COMPLIMENTARY LIVE INTERACTIVE CPE WEBCASTS

# EXPANDING HORIZONS IN IMMUNO-ONCOLOGY:

## *Health System Pharmacists' Perspectives*

University of Tennessee College of Pharmacy

Advanced Studies *in* Pharmacy.

***Supported by an educational grant from Bristol-Myers Squibb Company.***

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***R. Donald Harvey, PharmD, FCCP, BCOP, reports serving as a consultant for Amgen Inc/Onyx Pharmaceuticals (for oprozomib development); and serving on an advisory board for Baxter (for intravenous immunoglobulin [IVIG]), Bristol-Myers Squibb Company, and Takeda Pharmaceutical Company, Ltd (for ixazomib). Dr Harvey's spouse reports receiving grants/research support from Baxalta and Novo Nordisk; and serving as a consultant for Baxalta and Biogen Idec.***

# Agenda

***Activity Overview and Goals***

***Pharmacology and Clinical Use of Immunotherapies***

***Pharmacists' Role and the Interpretation of Gray Areas of Immunotherapy: Case Studies***

***Q & A***

# Learning Objectives

**The University of Tennessee College of Pharmacy takes responsibility for the content, quality, and scientific integrity of this CPE activity. Upon the conclusion of this activity, the participant should be able to:**

- **DIFFERENTIATE the mechanisms of active immunotherapies from that of targeted and cytotoxic therapies.**
- **EVALUATE clinical trial data and uses of PD-1 and CTLA-4 inhibitors in malignancies.**
- **RECOGNIZE unique disease response patterns associated with immunotherapy treatment.**
- **IDENTIFY strategies to recognize and manage adverse events related to immunotherapies.**

# CPE Information

**INTENDED AUDIENCE –** This activity is designed for health-system pharmacists. No prerequisites required.

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# Educational Grant

**The University of Tennessee College of Pharmacy would like to acknowledge an educational grant from *Bristol-Myers Squibb Company* which helped to make this activity possible.**

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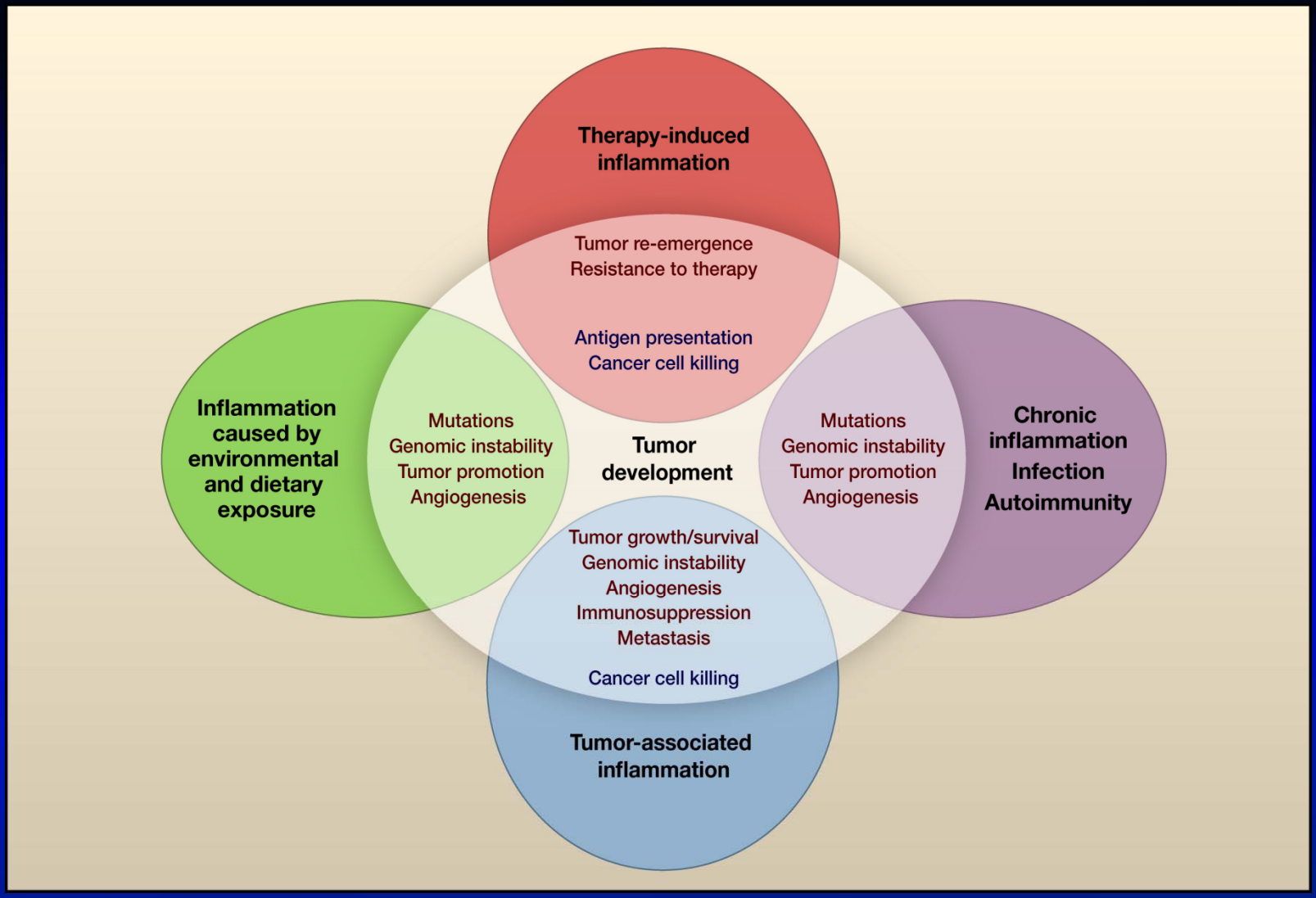
- Q&A
  - Please type in questions at any time during the presentation, using the “Ask a Question” tab located on the left of your screen.
  - The faculty will try to get to all of your questions during Q&A.
  - Slides are available on Event Resource tab
- Post-Test, Evaluation, and Certification

# Pharmacology and Clinical Use of Immunotherapies

# Cancer and the Immune System




Harvey RD, et al. *Clin Pharmacol Ther.* 2014;96:449-457. For educational purposes only.

# Anticancer Immunotherapy Postulates

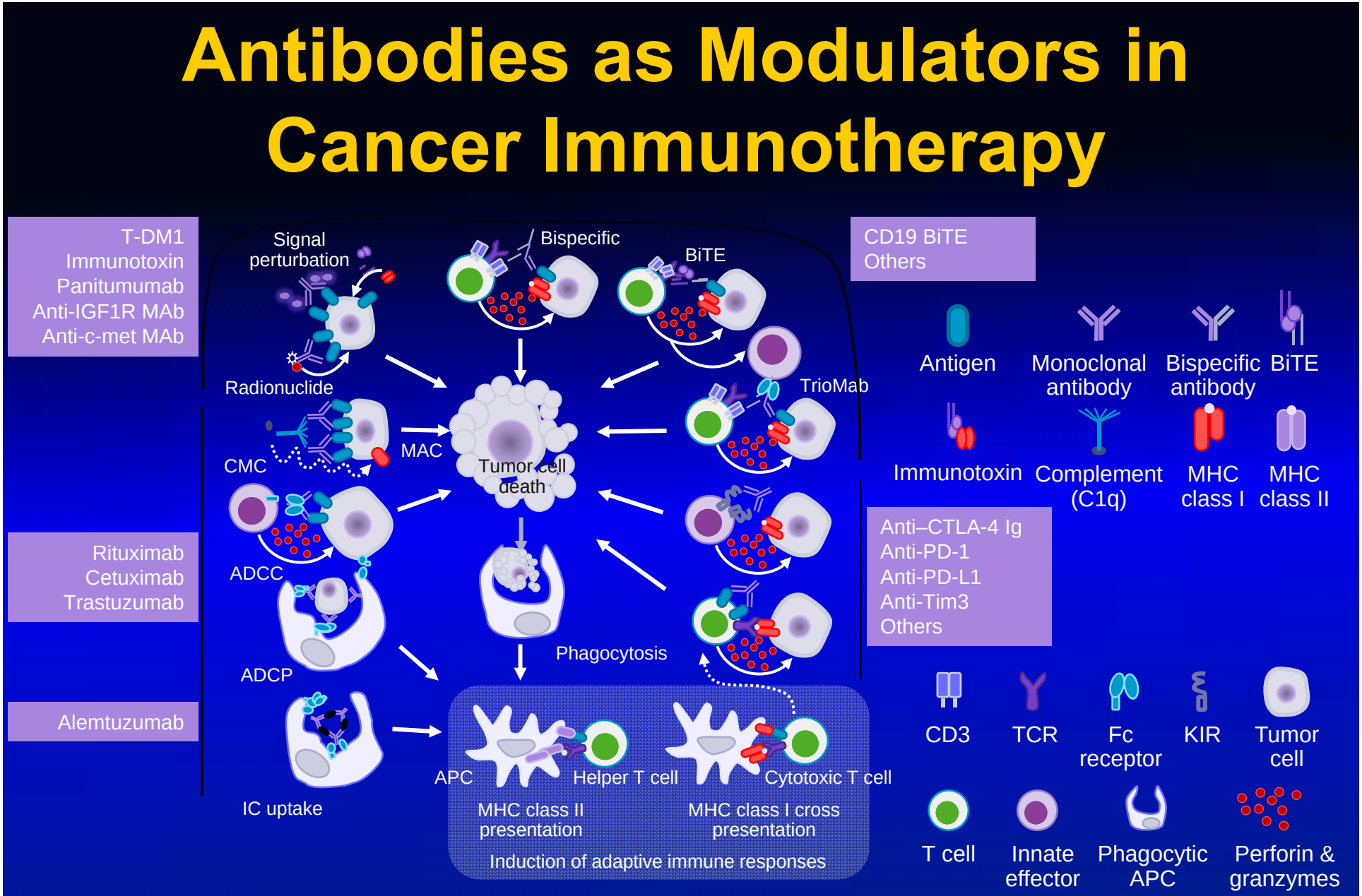
- No new truly curative anticancer agents have been developed in the last 20 years.
  - Multiple mechanisms of innate and acquired resistance
- The immune response has the ability to identify and disable escape routes.
- Immunotherapy can cure cancers.
  - Historically small patient numbers
  - Associated with substantial toxicity

# Immunotherapy Approaches

- Active
  - Vaccination
    - Autologous
    - Allogeneic
  - Cytokines
    - Interferon, interleukin-2, GM-CSF, denileukin diftitox
- Passive
  - Conventional naked and loaded monoclonal antibodies
- Passive leading to active
  - Ipilimumab, PD-1, PD-L1 antibodies

GM-CSF = granulocyte-macrophage colony-stimulating factor; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

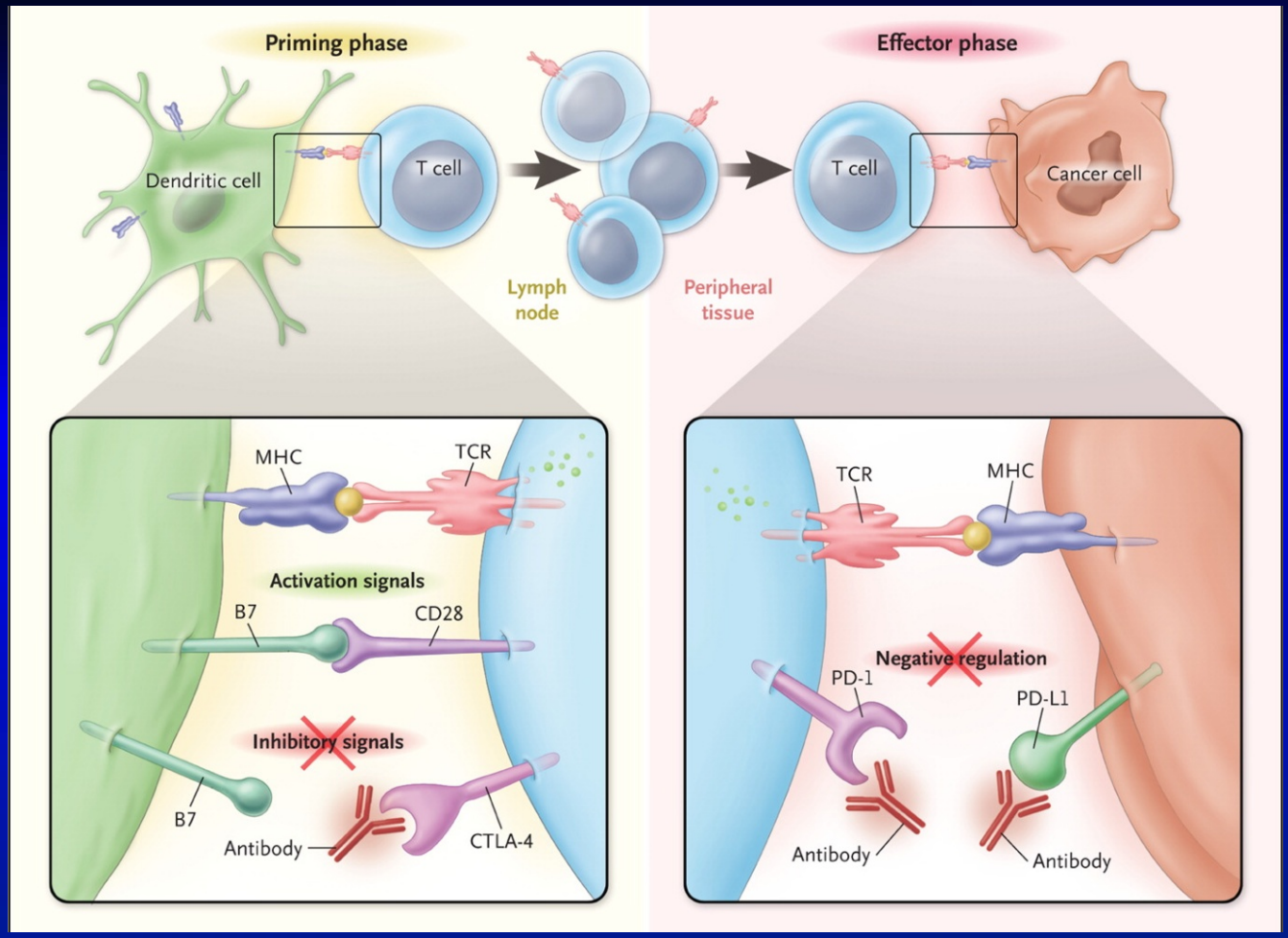
# Antibodies as Modulators in Cancer Immunotherapy




ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; APC = antigen-presenting cell; BiTE = bispecific T cell engager; CMC = complement-mediated cytotoxicity; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; IC = immune complex; Ig = immunoglobulin; IGF-1R = type I insulin-like growth factor receptor; KIR = killer cell immunoglobulin-like receptor; MAb = monoclonal antibody; MAC = membrane attack complex; MHC = major histocompatibility complex; TCR = T cell receptor; T-DM1 = trastuzumab-MCC-DM1.

Weiner LM, et al. *Cell*. 2012;148:1081-1084. For educational purposes only.

# CTLA-4 and PD-1/L1 Checkpoint Blockade




Ribas A. *N Engl J Med.* 2012;366:2517-2519. For educational purposes only.

# Comparison of CTLA-4 vs PD-1

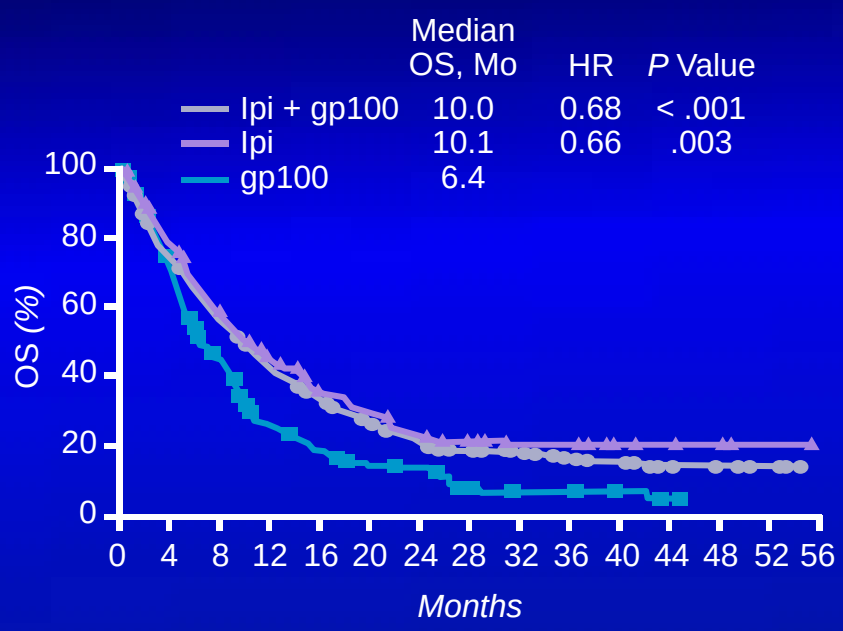
| CTLA-4 Pathway | PD-1 Pathway |
|---|---|
| Exclusively on T cells | On T, B, and NK cells |
| Ligands: CD80 and CD86 | Ligands: PD-L1 and PD-L2 |
| Ligands only expressed on APCs | Ligand expressed on APCs and tumor cells |
| CTLA-4–deficient mice suffer early, fatal autoimmune syndrome | PD-1–deficient mice develop strain-specific autoimmunity late in life |
| Blockade enhances proliferation of CD4+ and CD8+ T cells with increase in ratio to regulatory T cells | Blockade enhances CD8+ T cells greater than CD4+ with increase of CD8+ to Tregs and cytotoxicity of CD8+ |

NK = natural killer; Treg = regulatory T cell.

