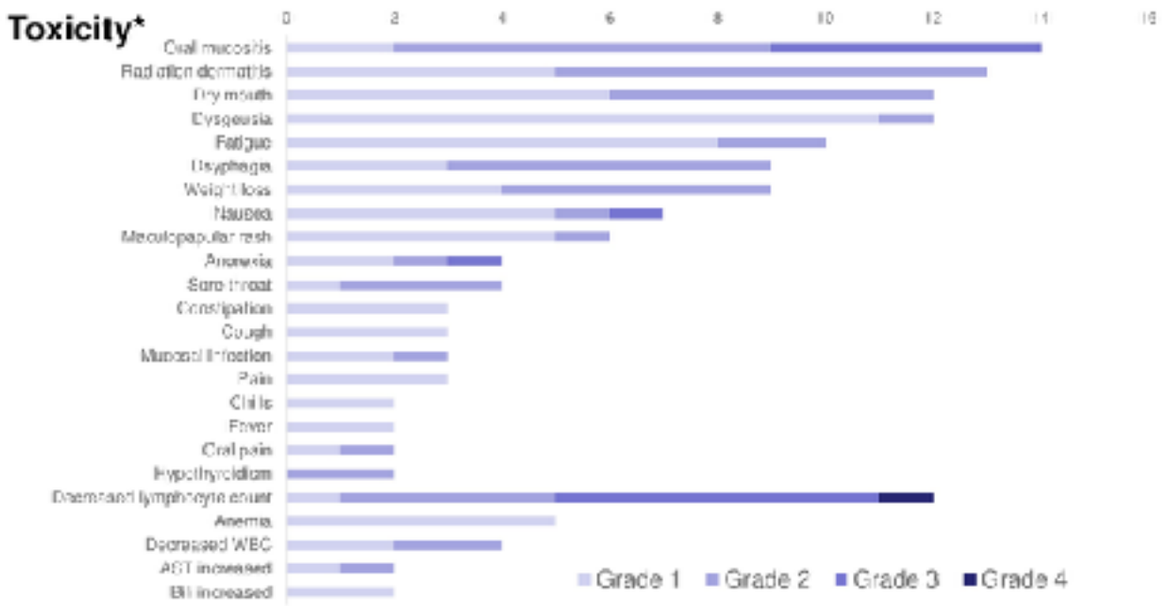
	# (of 16)			# (of 16)
Demographics			Site	
Male	15		Oral Cavity	1
White	13		Oropharynx	9
American Indian	1		Larynx	1
Unknown	2		Hypopharynx	1
Age	62.5 (median)		Supraglottic larynx	2
			Unknown	2
Smoking Status				
Never smoker	1		Reason for inclusion	
Former smoker	11		Abnl hearing	5
Current smoker	1		Abnl renal fcn	3
			CM	1
p16 status			Neuropathy	2
p16 +	8		Tinnitus	5
P16 -	6			
P16 Unknown	2			

	N0	N1	N2a	N2b	N2c	N3
T1	0	1	0	1	0	1
T2	0	1	0	2	2	0
T3	2	0	0	1	1	1
T4a	0	0	0	0	1	0
Tx	0	0	0	0	0	2

Pembrolizumab (Pembro) Concomitant with and Post 7 weeks of Radiation



Toxicity*



*any occurring at least twice, any attribution)

Methods

Inclusion

- AJCC v7 stage III-IVA SCCHN
- Ineligible for bolus CDDP for one of the following reasons:
  - Renal dysfunction
  - Abnormal hearing
  - Tinnitus
  - Neuropathy
  - Diabetes
  - Oncologist-certified ineligibility per SOC (must specify reason)
  - Patient refusal to take CDDP

Statistics

- Primary endpoint: mPFS 18 months from null of 10 months. 1 sided alpha 0.1, 80% power.
- Data presented here: All patients who have completed treatment have 30 days follow up from last pembrolizumab

Treatment Failures

- T2N2c HPV- SqCC Uvula. H/O IDDM, HLD, HTN and 70 pack year smoking history. Persistent dz post chemoradiotherapy; declined salvage surgery.
- T4AN2c HPV- BOT. H/O colon CA s/p Sx, chemo. Persistent dz post chemoradiotherapy; declined salvage surgery.
- T2N2b HPV- hypopharynx. H/O hearing loss, HTN, COPD, AF, GGA and gout. Solitary lung met 6 months post treatment, treated with SRS.

Other Data

- All patients completed 70Gy XRT
- 10 patients completed 6 cycles pembrolizumab and 1 patient completed 5.
- Current accrual at 26/20.

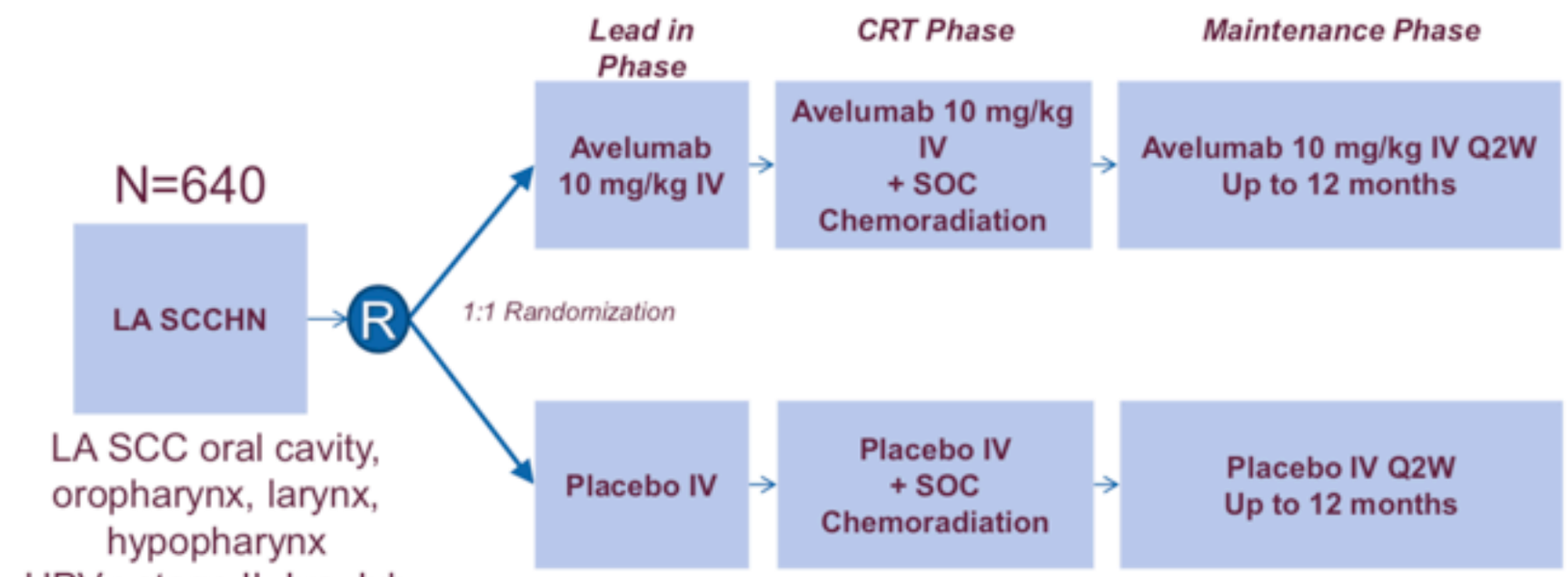
Conclusions

- Early data suggest limited toxicity and high feasibility of pembrolizumab combined with radiotherapy
- Treatment failure has been limited, however, even in the setting of a population with a high risk of failure given their high anatomic and biologic risk.
- Additional endpoints will include PFS, OS and correlative studies.

Funding for this study (NCT02508558) was provided by Merck. We thank the patients who participated and their families.

