Melanoma and introduction to immunotherapy

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Swiss Institute of Bioinformatics, Lausanne
Two simultaneous revolutions in stage IV melanoma

Targeted therapies

- BRAFi\(^1,2\):
  - 2nd Generation TKI:
    - Dual BRAF + MEK inhibition\(^4\)

Immune therapies

- CTLA-4 blockade\(^3\)
  - PD-1 blockade\(^5\)
  - Combined CTLA-4 + PD-1\(^6\)

Early clinical benefit

Late clinical benefit

Early and late clinical benefit

2nd generation strategies can both deliver early and late clinical benefits, challenging treatment plans

Overview of stage IV outcome

- Targeted therapies provide better early outcome...

- ... but immuno-oncology curves are crossing at around 14 months\(^1\)...

- ... and the difference seems to increase with time

\(^1\)Ugurel, *EJC* 2017
What is the best endpoint to describe such a benefit?

- mOS or mPFS are not adequate to describe the long term benefit
- P. Ascierto and G. Long have proposed to use landmark PFS
- PFS is not dependent on subsequent lines
- Another endpoint to drive stage IV development is CR rate...

1 Asierto, *Lancet Oncology* 2017
Overview of therapeutic options in melanoma
## Overview of therapeutic options in melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Loco-regional</th>
<th>Systemic</th>
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<tr>
<td></td>
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<tr>
<td>Stage I</td>
<td>Standard</td>
<td>No!</td>
</tr>
<tr>
<td>Stage II</td>
<td>Standard</td>
<td>No!</td>
</tr>
<tr>
<td>Stage III</td>
<td>Standard</td>
<td>Option? Cave!</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Option for selected</td>
<td>Option for palliation</td>
</tr>
</tbody>
</table>

A multidisciplinary team is needed specially for early stage disease!
Brief introduction to cancer immunotherapy
Escaping the immune system is a hallmark of cancer!

Hanahan & Weinberg, *Cell* 2011
Demonstration of the activity of cytotoxic T lymphocytes

Various types of tumor antigens

1) Differentiation
2) Overexpression
3) Cancer-Testis
4) Mutations
   (Neo-antigens)

P53 Antigen in MHC-1

P53 Mutation
PD-1/PD-L1 inhibition successes across multiple tumors

Nivolumab, pembrolizumab, and atezolizumab approval in multiple cancers

Somatic Mutation Frequency (/Mb)

- Nivolumab approval in RCC
- Nivolumab and Pembrolizumab approval in SCCHN
- Nivolumab and Atezolizumab approval in Bladder cancer
- Nivolumab, pembrolizumab, and atezolizumab approval in NSCLC
- Nivolumab and pembrolizumab approval in Melanoma

1. Lawrence, Nature. 2013
Immune phenotypes and immunotherapy

Adapted from
- Chen & Mellman, *Immunity*, 2013
Imperfect correlation between TIL and PD-L1 status

• Tumors can also be classified on the basis of their TIL and PD-L1 status
  • Type I: PD-L1 + TIL +
  • Type II: PD-L1 - TIL -
  • Type III: PD-L1 + TIL -
  • Type IV: PD-L1 - TIL +
• In melanoma, type I and II are the most prevalent
  • Type I: 38%
  • Type II: 41%
• Cave: such classifications provide a framework for further development but are oversimplifications of the underlying biology complexity
Immunotherapy: Checkpoints inhibitors

1. Relargage des antigènes
2. Présentation des antigènes
3. Activation des lymphocytes
4. Infiltration des lymphocytes dans la tumeur
5. Transfert des lymphocytes vers la tumeur
6. Reconnaissance des cellules tumorales
7. Destruction des cellules tumorales
8. Destruction des cellules tumorales

αCTLA-4
αPD-1
Checkpoints act at different stages of the immune cycle.
CTLA-4 blockade: ipilimumab (Yervoy)
Canonical mode of action (MoA) of ipilimumab

Activation

Inhibition

Dendritic Cell

CTLA-4

CD28

B7

Dendritic Cell

CTLA-4

Ipilimumab

Dendritic Cell

17th ESO-ESMO Masterclass in Clinical Oncology
However, ipilimumab MoA is much more complex!