Greenwald RJ, et al. *Ann Rev Immunol*. 2005;23:515-548; Chambers CA, et al. *Ann Rev Immunol*. 2001;19:565-594; Dong H, et al. *Nat Med.* 2002;8:793-800; Curran MA, et al. *Proc Natl Acad Sci U S A*. 2010;107:4275-4280; Pilon-Thomas S, et al. *J Immunol*. 2010;184:3442-3449.

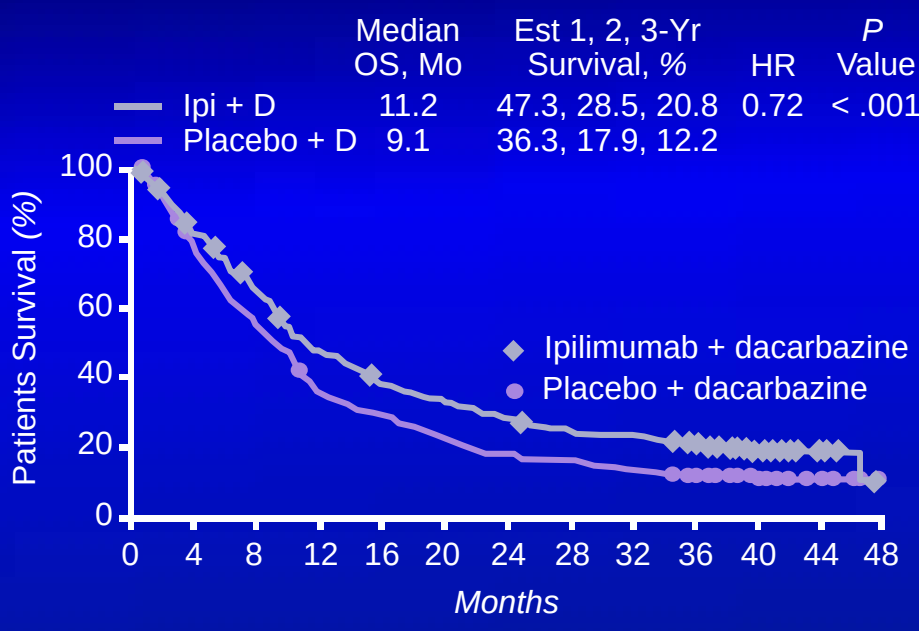
# Ipilimumab in Metastatic Melanoma: Durable OS

## Previously Treated Patients




Ipilimumab + gp100 vs gp100[1]

## Previously Untreated Patients

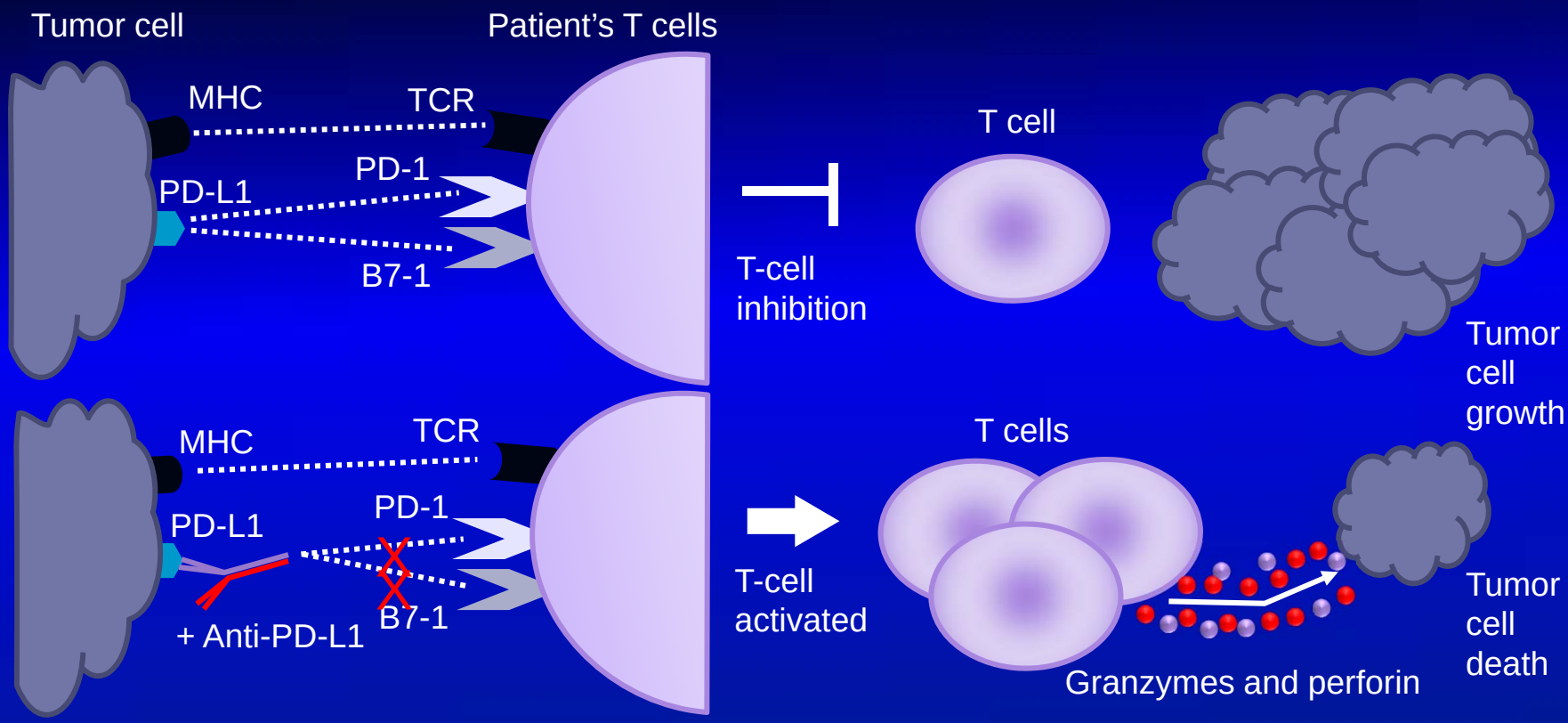



Ipilimumab vs Placebo[2]

D = dacarbazine; Ipi = ipilimumab; gp100 = glycoprotein 100; HR = hazard ratio; OS = overall survival.

1. Hodi FS, et al. *N Engl J Med*. 2010;363:711-723; 2. Robert C, et al. *N Engl J Med*. 2011;364:2517-2526. For educational purposes only.

# Anti–PD-1/PD-L1 Agents Inhibit Binding of PD-L1 to PD-1 and B7-1




- **Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical models**
- **Binding to PD-L1 leaves PD-1/PD-L2 interaction intact and may enhance efficacy and safety**

Herbst RS, et al. ASCO 2013. Abstract 3000. For educational purposes only.

# Clinical Development of Inhibitors of the PD-1 Immune Checkpoint

| Target | Antibody | Molecule | Development Stage |
|---|---|---|---|
| PD-1 | Nivolumab (BMS-936558) | Fully human IgG4 | Approved |
| | CT-011 | Humanized IgG1 | Phase II multiple tumors |
| | Pembrolizumab (MK-3475) | Humanized IgG4 | Approved |
| PD-L1 | BMS-936559 | Fully human IgG4 | Phase I |
| | MedI-4736 | Engineered human IgG1 | Phase I |
| | MPDL-3280A | Engineered human IgG1 | Phase II–III |

# Activity of Anti-PD-1/PD-L1 in Patients with Advanced Melanoma

| Agent | Pts, *n* | ORR (at Optimal Dose), *%* | Grades 3/4 Tx-Related AEs, *%* | 6-Mo PFS, *%* | 12-Mo PFS, *%* | Median PFS, *Mo* | 1-Yr OS, *%* | 2-Yr OS, *%* |
|---|---|---|---|---|---|---|---|---|
| Nivolumab (anti-PD-1)[1-3] | 104 | 31 (41) | 22 | 41 | 36 | 3.7 | 62 | 43 |
| Pembrolizumab (anti-PD-1)[4,5] | 135 | 38 (52) | 13 | NA | NA | >7 | 81 | NA |
| BMS559 (anti-PD-L1)[6] | 55 | 17 | 5 | NA | NA | NA | NA | NA |
| MPDL3280A (anti-PD-L1)[7] | 44 | 29* | 36 | 43 | NA | NA | NA | NA |

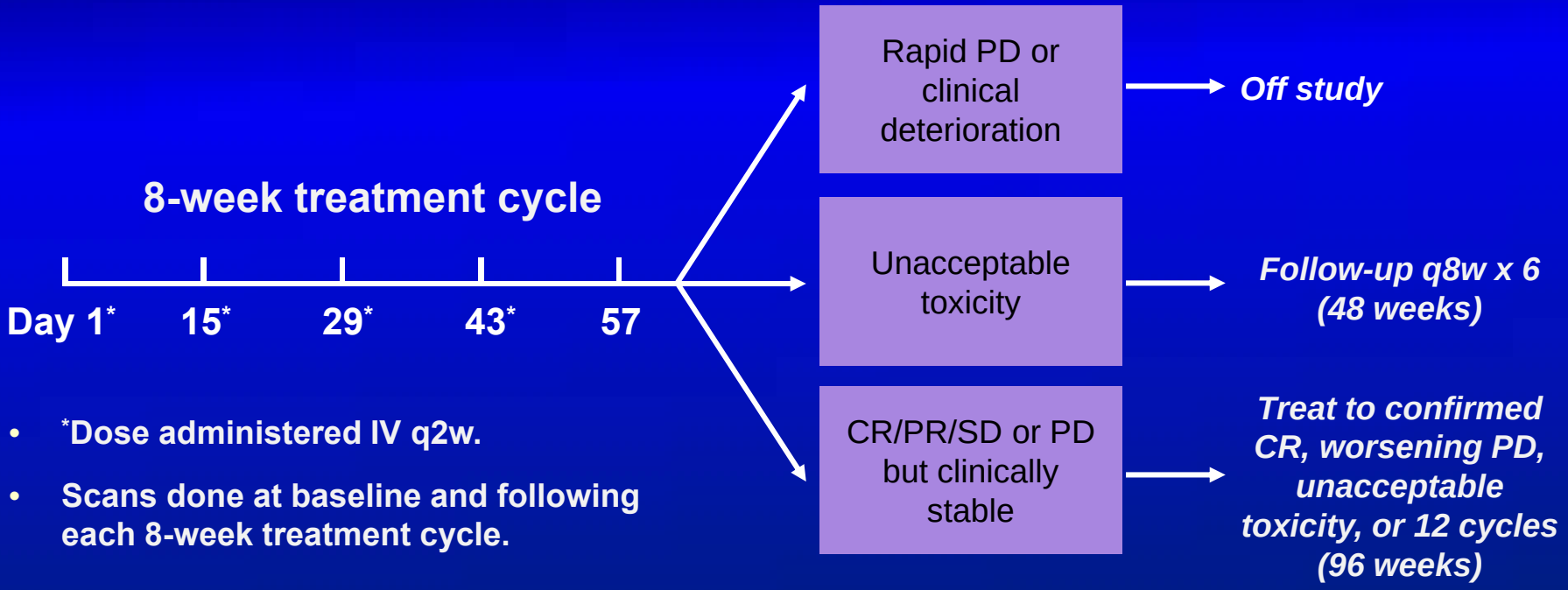
*Includes 4 patients with UM without a response.

AE = adverse event; NA = not applicable; ORR = objective response rate; PFS = progression-free survival; Tx = treatment; UM = uveal melanoma.

1. Topalian SL, et al. *J Clin Oncol*. 2014;32:1020-1030; 2. Sznol M, et al. ASCO 2013. Abstract 9006; 3. Topalian SL, et al. *N Engl J Med*. 2012;366:2443-2454; 4. Ribas A, et al. ASCO 2013. Abstract 9009; 5. Hamid O, et al. *N Engl J Med*. 2013;369:134-144; 6. Brahmer JR, et al. *N Engl J Med*. 2012;366:2455-2465; 7. Hamid O, et al. ASCO 2013. Abstract 9010.

# Phase I Nivolumab Multidose Regimen

- **Eligibility: Advanced melanoma, NSCLC, RCC, CRC, or CRPC with PD after 1 to 5 systemic therapies**
- **NSCLC Expansion Cohort: Patients randomized to 3 dose levels of nivolumab (1, 3, or 10 mg/kg)**




- *Dose administered IV q2w.
- Scans done at baseline and following each 8-week treatment cycle.

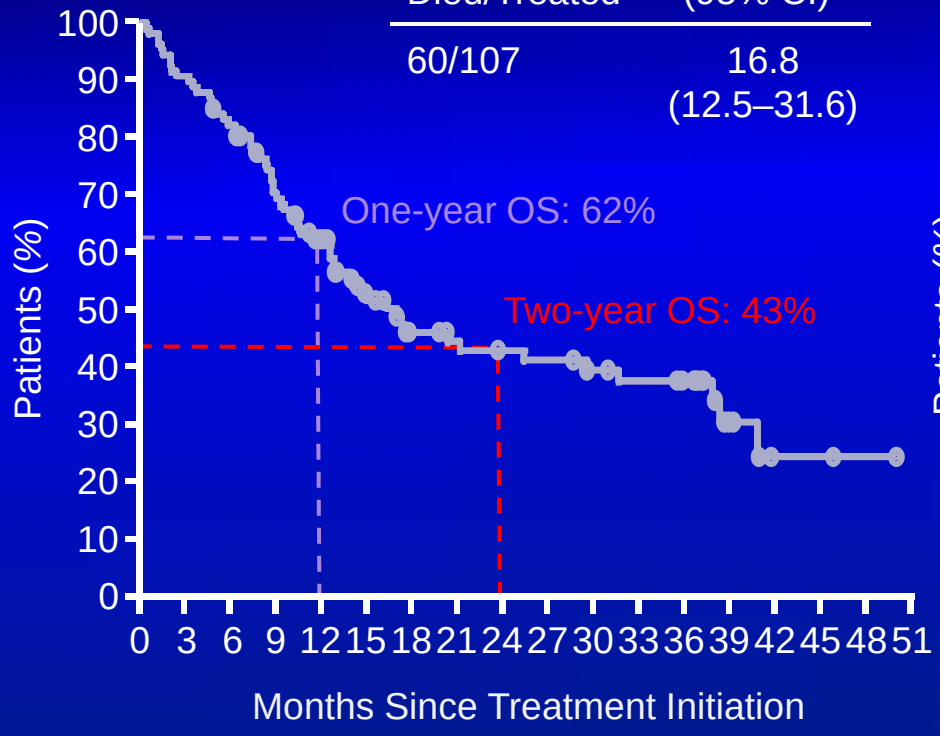
CR = complete response; CRC = colorectal carcinoma; CRPC = castration-resistant prostate cancer; IV = intravenously; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; q2w = every 2 weeks; q8w = every 8 weeks; RCC = renal cell cancer; SD = stable disease.

Brahmer JR, et al. *J Thorac Oncol*. 2013;8:S53-S54. Abstract MS09.4. For educational purposes only.

# Nivolumab Phase I Study: Survival of Patients with Melanoma

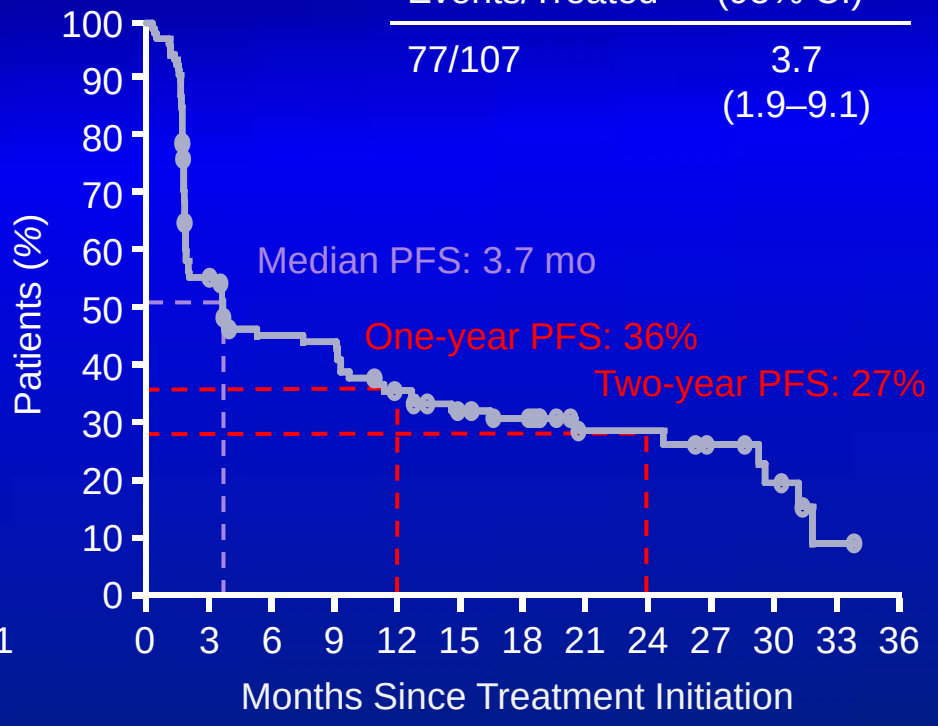
## OS

| Died/Treated | Median, Mo (95% CI) |
|---|---|
| 60/107 | 16.8 (12.5–31.6) |




## PFS

| Events/Treated | Median, Mo (95% CI) |
|---|---|
| 77/107 | 3.7 (1.9–9.1) |




CI = confidence interval.