JAVELIN Head and Neck 100 (B9991016)

Randomized, double blind Phase III trial NCT02952586



LA SCC oral cavity, oropharynx, larynx, hypopharynx
HPV-; stage II, Iva, Ivb
HPV+: T4 or N2c (AJCC 7) or N3
ECOG PS=0 or 1
No prior therapy

Primary Endpoint: PFS by investigator per modified RECIST v1.1

Stratification Factors

- **T stage (<T4 vs T4)**
- **N stage (N0/N1/2b vs N2c/N3)**
- **HPV (+ vs -) as measured by p16 IHC**

UC Sa
MOORES CA

MUNICH 2018 ESMO congress

1126TiP

Nivolumab and Ipilimumab in Combination with Radiotherapy in Patients with Locally Advanced Head and Neck Cancer

Sidney Kimmel Cancer Center
Jefferson Health | NCI – designated

Jennifer M Johnson, MD PhD[1], Voichita Bar Ad, MD[2], Emily Lorber, CRNP[1], Adam Luginbuhl, MD[3], Joseph Curry, MD[3], David Cognetti, MD[3], Scott Keith, PhD[1], Rita Axelrod, MD[1], Ralph Zinner, MD[1], Ulrich Rodeck, MD PhD[4], Larry Harshyne, PhD[5], Athanassios Argiris, MD PhD[1]

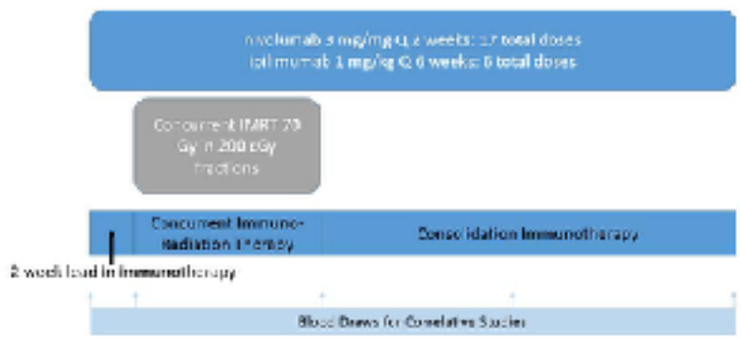
[1]Department of Medical Oncology [2]Department of Radiation Oncology [3]Department of Otolaryngology [4]Department of Dermatology and Cutaneous Biology [5]Department of Neurosurgery Thomas Jefferson University

#forefront

Background

- Definitive treatment of locally advanced squamous cell carcinoma of the head and neck often incorporates concurrent chemoradiotherapy.
- Platinum agents have been the backbone of systemic therapy in combined modality approaches. However, the addition of cisplatin to radiotherapy results in a modest survival benefit and is associated with multiple acute and late toxicities.
- Nivolumab (nivo), a fully human anti-programmed cell death-1 (PD-1) monoclonal antibody (mAb), has demonstrated a survival advantage when compared with standard treatment in patients with platinum-refractory recurrent or metastatic SCCHN[1].
- Combination of nivo with the CTLA-4 directed mAb ipilimumab (ipi) has yielded improvements in antitumor activity in melanoma and is under investigation in multiple other solid tumor types including SCCHN in the CheckMate 651 Trial NCT02741570[2].
- The combination of RT and immunotherapy leads to synergistic effects in the laboratory and has promise in early phase clinical trials[3-6].
- This clinical trial combines immunotherapy and RT to build upon these observations.

Trial Design



Statistical Considerations

- Goal Enrollment: 24 patients
- Designed in 2 stages with safety stopping rules.
- First stage = 12 patients. Enrollment was suspended until all 12 patients completed radiotherapy and toxicities assessed 2 weeks after radiotherapy completion.
- The grade 3-4 toxicity rate for nivolumab/ipilimumab combination therapy (without radiotherapy) is about 35% and has been well-characterized in multiple clinical trials.
- The toxicity of RT plus systemic therapy (cetuximab or cisplatin) is also well known (acceptable grade 3/4 mucositis about 60%, grade 3/4 dermatitis about 25%).
- For the stopping rules, we will only consider grade 4-5 in-field toxicities DURING radiation treatment and the two week period after the completion of radiation treatment.
- A true combined toxicity rate of 0.25 with clearly attributable 2 grade 4 mucositis, grade 4 dermatitis, or other grade 4 in-field events (eg bleeding, edema), any grade 5 toxicity that is attributable to treatment, or excessive toxicity leading to unacceptable interruption (e.g., >3 consecutive days) of or inability to complete radiation therapy will be considered unacceptable for this new regimen.

Inclusion Criteria

Disease:

- Newly Diagnosed and Untreated AJCC7th Edition Stage IVA-B SCCHN
- Oral Cavity
- Hypopharynx
- Larynx
- Oropharynx p16
- Oropharynx p16+ must have T4a, T4b, N2c, or N3 disease
- Nasopharyngeal is excluded

Patient:

- ECOG PS 0-1
- Adequate tumor available for PD-L1 testing
- Adequate Organ Function as determined by EBC, ANC, platelets, hemoglobin, total bilirubin, AST, ALT, and creatinine
- HIV, Hepatitis B, Hepatitis C negative
- No history of autoimmune disease
- No concurrent malignancies

Funding

Funding has been provided by Bristol Myers Squibb

NCT03162731

Objectives / Endpoints

Primary Objective:

- To investigate the safety of the combination of nivolumab and ipilimumab with radiation treatment for definitive management of patients with locally advanced squamous cell carcinoma of the head and neck.

Secondary Objectives:

- To estimate 1 year PFS in all patients treated.
- To assess overall response rate.
- To assess overall survival.

Exploratory Objectives:

- To explore whether PD-L1 expression is associated with treatment response
- To explore whether there is a net change in the Th1/Th2 ratio (IFN-g, IL-4, IL10) or cell subset frequencies (M2 monocytes, myeloid-derived suppressor cells) within a patient's peripheral blood either at baseline or in response to treatment is associated with treatment response
- To explore whether exosomes or other immune related serum biomarkers change after combination therapy

- We have documented extensive immune bias in the peripheral blood of astrocytoma patients and observed similar results in preliminary studies from HNSCC patients.
- Our novel in vitro assay include co-culture of human monocytes with various patient samples investigate polarization capacity.
- Astrocytoma derived exosomes and soluble factors can bias normal monocytes towards M2. HNSCC patient sera can also bias monocytes towards M2.
- PD-L1 is preferentially expressed on M2 monocytes and macrophages, making them targets of nivolumab.
- We will examine the ability of nivo and ipi to alter immune bias and look for correlations with treatment outcomes.

Status

- Stage 1 is complete with 12 out of 24 total patients accrued.
- All 12 stage 1 patients completed concurrent immuno radiation therapy.
- The trial re-opened to accrual on 9/25/2018.

Contacts

Jennifer.M.Johnson@Jefferson.edu

Athanassios.Argiris@Jefferson.edu

References

1. Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016 10;375(19):1856-1867.
2. Argiris A, Gillison M, Ferris RL, et al. A randomized, open-label, phase 3 study of nivolumab in combination with ipilimumab vs extreme regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as first-line therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: CheckMate 651. Annals of Oncology 2016 27(6): tdw070.
3. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: mechanisms and strategies. Science 2015 348(6230): 56-61.
4. Sun XS, Liu Q, Tao Y, et al. A phase II multicenter trial of pembrolizumab versus cetuximab, concomitant with radiotherapy (RT) in locally advanced LA squamous cell carcinoma of the head and neck (SCCHN): First results of the GORTEC 2015-01 "PembroRad" trial. J Clin Oncol. 2018 36:6008-6018.
5. Gillison M, Ferris RL, Zhang Q, et al. Safety Evaluations of Nivolumab (Anti-PD1) added to chemoradiotherapy platforms for patients with intermediate and high-risk locally-regionally advanced head and neck squamous cell carcinoma. 2018 in Multidisciplinary Head and Neck Cancers Symposium (Scottsdale, Arizona)

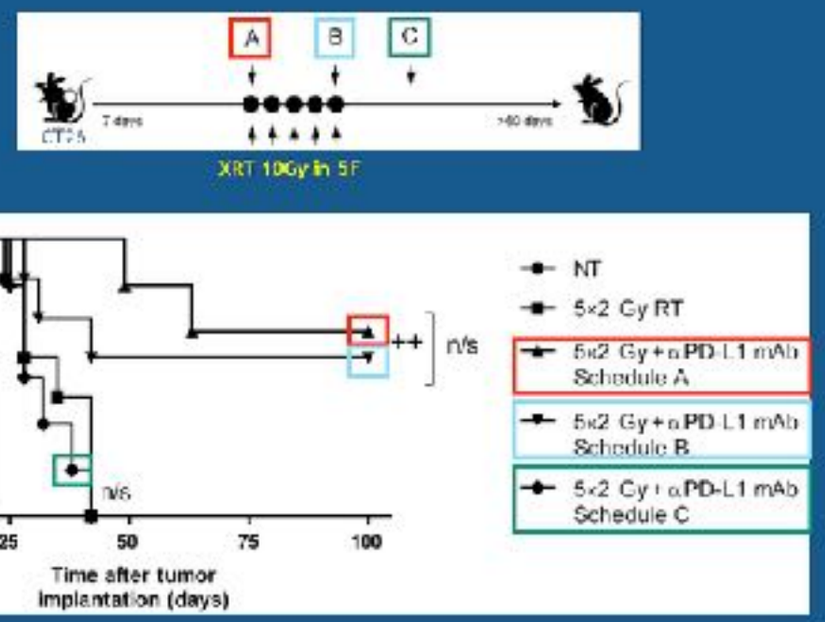
Phase II/III R trials with standard XRT + IO in LA HNSCC

