Key Clinical Missions

- Tertiary / Highly Complex Medicine
- Rare Tumors (> 25%)
- Care integrated with Clinical Research (~3800 pts/yr in Clinical Trials)

- Early Drug Development
  - (900 pts included in 2015: ~25% of CR program)

KEY MISSION INNOVATE and create ACCESS TO INNOVATION

INTEGRATION of RESEARCH and CARE to create TOMORROWS MEDICINE
THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION
Molecular Alterations in Melanoma

- **FGFR**
- **PTEN**
- **PI3K**
- **Akt**
- **TOR**
- **GRB2**
- **SOS**
- **Ras GDP**
- **N-Ras GTP**
- **C-Raf**
- **B-Raf**
- **MEK**
- **ERK**
- **ELK**
- **MITF**
- **CDK2/4**
- **Cyclin D**
- **p16**

- **Amplified in 10%-15%**
- **Amplified or mutated in 20%-40% acral and mucosal melanoma**
- **15% mutation**
- **50%-65% V600E mutation**
- **25%-50% loss**
- **Frequent loss**
- **Amplified in 30%**

Vemurafenib and Dabrafenib show similar efficacy

Chapman et al., NEJM 2011

Hauschild et al., Lancet 2012
Safety and efficacy of vemurafenib in 

**BRAF**$^{V600E}$ and **BRAF**$^{V600K}$ mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study


**OS** 9.7-13.6 mts  
**Gain:** 3.9 mts  
**HR 0.70**

**V600E (91%):** 13.3-10.0  
**HR = 0.75**

**V600K (9%):** 14.5–7.6  
**HR = 0.43**

**PFS** 1.6-6.9 mts  
**Gain 5.3 mts**

**HR 0.38**
SUCCESS AND FAILURE
Molecular Alterations in Melanoma

**BRAF + MEK Inhibitors**

- **FGFR**
- **PTEN**
- **PI3K**
- **Akt**
- **TOR**
- **PI3K**
- **Akt**
- **TOR**
- **N-Ras GDP**
- **C-Raf**
- **MEK**
- **ERK**
- **ELK**
- **MITF**
- **p16**
- **CDK2/4**
- **Cyclin D**
- **Kit**

- **Amplified or mutated in 20%-40% acral and mucosal melanoma**
- **15% mutation**
- **50%-65% V600E mutation**
- **Amplified in 10%-15%**
- **25%-50% loss**
- **Frequent loss**
- **Amplified in 30%**

Median Follow-up: $D + T = 11$ months and $Vem = 10$ months

$\approx 8$ weeks
Drug Development Challenges

- Tumor by evolution is “moving target”
  - Heterogeneity and Innate resistance
  - Acquired resistance/Additional mutations
  - Mono-Dimensional Thinking

We need to address:
- Nodes of Convergence of Pathways
- Cross Talk Complexity between pathways
eIF4F Node of Convergence
Ras/Raf – PI3K- Caspase cascade

Adapted from Sosman, Curr. Oncol. Rep. 11, 405 (2009)
eIF4F is a nexus of resistance to anti-BRAF and anti-MEK cancer therapies

Lise Boussemart\textsuperscript{1,2,3*}, Hélène Malka-Mahieu\textsuperscript{1,2,3*}, Isabelle Girault\textsuperscript{1*}, Delphine Allard\textsuperscript{1}, Oskar Hemmingsson\textsuperscript{1†}, Gorana Tomasic\textsuperscript{4}, Marina Thomas\textsuperscript{5}, Christine Basmadjian\textsuperscript{5}, Nigel Ribeiro\textsuperscript{6}, Frédéric Thuaud\textsuperscript{6}, Christina Mateus\textsuperscript{3}, Emilie Routier\textsuperscript{3}, Nyam Kamusu-Kom\textsuperscript{1}, Sandrine Agoussi\textsuperscript{1}, Alexander M. Eggermont\textsuperscript{2,3}, Laurent Désaubry\textsuperscript{5}, Caroline Robert\textsuperscript{1,2,3} & Stéphan Vagner\textsuperscript{1,2,3†}

In BRAF(V600)-mutant tumours, most mechanisms of resistance to drugs that target the BRAF and/or MEK kinases rely on reactivation of the RAS–RAF–MEK–ERK mitogen-activated protein kinase (MAPK) signal transduction pathway, on activation of the alternative PI(3)K–AKT–mTOR pathway (which is ERK independent) or on modulation of the caspase-dependent apoptotic cascade\textsuperscript{1–3}. All three pathways converge to regulate the formation of the eIF4F eukaryotic translation initiation complex, which binds to the 7-methylguanylate cap (m\textsuperscript{7}G) at the 5' end of messenger RNA, thereby modulating the translation of specific mRNAs\textsuperscript{3,5}. Here we show that the persistent formation of the eIF4F complex, comprising the eIF4E cap-binding protein, the eIF4G scaffolding protein and the eIF4A RNA helicase, is associated with resistance to anti-BRAF, anti-MEK and anti-BRAF plus anti-MEK drug combinations in BRAF(V600)-mutant melanoma, colon and thyroid cancer cell lines. Resistance to treatment and maintenance of eIF4F complex formation is associated with one of three mechanisms: reactivation of MAPK signalling, persistent ERK-independent phosphorylation of the inhibitory eIF4E-binding protein 4EBP1 or increased pro-apoptotic BCL-2-modifying factor (BMF)-dependent degradation of eIF4G. The development of an \textit{in situ} method to detect the eIF4E–eIF4G interactions shows that eIF4F complex formation is decreased in tumours that respond to anti-BRAF therapy and increased in resistant metastases compared to tumours before treatment. Strikingly, inhibiting the eIF4F complex, either by blocking the eIF4E–eIF4G interaction or by targeting eIF4A, synergizes with inhibiting BRAF(V600) to kill the cancer cells. eIF4F not only appears to be an indicator of both innate and acquired resistance but also is a promising therapeutic target. Combinations of drugs targeting BRAF (and/or MEK) and eIF4F may overcome most of the resistance mechanisms arising in BRAF(V600)-mutant cancers.
Drug Development Challenges

• Nodes of Convergence of Pathways

• Cross Talk Complexity between pathways
Differential response of BRAF inhibition in *BRAF* mutant melanoma vs colon cancer.

Kopetz et al., ASCO 2010

CROSS TALK and RESISTANCE

LETTER

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Ananth Prahallad*, Chong Sun*, Sidong Huang*, Federica Di Nicolantonio‡‡, Ramon Salazar‡, Davide Zecchin‡, Roderick L. Beijersbergen*, Alberto Bardelli‡,‡ & René Bernards

Human colon cancer growth in mice

No drug
EGFR inhibitor
BRAF inhibitor
BRAF+EGFR inhibitor
• Targeted Agents will be effective across different tumor types with that target
  – importance of organ of origin
  – Answer is NO

• For combination therapies one must demonstrate the antitumor effects for each individual agent
  – Answer is NO
A map of human cancer signaling

Qinghua Cui¹, Yun Ma², Maria Jaramillo³, Hamza Bari¹, Arit Awan¹, Song Yang⁴, Simo Zhang², Lixue Liu², Meng Lu², Maureen O’Connor-McCourt³, Enrico O Purisima¹,⁵ and Edwin Wang¹,⁵,*

Figure 3. Human oncoprote signaling map. The human cancer signaling map was extracted from the human signaling network, which was mapped with cancer-related genes.
Molecular profiling
Identification of the molecular alteration
Tumor Specimen
Molecular profiling
Targeted therapy according to the molecular profile
Identification of the molecular alteration
Precision Medicine: identify-hit the target
Rational Genomics: “Molecular Portraits” for targeted therapy allocation

Rapid through Clinical Trials

Logistics – Logistics – Logistics
Focus, time pressure, culture, infrastructure

Examples of Current Clinical Trials
SAFIR01 Molecular Screening in Breast Cancer

Which candidate target?

