

CONSENSUS OR CONTROVERSY?

Clinical Investigators Provide Perspectives on the Treatment of Metastatic Non-Small Cell Lung Cancer in Patients Without Targetable Tumor Mutations

**March 17, 2017
7:30 PM – 9:00 PM**

Faculty

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Heather Wakelee, MD**

Moderator

Neil Love, MD

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Disclosures for Dr Brahmer

Advisory Committee	Bristol-Myers Squibb Company, Merck
Consulting Agreements	Bristol-Myers Squibb Company, Celgene Corporation, Lilly, Merck
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Merck

Disclosures for Dr Langer

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Data and Safety Monitoring Board	Abbott Laboratories, Amgen Inc, Lilly, Peregrine Pharmaceuticals Inc, Synta Pharmaceuticals Corp

Disclosures for Dr Rizvi

Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Merck, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc
Ownership Interest	Gritstone Oncology

Disclosures for Dr Wakelee

Consulting Agreements	ACEA Biosciences Inc, Genentech BioOncology, Helsinn Group, Peregrine Pharmaceuticals Inc, Pfizer Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Exelixis Inc, Genentech BioOncology, Gilead Sciences Inc, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Roche Laboratories Inc, Xcovery
Grants	Clovis Oncology, Exelixis Inc, Gilead Sciences Inc, Pharmacyclics LLC, an AbbVie Company, Xcovery

Disclosures for Moderator Neil Love, MD

Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma, Agendia Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, CTI BioPharma Corp, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lexicon Pharmaceuticals Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, NanoString Technologies, Natera Inc, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro Inc, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

Module 3: Toxicities Associated with and Relative Contraindications to Immune Checkpoint Inhibition

How often do you believe pseudoprogression occurs with anti-PD-1/anti-PD-L1 therapy?



JULIE R BRAHMER, MD

6% of the time



COREY J LANGER, MD

Very rarely- if ever



HEATHER WAKELEE, MD

2.8% of the time



RAMASWAMY GOVINDAN, MD

Not much if imaging is at 8 weeks or later



JOEL W NEAL, MD, PHD







Rare (<5%)









GREGORY J RIELY, MD, PHD

Very rarely

Have you had any patients in whom anti-PD-1/anti-PD-L1 therapy was stopped because of toxicity, protocol requirements, et cetera, who experienced sustained responses after treatment was discontinued?

		RESPONSE OFF TREATMENT?	DURATION OF RESPONSE
	JULIE R BRAHMER, MD	Yes	4 years
	COREY J LANGER, MD	Yes	12 months
	HEATHER WAKELEE, MD	Yes	7 months and counting
	RAMASWAMY GOVINDAN, MD	Yes	1.5 years and counting
	JOEL W NEAL, MD, PHD	Yes	6 months
	GREGORY J RIELY, MD, PHD	Yes	6 months and counting

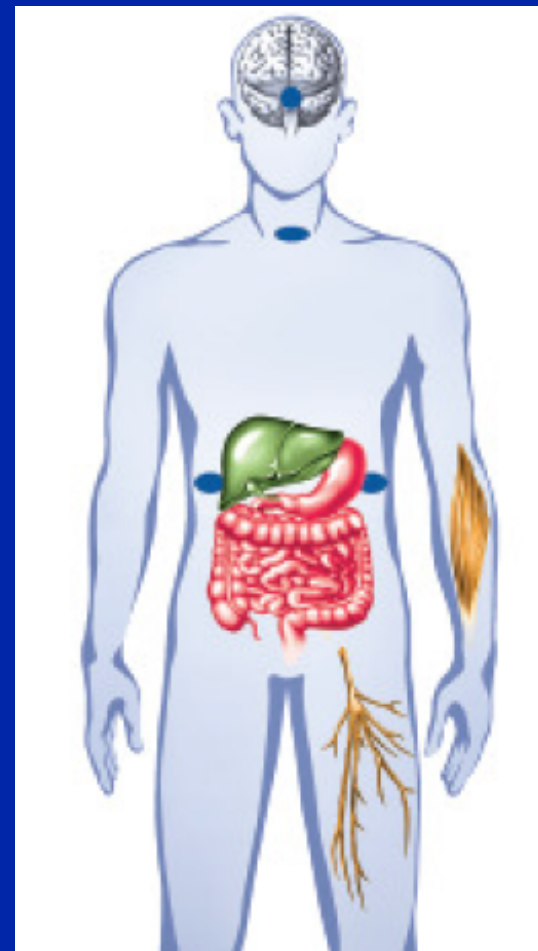
Are anti-PD-1/PD-L1 antibodies effective in patients with brain metastases? Have you observed any meaningful clinical responses to anti-PD-1/PD-L1 antibodies in a patient with brain metastases?

