Evolving Therapies in the Clinical Management of Melanoma

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Learning Objectives

1. Interpret clinical data supporting emerging targeted therapies
2. Evaluate clinical data supporting immunotherapies used in the treatment of advanced/metastatic melanoma
3. Formulate strategies to manage and mitigate potential adverse events of targeted therapies and immunotherapies used in the treatment of advanced/metastatic melanoma

Financial Disclosure

- Ms. Kottschade has acted as a consultant for Bristol-Myers Squibb and Array BioPharma; she has received research funding from Bristol-Myers Squibb.
- Dr. Markovic has nothing to disclose.
- Off-label/investigational uses will not be discussed in this presentation.

Presentation Overview

- Changes in staging criteria with the release of AJCC v. 8.0
- Updates of the following in the management of stage III disease:
  - Surgery
  - Immunotherapy
  - Targeted therapy
- Advances in systemic therapy for metastatic disease
- Management of toxicity for patients undergoing immunotherapy or targeted therapy for melanoma

Updates in Staging

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Updated Staging Criteria for Cutaneous Melanoma, AJCC v. 8.0

- Became effective January 1, 2018
- Most significant changes were with T1 lesions and stage III disease
- New sub-stage categories added for stage III and IV disease

Changes in T1 Lesions

- Mitotic rate removed as staging criterion for T1 tumors
- T1a is defined as
  - non-ulcerated and <0.8 mm in thickness
- T1b is defined as:
  - any melanoma 0.8 mm to 1.0 mm in thickness regardless of ulceration status OR
  - any ulcerated melanoma <0.8 mm in thickness

Changes in Stage III

- Addition of “in-transit/satellite/microsatellite” to each of the “N” subcategories
- Addition of new stage IIID subcategory
- Narrowing of patients in stage IIIA with upstaging of most stage III patients

SLNB = sentinel lymph node biopsy

Changes in Nomenclature for Stage IV Disease

- Traditionally "M" stage in melanoma based on anatomic location
- Fourth "M" sub-stage added to staging
  - "M1d" added to account for the presence of any CNS disease
- Additionally serum lactate dehydrogenase (LDH) has been added to all anatomic site categories defined as:
  - (0) not elevated
  - (1) elevated

Impact on Practice

- May increase the number of patients undergoing SLNB?
- Will more patients be getting adjuvant therapy unnecessarily?
- What to do with the “new” IIIA patients?

Updates in Stage III Management: Surgery

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Sentinel Lymph Node Biopsy

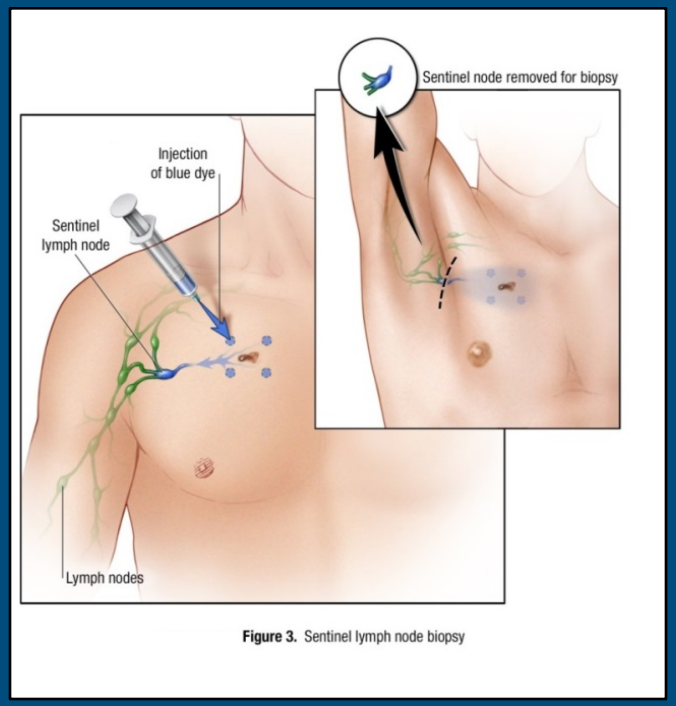


Figure 3. Sentinel lymph node biopsy

- MSLT-1: Is SLN biopsy necessary?
  - 2001 patients with melanoma (Breslow 1.2 to 3.5 mm)
  - Randomized to:
    - (1) WLE + OBS (delay CLND at relapse), vs
    - (2) WLE + SLN Bx + CLND
  - Result: SLN biopsy arm results in improved 10-year disease-free survival

CLND = complete lymph node dissection; OBS = observation; WLE = wide local excision.

Morton DL et al, *NEJM* 2014;370:599-609

Updates in Management of Stage III Disease: Surgery

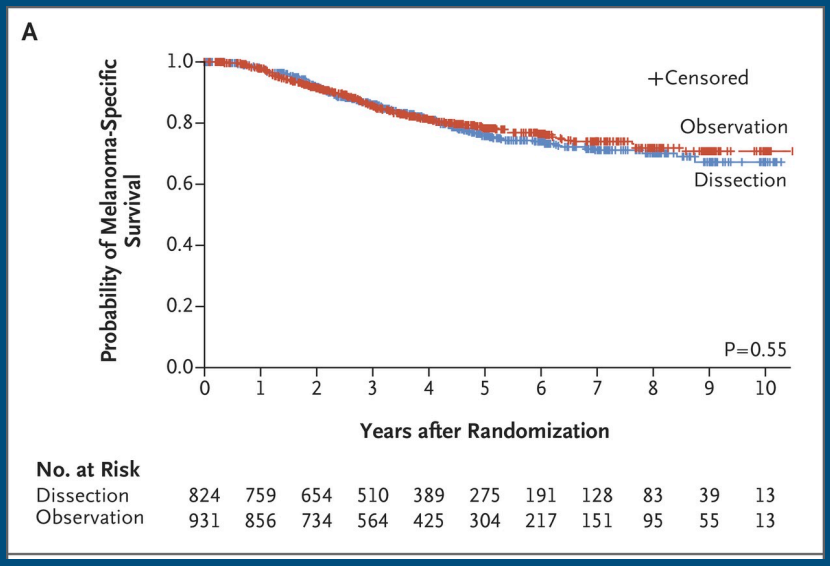
- MSLT-2: in SLN+ melanoma is CLND necessary?
  - 1934 patients with melanoma (1.2–3.5 mm) with SLN+ randomized to:
    (1) Observation
    (2) Completion lymph node dissection (CLND)
- Results
  - 3-year DFS: 63% vs 68% (p=0.05 in favor of CLND, primarily local Dz)
  - 3-year OS rate: 86% vs 86% (no difference)
  - Lymphedema: 6.3% vs 24.1% (worse with CLND)
  - Non SLN mets: powerful predictor of local recurrence (residual cancer)

DFS = disease-free survival; OS = overall survival.

Faries et al. *N Engl J Med* 2017;376:2211-2222

Updates in Management of Stage III Disease: Surgery

- MSLT-2, of note:
  - Size of SLN mets in >90% of cases is ≤ 1 mm
  - Breslow thickness in almost 80% of cases < 3.5 mm
  - Unknown: *OS outcomes in patients with delayed CLND vs upfront CLND*



Faries et al. *N Engl J Med* 2017; 376:2211-2222

Updates in Management of Stage III Disease: Impact on Practice

- Based on 3-year OS, immediate CLND is not superior to observation in SLN+ patients
- Based on 3-year RFS, immediate CLND primarily reduces risk of local (not systemic) relapse
- CLND → additional staging info in 6% patients[1]
- CLND not routinely recommended to patients with SLN micro-metastases (<1.0 mm)
- Close monitoring, sequential ultrasound follow-up
- Multidisciplinary evaluation and discussion with patients are needed

RFS = relapse-free survival

[1]Madu et al. *Eur J Cancer* 2017;87:212-215

Updates in Stage III Management: Adjuvant Therapy

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Updates in Management of Stage III Disease: Adjuvant Therapy

Approved drugs for the adjuvant therapy of stage III melanoma

Old Era (1996–2009)

- High-Dose Interferon (IFN)-α2b (US, EU), Low-Dose IFN-α2a (EU), pegylated IFN-α2b (US)[1]

New Era (2015–2018)

• ***Ipilimumab (US)**[2]	HR_{RFS}(Ipilimumab vs. Placebo)=0.75	(2015)
• **Nivolumab**[3]	HR_{RFS}(Nivolumab vs. Ipilimumab)=0.65	(2017)
• ***Dabrafenib plus Trametinib**[4]	HR_{RFS}(Dab+Tra vs. Placebo)=0.47	(2018)
• ***Pembrolizumab**[5]	HR_{RFS}(**Pembrolizumab** vs. **Placebo**)=0.57	(EXP/2018)

* Trials performed in identical patient populations at high risk of relapse: IIIA >1mm; IIIB/C

5-year relapse rates: stage IIIA, 37%; stage IIIB, 68%; stage IIIC, 89%[6]

[1]Eggermont AM, et al. *Lancet* 2014;383:816-27; [2]Eggermont AM, et al. *Lancet Oncology* 2015;16:522-30; [3]Weber J, et al. *N Engl J Med* 2017;377:1824-35; [4]Long GV, et al. *N Engl J Med* 2017;377:1813-23; [5]Eggermont AM, et al. *N Engl J Med* 2018;375:1845-55: 15 March; [6]Romano E, et al. *J Clin Oncol* 2010;28:3042-7.

Updates in Management of Stage III Disease: Adjuvant Therapy—Nivolumab

Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: Updated Results from a Phase 3 Trial (CheckMate 238)

Jeffrey Weber,[1] Mario Mandala,[2] Michele Del Vecchio,[3] Helen Gogas,[4] Ana M. Arance,[5] C. Lance Cowey,[6] Stéphane Dalle,[7] Michael Schenker,[8] Vanna Chiarion-Sileni,[9] Ivan Marquez-Rodas,[10] Jean-Jacques Grob,[11] Marcus Butler,[12] Mark R. Middleton,[13] Michele Maio,[14] Victoria Atkinson,[15] Reinhard Dummer,[16] Veerle de Pril,[17] Anila Qureshi,[17] Abdel Saci,[17] James Larkin,[18]* Paolo A. Ascierto[19]*

[1]NYU Perlmutter Cancer Center, New York, New York, USA; [2]Papa Giovanni XIII Hospital, Bergamo, Italy; [3]Medical Oncology, National Cancer Institute, Milan, Italy; [4]University of Athens, Athens, Greece; [5]Hospital Clinic de Barcelona, Barcelona, Spain; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, Texas, USA; [7]Hospices Civils de Lyon, Pierre Bénite, France; [8]Oncology Center Sf Nectarie Ltd., Craiova, Romania; [9]Oncology Institute of Veneto IRCCS, Padua, Italy; [10]General University Hospital Gregorio Marañón, Madrid, Spain; [11]Hôpital de la Timone, Marseille, France; [12]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [13]Churchill Hospital, Oxford, United Kingdom; [14]Center for Immuno-Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [15]Gallipoli Medical Research Foundation and University of Queensland, Brisbane, Australia; [16]University Hospital Zurich, Switzerland; [17]Bristol-Myers Squibb, Princeton, New Jersey, USA; [18]Royal Marsden NHS Foundation Trust, London, UK; [19]Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; *Contributed equally to this study.

Updates in Management of Stage III Disease: Adjuvant Therapy—Nivolumab

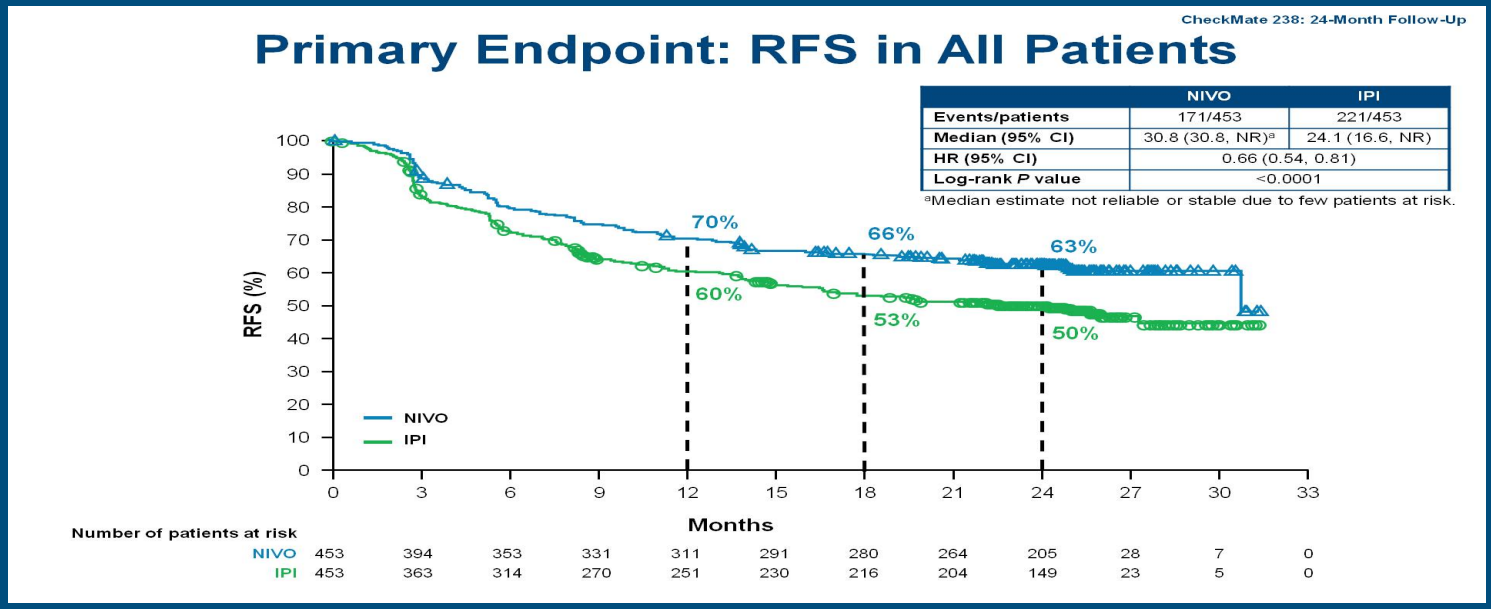
CheckMate 238: 24-Month Follow-Up

Key Eligibility Criteria

- At least 15 years of age
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Histologically confirmed melanoma metastatic to regional lymph nodes or with distant metastases surgically rendered free of disease
  - Stage IIIB, IIIC, or stage IV melanoma by the American Joint Committee on Cancer 2009 classification, 7th edition
  - Complete regional lymphadenectomy or resection was required within 12 weeks of randomization
- Patients with ocular/uveal melanoma, systemic corticosteroid use >10 mg/day of prednisone or equivalent, or previous systemic therapy for melanoma were excluded
  - Acral and mucosal melanoma were allowed