- Biopsy of metastatic sites
- Frozen sample
- CGH/hot spot mutations (PIK3CA/AKT)*
- eligible for phase I
  N= 400

**Primary endpoint:**
% of patients included in phase I/II trial according to the profile

Funded by **INCA**
Sanger 30 genes

**Target discovery**
- FGFR1
- FGFR2
- FGF4 amp
- NOTCH amp
- PIK3CA / AKT / PTEN alteration
- Genetic instability
- VEGFA amplification
- PAK1 ampli

**Trials**
- Trial A
- Trial B
- Trial C
- Trial D
- Trial E
- Trial F
- Trials X, Y...

**Funded by**
- André et al ESMO 2012, Lancet Oncol 2014
High level of expectation

Recruitment completed between May 2011 and August 2012

André ESMO 2012
Molecular alterations

Targetable alterations

Rare alterations

% of patients with available genomic result

29% molecular alteration
IN THE END ONLY 12% gets targeted therapy

André et al, Lancet Oncology 2014

mutations

copy number alterations
MOSCATO: MOlecular Screening for CAncer Treatment Optimization

Histological analysis
Molecular analysis
CGH, NGS --- WES
Gene-panel sequencing

14 calendar days
CGH+RNAseq+NGS - WES

TARGET IDENTIFIED IN 45-50%
Targeted therapy in 20-25%
1200 PATIENTS IN 4 Years
MATCH-R trial

Patients with + biomarker tumor exposed to a targeted therapy and an initial response

Sensitive → Resistant

In vitro Cell lines → Mouse avatar → Tumor biopsy or effusion
Biopsy metastatic site: NGS Array CGH

Molecular alteration Excluding EGFR mut and ALK trl

Chemotherapy 4 cycles

No PD

Targeted therapy According to Molecular alteration

Pemetrexed if Non-SCC

EGFR TKI if SCC

Followed up but not included

metastatic NSCLC first line chemotherapy

All histologies
<table>
<thead>
<tr>
<th>Genetic abnormality</th>
<th>Gene location</th>
<th>Squamous Cell Carcinoma</th>
<th>Adenocarcinoma</th>
<th>Therapeutic intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA amplification[</td>
<td>3q26.3</td>
<td>33%</td>
<td>6%</td>
<td>AZD2014 (TORC1/2)</td>
</tr>
<tr>
<td>FGFR1 amplification[</td>
<td>8p12</td>
<td>22%</td>
<td>1%</td>
<td>AZD4547 (FGFR)</td>
</tr>
<tr>
<td>PTEN mutation</td>
<td>10q23.3</td>
<td>10%</td>
<td>2%</td>
<td>AZD8186 (PI3Kbeta)</td>
</tr>
<tr>
<td>MET amplification</td>
<td>7q31.1</td>
<td>3-21%</td>
<td>3-21%</td>
<td>Volitinib</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>10q23.3</td>
<td>8-20%</td>
<td>8-20%</td>
<td>AZD8186 (PI3Kbeta)</td>
</tr>
<tr>
<td>KRAS mutation[</td>
<td>12p12.1</td>
<td>6%</td>
<td>21%</td>
<td>AZD6244 (MEK)i?? or combo with AZD2014</td>
</tr>
<tr>
<td>LKB1 mutation</td>
<td>19p13.3</td>
<td>5%</td>
<td>23%</td>
<td>AZD2014 (TORC1/2)</td>
</tr>
<tr>
<td>HER 2 amplification</td>
<td>17q11.2-q12; 17q21</td>
<td>3-5%</td>
<td>5-9%</td>
<td>AZD 8931 (pan-HER)</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>3q26.3</td>
<td>3%</td>
<td>3%</td>
<td>AZD2014 (TORC1/2)</td>
</tr>
<tr>
<td>RET translocation</td>
<td>10q11.2</td>
<td>2%</td>
<td>1%</td>
<td>AZD6474 (VEGFR, EGFR, RET)</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>7p34</td>
<td>2%</td>
<td>1-3%</td>
<td>AZD6244 (MEK)i</td>
</tr>
<tr>
<td>AKTI mutation</td>
<td>14q32.32</td>
<td>1%</td>
<td>Very rare</td>
<td>AZD5363 (Akt)</td>
</tr>
<tr>
<td>MET mutation</td>
<td>7q31.1</td>
<td>1%</td>
<td>2%</td>
<td>Volitinib</td>
</tr>
<tr>
<td>HER2 mutation</td>
<td>17q11.2-q12; 17q21</td>
<td>1%</td>
<td>2%</td>
<td>AZD 8931 (pan-HER)</td>
</tr>
</tbody>
</table>
Biopsy metastatic site: NGS CGH: 51 alterations

Molecular alteration Excluding HER2

Chemotherapy 6-8 cycles

No PD

Targeted therapy According to Molecular alteration

Chemotherapy continuation

Followed up but not included

metastatic Breast cancer patient 1st or 2nd line
Since 2010: Ongoing precision medicine programs
15 GR-initiated trials (high throughput genomics)

FUNDING TOTAL ~50 Million: Fondation GR (10), MCM Building (15), IHU (6), INCA (6), ARC (4), Philanthropia (2), WINconsort (4), EU-FP7 (3)
MOSCATO: MOlecular Screening for CAncer Treatment Optimization

- Biopsy
  - Histological analysis
  - Molecular analysis
    - CGH, NGS --- WES
    - Gene-panel sequencing

14 calendar days
CGH+RNAseq+NGS - WES

TARGET IDENTIFIED IN 45-50%
Targeted therapy in 20-25%
1200/1200 PATIENTS IN 3.5 Years
PROBLEMS with Molecular Portraits

• ATTRITION RATE
  • 100 pts with molecular portrait
  • 50 pts have target identified
  • 25 are actionable
  • 25% overall response rate
  • So in the end 6/100 patients benefit….

• INNATE RESISTANCE + ORGAN CONTEXT
NEEDS

• Higher Target Identification Rate
• Higher % of Actionable Targets
• Higher number / diversification of new drugs
• Rational intra/interpathway combinations

• Functional Genetics (Crosstalk)
  – Rene Bernards
• Nodes of convergence
  – Vagner, Robert
• Simplification of models
  – Master Regulators (Andrea Califano)
Problems with Targeted Drugs

• Lack of Durability of responses
  – Improvement with combo’s limited
  – Combo’s of non-active drugs can be active

• Lack of Transversality of impact across tumor types
  – Organ of origin
  – Context
A map of human cancer signaling

Qinghua Cui¹, Yun Ma², Maria Jaramillo³, Hamza Bari¹, Arif Awan¹, Song Yang⁴, Simo Zhang², Lixue Liu², Meng Lu², Maureen O’Connor-McCourt³, Enrico O Purisima¹,⁵ and Edwin Wang¹,⁵,⁶.

*Figure 3* Human oncogene-signaling map. The human cancer-signaling map was extracted from the human signaling network, which was mapped with cancer genes. Arrows indicate activation of the pathway.
THE MELANOMA PARADIGM
MUTATION DRIVEN DRUG DEVELOPMENT
INNOVATIVE IMMUNOMODULATION
REVOLUTION IN IMMUNOTHERAPY

BREAKING TOLERANCE
Immune-Checkpoint-Blockers

INHIBIT THE INHIBITOR

VS

ACTIVATE THE ACTIVATOR
Anti CTLA-4 Monoclonal Antibodies Perpetuate T Cell Activation Reawaken silenced Immune Responses

IL-2

T-cell

TCR

Antigen

CD28

MHC

B7

APC

IL-2

TCR

Antigen

CD28

MHC

B7

CTLA-4

IL-2

TCR

CD28

CTLA-4

Antigen

MHC

B7

Anti-CTLA-4 mAb
Balancing T cell activation: playing with T cell receptors

- PD-1 and CTLA4 play distinct roles in regulating T cell immunity.
- CTLA4 modulates early phases of T cell priming (naïve and memory T cells)
- PD-1 is expressed on antigen-experienced T cells (TILs and Tregs)
- PD-1/PDL-1 interaction downregulates overt inflammation in lesions
- PDL-1 expressed on Tumor Cells and Plasmoid DCs