Sznol M, et al. ASCO 2013. Abstract CRA9006. For educational purposes only

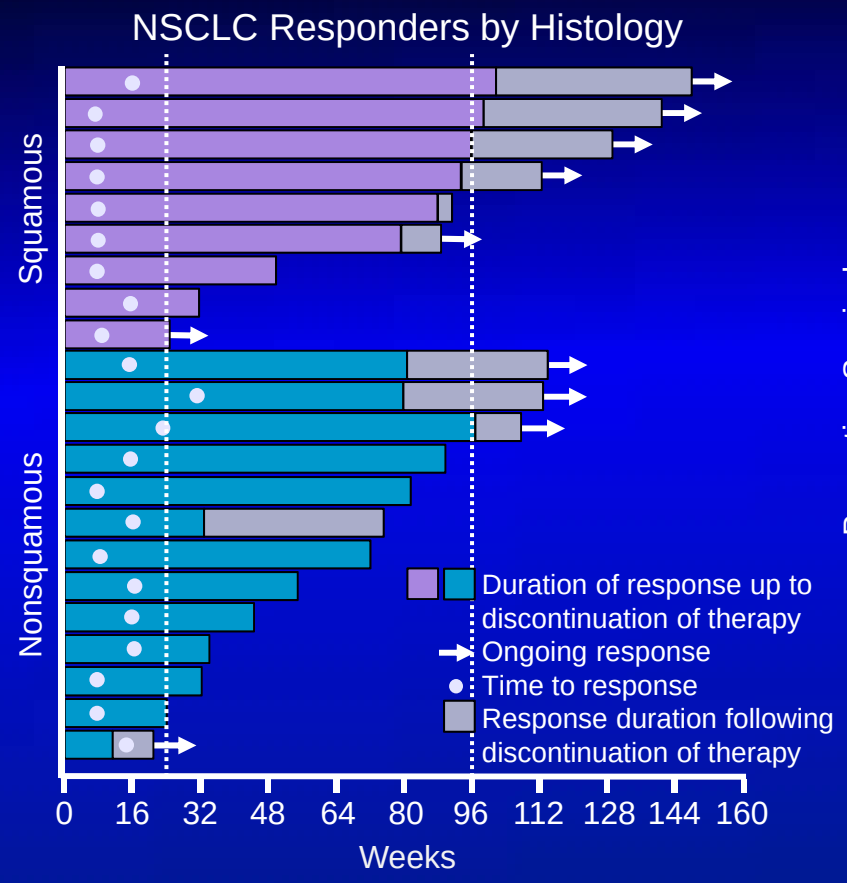
# PD-1 Blockade with Nivolumab: Toxicities

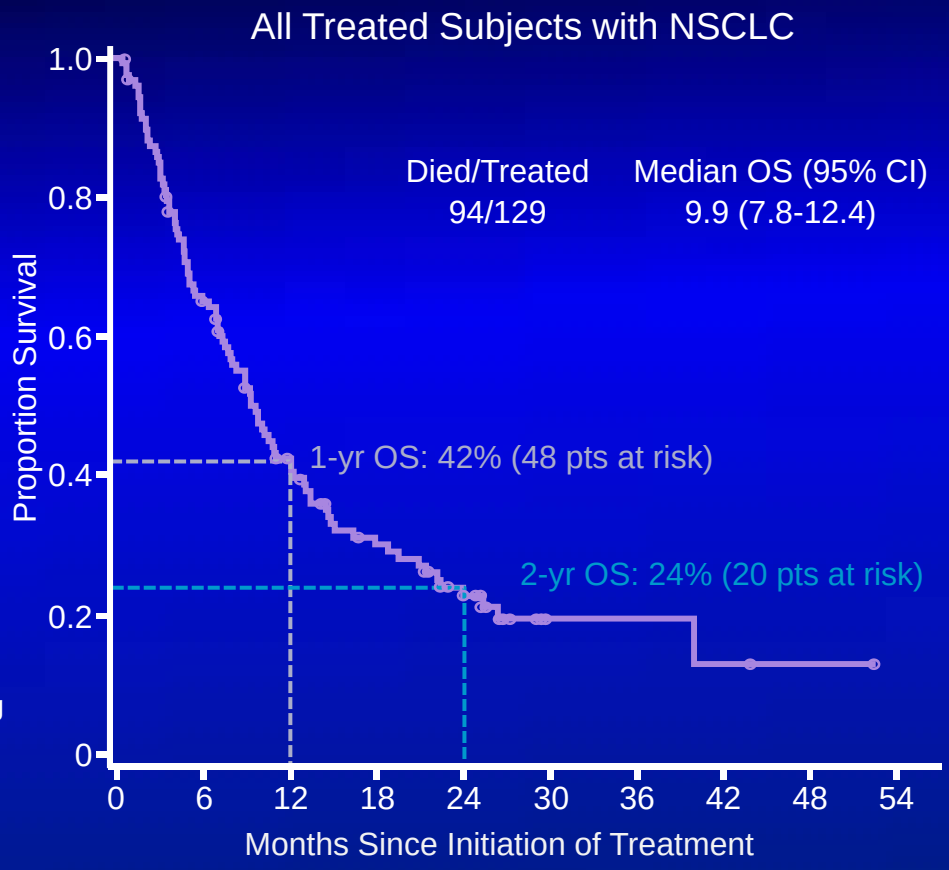
| Anti-PD-1–Related Adverse Event, *n* (%) | All Grades | Grade 3/4 |
|---|---|---|
| Any select event | 54 (58) | 5 (5) |
| Skin | 36 (38) | 2 (2) |
| Gastrointestinal | 18 (19) | 2 (2) |
| Endocrinopathies | 13 (14) | 2 (2) |
| Hepatic | 7 (7) | 1 (1) |
| Infusion reaction | 6 (6) | — |
| Pulmonary | 4 (4) | — |
| Renal | 2 (2) | 1 (1) |

- Early respiratory symptoms can be fatal pneumonitis
- Renal insufficiency can also occur rarely
- Endocrinopathies and enterocolitis are more characteristic of ipilimumab but may occur in patients receiving a PD-1–blocking drug

Sznol M, et al. ASCO 2013. CRA9006.
Topalian SL, et al. *N Engl J Med*. 2012;366:2443-2454.

# Nivolumab: Duration of Response and OS in NSCLC



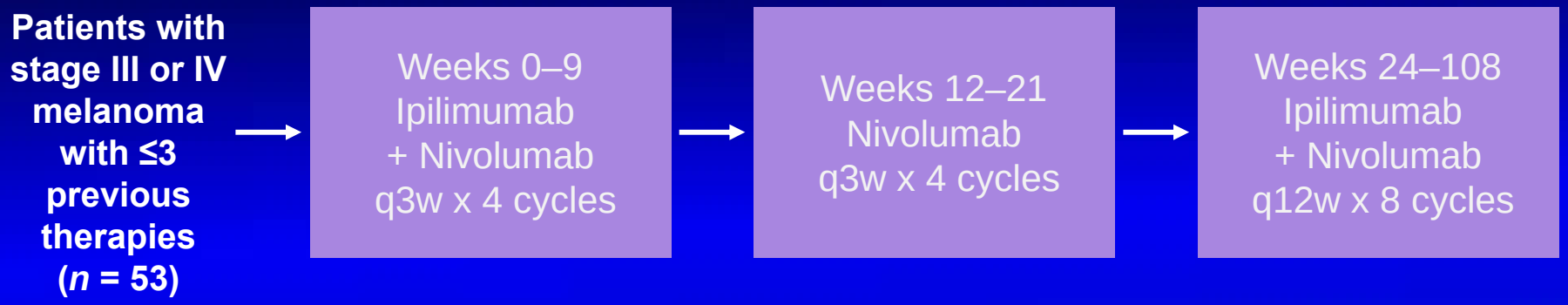




| Patients at Risk, *n* | 129 | 82 | 48 | 31 | 20 | 4 | 3 | 2 | 1 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|

Brahmer JR, et al. *J Thorac Oncol*. 2013;8:S365. Abstract MO18.03.

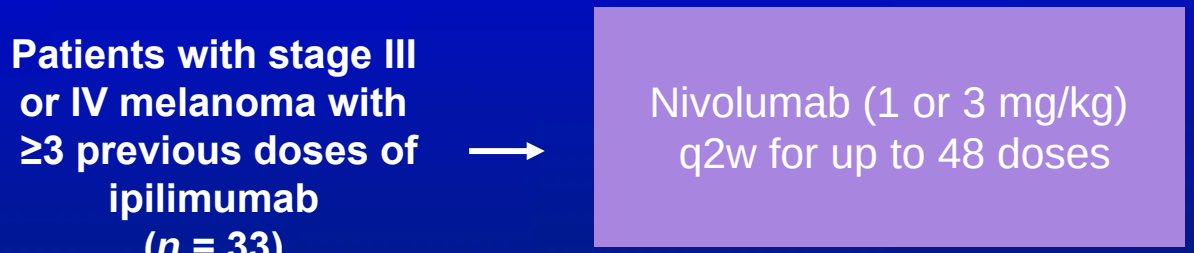
# Nivolumab + Ipilimumab: Phase I Study

- **Concurrent therapy study design:**




**Escalating doses of nivolumab (0.3–10 mg/kg) and ipilimumab (1–10 mg/kg)**

- **Sequenced therapy study design**




q3w = every 3 weeks; q12w = every 12 weeks.

Wolchok JD, et al. *N Engl J Med*. 2013; 369:122-133; Wolchok JD, et al. ASCO 2013. Abstract 9012.

# Nivolumab + Ipilimumab: Efficacy

## Clinical activity in concurrent regimen

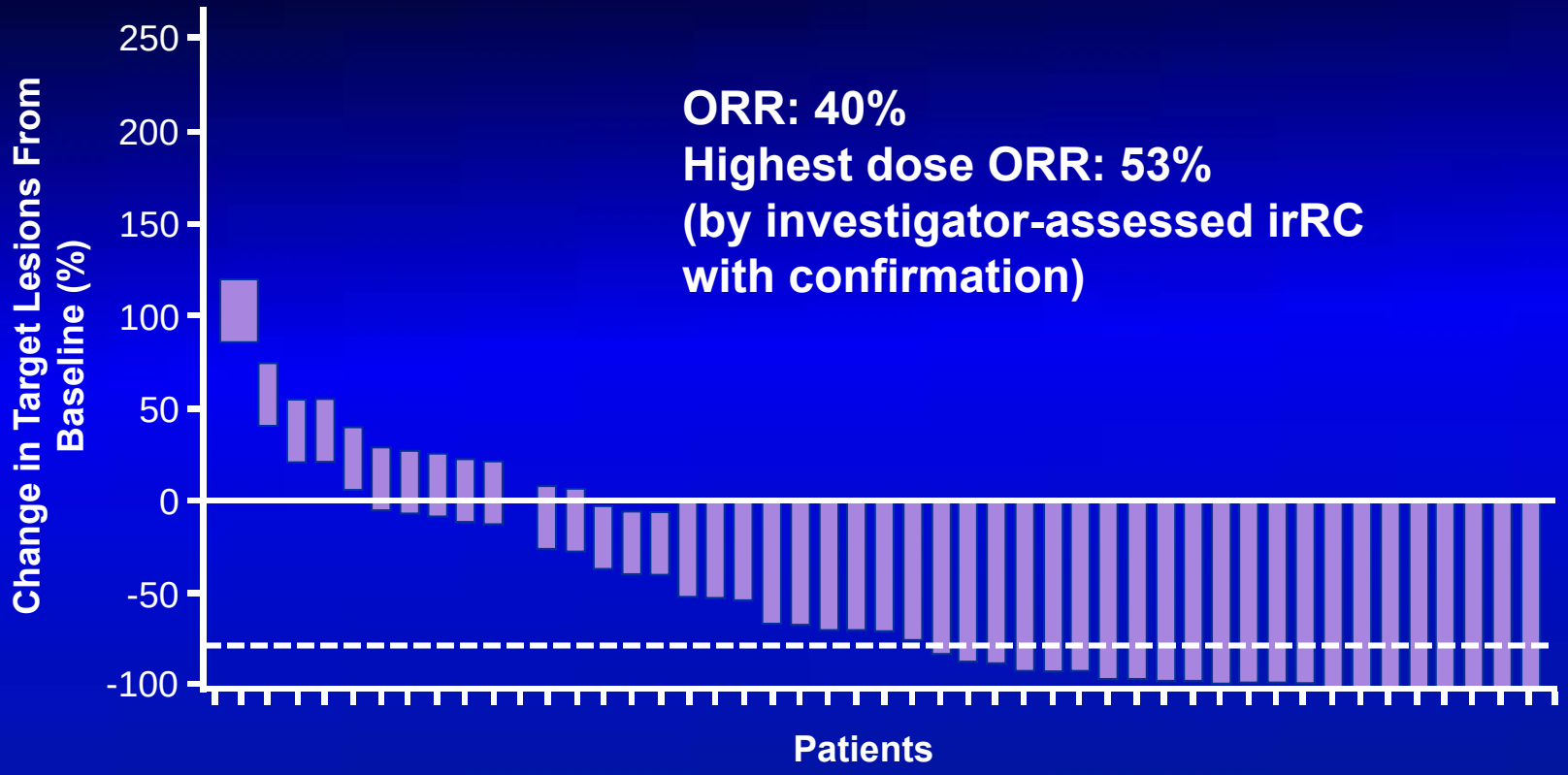
| Cohort | Nivolumab + Ipilimumab, mg/kg | Response Evaluable Patients, *n* | CR, *n* | PR, *n* | ORR, % | ≥80% Tumor Reduction at 12 Wks, *n* (%) |
|---|---|---|---|---|---|---|
| 1 | 0.3 + 3 | 14 | 1 | 2 | 21 | 4 (29) |
| 2 | 1 + 3 | 17 | 3 | 6 | 53 | 7 (41) |
| 2a | 3 + 1 | 15 | 1 | 5 | 40 | 5 (33) |
| 3 | 3 + 3 | 6 | 0 | 3 | 50 | 0 |
| All | - | 52 | 5 | 16 | 40 | 16 (31) |

## Clinical activity in sequenced regimen (*n* = 30)

- ORR: 20% (1 CR, 5 PR)
- 4 patients had ≥80% tumor reduction at first scheduled 8-week tumor assessment

Wolchok JD, et al. *N Engl J Med*. 2013; 369:122-133; Wolchok JD, et al. ASCO 2013. Abstract 9012.