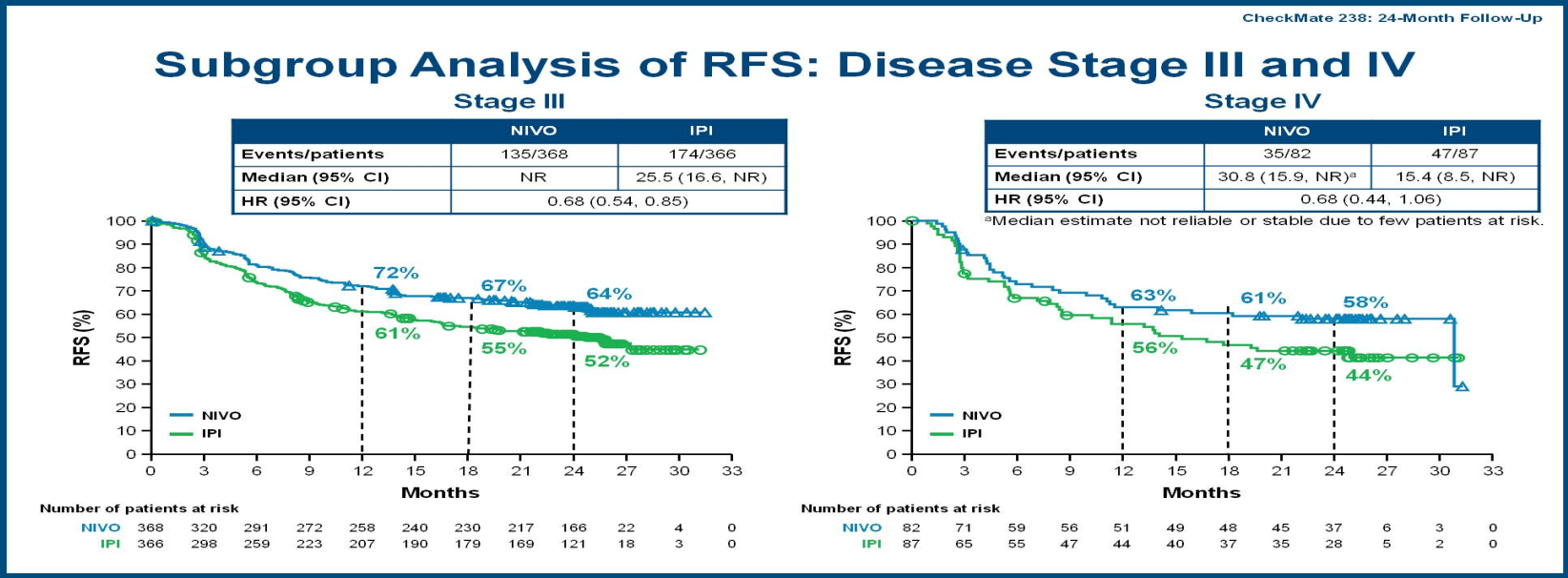
Weber et al. ASCO 2018

Updates in Management of Stage III Disease: Adjuvant Therapy—Nivolumab



Weber et al. ASCO 2018

Changes in Management of Stage III Disease: Adjuvant Therapy—Nivolumab



Weber et al. ASCO 2018

Updates in Management of Stage III Disease: Adjuvant Therapy—Nivolumab

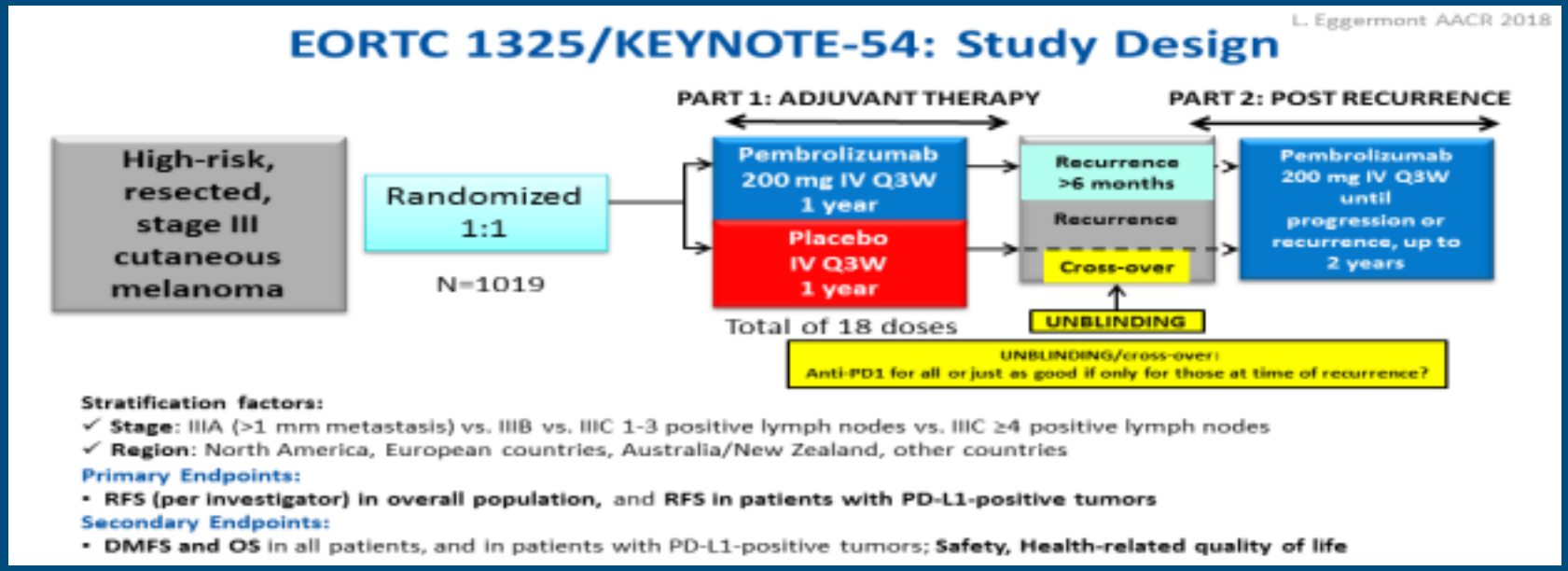
CheckMate 238: 24-Month Follow-Up

Summary

- With extended follow-up, NIVO demonstrated a sustained efficacy benefit vs the active comparator of IPI at 10 mg/kg in patients with resected stage IIIB/C or stage IV melanoma at high risk for recurrence
  - HR = 0.66 (95% CI 0.54, 0.81; *P* <0.0001) with estimated 24-month RFS rates of 63% for NIVO and 50% for IPI
  - Benefit for NIVO was observed across the majority of prespecified subgroups tested, including PD-L1 and *BRAF* mutation status
- NIVO showed a clinically and statistically significant improvement in DMFS vs IPI
- These more mature data continue to demonstrate durable clinical benefit with NIVO and further support its use for resected stage III or IV melanoma

Weber et al. ASCO 2018

Updates in Management of Stage III Disease: Adjuvant Therapy—Pembrolizumab



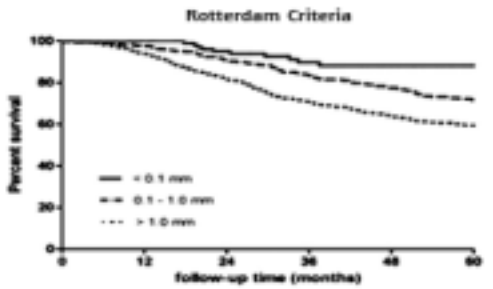
AAM Eggermont et al. AACR 2018

Updates in Management of Stage III Disease: Adjuvant Therapy—Pembrolizumab

L. Eggermont AACR 2018

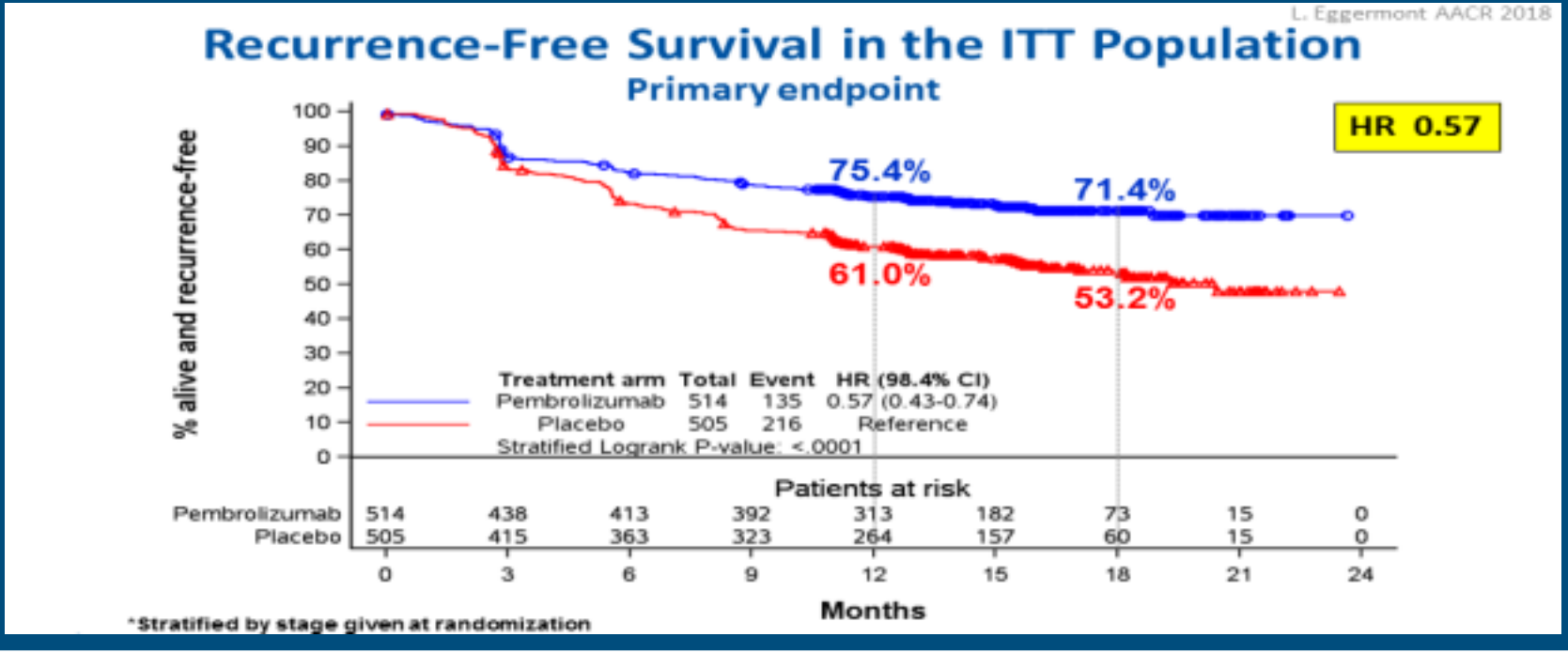
Key Eligibility Criteria

- At least 18 years of age
- Complete and adequate resection of stage III melanoma
- Histologically confirmed melanoma metastatic to lymph node
- **Stage IIIA (if N1a, at least 1 metastasis >1 mm);** stage **IIIB** or **IIIC** (no in transit meta)
- No prior systemic therapy for melanoma
- No autoimmune disease
- Documented NED following surgery
- Randomization within 13 weeks of surgery



Van der Ploeg, et al. *Eur J Cancer* 2014;50:111-20.

Updates in Management of Stage III Disease: Adjuvant Therapy—Pembrolizumab



AAM Eggermont et al. AACR 2018

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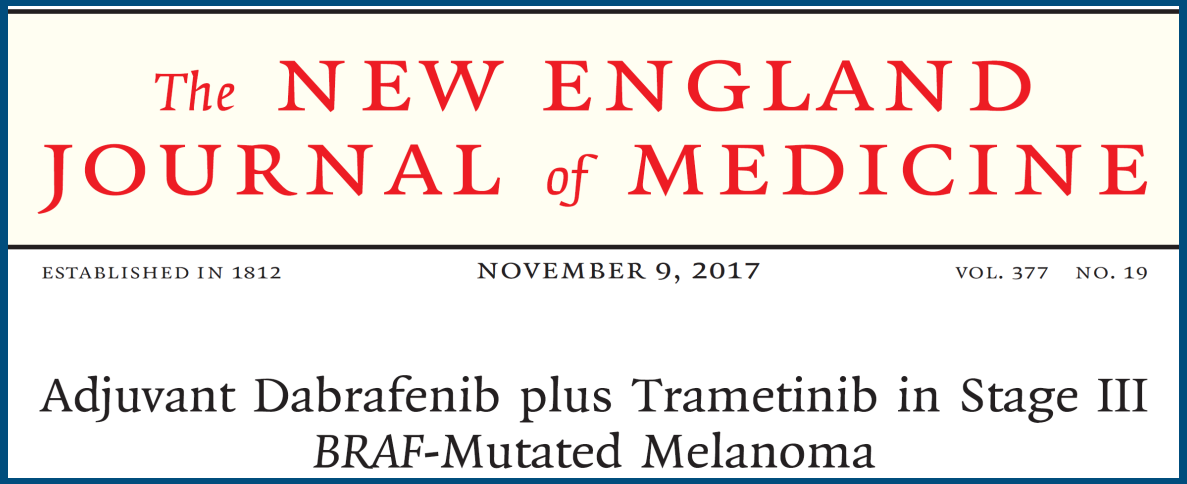
Updates in Management of Stage III Disease: Adjuvant Therapy—Pembrolizumab

Summary/Conclusions

- Study EORTC 1325/KEYNOTE-054 met its primary endpoint of a significant improvement in RFS with 200 mg I.V. Q3W **pembrolizumab** vs. **placebo**
  - **ITT overall population: HR = 0.57**, *P*<0.0001, **18 mos RFS difference: 18.2%**
  - **PD-L1+ population: HR = 0.54**, *P*<0.0001, **18 mos RFS difference: 19.7%**
- **Consistent results** across prespecified subgroups with HRs favoring **pembrolizumab** relative to **placebo**
- **Favorable safety profile**, where severe irAEs are rare, is generally consistent with that observed in advanced melanoma. There were many grade 1-2 thyroid events in about 1/5 pts, but severe endocrine events only in 9 pts (hypophysitis, diabetes, adrenal)
  - Most irAEs were managed and resolved with established treatment algorithms
- Data remain blinded for DMFS and OS (will be reported at future meetings)

Updates in Management of Stage III Disease: Adjuvant Dabrafenib/Trametinib

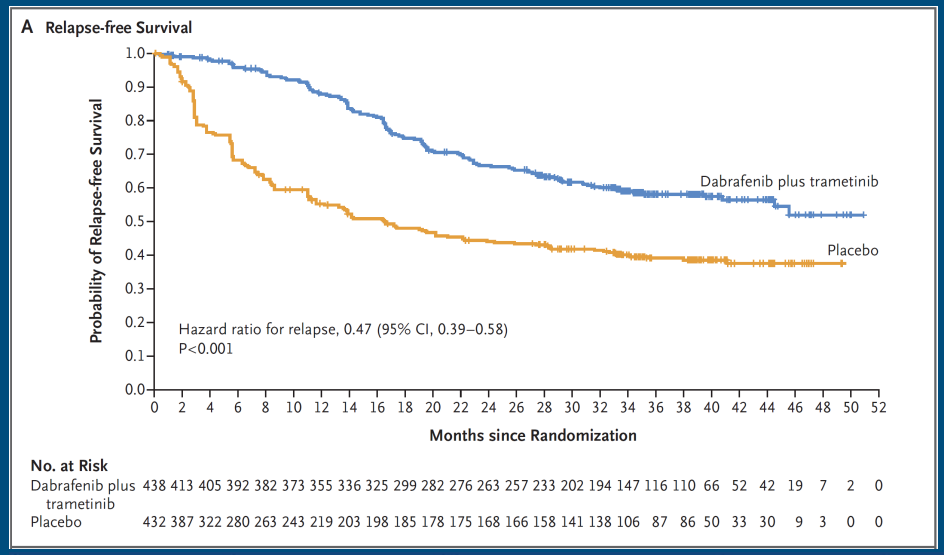
COMBI-AD

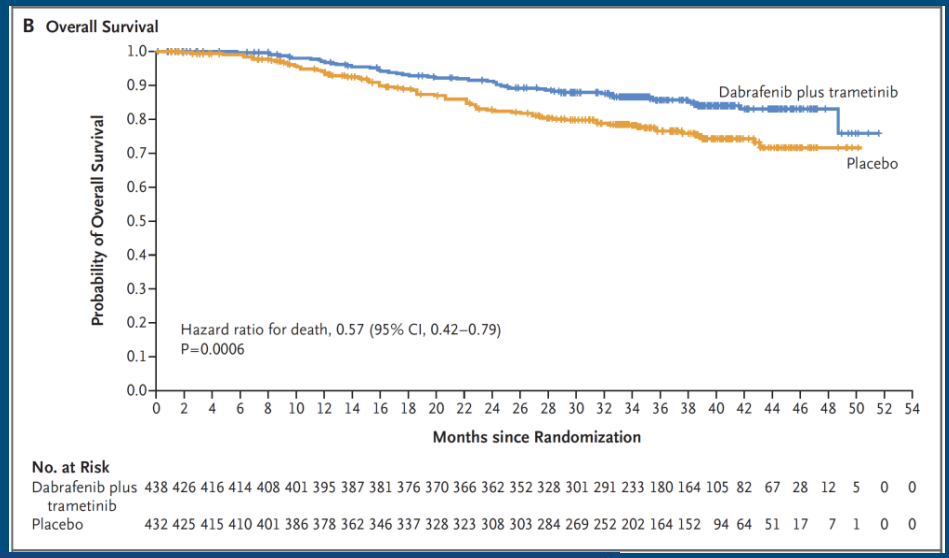


Phase 3: Dabrafenib 150 mg bid/trametinib 2 mg vs. placebo x 12 months
Primary end point: RFS
Secondary end point: OS, DMFS, freedom from relapse, safety

Long et al. *N Engl J Med* 2017;377:1813-1823

Updates in Management of Stage III Disease: Adjuvant Dabrafenib/Trametinib





	DT	Observation	HR	*P*-Value
3-year RFS	58%	39%	0.47	0.0000000000000153
3-year OS	86%	77%	0.57	0.0006