Immunotherapy strategies

Cytokines
- IFN
- IL2
- IL7
- IL21
- GM-CSF

Vaccination
- DC
- DNA
- RNA

Adoptive Tcell therapy
- Activated
- TCR engineered CARs

Immunocyte depletion
- Treg
- MDSC

MoAb-conjugates

- Activating receptors
  - CD28
  - OX40
  - GITR
  - CD137
  - HVEG

- Inhibitory receptors
  - CTLA-4
  - PD-1
  - TIM-3
  - BTLA
  - VISTA
  - LAG-3

- Agonistic antibodies
- Blocking antibodies

- T-cell stimulation
ANTI-CTLA4
Ipilimumab Data
Potential for long-term survival with IT anti-CTLA-4 (ipilimumab)

- Ipilimumab was the first therapy to improve overall survival in unresectable or metastatic melanoma in a randomised phase 3 trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, months</th>
<th>95% CI</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab + gp100</td>
<td>10.0</td>
<td>8.5–11.5</td>
<td>0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>10.1</td>
<td>8.0–13.8</td>
<td>0.66</td>
<td>0.003</td>
</tr>
<tr>
<td>gp100</td>
<td>6.4</td>
<td>5.5–8.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- In clinical trials, most adverse events associated with ipilimumab were immune related and managed using ipilimumab-specific treatment guidelines

- Most frequently reported adverse events associated with ipilimumab monotherapy (all grades) in a clinical study were: diarrhoea (27%), rash (26%) and pruritus (26%)

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma


**Fig 1.** Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.
Ipilimumab + DTIC in Melanoma in 1st line. IMPACT MEDIAN SURVIVAL only 2.1 MONTHS

DTIC may have rather limited the ipilimumab effect than enhance it. DTIC does NOT LEAD TO IMMUNOGENIC CELL DEATH and thus may be a poor combination therapy candidate.

Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial


EORTC 18071/CA184-029: Study Design

**INDUCTION**
- **High-risk, stage III, completely resected melanoma**
- **N=475**
  - **Ipi 10 mg/kg Q3W X4**
  - **MAINTENANCE Ipi 10 mg/kg Q12W up to 3 years**

**Placebo (Pbo)**
- **N=476**
  - **Placebo (Pbo) Q3W X4**
  - **MAINTENANCE Placebo (Pbo) Q12W up to 3 years**

Treatment up to a maximum 3 years, or until disease progression, intolerable toxicity, or withdrawal

**Stratification factors:**
- Stage (IIIA vs IIIB vs IIIC ≤3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

**Primary Endpoint: RFS**
- Secondary endpoints: DMFS and OS
Primary Endpoint: Recurrence-free Survival (IRC)

<table>
<thead>
<tr>
<th></th>
<th>Ipi</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>234/475</td>
<td>294/476</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.75 (0.64–0.90)</td>
<td></td>
</tr>
<tr>
<td>Log-rank $P$ value*</td>
<td>0.0013</td>
<td></td>
</tr>
<tr>
<td>2-Year RFS rate (%)</td>
<td>51.5</td>
<td>43.8</td>
</tr>
<tr>
<td>3-Year RFS rate (%)**</td>
<td>46.5</td>
<td>34.8</td>
</tr>
</tbody>
</table>

*Stratified by stage.
**Data are not yet mature.

Median: 17.1 mo
Median: 26.1 mo

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ipi</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>234</td>
<td>294</td>
</tr>
<tr>
<td>N</td>
<td>475</td>
<td>476</td>
</tr>
</tbody>
</table>

Patients Alive Without Recurrence (%)

- Ipi 10 mg/kg
- Pbo

*Stratified by stage.
**Data are not yet mature.
POST HOC ANALYSES

ULCERATED PRIMARY

VS

NON-ULCERATED PRIMARY
EORTC 18071: Importance of ULCERATION for RFS

<table>
<thead>
<tr>
<th></th>
<th>Microscopic and macroscopic Stage III</th>
<th>Microscopic Stage III* (sentinel nodes positive)</th>
<th>Macroscopic Stage III* (palpable nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerated</td>
<td>Ulcerated (N=400)</td>
<td>Ulcerated (N=187)</td>
<td>Ulcerated (N=213)</td>
</tr>
<tr>
<td>Non-ulcer</td>
<td>Non-ulcer (N=501)</td>
<td>Non-ulcer (N=201)</td>
<td>Non-ulcer (N=300)</td>
</tr>
<tr>
<td><strong>HR (CI)</strong></td>
<td>0.63 (0.45-0.88)†</td>
<td>0.53 (0.31-0.90)‡</td>
<td>0.68 (0.44-1.05)‡</td>
</tr>
<tr>
<td></td>
<td>0.82 (0.59-1.14)†</td>
<td>0.72 (0.40-1.31)‡</td>
<td>0.85 (0.57-1.28)‡</td>
</tr>
</tbody>
</table>

HR: hazard ratio for Ipi versus Pbo. CI: confidence interval at 95% (all patients) or Cl at 99% (subgroups *Post hoc analyses).

(1): Cox model stratified by stage at randomization (primary analysis).
†Cox model: treatment effect adjusted by type of lymph node (LN) involvement (micro vs macroscopic), no. of LN+ (1, 2-3, ≥4), ulceration (No, Yes), Breslow thickness (≤2, >2-4 or Unknown, >4 mm).
‡Cox model: as above, but without type of LN involvement.
Time to Onset of Grade 2-5 irAEs

10 mg/kg Ipilimumab (n=471)  
Placebo (n=474)

**Skin**
- Median time to onset (ipilimumab): 4.3 wks (range: 0.3–144.1)

**Gastrointestinal**
- Median time to onset (ipilimumab): 6.3 wks (range: 0.3–145.0)

**Hepatic**
- Median time to onset (ipilimumab): 8.7 wks (range: 1.9–48.0)

**Endocrine**
- Median time to onset (ipilimumab): 10.8 wks (range: 0.3–90.1)
DRUGS OF THE YEAR
2013/2014/2015/2016/2017.....

ANTI-PD1/PD1-L
CTLA-4 and PD-1/PDL1

**Mostly CENTRAL in LNN**

- Activation (cytokines, lysis, proliferation, migration to tumor)

**Mostly PERIPHERAL Tumor Microenvironment**

CTLA-4 Blockade (ipilimumab, tremelimumab)

PD-1 Blockade (nivolumab, pembrolizumab)

Dendritic cell

- MHC
- TCR
- B7
- CD28
- CTLA-4

T cell

- MHC
- TCR
- B7
- CD28
- CTLA-4

Tumor cell

- MHC
- TCR
- PD-1
- PD-L1
- PD-L2

anti-CTLA-4

anti-PD-1

anti-PD-1
Anti-PD1
Nivolumab
Pembrolizumab
Data
Efficacy and Safety of the Anti-PD-1 Monoclonal Antibody PEMBROLIZUMAB (MK-3475) in 411 Patients With Melanoma

Antoni Ribas,¹ F. Stephen Hodi,² Richard Kefford,³,⁴ Omid Hamid,⁵ Adil Daud,⁶ Jedd D. Wolchok,⁷ Wen-Jen Hwu,⁸ Tara C. Gangadhar,⁹ Amita Patnaik,¹⁰ Anthony M. Joshua,¹¹ Peter Hersey,⁴ Jeffrey Weber,¹² Roxana Dronca,¹³ Hassane Zarour,¹⁴ Kevin Gergich,¹⁵ Xiaoyun (Nicole) Li,¹⁵ Robert Iannone,¹⁵ S. Peter Kang,¹⁵ Scot Ebbinghaus,¹⁵ Caroline Robert¹⁶

¹University of California, Los Angeles, CA; ²Dana-Farber Cancer Institute, Boston, MA; ³Crown Princess Mary Cancer Centre, Westmead Hospital and Melanoma Institute Australia, Sydney, Australia; ⁴University of Sydney, Sydney, Australia; ⁵The Angeles Clinic and Research Institute, Los Angeles, CA; ⁶University of California, San Francisco, CA; ⁷Memorial Sloan-Kettering Cancer Center, New York, NY; ⁸MD Anderson Cancer Center, Houston, TX; ⁹Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; ¹⁰South Texas Accelerated Research Therapeutics, San Antonio, TX; ¹¹Princess Margaret Hospital, Toronto, Ontario; ¹²H. Lee Moffitt Cancer Center, Tampa, FL; ¹³Mayo Clinic, Rochester, MN; ¹⁴University of Pittsburgh, Pittsburgh, PA; ¹⁵Merck & Co., Inc., Whitehouse Station, NJ; ¹⁶Institut Gustave-Roussy, Villejuif, France
In patients with measurable disease at baseline by RECIST v1.1 by central review and ≥1 postbaseline assessment (n = 317).

