ESMO SUMMIT AFRICA 2020
Current Standards of Care and practice changing studies in Advanced Melanoma

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CONFLICT OF INTEREST DISCLOSURE

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Melanoma
Melanoma
Melanoma
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

Traitements approuvés dans le mélanome métastatique
Immune system in action
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
Advances in Melanoma Immunotherapy

NRAS
BRAF
MEK
ERK
CDK4/6
p14/p16
PI3K
PIK
AKT1
mTOR
PTEN

Differentiation
Cell membrane
Cytoplasm

Adenyl-cyclase
G protein

MITF
p14/p16
Cyclin D
CDK4/6
HDM2
p53
CREB
Rb
E2F

Apoptosis/survival
Proliferation

Transcription
Nucleus

NFκB
IKB

Transcription

MC1R
KIT
NRAS

50-60%
Rapid action of BRAF blockade

Hazard ratio, 0.37; 95% CI, 0.26 to 0.55; P<0.001
But transient action

Chapman et al NEJM 2011
Waggle et al JCO 2011
Anti-BRAF + anti-MEK combination decreases the risk of death of 30% vs anti-BRAF monotherapy and doubles the PFS.

Phase III
Nivolumab vs chemotherapy

Anti-PD-1
pembrolizumab vs ipilimumab

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 12 mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>NR (NR-NR)</td>
<td>74.1%</td>
<td>0.63 (0.47-0.83)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>NR (NR-NR)</td>
<td>68.4%</td>
<td>0.69 (0.52-0.90)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
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</table>

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

Robert et al NEJM 2015
Long term overall survival

Anti-PD1 pembrolizumab: 5 year OS 43.2%

Combination anti-CTLA-4+anti-PD1: ipilimumab+nivolumab
5 year OS 44% nivo and 52% ipi/nivo

Combined encorafenib+binimetinib 4 year OS 39%

Combined dabrafenib+trametinib
4 year OS : 37% and 5 year OS 34%

Robert et al Lancet Oncol 2019; Dummer et al ASCO 2019; Larkin et al ESMO 2019; Robert et al NEJM 2019
Overall survival for patients with metastatic melanoma

Response rates

- Anti-PD1/CTLA4: 50-55%
- Anti-PD1: 35-40%
- Anti-BRAF/MEK: 70%
- Anti-BRAF: 50%
- Anti-CTLA4: 15-20%
- Chemo: 10-15%
Can we cure some patients?
Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma


**Fig 3.** Disease-free survival (A) from time of experiencing complete response (CR) in all patients who achieved CR (n = 105) and (B) from time of discontinuation of pembrolizumab in patients who discontinued after CR for reasons other than progression (n = 89). The hash marks designate patients who were censored at that time point.

**Conclusion**
Patients with metastatic melanoma can have durable complete remission after discontinuation of pembrolizumab, and the low incidence of relapse after median follow-up of approximately 2 years from discontinuation provides hope for a cure for some patients. The mechanisms underlying durable CR require further investigation.
Checkmate 067
Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

Median OS, mo (95% CI)
- NIVO+IPI (n = 314): NR (38.2–NR)
- NIVO (n = 316): 36.9 (28.2–58.7)
- IPI (n = 315): 19.9 (16.8–24.6)

HR (95% CI) vs IPI
- 0.52 (0.42–0.64)
- 0.63 (0.52–0.76)
- –

HR (95% CI) vs NIVO*
- 0.83 (0.67–1.03)
- –
- –

No. at risk
- NIVO+IPI: 314, 292, 265, 248, 227, 222, 210, 201, 199, 193, 187, 181, 179, 172, 169, 164, 163, 159, 157, 155, 150, 92, 14, 0
- NIVO: 316, 292, 266, 245, 231, 214, 201, 191, 181, 175, 171, 164, 158, 150, 145, 142, 141, 139, 137, 135, 130, 78, 14, 0
- IPI: 315, 285, 253, 227, 203, 181, 163, 148, 135, 128, 113, 107, 100, 95, 94, 91, 87, 84, 81, 77, 73, 36, 12, 0

HR = 0.83 (95% CI, 0.67–1.03)

Larkin et al ESMO 2019
Checkmate 067
OS by LDH Level

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline LDH levels

**OS (%):**

- **LDH ≤ ULN**
  - NIVO+IPI (n = 199)
  - NIVO (n = 197)
  - IPI (n = 194)

| LDH ≤ ULN | Median, mo (95% CI) | HR (95% CI) vs IPI | HR (95% CI) vs NIVO
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<tr>
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<tbody>
<tr>
<td>NIVO+IPI</td>
<td>NR</td>
<td>0.48 (0.37–0.64)</td>
<td>0.83 (0.62–1.12)</td>
</tr>
<tr>
<td>NIVO</td>
<td>NR (40.2–NR)</td>
<td>0.58 (0.44–0.76)</td>
<td>–</td>
</tr>
<tr>
<td>IPI</td>
<td>28.8 (22.7–34.0)</td>
<td>–</td>
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- **LDH > ULN**
  - NIVO+IPI (n = 114)
  - NIVO (n = 112)
  - IPI (n = 115)

| LDH > ULN | Median, mo (95% CI) | HR (95% CI) vs IPI | HR (95% CI) vs NIVO
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<tbody>
<tr>
<td>NIVO+IPI</td>
<td>17.4 (10.7–42.6)</td>
<td>0.58 (0.43–0.79)</td>
<td>0.82 (0.59–1.13)</td>
</tr>
<tr>
<td>NIVO</td>
<td>16.0 (11.7–21.7)</td>
<td>0.71 (0.53–0.96)</td>
<td>–</td>
</tr>
<tr>
<td>IPI</td>
<td>10.9 (8.4–13.1)</td>
<td>–</td>
<td>–</td>
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</table>