Long et al. *N Engl J Med* 2017;377:1813-1823

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Impact on Practice

- Translating results to “new” patients that are IIIA?
- Lack of tissue available for BRAF testing?
- No direct head-to-head comparison in BRAFm population of targeted vs. immunotherapy in the adjuvant setting
- What to do with patients that relapse on adjuvant therapy?
- Risk for lifelong toxicity for patients on adjuvant immunotherapy

Updates in Systemic Therapy in Metastatic Disease

Svetomir N. Markovic, MD, PhD

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Systemic Rx for Metastatic Melanoma

- Massive progress since 2011
- BRAF mutation guided therapy with BRAFi/MEKi:
  - vemurafenib + cobimetinib
  - dabrafenib + trametinib
  - encorafenib + binimetinib
- Immunotherapy
  - Anti-CTLA4: ipilimumab
  - Anti-PD1: nivolumab, pembrolizumab

Systemic Therapy for Metastatic Disease

Overall Survival in COLUMBUS: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) vs Vemurafenib (VEM) or ENCO in *BRAF*-Mutant Melanoma

Reinhard Dummer, Paolo A. Ascierto, Helen J. Gogas, Ana Arance, Mario Mandala, Gabriella Liszkay, Claus Garbe, Dirk Schadendorf, Ivana Krajsova, Ralf Gutzmer, Vanna Chiarion-Sileni, Caroline Dutriaux, Jan Willem B. de Groot, Naoya Yamazaki, Carmen Loquai, Laure A. Moutouh-de Parseval, Michael D. Pickard, Victor Sandor, Caroline Robert, Keith T. Flaherty

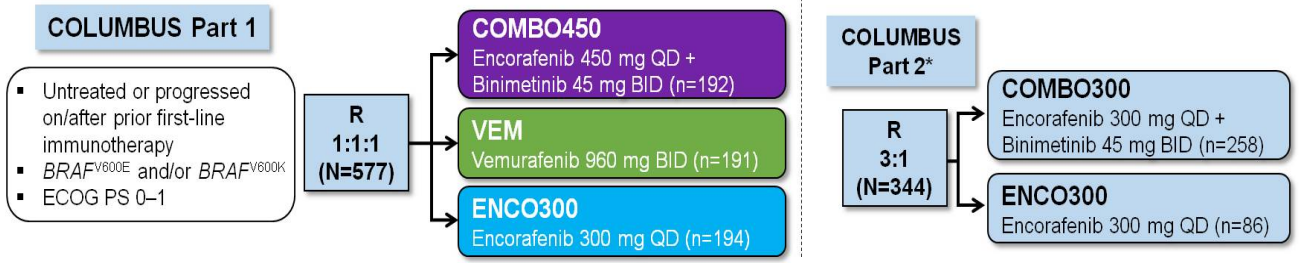
Updates in Systemic Therapy: COLUMBUS

- BRAFi/MEKi combinations are established as a standard of care for the treatment of advanced *BRAF*^{V600}-mutant melanoma with median PFS (≈12 months) and OS (≈24 months)[1-3]
- Approved combinations have unique toxicities that may impact the ability to deliver optimal treatment
  - Dabrafenib/trametinib is associated with pyrexia[2,3]
  - Vemurafenib/cobimetinib is associated with photosensitivity[4]
- **ENCO** has a unique pharmacologic profile with an on-target dissociation half-life of >30 hours, leading to sustained target inhibition[5]
- **BINI** has a shorter half-life than other MEKi; dose modification may be easier[6]
- Promising clinical activity and tolerability were demonstrated with ENCO + BINI in a phase 1b/II study[5,7]

BINI=binimetinib; BRAFi=BRAF inhibitor; ENCO=encorafenib; MEKi=MEK inhibitor; OS=overall survival; PFS=progression-free survival

1. Chapman PB, et al. *N Engl J Med*. 2011;364(26):2507-2516.
2. Robert C, et al. *N Engl J Med*. 2015;372(1):30-39.
3. Long GV, et al. *Lancet*. 2015;386(9992):444-451.
4. Ascierto PA, et al. *Lancet Oncol*. 2016;17:1248-1260.
5. Delord JP, et al. *Clin Cancer Res*. 2017;23:5339-5548.
6. Data on File. Array BioPharma Inc.
7. Sullivan RJ, et al. *J Clin Oncol*. 2015;33:9007.

Updates in Systemic Therapy: COLUMBUS



Efficacy update with additional follow-up of 18 months:

OS:

- Secondary endpoint†
- Planned after 232 events in the COMBO450 and VEM groups combined
- Median duration of follow-up‡: 36.8 months

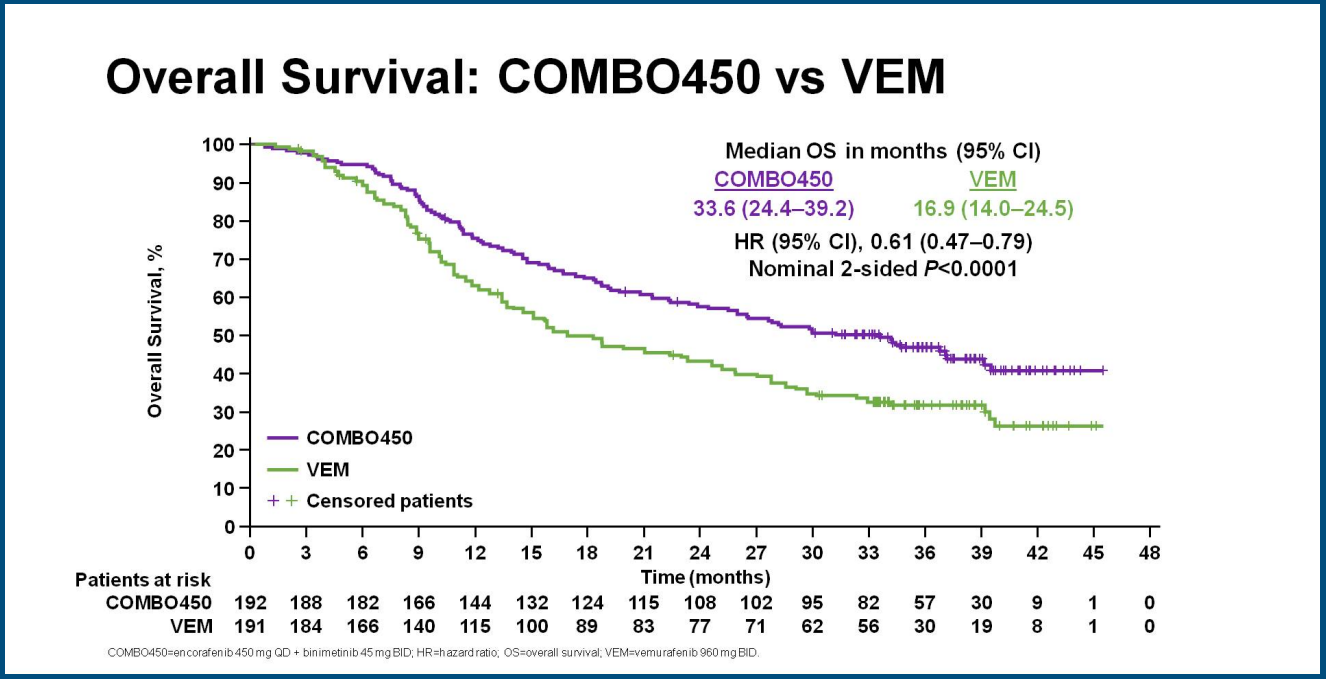
PFS:

- Primary endpoint
- Median duration of follow-up‡: 32.1 months

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PFS=progression-free survival; R=randomization; VEM=vemurafenib 960 mg BID.
*Amendment requested by FDA.
†Included in hierarchical testing approach.
‡Median follow-up of patients assessed using reverse Kaplan-Meier approach (i.e. median potential follow-up).

Dummer et al. ASCO 2018

Updates in Systemic Therapy: COLUMBUS



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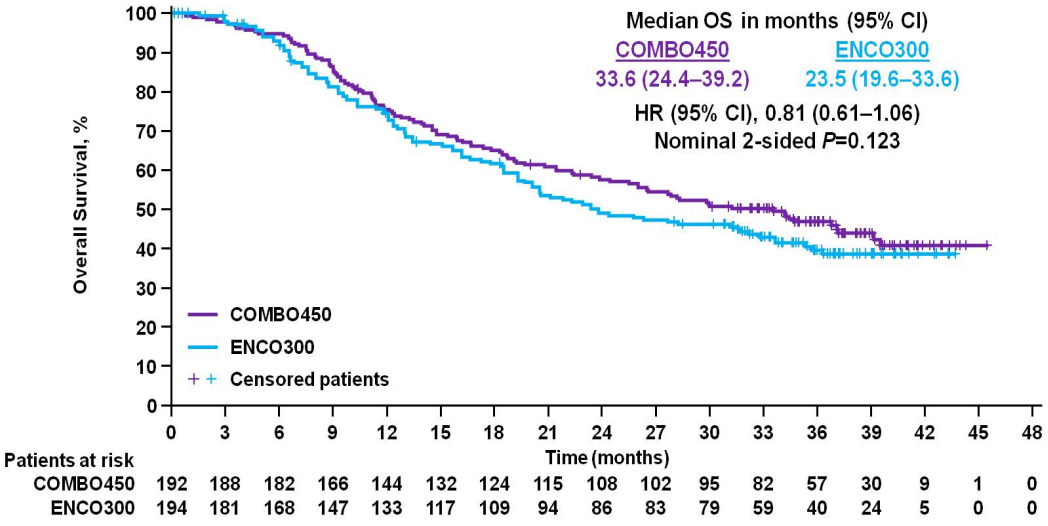
Updates in Systemic Therapy: COLUMBUS

Overall Survival: COMBO450 vs ENCO300

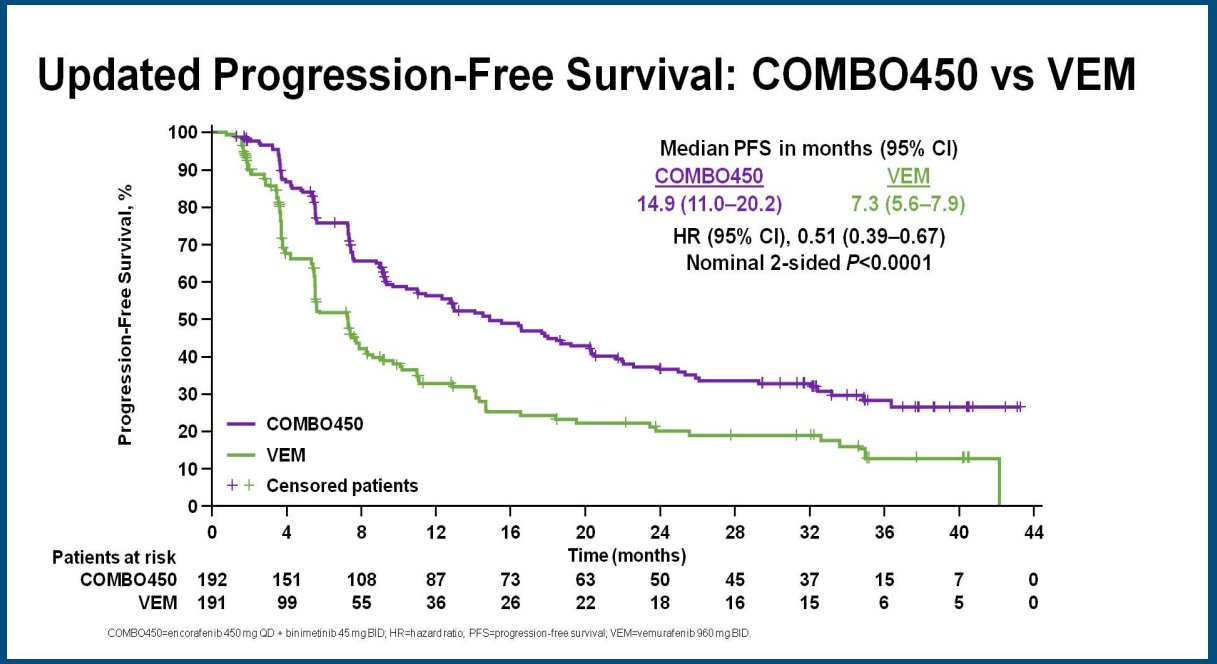


Patients at risk																
COMBO450	192	188	182	166	144	132	124	115	108	102	95	82	57	30	9	1	0
ENCO300	194	181	168	147	133	117	109	94	86	83	79	59	40	24	5	0	0

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300=encorafenib 300 mg QD; HR=hazard ratio; OS=overall survival.

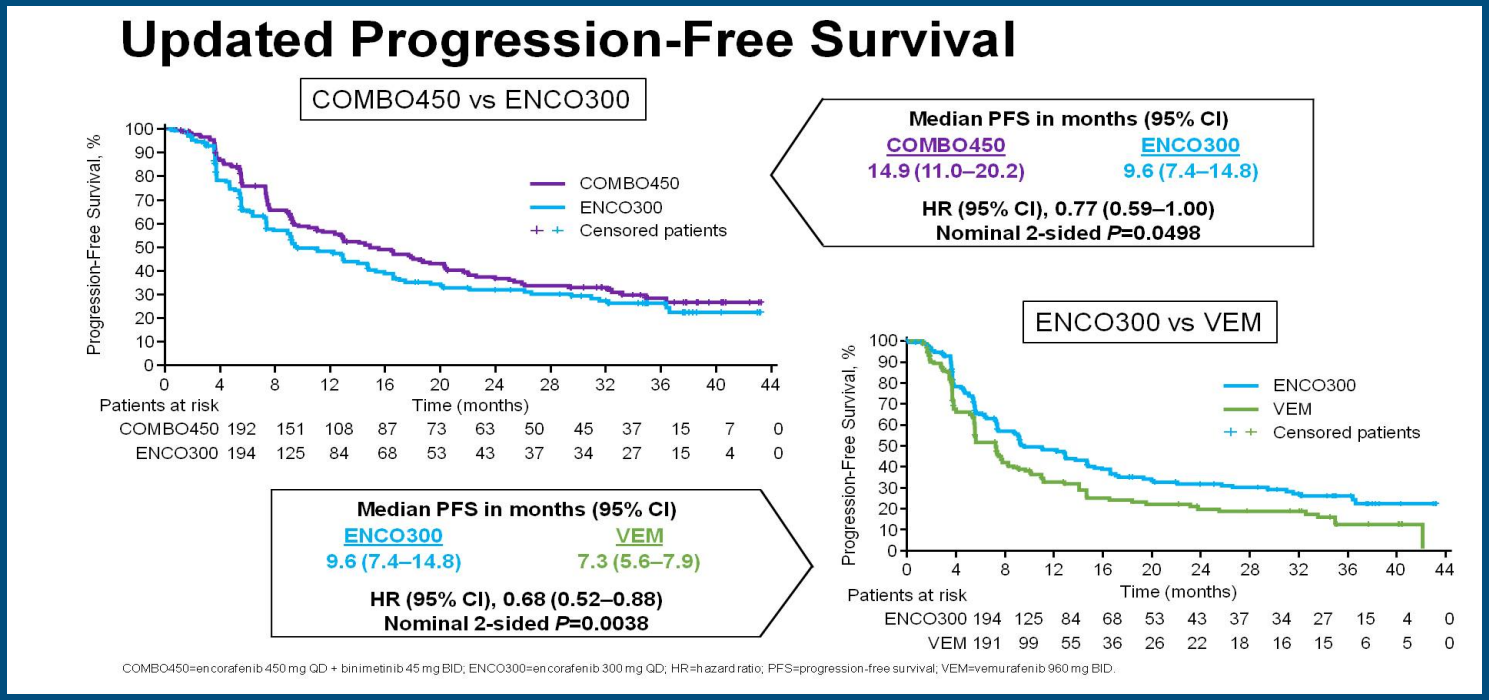
Dummer et al. ASCO 2018

Updates in Systemic Therapy: COLUMBUS



Dummer et al. ASCO 2018

Updates in Systemic Therapy: COLUMBUS



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Updates in Systemic Therapy: COLUMBUS

- COMBO450 showed improved OS vs VEM: 33.6 mo vs 16.9 mo (HR 0.61; nominal 2-sided *P*<0.0001)
- Updated PFS results remained the same as previously reported: median PFS 14.9 mo[1]
- Performance of VEM in COLUMBUS was consistent with historical data for ORR, PFS, and OS[2,3]
- Use of subsequent systemic therapies in COLUMBUS was similar to phase 3 studies of established BRAFi/MEKi therapies[2,4]
- COMBO450 showed a favorable tolerability profile and no new safety concerns

Encorafenib plus binimetinib combination therapy provides a new efficacy benchmark for targeted therapy and it is a promising treatment option for patients with *BRAF*^{V600}-mutant melanoma

BRAFi=BRAF inhibitor; COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; HR=hazard ratio; MEKi=MEK inhibitor; OS=overall survival; PFS=progression-free survival; VEM=vemurafenib 960 mg BID.

