MELANOMA TREATMENT
COMBINING IMMUNOTHERAPY AND
TARGETED THERAPY

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Disclosure

Non-approved drugs and off-label use of drugs will be discussed
Overall Survival for Metastatic Melanoma

Survival data from 42 Phase II trials with over 2,100 stage IV patients:

- 12 month OS: 25.5%,
- median OS: 6.2 months

Adapted from Korn 2008

P Chapman et al NEJM 2011

Rapid effect of BRAF-inhibitor
Rapid but transient effect of BRAF-inhibitor

Hazard ratio, 0.37; 95% CI, 0.26 to 0.55; P<0.001
Rapid but transient effect of BRAF-inhibitor
COMBINATION ANTI-BRAF + ANTI-MEK

Vemurafenib (n = 352)\textsuperscript{a}
Median OS, 17.8 mo (95% CI, 15.6-20.7)
- 128 censored pts, 89 (70%) ongoing f/u,
of which 10 (11%) are still on study tx

HR, 0.68 (95% CI, 0.56-0.83)

2-y OS, 53%
3-y OS, 45%
2-y OS, 39%
3-y OS, 31%

Patients at risk, n
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
D + T & 352 & 311 & 245 & 201 & 171 & 150 & 127 & 33 \\
Vem & 352 & 289 & 203 & 154 & 119 & 103 & 81 & 22 \\
\hline
\end{tabular}

C Robert ESMO 2016
Different types of resistances

- Primary resistance
- Secondary resistance
- Dissociated response
Anti-CTLA-4
Ipilimumab

Pre-treated-pts
+/- gp100
HLA-A2
3mg/kg
Re-induction possible

naive-pts
+ DTIC
10 mg/kg
Maintenance possible

Hodi et al 2010 NEJM
Robert et al NEJM 2011
Anti-PD1 Immunotherapy: Two positive Phase III

Nivolumab vs chemotherapy  pembrolizumab vs ipilimumab

Decrease of the risk of death
58% vs chemotherapy
31 to 37% vs ipilimumab

Combination of anti-CTLA-4 + anti-PD1

Larkin et al AACR 2016
Combination of anti-CTLA-4 + anti-PD1

Database lock: Sept 13, 2016, minimum f/u of 28 months

Larkin et al AACR 2016
First-line therapy: Overall survival

Mean survival curves created by weighted averaging of digitised Kaplan-Meier survival curves of metastatic melanoma patients treated in selected clinical trials.

Longer Follow-up

Ugurel S et al Eur J Cancer In Press
Longer Follow-up

Uğurel S et al Eur J Cancer In Press
PDGFR; IGF-1R, EGFR, MET

Resistance mechanisms

MAPK reactivation only: 52-58%
• RAS mut 20%
• BRAF Splice vrt: 10-16%
• BRAF amplific: 13%
• MEK1/2 mut: 7%
• CDKN2A: 2-5%

Cell growth, prolif, survival

Shi et al Cancer Discov 2014
Van Allen et al Cancer Discov 2014
Rizos et al Clin Cancer Res 2014
Johnson et al Eur J Cancer 2015
PI3K pathway activation only: 5%
- AKT mut
- PTEN del

Cell growth, prolif, survival

PDGFR; IGF-1R, EGFR, MET

NRAS

CRAF → BRAF* → MEK → ERK

PI3K

AKT1

mTOR

Cyclin D

CDK4/6

Rb

E2F

PTEN

IKB

NFkB

Shi et al Cancer Discov 2014
Van Allen et al Cancer Discov 2014
Rizos et al Clin Cancer Res 2014
Johnson et al Eur J Cancer 2015
Both pathways are activated 18-20%.

Cell growth, prolif, survival
Cell growth, prolif, survival

- NRAS
- NRAS
- CRAF
- BRAF*
- MEK
- ERK
- PI3K
- PTEN
- mTOR
- IκB
- NFκB
- Cyclin D
- CDK4/6
- Rb
- E2F

- PDGFR; IGF-1R, EGFR, MET

Resistance mechanisms

None: 25%

Shi et al Cancer Discov 2014
Van Allen et al Cancer Discov 2014
Rizos et al Clin Cancer Res 2014
Johnson et al Eur J Cancer 2015
Cap-dependent translation initiation complex

Ribosomes

mRNA

eIF4F complex
The sustained activation of the eIF4F complex is associated in BRAF-mutant cancer cell lines

✓ with multiple mechanisms of resistance to BRAF inhibitor
✓ with resistance to anti-BRAF + anti-MEK combinations

in NRAS-mutant cancer cell lines

✓ with resistance to anti-MEK

Boussemart, Malka-Mahieu, Girault et al. Nature 2014
Malka-Mahieu et al., Cell Cycle 2016
Malka-Mahieu et al., Clin Cancer Res 2017
Non-genomic alteration lead to resistance

- Frequent non-genomic and immune alterations in acquired MAPKi-resistant melanoma
- Methylome (CpG)/transcriptome-wide alterations in functionnal genes
- c-MET, LEF1, and YAP1 dysregulation reduces MAPK addiction and apoptotic sensitivity

Hugo et al Cell 2015
Drug-dependency: towards an intermittent dosing regimen

Murine BRAF mutant xenograft model

Das Thakur et al. Nature 2013
Ex of early rechallenge

PET-CT July 2016

CT scan August 2016

PET-CT December 2016

Symptoms +

Anti- BRAF + Anti-MEK

After 5 days of wash out

Symptoms +++

Anti- BRAF + Anti-MEK
Genetic resistances to immunotherapies

- Mutation-derived modification of the INF-γ signaling pathway or loss of CI I expression

Zaretsky et al, NEJM 2016

Gao et al et al, Cell 2016
But durable interferon signaling leads to resistance via STAT1-induced epigenetic changes.
How is the immune system involved in response to targeted agents?

