Immunootherapy in Unresectable or Metastatic Melanoma:
Where Do We Stand?

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Overview

• Background

• Immunotherapy clinical decision questions 2016

• Optimizing immunotherapy – a look to the future
Immunotherapy for Melanoma

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Checkpoint Inhibitors
Checkpoint Inhibitors Approved for Melanoma

- Anti-CTLA4 antibody: ipilimumab
- Anti-PD-1 inhibitors: pembrolizumab, nivolumab
- Combination anti-CTLA4 and anti-PD-1 (ipilimumab and nivolumab)
Overview

• Background

• **Immunotherapy clinical decision questions 2016**

• Optimizing immunotherapy – a look to the future
Immunotherapy for Melanoma
Questions in the Clinic

• Is checkpoint inhibition with CTLA-4 better than chemotherapy and vaccines?
• Is anti-PD-1 better than chemotherapy second line after anti-CTLA-4?
• Is anti-PD-1 better than ipilimumab first line?
• Is combination anti-CTLA-4 and anti-PD-1 better than either one alone?
• What is the correct sequence of treatment for $BRAF^+$ patients?
Clinical Results With Ipilimumab
(2nd and 1st Line)
Ipilimumab vs Vaccine and Ipi + DTIC vs DTIC

HR: 0.66 and 0.68
Pretreated pts
Ipi 3 mg/kg +/- gp100

HR: 0.72
First line
Ipi 10 mg/kg + DTIC


Ipilimumab (anti-CTLA-4) is better than chemotherapy or vaccines
Immunotherapy for Melanoma
Questions in the Clinic

• Is checkpoint inhibition with CTLA-4 better than chemotherapy and vaccines?

• Is anti-PD-1 better than chemotherapy second line after anti-CTLA-4?

• Is anti-PD-1 better than ipilimumab first line?

• Is combination anti-CTLA-4 and anti-PD-1 better than either one alone?

• What is the correct sequence of treatment for $BRAF^+$ patients?
KEYNOTE-002 (NCT01704287): International, Randomized, Pivotal Study Pembrolizumab Post Ipilimumab

**Patients**
- Advanced melanoma
- PD within 24 weeks after ≥2 IPI doses
- Previous BRAF or MEK inhibitor (if BRAF mutant)
- ECOG PS 0-1
- Resolution of IPI-related AEs
- No chronic systemic steroid therapy (>10 mg/day prednisone or equivalent)
- No active autoimmune disease

**Stratification factors:**
- ECOG PS (0 vs 1)
- LDH (normal vs elevated)
- BRAF status (mutant vs wild type)

**Primary endpoints:** PFS and OS
**Secondary endpoints:** ORR, duration of response, safety

KEYNOTE-002: Progression-Free Survival
(Post Ipilimumab, RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 6 mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 Q3W</td>
<td>2.9 (2.8-3.8)</td>
<td>34%</td>
<td>0.57 (0.45-0.73)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>N = 180</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembro 10 Q3W</td>
<td>2.9 (2.8-4.7)</td>
<td>38%</td>
<td>0.50 (0.39-0.64)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>N = 181</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2.7 (2.5-2.8)</td>
<td>16%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>N = 179</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After ipilimumab, anti-PD-1 is better than chemotherapy
Immunotherapy for Melanoma
Questions in the Clinic

• Is checkpoint inhibition with CTLA-4 better than chemotherapy and vaccines?
• Is anti-PD-1 better than chemotherapy second line after anti-CTLA-4?
• Is anti-PD-1 better than ipilimumab first line?
• Is combination anti-CTLA-4 and anti-PD-1 better than either one alone?
• What is the correct sequence of treatment for $BRAF^+$ patients?
KEYNOTE-006 Study Design

Patients
- Unresectable, stage III or IV melanoma
- ≤1 previous therapy, excluding anti–CTLA-4, PD-1, or PD-L1 agents
- Known BRAF status
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

Stratification factors:
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive vs negative)

Pembrolizumab
- 10 mg/kg IV q 2 weeks for 2 years

Pembrolizumab
- 10 mg/kg IV q 3 weeks for 2 years

Ipilimumab
- 3 mg/kg IV q 3 weeks x 4 doses

R 1:1:1

- Primary endpoints: PFS and OS
- Secondary endpoints: Overall response rate (ORR), duration of response (DoR), safety

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1

aPrior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
bDefined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).