Larkin et al ESMO 2019
Higher Proportion of Patients Alive and Treatment-Free at 5 Years With NIVO+IPI

Population analyzed: patients who were alive and followed on study

- **On study therapy**
- **Received subsequent systemic therapy**
- **Treatment-free (off study treatment and never received subsequent systemic therapy)**

### NIVO+IPI (n = 151)
- 74% (n = 112)
- 18% (n = 27)
- 8% (n = 12)

### NIVO (n = 130)
- 58% (n = 75)
- 24% (n = 31)
- 18% (n = 24)

### IPI (n = 67)
- 55% (n = 37)
- 45% (n = 30)

Median follow-up: 63.5 mo (range 56.9−68.7) for NIVO+IPI, NIVO, and IPI groups.

Larkin et al ESMO 2019
Standards of care for metastatic melanoma (besides clinical trials)

- **BRAF V600:**
  - targeted anti-BRAF+ MEK or immunotherapy with anti-PD1 +/- anti-CTLA4
  - targeted anti-BRAF+ MEK or immunotherapy with anti-PD1 +/- anti-CTLA4
  - Chemotherapy

- **BRAF WT**
  - immunotherapy with anti-PD1 +/- anti-CTLA4
  - chemotherapy
Ongoing trials
Clinical Trials Combining BRAFi + MEKi + anti–PD-1/L1

Dabrafenib + trametinib + durvalumab¹

Dabrafenib + trametinib + pembrolizumab² ³

Vemurafenib + cobimetinib + atezolizumab⁴

Dabrafenib + trametinib + spartalizumab⁵

BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. a Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. b Patients with PR and 100% change in SOD have (a) 100% change for all target lesions and (b) non-CR/non-PD response for nontarget lesions.


Presented by R Dummer at AACR 2018
Dabrafenib + trametinib +/- Pembrolizumab (Keynote 022)

ORR: 63.3% in triple combination

ORR: 71.7% in double combination

Ascierto et al Nat Med 2019
### Progression-Free Survival

**Median (95% Cl), mo**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + D + T</td>
<td>16.9 (11.3-27.9)</td>
<td>0.53 (0.34-0.83)</td>
</tr>
<tr>
<td>Placebo + D + T</td>
<td>10.7 (7.2-16.8)</td>
<td></td>
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</tbody>
</table>

**Progression-Free Survival (%)**

- **12-mo PFS**
  - Pembro + D + T: 62% (47%)
  - Placebo + D + T: 41% (16%)

- **24-mo PFS**
  - Pembro + D + T: 41% (16%)

**Based on Kaplan-Meier estimate of PFS, per investigator assessment.**

**Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.**

Data cutoff: Jun 26, 2019.

*Ferruci et al SMR 2019*
Overall Survival

Events, Median\textsuperscript{a} (95% CI, mo) HR\textsuperscript{b} (95% CI)\textsuperscript{b}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + Durvalumab + Tremelimab</td>
<td>26 (43.3)</td>
<td>NR (23.9-NR)</td>
<td>0.64 (0.38-1.06)</td>
</tr>
<tr>
<td>Placebo + Durvalumab + Tremelimab</td>
<td>36 (60.0)</td>
<td>26.3 (18.2-NR)</td>
<td></td>
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</tbody>
</table>

\textsuperscript{a}Based on Kaplan-Meier estimate of overall survival.
\textsuperscript{b}Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Data cutoff: Jun 26, 2019.

Ferruci et al SMR 2019
Phase II Randomized trial SEquential COMBo Immuno and Target therapy (SECOMBIT)

- 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

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
Objective: do we improve patients outcome if immunotherapy is preceded by a short course of targeted therapy?

Key eligibility criteria

- Aged $\geq$ 18 years
- Treatment-naïve patients
- Presence of $BRAF^V600E$ or $V600K$ mutation in tumour tissue prior to enrolment
- ECOG PS 0–1

Multicentre, two-arm, open-label, randomised comparative Phase 2 study

Randomisation

- ENCO 450 mg PO QD + BINI 45 mg PO BID
- NIVO 3 mg/kg Q3W + IPI 1 mg/kg Q3W for 4 doses then NIVO 480 mg IV Q4W

After 12 weeks

- NIVO 3 mg/kg Q3W + IPI 1 mg/kg Q3W for 4 doses then NIVO 480 mg IV Q4W
- ENCO 450 mg PO QD + BINI 45 mg PO BID until progression 2

Progression

Investigator Choice until progression 2

Primary endpoint

- PFS

Secondary endpoints

- OS
- CR
- ORR
- PFS2*
- Safety

*PFS2 is defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first
Combination of Immunotherapies

IDO inhibitor? Yes

Oncolytic virus? TVEC? ?

TLR9 agonist? ?

• Long term results show a 5 year OS rate between 34% with targeted agents to 52% with ipilimumab+nivolumab

• The most effective regimen is also the most toxic

• Stopping Immunotherapy can be considered for complete responders

• Perspectives: New combinations and sequential regimen