Percentage changes >100% were truncated at 100%.

Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas
Time to and Durability of Response: Swimmer Plot Pembrolizumab in advanced melanoma

- 88% of responses ongoing\(^a\)
- Median response duration not reached (range, 6+ to 76+ weeks)

\(^a\)Ongoing response defined as alive, progression free, and without new anticancer therapy.
Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas
Pembrolizumab ORR Based on Tumor PD-L1 Expression

ORR by PD-L1 Positivity Across Doses/Schedules n=113

Unselected  PD-L1+  PD-L1–

Overall Response Rate

0  10  20  30  40  50  60

Proportion PD-L1+

86%  77%  55%

Overall response rate to Pembro:

Unselected  51%  32%  39%
PD-L1+  57%  39%  59%
PD-L1–  20%  9%  14%

• Differences in PD-L1 positivity may partly explain ORR differences between dosing cohorts

1-sided P values calculated by logistic regression, adjusting for dose/schedule.
PD-L1 positivity defined as staining in ≥1% of tumor cells.
Analysis cut-off date: 18 October 2013.
1. Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.

Presented by: Richard Kefferd
PD-L1 positivity defined as staining in ≥1% of tumor cells.
Analysis cut-off date: 18 October 2013.
1. Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.
Nivolumab in Previously Untreated Melanoma without BRAF Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.
Anti-PD1 vs DTIC in BRAF wild type Advanced Melanoma

A Overall Survival

Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73) P<0.001

Patients Surviving (%)

Patients Who Died
no./total no.

Median Survival
mo (95% CI)

Nivolumab
50/210
Not reached

Dacarbazine
96/208
10.8 (9.3–12.1)

No. at Risk

Nivolumab 210 185 150 105 45 8 0
Dacarbazine 208 177 123 82 22 3 0

Months
BRAFinh in BRAFmutant compared to anti-PD1 in Wildtype Advanced Melanoma

OS 9.7-13.6 mts
Gain: 3.9 mts
HR 0.70

PFS 1.6-6.9 mts
Gain: 5.3 mts
HR 0.38
Nivolumab activity equal in BRAF wild type / V600 Mutant

Efficacy and Safety of Nivolumab in Patients With BRAF V600 Mutant and BRAF Wild-Type Advanced Melanoma: A Pooled Analysis of 4 Clinical Trials

James Larkin, MD, PhD; Christopher D. Lao, MD, MPH; Walter J. Urba, MD, PhD; David F. McDermott, MD; Christine Horak, PhD; Joel Jiang, PhD; Jedd D. Wolchok, MD, PhD

CONCLUSIONS AND RELEVANCE  The results of this retrospective analysis suggest that nivolumab has similar efficacy and safety outcomes in patients with wild-type or mutant BRAF, regardless of prior BRAF inhibitor or ipilimumab treatment.

Nivolumab activity equal in BRAF wild type / V600 Mutant
Durable, Long-term Survival in Previously Treated Patients With Advanced Melanoma Who Received Nivolumab Monotherapy in a Phase I Trial

F. Stephen Hodi,1 Harriet M. Kluger,2 Mario Sznol,2 Richard D. Carvajal,3 Donald P. Lawrence,4 Michael B. Atkins,5 John D. Powderly,6 William H. Sharfman,7 Igor Puzanov,8 David C. Smith,9 Philip D. Leming,10 Evan J. Lipson,7 Janis M. Taube,7 Robert A. Anders,7 Christine E. Horak,11 Joel Jiang,11 David F. McDermott,12 Jeffrey A. Sosman,8 Julie R. Brahmer,7 Drew M. Pardoll,7 Suzanne L. Topalian7

1Dana Farber Cancer Institute, Boston, MA, USA; 2Yale University School of Medicine and Smilow Cancer Center, Yale-New Haven Hospital, New Haven, CT, USA; 3Columbia University Medical Center, New York, NY, USA; 4Massachusetts General Hospital Cancer Center, Boston, MA, USA; 5Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; 6Carolina BioOncology Institute, Huntersville, NC, USA; 7The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 8Vanderbilt University Medical Center, Nashville, TN, USA; 9University of Michigan, Ann Arbor, MI, USA; 10The Christ Hospital Cancer Center, Cincinnati, OH, USA; 11Bristol-Myers Squibb, Princeton, NJ, USA; 12Beth Israel Deaconess Medical Center, Boston, MA, USA
Overall Survival at 5 Years of Follow-up Nivolumab in Advanced Melanoma

Number of Patients at Risk

<table>
<thead>
<tr>
<th>All Patients</th>
<th>107</th>
<th>86</th>
<th>64</th>
<th>51</th>
<th>49</th>
<th>43</th>
<th>41</th>
<th>36</th>
<th>29</th>
<th>17</th>
<th>15</th>
<th>12</th>
<th>3</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO 3 mg/kg</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Probability of Survival

- All Patients (events: 69/107), median and 95% CI: 17.3 (12.5–37.8)
- NIVO 3 mg/kg (events: 11/17), median and 95% CI: 20.3 (7.2–NR)

Database lock Oct 2015
Summary of Overall Survival

<table>
<thead>
<tr>
<th>Landmark timepoint</th>
<th>OS Rate, % (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients (N = 107)</td>
</tr>
<tr>
<td>12-month</td>
<td>63 (53–71)</td>
</tr>
<tr>
<td>24-month</td>
<td>48 (38–57)</td>
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<tr>
<td>36-month</td>
<td>42 (32–51)</td>
</tr>
<tr>
<td>48-month</td>
<td>35 (26–44)</td>
</tr>
<tr>
<td>60-month</td>
<td>34 (25–43)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>17.3 (12.5–37.8)</td>
</tr>
</tbody>
</table>

*Based on Kaplan-Meier estimates
NR, not reached

Database lock Oct 2015
Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*
Pembrolizumab vs ipilimumab: OS

B Overall Survival

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Month 0</th>
<th>Month 2</th>
<th>Month 4</th>
<th>Month 6</th>
<th>Month 8</th>
<th>Month 10</th>
<th>Month 12</th>
<th>Month 14</th>
<th>Month 16</th>
<th>Month 18</th>
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</thead>
<tbody>
<tr>
<td>Pembrolizumab, Q2W</td>
<td>279</td>
<td>266</td>
<td>248</td>
<td>233</td>
<td>219</td>
<td>212</td>
<td>177</td>
<td>67</td>
<td>19</td>
<td>0</td>
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<tr>
<td>Pembrolizumab, Q3W</td>
<td>277</td>
<td>266</td>
<td>251</td>
<td>238</td>
<td>215</td>
<td>202</td>
<td>158</td>
<td>71</td>
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<tr>
<td>Ipilimumab</td>
<td>278</td>
<td>242</td>
<td>212</td>
<td>188</td>
<td>169</td>
<td>157</td>
<td>117</td>
<td>51</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>
CHANGING ADJUVANT LANDSCAPE MELANOMA

- **To be reported:**
  - Ipilimumab Trials
    - EORTC 18071: DMFS/OS analysis adjuvant ipilimumab
    - ECOG 1609: Ipilimumab 3 vs 10 vs HDI
  - BRAFi (+ MEKi) Trials
    - Adjuvant vemurafenib (?)
    - Adjuvant dabrafenib + trametinib