		EFFECTIVE IN BRAIN METS?	OBSERVED RESPONSES?
	JULIE R BRAHMER, MD	Yes, about as effective as with systemic metastases	Yes
	COREY J LANGER, MD	Yes, but less effective than with systemic metastases	No
	HEATHER WAKELEE, MD	Yes, about as effective as with systemic metastases	Yes
	RAMASWAMY GOVINDAN, MD	Yes, about as effective as with systemic metastases	Yes
	JOEL W NEAL, MD, PHD	Yes, but less effective than with systemic metastases	No
	GREGORY J RIELY, MD, PHD	Yes, about as effective as with systemic metastases	No

Immune-Related Adverse Events (irAEs) Associated with Immune Checkpoint Inhibitors

Occasional (5%-20%) irAEs Grade 3/4 uncommon

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor and sensory neuropathies
- Arthritis



Less common: hematologic; cardiovascular; ocular; renal

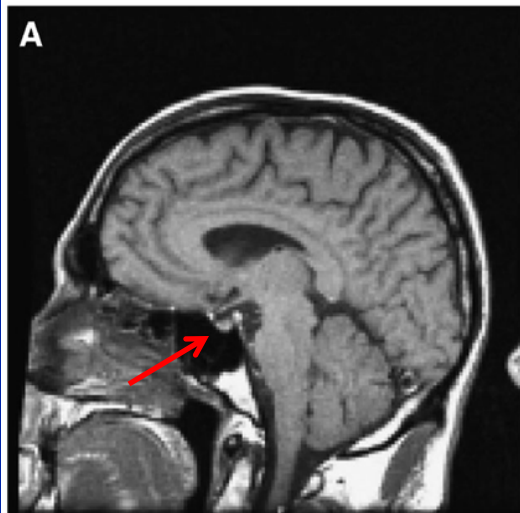
Rash and pruritus

- Patients should immediately report symptoms
- Treatment
 - Mild: Supportive care, increase monitoring
 - Antihistamines, topical non-Rx strength steroids
 - Moderate: Hold treatment, consider steroids (oral)
 - Severe: Permanently discontinue, start steroids

Diarrhea and colitis

- Symptoms occur after an average of 6-7 weeks
 - Diarrhea, abdominal pain, mucus/blood in stool
 - Peritoneal signs, bowel perforation, ileus
- Patients should immediately report bowel changes; rule out infectious/alternative causes
- Treatment
 - **Mild**: Supportive care, increase monitoring
 - **Moderate**: Hold treatment, consider steroids
 - **Severe**: Permanently discontinue, start steroids
 - Consider infliximab, GI consultation
 - Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis

Hypophysitis and endocrinopathies



6/30/04 - Baseline (4.5 mm)



12/3/04 - Headache/fatigue (10.8 mm)

- Can present with severe HA
- Differential includes CNS mets
- MRI with pituitary cuts
- Pituitary dysfunction may be reversible or permanent
 - Adrenal insufficiency
 - Hypothyroid

Adrenal insufficiency

- Nonspecific complaints
 - Fatigue, fevers, nausea
- Consider endocrinopathies early, especially with fatigue
 - Risk of adrenal crisis
- Check TSH, cortisol, ACTH, consider others
 - Initiate replacement therapy, referrals
- Patient education
 - Stress dosing, communication to providers

Liver toxicity

- Monitor liver function tests before each dose
- Rule out viral hepatitis, disease progression
- Treatment of mild elevation
 - Increase frequency of monitoring
- AST/ALT > 2.5-5x ULN or bilirubin > 1.5-3x ULN
 - Hold treatment, increase monitoring
- AST/ALT > 5x ULN or bilirubin > 3x ULN
 - Permanently discontinue, start steroids