1 Blocking CTLA4 inhibitory signal$^1$

2 Treg depletion by ADCC$^2$

3 Blocking IDO expression by APC$^3$

4 Blocking inhibitory cytokines$^3$

5 Blocking CD80 capture$^3$

6 Blocking CTLA4 ligands capture$^3$

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Long term benefit of CTLA-4 blockade: pooled analysis

- Long term benefit can be in part explained by the larger number of antigen recognized
- Upon loss of an antigen by the tumors, growth can be controlled by the other ones
- Ipilimumab has been shown to increase the antigenic repertoire

* Schadendorf, JCO 2015
1. PD-L1 expression induced by IFN


2. PD-L1 expression resulting from oncogenic events

Green, *Blood* 2010:
9p24.1 amplification leads to increased PD-L1 expression in Hodgkin
 PD-1 / PD-L1 pathway: biological interpretation

Tumor cell

PD-L1

Lymphocyte

INF-γ

=
**PD-1/PD-L1 inhibition successes across multiple tumors**

- Nivolumab, pembrolizumab, and atezolizumab approval in NSCLC
- Nivolumab, pembrolizumab, and atezolizumab approval in Melanoma
- Nivolumab and pembrolizumab approval in Lung SQ
- Nivolumab and pembrolizumab approval in Lung AD
- Nivolumab and pembrolizumab approval in Bladder cancer
- Nivolumab and pembrolizumab approval in SCCHN
- Nivolumab approval in RCC

1. Lawrence, Nature. 2013

**Somatic Mutation Frequency (/Mb)**

- Rhabdoid tumor
- Ewing sarcoma
- Thyroid
- AML
- Medulloblastoma
- Carcinoid
- Neuroblastoma
- Prostate
- CLL
- Low-grade glioma
- Breast
- Pancreas
- Multiple myeloma
- Kidney clear cell
- Kidney papillary cell
- Ovarian
- Glioblastoma
- Cervical
- DLBCL
- Head and neck
- Colorectal
- Esophageal
- Adenocarcinoma
- Stomach
- Bladder
- Lung AD
- Lung SQ
- Melanoma
- Carcinoid
- Neuroblastoma
- Prostate
- CLL
- Low-grade glioma
- Breast
- Pancreas
- Multiple myeloma
- Kidney clear cell
- Kidney papillary cell
- Ovarian
- Glioblastoma
- Cervical
- DLBCL
- Head and neck
- Colorectal
- Esophageal
- Adenocarcinoma
- Stomach
- Bladder
- Lung AD
- Lung SQ
- Melanoma
Toxicity management: detailed guidelines exist, e.g. ESMO

Haanen, Ann Oncol. 2017
Clinical management of stage III melanoma
Results from MSLT-2: no benefit to radical lymphadenectomy

Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. (Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)
Important:
The control arm is not follow-up, but active surveillance with 4 monthly ultrasounds!
Results from MSLT-2: no benefit to radical lymphadenectomy
Possible stage III melanoma management algorithm

- **pT1b-T4b cN0 cM0**

  - **SLNB**
    - **Adjuvant criteria?**
      - **No**
        - **US FU**
        - **CLND**
      - **Yes**
        - **Adjuvant**
        - **CLND**
        - **Relapse**
  - **Std. FU**
    - **Relapse**
    - **CLND**
    - **Adjuvant**

- **Adjuvant criteria?**
  - **No**
  - **Yes**
Adjuvant treatments
With 11% gain at 5 years, 89% of the population is exposed to treatment with no benefit and the number needed to treat is 9.1 compared to 35 for INF\(^1\)

\(^1\)Mocellin, Cochrane Review, 2013
**EORTC 18071/CA184-029: adjuvant ipilimumab**

Randomized, double-blind, phase 3 study evaluating the efficacy and safety of ipilimumab in the adjuvant setting for high-risk melanoma

- **Stratification factors:**
  - Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
  - Regions (North America, European countries and Australia)

**Enrollment Period:** June 2008 – July 2011

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

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>MAINTENANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipilimumab 10 mg/kg</strong></td>
<td><strong>Ipilimumab 10 mg/kg</strong></td>
</tr>
<tr>
<td><strong>Q3W X4</strong></td>
<td><strong>Q12W up to 3 years</strong></td>
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</table>