- **To be launched:** Anti-PD1 Trials
  - EORTC 1235: adjuvant pembrolizumab
  - ECOG/SWOG: adjuvant pembrolizumab vs HDI
  - BMS: adjuvant ipilimumab vs nivolumab
Sample size needed: N=950 patients (randomized)
Randomization < 12 weeks after complete lymph node dissection
  • Stratify by Stage; by region (Europe, Australia, N.America)

AT RELAPSE: unblinding: ALL PLACEBO PATIENTS CAN GET PEMBRO
AT RELAPSE for Pembro patients: physicians choice
PREDEFINED GROUP OF INTEREST: PDL-1 positive patients
  • Coordinator: Caroline Robert  Study Chair: Alexander Eggermont

Eligible patient

R
(double blind)

Placebo
i.v., q3 wks for 12 mts or until disease progression, unacceptable toxicity or withdrawal

200 mg anti-PD1 (Pembrolizumab)
i.v., q3 wks for 12 mts, or until disease progression, unacceptable toxicity or withdrawal
Anti-PD1 (nivolumumab) (pembrolizumab)

TRANSVERSAL IMPACT
Pembrolizumab Antitumor Activity

Melanoma\(^1\) (N=411) KEYNOTE-001

NSCLC\(^2\) (N=262) KEYNOTE-001

H\&N Cancer\(^3\) (N=61) KEYNOTE-012

Urothelial Cancer\(^4\) (N=33) KEYNOTE-012

Gastric Cancer\(^5\) (N=39) KEYNOTE-012

TNBC\(^6\) (N=32) KEYNOTE-012

cHL\(^7\) (N=29) KEYNOTE-013

Anti-PD1
(nivolumumab)
(pembrolizumab)

LUNG CANCER
Nivolumab vs Docetaxel in NSCLC 2\textsuperscript{nd} line
Overall Survival \textsuperscript{(FDA et al. 2015)}

Figure 1: Overall Survival - Trial 2

- OPDIVO
- Docetaxel

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>OPDIVO</th>
<th>Docetaxel</th>
</tr>
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<tbody>
<tr>
<td>135</td>
<td>113</td>
<td>103</td>
</tr>
<tr>
<td>137</td>
<td>86</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>69</td>
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<td>7</td>
<td>2</td>
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<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Read, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Habrison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

CONCLUSIONS
Among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level. (Funded by Bristol-Myers Squibb; CheckMate 017 ClinicalTrials.gov number, NCT01642004.)
Nivolumab vs Docetaxel 2nd line
Squamous NSCLC

Median Overall Survival
mo (95% CI)
Nivolumab (N=135) 9.2 (7.3–13.3)
Docetaxel (N=137) 6.0 (5.1–7.3)

1-Yr Overall Survival
% of patients (95% CI)
Nivolumab 42 (34–50)
Docetaxel 24 (17–31)

No. of Deaths
Nivolumab 86
Docetaxel 113

Hazard ratio for death, 0.59 (0.44–0.79)
P<0.001

No. at Risk
Nivolumab 135 113 86 69 52 31 15 7 0
Docetaxel 137 103 68 45 30 14 7 2 0

Months
Nivolumab vs Docetaxel in 2\textsuperscript{nd} line in Squamous NSCLC

A Duration of Response

Patients with Ongoing Response

- Nivolumab: 63% (17 of 27 patients with response)
- Docetaxel: 33% (4 of 12 patients with response)

B Progression-free Survival

Median Progression-free Survival (mo) (95% CI)
- Nivolumab (N=135): 3.5 (2.1–4.9)
- Docetaxel (N=137): 2.8 (2.1–3.5)

1-Yr Progression-free Survival (% of patients) (95% CI)
- Nivolumab: 21 (14–28)
- Docetaxel: 6 (3–12)

No. of Events
- Nivolumab: 105
- Docetaxel: 122

Hazard ratio for disease progression or death, 0.62 (0.47–0.81) P<0.001

No. at Risk
- Nivolumab: 135
- Docetaxel: 137

Months

0 3 6 9 12 15 18 21 24
### Nivolumumab activity Squamous NSCLC PD-L1 Expression

#### C Overall and Progression-free Survival According to PD-L1 Expression Level

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
<th>Unstratified Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>63</td>
<td>56</td>
<td>0.69 (0.45–1.05)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>54</td>
<td>52</td>
<td>0.58 (0.37–0.92)</td>
</tr>
<tr>
<td>≥5%</td>
<td>42</td>
<td>39</td>
<td>0.53 (0.31–0.89)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>75</td>
<td>69</td>
<td>0.70 (0.47–1.02)</td>
</tr>
<tr>
<td>≥10%</td>
<td>36</td>
<td>33</td>
<td>0.50 (0.28–0.89)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>81</td>
<td>75</td>
<td>0.70 (0.48–1.01)</td>
</tr>
<tr>
<td>Not quantifiable at baseline</td>
<td>18</td>
<td>29</td>
<td>0.39 (0.19–0.82)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression-free survival</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
<th>Unstratified Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1%</td>
<td>63</td>
<td>56</td>
<td>0.67 (0.44–1.01)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>54</td>
<td>52</td>
<td>0.66 (0.43–1.00)</td>
</tr>
<tr>
<td>≥5%</td>
<td>42</td>
<td>39</td>
<td>0.54 (0.32–0.90)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>75</td>
<td>69</td>
<td>0.75 (0.52–1.08)</td>
</tr>
<tr>
<td>≥10%</td>
<td>36</td>
<td>33</td>
<td>0.58 (0.33–1.02)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>81</td>
<td>75</td>
<td>0.70 (0.49–0.99)</td>
</tr>
<tr>
<td>Not quantifiable at baseline</td>
<td>18</td>
<td>29</td>
<td>0.45 (0.23–0.89)</td>
</tr>
</tbody>
</table>
Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer


CONCLUSIONS
Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel. (Funded by Bristol-Myers Squibb; CheckMate 057 ClinicalTrials.gov number, NCT01673867.)
Nivolumab vs Docetaxel in 2\textsuperscript{nd} line NONSquamous NSCLC

A Overall Survival

Overall Survival (% of patients)

No. of Deaths/Total No. of Patients

Nivolumab 190/292
Docetaxel 223/290

No. at Risk

Nivolumab 292 232 194 169 146 123 62 32 9 0
Docetaxel 290 244 194 150 111 88 34 10 5 0

Median Overall Survival (95\% CI)

Nivolumab 12.2 (9.7–15.0) mo
Docetaxel 9.4 (8.1–10.7)

1-Yr Overall Survival Rate (95\% CI)

Nivolumab 51 (45–56) \%
Docetaxel 39 (33–45) \%

Hazard ratio for death, 0.73 (96\% CI, 0.59–0.89) P=0.002
Nivolumab vs Docetaxel in 2\textsuperscript{nd} line in NONSquamous NSCLC

\textbf{B} Duration of Response

- Patients with Response
  - Nivolumab
  - Docetaxel

- Time to first response
  - During nivolumab treatment
  - During docetaxel treatment
  - After discontinuation of treatment
  - Ongoing response

- 52\% (29 of 56 patients with ongoing response)
- 14\% (5 of 36 patients with ongoing response)

\textbf{C} Progression-free Survival

- No. of Events/Total No. of Patients:
  - Nivolumab: 234/292
  - Docetaxel: 245/290

- Median Progression-free Survival (95\% CI):
  - Nivolumab: 2.3 (2.2–3.3) months
  - Docetaxel: 4.2 (3.5–4.9) months

- 1-Yr Progression-free Survival Rate (95\% CI):
  - Nivolumab: 19 (14–23)\%  
  - Docetaxel: 8 (5–12)\%

- Hazard ratio for disease progression or death:
  - 0.92 (95\% CI, 0.77–1.11); P=0.39

\textbf{No. at Risk}

- Nivolumab: 292, 128, 82, 58, 46, 35, 17, 7, 2, 0
- Docetaxel: 290, 156, 87, 38, 18, 6, 2, 1, 1, 0
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leightl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Luncseford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

