Immunotherapy of Melanoma

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Overview

- Metastatic Melanoma
- Adjuvant therapy for High-risk
- Practical Questions
- Future Directions
Overview

- Metastatic Melanoma
- Adjuvant therapy for High-risk
- Practical Questions
- Future Directions
Today’s Immunotherapy = Checkpoint Inhibitors
Check-Point Inhibitors Approved for Melanoma

- Anti CTLA4 antibody: Ipilimumab
- Anti PD-1 inhibitors: pembrolizumab, nivolumab
- Combination anti CTLA-4 and anti-PD1 (ipilimumumab and nivolumab)
Clinical Results with Ipilimumab (2nd and 1st line)
Ipilimumab vs vaccine and Ipi + DTIC vs DTIC

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

Hodi FS, et al. *N Engl J Med*. 2010;363:711-23.

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

Robert C, et al. *N Engl J Med*. 2011;364:2517-26.
Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma

Overall Survival (%)

Years

[Graph showing survival data over 10 years]

1. Schadendorf et al. J Clin Oncol 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.
Keynote-006 Front-line Pembrolizumab vs Ipilimumab

Patients

- Unresectable, stage III or IV melanoma
- ≤1 prior therapy, excluding anti-CTLA-4, PD-1, or PD-L1 agents
- Known \(BRAF\) status\(^b\)
- 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\(^c\) vs negative)

- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

Pembrolizumab

- 10 mg/kg IV Q2W
- Pembrolizumab 10 mg/kg IV Q3W
- Ipilimumab 3 mg/kg IV Q3W x 4 doses

\(^a\)Patients enrolled from 83 sites in 16 countries.

\(^b\)Prior 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.

\(^c\)Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.
## Tumor Response (irRC, investigator)

|               | Pembrolizumab | Ipilimumab |
|---------------|---------------|------------|
|               | N = 556       | N = 278    |
| ORR, % (95% CI)| 42 (38-46)    | 16 (12-21) |
| Best overall response, % (95% CI) |            |            |
| CR            | 13 (11-16)    | 3 (1-6)    |
| PR            | 29 (25-33)    | 14 (10-18) |
| SD            | 21 (18-25)    | 25 (20-31) |
| PD            | 29 (26-33)    | 39 (33-45) |

Analysis includes all randomized patients with measurable disease at baseline who received ≥1 pembrolizumab dose. Data cutoff date: Nov 3, 2016.
Overall Survival
Median Follow-Up 45.9 (0.3-50.0) Months

|                | All Patients | Treatment-Naive Patients |
|----------------|--------------|--------------------------|
|                | Events, n    | HR* (95% CI)             | Median, mo (95% CI) |
| pembrolizumab   | 309          | 0.73 (0.61-0.89)         | 32.7 (24.5-41.6)   |
| ipilimumab      | 164          | -                        | 15.9 (13.3-22.0)   |

*Based on Cox regression model with treatment as covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative), and ECOG (0 vs 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum was excluded from treatment comparison. °Derived by the product-limit (Kaplan-Meier) method for censored data. Data cutoff: Dec 4, 2017.
Blocking CTLA-4 and PD-1
CA209-067: 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:
- 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.
**Updated Response To Treatment**

|                        | NIVO+IPI (N=314) | NIVO (N=316) | IPI (N=315) |
|------------------------|------------------|--------------|-------------|
| ORR, % (95% CI)*       | 58.9 (53.3–64.4) | 44.6 (39.1–50.3) | 19.0 (14.9–23.8) |
| Best overall response — % |                  |              |             |
| Complete response      | 17.2             | 14.9         | 4.4         |
| Partial response       | 41.7             | 29.7         | 14.6        |
| Stable disease         | 11.5             | 9.8          | 21.3        |
| Progressive disease    | 23.6             | 38.6         | 51.1        |
| Unknown                | 6.1              | 7.0          | 8.6         |
| Median duration of response, months (95% CI) | NR (NR–NR) | 31.1 (31.1–NR) | 18.2 (8.3–NR) |

*By RECIST v1.1; NR = not reached.