**Overall Survival**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro q2w</td>
<td>122</td>
<td>0.68 (0.53-0.87)</td>
<td>.00085</td>
</tr>
<tr>
<td>Pembro q3w</td>
<td>119</td>
<td>0.68 (0.53-0.86)</td>
<td>.00083</td>
</tr>
<tr>
<td>Ipi</td>
<td>142</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Final analysis data cutoff date: Dec 3, 2015.

Anti-PD-1 is better than ipilimumab front line
Immunotherapy for Melanoma
Questions in the Clinic

• Is checkpoint inhibition with CTLA-4 better than chemotherapy and vaccines?
• Is anti-PD-1 better than chemotherapy second line after anti-CTLA-4?
• Is anti-PD-1 better than ipilimumab first line?
• Is combination anti-CTLA-4 and anti-PD-1 better than either one alone?
• What is the correct sequence of treatment for \textit{BRAF}^+ patients?
CheckMate-067: Study Design

- Randomized, double-blind, phase II 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

NIVO 1mg/kg + IPI 3mg/kg Q3W for 4 doses then NIVO 3mg/kg Q2W
n = 314

NIVO 3mg/kg Q2W + IPI-matched placebo
n = 316

IPI 3mg/kg Q3W for 4 doses + NIVO-matched placebo
n = 315

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.

Progression-Free Survival (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 (95% CI) vs NIVO</td>
<td>0.76 (0.60-0.92)**</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank P<.00001 vs IPI  **Exploratory endpoint

## Safety Summary

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI (n = 313)</th>
<th>NIVO (n = 313)</th>
<th>IPI (n = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Treatment-related adverse event (AE)</td>
<td>95.5</td>
<td>55.0</td>
<td>82.1</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>36.4</td>
<td>29.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Initial Report of Overall Survival Rates From a Randomized Phase II Trial Evaluating the Combination of Nivolumab and Ipilimumab in Patients With Advanced Melanoma

**OS at 2 Years of Follow-up (All Randomized Patients)**

- **30/47 (64%)** of patients randomized to IPI crossed over to receive any systemic therapy at progression.

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 95)</th>
<th>IPI (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS, months (95% CI)</strong></td>
<td>NR (11.9–NR)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.74 (0.43–1.26)*</td>
<td></td>
</tr>
</tbody>
</table>

*Exploratory endpoint

NR = not reached

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Combination anti-ipilimumab and anti-PD-1 is better than ipilimumab and maybe better than anti-PD-1
Immunotherapy for Melanoma
Questions in the Clinic

• Is checkpoint inhibition with CTLA-4 better than chemotherapy and vaccines?
• Is anti-PD-1 better than chemotherapy second line after anti-CTLA-4?
• Is anti-PD-1 better than ipilimumab first line?
• Is combination anti-CTLA-4 and anti-PD-1 better than either one alone?
• What is the correct sequence of treatment for BRAF+ patients?
**BRAF Mutation**

- **Growth Factors**
  - RAS
  - BRAF
  - MEK
  - ERK

**BRAF** mutation is present in ~50% of melanomas.

Increased cell proliferation and survival.
**Study Rationale**

**BRAFi (dabrafenib)**
- PFS HR, 0.37 vs DTIC\(^1\)
- Hyperproliferative skin AEs

**BRAFi (vemurafenib)**
- PFS HR, 0.38 vs DTIC\(^2\)
- Hyperproliferative skin AEs

**MEKi (trametinib)**
- PFS HR, 0.45 vs chemotherapy\(^3\)

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**RAS**

**mutBRAF**

**MEK**

**pERK**

Proliferation, Survival, Invasion, Metastasis

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**BRAFi + MEKi ph III studies**