Study	Ph	Population	Arms	Adjuvant
CA2099TM	III	N=1046 (2 cohorts, placebo controlled) CDDP unfit, intermediate/high risk	XRT + CDDP w/wo Nivolumab XRT + Nivolumab vs. Cetuximab	Nivo vs placebo Nivo vs placebo
KEYNOTE-412	III	N=780 Intermediated or high risk	XRT + CDDP + Pembrolizumab XRT + CDDP + Placebo	Pembrolizumab Placebo
REACH*	III	N=688 Stage III/Iva LA HNSCC	XRT + Avelumab + Cetuximab XRT + CDDP or Cetuximab	Avelumab
JAVELIN HN100	III	N=640 Intermediate or high risk	XRT + Avelumab + CDDP XRT + CDDP + Placebo	Avelumab Placebo
NRG-HN004	II/III	N=533 CDDP unfit, intermediate/high risk	XRT + Durvalumab XRT + Cetuximab	Durvalumab
PembroRad*	II	N=133 Stage III/IV LA HNSCC, CDDP unfit	XRT + Pembrolizumab XRT + Cetuximab	
KEYCHAIN	II	N=122 P16+, High or intermediate-risk	XRT + Pembrolizumab XRT + CDDP	Pembrolizumab
UPC 15-132	II	N=44 Intermediate or high risk	XRT + CDDP XRT + CDDP + Pembrolizumab	Pembrolizumab Pembrolizumab

Phase (NCT No.)	N	Line	Treatment	Estimated Study Completion
Phase III Javelin 100 (NCT02952586)	640	LA-HNSCC (Neoadjuvant/ concurrent-adjuvant)	CRT +/- avelumab vs placebo	2022

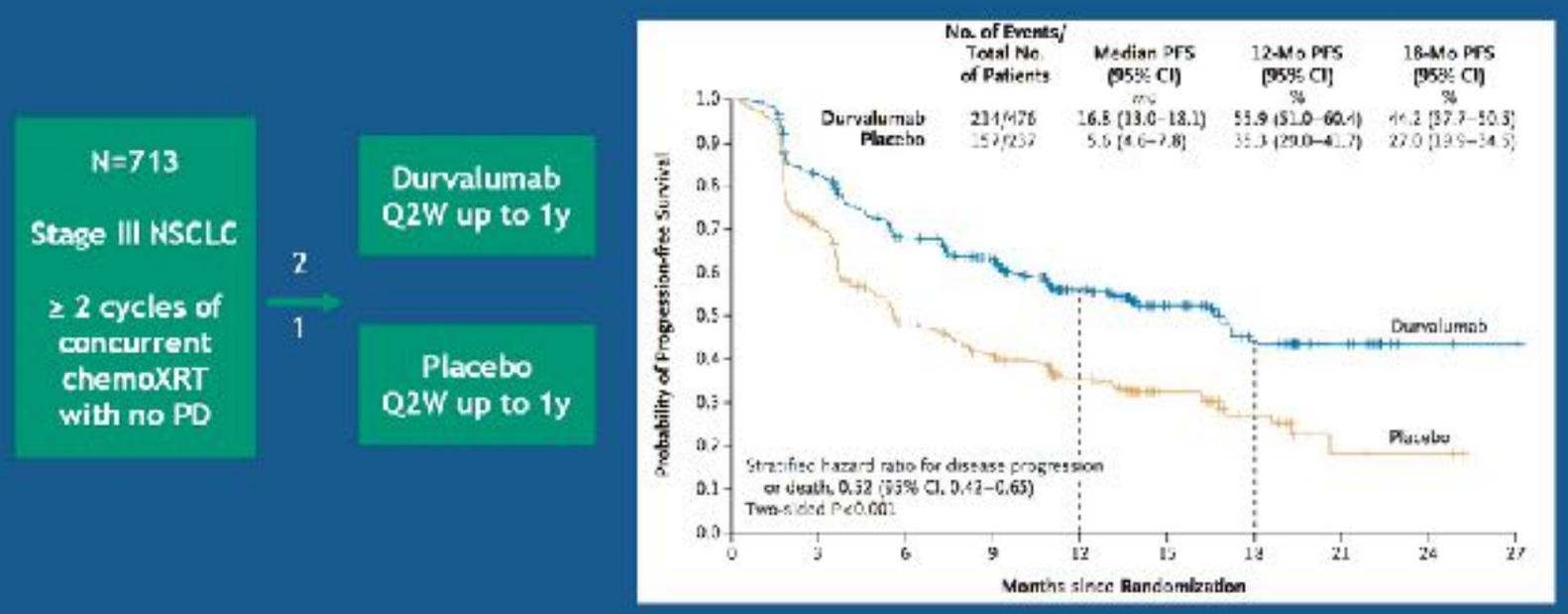
INMUNOTERAPIA ADYUVANTE

What is the best "timing"? Concurrent vs adjuvant



- Modelos murinos en cáncer de colon.
- RT 10 Gy (5d)
- Anti- PD-L1 en tres momentos: A en d1, B en d5, C en d12.
- A y B (concomitante) mayor supervivencia.

What is the best "timing"? Concurrent vs adjuvant



Datos de fase III PACIFIC en NSCLC (CRT->Durva)

What is the best "timing"? Concurrent vs adjuvant

UPCI 15-132

Stage III/IVb intermediate/high-risk oral cavity, oropharynx, hypopharynx, Larynx, unknown primary

ECOG 0-1

Randomization

CRT 7 wks

Sequential 24 wks

IMRT + cisplatin → Pembrolizumab

Pembrolizumab → 1 wk → IMRT + cisplatin

Stratification: p16 and nodal status

Primary objectives:
1y PFS,
1y failure rate
Toxicity

The concurrent versus adjuvant strategy is being tested in HNSCC.

PI: Ferris R, Bauman J

Adjuvant anti-PD-L1 in LA HNSCC

IMvoke010

PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED

- LA HNSCC (N=400)
- Oral cavity, larynx, hypopharynx, HPV- OPSCC
  - -T3-T4a, N2-N3
- HPV+ OPSCC
  - -T1-2, N3, ≥ 10 ppy
  - -T3-4, N3, regardless ppy
- completed definitive local therapy (sx alone excluded)
- no PD 10-12 wks

R

Atezolizumab Q3W x 1 year

Placebo Q3W x 1 year

Co-primary objectives:
- EFS and OS

MUNICH 2018 ESMO congress

Poster #1117TiP
Abstract #1012

IMvoke010: Randomized Phase III Study of Atezolizumab as Adjuvant Monotherapy After Definitive Therapy of Squamous Cell Carcinoma of the Head and Neck

Robert I. Haddad,[1] Deborah J. Wong,[2] Ye Guo,[3] Jerome Fayette,[4] Ezra E.W. Cohen,[5] Matthew Kowgier,[6] Alan Sandler,[7] Christina Matheny,[7] Fairooz Kabbinavar,[7] David Raben[8]

[1]Dana-Farber Cancer Institute, Boston, MA, United States; [2]University of California Los Angeles, Los Angeles, CA, United States; [3]Tongji University East Hospital, Shanghai, China; [4]Centre Léon Bérard, Lyon, France; [5]University of California San Diego, La Jolla, CA, United States; [6]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [7]Genentech, Inc., South San Francisco, CA, United States; [8]University of Colorado, Denver, CO, United States

BACKGROUND

Current treatments for locally advanced squamous cell carcinoma of the head and neck (SCCHN)

- > 90% of all tumours in the head and neck region are squamous cell carcinomas
- The majority of patients with squamous cell carcinoma of the head and neck (SCCHN) present with locally advanced disease (stage III–IVB), which is associated with poor survival outcomes[1]
- Definitive local therapy for the treatment of locally advanced SCCHN can include combinations of surgery, radiation therapy and chemotherapy to optimise the chances for long-term disease control and improved survival
  - After completing definitive local therapy, patients are monitored for local recurrence and/or distant metastases as standard of care
  - To date, the use of additional maintenance or adjuvant chemotherapy in patients who have residual disease and/or high-risk features after completion of definitive local therapy has not demonstrated any benefit

Cancer immunotherapy in SCCHN: PD-L1 and atezolizumab

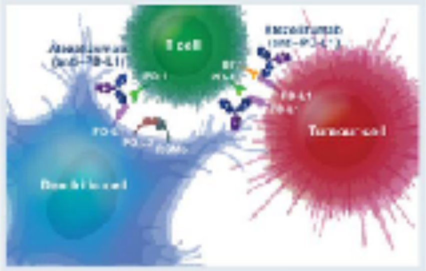
Programmed death-ligand 1 (PD-L1) expression in SCCHN

