Management of Side Effects for Patients Receiving Multimodality Therapy in Thoracic Oncology

Marianne Davies, DNP, RN, CNS, ACNP, AOCNP®
Yale University School of Nursing & Medicine
Yale Comprehensive Cancer Center

Beth Eaby-Sandy, MSN, CRNP
Abramson Cancer Center, Hospital of the University of Pennsylvania

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Learning Objectives

1. Identify strategies to mitigate adverse events (AEs) of checkpoint inhibitors
2. Evaluate emerging data regarding managing AEs of EGFR and ALK inhibitors
3. Formulate plans to mitigate AEs associated with radiotherapy

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Overview and Locally Advanced Non–Small Cell Lung Cancer (NSCLC)

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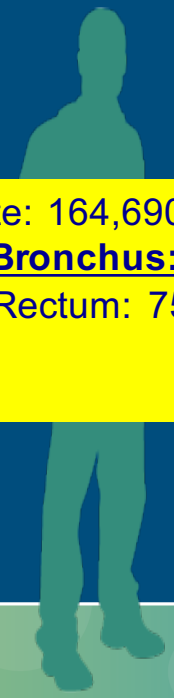
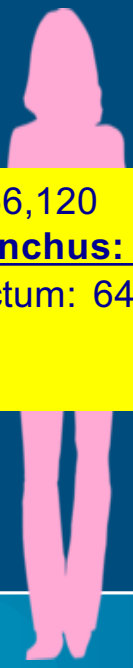
NSCLC: Scope of the Problem

Estimated Number of New Cases in US by Sex: 2018



1. Prostate: 164,690
2. **Lung/Bronchus: 121,680**
3. Colon/Rectum: 75,610

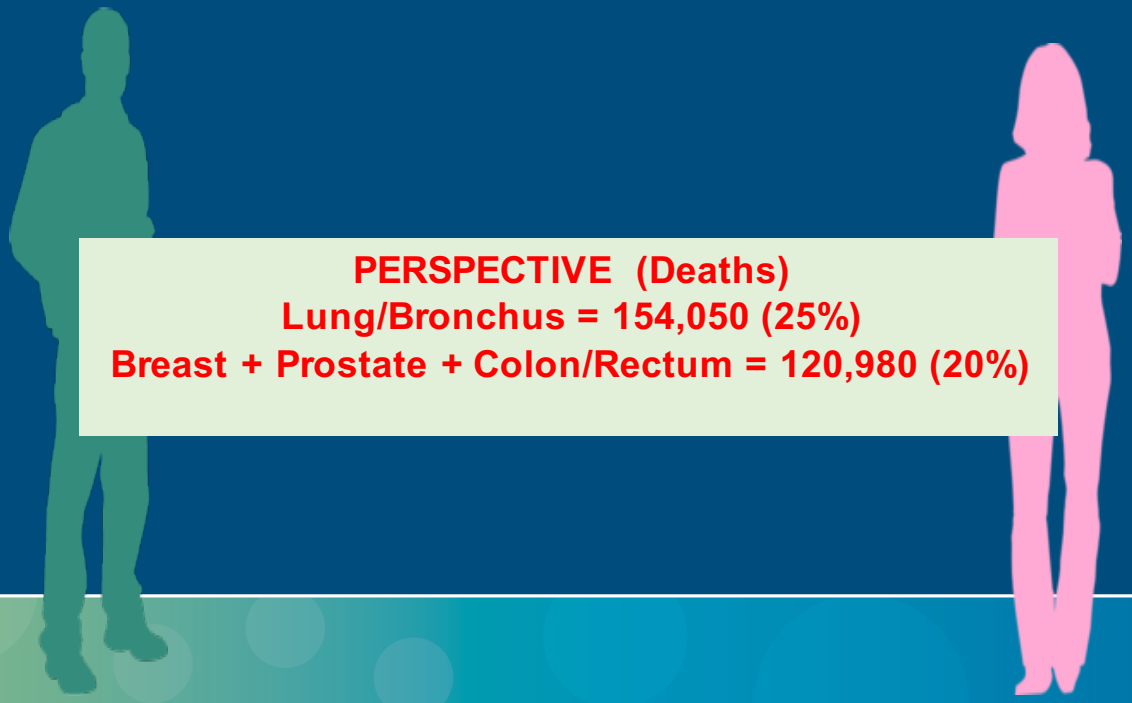


1. Breast: 266,120
2. **Lung/Bronchus: 112,350**
3. Colon/Rectum: 64,640

American Cancer Society. Cancer Facts and Figures 2018.