- At the 18-month DBL, the CR rate for NIVO+IPI, NIVO and IPI was 12.1%, 9.8% and 2.2%, respectively

Database lock: Sept 13, 2016, minimum f/u of 28 months
CM-67 Progression-Free Survival

|                      | NIVO+IPI (N=314) | NIVO (N=316) | IPI (N=315) |
|----------------------|------------------|--------------|-------------|
| Median PFS, mo (95% CI) | 11.5 (8.7–19.3)  | 6.9 (5.1–9.7) | 2.9 (2.8–3.2) |
| HR (95% CI) vs. IPI  | 0.43 (0.35–0.52) | 0.55 (0.45–0.66) | --          |
| HR (95% CI) vs. NIVO | 0.78 (0.64–0.96) | --           | --          |
CM-67 Overall Survival

|                        | NIVO + IPI (N=314) | NIVO (N=316) | IPI (N=315) |
|------------------------|---------------------|--------------|-------------|
| Median OS, months (95% CI) | 38.2-NR            | 37.6 (29.1-NR) | 19.9 (16.9-24.6) |
| HR (99.5% CI) vs. IPI  | 0.55 (0.45–0.69)*  | 0.65 (0.53–0.80)* | -            |
| HR (99.5% CI) vs. NIVO | 0.85 (0.68–1.07)   | -            | -            |

Database lock May 24, 2017
Wolchok, NEJM, 2017
Decision Point...

Immunotherapy

- PD-1 alone
- PD-1/CTLA-4 Combination
Safety Summary

- With an additional 19 months of follow-up, safety was consistent with the initial report

| Patients reporting event, % | NIVO+IPI (N=313) | NIVO (N=313) | IPI (N=311) |
|-----------------------------|------------------|--------------|-------------|
|                             | Any Grade        | Grade 3-4    | Any Grade   | Grade 3-4    | Any Grade | Grade 3-4 |
| Treatment-related adverse event (AE) | 95.8 | 58.5 | 86.3 | 20.8 | 86.2 | 27.7 |
| Treatment-related AE leading to discontinuation | 39.6 | 31.0 | 11.5 | 7.7 | 16.1 | 14.1 |
| Treatment-related death, n (%) | 2 (0.6)a | 1 (0.3)b | 1 (0.3)b |

- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)

- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

aCardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.

bNeutropenia (NIVO, n=1); colon perforation (IPI, n=1).1

1. Larkin J, et al. NEJM 2015;373:23–34.
Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs

Toxicity Earlier
Longer Time to Resolution

Circles represent medians; bars signify ranges

Larkin J et al ECC 2015
### OS by Tumor PDL-1 Expression at a 1% Cutoff

**PD-L1 Expression Level <1%**

| ≥1% PD-L1 | NIVO+IPI | NIVO | IPI |
|-----------|----------|------|-----|
| Median OS, mo (95% CI) | NR (26.5–NR) | 23.5 (13.0–NR) | 18.6 (13.7–23.2) |
| HR (95% CI) vs NIVO | 0.74 (0.52–1.06) | — | — |

**PD-L1 Expression Level ≥1%**

| ≤1% PD-L1 | NIVO+IPI | NIVO | IPI |
|-----------|----------|------|-----|
| Median OS, mo (95% CI) | NR | NR | 22.1 (17.1–29.7) |
| HR (95% CI) vs NIVO | 1.03 (0.72–1.48) | — | — |

- **ORR** of 54.5% for **NIVO+IPI** and 35.0% for **NIVO**

### OS by Tumor PDL-1 Expression Level at a 1% Cutoff

**Patients at Risk**

| Treatment | NIVO+IPI | NIVO | IPI |
|-----------|----------|------|-----|
| NIVO+IPI  | 123 | 112 | 111 |
| NIVO      | 117 | 103 | 96  |
| IPI       | 113 | 96  | 87  |

- **ORR** of 54.5% for **NIVO+IPI** and 35.0% for **NIVO**

**Patients at Risk**

| Treatment | NIVO+IPI | NIVO | IPI |
|-----------|----------|------|-----|
| NIVO+IPI  | 155 | 144 | 132 |
| NIVO      | 171 | 165 | 158 |
| IPI       | 164 | 155 | 138 |