- SCCHN evades host cellular immune response through upregulation of T-cell suppressive ligands, including PD-L1
  - On activated T cells, PD-L1 interacts with programmed death-1 (PD-1) and B7.1 (CD80) and prevents killing of tumour cells
  - Nonclinical data suggest that PD-L1 expression is high in the oropharyngeal area and in both human papillomavirus (HPV)-positive and HPV-negative SCCHN
- The recent approvals of 2 anti-PD-1 agents in SCCHN, nivolumab (approved in the EU and US) and pembrolizumab (approved in the US only), highlight the efficacy of targeting PD-L1/PD-1 signalling in this disease

Atezolizumab

- Atezolizumab is an anti-PD-L1 monoclonal antibody that selectively inhibits PD-L1 from binding to its receptors PD-1 and B7.1 (Figure 1)
  - By blocking the interactions of PD-L1 with its receptors PD-1 and B7.1 while leaving the PD-L2/PD-1 interaction intact—potentially preserving peripheral immune homeostasis—atezolizumab can reinvigorate suppressed T cells to kill cancer cells
  - Single-agent atezolizumab is approved for metastatic urothelial carcinoma and non-small cell lung cancer (NSCLC) in several treatment settings

Figure 1. Atezolizumab Inhibits PD-L1 in the Tumour Microenvironment



Rationale for studying atezolizumab in SCCHN

- Targeting the PD-L1/PD-1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have experienced failure of standard-of-care therapies
- Efficacy results from a cohort of patients with recurrent/metastatic SCCHN in the Phase I PCD4989g study suggest that single-agent atezolizumab offers a potential clinical benefit
  - In a heavily pre-treated cohort of patients with SCCHN, atezolizumab demonstrated promising clinical activity, with encouraging response and long-term survival data
    - Objective response rate was 22% (n = 6 of 32 [partial responses]) and median duration of response was 7.4 months in all patients
    - Median progression-free survival and overall survival (OS) were 2.6 and 6.0 months in all patients, respectively
    - One-, 2- and 3-year OS rates were 38%, 21% and 12% in all patients, respectively
  - Response with atezolizumab was observed independently of PD-L1 expression or HPV status in patients with advanced SCCHN
- Given the evidence of the clinical activity of atezolizumab in advanced and metastatic SCCHN, atezolizumab offers the potential for clinical benefit in patients with SCCHN in the adjuvant setting

CLINICAL TRIAL DESIGN

- IMvoke010 is a Phase III, global, double-blind, placebo-controlled study of atezolizumab as adjuvant therapy in patients with locally advanced SCCHN who are at high risk for disease recurrence or progression after completing definitive local therapy
- The study design for IMvoke010 is shown in Figure 2
- Key inclusion and exclusion criteria are shown in Table 1

Figure 2. IMvoke010 Study Design

Q3W, every 3 weeks; R, randomisation; SCCHN, squamous cell carcinoma of the head and neck.

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Histologically or cytologically confirmed SCCHN that is locally advanced per the AJCC 8th Edition Cancer Staging Manual (stage III HPV-positive oropharyngeal carcinoma or stage IVA or IVB HPV-negative tumour involving the oral cavity, oropharynx, larynx, or hypopharynx)	Received surgery alone or radiotherapy alone as definitive local therapy, or received prior neoadjuvant treatment or any systemic anti-cancer therapy without definitive local therapy
HPV status as determined locally by p16 immunohistochemistry, in situ hybridisation, or polymerase chain reaction–based assay	Squamous cell carcinoma of the nasopharynx
Completed definitive local curative therapy and have scans confirming CR, PR or SD after completion of definitive local therapy	Evidence of disease progression or metastatic disease during or following definitive local therapy
Absence of metastatic disease	History of autoimmune disease
≥ 18 years of age	Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
ECOG PS 0 or 1	

AJCC, American Joint Committee on Cancer; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Study objectives

- To evaluate the efficacy of atezolizumab compared with placebo
- Co-primary endpoints:
  - Independent review facility (IRF)-assessed event-free survival (EFS) and OS
- Secondary endpoints:
  - Investigator-assessed EFS, IRF-assessed and investigator-assessed EFS and OS rates at specific time points, and patient-reported outcomes
- Key additional and exploratory outcome measures: pharmacokinetics, immunogenicity, biomarker studies and patient-reported outcomes
- To evaluate the safety and tolerability of atezolizumab

ENROLMENT

- Approximately 400 patients will be enrolled in 18 countries

Figure 3. Enrolment Sites

- Australia
- Brazil
- Canada
- China
- France
- Germany
- India
- Italy
- Poland
- Republic of Korea
- Russian Federation
- South Africa
- Spain
- Taiwan
- Thailand
- Turkey
- United Kingdom
- United States

FURTHER INFORMATION

- For more information on IMvoke010: https://clinicaltrials.gov/ct2/show/NCT03452137

REFERENCES

1. Sanderson RJ, et al. Br Med J. 2002;325:822-827.
2. Adelstein DJ, et al. J Clin Oncol. 2003;21:92-98.
3. [illegible]
4. [illegible]
5. [illegible]
6. [illegible]
7. [illegible]
8. OPDIVO (nivolumab) [summary of product characteristics]. Bristol-Myers Squibb Pharma EEIG: Uxbridge, UK; 2015.
9. OPDIVO (nivolumab) [prescribing information]. Bristol-Myers Squibb Company: Princeton, NJ; 2015.
10. [illegible]
11. KEYTRUDA (pembrolizumab) [prescribing information]. Merck & Co., Inc. Whitehouse Station, NJ; 2017.
12. [illegible]
13. Herbst RS, et al. Nature. 2014;515:563-567.
14. Chen DS, et al. Clin Cancer Res. 2012;18:6580-6587.
15. TECENTRIQ (atezolizumab) [prescribing information]. Genentech USA, Inc.: South San Francisco, CA; 2016.
16. TECENTRIQ (atezolizumab) [summary of product characteristics]. Roche Registration GmbH: Grenzach-Wyhlen, Germany; 2017.
17. Chen DS, Mellman I. Immunity. 2013;39:1-10.
18. [illegible]

ACKNOWLEDGEMENTS

- The patients and their families
- The investigators and clinical study sites
- This study is sponsored by F. Hoffmann-La Roche, Ltd
- Medical writing/editorial support for this poster was provided by Jonathan Lee, PhD, of Health Interactions and funded by F. Hoffmann-La Roche

Phase II Multi-site Investigation of Neoadjuvant Pembrolizumab and Adjuvant Concurrent Radiation and Pembrolizumab with or without Cisplatin in Resected Head and Neck Squamous Cell Carcinoma

University of CINCINNATI

Trisha M. Wise-Draper[1], Matthew O. Old[2], Francis P. Worden[3], Paul E. O'Brien[4], Ezra E.W. Cohen[5], Neal Dunlap[6], Michelle L. Mierzwa[3], Keith Casper[3], Sarah Palackdharry[1], Benjamin Hinrichs[1], Alfredo Molinolo[5], Vinita Takiar[1], Jonathan Mark[1], Alice Tang[1], Muhammad Kashif Riaz[1], John C. Morris[1], Nooshin Hashemi[1], Changchun Xie[1], Maura L. Gillison[8]

University of Cincinnati Cancer Institute, Cincinnati, OH[1]; The Ohio State University, Columbus, OH[2]; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI[3]; Medical University of South Carolina, Charleston, SC[4]; University of California, San Diego, La Jolla, CA[5]; University of Louisville, James Graham Brown Cancer Center, Louisville, KY[6]; University of Michigan, Ann Arbor, MI[7]; The University of Texas MD Anderson Cancer Center, Houston, TX[8]

Background

- In healthy conditions, the receptor ligand interaction between PD-1, expressed on activated T-cells, and PD-L1 serves as a checkpoint mechanism to downregulate excessive immune responses. Binding of PD-L1 to PD-1 inhibits T-cell activation through the T-cell receptor.
- PD-L1 is up-regulated in many cancers, including head and neck squamous cell carcinoma (HNSCC), and the pathway is often hijacked by tumors as a means to hide from immune detection.
- Pembrolizumab is a highly selective anti-PD-1 humanized monoclonal antibody (IgG4/κ) designed to directly block the interaction between PD-1 and its ligand.
- Pembrolizumab treatment resulted in a 18% overall response rate in metastatic and recurrent HNSCC (KEYNOTE-012).
- Interestingly, Dr. John Morris' laboratory has shown that not only MHC-1 but that PD-L1 expression is also increased in response to radiation, *in vitro* and *in vivo*, suggesting a possible mechanism of resistance to radiation (Figure 1A and B).
- In addition, mice pre-treated with anti-PD-L1 antibody one week prior to radiation resulted in increased survival of mice bearing HNSCC tumors compared to mice treated five days post-radiation and radiation alone (Figure 1C).