Pneumonitis

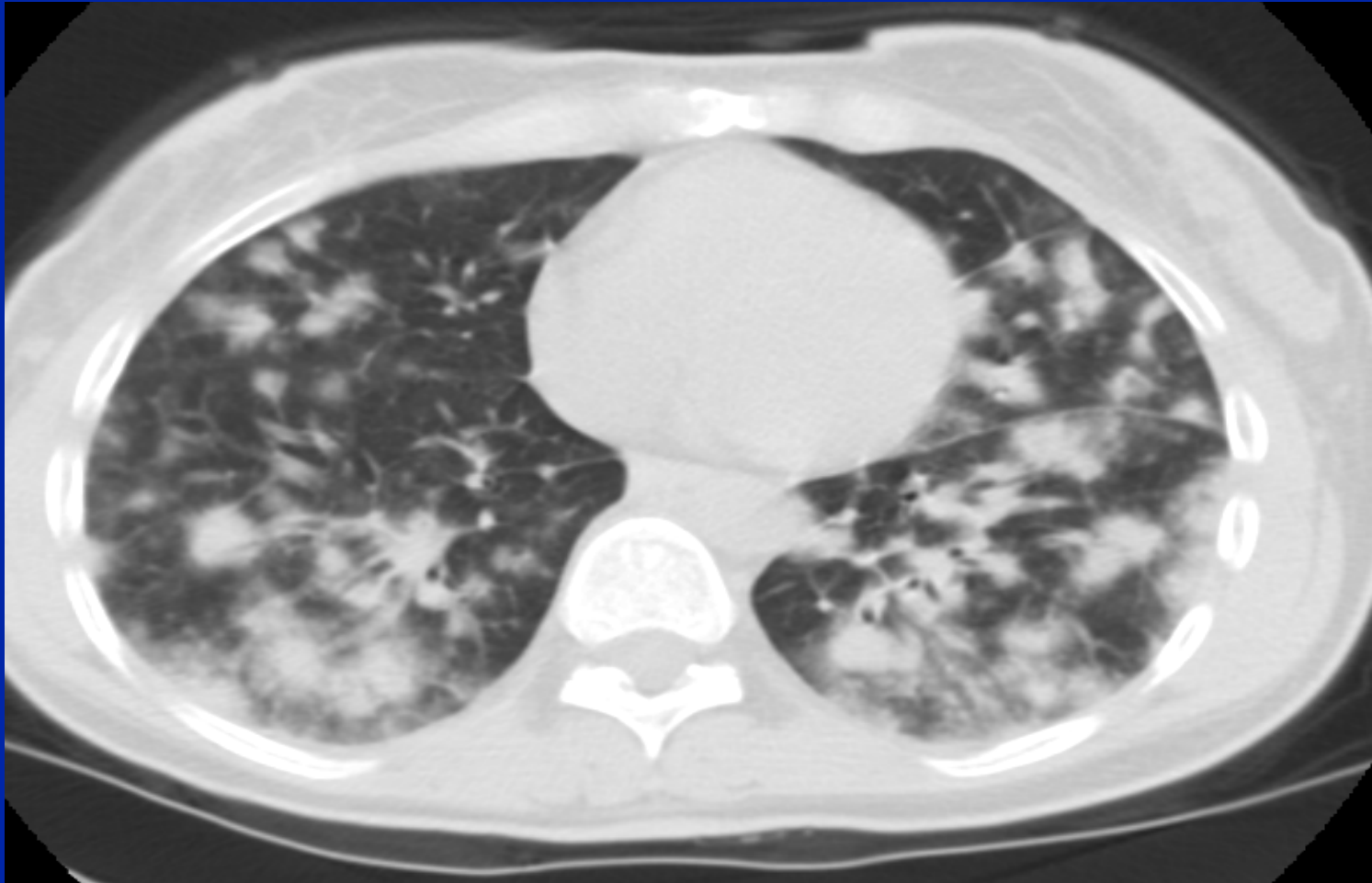








Image courtesy of Mike Postow, MD

Pneumonitis Management

1. Radiographic changes: monitor
2. Mild to moderate symptoms: high-dose prednisone, consider hospitalization/pulmonary evaluation
3. Severe symptoms or hypoxia: high-dose steroid, hospitalize, pulmonary evaluation, bronchoscopy

****Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis****

For a patient who has received all standard treatments and with a life expectancy of 6 to 12 months because of metastatic disease, would you discuss the option of an anti-PD-1/anti-PD-L1 antibody if the patient had the following condition and currently did not require active treatment for it...

		CROHN'S DISEASE	MS	LUPUS	RA	PSORIASIS
	JULIE R BRAHMER, MD	Yes	Yes	No	Yes	Yes
	COREY J LANGER, MD	Yes	Yes	Yes	Yes	Yes
	HEATHER WAKELEE, MD	Yes	No	No	Yes	Yes
	RAMASWAMY GOVINDAN, MD	No	No	No	Maybe	Maybe
	JOEL W NEAL, MD, PHD	Yes	Yes	Yes	Yes	Yes
	GREGORY J RIELY, MD, PHD	Yes	Yes	Yes	Yes	Yes

Toxicity of Anti-PD-1 Antibodies in Patients with Preexisting Autoimmune Disorders

Retrospective study of 52 patients with melanoma and preexisting autoimmune disease (AD)

Immune toxicity characteristic (N = 52)	Number (%)
Flare of AD on anti-PD-1	
Yes	20 (38%)
No	32 (62%)
Median time to flare	38 days
Grade of flare	
Grade 1-2	17 (33%)
Grade 3	3 (6%)
Grade 4	0 (0%)

- Anti-PD-1 antibodies induced relatively frequent immune toxicities that were often mild and easily managed without the need for treatment discontinuation.