This article was published on April 19, 2015, at NEJM.org.
Role PD-L1 expression in Pembrolizumab NSCLC Therapy
Nivolumab Versus Investigator’s Choice (IC) for Recurrent or Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (SCCHN): CheckMate-141

Maura L. Gillison,1 George Blumenschein, Jr,2 Jerome Fayette,3 Joel Guigay,4 A. Dimitrios Colevas,5 Lisa Licitra,6 Kevin Harrington,7 Stefan Kasper,8 Everett E. Vokes,9 Caroline Even,10 Francis Worden,11 Nabil F. Saba,12 Lara Carmen Iglesias Docampo,13 Robert Haddad,14 Tamara Rordorf,15 Naomi Kiyota,16 Makoto Tahara,17 Manish Monga,18 Mark Lynch,18 William J. Geese,18 Justin Kopit,18 James W. Shaw,18 Robert L. Ferris19

1The Ohio State University, Columbus, OH, USA; 2MD Anderson Cancer Center, Houston, TX, USA; 3Centre Leon Berard, Lyon, France; 4Centre Antoine Lacassagne, Nice, France; 5Stanford Cancer Institute, Stanford, CA, USA; 6IRCCS Istituto Nazionale Tumori, Milan, Italy; 7Institute of Cancer Research, London, UK; 8University Hospital Essen, Essen, Germany; 9University of Chicago, Chicago, IL, USA; 10Institut Gustave Roussy, Villejuif Cedex, France; 11University of Michigan, Ann Arbor, MI, USA; 12Winship Cancer Institute, Emory University, Atlanta, GA, USA; 13Hospital Universitario 12 de Octubre, Madrid, Spain; 14Dana-Farber Cancer Institute, Boston, MA, USA; 15Universitätsspital Zurich, Zurich, Switzerland; 16Kobe University Hospital, Kobe-City, Japan; 17National Cancer Center Hospital East, Kashiwa, Japan; 18Bristol-Myers Squibb, Princeton, NJ, USA; 19University of Pittsburgh Medical Center and Cancer Institute, Pittsburgh, PA, USA
Overall Survival in SCCHN: Nivolumab vs Investigator's Choice 2\textsuperscript{nd} line

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (97.73% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.5 (5.5–9.1)</td>
<td>0.70 (0.51–0.96)</td>
<td>0.010</td>
</tr>
<tr>
<td>Investigator’s Choice (n = 121)</td>
<td>5.1 (4.0–6.0)</td>
<td>1.00 (0.87–1.14)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

1-year OS rate (95% CI)

- Nivolumab: 36.0% (28.5–43.4)
- Investigator’s Choice: 16.6% (8.6–26.8)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Investigator’s Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>240</td>
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<td>Months</td>
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</tbody>
</table>

Overall Survival (% of patients)
Overall Survival in SCCHN by PD-L1 Expression

**PD-L1 Expression ≥ 1%**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 88)</td>
<td>8.7 (5.7–9.1)</td>
<td>0.55 (0.36–0.83)</td>
</tr>
<tr>
<td>Investigator’s Choice (n = 61)</td>
<td>4.6 (3.8–5.8)</td>
<td></td>
</tr>
</tbody>
</table>

**PD-L1 Expression < 1%**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 73)</td>
<td>5.7 (4.4–12.7)</td>
<td>0.89 (0.54–1.45)</td>
</tr>
<tr>
<td>Investigator’s Choice (n = 38)</td>
<td>5.8 (4.0–9.8)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Safety and Efficacy of Pembrolizumab (MK-3475) in Patients with Malignant Pleural Mesothelioma (MPM): Preliminary Results from KEYNOTE-028

Evan Alley,¹ L. Rhoda Molife,² Armando Santoro,³ Kim Beckey,⁴ Shuai Sammy Yuan,⁴ Jonathan Cheng,⁴ Bilal Piperdi,⁴ Jan H.M. Schellens⁵

¹University of Pennsylvania, Philadelphia, PA; ²Royal Marsden Hospital, London, UK; ³Istituto Clinico Humanitas, Milan, Italy; ⁴Merck & Co, Inc., Kenilworth, NJ, USA; ⁵Netherlands Cancer Institute, Plesmanlaan, Netherlands
Pembrolizumab in Mesothelioma

*Includes patients with ≥1 postbaseline tumor assessment (n = 23).
Analysis cut-off date: January 20, 2015.
Pembrolizumab in Mesothelioma

![Graph showing changes in tumor assessment over time for different histological subtypes of mesothelioma.]

*Includes patients with ≥1 postbaseline tumor assessment (n = 23).
Analysis cut-off date: January 20, 2015.
PEMBROLIZUMAB in GASTRIC CANCER:

39 pts, median FU: 8.8 months. 2/3 of pts had ≥ two prior therapies, 30% achieved PR 50% of pts some degree of tumor shrinkage median duration of response: 24 weeks (range 8+ to 33+ wks)

Analysis cut-off date: November 10, 2014.
Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial


Conclusion
Nivolumab demonstrated antitumor activity with a manageable safety profile across the three doses studied in mRCC. No dose-response relationship was detected as measured by PFS. These efficacy and safety results in mRCC support study in the phase III setting.

J Clin Oncol 33:1430-1437. © 2014 by American Society of Clinical Oncology
NO DOSE-RESPONSE EFFECT In RCC

Fig 2. (A) Progression-free and (B) overall survival by treatment arm (randomly assigned patients). Tick marks represent censored observations.

Fig 3. Duration of response in patients who achieved objective response by dose treatment arm. Based on data cutoff date of March 5, 2014.
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma


CONCLUSIONS

Among patients with previously treated advanced renal-cell carcinoma, overall survival was longer and fewer grade 3 or 4 adverse events occurred with nivolumab than with everolimus. (Funded by Bristol-Myers Squibb; CheckMate 025 ClinicalTrials.gov number, NCT01668784.)
Nivolumab in 2nd line in RCC

![Graph showing Kaplan-Meier Curve for Overall Survival.](image)

**Figure 1.** Kaplan–Meier Curve for Overall Survival.

CI denotes confidence interval, and NE not estimable.
Nivolumab in 2\textsuperscript{nd} line in RCC
No clear impact PD-L1 Expression

**Figure 3.** Kaplan–Meier Curve for Overall Survival, According to Programmed Death 1 Ligand (PD-L1) Expression Level.
MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles¹, Joseph Paul Eder², Gregg D. Fine³, Fadi S. Braiteh⁴, Yohann Loriot⁵, Cristina Cruz⁶, Joaquim Bellmunt⁷, Howard A. Burris⁸, Daniel P. Petrylak², Siew-leng Teng³, Xiaodong Shen³, Zachary Boyd³, Priti S. Hegde³, Daniel S. Chen³ & Nicholas J. Vogelzang⁹
Pembrolizumab in Triple Negative Breast Cancer

J Clin Oncol. 2016 May 2. pii: JCO648931. [Epub ahead of print]

Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study.
Nanda R¹, Chow LQ², Dees EC², Berger R², Gupta S², Geva R², Pusztai L², Pathiraja K², Aktan G², Cheng JD², Karantza V², Buisseret L².

RESULTS:
Among 111 patients with TNBC whose tumor samples were screened for PD-L1 expression, 58.6% had PD-L1-positive tumors. Among the 27 patients who were evaluable for antitumor activity, the overall response rate was 18.5%, the median time to response was 17.9 weeks (range, 7.3 to 32.4 weeks), and the median duration of response was not yet reached (range, 15.0 to ≥ 47.3 weeks).

CONCLUSION:
clinical activity and a potentially acceptable safety profile of pembrolizumab given every 2 weeks to patients with heavily pretreated, advanced TNBC.