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>MAINTENANCE</th>
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<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>Q3W X4</strong></td>
<td><strong>Q12W up to 3 years</strong></td>
</tr>
</tbody>
</table>

**R**

- N=475
- N=476

N=951
EORTC 18071: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Deaths/patients</td>
<td>162/475</td>
<td>214/476</td>
</tr>
<tr>
<td>Hazard ratio (95.1% CI)*</td>
<td>0.72 (0.58 - 0.88)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value*</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Stratified by stage at randomization

CI = confidence interval; NR = not reached.
Checkmate-238: adjuvant nivolumab vs. ipilimumab

Patients with high-risk, completely resected stage IIIB/IIIC or stage IV melanoma

n = 453

Stratified by:
1) Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c
2) PD-L1 status at a 5% cutoff in tumor cells

Enrollment period: March 30, 2015 to November 30, 2015

Follow-up
Maximum treatment duration of 1 year

NIVO 3 mg/kg IV Q2W and
IPI placebo IV Q3W for 4 doses then Q12W from week 24

IPI 10 mg/kg IV Q3W for 4 doses then Q12W from week 24 and
NIVO placebo IV Q2W

Weber, ESMO 2017
Checkmate-238: primary endpoint – relapse free survival

<table>
<thead>
<tr>
<th></th>
<th>NIVO</th>
<th>IPI</th>
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</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>154/453</td>
<td>206/453</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR (16.6, NR)</td>
</tr>
<tr>
<td>HR (97.56% CI)</td>
<td>0.65 (0.51, 0.83)</td>
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</tr>
<tr>
<td>Log-rank P value</td>
<td>&lt;0.0001</td>
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</table>

Number of patients at risk:

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<tr>
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<th>NIVO</th>
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<td>453</td>
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<td>3/6</td>
<td>399</td>
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<td>9/12</td>
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<td>24/27</td>
<td>249</td>
<td>184</td>
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<tr>
<td>27/27</td>
<td>71</td>
<td>56</td>
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Weber, ESMO 2017
Adjuvant BRAFi + MEKi: COMBI-AD

Key eligibility criteria
• Completely resected, high-risk stage IIIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
• BRAF V600E/K mutation
• Surgically free of disease ≤ 12 weeks before randomization
• ECOG performance status 0 or 1
• No prior radiotherapy or systemic therapy

Stratification
• BRAF mutation status (V600E, V600K)
• Disease stage (IIIA, IIIB, IIIC)

Treatment: 12 months
Dabrafenib 150 mg BID + trametinib 2 mg QD (n = 438)
2 matched placebos (n = 432)

Follow-up until end of study

Primary endpoint: RFS
Secondary endpoints: OS, DMFS, FFR, safety
Adjuvant BRAFi + MEKi: COMBI-AD

Proportion Alive and Relapse Free

<table>
<thead>
<tr>
<th>Months From Randomization</th>
<th>Proportion Alive and Relapse Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 y</td>
<td>88%</td>
</tr>
<tr>
<td>2 y</td>
<td>67%</td>
</tr>
<tr>
<td>3 y</td>
<td>58%</td>
</tr>
</tbody>
</table>

1 y, 56%
2 y, 67%
3 y, 58%

**Dabrafenib plus trametinib**

- Events, n (%): 166 (38)
- Median (95% CI), mo: NR (44.5-NR)
- HR (95% CI): 0.47 (0.39-0.58); $P < .001$

**Placebo**

- Events, n (%): 248 (57)
- Median (95% CI), mo: 16.6 (12.7-22.1)
- HR (95% CI): $P = .0000000000000153$

No. at Risk

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<thead>
<tr>
<th>Dabrafenib plus trametinib</th>
<th>Placebo</th>
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NR, not reached.