NSCLC: Scope of the Problem

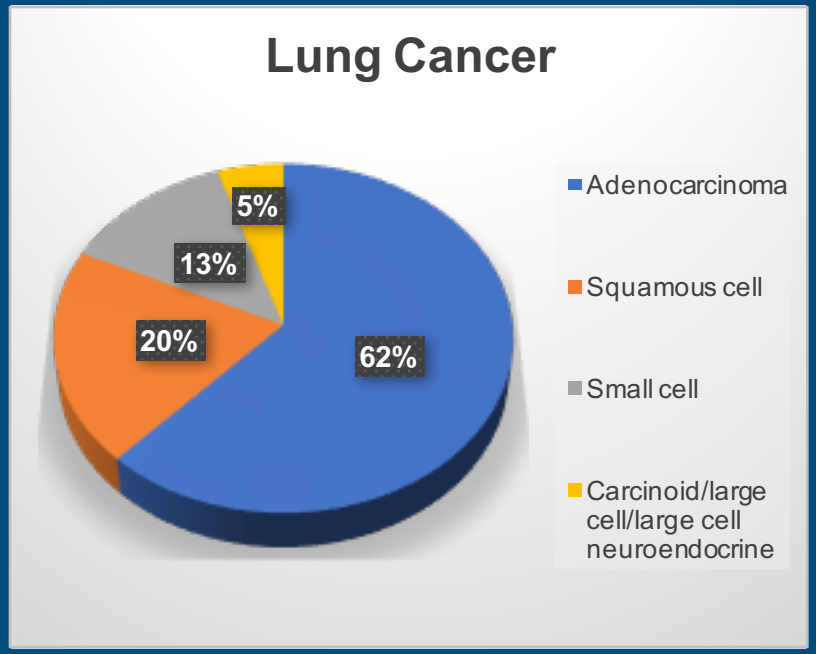
Estimated Number of Deaths in US by Sex: 2018



PERSPECTIVE (Deaths)
Lung/Bronchus = 154,050 (25%)
Breast + Prostate + Colon/Rectum = 120,980 (20%)

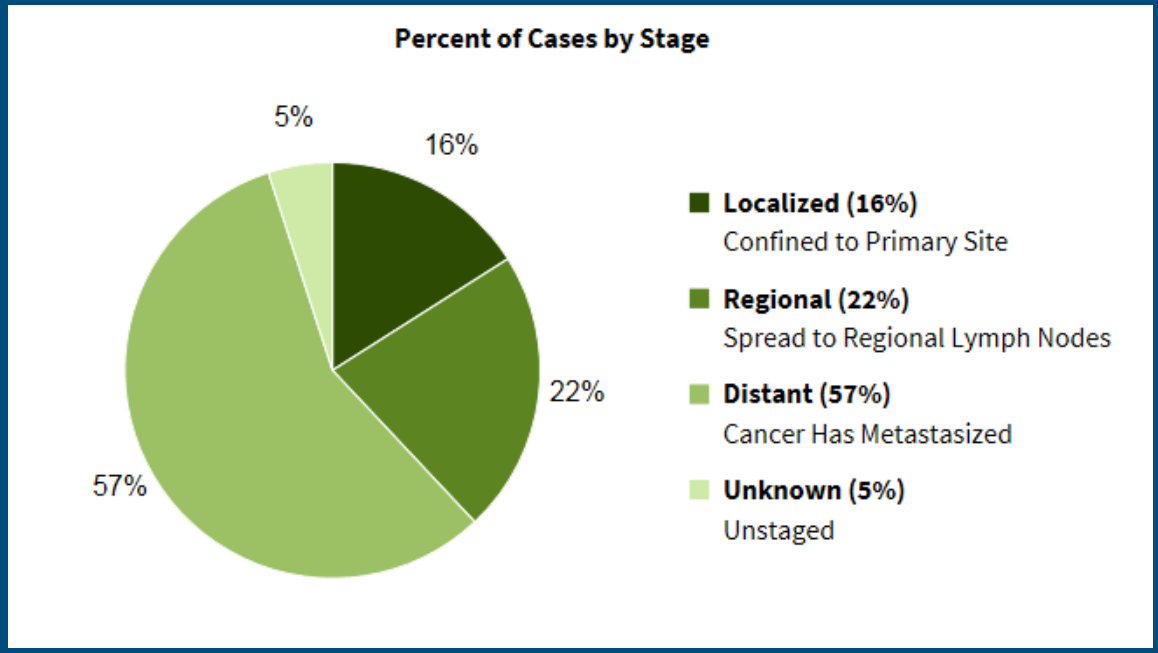
American Cancer Society. Cancer Facts and Figures 2018.