A single-agent phase II study examining a 200-mg dose given once every 3 weeks (ClinicalTrials.gov identifier: NCT02447003) is ongoing.
CONCLUSIONS

In this study, first-line therapy with pembrolizumab in patients with advanced Merkel-cell carcinoma was associated with an objective response rate of 56%. Responses were observed in patients with virus-positive tumors and those with virus-negative tumors. (Funded by the National Cancer Institute and Merck; ClinicalTrials.gov number, NCT02267603.)
Pembrolizumab in Merkel Cell Carcinoma
RR 56% and PFS

A
Viral Status (N=24)
- Negative
- Positive

B
Viral Status (N=24)
- Negative
- Positive

C
Patients with Evidence of Response
- Complete response
- Partial response
- Stable disease
- Progressive disease
- Ongoing complete response
- Ongoing partial response
- Receipt of treatment
According to Moskowitz (MSKCC), it is believed that classic Hodgkin’s lymphoma may represent a uniquely vulnerable target for PD-1 blockade. Specifically, amplification of 9p24.1 is frequent in the disease and results in the overexpression of PD-L1 and PD-L2.

**ORR** 86%
**CR** 21%
**PR** 45%
**SD** 21%

**DURABILITY:** Seventeen of the 19 responses were ongoing
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


BACKGROUND
Somatic mutations have the potential to encode “non-self” immunogenic antigens. We hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.
# Pembrolizumab in Mismatched Repair Deficient Tumors

## Table 2. Objective Responses According to RECIST Criteria.

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N=10)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N=18)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)†</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%)† ‡</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
<td>40 (12–74)</td>
<td>0 (0–19)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — %‡</td>
<td>90 (55–100)</td>
<td>11 (1–35)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
<td>Not reached</td>
<td>NA‡</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
<td>28 (13–35)</td>
<td>NA‡</td>
<td>12 (10–13)</td>
</tr>
</tbody>
</table>
Pembrolizumab in Mismatched Repair Deficient Tumors

B Radiographic Response

- Mismatch repair–proficient colorectal cancer
- Mismatch repair–deficient colorectal cancer
- Mismatch repair–deficient noncolorectal cancer

Change from Baseline in the Sum of Longest Diameters (%)

- 20% increase (progressive disease)
- 30% decrease (partial response)
Pembrolizumab in Mismatched Repair Deficient Tumors

A  Progression-free Survival in Cohorts with Colorectal Cancer

- Probability of Progression-free Survival
- Months
- No. at Risk:
  - Mismatch repair-deficient: 11, 8, 6, 2, 0, 0
  - Mismatch repair-proficient: 21, 2, 1, 0, 0

B  Overall Survival in Cohorts with Colorectal Cancer

- Probability of Overall Survival
- Months
- No. at Risk:
  - Mismatch repair-deficient: 11, 9, 7, 5, 1, 0
  - Mismatch repair-proficient: 21, 12, 5, 1, 1, 0

P < 0.001 by log-rank test
P = 0.03 by log-rank test
Anti-PD1 is most important drug in history cancer medicine

- **IMMUNOTHERAPY: TRANSVERSAL IMPACT**

  - Melanoma: approved 2014, will take all first line + adjuvant
  - Renal: approval 2016, all the way to first line?
  - Bladder: (ASCO/ESMO 2014/15) will take first line
  - Lung: approved 2015, will take first line + adjuvant
  - Mesothelioma: AACR 2016
  - Head and Neck: (ASCO 2015) like lung: major results in 2015
  - Oesoph/Stomach: (ASCO GI 2015) may take first place
  - HCC: (ASCO 2015) potentially in first place
  - MSI CRC tumors: 60% response rate (ASCO 2015) various types
  - Various Mismatched Repair Deficient: 60% response rate (ASCO 15)
  - Anal Cancer: ESMO 2015
  - Merkel Cell: NEJM 2016
  - Hodgkin: approval in 2016? (ASH 2014)
  - TNBC?: JCO 2016
Mutational Load and Sensitivity to anti-CTLA4/PD1

MSI tumors (CRC and others): 60% response rate (ASCO 2015)
CRC MSI: RR 62%; CRC RR 0%; Others MSI RR 60% !!
Tumor antigens and response to Ab CTLA-4

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanjun Li, M.D., Ph.D., Ceyhan Elipenahi, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Luis Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.
IMMUNO – COMBOS

INHIBITOR COMBOS
Anti-CTLA4 + Anti-PD1
Initial Report of Overall Survival Rates From a Randomized Phase II Trial Evaluating the Combination of Nivolumab and Ipilimumab in Patients With Advanced Melanoma: CHECKMATE 069


1Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2University of Louisville, Louisville, KY, USA; 3New York University, New York, NY, USA; 4Gustave Roussy, Villejuif-Paris-Sud, France; 5Huntsman Cancer Institute, Salt Lake City, UT, USA; 6Beth Israel Deaconess Medical Center, Boston, MA, USA; 7Washington University, St Louis, MO, USA; 8Institut Universitaire du Cancer, Toulouse, France; 9Greenville Health System, Greenville, SC, USA; 10St Luke’s Cancer Center and Temple University, Bethlehem, PA, USA; 11University of New Mexico, Albuquerque, NM, USA; 12Cleveland Clinic, Cleveland, OH, USA; 13California Pacific Center for Melanoma Research, San Francisco, CA, USA; 14Duke University, Durham, NC, USA; 15Oregon Health & Science University, Portland, OR, USA; 16Dana-Farber Cancer Institute, Boston, MA, USA; 17Bristol-Myers Squibb, Princeton, NJ, USA.
Eligible patients with unresectable stage III or IV melanoma
- Treatment-naïve
- BRAF WT (N = 109) or BRAF MT (N = 33)
- Stratified by BRAF status

Treat until disease progression\textsuperscript{a} or unacceptable toxicity
- IPI-treated patients could receive NIVO monotherapy after disease progression

\textsuperscript{a}Treatment beyond initial investigator-assessed RECIST v1.1-defined progression is permitted in patients experiencing clinical benefit and tolerating study therapy. Upon confirmed progression and change of treatment, all patients were unblinded.

MT = mutation-positive; PFS = progression-free survival; Q3W = every 3 weeks; R = randomization; WT = wild-type
# Response to Treatment
(11 months of follow-up)

<table>
<thead>
<tr>
<th></th>
<th>BRAF WT</th>
<th>All Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO+IPI (N = 72)</td>
<td>IPI (N = 37)</td>
</tr>
<tr>
<td>Objective Response Rate – % (95% CI)a</td>
<td>61 (49–72)</td>
<td>11 (3–25)</td>
</tr>
<tr>
<td>Best Overall Response – %b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

*aProportion of patients with a confirmed complete or partial response; 95% CI is based on Clopper and Pearson method.

*bAs assessed by the investigator with the use of the Response Evaluations Criteria in Solid Tumors, version 1.1.

Tumor Burden Change From Baseline at 2 Years of Follow-up (All Randomized Patients)

- **NIVO + IPI**
  - Median change: -70%

- **IPI**
  - Median change: +5%

* = confirmed responder

Database lock Feb 2016
PFS at 2 Years of Follow-up
(BRAF Wild-type Patients)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI</th>
<th>IPI</th>
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</thead>
<tbody>
<tr>
<td>Death or disease progression, n/N</td>
<td>31/72</td>
<td>28/37</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (8.6-NR)</td>
<td>4.4 (2.8–5.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.35 (0.21–0.59)</td>
<td>&lt;0.0001</td>
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<tr>
<td>P value</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

NR = not reached
PFS at 2 Years of Follow-up (All Randomized Patients)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or disease progression, n/N</td>
<td>43/95</td>
<td>35/47</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (7.36–NR)</td>
<td>3.0 (2.7–5.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.36 (0.22–0.56)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NR = not reached

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI</th>
<th>IPI</th>
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</thead>
<tbody>
<tr>
<td>Months</td>
<td>95</td>
<td>69</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>
OS at 2 Years of Follow-up (BRAF Wild-type Patients)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 72)</th>
<th>IPI (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR</td>
<td>24.8 (10.3–NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.58 (0.31–1.08)*</td>
<td>*Exploratory endpoint</td>
</tr>
</tbody>
</table>