- **ORR** of 65.2% for **NIVO+IPI** and 55.0% for **NIVO**

- Months: 0 3 6 9 12 15 18 21 24 27 30 33 36 39
- OS (%): 0 10 20 30 40 50 60 70 80 90 100

- OS (%): 0 10 20 30 40 50 60 70 80 90 100

- Months: 0 3 6 9 12 15 18 21 24 27 30 33 36 39

- Patients at risk:
  - NIVO+IPI: 123
  - NIVO: 117
  - IPI: 113

- Patients at risk:
  - NIVO+IPI: 155
  - NIVO: 171
  - IPI: 164
Overview

- Metastatic Melanoma
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Key eligibility criteria

- Stage IIIA, IIB, or IICC melanoma metastatic to lymph node
- Complete and adequate resection of stage III melanoma
- No prior systemic therapy

Stratified by:
- Stage (IIIA vs IIB vs IICC 1-3 positive lymph nodes vs IICC ≥ 4 positive lymph nodes)
- Region of the world

Randomized, double-blind, phase 3 study

INDUCTION

- Ipilimumab 10 mg/kg
  - Q3W × 4 (n = 475)
- Placebo
  - Q3W × 4 (n = 476)

MAINTENANCE

- Ipilimumab 10 mg/kg
  - Q12W up to 3 years
- Placebo
  - Q12W up to 3 years

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

Primary endpoint
- RFS

Secondary endpoints
- OS, DMFS, safety, HRQOL

DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q12W, every 12 weeks; RFS, relapse-free survival.

1. Eggermont AM, et al. J Clin Oncol 2014;32:5s(suppl; abstr LBA9008); 2. Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR].
EORTC 18071
Ipilimumab vs Placebo

Safety Summary

|                          | Ipilimumab | Placebo |
|--------------------------|------------|---------|
| (n = 471)                |            |         |
| Any AE, %                | Any Grade  | Grade 3/4 |
|                          | 98.7       | 54.1    |
| Treatment-related AE, %  | 94.1       | 45.4    |
| Treatment-related AE leading to discontinuation, % | 48.0 | 32.9 |
| Any immune-related AE, % | 90.4       | 41.6    |

Deaths due to drug-related AEs
- 5 patients (1.1%) in the ipilimumab group
  - 3 patients with colitis (2 with gastrointestinal perforations)
  - 1 patient with myocarditis
  - 1 patient had multiorgan failure with Guillain-Barré

Eggermont et al. NEJM 2016
Patients with:
• High-risk, completely resected stage IIIB/IIIC or stage IV (AJCC 7th edition) melanoma
• No prior systemic therapy
• ECOG 0-1

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

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

Follow-up
Maximum treatment duration of 1 year

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

Jeffrey Weber, Oral Presentation ASCO 2018
Primary Endpoint: RFS in All Patients

| Months | Number of patients at risk |
|--------|---------------------------|
| 0      | NIVO 453 | 453 |
| 10     | NIVO 394 | 394 |
| 20     | NIVO 353 | 353 |
| 30     | NIVO 331 | 331 |
| 40     | NIVO 291 | 291 |
| 50     | NIVO 280 | 280 |
| 60     | NIVO 264 | 264 |
| 70     | NIVO 205 | 205 |
| 80     | NIVO 283 | 283 |
| 90     | NIVO 94  | 94  |
| 100    | NIVO 331 | 331 |

**Events/patients**

|          | NIVO | IPI  |
|----------|------|------|
| 0        | 171  | 221  |

**Median (95% CI)**

|                | NIVO | IPI  |
|----------------|------|------|
| 30.8 (30.8, NR)a | 24.1 | (16.6, NR) |

**HR (95% CI)**

|                | NIVO | IPI  |
|----------------|------|------|
| 0.66 (0.54, 0.81) |     |      |

**Log-rank P value**

|                | NIVO | IPI  |
|----------------|------|------|
| <0.0001        |      |      |

aMedian estimate not reliable or stable due to few patients at risk.