# Nivolumab + Ipilimumab: Tumor Response with Concurrent Therapy

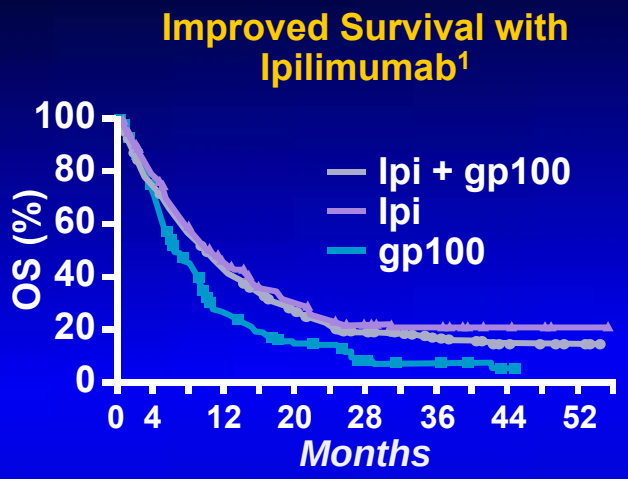


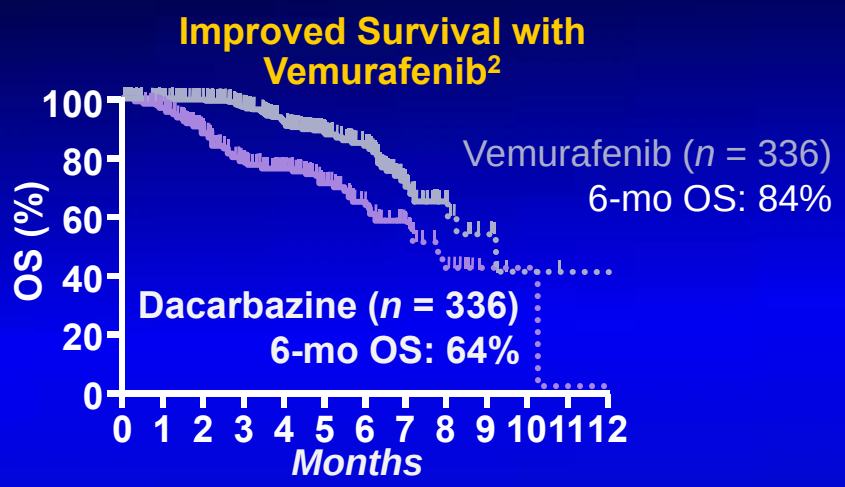

**Objective responses were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22) (*P* > .99).**

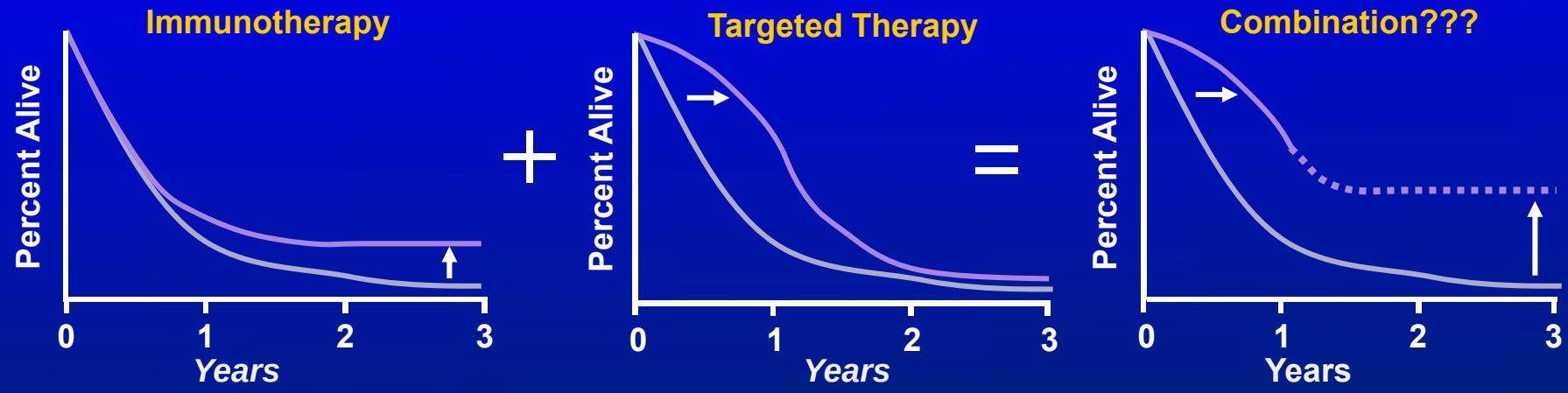
irRC = immune-related response criteria.

Wolchok JD, et al. *N Engl J Med.* 2013;369:122-133.

# Combining Immunotherapy and Targeted Therapy for Melanoma




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

# Ipilimumab + Vemurafenib Liver Toxicities in Phase I Testing

| Patient Number | Doses of Ipilimumab Before ALT-AST Elevation, *n* | Time to Onset of ALT-AST Elevation After First Dose Ipilimumab, Days | Treatment | Time to Resolution of ALT-AST Elevation, Days | Toxicity Relapse With Repeated Ipilimumab |
|---|---|---|---|---|---|
| **Cohort 1*** | | | | | |
| 4 | 1 | 21 | GCS; Vem discontinued for 5 days then restarted with dose reduction; Ipi permanently discontinued | 4 | NA |
| 5 | 2 | 26 | GCS; Vem discontinued for 4 days then restarted with dose reduction; Ipi continued (2 doses) | 6 | No |
| 6† | 1 | 21 | GCS; Vem discontinued for 5 days then restarted with dose reduction; Ipi continued (1 dose) | 6 | No |
| 8 | 1 | 19 | GCS; Vem discontinued for 4 days then restarted with dose reduction; Ipi continued (1 dose) | 12 | Yes |
| **Cohort 2‡** | | | | | |
| 10 | 1 | 15 | GCS; Vem discontinued for 7 days then restarted with dose reduction; Ipi permanently discontinued (1 dose) | 10 | NA |
| 16§ | 1 | 13 | Vem and Ipi permanently discontinued | 20 | NA |

*Cohort 1: 1-month run-in of single-agent vemurafenib 960 mg bid followed by 4 infusions of ipilimumab 3 mg/kg every 3 weeks plus vemurafenib; †Patient also had grade 2 increase in total bilirubin; ‡Cohort 2: vemurafenib 760 mg bid plus ipilimumab 3 mg/kg every 3 weeks; § Patient also had grade 3 increase in total bilirubin.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; bid = twice a day; GCS = glucocorticosteroid; Vem = vemurafenib.

Ribas A, et al. *N Engl J Med.* 2013;368:1365-1366. 

# Clinical Pharmacology of Novel Immunotherapeutics

- The optimal predictor for response to CTLA-4 and PD-1/PD-L1 inhibitors is still unclear.
  - Ongoing studies assessing chronicity and predictive power of PD-L1 expression
  - To date, conflicting results
    - Variability in assays, tumor heterogeneity
- Investigation of systemic effects of CTLA-4 and PD-1/PD-L1 blockade is incomplete.
  - Role of cytokine changes on adverse events
  - Effect on hepatic drug metabolism

# Pharmacists' Role and the Interpretation of Gray Areas of Immunotherapy: Case Studies

# Case 1

- A 69-year-old woman with no prior significant PMH developed a primary skin melanoma in the left thigh area that was 1.4 mm thick at the time of diagnosis. At the time of excision, the left inguinal sentinel lymph node biopsy was positive.
- A follow-up PET scan showed an abdominal nodule approximately 3 cm.
- No other abnormalities were noted.

PET = positron emission tomography; PMH = past medical history.

# Case 1 (cont'd)

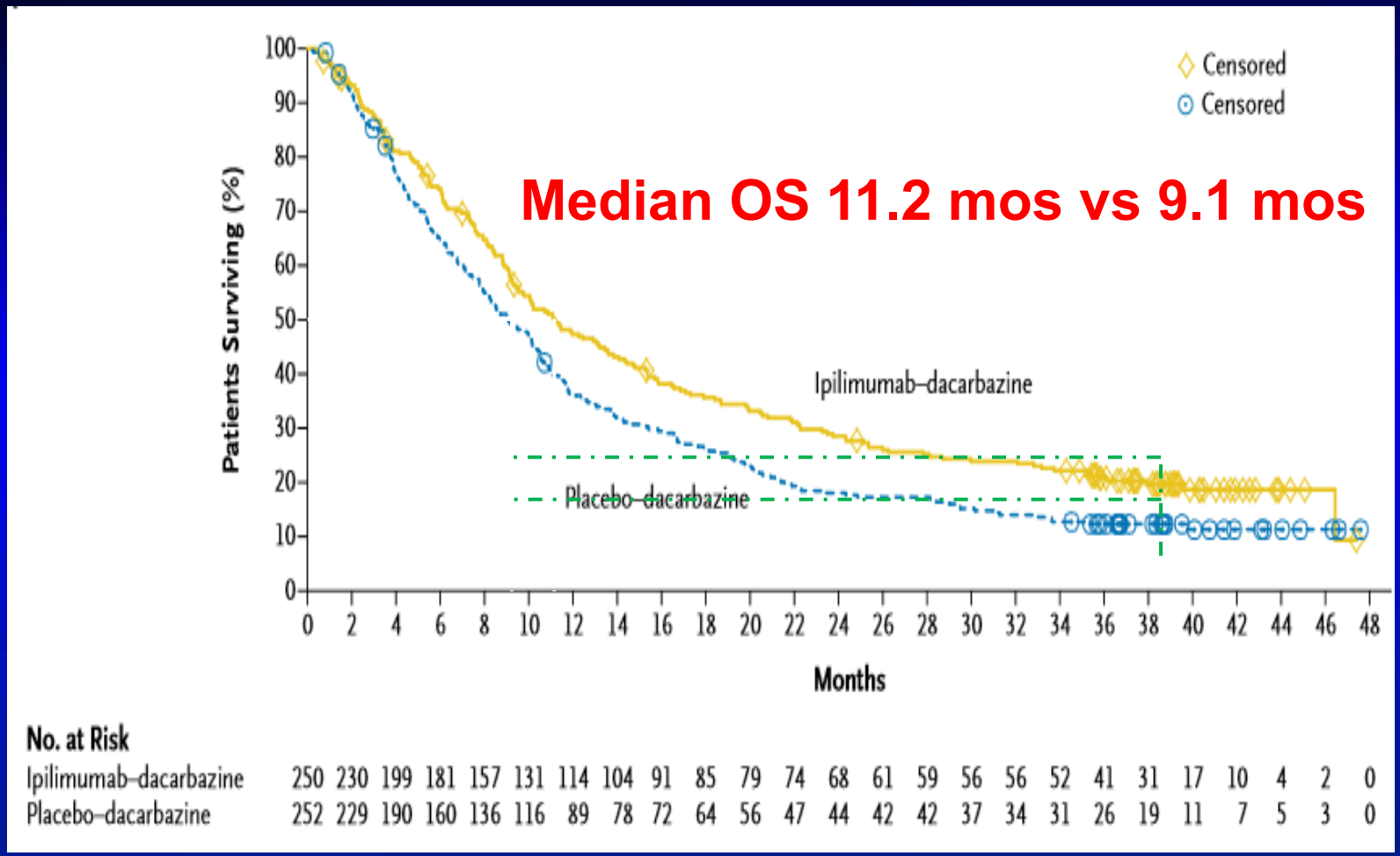
- PMH:  Not contributory – otherwise healthy
- Drug history: NKDA – no current drugs
- Physical exam and labs within normal limits, except for noted skin lesion (nearly healed)
- BRAF is wild type.

NKDA = no known drug allergies.

# 1. What therapy would you recommend?

A. Dacarbazine
B. Interleukin-2
C. Ipilimumab
D. Pembrolizumab
E. Nivolumab and ipilimumab

# Dacarbazine +/- Ipilimumab (First Line)

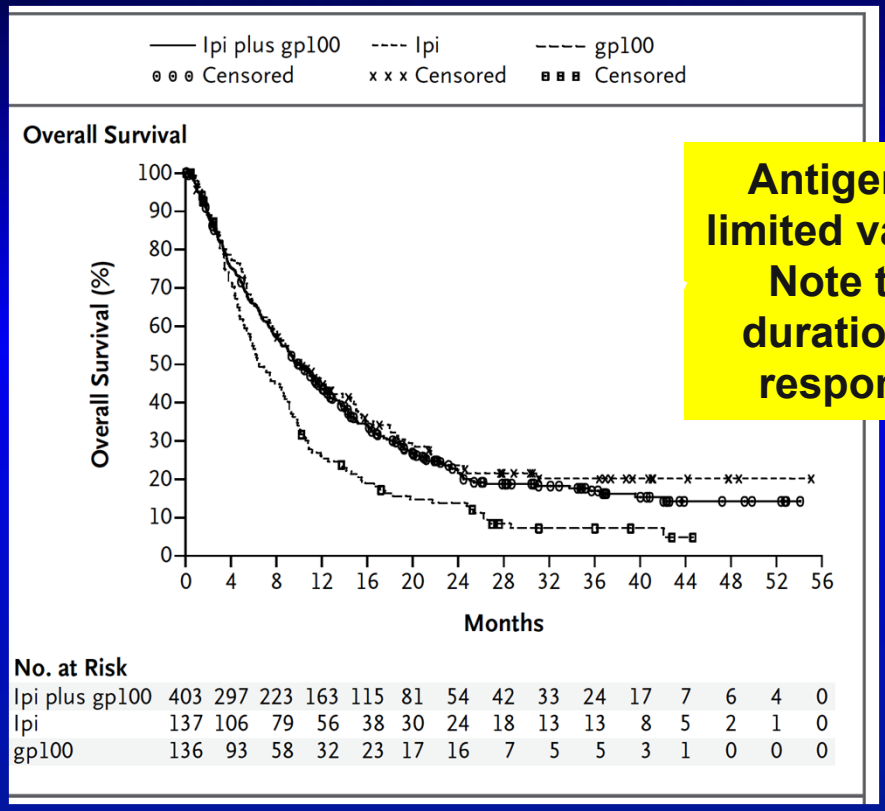



mos = months; OS = overall survival.

Robert. *N Engl J Med*. 2011;364:2517. For educational purposes only.

# Ipilimumab and High-Dose IL-2

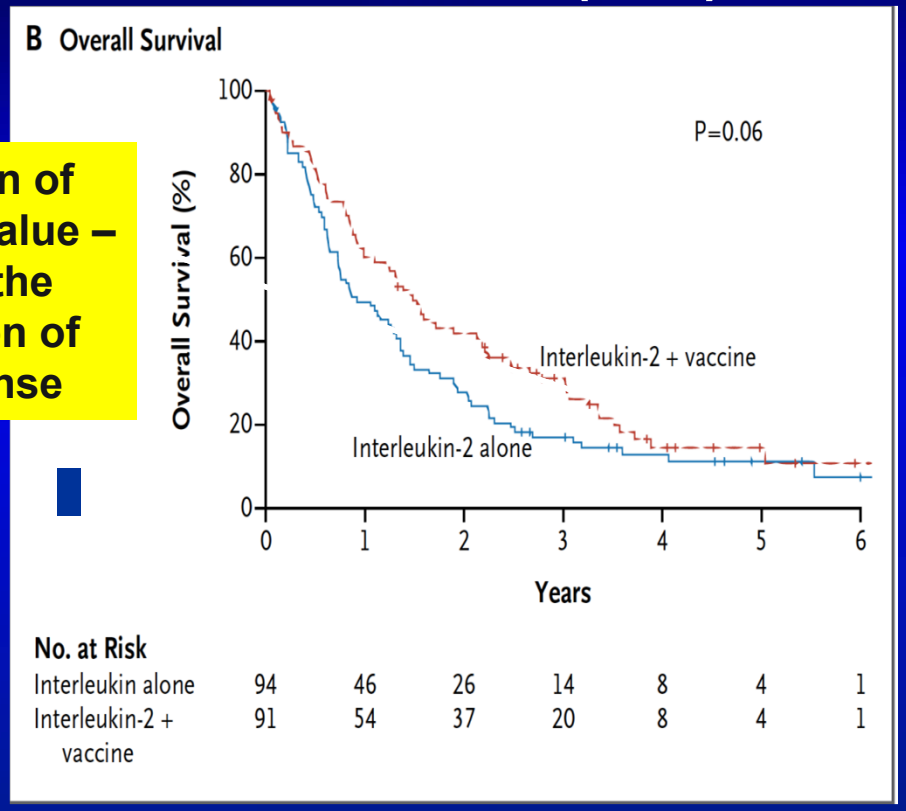
## Ipilimumab (Ipi)




Hodi et al. *N Engl J Med*. 2010;363:711-723.
For educational purposes only.

**Antigen of limited value – Note the duration of response**

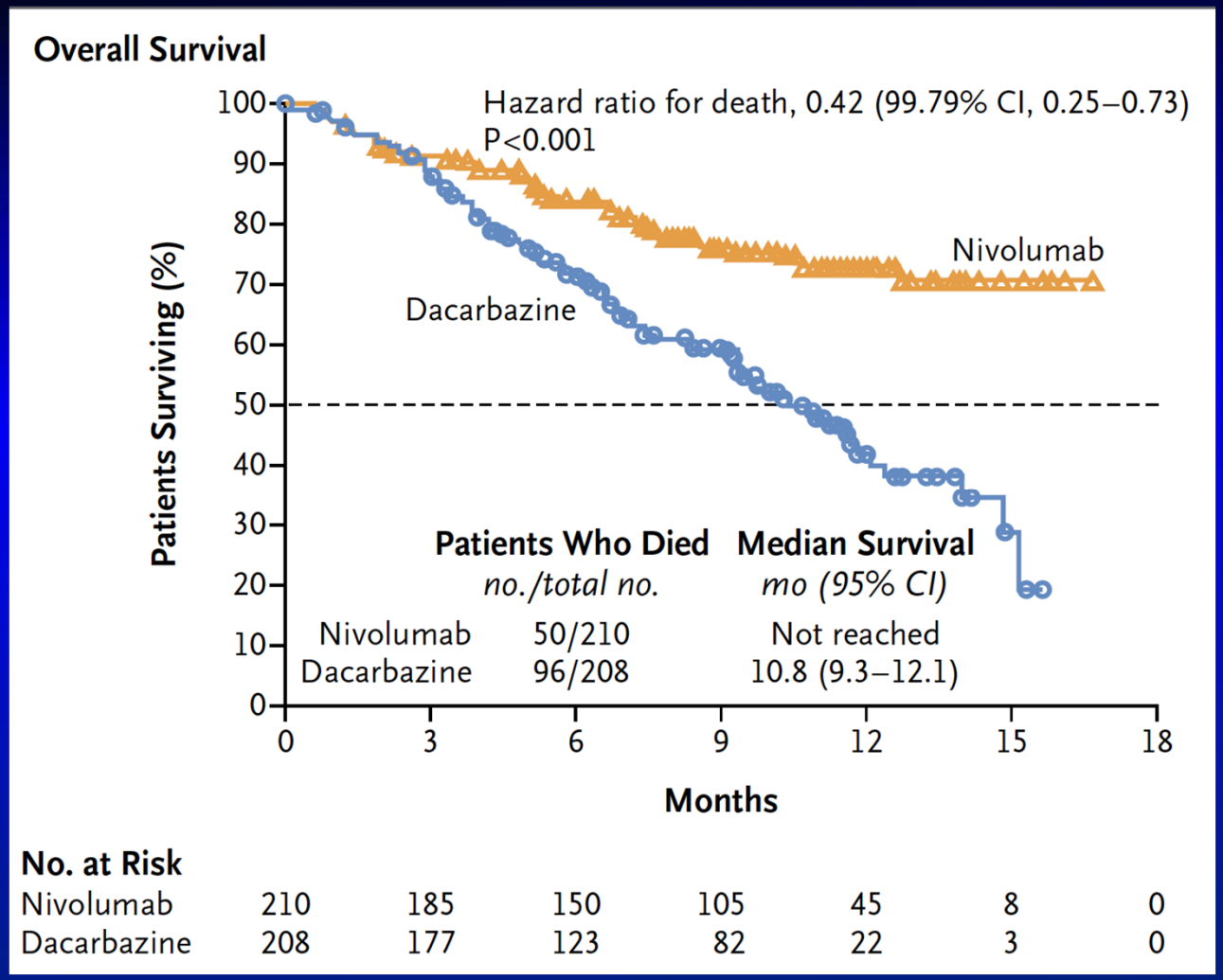
## gp100 Peptide Vaccine and Interleukin-2 (IL-2)




Schwartzentruber et al. *N Engl J Med*. 2010;364:2119-2127.
For educational purposes only.

gp100 = glycoprotein 100.