1. Dummer R, et al. *Lancet Oncol.* 2018;19:603-615.
2. Ascierto PA, et al. *Lancet Oncol.* 2016;17:1248-1260.
3. Robert C, et al. *Eur J Cancer.* 2015;51:S663-S664.
4. Long GV, et al. *Ann Oncol.* 2017;28:1631-1639.

Updates Systemic Therapy: Immunotherapy

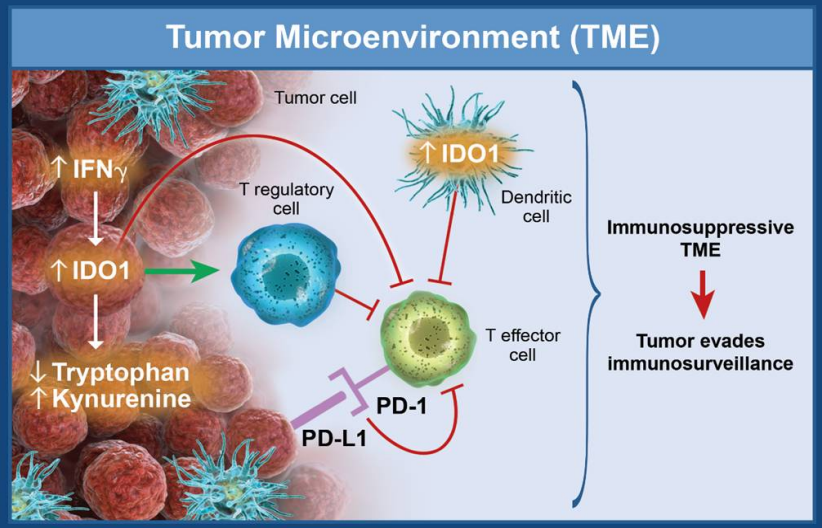
Epacadostat Plus Pembrolizumab Versus Pembrolizumab Alone in Patients With Unresectable or Metastatic Melanoma: Results of the Phase 3 ECHO-301/KEYNOTE-252 Study

Georgina V. Long,[1] Reinhard Dummer,[2] Omid Hamid,[3] Thomas Gajewski,[4] Christian Caglevic,[5] Stephane Dalle,[6] Ana Arance,[7] Matteo S. Carlino,[8] Jean-Jacques Grob,[9] Tae Min Kim,[10] Lev Demidov,[11] Caroline Robert,[12] James Larkin,[13] James R. Anderson,[14] Janet Maleski,[15] Mark Jones,[15] Scott J. Diede,[14] Tara C. Mitchell[16]

[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; [2]University Hospital Zürich, Zurich, Switzerland; [3]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [4]University of Chicago Medical Center, Chicago, IL, USA; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Hospices Civils De Lyon, Cancer Research Center of Lyon, Claude Bernard University Lyon, Pierre Benite, France; [7]Hospital Clinic de Barcelona, Barcelona, Spain; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [9]Aix-Marseille University, Marseille, France; [10]Seoul National University Hospital, Seoul, South Korea; [11]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [12]Gustave Roussy Comprehensive Cancer Center, Villejuif, France; [13]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Incyte Corporation, Wilmington, DE, USA; [16]Abramson Cancer Center of the University of Philadelphia, Philadelphia, PA, USA.

Updates in Systemic Therapy: ECHO-301/KEYNOTE-252

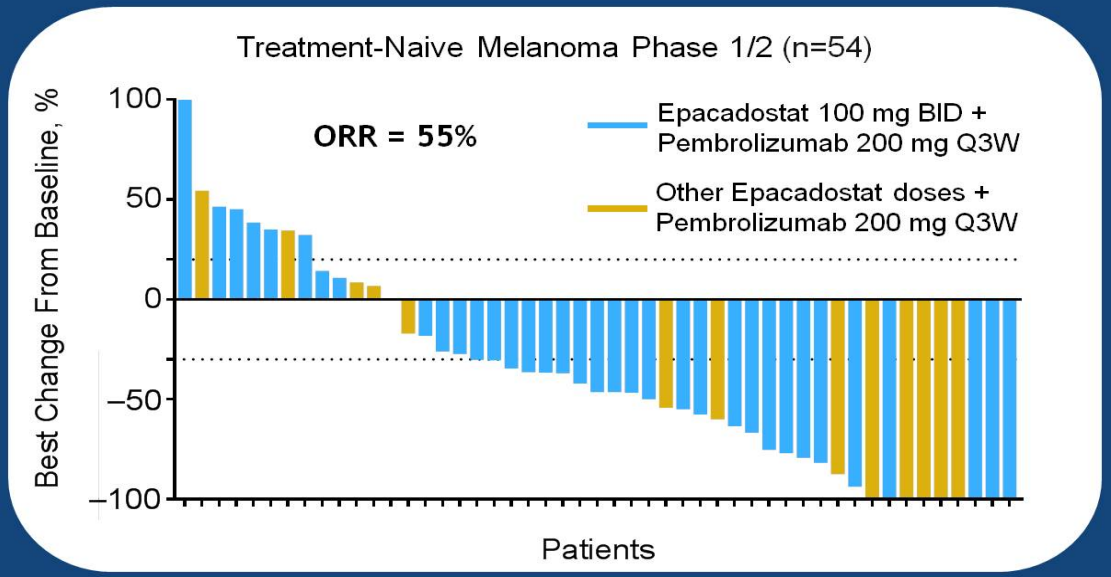
- Upregulation of IDO1 is a potential mechanism to evade immunosurveillance
  - ↓ Tryptophan ↑ Kynurenine
  - ↓ T_{eff} and NK cells
  - ↑ T_{reg} cells, MDSCs, TAMs
- Epacadostat: IDO1 enzyme inhibitor
- Pembrolizumab: anti-PD-1 humanized antibody



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; T_{eff}, effector T cell; T_{reg}, regulatory T cell.

Long et al. ASCO 2018

Updates in Systemic Therapy: ECHO-301/KEYNOTE-252



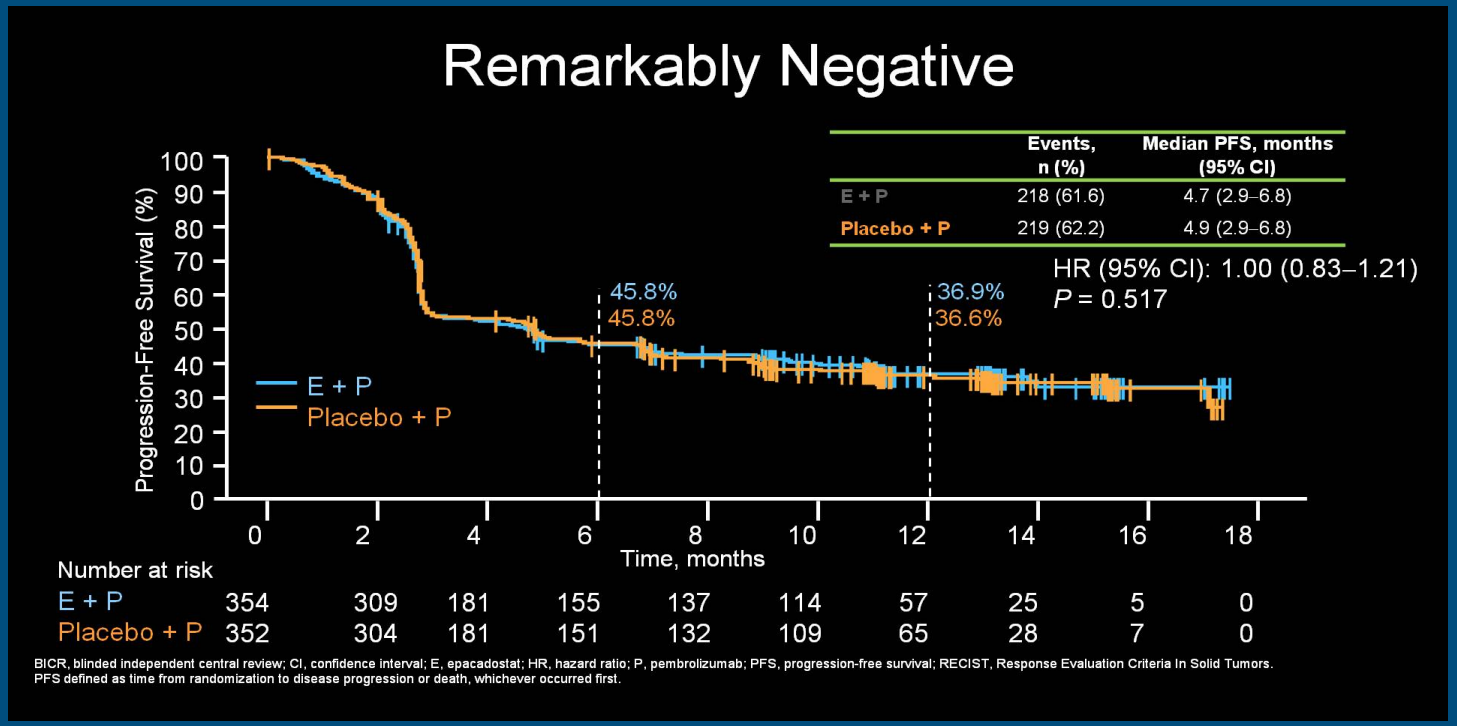
BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Hamid O, et al. *Ann Oncol.* 2017;28(suppl 5):1214O.

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

Long et al. ASCO 2018

Updates in Systemic Therapy: ECHO-301/KEYNOTE-252



Long et al. ASCO 2018

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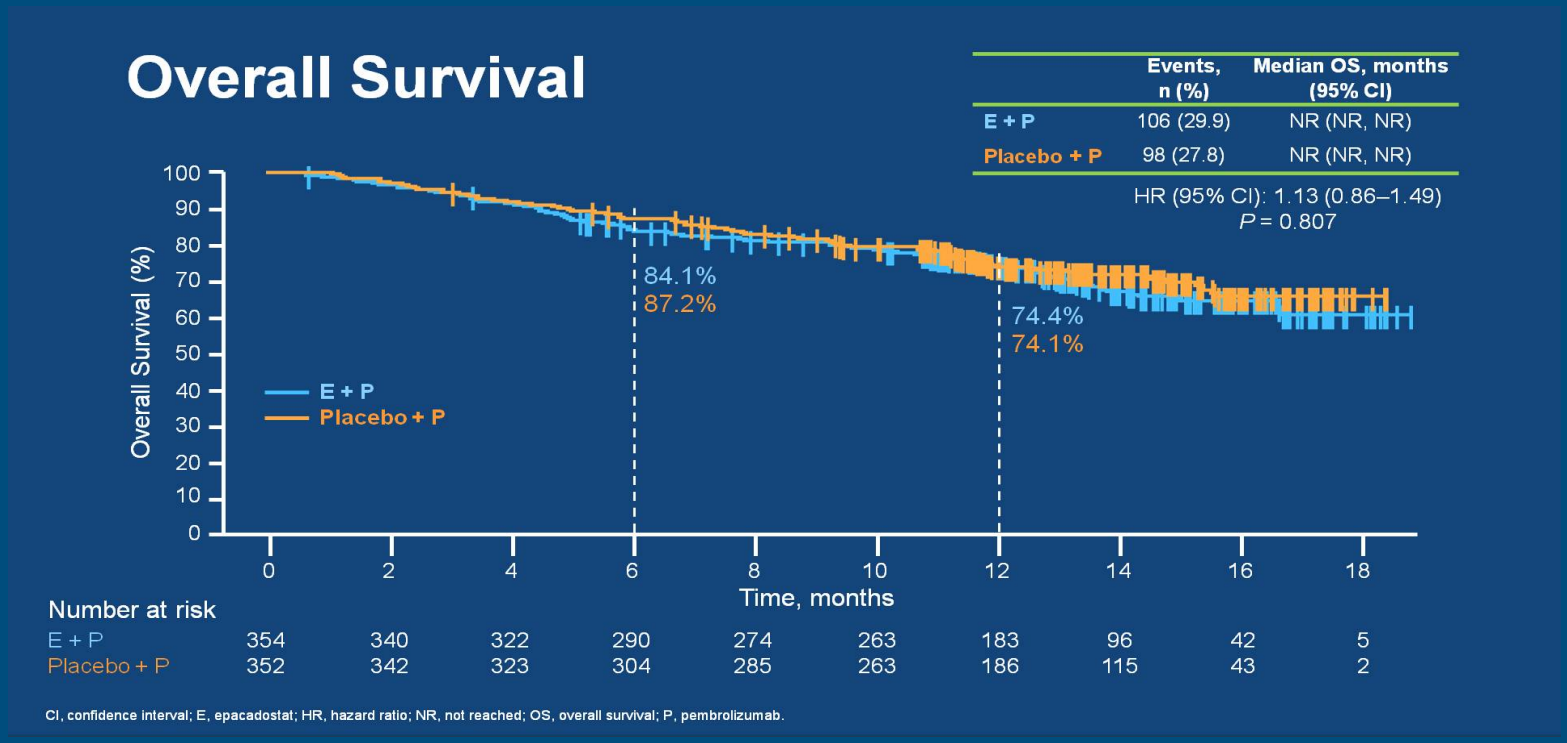
Updates in Systemic Therapy: ECHO-301/KEYNOTE-252



Long et al. ASCO 2018

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Updates in Systemic Therapy: ECHO-301/KEYNOTE-252

- The addition of epacadostat to pembrolizumab did not result in greater clinical benefit than pembrolizumab alone
- Trial was recommended to be stopped since it did not meet primary endpoint of PFS, and OS was not expected to reach statistical significance
- Additional analyses
  - IDO1 expression; tumor mutational burden; RNAseq
  - Do we need randomized phase II trial prior to phase III trial?

Management of Toxicity

Lisa A. Kottschade, APRN, MSN, CNP

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Immunotherapy

Can “cure” cancer, but…

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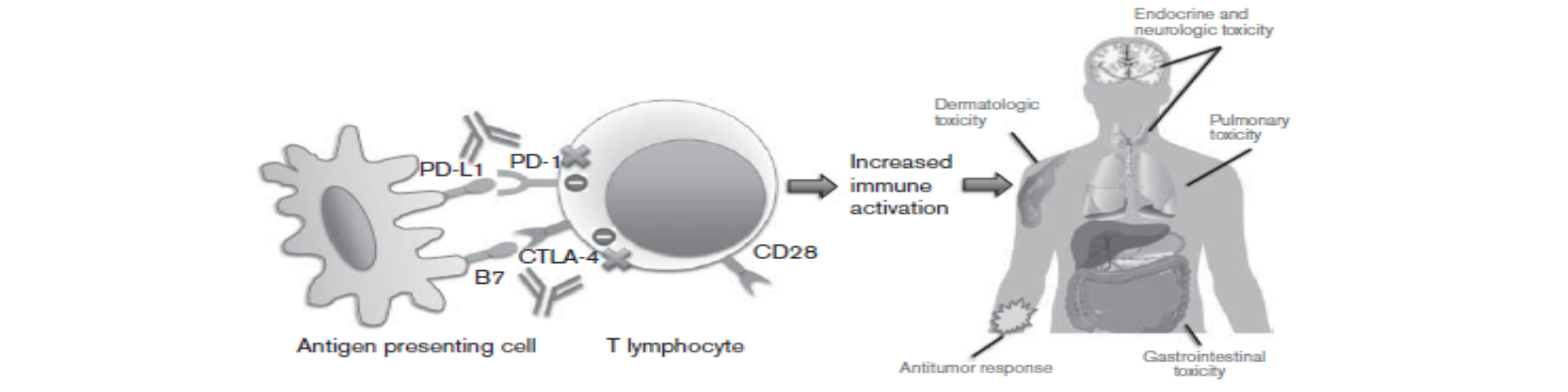
Immune-related Adverse Events (irAE)

- Definition: Adverse events that occur via the activation of a patient's immune system that can occur in any tissue, organ, or system
  - Can be SEVERE and sometimes FATAL

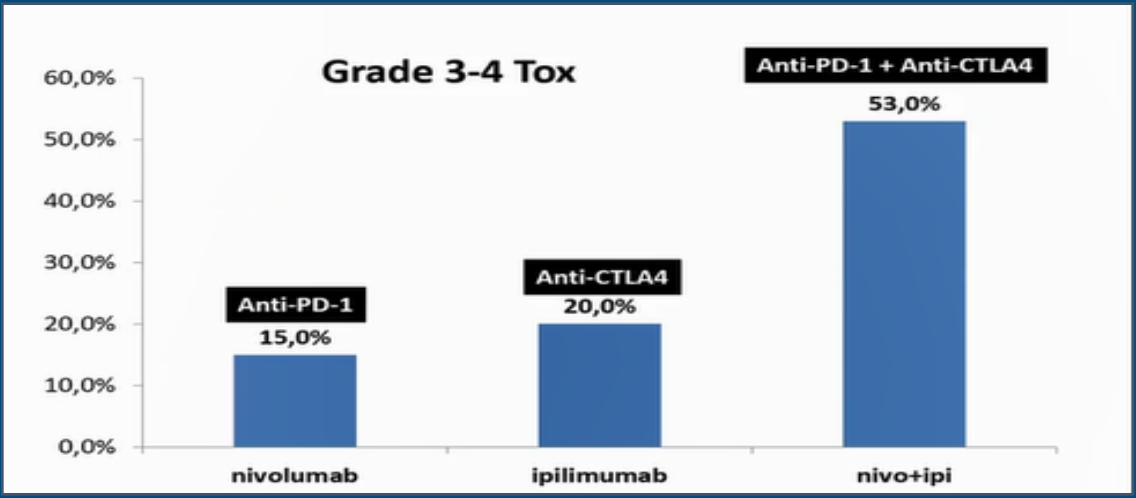


Kottschade, L, et al. *Melanoma Res*. 2016;26(5):469-480.