Figure 1. Anti-PD-L1 therapy prior to radiation results in increased survival. MHC-1 and PD-L1 expression was shown to be upregulated in murine head and neck cancer lines (HPV+ and HPV-) with increasing doses of radiation both in vitro (a) and in vivo, with mice bearing HNSCC tumors (b). Mice pre-treated with anti-PD-L1 antibody 1 week prior to radiation (1) survived significantly longer than mice treated five days post-radiation(2) and radiation alone(3) (c).

Hypothesis: ***The addition of Pembrolizumab prior and concurrently to combined radiation or cisplatin and radiation (CRT) after surgical resection in clinical high risk HNSCC will result in enhanced tumor response.***

Methods

- Multi-site Phase II Trial (UC, UCSD, UMich, OSU, MUSC, Univ of Louisville, MD Anderson, Case Western)
- Primary Objectives: 1. Determine the frequency and severity of side effects of pembrolizumab when administered in combination with radiation alone or cisplatin and radiation therapy (CRT) in patients undergoing adjuvant treatment for resected HNSCC. 2. To estimate the 1 and 3 year disease free survival (DFS) combining pembrolizumab with adjuvant CRT in patients with resected high risk HNSCC. 3. To estimate the 1 and 3 year disease free survival (DFS) combining pembrolizumab with adjuvant radiation in patients with resected intermediate risk HNSCC.
- Statistical analysis was based upon RTOG 9501 historical controls with DFS at 1 year and 3 years being 66% and 47% respectively for patients with high risk features undergoing CRT. We expected that at least 50% of patients (~40 patients) based on defined inclusion criteria will have high risk disease confirmed at resection (+ECE or + margins). With an expected sample size of at least N=40 in the CRT arm, and adding pembrolizumab to cisplatin and radiation, we expect to reach over 80% power to detect an increase of 21% in RFS at year 1 (87% RFS compared to 66% at 1 year) using exact test at significance level, alpha=0.025 (one-sided). In comparison, assuming that we will reach a similar 1 year DFS of 58% in the radiation alone arm, by adding pembrolizumab, and assuming N=40, we expect to reach over 80% power to detect an increase of 22% in RFS at 1 year (80% RFS compared to 58% at 1 year).
- Safety analysis includes all patients receiving at least 1 dose of treatment and adverse events are graded using CTCAE v4.03.

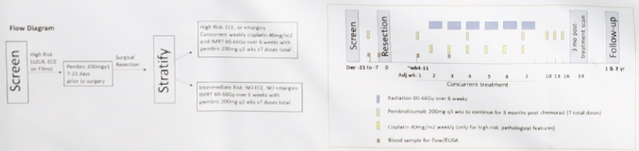


Figure 2. Clinical Trial Schema. Eligible patients with high-risk (Stage III/IV) locally advanced HNSCC were consented to receive pembrolizumab 200 mg I.V. 1-3 weeks before planned surgical resection. Pretreatment biopsies and resection specimens were archived for H&E and immunohistochemistry. Peripheral blood (red boxes) was collected for functional analysis pre-pembrolizumab, post-pembrolizumab prior to surgery, and post surgery prior to adjuvant week 1 and 3 (see schema). Patients are followed for disease-free and overall survival. Safety was determined by delays in SOC treatment.

Results

Patient Characteristics

Characteristic	(N= 34)
Age	
Median - yr	55
Range - yr	27-76
Sex- no. (%)	
Male	23 (68)
Female	11 (32)
Racial or Ethnic Group - no. (%)	
White	33 (97)
Hispanic	1 (3)
Black	0 (0)
Other	0 (0)
Smoker >10 pk year (%)	
Yes	17 (50)
No	17 (50)
Alcohol use >5 drinks/wk (%)	
Yes	12 (35)
No	22 (65)
ECOG performance score- no. (%)	
Zero	25 (74)
One	9 (26)
Site of Tumor - no. (%)	
Oral Cavity	30 (88)
Larynx	4 (12)
Clinical Stage - no. (%)	
T Stage	
T<	
T1	2 (6)
T2	4 (12)
T3	6 (18)
T4	21 (62)
N Stage	
N0	6 (18)
N1	3 (9)
N2a	1 (3)
N2b	13 (35)
N2c	11 (32)

- 34/80 patients have been enrolled
- Four patients have withdrawn (2 due to decision to receive treatment closer to home and 2 due to secondary thyroid cancer)
- 16/16 patients completed safety lead-in without Dose Limiting Toxicity which was defined as delay in standard of care (> 7 days delay in surgery, >3 days for radiation, and/or >7 days for cisplatin dose)

Pembrolizumab Induces Pathological Treatment Effect

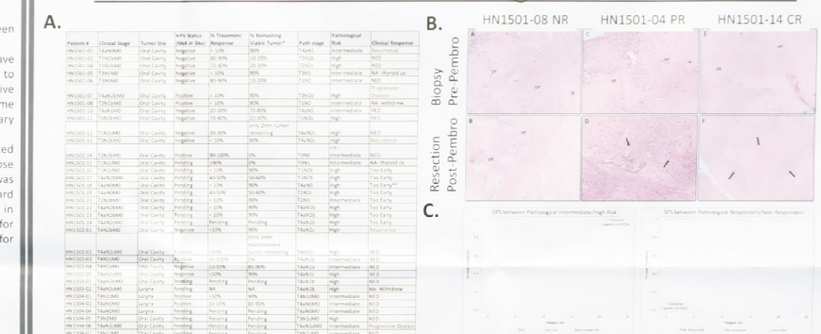


Figure 3. Neoadjuvant pembrolizumab results in pathological treatment effect in tumors. A. Table demonstrating clinical and pathological stage of each patient and pathological response after neoadjuvant pembrolizumab. 19/34 (56%) of patients had high pathological risk features. 14/27 (52%) of patients tissues examined, demonstrated a pathological response which was characterized by >10% treatment effect (TE) or decreased viable tumor (HN1502-02). TE was defined as tumor necrosis and/or histiocytic inflammation and giant cell reaction to keratinaceous debris. TE percentage was determined by dividing estimates of area showing these features by the total area showing residual viable tumor (VT) and TE. Clinical response was assessed at three months post radiation or at time of relapse with imaging and clinical exam.. NED= no evidence of disease. B. Representative images from patients' biopsy (pre-pembro) and resection (post-pembro) demonstrating a patient with no pathological response (HN1501-08) with a lot of VT and those with moderate (HN1501-04) and complete response (HN1501-14) and intense immune infiltration (arrows). C. Disease free survival (DFS) was evaluated between patients with high vs. intermediate risk pathological features (left) and patients with TE (responders) vs. no TE (non-responders) and was calculated from treatment allocation to date of relapse or last date known alive. Kaplan Meier Curves are displayed and survival probability was compared using logrank between the two groups.

Pembrolizumab induces anti-tumor immune signature in those with TE

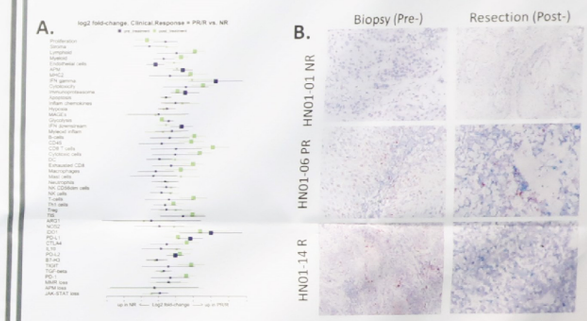


Figure 4. Pembrolizumab increases pro-inflammatory anti-tumorigenic response. A. Biopsy and Resection tissue from 11 patients were harvested for RNA and subjected to nanostring technology. Expression was correlated with pathological partial responders (PR) and responders (R) compared to non-responders (NR). R was defined as >90% TE, PR was >10% TE and non-responders was <10% TE. Large boxes indicate significance. Blue boxes show differential expression at baseline between NR and PR/R whereas green boxes are changes in expression after pembrolizumab treatment. B. RNAscope was used to detect PD-L1 (red) and CD8 (blue) RNA expression in biopsy and resection tissue. All Pictures are at 200x.