Adjuvant BRAFi + MEKi: COMBI-AD

17th ESO-ESMO Masterclass in Clinical Oncology
Targeted therapies for stage IV melanoma
Targeted therapies in stage IV melanoma: main trials

**Preclinical programs:**
- Allosteric inhibitors

**Targeted therapies in stage IV melanoma:**

**COMBI-v**: BRAF\(^{V600}\)
- D+T vs. vemurafenib
- RR 64%, mPFS 11.4m
- HR OS/PFS: 0.69/0.75

**COMBI-d**: BRAF\(^{V600}\)
- D+T vs. dabrafenib
- RR 67%, mPFS 9.3m
- HR OS/PFS: 0.63/0.75

**Co-BRIM**: BRAF\(^{V600}\)
- V + cobi vs. V
- RR 68%, mPFS 9.9m
- HR OS/PFS: 0.51/0.65

**COLOMBUS**: BRAF\(^{V600}\)
- enco + bini / enco / V
- RR 63%, mPFS 14.9
- HR OS/PFS: NA/0.54

**BREAK-3**: BRAF\(^{V600}\)
- dabrafenib vs. DTIC
- RR 47%, mPFS 5.1m
- HR OS/PFS: 0.61/0.30

**BRIM-3**: BRAF\(^{V600}\)
- vemurafenib vs. DTIC
- RR 57%, mPFS 6.9m
- HR OS/PFS: 0.70/0.38

**NEMO**: NRAS\(^{mut}\)
- binimetinib (MEK162)
- RR 15%, mPFS 2.8m
- HR OS/PFS: 1.0 / 0.62

**Metric**: BRAF\(^{V600}\)
- trametinib vs DTIC
- RR 22%, mPFS 4.8m
- HR OS/PFS: 0.54/0.45

**Preclinical & clinical:**
- Allosteric and ATP competitors
  - GDC-0994 in phase I

---

N = 947 screened

- BRF V600E/K
- Unresectable stage IIIC/IV
- Treatment naive
- ECOG PS 0/1
- No brain metastases, unless:
  - Treated
  - Stable ≥ 12 weeks

Stratification
- BRF-mutant (V600E vs K)
- LDH (> ULN vs ≤ ULN)

Primary Endpoint: investigator-assessed PFS
Secondary Endpoints: OS, overall response rate (ORR), duration of response, safety

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; QD, once daily; ULN, upper limit of normal.

Presented by Keith Flaherty, ASCO 2016
COMBI-d: 3 year survival estimates

Progression-Free Survival

Dabrafenib + Trametinib (n = 211)

Dabrafenib + Placebo (n = 212)

Overall Survival

Dabrafenib + Trametinib (n = 211)

Dabrafenib + Placebo (n = 212)

58% of D+T patients alive at 3 years still on D+T

Presented By Keith Flaherty at 2016 ASCO Annual Meeting
Baseline Factors Influencing OS in Combi-d, Combi-v and Ph-II

Regression tree analysis based on:
- BMI
- Age
- LDH (N, > 1-ч Ϯdž ULN, ш Ϯdž ULN)
- Sex
- ECOG
- Visceral disease
- Number of sites
- Prior adjuvant immunotherapy

5 prognostic subgroups with very large OS differences

Adapted from:
GV. Long, SMR 2015, JCO 2016
K. Flaherty, ASCO 2016
Counteracting BRAF/MEKi resistance mechanisms
Strategies to overcome BRAFi + MEKi resistance

• Combination based on molecular escape
  • E.g: LOGIC-2 trial

• Sequential regimens
  • Ongoing

• Treatment beyond PD
  • +/- local therapy

• Engaging the immune system
  • Synergistic with combo?
Example of rational combination trial: LOGIC-2

- Strategies for rational combination at PD based on molecular escapes are now emerging
- An example is the LOGIC-2 trial: NCT02159066
  - Primary endpoint: ORR
  - Secondary endpoints: PFS, OS, ...
- Recruitment has been completed
- First data expected for 12.2017!

140 stage IV $\text{BRAF}^{\text{V600}}$ patients

- Binimetinib (MEK)
- Encorafenib (BRAF)

CDK4/6 inhibitor or
FGFR inhibitor or
PI3K inhibitor or
MET inhibitor or

LEE011
BGJ398
BKM120
INC280

Mandatory baseline and PD biopsies
Adding CDK4i to the BRAFi and MEKi backbone?