Frequency of irAEs

Table 1 Frequency of common immune-related adverse events of select pivotal clinical trials in melanoma

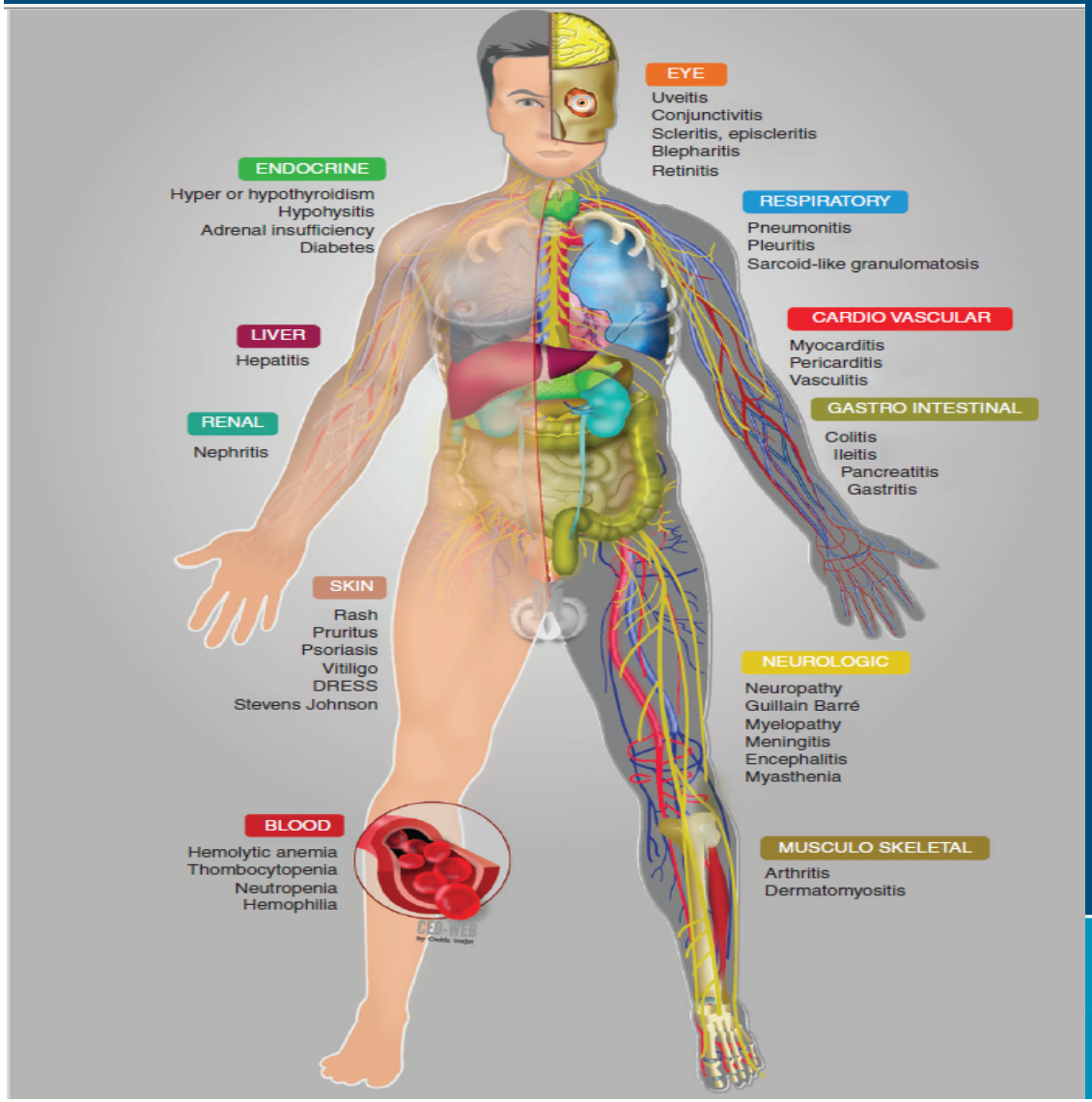
	Anti-PD1		Anti-CTLA-4	Combination
Toxicity	Pembroliziumab	Nivolumab	Ipilimumab	Ipilimumab/nivolumab
Any irAE	72.9 (10.1) 79.5 (13.3)	82.1 (16.3)	73.0 (19.9) 37.0 (10.9) 80.2 (22.9)	95.5 (55)



Larkin, J, et al. *N Engl J Med*. 2015;373(1):23-34; Kottschade, L, et al. *Melanoma Res*. 2016;26(5):469-480.

Clinical Spectrum of irAEs

Dermatologic, gastrointestinal, hepatic, endocrine, pulmonary



Michot, JM, et al. *Eur J Cancer*. 2016;54:139-148.

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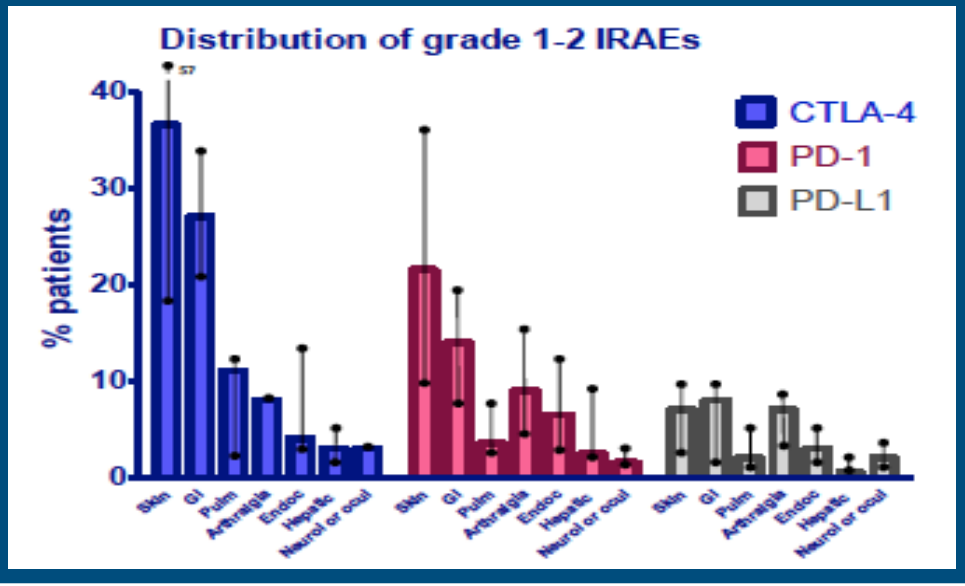
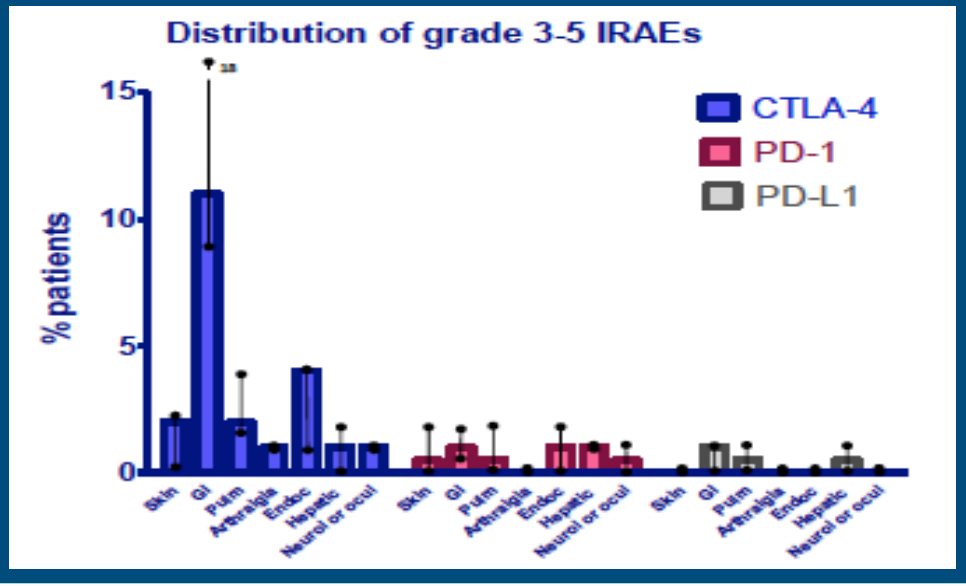
A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors†

T. W. Chen[1,2], A. R. Razak[1,2], P. L. Bedard[1,2], L. L. Siu[1,2] & A. R. Hansen[1,2*]

[1]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre–University Health Network, Toronto; [2]Department of Medicine, University of Toronto, Toronto, Canada





- Most commonly reported low-grade irAE: rash/pruritis
- irAE more commonly reported for anti-CTLA4 therapy
  - Diarrhea & colitis more common for anti-CTLA4 therapy

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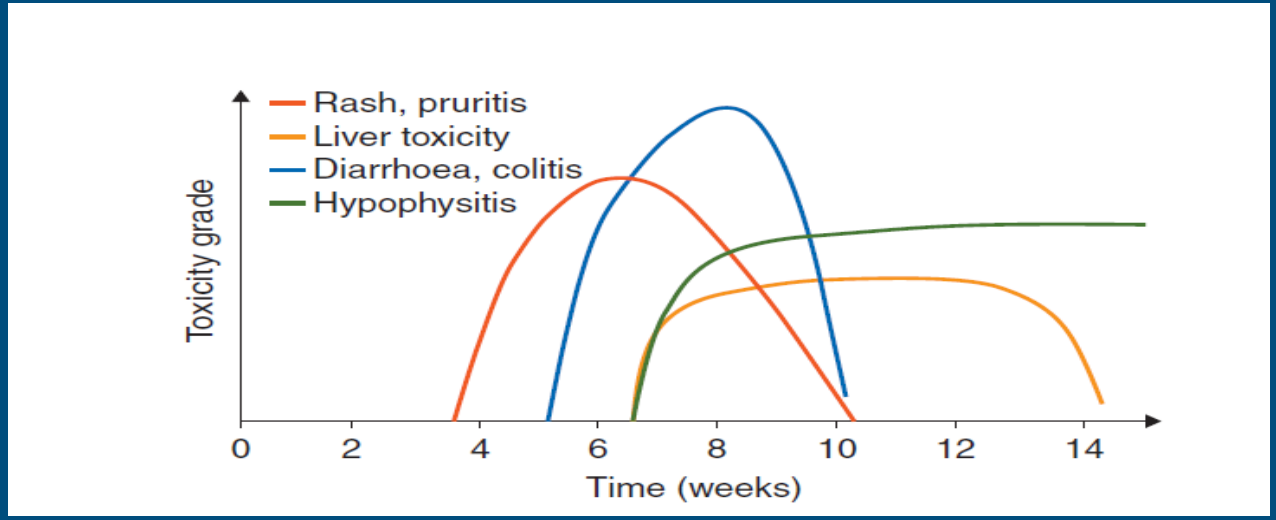
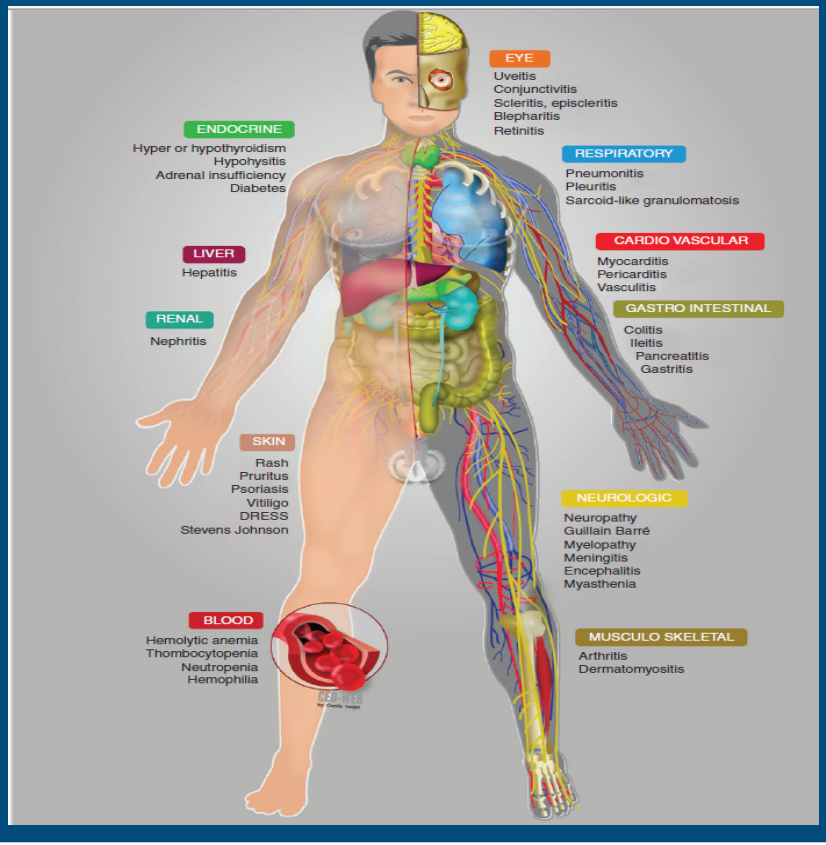
Kinetics of Appearance of irAEs



Weber, J. S., et al. (2012). *J Clin Oncol* **30**(21): 2691-2697.