Lung Cancer: Histology Matters



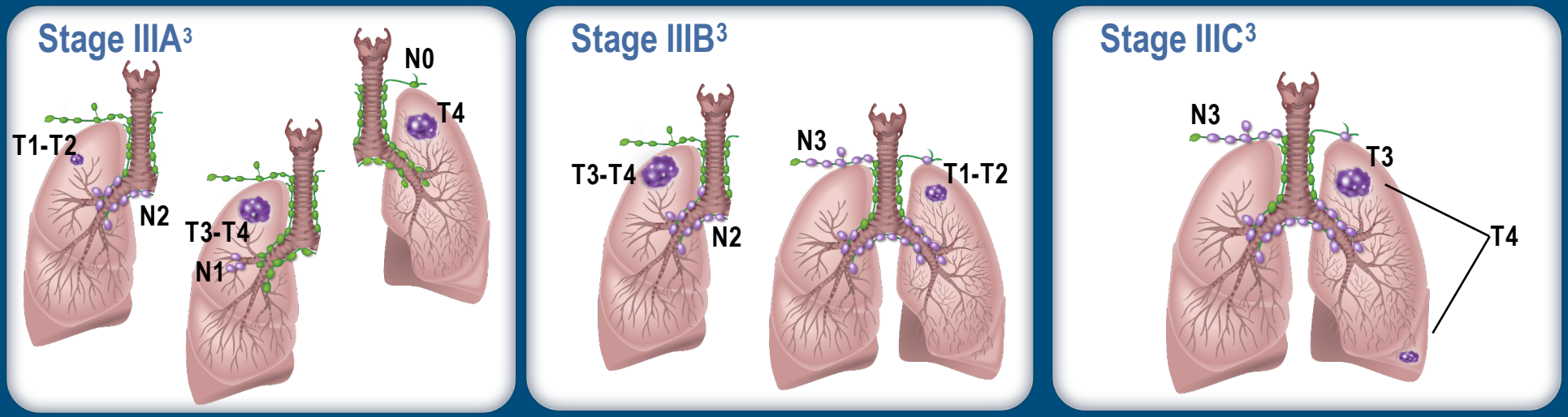
- Adenocarcinoma
  - Most likely to harbor a genetic mutation
  - Most common type in non-smokers
- Squamous cell
  - Generally more centrally located
- SCLC
- Large cell
  - Often associated with neuroendocrine features, but not a small cell

Lung Cancer Stages and Survival



https://seer.cancer.gov/statfacts/html/lungb.html

Locally Advanced/Stage III NSCLC



Most stage III NSCLC is not easily resectable; majority receive concurrent chemotherapy and radiation

5-Year Survival Rates for Stage III NSCLC Post-Chemo/Radiation

- CALGB 39801 Pac/Carbo/XRT: 4-19% depending on prognostic factors
- SWOG 9019, 9504: Etopo/Cis/XRT: 15%, 29%
- Meta-analysis of stage III chemo/radiation trials 15.1%

Vokes, EE, et al. Clin Lung Canc 2009; Ablain KS et al. JCO 2002; Gandara DR, et al JCO 2005;Stinchcombe, TE, et al. JTO 2009

Locally Advanced NSCLC/Stage III

- About 30% of patients diagnosed with NSCLC
- Standard of care concurrent chemo plus radiation
- Median PFS is 8-10 months with chemo plus radiation
- 5-year survival rate only about 15%
- No advances in this population for several years
  - 3 common regimens
    - Weekly paclitaxel/carboplatin
    - Every-3-week pemetrexed/carboplatin
    - 28-day cycle of etoposide/cisplatin (SWOG regimen)
- New data adding immunotherapy in 2018!