All Adverse Events

CTCAE Category	Adverse Event	RT (n=15) Any Grade no.	%	Grade 1	Grade 2	Grade 3	Grade 4	CRT (n=19) Any Grade no.	%	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders	Anemia	3	20%	3	0	0	0	8	42%	1	7	0	0
	Febrile neutropenia	0	0%	0	0	0	0	2	11%	0	0	2	0
Cardiac Disorders	Heart Failure	0	0%	0	0	0	0	1	5%	0	0	1	0
	Myocardial infarction	0	0%	0	0	0	0	1	5%	0	0	1	0
Ear and labyrinth disorders	Venous injury	0	0%	0	0	0	0	1	5%	0	0	1	0
	Tinnitus	0	0%	0	0	0	0	6	32%	6	0	0	0
Endocrine disorders	Hyperthyroidism	2	13%	2	0	0	0	2	11%	2	0	0	0
	Autoimmune Colitis	0	0%	0	0	0	0	1	5%	0	1	0	0
Gastrointestinal disorders	Constipation	5	33%	3	2	0	0	1	5%	1	0	0	0
	Diarrhea	1	7%	1	0	0	0	7	37%	3	2	0	0
	Duodenal hemorrhage	1	7%	0	0	1	0	0	0%	0	0	0	0
	Dysphagia	3	20%	1	2	0	0	6	32%	0	2	4	0
	Oral pain	3	20%	2	1	0	0	3	16%	0	3	0	0
	Mucositis	3	20%	0	1	2	0	10	53%	4	6	0	0
	Nausea	4	27%	3	1	0	0	9	47%	5	2	2	0
	Vomiting	2	13%	2	0	0	0	8	42%	5	1	2	0
General disorders and administration site conditions	Edema Face	2	13%	2	0	0	0	3	16%	2	3	0	0
	Fatigue	4	27%	2	1	1	0	7	37%	4	3	0	0
	Pain	6	40%	4	1	1	0	7	37%	2	5	0	0
Infections and infestations	Mucosal infection	2	13%	1	1	0	0	5	26%	1	3	1	0
Injury, poisoning and procedural complications	Dermatitis radiation	5	33%	3	1	1	0	5	26%	2	3	0	0
Investigations	AST increased	0	0%	0	0	0	0	3	16%	2	0	1	0
	Lymphocyte count decreased	3	20%	1	1	0	1	2	11%	0	0	2	0
	Platelet count decreased	0	0%	0	0	0	0	5	26%	3	1	1	0
	Weight loss	6	40%	5	1	0	0	4	21%	2	1	1	0
	White blood cell count decreased	1	7%	1	0	0	0	4	21%	0	2	2	0
Metabolism and nutrition disorders	Anorexia	2	13%	1	1	0	0	3	16%	1	1	1	0
	Dehydration	2	13%	0	2	0	0	2	11%	0	1	1	0
	Hyperglycemia	1	7%	1	0	0	0	3	16%	2	0	1	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	7%	0	1	0	0	0	0%	0	0	0	0
Nervous system disorders	Dysgeusia	4	27%	3	1	0	0	1	5%	1	0	0	0
Psychiatric disorders	Insomnia	2	13%	1	1	0	0	5	26%	3	2	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	13%	2	0	0	0	2	11%	1	1	0	0
	Sore Throat	4	27%	3	1	0	0	4	21%	1	3	0	0
Skin and subcutaneous tissue disorders	Rash	5	33%	4	1	0	0	3	16%	2	1	0	0
	Hypertension	2	13%	0	1	1	0	3	16%	1	1	1	0
Vascular disorders	Lymphedema	5	33%	5	0	0	0	2	11%	2	0	0	0

Pembrolizumab Related Adverse Events

CTCAE Category	Adverse Event	Any Grade no.	%	Grade 1	Grade 2	Grade 3	Grade 4
Endocrine disorders	Hyperthyroidism	1	3%	1	0	0	0
	Hypothyroidism	1	3%	0	1	0	0
Gastrointestinal disorders	Autoimmune Colitis	1	3%	0	0	1	0
	Diarrhea	1	3%	0	1	0	0
	Duodenal hemorrhage	1	3%	0	0	1	0
	Mucositis	1	3%	0	0	1	0
	Nausea	3	9%	2	0	1	0
	Vomiting	1	3%	0	0	1	0
General disorders and administration site conditions	Fatigue	3	9%	2	1	0	0
	Pain	1	3%	1	0	0	0
Investigations	ALT increased	1	3%	0	1	0	0
Metabolism and nutrition disorders	Anorexia	1	3%	1	0	0	0
	Hypomagnesemia	1	3%	1	0	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	3%	0	1	0	0
Nervous System Disorders	Headache	1	3%	1	0	0	0
	Syncope	1	3%	0	0	1	0
Respiratory, thoracic and mediastinal disorders	Cough	1	3%	0	1	0	0
	Dry skin	1	3%	1	0	0	0
Skin and subcutaneous tissue disorders	Pruritis	1	3%	1	0	0	0
	Rash	1	3%	1	0	0	0
Vascular Disorders	Lymphedema	1	3%	1	0	0	0

Table 3. Adverse Events. The left table indicates all reported adverse events in the first 34 patients. The most common AEs were anemia, mucositis, fatigue and nausea. Decrease in cellular counts and nausea and vomiting were more common in those that received cisplatin. The most common pembrolizumab related AEs were nausea and fatigue.

Conclusions

- Pembrolizumab induces a pathological response in >50% tumors after just 1 administration
- Neoadjuvant and adjuvant pembrolizumab is safe with minimal related Adverse Events and no unexpected events
- Pembrolizumab results in increased anti-tumor inflammatory response in patients with pathological response

Acknowledgements

The phase II study was supported by Merck. Correlative analysis was supported by a KL2 awarded to Dr. Wise-Draper as part of a CTSA grant at the University of Cincinnati as well as a grant from the DoD. We would like to thank the University of Cincinnati Cancer Institute Clinical Trials Coordinators and our pathology tissue core for the success of this study.

CONCLUSIONES

- Como ha ocurrido en otras patologías, existe interés trasladar el beneficio de IT en enfermedad avanzada a enfermedad precoz/localmente avanzada.
- A día de hoy no existen datos que justifiquen su uso en la práctica clínica habitual.
- El racional del efecto coadyuvante de RT e IT genera un futuro esperanzador en este campo, a la espera de los resultados en términos de efectividad.
- En cuanto a seguridad, la inmunoterapia no parece añadir mayor toxicidad que la esperada en la mayoría de estudios.
- Quedan muchas dudas pendientes de aclarar: ¿tiempo de IT adyuvante?, ¿dosis similar o menor que en enf avanzada? ¿cómo seleccionar los pacientes que realmente se van a beneficiar - factores productivos de respuesta - biomarcadores?
- Es de especial interés intentar ofrecer a nuestros pacientes la posibilidad de participar en EC.

2018 ASCO ANNUAL MEETING

A randomized phase III study of Nimotuzumab in combination with concurrent radiotherapy and Cisplatin versus radiotherapy and Cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck

ELIGIBILITY CRITERIA
- Age ≥ 18 years
- SCC of oral cavity/ oropharynx/ hypopharynx/ larynx
- Stage III / IV, no distant metastasis
- Definitive CRT
- Adequate organ function

Stratify
- T-group (T0,1,2 vs T3,4)
- N-group (N0,1 vs N2,3)
- Site (Oropharynx versus non oropharynx)
- Technique of radiation (conventional versus others)

Randomized 1:1 Open Label

n=268 → Nimotuzumab (200mg) - weekly cisplatin 30mg/m² with of RT (NCRT)

n=268 → Weekly cisplatin 30mg/m² with RT (CRT)

RT: 70 Gy/35 #/-7 weeks

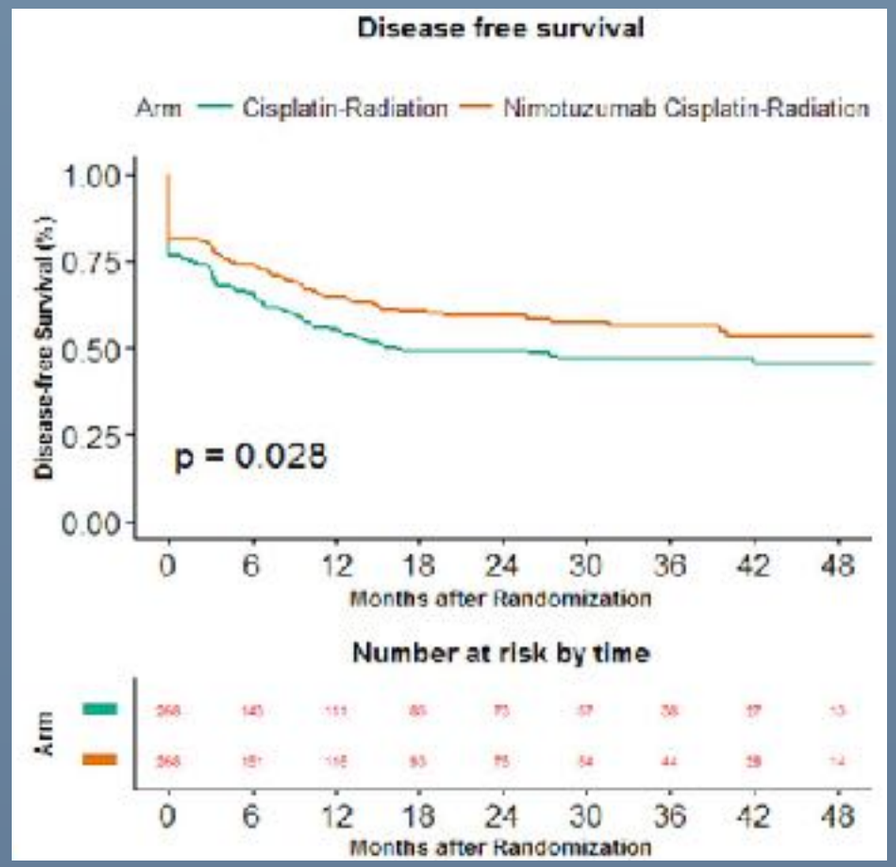
Follow-up: Weekly during CRT, then Q3 months x 2 years, then Q6 monthly