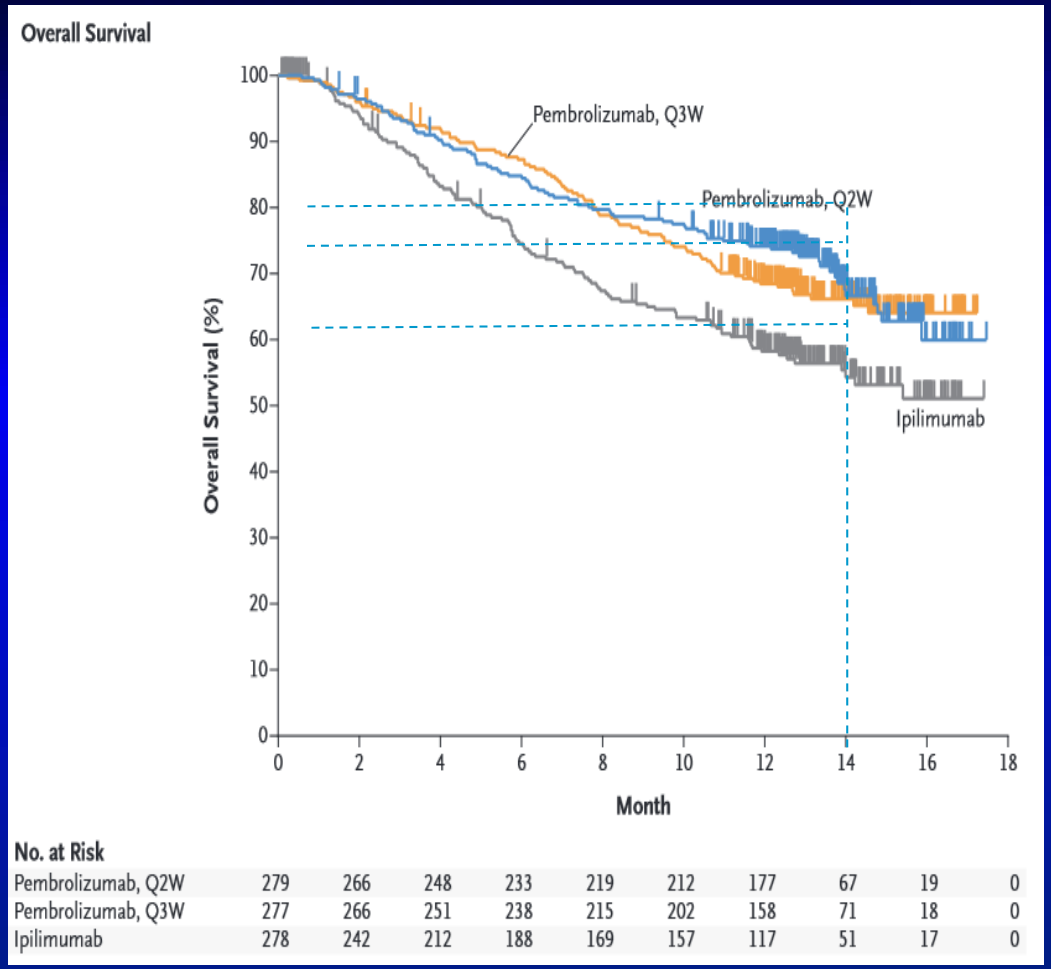
# Nivolumab vs Dacarbazine (First-line BRAF WT)




CI = confidence interval; WT = wild type.

Robert et al. *N Engl J Med*. 2015;372:320-330. For educational purposes only.

# Ipilimumab vs Pembrolizumab in Metastatic Melanoma (KEYNOTE-006)




No. at Risk

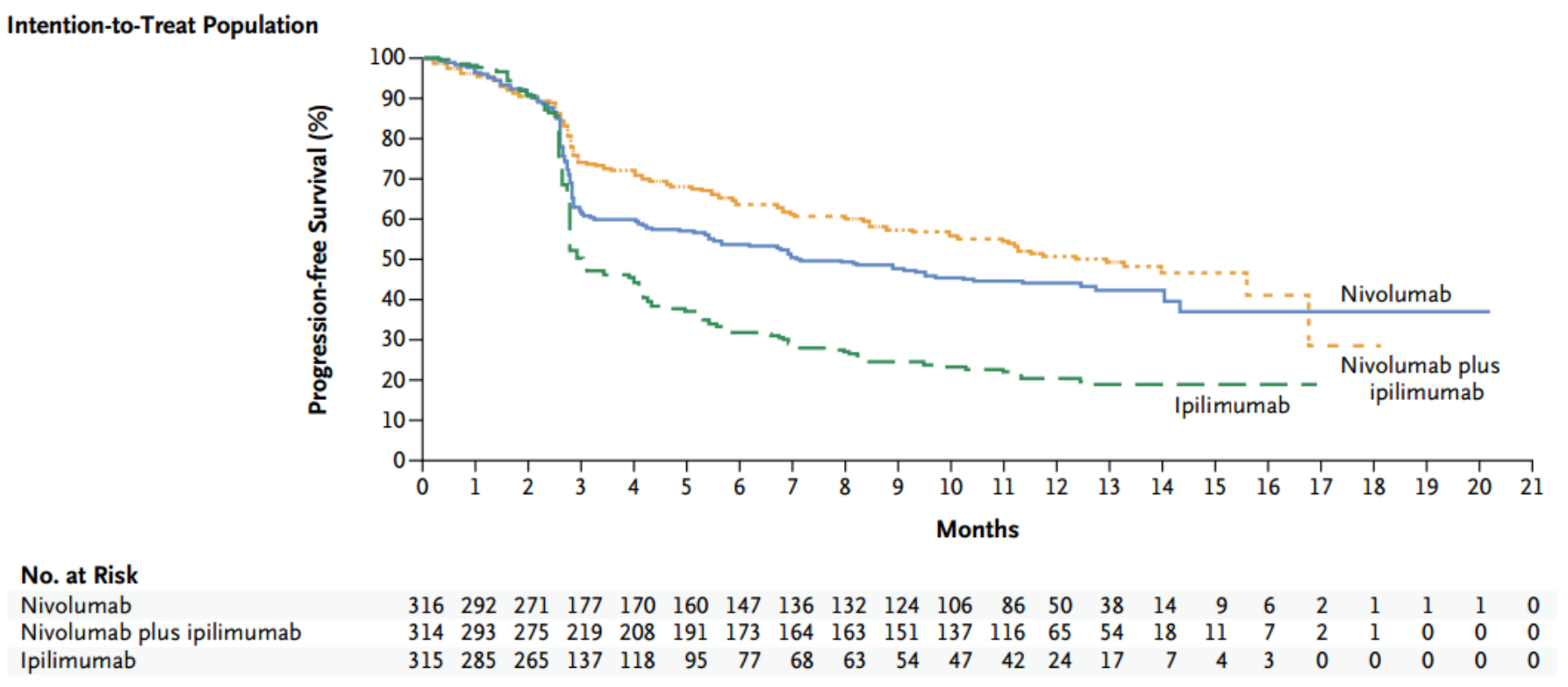
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab, Q2W | 279 | 266 | 248 | 233 | 219 | 212 | 177 | 67 | 19 | 0 |
| Pembrolizumab, Q3W | 277 | 266 | 251 | 238 | 215 | 202 | 158 | 71 | 18 | 0 |
| Ipilimumab | 278 | 242 | 212 | 188 | 169 | 157 | 117 | 51 | 17 | 0 |

**One-year OS**
**Pembro q2w = 74%**
**Pembro q3w = 68%**
**Ipilimumab = 58%**

**HR = 0.63, *P* = .0005**
**HR = 0.69, *P* = .0036**

HR = hazard ratio; q2w = every 2 weeks; q3w = every 3 weeks.
Robert et al. *N Engl J Med*. 2015;367:1694-1703. For educational purposes only.

# Ipilimumab vs Nivolumab vs the Combination in Metastatic Melanoma




**Median PFS**
**Ipi = 2.9 mo**

**Nivo = 6.9 mo**
**Ipi plus Nivo = 11.5 mo**

**HR = 0.42, *P* <.001**

Nivo = nivolumab; PFS = progression-free survival.

Larkin et al. *N Engl J Med*. 2015;373:23-34. For educational purposes only.

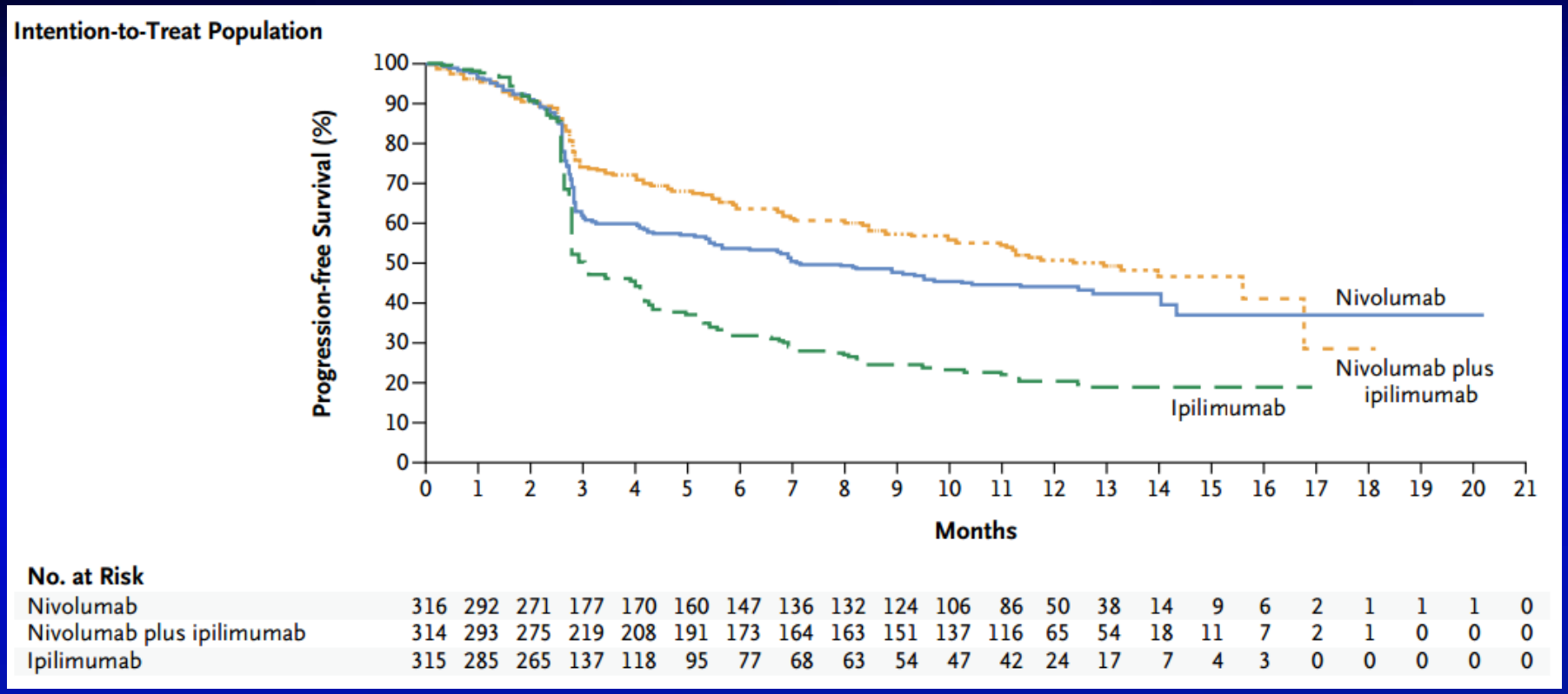
# Summary of First-line Drug Choices

- Dacarbazine approved 1975 (no placebo-controlled trials)
- Ipilimumab >dacarbazine
- Nivolumab >dacarbazine
- Pembrolizumab >ipilimumab
- Nivolumab and ipilimumab >ipilimumab
- Dacarbazine and ipilimumab monotherapy inferior first-line choices

2. **Would you use nivolumab and ipilimumab together instead of in sequence?**

   A. **Yes**
   B. **No**

# Ipilimumab and Nivolumab Together



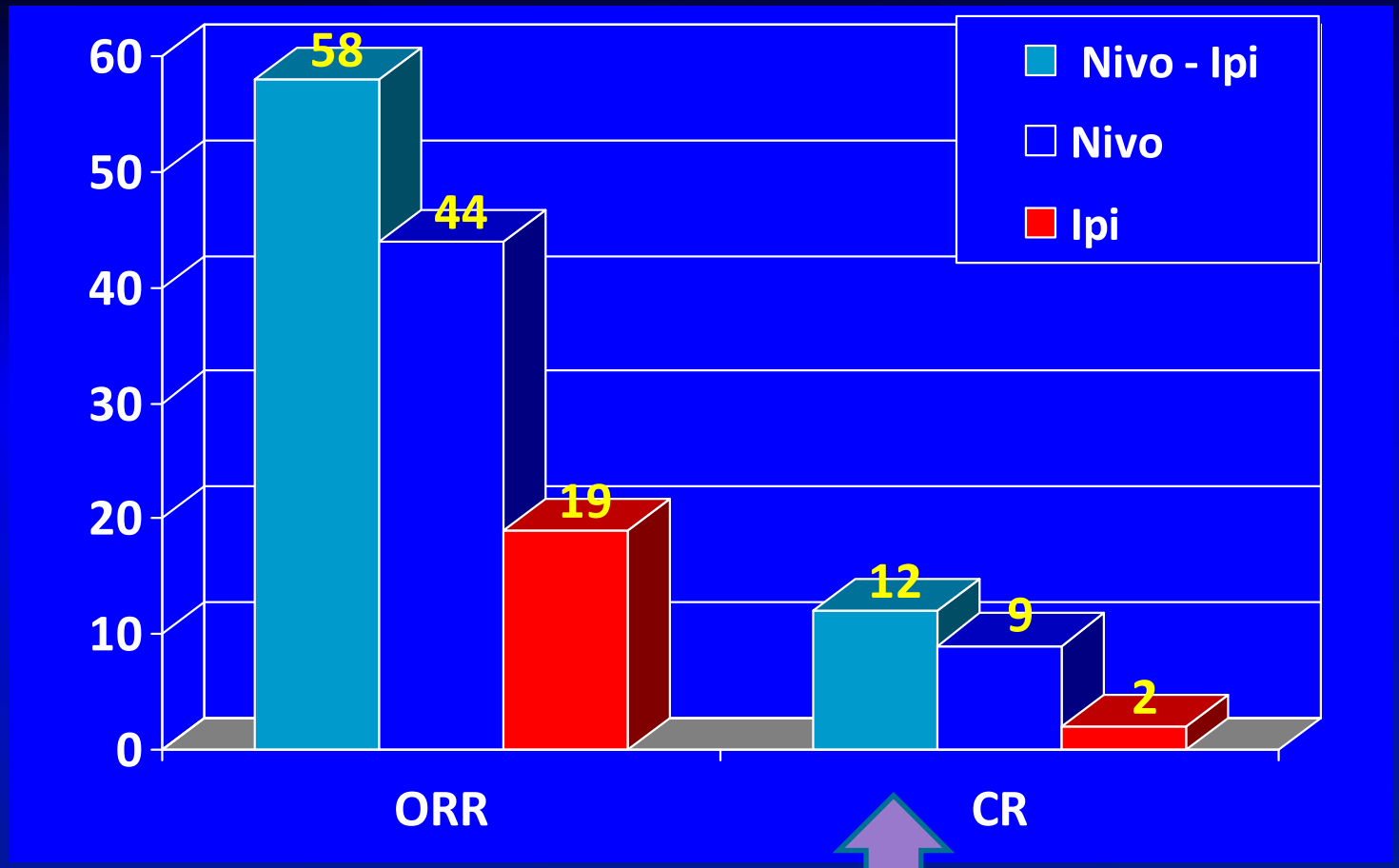

**Median PFS**
**Ipi = 2.9 mo**

**Nivo = 6.9 mo**
**Ipi plus Nivo = 11.5 mo**

**HR = 0.42, *P* <.001**

Larkin et al. *N Engl J Med*. 2015;373:23-34. For educational purposes only.