Hugo et al Cell 2015
Combining or Sequencing?

• Sequencing at progression?
• Before progression?
In a murine model

• In a syngeneic BRAFV600E mutant melanoma mouse model
• Increased T cell homing with D and/or T
• No impaired T cell function with T
• Up-regulation of PD-L1 and superiority of the triple combination

Keynote 022: Combination pembrolizumab + dabrafenib + trametinib

Grade 3 AE: 40%

Ribas et al. ASCO 2016
Vemurafenib + cobimetinib + atezolizumab

<table>
<thead>
<tr>
<th>Screening</th>
<th>Vem + Cobi run-in</th>
<th>Atezo + Vem + Cobi</th>
</tr>
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<tbody>
<tr>
<td>Up to 28 d</td>
<td>28 d</td>
<td>C1</td>
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- **Vem (PO BID)**
  - 960 mg

- **Cobi (PO QD, 21/7)**
  - 60 mg

- **Atezo (IV q2w)**
  - 800 mg

Hwu et al ESMO 2016
Roche C039262
Phase III Study

N = 500
- Previously Untreated
- Advanced BRAF V600 Mutant Melanoma
- PS 0 - 1
- Measurable disease by RECIST 1.1

Days 1-21
Cobimetinib 60 mg QD + Vemurafenib 960 mg BID

Days 22-28
Vemurafenib 960 mg BID

1:1

Days 22-28
Vemurafenib 720 mg BID + Vemurafenib Placebo

Atezolizumab Placebo Q2W + Cobimetinib 60 mg QD 21/7 + Vemurafenib 960 mg BID

Atezolizumab 840 mg Q2W + Cobimetinib 60 mg QD 21/7 + Vemurafenib 720 mg BID + Vemurafenib Placebo

28-day run-in

Tx until PD or toxicity
Novartis CPDR001F2301
Phase III Study

Part 1: Open-label safety run-in part
Part 2: Open-label biomarker part
Part 3: Double-blind, randomized part

Safety Run-In (N= 6/cohort)
Dabrafenib (D) + Trametinib (T) + PDR001

Pt population:
• BRAF V600 mutant unresectable or metastatic melanoma
• 1L setting
• PS 0-1

Determine PDR001 regimen

Randomized, Double-blind
(N=440, R 1:1)

Pt population:
• BRAF V600 mutant unresectable or metastatic melanoma
• 1L setting
• PS 0-2
• Elevated LDH

D + T + PDR001 (regimen determined in safety run-in)

D + T + Placebo

Biomarker Cohort (N = 20)
• Enrolment start after Cohort Dose Level 1 LPFV achieved
• D + T run in for 4 wks, then D+T+PDR 400mg q4w
Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma (NCT02224781)

Main objective OS

PI: Michael Atkins; ECOG-ACRIN Cancer Research Group
Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) followed by combo target therapy (dabrafenib/trametinib) and vice-versa.

- Patients with metastatic BRAF V600 mutated melanoma
- Sample size 230 pts

This study is designed as a phase II randomized trial with no formal comparative test.

**Endpoints:**
- **Primary** – OS
- **Secondary** – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR;
- Duration of Response, Toxicity, Biomarkers study

P Ascierto PI
Unresectable stage III or IV melanoma BRAF V600 mutated

No clinically significant tumor-related symptoms or evidence of rapidly progressive disease

ECOG 0-1

No previous systemic therapy with BRAF, MEK, CTLA-4, PDL1, PD1 inhibitors

Non-symptomatic brain metastases allowed

Systemic treatment with <10 mg daily prednisone equivalents allowed

Ipilimumab 1mg/kg Q3W 4 doses

a-PD-1

Brafi+ MEKi 2 months

Ipilimumab 1mg/kg Q3W 4 doses

a-PD-1
Many avenues are explored to overcome the resistance

+ radiotherapy
+ other IT
  - 41BB
  - OX-40
  - CD40
  - GITR
  - ICOS
  - IDO
+ other checkpoint-I
  - TIM 3; LAG 3
+ macrophage-I
  - CSFR1
+ chemo
+ local tt
  - Ipi
  - Oncol virus
  - TLR agonist
+ cancer vaccines
+ targeted therapies
  - BRAF, MEK
+ epigenetic modifiers
  - HDAC
+ Adopt C T
+ NK activation
We will also have to overcome

- Toxicity

- Financial issues

Ledford H, Nature 2013
Conclusion

• We are in a therapeutic revolution
• New challenges are fighting resistance mechanisms and identifying predictive biomarkers
• Combining or sequencing targeted therapies and immunotherapies are largely explored
• Preliminary results are encouraging but it is too early to recommend combination outside of clinical trials
Ensemble contre le mélanome
What strategy to adopt?

- Cellular adaptation: drug holiday
- Cycle between S and R: rechallenges
- Altered proportion of R and S cells with distinct growth: regrowth during drug holiday but re-sensitisation at rechallenge
- Slow growing sensitive
- Distinct sensitivity to agents A and B might beneficiate from treatment beyond PD, combination with a third agent, drug holiday

*Kuczynski et al Nat Rev Clin Oncol. 2013 Drug rechallenge and treatment beyond progression*