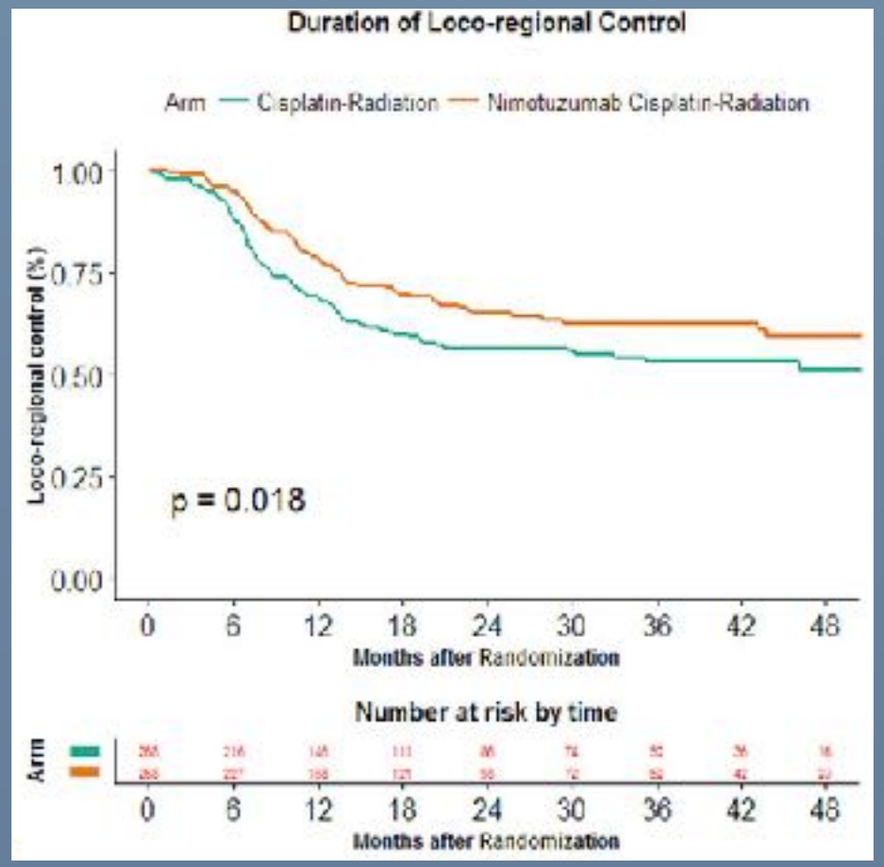
Primary Endpoint
- Progression free survival (PFS)
- Duration between date of randomization to time of progression
- Progression - RECIST criteria version 1.1.

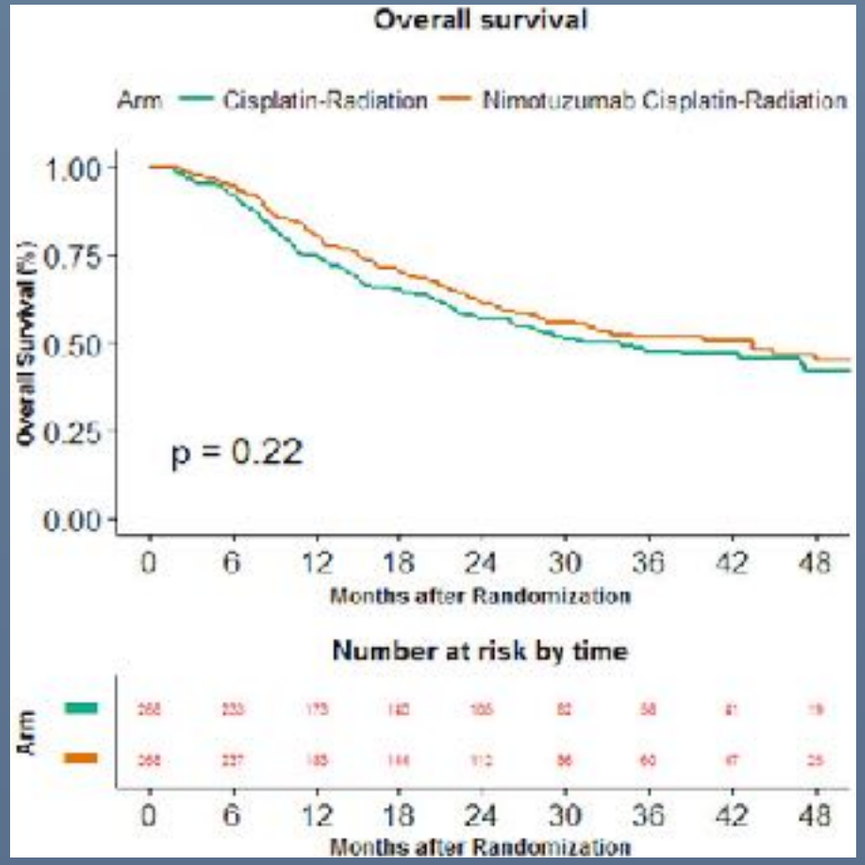
Secondary Endpoints
- Disease free survival (DFS)
- Time to locoregional control (LRC)
- Overall Survival (OS)
- Adverse event rate (CTCAE version 4.02)

Variable	Cisplatin - Radiotherapy arm	Nimotuzumab-cisplatin - Radiotherapy arm	P value
Median number of cisplatin cycles	7 (IQR 7-7)	7 (IQR 7-7)	0.389
Proportion of patients receiving ≥7 cycles cisplatin	219 (81.7%)	226 (84.3%)	0.421
Proportion of patients requiring cisplatin dose reduction	21 (7.8)	26 (9.7)	0.445
Proportion of patients with > 200 mg/m2 of cisplatin	211 (78.7%)	208 (77.6%)	0.754
Median number of Nimotuzumab cycles	Not applicable	7 (IQR 7-7)	-
Proportion of patients receiving ≥7 cycles Nimotuzumab	Not applicable	226 (84.3%)	-

Variable	Cisplatin - Radiotherapy arm	Nimotuzumab-cisplatin - Radiotherapy arm	P value
Median radiotherapy dose	70 Gy (IQR 70-70Gy)	70 Gy (IQR 70-70 Gy)	0.713
100 % of planned radiotherapy dose completed	252 (94.0%)	250 (93.3%)	0.723
Conventional IMRT Not received	229 (85.4%) 38 (14.2%) 1 (0.4%)	238 (88.8%) 29 (10.8%) 1 (0.4%)	0.240
Time for completion of radiation	51 (IQR 49-54)	51 (IQR 49-54)	0.630
Radiation completion time > 63 days	7 (2.6%)	5 (1.9%)	0.559
Proportion of patients with gaps greater than 2 days	72 (26.9%)	80 (29.9%)	0.443
Median cumulative duration of gap	5 (IQR 3-9)	5 (IQR 3-8)	0.824