**Dabrafenib + trametinib (D + T)**
- PFS HR, 0.67 vs dabrafenib\(^4\)
- OS HR, 0.71 vs dabrafenib\(^4\)

**Vemurafenib + cobimetinib**
- PFS HR, 0.58 vs vemurafenib\(^6\)
- OS HR, 0.70 vs vemurafenib\(^6\)

Decreased hyperproliferative skin AEs\(^4,5,6\)

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**References**


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AE, adverse event; BRAF, v-Raf murine sarcoma viral oncogene homolog B; BRAFi, BRAF inhibitor; DTIC, dacarbazine; HR, hazard ratio; MEK, mitogen-activated protein kinase kinase; MEKi, MEK inhibitor; mut, mutant; OS, overall survival; pERK, phospho-extracellular signal-regulated kinase; PFS, progression-free survival; ph, phase.
COMBI-d: PFS and OS\textsuperscript{a}

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

**Progression-Free Survival**

- **Dabrafenib + Trametinib (n = 211)**
  - 2-yr PFS, 30\%
  - 3-yr PFS, 22\%
- **Dabrafenib + Placebo (n = 212)**
  - 2-yr PFS, 16\%
  - 3-yr PFS, 12\%

<table>
<thead>
<tr>
<th>Months From Randomization</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>D + T</td>
<td>211 137 84 69 54 45 31 0</td>
</tr>
<tr>
<td>D + Pbo</td>
<td>212 110 67 41 29 11 7 1 0</td>
</tr>
</tbody>
</table>

**Overall Survival**

- **Dabrafenib + Trametinib (n = 211)**
  - 2-yr OS, 52\%
  - 3-yr OS, 44\%
- **Dabrafenib + Placebo (n = 212)**
  - 2-yr OS, 43\%
  - 3-yr OS, 32\%

<table>
<thead>
<tr>
<th>Months From Randomization</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>D + T</td>
<td>211 187 143 111 96 86 76 13 0</td>
</tr>
<tr>
<td>D + Pbo</td>
<td>212 175 138 104 84 69 57 7 0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Intent-to-treat population; \textsuperscript{b} Dabrafenib + placebo includes 26 patients who crossed over to combination arm; +, censored.

Antitumoral Response: Targeted Therapies vs Immunotherapies (CTLA-4 Antibodies)

EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo

ECOG and SWOG protocol – Atkins, Chmielowski
Anticipated opening 6/2015

ECOG PS
1. 0
2. 1

LDH
1. Normal
2. Elevated

PD

Arm 1:
Ipi 3/Nivo 1 mg/kg q 3wks x 4 +Maint Nivo

D 150 BID / T 2 mg Qd

Arm 2:
D 150 BID / T 2 mg Qd

Ipi 3/Nivo 1 mg/kg q 3wks x 4 +Maint Nivo

Immunotherapy for Melanoma Answers in August 2016?

• Is checkpoint inhibition with CTLA-4 better than chemotherapy and vaccines?  
  – YES!

• Is anti-PD-1 better than chemotherapy second line after anti-CTLA-4?  
  – YES!
• Is anti-PD-1 better than ipilimumab first line?  
  – YES!

• Is combination anti-CTLA-4 and anti-PD-1 better than either one alone?  
  – MAYBE!

• What is the correct sequence of treatment for BRAF+ patients?  
  – NOT SURE!
Overview

• Background
• Immunotherapy clinical decision questions 2016
• Optimizing immunotherapy – a look to the future
How Can Immunotherapy be Optimized and Improved?

• **Addition of other checkpoint modulators**

• **BRAF/MEK combination**

• **Reduce toxicity of combination therapy**
  – Lower dose ipilimumab

• **Can we “injure” the tumor to render it more vulnerable to systemic immune attack?**
  – Oncolytic therapy
  – Radiation/chemotherapy
T-Cell Immune Checkpoints

Activating receptors:
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

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

Agonistic Abs

Blocking Abs

T cell stimulation

How Can Immunotherapy be Optimized and Improved?