# Ipilimumab and Nivolumab Together



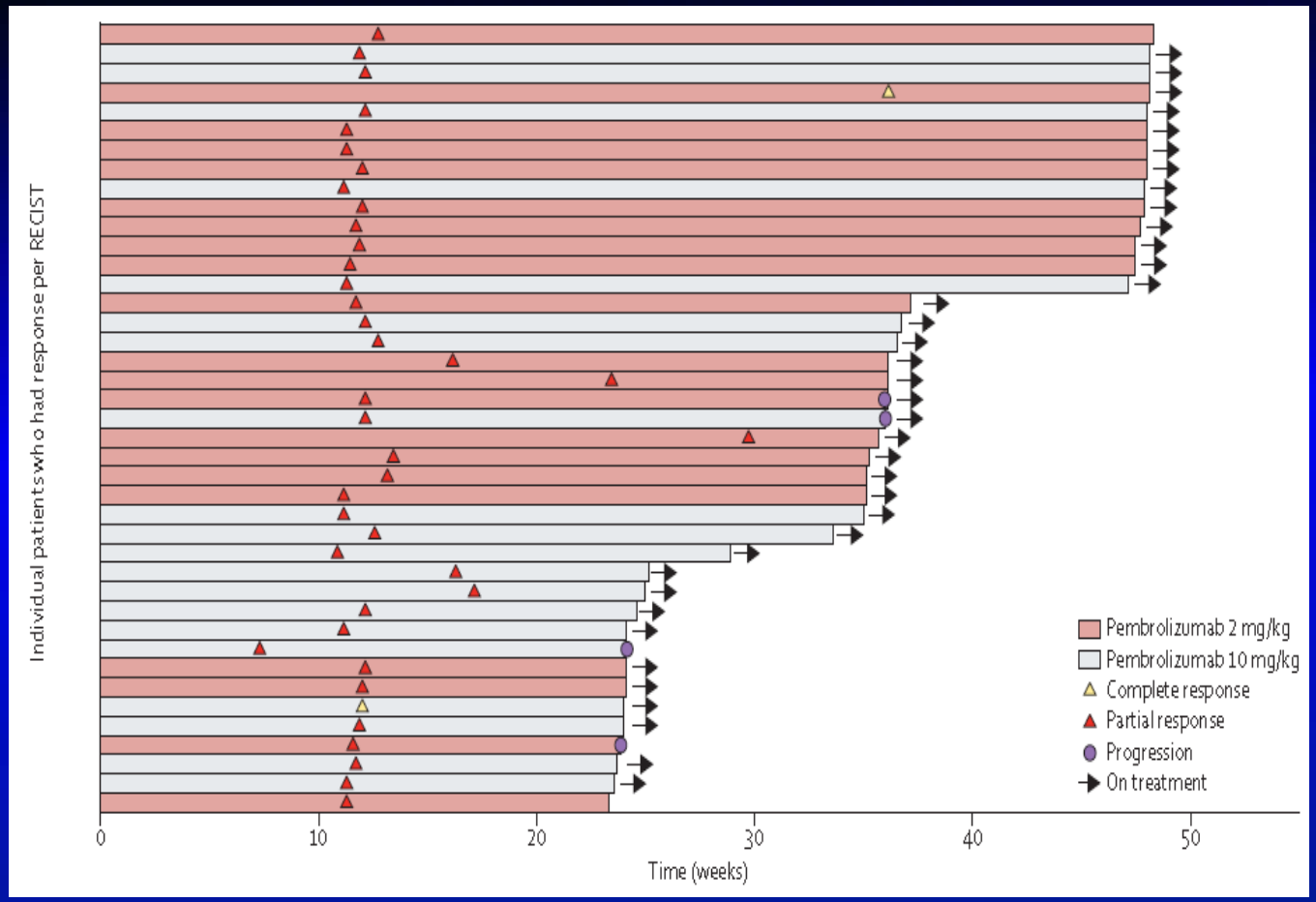

CR = complete response; ORR = objective response rate.

Larkin et al. *N Engl J Med*. 2015;373:23-34.

# Sequential Ipilimumab and Nivolumab

- Although they are both classified as immune checkpoint inhibitors, they work differently.
- Clear evidence that there is no cross-resistance

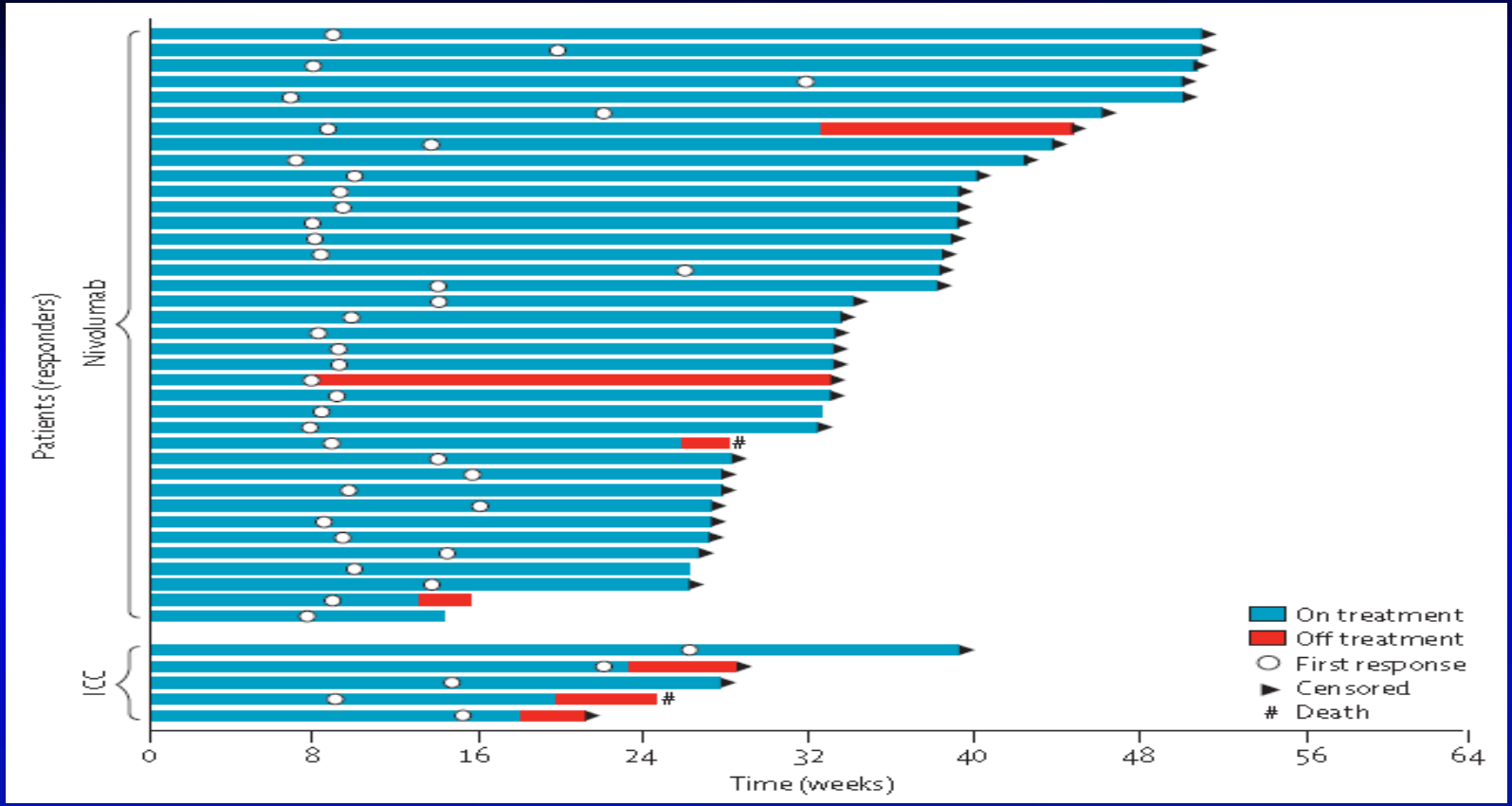
# Pembrolizumab After Ipilimumab




- **Responses appear to be durable**

Roberts et al. *Lancet*. 2014;384:1109-1117. For educational purposes only.

# Nivolumab After Ipilimumab



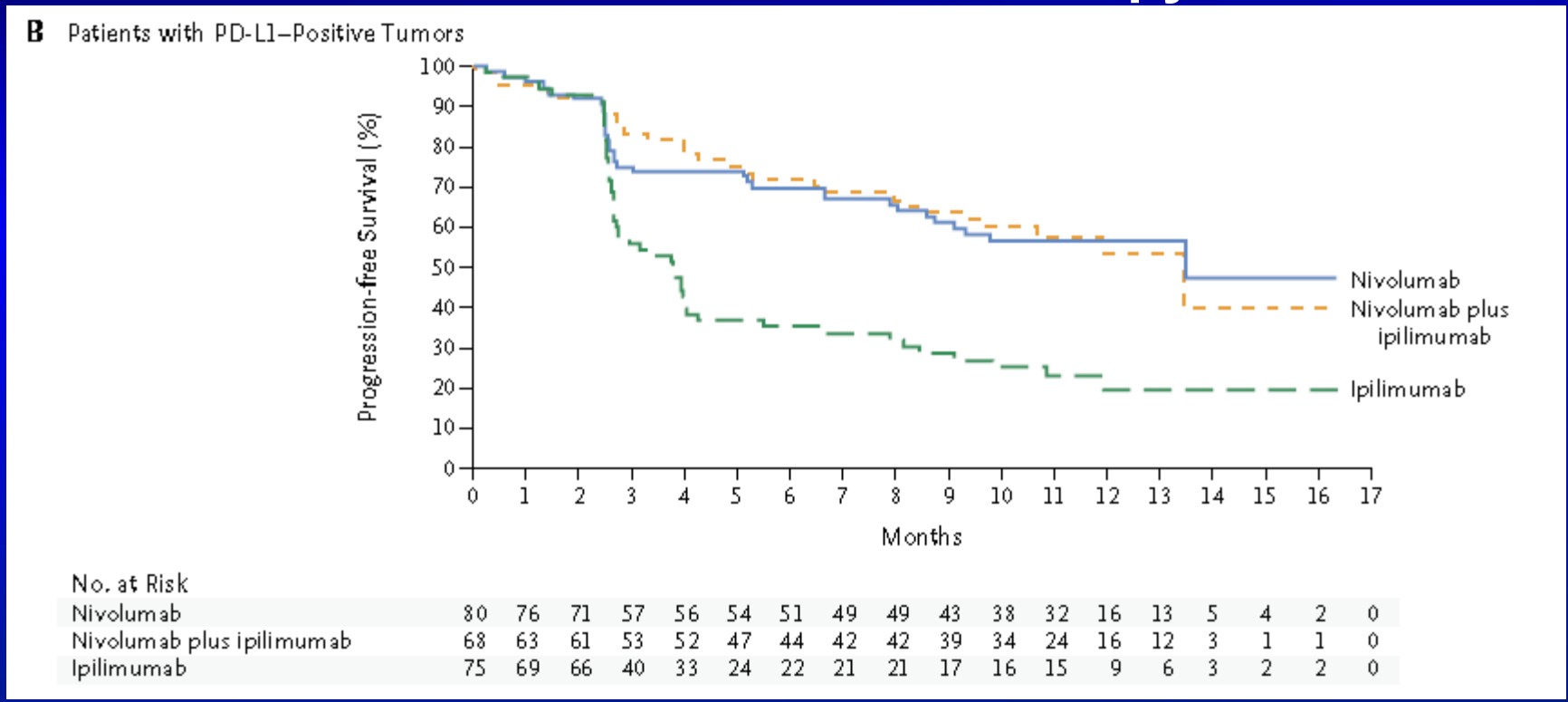

- **Responses appear to be durable**

ICC = investigator's choice of chemotherapy.

Weber et al. *Lancet Oncol*. 2015;16:375-384. For educational purposes only.

# Ipilimumab Does Not Add Value to High PD-L1–Expressing Tumors

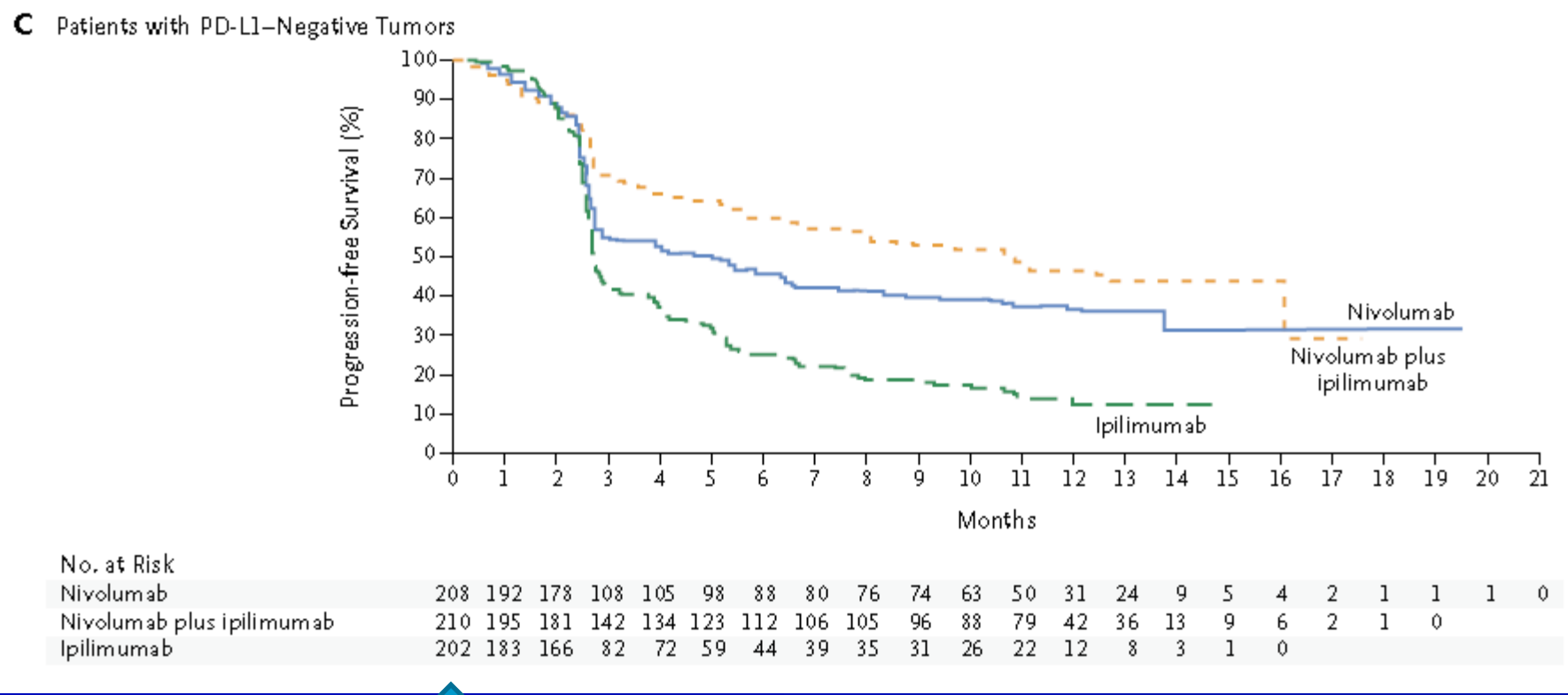
- **PD-L1 expression may predict which patients should be treated with nivolumab monotherapy**




PD-L1 = programmed death-ligand 1.

Larkin et al. *N Engl J Med*. 2015;373:23-34. For educational purposes only.

# The Combination Is Best




**72%**

## No evidence of ipilimumab efficacy after a PD-1

PD-1 = programmed death 1.

Larkin et al. *N Engl J Med*. 2015;373:23-34. For educational purposes only.

# Can We Afford the Combination?

- Ipilimumab 3 mg/kg x 4 doses – $33 985 per dose (5 x 50-mg vials)
- Nivolumab 3 mg/kg q2w until progression – $7 201 per dose (3 x 100-mg vials)
- Pembrolizumab 2 mg/kg q3w until progression (4 x 50-mg vials ) ~ $9 128
- Combination of ipilimumab 3 mg/kg q3w x 4 and nivolumab 1 mg/kg q3w x 4 – $36 385 per cycle, then nivolumab 3 mg/kg q2w

Assumes 85-kg patient. Good RX.com Web site. Available at: http://www.good Rx.com. Accessed November 5, 2015.