Jeffrey Weber, Oral Presentation ASCO 2018
• There were no treatment-related deaths in the NIVO group
• There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Weber, J et al ESMO 2017
**EORTC 1325/KEYNOTE-54: Study Design**

**PART 1: ADJUVANT THERAPY**
- Pembrolizumab 200 mg IV Q3W 1 year
- Placebo IV Q3W 1 year
- Total of 18 doses
- N=1019

**PART 2: POST RECURRENT**
- Pembrolizumab 200 mg IV Q3W until progression or recurrence, up to 2 years
- Recurrence >6 months
- Recurrence
- Cross-over

**Stratification factors:**
- **Stage:** IIIA (>1 mm metastasis) vs. IIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
- **Region:** North America, European countries, Australia/New Zealand, other countries

**Primary Endpoints:**
- RFS (per investigator) in overall population, and RFS in patients with PD-L1-positive tumors

**Secondary Endpoints:**
- DMFS and OS in all patients, and in patients with PD-L1-positive tumors; Safety, Health-related quality of life
Recurrence-Free Survival in the ITT Population

Primary endpoint

% alive and recurrence-free

Treatment arm | Total | Event | HR (98.4% CI)
--- | --- | --- | ---
Pembrolizumab | 514 | 135 | 0.57 (0.43-0.74)
Placebo | 505 | 216 | Reference

Stratified Logrank P-value: <.0001

| Patients at risk | 514 | 438 | 413 | 392 | 313 | 182 | 73 | 15 | 0 |
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Pembrolizumab | 505 | 415 | 363 | 323 | 264 | 157 | 60 | 15 | 0 |
Placebo | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

*Stratified by stage given at randomization

HR 0.57

The future of cancer therapy
Interferon
Overview

• Metastatic Melanoma
• Adjuvant therapy for High-risk
• Practical Questions
• Future Directions
Practical Questions

• What is the correct duration?
  – Are responses durable after stopping treatment?

• What is the correct first choice for BRAF+ patients?
Disposition of Patients Completing ≥94 Weeks of Pembrolizumab Treatment

556 patients received pembrolizumab

103 (18.5%) completed 2 year pembrolizumab treatment

Median follow-up after ≥94 weeks pembro: 20.3 (0.03-24.8) mo

28 (27.2%) CR
- 26 patients had an ongoing response
- 2 (7.1%) confirmed PD\(^a\)
- 3 received 2nd course of pembrolizumab\(^b\)

65 (63.1%) PR
- 56 patients had an ongoing response
- 9 (13.8%) confirmed PD\(^a\)
- 4 received 2nd course of pembrolizumab

10 (9.7%) SD
- 7 patient had an ongoing SD
- 3 (30%) confirmed PD\(^a\)
- 1 received 2nd course of pembrolizumab

\(^a\)Confirmed PD by investigator per irRC (confirmatory scan or no subsequent scan or not evaluable). An additional 5 pts with unconfirmed progressive disease were observed. \(^b\)Includes 1 patient who discontinued early with CR and then progressed. Data cutoff: Dec 4, 2017.
PFS<sup>a</sup> in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 103)

*Per immune-related response criteria by investigator review; time is measured from last dose of pembrolizumab. Data cutoff: Dec 4, 2017.
Duration of Response in Patients With ≥94 Weeks of Pembrolizumab (n = 103)

- 89% (86%) patients who completed 2 years on pembrolizumab were progression-free at 20 months after end of therapy

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Abstract 9503, 2018 ASCO Annual Meeting
Practical Questions

• What is the correct duration?
  – Are responses durable after stopping treatment?