Trial of Durvalumab Post-Chemo/Radiation

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

2:1 randomization, stratified by age, sex, and smoking history N=713

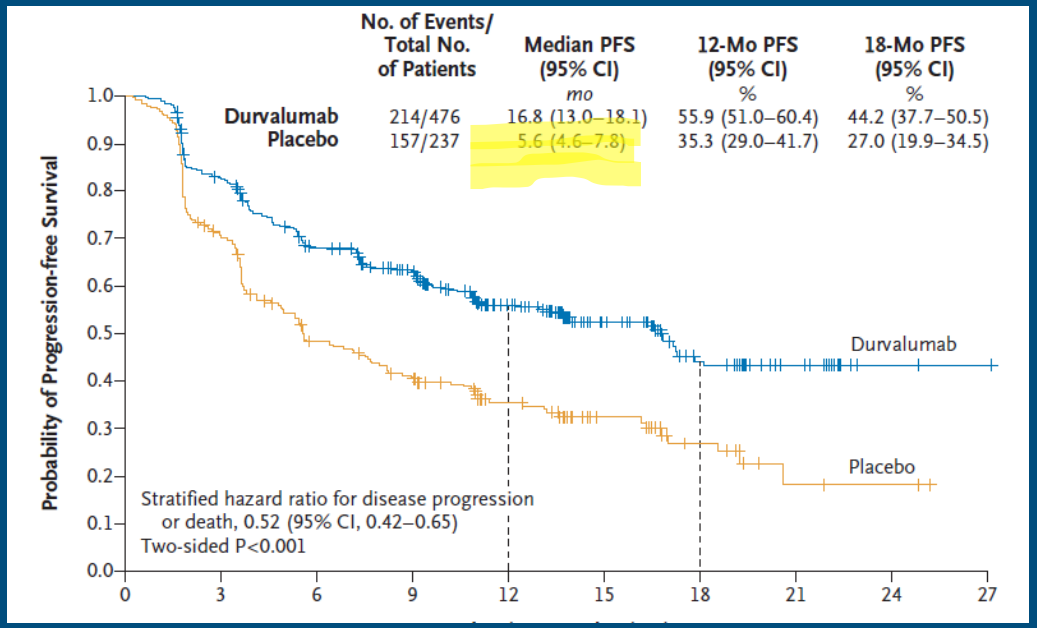
Co-primary endpoints
- PFS by BICR using RECIST v1.1*
- OS

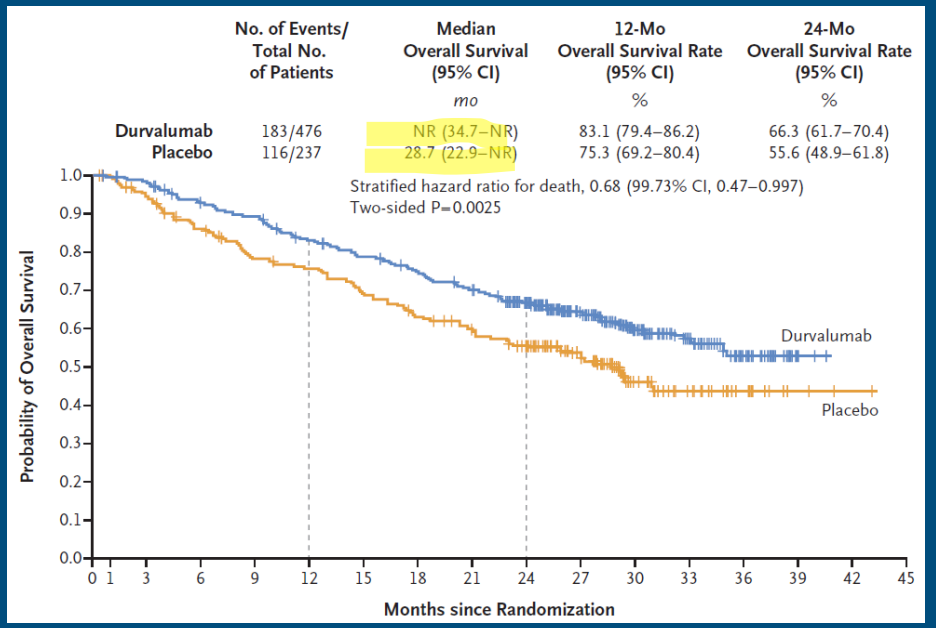
Key secondary endpoints
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.
ClinicalTrials.gov number: NCT02125461

Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-29.