- Results from a phase I/II trial testing the triple combination of BRAF, MEK and CDK4 presented at ASCO\(^1\)
  - 42 patient in the phase II, BRAFi naïve were given
    - encorafenib 200 mg (BRAF)
    - binimetinib 45 mg (MEK)
    - ribociclib 600 mg (CDK4) (3w out of 4)
  - ORR was 52% compared to 63% in combo arm of COLOMBUS
  - mPFS 9.2 m compared to 14.9 m in combo arm of COLOMBUS
  - Explanation?
    - Lower dosage of BRAF and / or MEK?
    - High discontinuation rate?
    - PK/PD with triple combination?

\(^1\)Abstract 9518, Ascierto, ASCO 2017, Discussed by G. McArthur
Strategies to overcome BRAFi + MEKi resistance

• Combination based on molecular escape
  • E.g: LOGIC-2 trial

• Sequential regimens
  • Ongoing

• Treatment beyond PD
  • +/- local therapy

• Engaging the immune system
  • Synergistic with combo?
Rechallenge: prospective trial!

- BRAF + MEKi rechallenge, prospective phase II trial
- Patients having failed BRAFi or BRAF + MEKi with a drug free interval of 3+ months
- RR 32% (8/25)
- Baseline BRAF v600 Mut cfDNA was not associated with clinical benefit, but responders had a statistically more important cfDNA decline at W2

- Could resistance mechanisms predict clinical benefits in rechallenge?

Schreuer, Lancet Oncol 2017
Immuno-therapies for stage IV melanoma
Therapeutic opportunities: towards a rational selection of PD-1 based combos?
A large number of checkpoints are targeted in clinical trials

Activating Checkpoints
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Checkpoints
- CTLA-4
- PD-1
- TIM-3
- BTLA
- LAG-3
- VISTA
- TCR

Adapted from Mellman, Nature 2011

12*11=132 possible doublets.
☞ We need to guide trial development!

Blocking MABs

Combinatorial issue!
Towards a rational selection of PD-1 based combo?

- PD-L1 positivity ≥ 1% → αPD-1 alone?
- PD-L1 positivity < 1% → αPD-1 + αCTLA-4?
- High content in TAM → αPD-1 + αCSF1R?
- High IDO expression → αPD-1 + IDOi?
- T cell exhaustion, LAG3+? → αPD-1 + αLAG3?
- T cell exhaustion, TIM3+? → αPD-1 + αTIM3?

- Either baseline or on treatment biopsies can help guide decision
- All combos are being tested within clinical trials
- Complex biomarker will help optimal patient selection
# Selected PD-1-based checkpoint combos tested for melanoma

<table>
<thead>
<tr>
<th>Indication, clinical phase</th>
<th>Compound</th>
<th>Checkpoint target</th>
<th>PD-1 inhibitor</th>
<th>Clinical Trial.gov ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma, P I-II</td>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Pembrolizumab</td>
<td>NCT02089685</td>
</tr>
<tr>
<td>Solid tumors, P I-II</td>
<td>BMS-986218</td>
<td>CTLA-4</td>
<td>Nivolumab</td>
<td>NCT03110107</td>
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<td>Solid tumors, P I-II</td>
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<td>NCT01968109</td>
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<td>LAG-3</td>
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<td>Solid tumors, P I-II</td>
<td>Lirilumab</td>
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<td>Nivolumab</td>
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<td>Solid tumors, P I-II</td>
<td>BMS-986207</td>
<td>TIGIT</td>
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<td>Solid tumors, P I</td>
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<td>Pembrolizumab</td>
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<td>Enoblituzumab</td>
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<td>Pembrolizumab</td>
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<td>Melanoma, P III</td>
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<td>IDO</td>
<td>Pembrolizumab</td>
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<td>BMS-986205</td>
<td>IDO</td>
<td>Nivolumab</td>
<td>NCT02658890</td>
</tr>
<tr>
<td>Solid tumors, P I-II</td>
<td>Urelumab</td>
<td>CD137 (4-1BB)</td>
<td>Nivolumab</td>
<td>NCT02253992</td>
</tr>
<tr>
<td>Solid tumors, P I-II</td>
<td>BMS-986156</td>
<td>GITR</td>
<td>Nivolumab</td>
<td>NCT02598960</td>
</tr>
<tr>
<td>Solid tumors, P I-II</td>
<td>BMS-986178</td>
<td>OX40</td>
<td>Nivolumab</td>
<td>NCT02737475</td>
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<tr>
<td>Solid tumors, P I-II</td>
<td>Varlilumab</td>
<td>CD27</td>
<td>Nivolumab</td>
<td>NCT02335918</td>
</tr>
</tbody>
</table>
Rational combination or rational sequencing?