Less Commonly Reported irAEs

- Diabetic ketoacidosis
- Primary/secondary adrenal insufficiency
- Graves-like disease



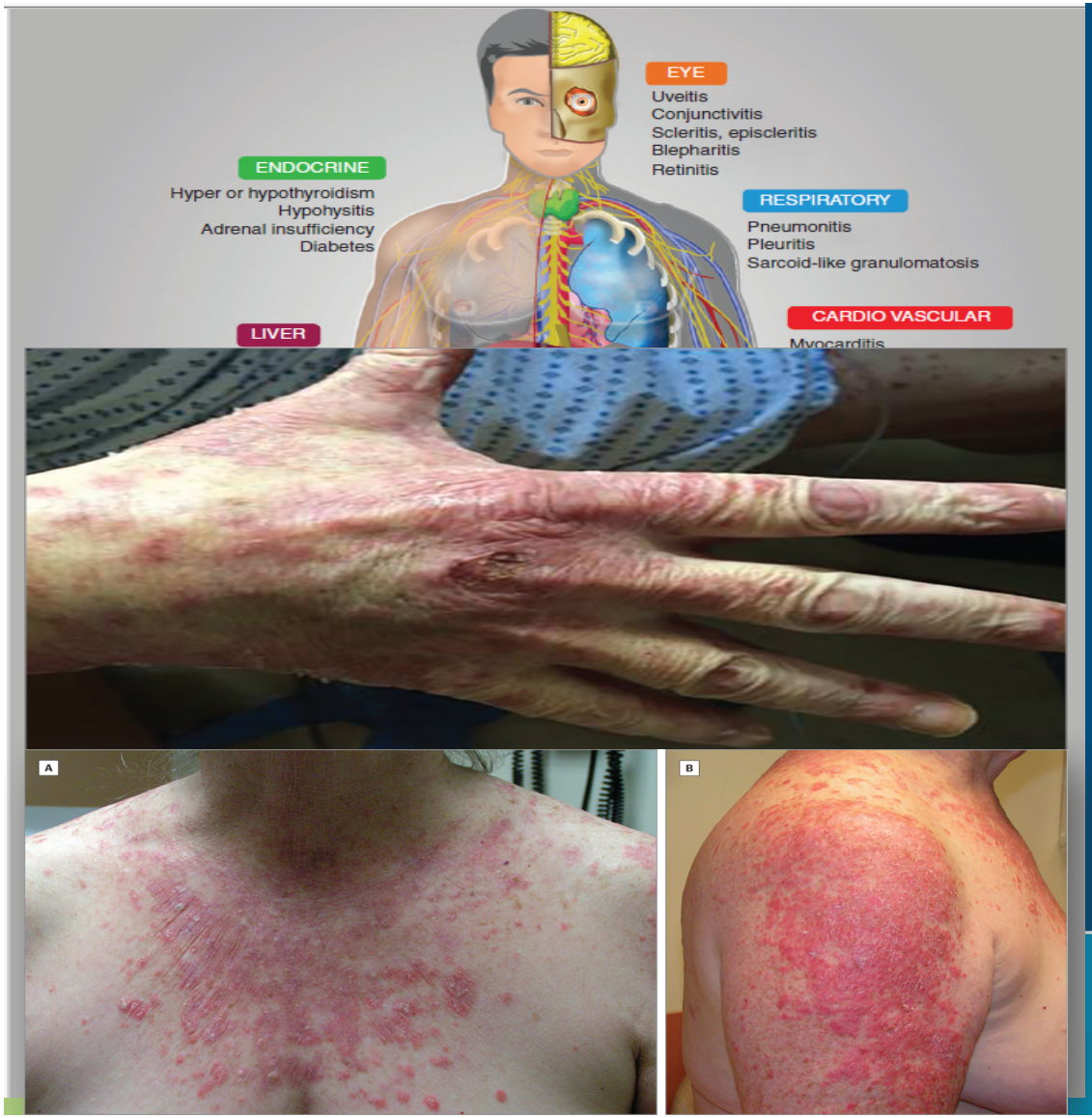
- Pneumonitis
- ARDS
- NSIP
- AEP
- Pleural inflammation
- Airway disease
- Sarcoid-like reaction

Neurologic
- Peripheral neuropathy
- Autoimmune encephalitis
- AIDP

Rheumatologic*

Michot, JM, et al. *Eur J Cancer*. 2016;54:139-148.

Clinical Pearls in the Management of irAEs From Immune Checkpoint Inhibitors



Dermatologic irAEs

- Most frequent for both anti-CTLA-4 and anti-PD-1 blockade (40% single agent-60% combo therapy)
  - Diffuse maculopapular rash and/or pruritis
  - Vitiligo
- Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported
- Many patients will have pruritus in the absence of rash (10-30%)
- Can be just, if not more bothersome than physical rash

Michot, JM, et al. *Eur J Cancer*. 2016;54:139-148.

Management of Rash/Pruritus

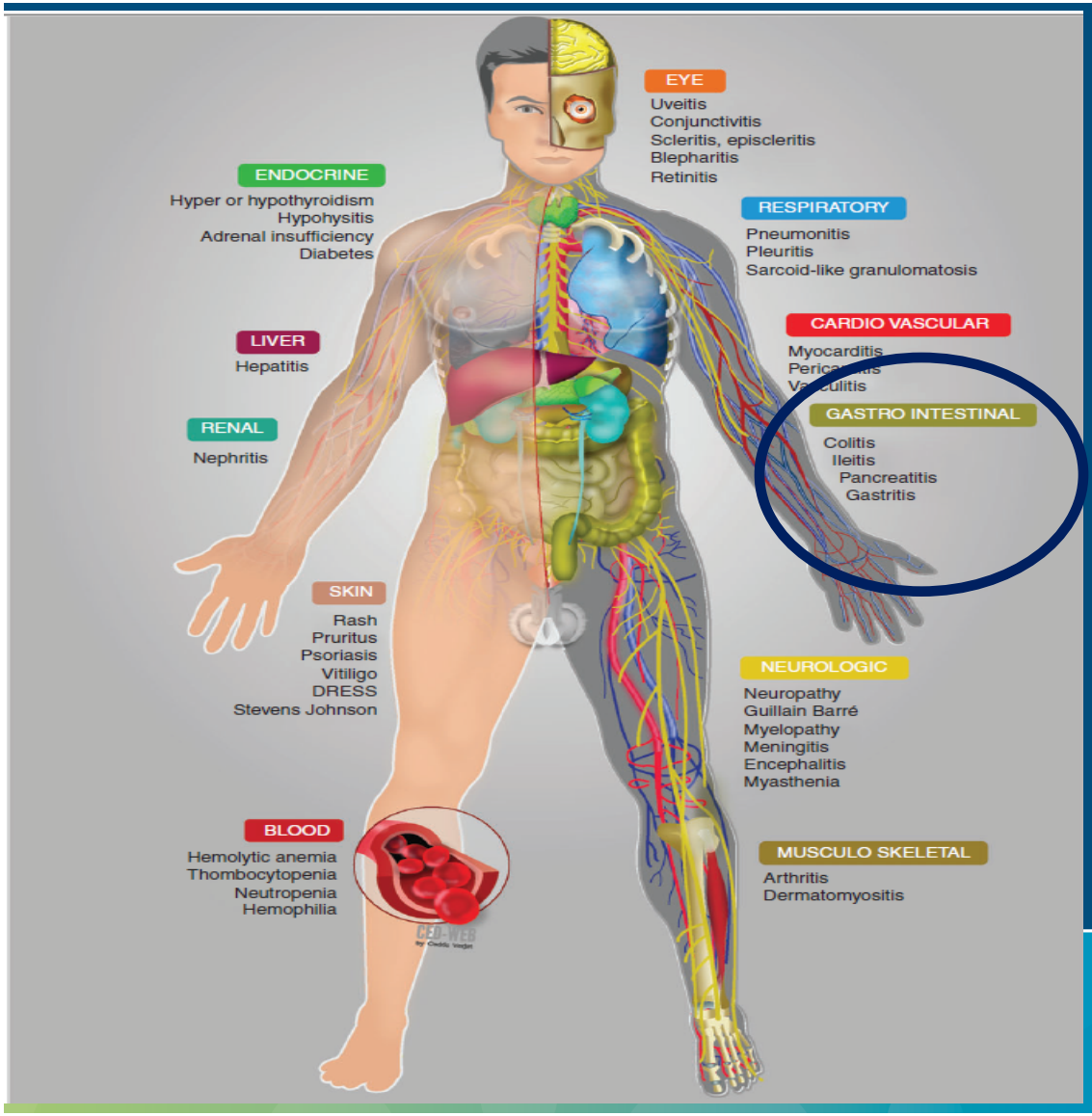
- Based on amount of BSA involved
- For <20% of BSA involved
  - Manage symptomatically
    - Topical agents (steroids/emollients/antihistamine cream)
    - And/or oral antihistamines
    - Any progression or lack of resolution (see below)
    - Continue agent cautiously

Management of Rash/Pruritus (cont.)

- For 20-50% of BSA involved
  - As above with the addition of oral steroids
  - Prednisone 0.5 mg-1 mg/daily (or equivalent)
  - Consider dermatologic consult
  - Hold agent
- For >50% of BSA involved
  - Steroid therapy at 1-2 mg/kg
  - Referral to dermatology
  - Hold agent, may need to discontinue

Management of Vitiligo

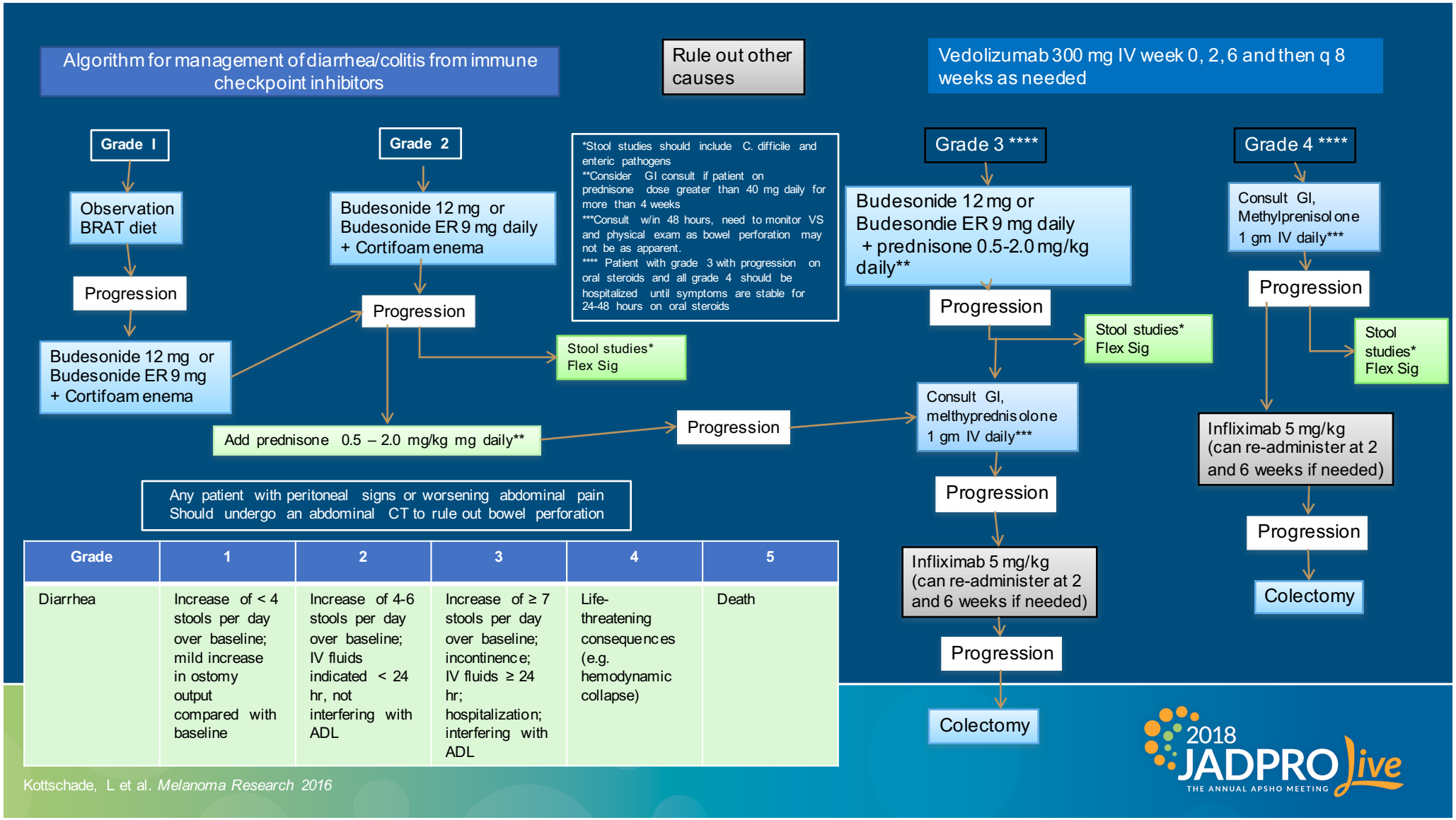
- Self-limiting, may be predictive of better outcomes and does not require intervention
- Likely permanent
- Patients should be cautioned about sun-protection in de-pigmented areas



Gastrointestinal

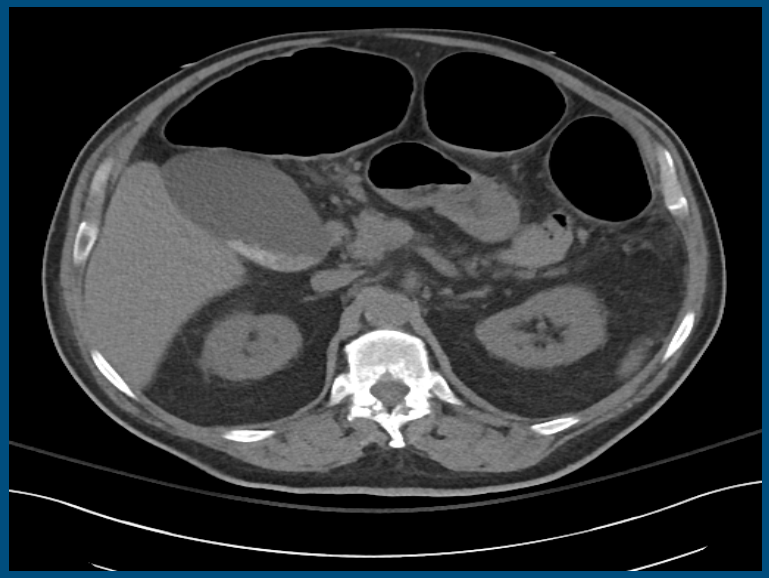
- Both diarrhea (increase in stool frequency) and colitis (diarrhea & abdominal pain with imaging/endoscopic evidence of colonic inflammation) more common with anti-CTLA-4 (30%)-combo therapy (50%)
- Colitis: Shares histologic features of Crohn's disease
  - Fatal bowel perforation reported in 1% of patients treated with ipilimumab

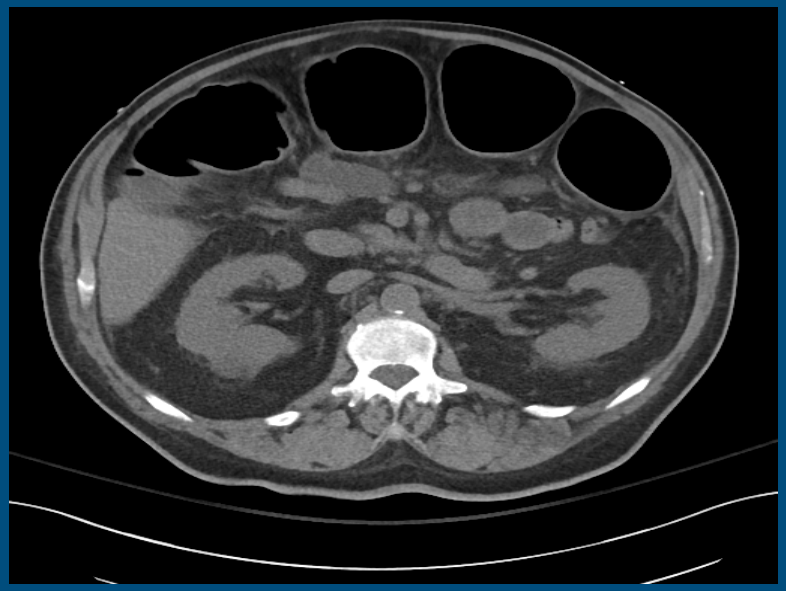
Michot, JM, et al. *Eur J Cancer*. 2016;54:139-148.