• What is the correct first choice for BRAF+ patients?
**MAPK Pathway Targeted Therapy**

**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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**BRAFi + MEKi ph III studies**

**Dabrafenib + trametinib (D + T)**
- PFS HR, 0.67 vs dabrafenib\(^4\)
- OS HR, 0.71 vs dabrafenib\(^4\)
- PFS HR, 0.56 vs vemurafenib\(^5\)
- OS HR, 0.69 vs vemurafenib\(^5\)

**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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1. Hauschild A, et al. *Lancet*. 2012;380(9839):358-365.
2. McArthur GA, et al. *Lancet Oncol*. 2014;15(3):323-332.
3. Flaherty KT, et al. *N Engl J Med*. 2012;367(2):107-114.
4. Long GV, et al. *Lancet*. 2015;386(9992):444-451.
5. Robert C, et al. *N Engl J Med*. 2015;372(1):30-39.
6. Atkinson V, et al. Presented at: Society for Melanoma Research 2015 Congress.
Decision Point….

- BRAF mutation test
  - BRAF<sup>V600</sup> mutation negative: Immunotherapy
  - BRAF<sup>V600</sup> mutation positive: Immunotherapy or MAP-K Targeted Therapy
KEYNOTE-001: Phase I RECIST Response (v1.1)

Total population n=581
ORR 33%
CR 8%

Medians:
- IPI-T: 71%
- IPI-N: 36%

Median Change:
- Total: -36%

Treatment naïve n=152
ORR 45%
CR 14%

Medians:
- 2 mg/kg Q3W: 80%
- 10 mg/kg Q3W: 80%
- 10 mg/kg Q2W: 80%

Analysis cut-off date: October 18, 2014; Median follow up 21 mo

Daud A et al ASCO 2015
# BRAF Inhibitors

| Phase | Vemurafenib\(^1\) | Dabrafenib\(^2\) |
|-------|------------------|------------------|
|       | Phase 1 2 3      | Phase 1 2 3      |
| RR    | 56% 57% 57%      | 56% 59% 59%      |
| PFS   | 6.7 6.9 5.5      | 6.3 6.9          |
| OS    | 13.8 15.9 13.6   | 13.1 18.2        |

1. Chapman PB, et al. *N Engl J Med* 2011;364:2507–2516 (updated Chapman et al. ASCO 2012); Sosman JA, et al. *N Engl J Med* 2012;366:707–714;
2. Hauschild A, et al. *Lancet* 2012;380:358–365 (updated Hauschild et al. ASCO 2013); Ascierto PA, et al. *J Clin Oncol* 2013; 31:3205–3211.
Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)
Contemplating the Options
Anti-PD1 therapy
BRAF-targeted therapy

Arm A:
Ipilimumab 3mg/kg IV q 3wks x 4
Nivolumab 1mg/kg IV q 3wks x 4
Followed by Nivolumab 3 mg/kg IV q2 wks x 42

Dabrafenib 150mg po BID
Trametinib 2 mg daily

Arm B:
Dabrafenib 150mg po BID
Trametinib 2 mg daily

Ipilimumab 3mg/kg IV q 3wks x 4
Nivolumab 1 mg/kg IV q3 wks x 4
Followed by Nivolumab 3 mg/kg IV q3 wks x 42

PD1

ECOG PS
0
1
Serum LDH

Randomize
Overview

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T-Cell Immune Checkpoints

Presented By Scott Gettinger at 2014 ASCO Annual Meeting

Mellman I et al. Nature. 2011;480:481–489.
The T Cell-Inflamed Tumor Microenvironment is Characterized by Expression of Immune-Inhibitory Pathways and Predicts Outcomes to Immunotherapy

- CD8
- FoxP3
- PD-L1
- IDO

Spranger et al., Science Trans. Med. 2013
Harlin et al. Clin Can Res 2009
Ribas et al. J Clin Oncol 33, 2015 (suppl; abstr 3001)
Combining Immunotherapy and Targeted Therapy for Melanoma?