- Addition of other checkpoint modulators
- **BRAF/MEK** combination
- Reduce toxicity of combination therapy
  - Lower dose ipilimumab
- Can we “injure” the tumor to render it more vulnerable to systemic immune attack?
  - Oncolytic therapy
  - Radiation/chemotherapy
### BRAF-MEK-PDL1
Dabrafenib + Trametinib + Durvalumab

<table>
<thead>
<tr>
<th>Clinical activity</th>
<th>Cohort A (n = 26) D + T + M</th>
<th>Cohort B (n = 19) T + M</th>
<th>Cohort C (n = 15) T → M (sequential)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>18 (69)</td>
<td>4 (21)</td>
<td>2a (13)</td>
</tr>
<tr>
<td>DCR (CR + PR + SD), n (%)</td>
<td>26 (100)</td>
<td>15 (79)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>SD ≥12 weeks, n (%)</td>
<td>4 (15)</td>
<td>10 (53)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Ongoing responders, n/N (%)</td>
<td>16/18 (89%)</td>
<td>4/4 (100%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Range of duration of ongoing response, weeks</td>
<td>7.7+ to 50.6+</td>
<td>7.9+ to 24.7+</td>
<td>7.0+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event (AE), n (%)a</th>
<th>Cohort A (n = 26) D + T + M</th>
<th>Cohort B (n = 20) T + M</th>
<th>Cohort C (n = 19) T → M (sequential)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>26 (100)</td>
<td>20 (100)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>12 (46)</td>
<td>9 (45)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>8 (31)</td>
<td>4 (20)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>AE leading to discontinuation of any drug</td>
<td>3 (12)</td>
<td>3 (15)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AE related to MEDI4736</td>
<td>14 (54)</td>
<td>7 (35)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>AE related to dabrafenib and/or trametinib</td>
<td>22 (85)</td>
<td>19 (95)</td>
<td>15 (79)</td>
</tr>
</tbody>
</table>

How Can Immunotherapy be Optimized and Improved?

• Addition of other checkpoint modulators
• BRAF/MEK combination
• Reduce toxicity of combination therapy
  – Lower dose ipilimumab
• Can we “injure” the tumor to render it more vulnerable to systemic immune attack?
  – Oncolytic therapy
  – Radiation/chemotherapy
KEYNOTE-029: Study Design

**Dose Run-In (Part 1A)**
- **Patients**
  - Advanced or metastatic melanoma, any number of prior therapies, OR
  - Advanced clear cell RCC, ≥1 prior therapy
  - No prior anti-CTLA4 or anti-PD1/PD-L1
  - ECOG PS 0 or 1

  ![Diagram](image)
  - Pembro 2 mg/kg q3W up to 24 months + IPI 1 mg/kg q3W x 4 doses
  - Tolerable based on DLT rate
  - Stop development of pembro + ipi

**Primary endpoint:**
Dose-limiting toxicity (DLT) rate

**Dose Expansion (Part 1B)**
- **Patients**
  - Advanced melanoma
  - Any number of prior therapies
  - No prior anti-CTLA4 or anti-PD1/PD-L1
  - ECOG PS 0 or 1

  ![Diagram](image)
  - Yes
  - No

**Primary endpoint:**
Safety

**Secondary endpoints:**
ORR, DOR, and PFS (per RECIST v1.1) and OS

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**National Institutes of Health. Available at: www.clinicaltrials.gov/ct2/show/NCT02089685.**
**Accessed June 5, 2016.**