Grade	1	2	3	4	5
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated < 24 hr, not interfering with ADL	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hr; hospitalization; interfering with ADL	Life-threatening consequences (e.g. hemodynamic collapse)	Death

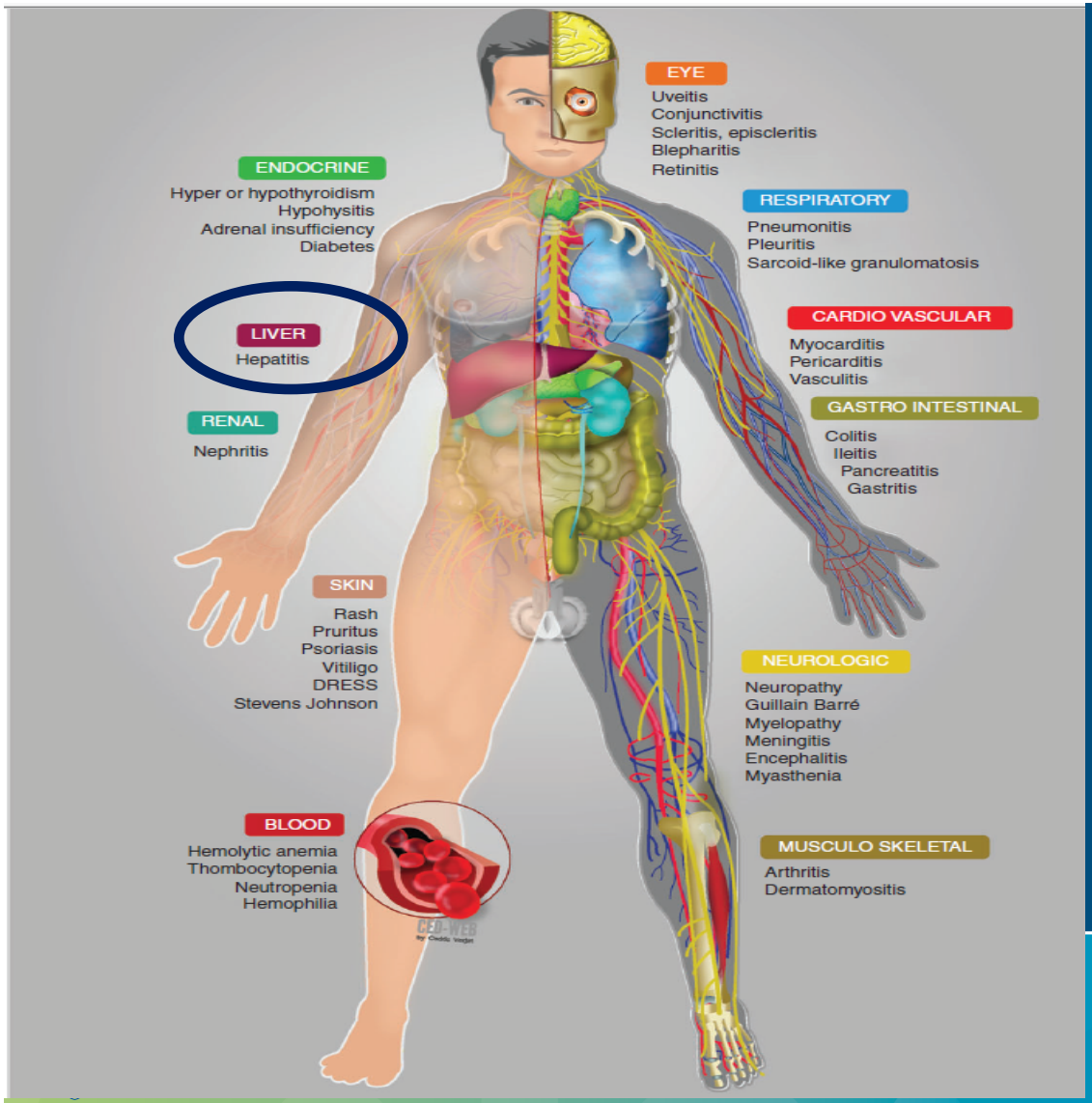
Kottschade, L et al. *Melanoma Research 2016*





Patient with grade 4 colitis from Ipi/Nivo. Self-medicated with loperamide. Presented to the ED with sepsis and hypotension, diagnosed with toxic megacolon. Required ICU admission and pressor support. Responded well to high-dose methylprednisolone and decompression.

Images courtesy of Lisa Kottschade, Mayo Clinic.



Hepatic irAEs

- Hepatotoxicity – asymptomatic transaminitis and/or hyperbilirubinemia
  - 30% in combination therapy (15% grade 3-4)
  - <10% in monotherapy
  - 0.2% hepatic failure

Rule out new or progressive hepatic involvement by malignancy

Management of Hepatic Toxicity

- AST or ALT > 3x and ≤ 5.0x ULN and/or total bili ≤ 3.0 x ULN
  - Rule out other causes (infection, malignancy)
  - Monitor LFTs 1-2 weekly until resolution to < grade 2 (or baseline)
  - For patients continuing to trend up or no resolution within 2 weeks start steroids at 0.5-1.0 mg/kg prednisone
- AST or ALT > 5.0x ULN and/or total bili > 3.0 x ULN
  - As above
  - Start steroids at 1-2 mg/kg prednisone

* In patients with abnormal LFTs at baseline, monitor for increase of LFTs and treat based on the parameters above

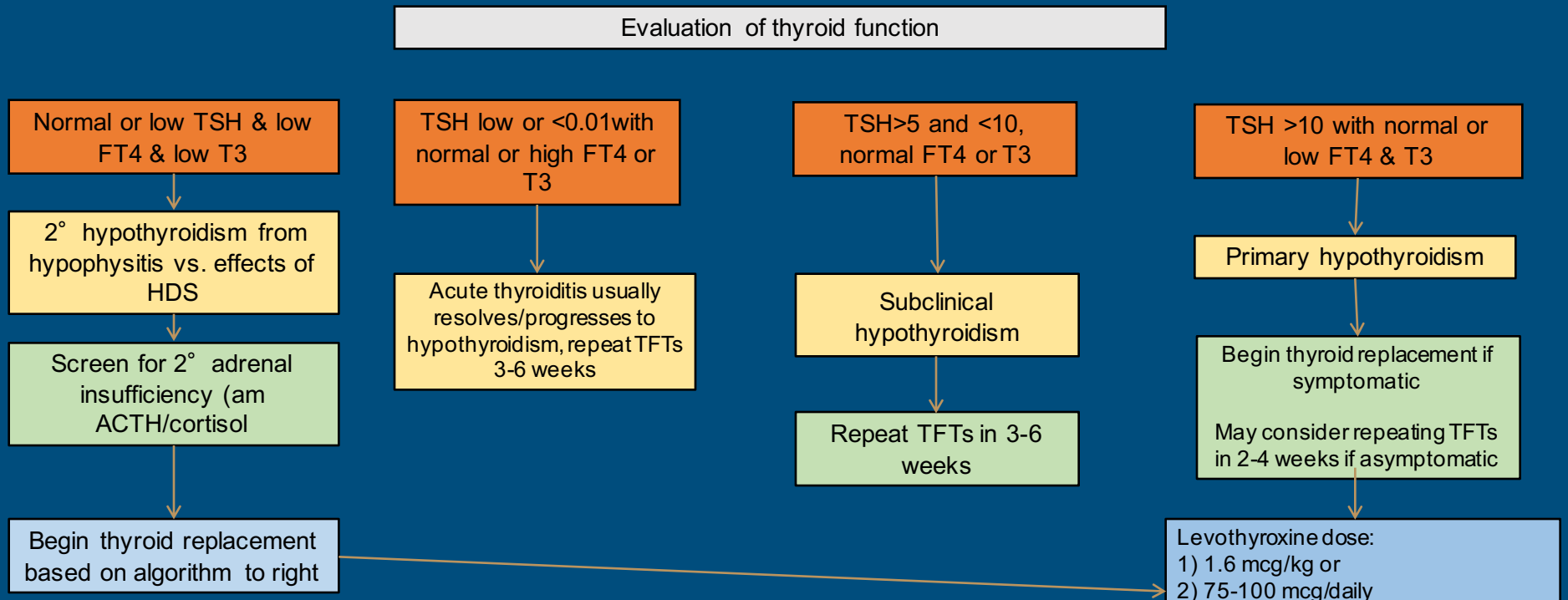
**For patients with persistently elevated LFTs or that are refractory to steroids consider hepatobiliary consult, consider mycophenolate

Endocrine irAEs

- Thyroid dysfunction (0-15%)[1,2]
  - Acute/inflammatory/painless thyroiditis associated thyrotoxicosis (↓TSH, ↑FT4 and/or T3)
    - Higher incidence in combination therapy (40%)
    - Resolution to euthyroid or progress to overt hypothyroidism (TSH >10); minority regain function

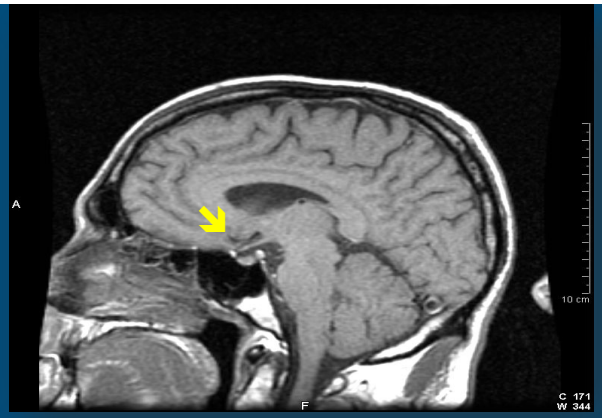
[1]Corsello, SM, et al. *J Clin Endocrinol Metab* 2013;98(4):1361-1375.
[2]Delivanis, DA, et al. *J Clin Endocrinol Metab* 2017;102(8).

Thyroiditis

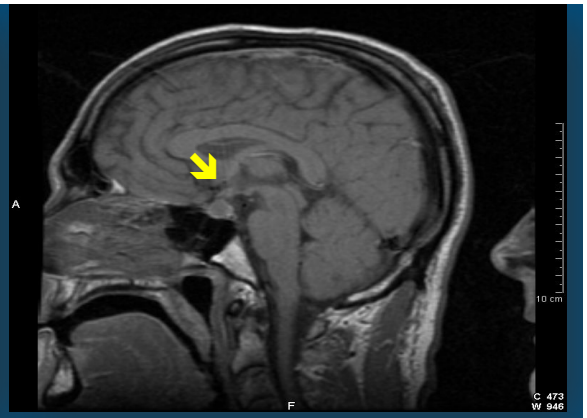


Kottschade, L et. al- *Melanoma Research 2016*

Endocrine irAEs (cont.)



Pre-ipilimumab

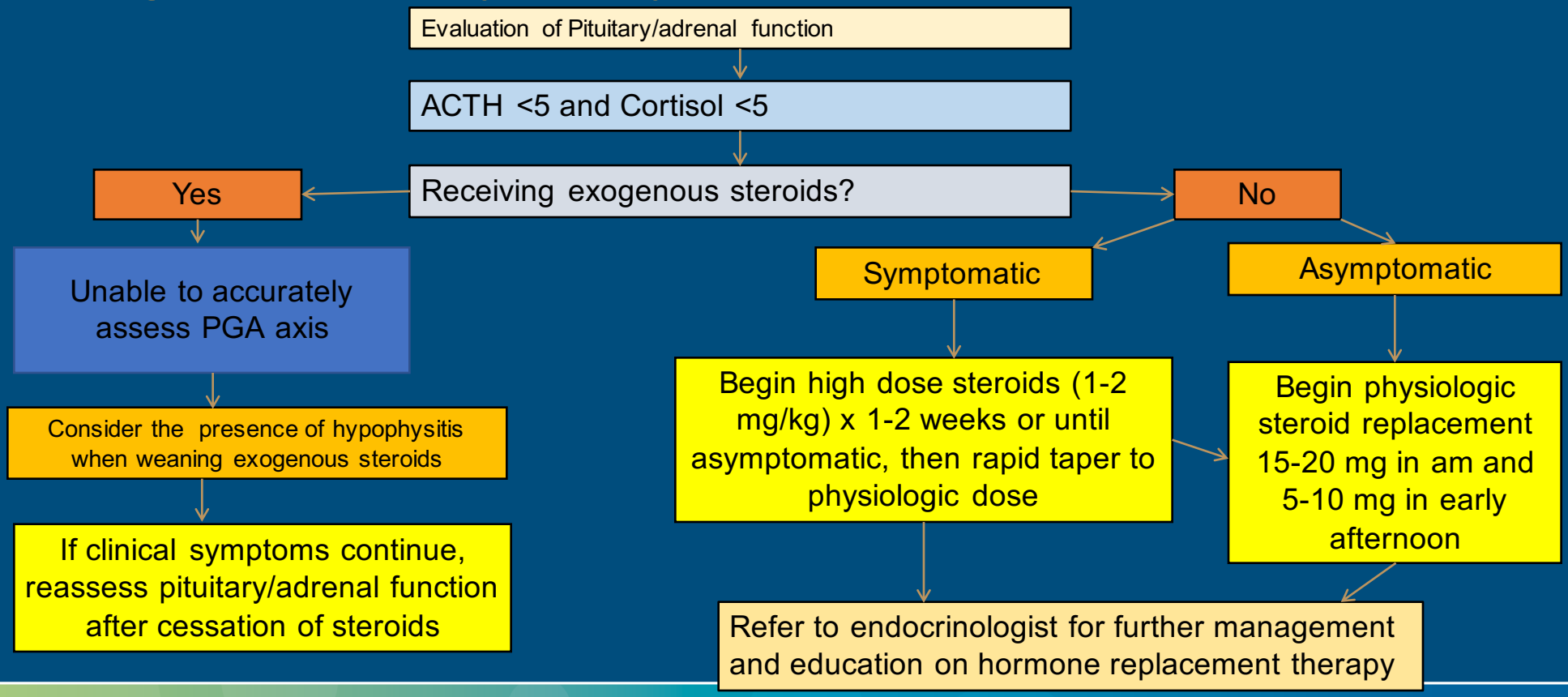


Post-ipilimumab

- Hypophysitis[1]
  - Clinically present with fatigue (the "run over by a truck" phenomenon) abrupt onset headache, possible visual changes/nausea/vomiting
  - Low or undetectable ACTH & AM cortisol levels
  - Enlarged pituitary on MRI (75%)
  - Differential: must consider CNS involvement by malignancy

[1]Ryder, M., et al. (2014). *Endocr Relat Cancer* **21**(2): 371-381.

Management of Hypophysitis



Endocrinopathies (cont.)

- Primary adrenal insufficiency/Adrenal crisis
  - Diagnosed by presence of volume depletion, electrolyte abnormalities, and low or undetectable am cortisol and **high ACTH**
- Hospitalize with fluid replacement, correct electrolytes and high dose steroids (1-2 mg/kg)
- Most PGA abnormalities do not resolve and patients require physiologic lifelong glucocorticoid replacement
- Patients need to be instructed in stress dose/sick day steroid dosing

  * Patients who remain asymptomatic and are on maintenance dosing only can be rechallenged*

Pneumonitis

- May present asymptomatically (only seen radiographically)
- DOE, SOB at rest, orthopnea
- Dry nagging cough (deep in chest)
- Chest pain
- Afebrile
- Differential: pulmonary embolism, progression of disease, infection

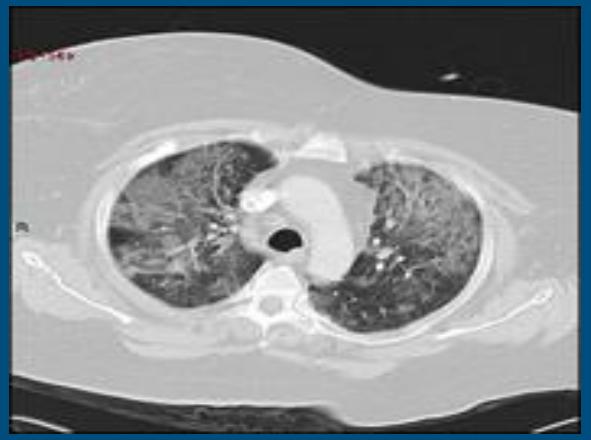
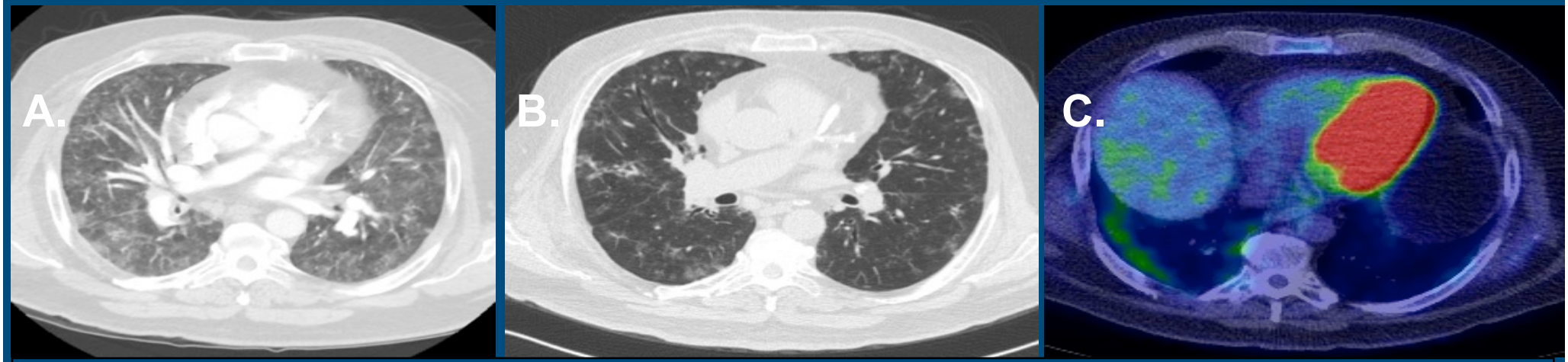


Image courtesy of Lisa Kottschade, Mayo Clinic.