NR = not reached

- 22/37 (60%) of patients randomized to IPI crossed over to receive any systemic therapy at progression
• 30/47 (64%) of patients randomized to IPI crossed over to receive any systemic therapy at progression.
<table>
<thead>
<tr>
<th>Any subsequent therapy</th>
<th>NIVO+IPI (N = 95)</th>
<th>IPI (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PD-1 agents</td>
<td>18 (17)</td>
<td>62 (29)</td>
</tr>
<tr>
<td>BRAF inhibitor</td>
<td>4 (4)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>MEK inhibitor</td>
<td>3 (3)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Investigational agent</td>
<td>4 (4)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td>18 (17)</td>
<td>36 (17)</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>12 (11)</td>
<td>28 (13)</td>
</tr>
</tbody>
</table>

- Median time to subsequent therapy: Not reached for NIVO+IPI and 6.1 months (95% CI: 4.2–7.4) for IPI

*a*Patients may have received more than one subsequent therapy

*b*Including 26 (55%) patients who received NIVO after progression on IPI (per protocol); 3 additional patients received NIVO or pembrolizumab off study
Similar Efficacy Regardless of Tumor PD-L1 Status (All Randomized Patients, NIVO + IPI)

<table>
<thead>
<tr>
<th>ORR (11 months)*</th>
<th>PFS Rate (2 Year)*</th>
<th>OS Rate (2 Year)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 ≥5%</td>
<td>PD-L1 &lt;5%</td>
<td>67%</td>
</tr>
<tr>
<td>58%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>48%</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

*Of the 94 all randomized patients treated with the combination, 80 (85%) had quantifiable PD-L1 expression. 30% had PD-L1 tumor expression ≥5% and 70% had PD-L1 tumor expression <5%.
Nivo + Ipi vs Nivolumab vs Ipilimumab in Melanoma: CHECKMATE 067

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone

Unresectable or Metastatic Melanoma
- Previously untreated
- 945 patients

Randomize 1:1:1

Stratify by:
- PD-L1 expression*
- BRAF status
- AJCC M stage

N=314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression** or unacceptable toxicity

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.
## Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong>*</td>
<td>57.6 (52.0–63.2)</td>
<td>43.7 (38.1–49.3)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td>Two-sided P value vs IPI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td><strong>Best overall response — %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>11.5</td>
<td>8.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>46.2</td>
<td>34.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.1</td>
<td>10.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22.6</td>
<td>37.7</td>
<td>48.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Duration of response (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR (13.1, NR)</td>
<td>NR (11.7, NR)</td>
<td>NR (6.9, NR)</td>
</tr>
</tbody>
</table>

*By RECIST v1.1. NR, not reached.
PFS (Intent-to-Treat)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.4)</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank P<0.00001 vs. IPI
**Exploratory endpoint
**PFS by PD-L1 Expression Level (5%)**

**Ipilimumab vs Nivolumab vs Combo**

### PD-L1 ≥5%

<table>
<thead>
<tr>
<th></th>
<th>mPFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>14.0</td>
<td>0.40</td>
</tr>
<tr>
<td>NIVO</td>
<td>14.0</td>
<td>0.40</td>
</tr>
<tr>
<td>IPI</td>
<td>3.9</td>
<td>--</td>
</tr>
</tbody>
</table>

### PD-L1 <5%

<table>
<thead>
<tr>
<th></th>
<th>mPFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>11.2</td>
<td>0.42</td>
</tr>
<tr>
<td>NIVO</td>
<td>5.3</td>
<td>0.60</td>
</tr>
<tr>
<td>IPI</td>
<td>2.8</td>
<td>--</td>
</tr>
</tbody>
</table>

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.*

(Wolchok, ASCO 2015)
<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=313)</th>
<th>Nivolumab plus Ipilimumab (N=313)</th>
<th>Ipilimumab (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (Any)</td>
<td>311 (99.4)</td>
<td>312 (99.7)</td>
<td>308 (99.0)</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>136 (43.5)</td>
<td>215 (68.7)</td>
<td>173 (55.6)</td>
</tr>
<tr>
<td>Treatment-related adverse event†</td>
<td>257 (82.1)</td>
<td>299 (95.5)</td>
<td>268 (86.2)</td>
</tr>
<tr>
<td></td>
<td>51 (16.3)</td>
<td>172 (55.0)</td>
<td>85 (27.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (19.2)</td>
<td>138 (44.1)</td>
<td>103 (33.1)</td>
</tr>
<tr>
<td></td>
<td>7 (2.2)</td>
<td>29 (9.3)</td>
<td>19 (6.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>107 (34.2)</td>
<td>110 (35.1)</td>
<td>87 (28.0)</td>
</tr>
<tr>
<td></td>
<td>4 (1.3)</td>
<td>13 (4.2)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>59 (18.8)</td>
<td>104 (33.2)</td>
<td>110 (35.4)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>6 (1.9)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>81 (25.9)</td>
<td>126 (40.3)</td>
<td>102 (32.8)</td>
</tr>
<tr>
<td></td>
<td>2 (0.6)</td>
<td>15 (4.8)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (13.1)</td>
<td>81 (25.9)</td>
<td>50 (16.1)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>7 (2.2)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (5.8)</td>
<td>58 (18.5)</td>
<td>21 (6.8)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34 (10.9)</td>
<td>56 (17.9)</td>
<td>39 (12.5)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4 (1.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase level</td>
<td>12 (3.8)</td>
<td>55 (17.6)</td>
<td>12 (3.9)</td>
</tr>
<tr>
<td></td>
<td>4 (1.3)</td>
<td>26 (8.3)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (6.4)</td>
<td>48 (15.3)</td>
<td>23 (7.4)</td>
</tr>
<tr>
<td></td>
<td>1 (0.3)</td>
<td>8 (2.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase level</td>
<td>12 (3.8)</td>
<td>48 (15.3)</td>
<td>11 (3.5)</td>
</tr>
<tr>
<td></td>
<td>3 (1.0)</td>
<td>19 (6.1)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>27 (8.6)</td>
<td>47 (15.0)</td>
<td>13 (4.2)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (1.3)</td>
<td>37 (11.8)</td>
<td>36 (11.6)</td>
</tr>
<tr>
<td></td>
<td>2 (0.6)</td>
<td>24 (7.7)</td>
<td>27 (8.7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24 (7.7)</td>
<td>33 (10.5)</td>
<td>19 (6.1)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (7.3)</td>
<td>32 (10.2)</td>
<td>24 (7.7)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (4.5)</td>
<td>32 (10.2)</td>
<td>13 (4.2)</td>
</tr>
<tr>
<td></td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse event leading to discontinuation</td>
<td>24 (7.7)</td>
<td>114 (36.4)</td>
<td>46 (14.8)</td>
</tr>
<tr>
<td></td>
<td>16 (5.1)</td>
<td>92 (29.4)</td>
<td>41 (13.2)</td>
</tr>
</tbody>
</table>
Immunotherapy combo strategies
Breaking Tolerance is Prerequisite?

Cytokines
- IFN
- IL2
- IL7
- IL21
- GmCSF

Adoptive Tcell therapy
- Activated
- TCR engineered CARs

Vaccination
- DC
- DNA
- RNA

Immunocyte depletion
- Treg
- MDSC

MoAb-conjugates
Immunotherapy + Other Modalities
Guidance by Immunogenic Cell Death
Zitvogel & Kroemer

PREDICTIONS

- IMMUNO COMBOS will dominate the scene for years to come
- Breaking tolerance is first prerequisite and will get Nobel Price
- Will be backbone for any treatment of metastatic melanoma patients and many tumors to come
- Anti-PD-1/PD-L1 is key. Anti-CTLA4 remains key for “tail effect”? 
- Neoantigens / private antigens: sequencing and TcR cloning will lead further understanding” “let the body decide what is key !!
- Will cure / “clinically cure” > 50% of advanced melanoma patients over next 5 years. Will stabilize 50% of many tumor types: "new ceiling", to be broken with new insights
THANK YOU

COME VISIT GUSTAVE ROUSSY
Cancer Campus Grand Paris