# 3. Should we be doing PD-L1 testing?

A. Yes
B. No

# PD-L1 Testing with Pembrolizumab

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.**

**KEYTRUDA® (pembrolizumab) for injection, for intravenous use**
**KEYTRUDA® (pembrolizumab) injection, for intravenous use**
**Initial U.S. Approval: 2014**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1.2) | 10/2015 |
| Dosage and Administration (2.1, 2.3) | 10/2015 |
| Dosage and Administration (2.4) | 01/2015 |
| Warnings and Precautions (5.1, 5.2, 5.4, 5.6) | 10/2015 |
| Warnings and Precautions (5.4, 5.6, 5.7) | 06/2015 |

**----------INDICATIONS AND USAGE----------**

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:

- patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. (1.1)
- patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

Continued approval for these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1, 1.2)

**----------DOSAGE AND ADMINISTRATION----------**

- Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks. (2.2)
- Dilute prior to intravenous infusion. (2.4)

**----------DOSAGE FORMS AND STRENGTHS----------**

- For injection: 50 mg lyophilized powder in single-use vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial (3)

**----------CONTRAINDICATIONS----------**

None. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- Immune-mediated Pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated Hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
- Immune-mediated Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- Infusion-related reactions: Stop infusion and permanently

decreased appetite, constipation, arthralgia, and diarrhea. (6.1)
- NSCLC included fatigue, decreased appetite, dyspnea and cough. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------USE IN SPECIFIC POPULATIONS----------**

Lactation: Discontinue nursing or discontinue KEYTRUDA. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 10/2015**

FDA = US Food and Drug Administration; NSCLC = non-small cell lung cancer.

# PD-L1 IHC 22C3 pharmDx for Autostainer Link 48 NEW

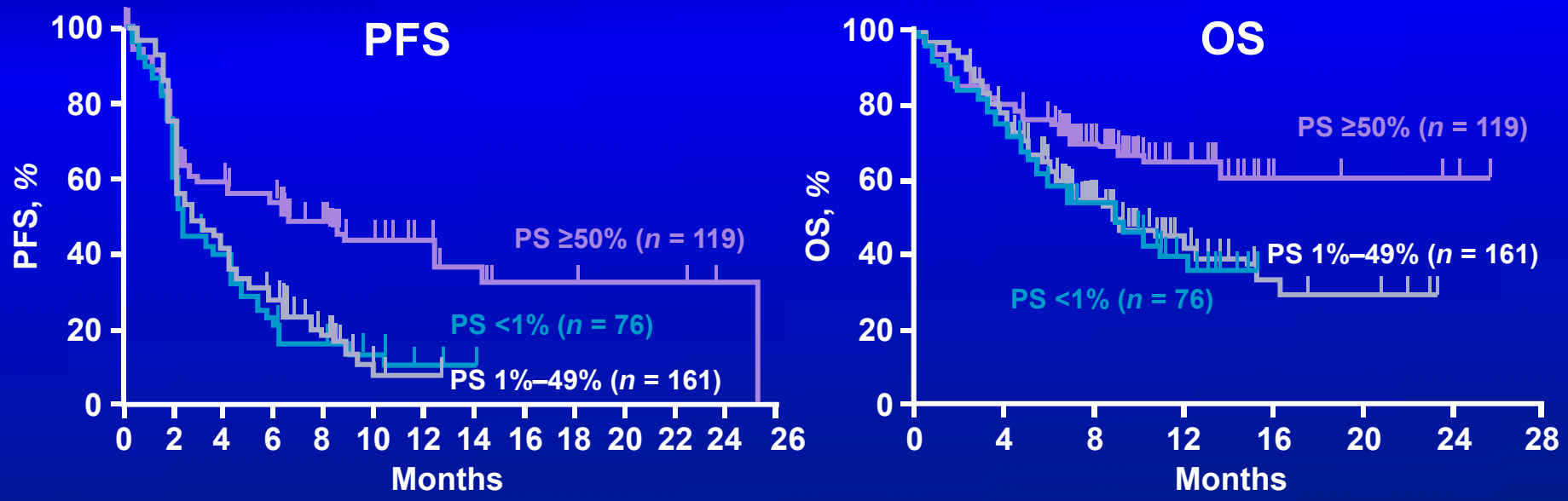
PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on Autostainer Link 48. PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining. The specimen should be considered PD-L1 positive if TPS ≥ 50% of the viable tumor cells exhibit membrane staining at any intensity.

Carpinteria, CA: Dako North America, Inc.

PD-L1 IHC 22C3 pharmDx for Autostainer Link 48. Dako Web site. Available at: http://www.dako.com/us/ar39/p250165/prod_products.htm. Accessed November 4, 2015.

# KEYNOTE-001: Pembrolizumab Efficacy by PD-L1 Expression

| ORR by RECIST, % (95% CI) | *N* | All Cohorts |
|---|---|---|
| **Percent PD-L1 staining** | | |
| ▪ ≥50% | 73 | 45.2 (33.5–57.3) |
| ▪ 1%–49% | 103 | 16.5 (9.9–25.1) |
| ▪ <1% | 28 | 10.7 (2.3–28.2) |




**Proportion score for 356 patients in training, validation groups with slides sectioned within ≤6 months of staining**

PS = proportion score; RECIST = Response Evaluation Criteria in Solid Tumors.

Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028. For educational purposes only.

# Response Based on PDL-1 Status

| Setting | Treatment | Objective Response Rate, % | | | Assay (mAb) |
|---|---|---|---|---|---|
| | | Unselected | PD-L1+ | PD-L1– | |
| Solid tumors (n = 42) | Nivo | 21 | 36 | 0 | Tumor (5H1) |
| Melanoma (n = 44) | Nivo | 32 | 67 | 19 | Tumor (28-8) |
| Melanoma (n = 34) | Nivo | 29 | 44 | 17 | Tumor (28-8) |
| Melanoma (n = 113) | Pembro | 40 | 49 | 13 | Tumor (22C3) |
| NSCLC (n = 129) | Pembro | 19 | 37 | 11 | Tumor (22C3) |
| HNSCC (n = 55) | Pembro | 18 | 46 | 11 | Tumor (22C3) |
| Melanoma (n = 411) | Pembro | 40 | 49 | 13 | Tumor (22C3) |
| Solid tumors (n = 94) | MPDL | 21 | 36 | 13 | TIL |
| Melanoma (n = 30) | MPDL | 29 | 27 | 20 | TIL |
| NSCLC (n = 53) | MPDL | 23 | 46 | 15 | TIL |
| Bladder (n = 65) | MPDL | 26 | 43 | 11 | TIL |
| Solid tumors (n = 179) | MEDI | 11 | 22 | 4 | NR (SP263) |

HNSCC = head and neck squamous cell carcinoma; mAb = monoclonal antibody; NR = neutral red; Pembro = pembrolizumab; TIL = tumor-infiltrating lymphocyte.

Mahoney KM. *Oncology*. 2014;28:39-48. For educational purposes only.

# PD-L1 Testing Is Controversial

- Different assays used in published literature
- Different definitions of PD-L1 positive
- Is it better to test archival or fresh tissue?
- Do you biopsy the primary tumor or a metastatic site?
- Is it important to the same degree in all tumors?
- Is expression stable over time?
- Pembrolizumab is approved in PL-1–expressing tumors with FDA-approved testing kit.

# The Great Unknown

- No data for:
  - Pembrolizumab and ipilimumab
  - 22C3 pharmDx* to predict outcome with nivolumab +/- ipilimumab in melanoma
  - Nivolumab efficacy with a TPS of 50%
  - Is it safe to extrapolate data?

*Carpinteria, CA: Dako North America, Inc.

TPS = tumor proportion score.

# Case 1 (cont'd)

- PD-L1 was tested and the TPS was 10% positive (not performed with the 22C3 pharmDx* assay).
- Treatment with pembrolizumab 2 mg/kg IV every 3 weeks was started.
- Just before the third dose (6 weeks from the 1st dose), a scan was performed and the abdominal mass had increased by 50%.

*Carpinteria, CA: Dako North America, Inc.

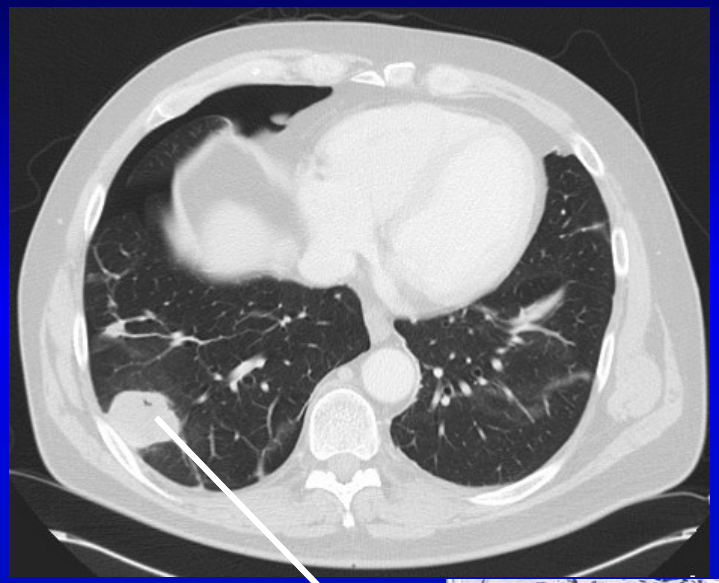
IV = intravenous.

## 4. How would you manage the patient now?

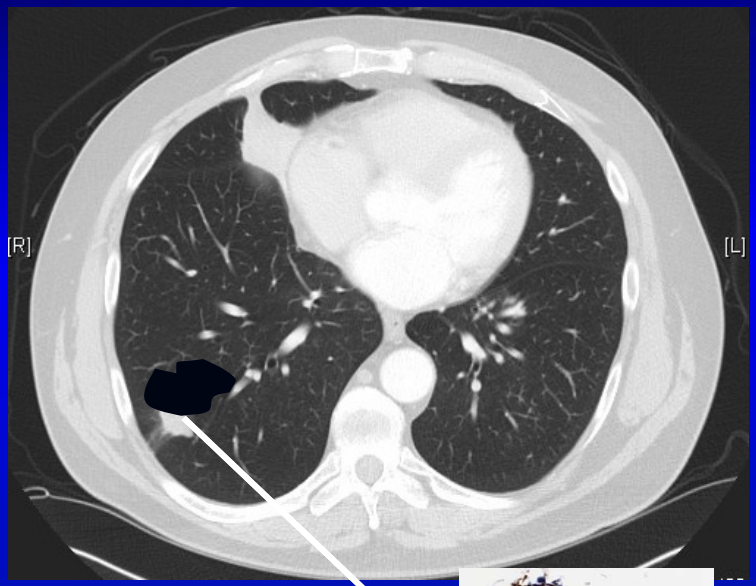
A. Continue pembrolizumab
B. Switch to nivolumab
C. Switch to ipilimumab
D. Switch to dacarbazine
E. Move to best supportive care

# Pseudoprogression with Pembrolizumab

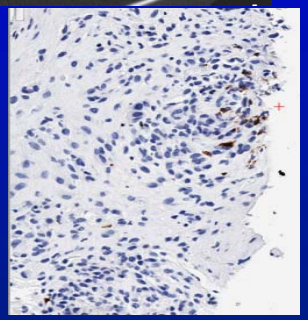
**Baseline**

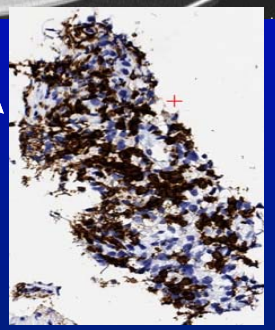


**Treatment**




**CD8+ IHC**

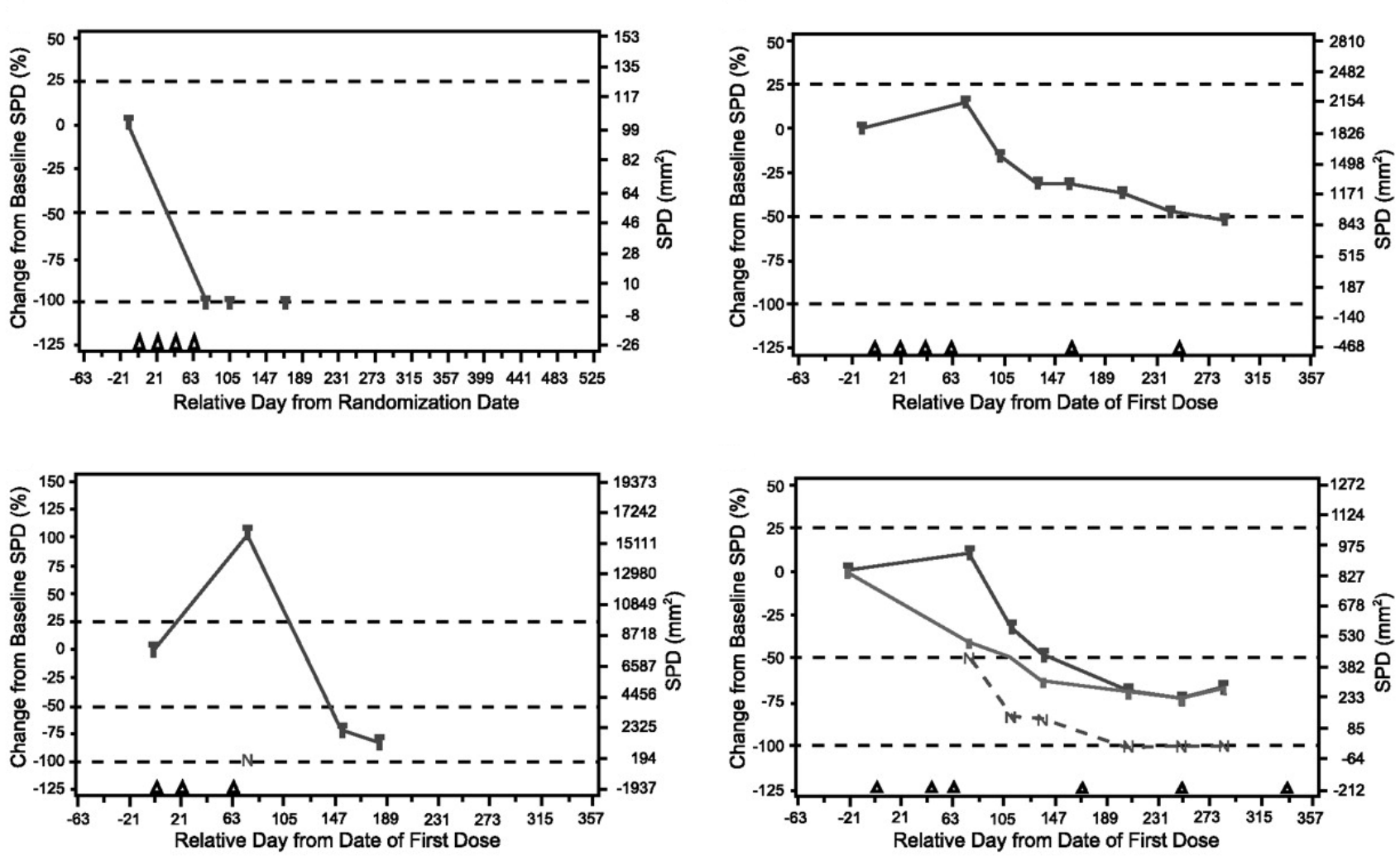




IHC = immunohistochemistry.

Ribas A, et al. ASCO 2013. Abstract 9009.

# Patterns of Response to Ipilimumab Observed in Advanced Melanoma




SPD = sum of the product of perpendicular diameters.

Wolchok et al. *Clin Cancer Res*. 2009;15:7412-7420. For educational purposes only.

# Immune-Related Response Criteria (irRC)

| | WHO | irRC |
|---|---|---|
| CR | Disappearance of all lesions not less than 4 weeks apart | Disappearance of all lesions not less than 4 weeks apart |
| PR | ≥50% decrease in SPD of all index lesions compared with baseline in 2 observations | ≥50% decrease in SPD of all index lesions compared with baseline in 2 observations |
| SD | Not PR, CR, or PD | Not PR, CR, or PD |
| PD | At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point) | At least 25% increase in tumor burden compared with nadir in 2 consecutive observations at least 4 weeks apart |
| New lesions | Always represent PD | Incorporated into tumor burden if possible |

PD = progressive disease; PR = partial response; SD = stable disease; WHO = World Health Organization.

Wolchok JD, et al. *Clin Cancer Res.* 2009;15:7412

# Follow-Up

- Pembrolizumab was continued and the scan 4 weeks later revealed tumor shrinkage by 50%.
- When asked about toxicity, the patient says that she has been having diarrhea for the last week, which is occasionally bloody.
- The loperamide she has been taking "doesn't work too well" and she requests a prescription for something stronger.

# 5. How do you manage this patient now?

A. Refer the patient to an emergency department with the directions to begin treatment immediately with intravenous hydration and dexamethasone at 4 mg every 6 hours.