Radiological Manifestations of Immune Checkpoint Inhibitor Induced Pneumonitis



A. Acute inflammatory pneumonitis, B. Chronic fibrotic changes, C. FDG-avid peripheral infiltrates.

- Clinical spectrum varies ranging from asymptomatic radiographic changes to acute hypoxemic respiratory failure

Kottschade, L, et al. *Melanoma Res* 2016;26(5):469-480.

Rheumatologic irAEs

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CORRESPONDENCE

Anti-CTLA4 Antibody–Induced Lupus Nephritis

N Engl J Med 2009; 361:211-212 | July 9, 2009 | DOI: 10.1056/NEJMc0904283

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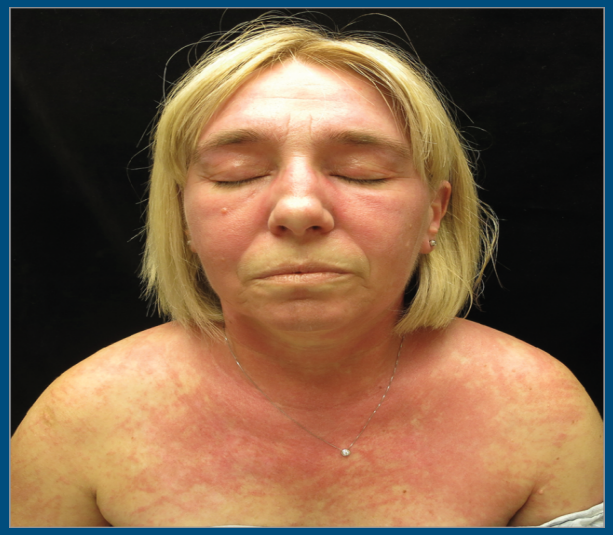

Drug-Associated Dermatomyositis Following Ipilimumab Therapy

A Novel Immune-Mediated Adverse Event Associated With Cytotoxic T-Lymphocyte Antigen 4 Blockade FREE

Shirwa Sheik Ali, BSc[1]; Allison L. Goddard, MD[2,3]; Jason J. Luke, MD[4]; Hilary Donahue, PA[4]; Derrick J. Todd, MD, PhD[5]; Andrew Werchniak, MD[2,3]; Ruth Ann Vleugels, MD, MPH[2]

DOI 10.1002/art.38282

Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of CTLA-4

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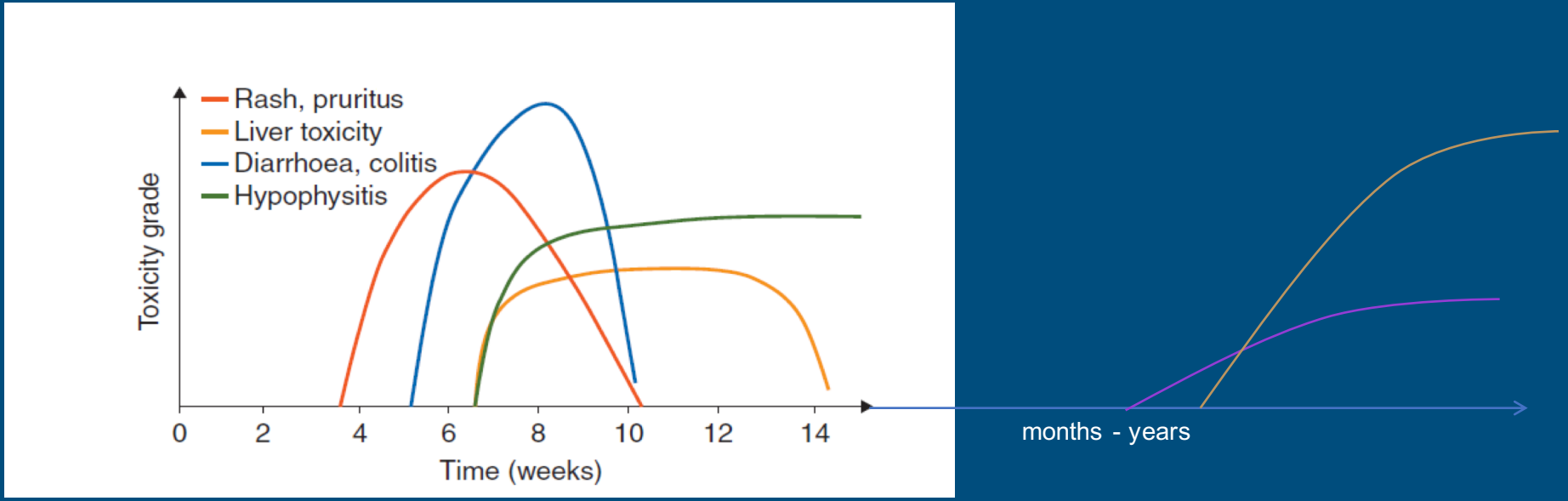
Rheumatologic irAEs: Observations



- Can occur many months after initiation and even discontinuation of ICI
- Can be steroid-refractory and chronic
- Typical disease-associated autoantibodies not seen

Weber, JS, et al. *J Clin Oncol. 2012*;30(21):2691-2697.

Ongoing Challenges

- Inconsistent reporting of irAE
- Current grading of toxicities may not adequately capture/characterize severity of all irAE
  - Many irAEs likely underreported
- Relative novelty of ICI and toxicity spectrum = barrier to early recognition, referral and treatment

The Unknowns

- When/if to re-challenge with ICI
- Impact of chronic steroid use and/or immunosuppressive agent on overall survival/cancer regression
- Biomarkers for risk for, and pathologic basis of irAE development

Clinical Pearls in the Management of Adverse Events in Targeted Therapy

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Background

- Approximately 40-60% of melanomas have a somatic mutation of BRAF at V600
- First approval in 2011 with most recent combo (3rd in class) approved in 2018.
- Significant improvement in PFS and OS with combinations vs BRAFi alone

Pyrexia

- One of most common AEs of combo therapy (more common with DT than VC or EB)
- Incidence
  - Around 50% all grades; 5% grade 3 or 4(DT)
  - Around 15% all grades; 4% grade 3; 0% grade 4 (EB)
- Severe reactions may include chills, rigors, hTN, dehydration, renal failure
- Patients may experience chills in absence of fever

VC = vemurafenib/cobimetinib; DT = dabrafenib/trametinib; EB = encorafenib/binimetinib.

Dermatologic AEs

- Varying types of rash presentation
  - Acneform type rash, most common
    - DT: 32% all grades; 1% grade 3-4
    - VC: 16% all grades; 2% grade 3-4
    - EB: 13% all grades; 1-2% grade 3-4
- Photosensitivity
    - DT and EB: not reported
    - VC: 46% all grades; 4% grade 3-4
- Steven's Johnson syndrome, TENS, and DRESS syndrome have been reported (more common with VC)
- Palmar-plantar erythrodysesthesia (hand-foot syndrome), more common with DT
- Risk for radiation recall and radiation dermatitis when used together

Secondary Cutaneous Malignancies

- Squamous cell carcinoma (cuSCC) and keratocanthoma (KA)- ~6% in combo; significantly higher in monotherapy ~20%
- Basal cell carcinoma ~4.5% in combo; ~2.4% in monotherapy
- Secondary primary melanoma ~ 0.8% in combo; higher in monotherapy ~2.4%
  - Interestingly many are BRAF wild type

Hepatotoxicity

- Common AE of combo therapy
  - Usually presents as transaminitis
  - Present in up to 30-40% of patients all grades
  - ~5-8% grade 3-4
- Exercise caution in patients switching to targeted therapy who have recently been treated with immunotherapy
  - Fatal hepatotoxicity has been seen

Cardiac Toxicity

- Prolonged QTc for patients on VC
  - Exact incidence unknown
  - Direct side effect from vemurafenib
  - Not seen with DT, theoretical with EB
- Cardiomyopathy (LVEF↓)
  - Defined as ≥ 10% decrease in LVEF from baseline
  - Incidence rate ~6%
  - Usually a class effect of MEKi, but isolated cases seen with BRAFi alone

Other Rare/Serious AEs

- Rhabdomyolysis
  - Asymptomatic increases in creatine phosphokinase
    - ~79% in VC therapy
    - 16% in EB therapy
  - Grade 3-4 in approximately 14%
- Uveitis/iritis/serous retinopathy
- Pneumonitis (interstitial lung disease (ILD): class effect of MEKi
- Hyperglycemia: Seen mostly with dabrafenib
- Hemorrhage and/or DVT
- Panniculitis

Pyrexia Management

For initial pyrexia episodes

- For fevers <101
  - Continue agents
  - Administer anti-pyretics as needed
  - Push fluids
- For fevers >101° but <104°
  - Hold dabrafenib until fever returns to normal (trametinib can be cautiously continued)
  - Administer anti-pyretics as needed
  - Can restart BRAFi at half-dose (MEKi full dose) and dose escalate every few days as tolerated
  - May use anti-pyretics prophylactically when rechallenging
- For fevers >104° (without other complications, i.e., hypotension, dehydrations, etc.)
  - Hold agents until fever returns to normal
  - Can restart agents at half-dose, do not dose escalate

Pyrexia Management (cont.)

- For refractory, complicated or subsequent febrile episodes:
- Rule out infection
- If pyrexia has not resolved within 3 days of onset; is accompanied by complications (i.e., hTN, dehydration, etc.), start prednisone 10 mg daily
- For patients with recurrent pyrexia, hold agents again; consider starting low dose prednisone (5-10 mg)
  - Once pyrexia is resolved, may rechallenge at half dose
  - Continue prednisone during rechallenge
  - If patient tolerates rechallenge- can taper steroids
    - *Note some patients will not tolerate steroid taper

Dermatologic Management Strategies

- Rash
- Acneform rash can be managed with minocycline 100 mg BID, if progresses initiate steroids
- *Patients who have rash with any of the following: blistering skin, sores in their mouth, peeling, fever, or redness or swelling of hands, face, etc. should immediately be ruled out for SJS or TENS.
- Photosensitivity
  - Very common, unique to vemurafenib
  - Can happen with only minutes of sun exposure
  - Instruct patients to use good photoprotection (SPF 30+), cover up, tinted windows, etc.
  - Manage symptomatically
- Secondary cutaneous malignancies
  - Manage as per standard of care
  - Can continue agents
  - Derm follow-up q 3-4 months

Cardiac Toxicity

- QTc management
  - For vemurafenib, repeat ECG 2 weeks after drug start, and monthly x3 and then every 3 months while on therapy
  - Hold vemurafenib for QTc >500 ms
  - May reinitiate once QTc <500 ms, at reduced dose
  - If QTc remains >500ms or increased >60 ms over baseline and all other risk factors are controlled for, permanently discontinue vemurafenib

Cardiac Toxicity (cont.)

- Decreased LVEF
  - Repeat ECHO at 1 month and every 3-4 months while on treatment.
  - For asymptomatic LVEF decrease of 10% (from baseline) or LVEF of 40-50%, hold MEKi for 2 weeks and repeat ECHO, if recovered, can restart MEKi at next lower dose level
  - For symptomatic LVEF; decrease of >20% (from baseline) or LVEF of 39-20%: hold MEKi for 4 weeks and repeat ECHO, if recovered (i.e., LVEF above LLN, symptoms resolved, and decrease from baseline <10%), can restart MEKi at next lower dose level
  - If the above criteria are not met or patient is not recovered after 4 weeks, permanently discontinue MEKi
- In patients who have restarted MEKi after dx of cardiomyopathy, repeat ECHOs more frequently for the first 4 months

Take-Home Points

- Many side effects from BRAFi and MEKi therapy, will resolve or lessen with holding agent and/or dose reductions.
- Be very cautious in patients who have recently transitioned from immunotherapy as there may be cross-toxicity (i.e., diarrhea, rash, and hepatotoxicity).
- BRAFi and MEKi agents must be held during radiation (including SRS) and for a few days after completion, due to increased skin and/or organ toxicity.

A Brief Look to the Future

Svetomir N. Markovic MD, PhD

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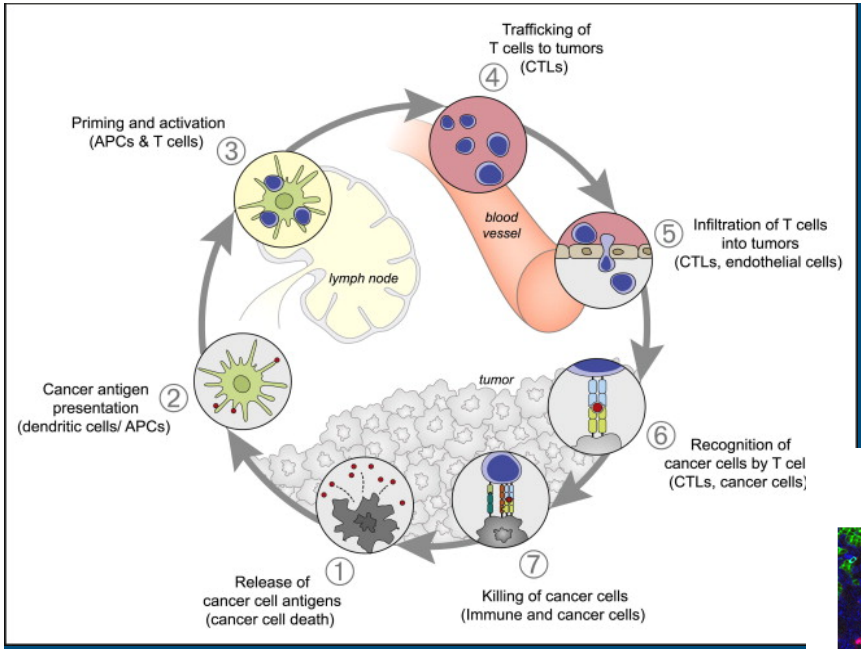
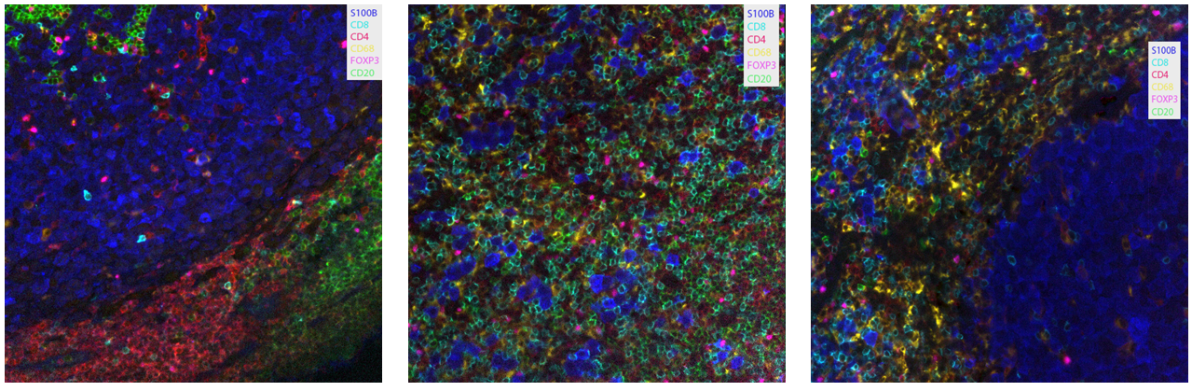


Chen et al, Immunity 39:1, 2013

Ongoing efforts:

- Resolve the complexity of the TME
- Understand systemic immune homeostasis of cancer
- Enable complex analysis of dynamic systems (time and space)
- Improve drug delivery platforms



S100B/CD8/CD4/CD68/FOXP3/CD20

Summary

- New AJCC staging substratified patients in stage III to provide better clarity.
- Patients with stage IV disease that includes CNS involvement are staged separately.
- Patients with SLN-positive disease do not benefit from CLND.
- Nivolumab is superior to ipilimumab for the adjuvant treatment of high-risk melanoma.

Summary (cont.)

- Pembrolizumab is superior to placebo for the adjuvant treatment of high-risk melanoma in terms of RFS. DMFS and OS benefit are still immature.
- Dabrafenib/trametinib are superior to placebo for the adjuvant treatment of high-risk melanoma in patients who harbor a BRAF mutation.
- Encorafenib/binimetinib represent a 3rd in class option for patients with metastatic melanoma, with a more favorable side-effect profile.
- The addition of epicadostat (IDO inhibitor) in combination with pembrolizumab did not improve PFS or OS in patients with metastatic melanoma.

Thank you!

QUESTIONS
AND DISCUSSION

SMARTIE

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If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.

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