Possible strategies for I-O sequences or combos

1. Sequencing
   - PD-1
   - PD
   - 2nd I-O agent

2. Combo at relapse
   - PD-1
   - PD
   - PD-1
   - 2nd I-O agent

3. Combo at start
   - PD-1
   - 2nd I-O agent

Depending on the type of resistance mechanism, one strategy or the other might be more appropriate to obtain maximal global PFS. Biomarkers are required to guide such strategies.
Rational selection of PD-1 based combo at start

PD-1 + CTLA-4 inhibitor
data: Checkmate-067
CheckMate 067: Study Design

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:
- BRAF status
- AJCC M stage
- Tumor PD-L1 expression <5% vs ≥5%

Treat until progression or unacceptable toxicity

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

N=314

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=316

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

N=315

Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

*The study was not powered for a comparison between NIVO and NIVO+IPI
Improved survival for the PD-1 arms compared to CTLA-4

PD-1 or PD-1 + CTLA-4 are both valid first lines for stage IV melanoma

Wolchok, NEJM 2017
Imperfect current biomarkers for patient selection

- No good predictive biomarkers have been identified that allow to strongly separate the patient populations
  - PD-L1 and BRAF allow to select population with higher benefit, but the biomarker negative population still derives benefit

No clear PD-L1 cutoff
- 1% (44% of pts) as basis for patient discussion?

1 Wolchok, NEJM 2017
Imperfect current biomarkers for patient selection

- No good predictive biomarkers have been identified that allow to strongly separate the patient populations
- PD-L1 and BRAF allow to select population with higher benefit, but the biomarker negative population still derives benefit

ROC curves confirm the poor performance of PD-L1 to guide patient selection: Fig. S4

1 Wolchok, NEJM 2017
Towards complex, multidimensional predictive biomarkers
Searching for better biomarkers for stage IV patient selection

Wolchok, NEJM 2017
Checkmate-038 prospective biomarker study\textsuperscript{1}

- 68 advanced melanoma patients
- Multidimensional biomarker analysis at baseline and on treatment reveals molecular actions of anti-PD-1 therapy
  a) Anti-PD-1 therapy induces changes in the mutational burden of tumors
  b) Distinct changes in gene expression programs associate with clinical response
  c) Shifts in the TCR repertoire occur following immune checkpoint blockade
- This study is one example of the level of information that need to be integrated for complex biomarker research
- Many more to come!

\textsuperscript{1}Riaz, Cell 2017 (in print)
Conclusion and outlook
Conclusion: modern treatment of melanoma, a whole new world!

• In less than 10 years, the treatment of melanoma has been completely rewritten
• Two strategies have provided unprecedented overall survival benefits
  • Targeted and immuno-therapies
• Our challenge for the years to come is
  • to optimally combine and/or sequence them
  • to define predictive biomarkers for precise patient selection and maximal benefit, i.e. a cure!
Possible treatment algorithm for stage IV melanoma

1st Line
- Trial
- PD-1
- PD-1/CLTA-4
- BRAF WT

2nd Line
- Trial
- CTLA-4
- Chemo
- I-O Re-challenge
- BRAFi/MEKi

3rd Line
- Trial
- Chemo
- Chemo
- MEKi

BRAF Mutated
- Trial
- PD-1
- PD-1/CLTA-4
- BRAFi/MEKi

NRAS Mutated
- Trial
- PD-1
- PD-1/CLTA-4
- MEKi

PD-1
CTLA-4
BRAFi
Chemo

ESMO/ESO Masterclass in Clinical Oncology
March 25th 2018, Berlin, Germany
Thank you for your attention!