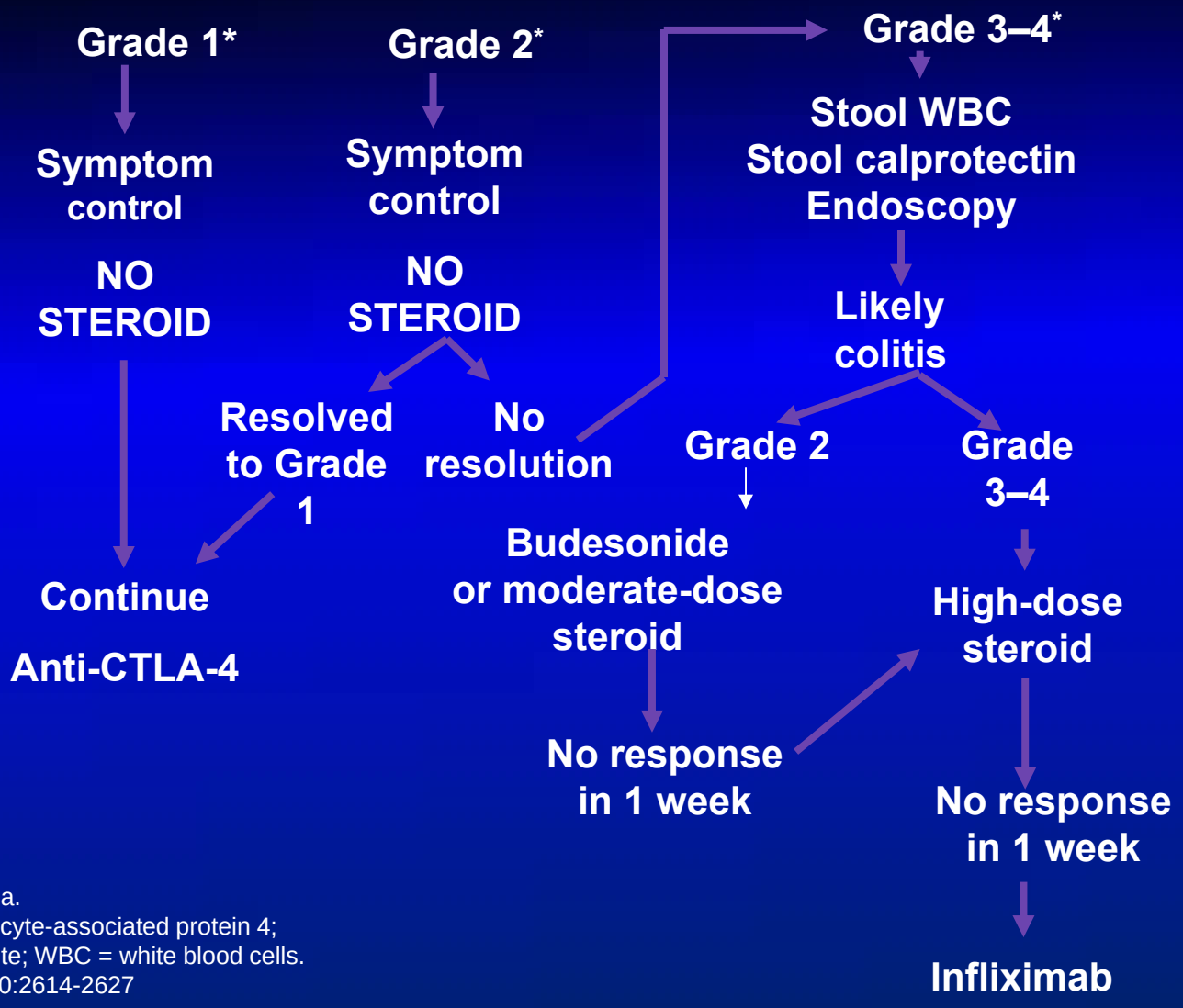
B. Comfort the patient by stating that occasional episodes of loose stools are actually frequent in the population and could be related to diet and recommend no further evaluation before her next infusion of pembrolizumab.

C. Obtain a full history including the frequency and severity of the gastrointestinal symptoms, recommend a stringent diet, oral hydration, and loperamide and follow up with the patient in the next day to assess the status of the loose stools.

D. Continue the pembrolizumab infusions, but prescribe oral prednisone 60 mg/day for 5 days, followed by a 1-month taper.

E. Not sure

# Management Algorithm for Diarrhea




*NCI Common Toxicity Criteria.
CTLA-4 = cytotoxic T-lymphocyte-associated protein 4;
NCI = National Cancer Institute; WBC = white blood cells.
O'Day et al. *Cancer*. 2007;110:2614-2627

6. Which of the following adverse events may also occur with immune checkpoint inhibitors?

A. Thyroiditis
B. Uveitis
C. Nephritis
D. Thrombocytopenia
E. All of the above

# Immune Checkpoint Inhibitor AEs

**Comparison of Immune-Related Adverse Events Between Anti–PD-1/PD-L1 Drugs and Ipilimumab**

| | Ipilimumab (%)[42] | Nivolumab/ BMS-936558 (%)[23] | Pembrolizumab/ MK-3475 (%)[21] | Pidilizumab/ CT-011 (%)[35] | BMS-936559 (%)[20] | MPDL3280A (%)[39] |
|---|---|---|---|---|---|---|
| Colitis | 7.6/5.3 | 14 | 13 | 0 | 9 | 39 |
| Dermatological | 43/1.5 | 23 | 21/2 | | | |
| Diarrhea | 33/5 | 18 | 20/1 | | | |
| Fatigue | 42/7 | 32 | 30/1 | | | |
| Hepatic | | | 13/1 | | | |
| Hypothyroid | | | 8/1 | | | |
| Hypophysitis | 1.5/1.5 | | | | | |
| Infusion reactions | | | | | 10 | |
| Pneumonitis | | /1 | 4/0 | | | 0/0 |
| Pruritus | | | 21 | | | |
| **Total grade 3/4** | **45.8** | | | | | |
| **Total immune-related** | **96.9** | **0** | **79** | **61** | **39** | **0** |

AE = adverse event;.

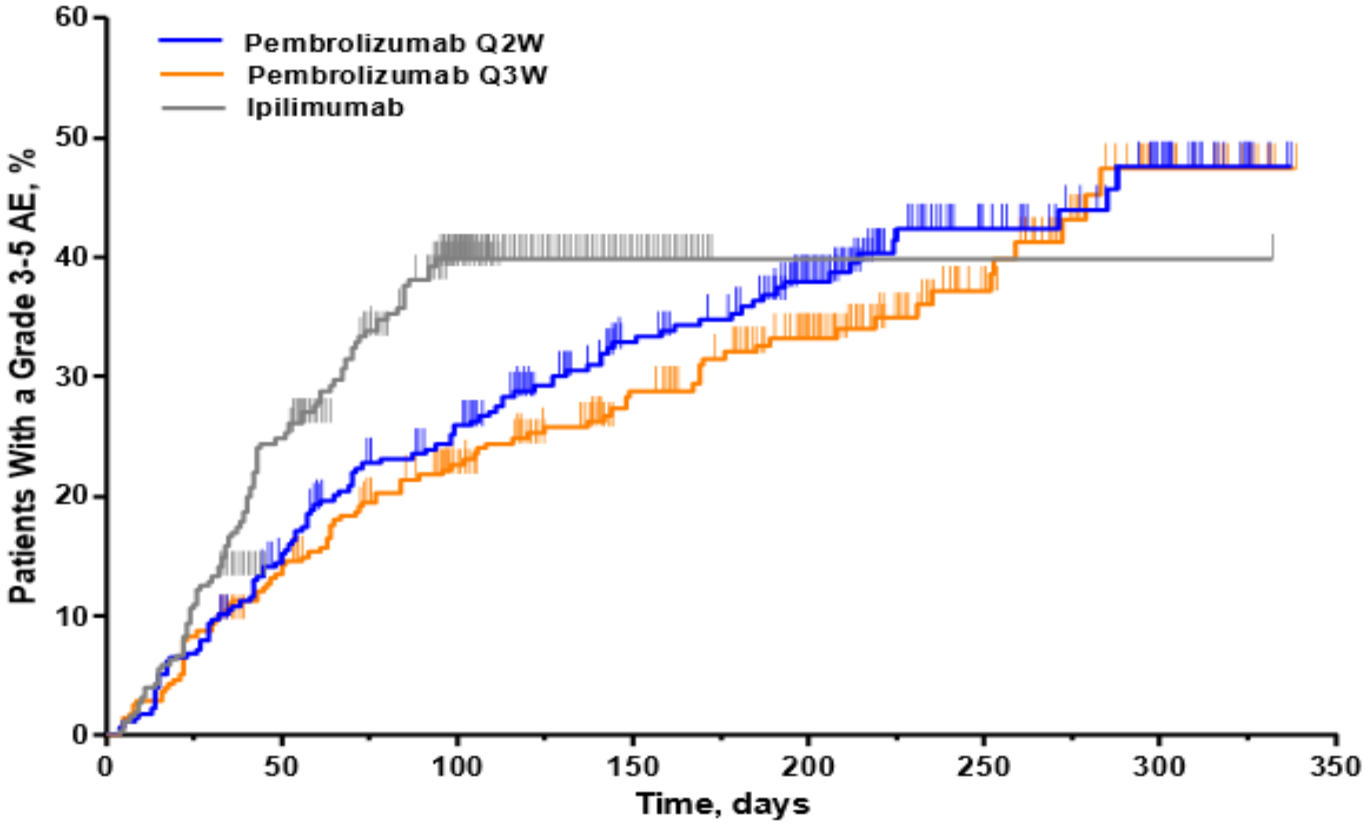
Dolan et al. *Cancer Control*. 2014;21:231-237. For educational purposes only.

# Toxicity for Nivolumab, Ipilimumab, or the Combination (Grades 3 and 4)

| Event | Nivolumab | Nivo + Ipi | Ipilimumab |
|---|---|---|---|
| Tx-related AE | 16.3% | 55% | 27.3% |
| Diarrhea | 2.2% | 9.3% | 6.1% |
| Fatigue | 1.3% | 4.2% | 1% |
| Pruritus | 0 | 1.9% | 0.3% |
| Rash | 0.6% | 4.8% | 1.9% |
| Vomiting | 0.3% | 2.6% | 0.3% |
| Inc. liver enzymes | 1.3% | 8.3% | 1.6% |
| Hypothyroidism | 0 | 0.3% | 0 |
| Colitis | 0.6% | 7.7% | 8.7% |
| Tx-related AE leading to D/C | 7.7% | 36.4% | 14.8% |

D/C = discontinuation; Inc. = including; Tx = treatment.

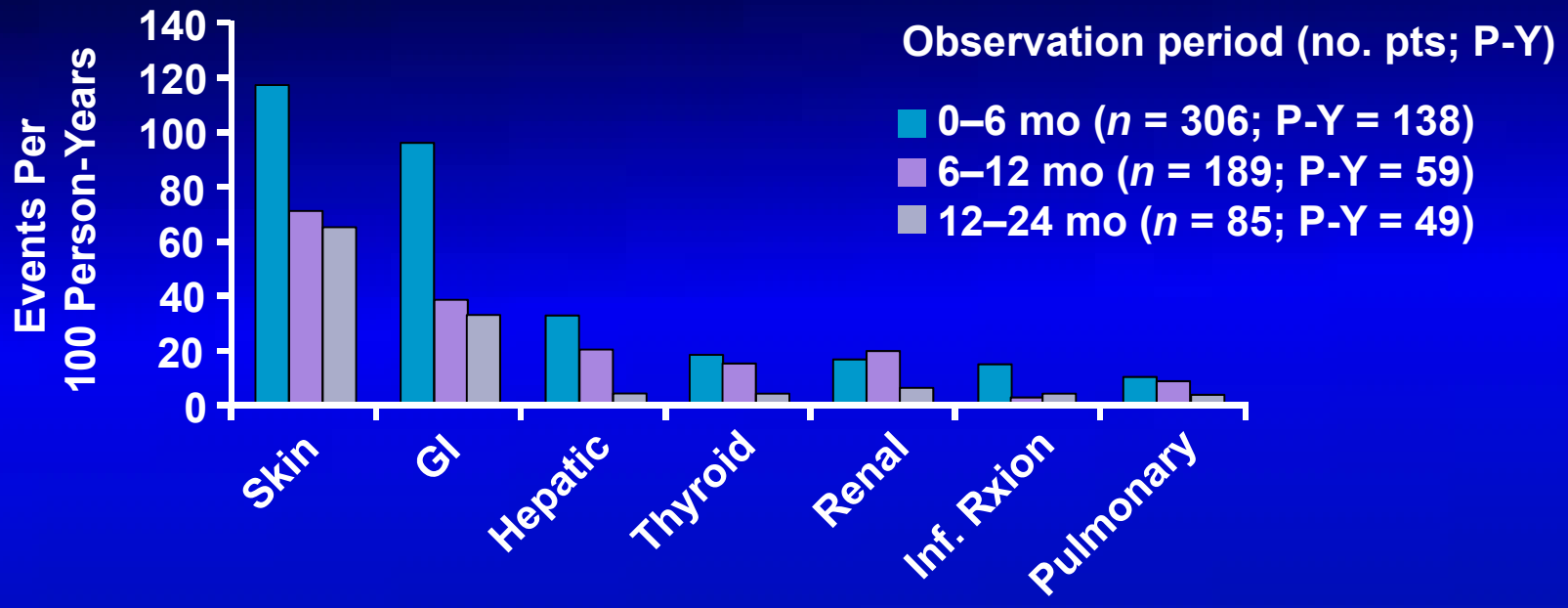
# Differences in Toxicity and Schedule




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pembrolizumab Q2W | 278 | 230 | 188 | 139 | 98 | 45 | 22 | 1 |
| Pembrolizumab Q3W | 277 | 233 | 179 | 140 | 97 | 47 | 17 | 0 |
| Ipilimumab | 256 | 182 | 6 | 1 | 1 | 1 | 1 | 0 |

Supplement to: Robert C, et al. *N Engl J Med.* 2015;372:2521-32. For educational purposes only.

# Nivolumab Toxicity Over Time




**Overall 17% had Grade 3 to 4 toxicities.**

GI = gastrointestinal; Inf. Rxion = infusion reaction; P-Y = person-year.

Topalian SL, et al. *J Clin Oncol.* 2014;32:1020-1030. For educational purposes only.

# Less Common Immune-Related Adverse Events

- Hematologic (hemolytic anemia, thrombocytopenia)
- Cardiovascular (myocarditis, pericarditis, vasculitis)
- Ocular (blepharitis, conjunctivitis, iritis, scleritis, uveitis)
- Renal (nephritis)
- Several case reports of rare autoimmune-based toxicities in patients treated with ipilimumab
  - Lupus nephritis
  - Inflammatory enteric neuropathy
  - Tolosa-Hunt syndrome
  - Myocardial fibrosis
  - Acquired hemophilia A
  - Autoimmune polymyositis

# Key Role for Pharmacists

- Discussion of “Med Rec” findings with physician (monitor for autoimmune disease and/or immunosuppression treatment)
- Monitoring/managing dermatologic and GI toxicity; early intervention with steroids
- Anticipate drug-drug interactions – how soon can checkpoint inhibitor be restarted following AE
- Costs/acquisition
- Know how to manage adverse events

# PD-1/PD-L1 Inhibition: Managing for Treatment-Related Adverse Events

**Any grade 1 AE or isolated hypothyroidism**

↓

**Symptom management or replacement therapy for hypothyroidism**

↓

**Continue PD-1 treatment and monitor**

- **Grade 2 pneumonitis, nephritis, colitis, hepatitis**
- **Symptomatic hypophysitis**
- **Any grade 3 AE**

↓

- **Hold PD-1 treatment and administer steroids**
- **After improvement to ≤grade 1, taper steroids over at least 1 month**

**Resume if:**
**AE remains at grade 0/1 after steroid taper**

**Permanently discontinue if:**

- **No improvement to ≤grade 1 within 12 weeks**
- **Cannot taper steroids to ≤10 mg/day of prednisone or equivalent within 12 weeks**

Nivolumab Immune-Mediated Adverse Reactions Management Guide. BMS.com Web site. Available at https://bmsdm.secure.force.com/opdivohcp/servlet/servlet.FileDownload?file=00Pi000000GL6RoEAL. Updated March 2015. Accessed November 2015. A Guide to Monitoring Patients During Treatment with Pembrolizumab: A resource for adverse reaction management adverse reaction management guide. Keytruda Web site. Available at: https://www.keytruda.com/static/pdf/adverse-reaction-management-tool.pdf. Updated 2015; Accessed November 2015.

# PD-1/PD-L1 Inhibition: Managing for Treatment-Related Adverse Events

- Grade 3/4 pneumonitis
- Grade 3/4 nephritis
- Grade 3/4 infusion-related reaction
- Any life-threatening or grade 4 AE
- Any severe or grade 3 recurrent AE

**Hepatitis associated with:**

- AST/ALT >5 x ULN
- AST/ALT ≥50% ↑ from baseline lasting ≥1 week*
- Total bilirubin >3 x ULN

→ **Initiate steroid therapy**

→ **Permanently discontinue PD-1 treatment**

*In patients with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

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# Summary

- Currently multiple drugs are available. Pembrolizumab and nivolumab, approved after ipilimumab, are both more effective than ipilimumab alone in first line.
- The combination of nivolumab and ipilimumab showed the best overall response, CR, and PFS.
- Response appears to be durable for ipilimumab, pembrolizumab, and nivolumab.
- The role of PD-L1 testing outside of a research protocol is limited to NSCLC patients where it is required for pembrolizumab therapy.
- If the projected data hold true for first-line treatment and durability, curing metastatic melanoma could become a possibility!

# Q&A

To submit a question, please use the "Ask a Question" tab located on the left side of your screen.

# Thank you!

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COMPLIMENTARY LIVE INTERACTIVE CPE WEBCASTS

# EXPANDING HORIZONS IN IMMUNO-ONCOLOGY:

## *Health System Pharmacists' Perspectives*

University of Tennessee College of Pharmacy

Advanced Studies *in* Pharmacy.

***Supported by an educational grant from Bristol-Myers Squibb Company.***