Immune-Mediated AEs: Incidence

Any: 58%
Grade 3-4: 25%

- Hypothyroidism: Grade 1-2 (16%), Grade 3-4 (14%)
- Hyperthyroidism: Grade 1-2 (10%), Grade 3-4 (6%)
- Hypophysitis: Grade 1-2 (8%), Grade 3-4 (8%)
- Pneumonitis: Grade 1-2 (8%), Grade 3-4 (8%)
- Hepatitis: Grade 1-2 (8%), Grade 3-4 (8%)
- Colitis: Grade 1-2 (8%), Grade 3-4 (8%)
- Skin reactions: Grade 1-2 (8%), Grade 3-4 (8%)
- Thyroiditis: Grade 1-2 (8%), Grade 3-4 (8%)
- Adrenal insufficiency: Grade 1-2 (8%), Grade 3-4 (8%)
- Infusion reaction: Grade 1-2 (8%), Grade 3-4 (8%)
- Pancreatitis: Grade 1-2 (8%), Grade 3-4 (8%)
- Uveitis: Grade 1-2 (8%), Grade 3-4 (8%)
- Nephritis: Grade 1-2 (8%), Grade 3-4 (8%)
- T1DM: Grade 1-2 (8%), Grade 3-4 (8%)
- Myositis: Grade 1-2 (8%), Grade 3-4 (8%)

*aIncludes grade 3 rash (n = 6), grade 3 drug reaction (n = 3), grade 3 pemphigoid (n = 1), and grade 2 exfoliative dermatitis (n = 1)
Data cutoff date: March 17, 2016

Best Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)

Data cutoff date: March 17, 2016

Change From Baseline, %

Median change:  
-54.5%

ORR = 57%

How Can Immunotherapy be Optimized and Improved?

• Addition of other checkpoint modulators
• BRAF/MEK combination
• Reduce toxicity of combination therapy
  – Lower dose ipilimumab
• Can we “injure” the tumor to render it more vulnerable to systemic immune attack?
  – Oncolytic therapy
  – Radiation/chemotherapy
Soft Tissue/Skin Metastases
Role for Intrallesional Oncolytic Therapy?

- Soft tissue and skin metastases occur frequently in melanoma
- Local-regional control is clinically important
- Systemic Therapy may not always be possible or appropriate
- Newer IL agents produce systemic responses
  - Combination with PD-1 agents an attractive strategy
3% – 10% of primary melanoma develop local/in-transit recurrences
- High-risk groups: thick, ulcerated, positive SLN, lower extremity

Source of significant morbidity

Greater than 50% risk of distant disease and death

AJCC, American Joint Committee on Cancer; SLN, sentinel lymph node
Several Intralesional Oncolytic Therapies in Development

- Talimogene laherparepvec (FDA approved)
- PV-10 (phase II, 50% RR, phase III trial ongoing)
- IL-12
- HF-10
- Coxsackie virus (CVA21)
How Do We Measure Response to Immunotherapy?
Patterns of Response to Ipilimumab in Melanoma

Response in baseline lesions

“Stable disease” with slow, steady decline in tumor volume

Response after initial decrease in tumor volume

Reduction in total tumor burden after the appearance of new lesions

Comparison Between WHO Criteria and the irRC

To systematically characterize additional patterns of response in patients with advanced melanoma, underlying WHO criteria were evolved into immune-related response criteria (irRC)

<table>
<thead>
<tr>
<th>WHO</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>New, measurable lesions (i.e., ≥5 × 5 mm)</td>
<td>Incorporated into tumor burden</td>
</tr>
<tr>
<td>New, nonmeasurable lesions (i.e., &lt;5 × 5 mm)</td>
<td>Do not define progression (but preclude irCR)</td>
</tr>
<tr>
<td>Non-index lesions</td>
<td>Contribute to defining irCR (complete disappearance required)</td>
</tr>
<tr>
<td>CR</td>
<td>Disappearance of all lesions in two consecutive observations not less than 4 wk apart</td>
</tr>
<tr>
<td>PR</td>
<td>≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions</td>
</tr>
<tr>
<td>SD</td>
<td>50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions</td>
</tr>
<tr>
<td>PD</td>
<td>At least 25% increase in tumor burden compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)</td>
</tr>
</tbody>
</table>

Summary & Conclusions

• Immunotherapy with checkpoint inhibitors is a front-line option for all patients
  – Anti-PD1 beats anti-CTLA4
  – Both beat chemotherapy
  – Combinations look better than single agent

• BRAF-mutated patients may receive MAP-kinase–directed therapy or immunotherapy
  – Combination BRAF/MEK is better than BRAF alone

• New combinations are being explored
  – Increase efficacy
  – Reduce toxicity