Significant Improvement in PFS and OS in Favor of Durvalumab Post Chemo/Radiation





Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-29. Antonia SJ, et al. *N Engl J Med*. 2018

General Toxicities From Chemo/Radiation in NSCLC

- Esophagitis
- Pancytopenia
- XRT skin burns
- Nausea
- Fatigue
- XRT pneumonitis

- But these vary across…
  - Patients
  - XRT techniques
  - Concurrent chemotherapy regimen

Vokes, EE, et al. Clin Lung Canc 2009; Gandara DR, et al JCO 2005;Stinchcombe, TE, et al. JTO 2009

Toxicities of Chemo/Radiation Followed by Durvalumab

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0

Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-29.

Management Strategies

- Esophagitis: Supportive care, most pharmacologic stuff doesn't work well…
- Pancytopenia: Check weekly counts and treat/educate accordingly
- XRT skin burns: Topical preps (less of an issue with new XRT techniques?)
- Nausea: Proper prophylaxis depending on emetogenicity of regimen
- Fatigue: Energy conservation
- XRT pneumonitis: Educated about symptoms and when likely to occur

Advanced NSCLC

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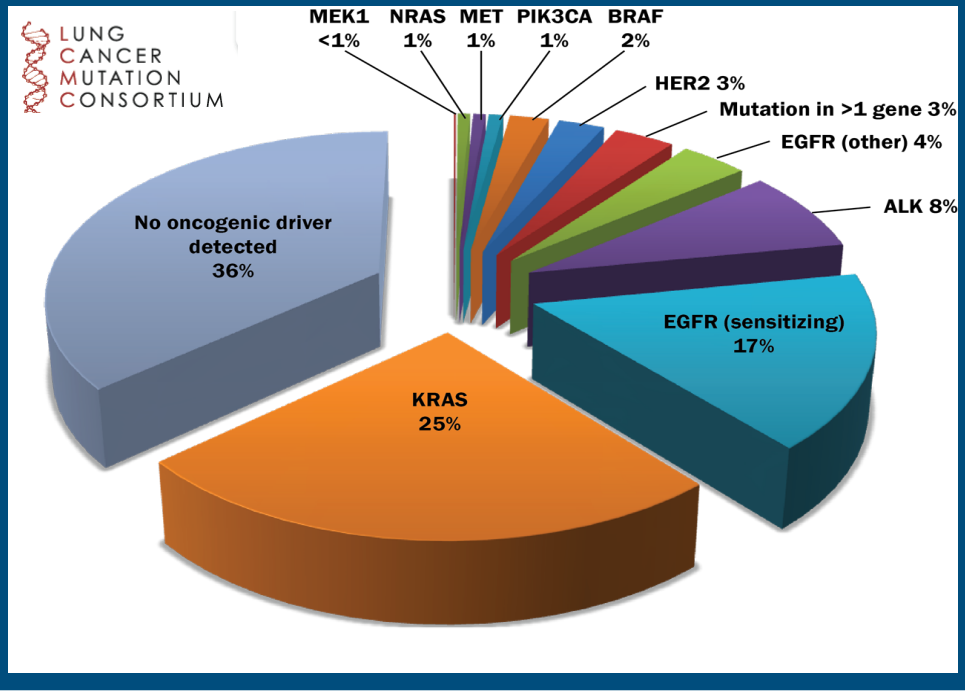
NSCLC: Treatment Decision Variables

- Histology
  - Non-squamous NSCLC
  - Squamous NSCLL
- Molecular driver mutations
  - EGFR
  - ALK
  - ROS1
  - BRAF
  - PD-L1
- Molecular drivers considerations
  - Consider in never-smokers
  - Mixed histologies

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancer to Select Targeted Drugs