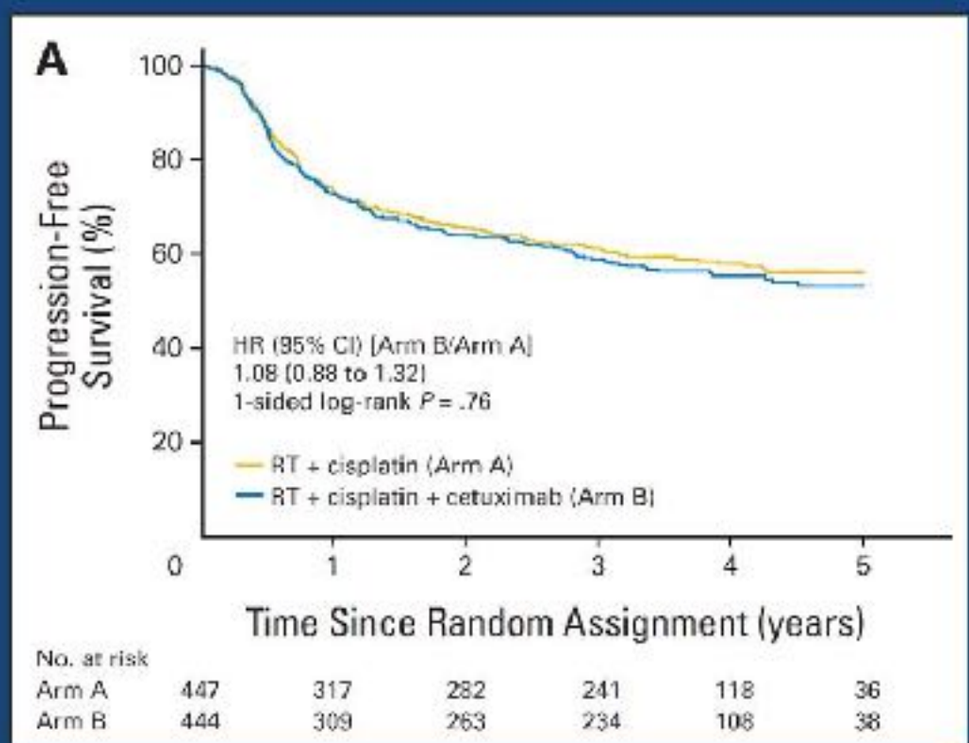




Variable	Cisplatin - Radiotherapy arm		Nimotuzumab-cisplatin - Radiotherapy arm		P value
	All Grades	Grade 3-5	All Grades	Grade 3-5	Grade 3-5
Mucositis	252 (96.9%)	145 (55.8%)	256 (97.0%)	176 (66.7%)	0.010
Radiation dermatitis	238 (91.5%)	76 (29.2%)	234 (88.6%)	73 (27.7%)	0.689
Odynophagia	252 (96.9%)	98 (37.7%)	257 (97.3%)	109 (41.3%)	0.400
Dysphagia	226 (86.9%)	75 (28.8%)	229 (86.7%)	80 (30.3%)	0.715
Nausea	124 (47.7%)	2(0.8%)	127 (48.1%)	4 (1.5%)	0.422
Vomiting	78 (30.0%)	4(1.5%)	77 (29.2%)	3(1.1%)	0.689
Weight loss	133 (51.2%)	2 (0.8%)	160 (60.6%)	3 (1.1%)	0.666
Maculopapular rash	6 (2.3%)	-	19 (17.2%)	-	-
Increased serum creatinine	26 (9.9%)	-	24 (9.0%)	2 (0.8%)	0.160
Increased SGOT	48 (18.3%)	3(1.1%)	41(15.4%)	2 (0.8%)	0.641
Increased SGPT	75 (28.6%)	3(1.1%)	85 (32.0%)	4 (1.5%)	0.719
Hyponatremia	236 (90.1%)	82 (31.3%)	237 (89.1%)	89 (33.5%)	0.596
Hypokalemia	10 (3.8%)	3 (1.1%)	16 (6.0%)	2 (0.8%)	0.641
Hypomagnesemia	79 (30.2%)	-	89 (33.5%)	-	-

Hospitalization because of toxicities was higher in NCRT arm [58 patients (21.6%) versus 41 patients (15.3%); *P*=0.058]

Adding cetuximab to radiation + cisplatin did not improve outcome



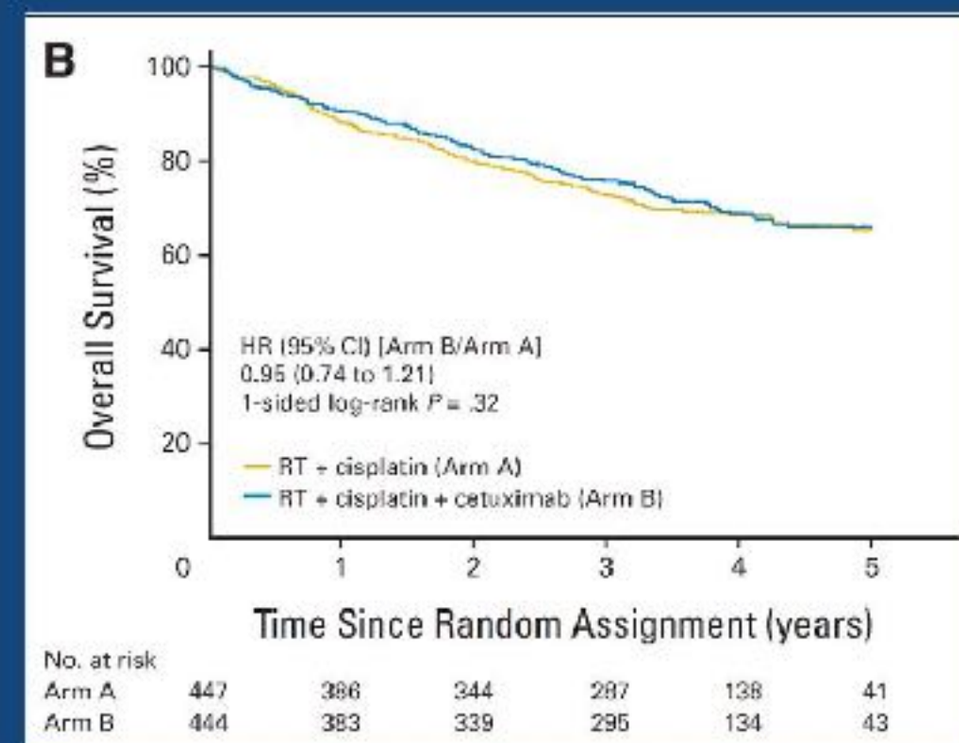
RTOG 0522

Stage III & IV
M0
HNSCC

Randomize

Cetuximab + Cisplatin 100mg/m^2 + Radiotherapy

Cisplatin 100mg/m^2 + Radiotherapy

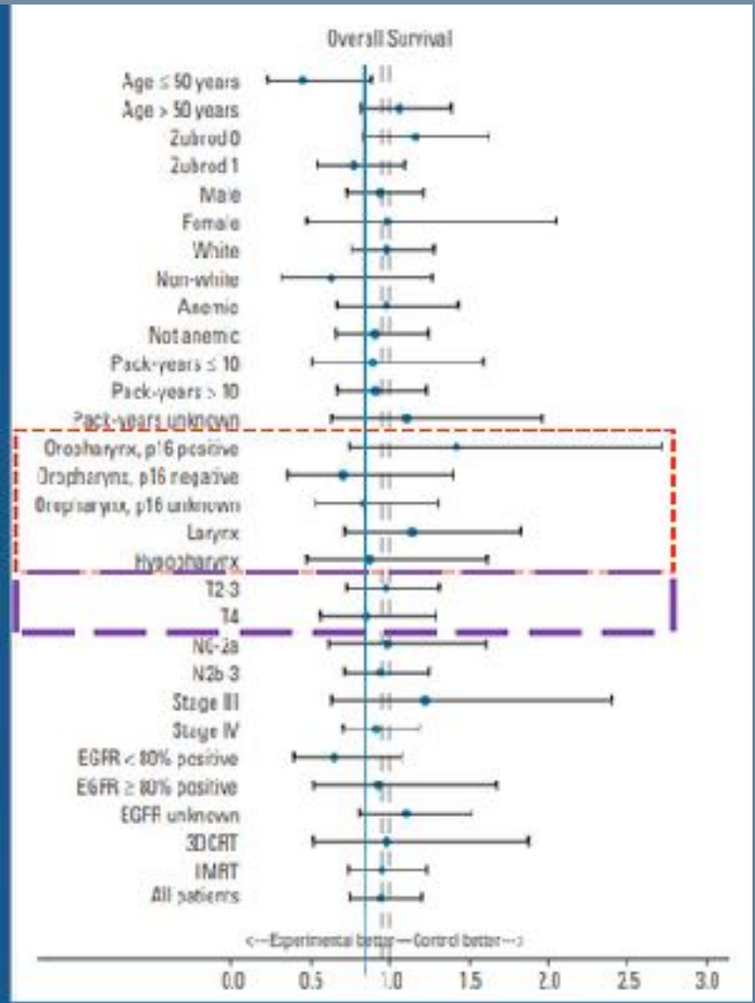


Ang, et al. JCO 2014

Difference with previous study

Factors	RTOG 0522-Cetuximab arm	Nimotuzumab arm
Patient characteristics		
HPV Negative	26.8%	94%
Hypo pharynx	6.4%	23.1%
T3-T4	60%	84.7%
Treatment		
Radiation interruptions (any cause)	51.8%	34.3%
Cisplatin 160 or above*	88.5%	92.9%

*-As data in RTOG 0522 available for 160mg/m2



Ang et al. J Clin Oncol. 2014 Sep 20;32(27):2940-50

¿Por qué difieren los resultados?

- CDDP 100mg/m2 c/21 vs. 30mg/m2 semanal (no estándar).
- CDDP >160mg/m2 similar
- Poblaciones distintas: >HPV- con Nimo (peor pronóstico); >T3/4 con Nimo; IMRT 13 (Nimo) vs.86%.

RESULTADOS ALENTADORES. DEBERÍA ESTUDIARSE CON CDDP 100mg/m2.