Improved Survival With Ipilimumab in Patients with Metastatic Melanoma

Improved Survival With Vemurafenib in Melanoma With BRAF V600E Mutation

1. Hodi FS, et al. *N Engl J Med*. 2010;363(8):711-723. 2. Chapman PB, et al. *N Engl J Med*. 2011;364(26):2507-2516.

Modified from: Ribas A, et al. *Clin Cancer Res*. 2012;18(2):336-341.
Targeted-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib +Durvalumab

Dabrafenib+Trametinib +Pembrolizumab

Vemurafenib+Cobimetinib +Atezolizumab

Multiple Triplet Combinations Launching Into Phase III:

- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab
IDO Inhibitors: Background

- Upregulation of IDO1 is a potential mechanism to evade immunosurveillance
  - ↓ Tryptophan ↑ Kynurenine
  - ↓ Teff and NK cells
  - ↑ Treg cells, MDSCs, TAMs
- Epacadostat: IDO1 enzyme inhibitor
- Pembrolizumab: anti-PD-1 humanized antibody

IDO1, indoleamine 2,3 dioxygenase 1; IFNγ, interferon gamma; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed death ligand-1; TAM, tumor-associated macrophage; Teff, effector T cell; Treg, regulatory T cell.
Phase I/II Combination Epacadostat + Pembrolizumab

• Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
• MTD of epacadostat not reached
• Phase 2: Epacadostat 100 mg PO BID

Phase 1/2 efficacy in treatment-naive melanoma:
- ORR = 55%
- Median PFS = 22.8 mo (12.4 mo all melanoma)

ECHO-202 / KEYNOTE-037
- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID

Hamid O, et al. Ann Oncol. 2017;28(suppl 5):1214O.
Phase III Randomized Placebo Controlled Trial

Key Eligibility Criteria
- Unresectable stage III or IV melanoma, advanced/metastatic disease
  - Patients with \textit{BRAF} mutation could have received prior \textit{BRAF}/MEK therapy
  - Prior anti-CTLA-4 or interferon in adjuvant setting permitted
- ECOG performance status 0–1
- No active CNS metastases

Stratification
- PD-L1 status (positive\(^a\) vs negative)
- \textit{BRAF} mutation status
  - Wild type
  - Mutant with prior \textit{BRAF}-directed therapy
  - Mutant without prior \textit{BRAF}-directed therapy

Primary endpoints: PFS (RECIST v1.1) and OS
Secondary endpoints: ORR (RECIST v1.1), DOR, safety

\textbf{BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.}

\(^{a}\geq 1\%\) staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).
Progression-Free Survival

Number at risk

|                  | E + P | Placebo + P |
|------------------|-------|-------------|
| 0                | 354   | 352         |
| 2                | 309   | 304         |
| 4                | 181   | 181         |
| 6                | 155   | 151         |
| 8                | 137   | 132         |
| 10               | 114   | 109         |
| 12               | 57    | 65          |
| 14               | 25    | 28          |
| 16               | 5     | 7           |
| 18               | 0     | 0           |

Events, n (%) | Median PFS, months (95% CI)

| E + P | 218 (61.6) | 4.7 (2.9–6.8) |
| Placebo + P | 219 (62.2) | 4.9 (2.9–6.8) |

HR (95% CI): 1.00 (0.83–1.21)  
P = 0.517

BICR, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.  
PFS defined as time from randomization to disease progression or death, whichever occurred first.

Georgina V. Long
Summary & Conclusions

- Immunotherapy with checkpoint inhibitors is standard of care for most patients
  - Single agent PD1
  - Combination PD-1/CTLA-4
- For BRAF+ patients the choice is based on clinical judgment
- It has recently been approved for adjuvant therapy
- Future therapies will address better combinations and overcoming resistance
How I Treat Metastatic Melanoma

Diagnosis of metastatic melanoma

BRAF mutation test

BRAF$^{V600}$ mutation positive

BRAF$^{V600}$ mutation negative

BRAF/MEK combo
Anti PD-1
Combo antiCTLA4/anti PD-1
Ipilimumab

Anti PD-1
Combo anti CTLA4/antiPD-1
Ipilimumab
How I treat High Risk Melanoma Adjuvant Therapy

Sentinel Node Biopsy Positive
BRAF mutation test

- BRAF<sup>V600</sup> mutation negative
  - Anti-PD1
- BRAF<sup>V600</sup> mutation positive
  - Anti-PD1
  - Or
  - Dabrafenib + Trametinib
Clinical Trials!