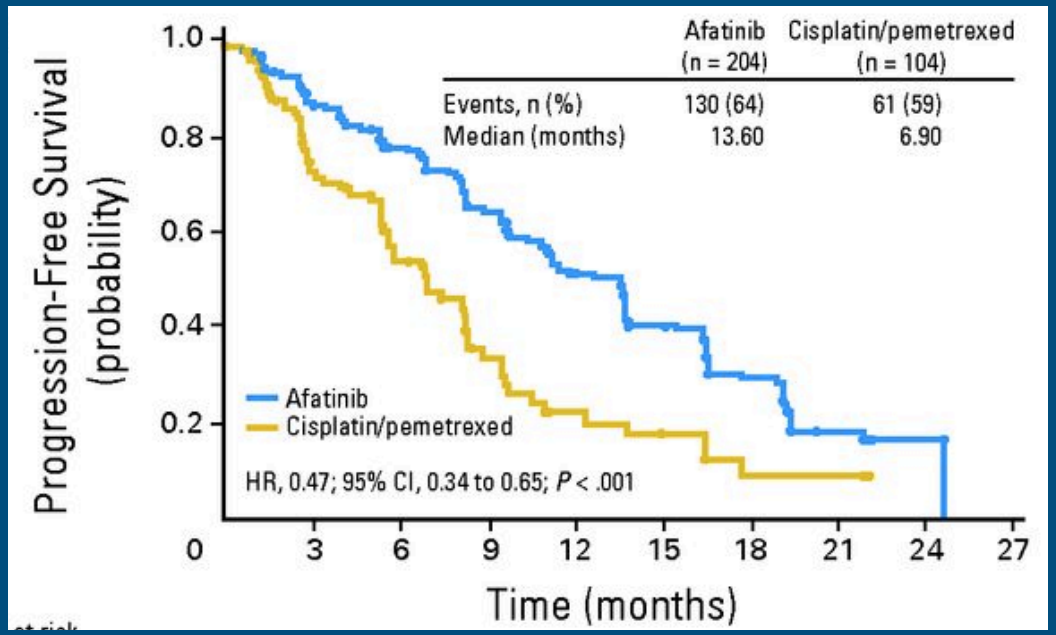
Kris M, et al. *JAMA*. 2014 May 21; 311(19): 1998–2006.

EGFR Mutant NSCLC

- Paradigm of oncogene driven solid tumor
- Occurs in about 20% of lung cancers
- More common in women than men (22% vs. 15%)
- More common in Asians than Caucasians (55% vs. 18%)
- More common in never-smokers (43%) than former (14%) or current smokers (5%)
- (But, if we only looked in women or never-smokers, we'd miss 57% of EGFR mutant NSCLC)

D'Angelo et al, JCO 2011; Dogan et al CCR 2012

In Patients With EGFR-Mutant NSCLC, First/Second-Generation EGFR TKIs Are Superior to Platinum-Based Doublets



What Causes Acquired Resistance?

Diagnosed with *EGFR* mutant NSCLC

↓

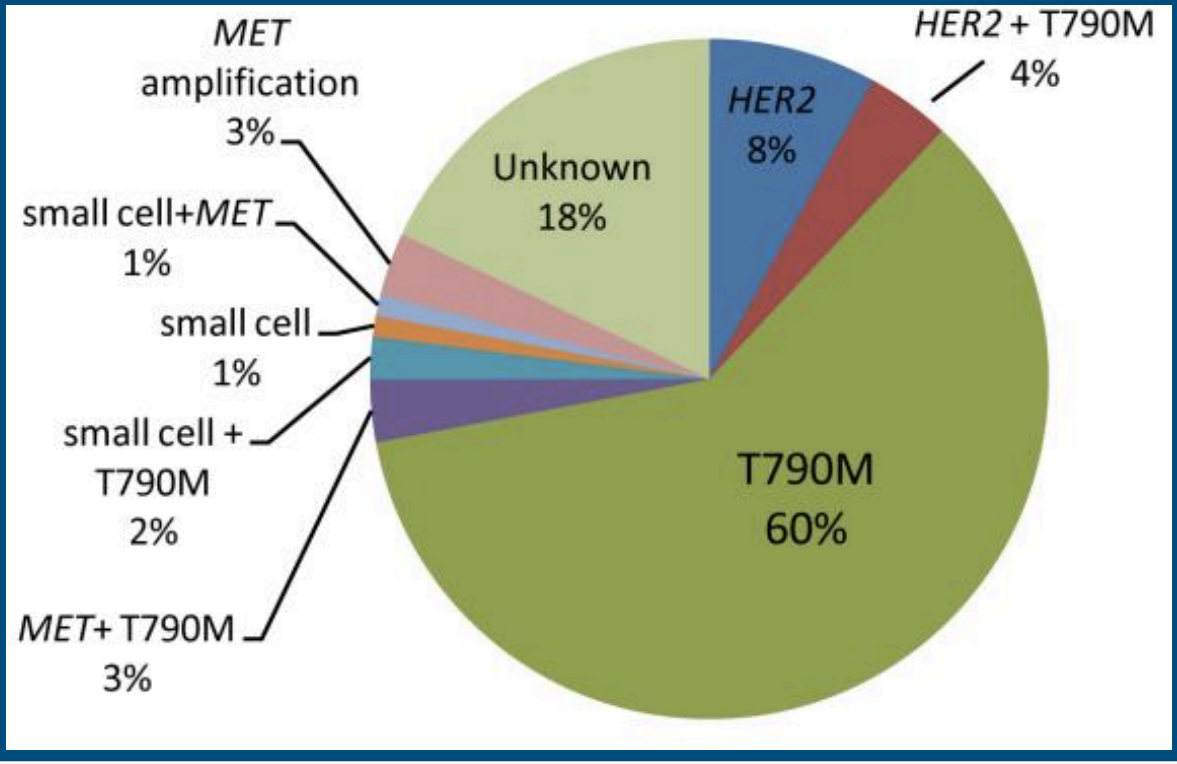
1st/2nd Generation EGFR TKI

↓

Development of Clinical Resistance to EGFR TKI

↓

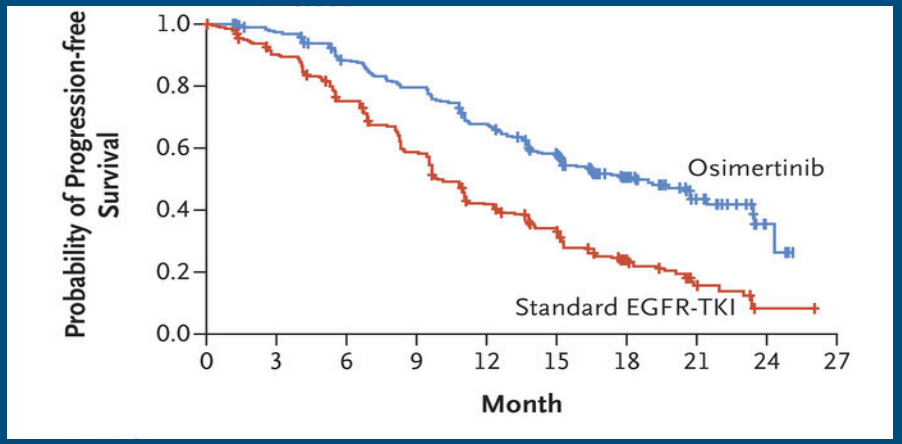
Biopsy to understand mechanism of resistance

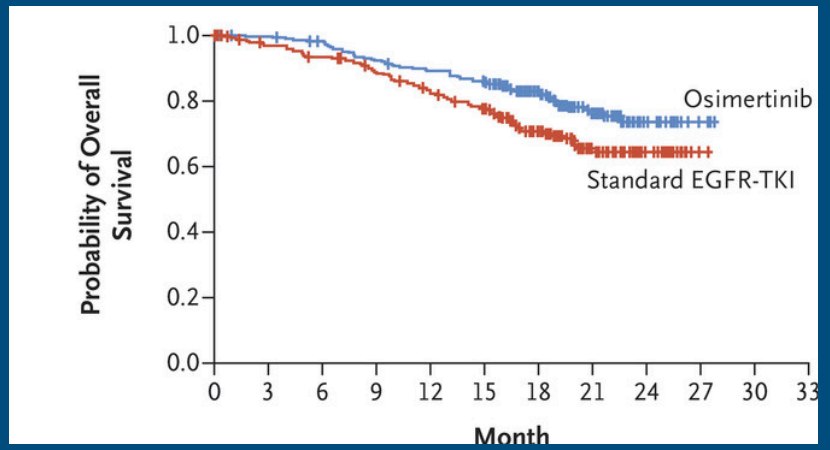


Yu et al, CCR 2013

FLAURA: Osimertinib vs. Gefitinb/Erlotinib

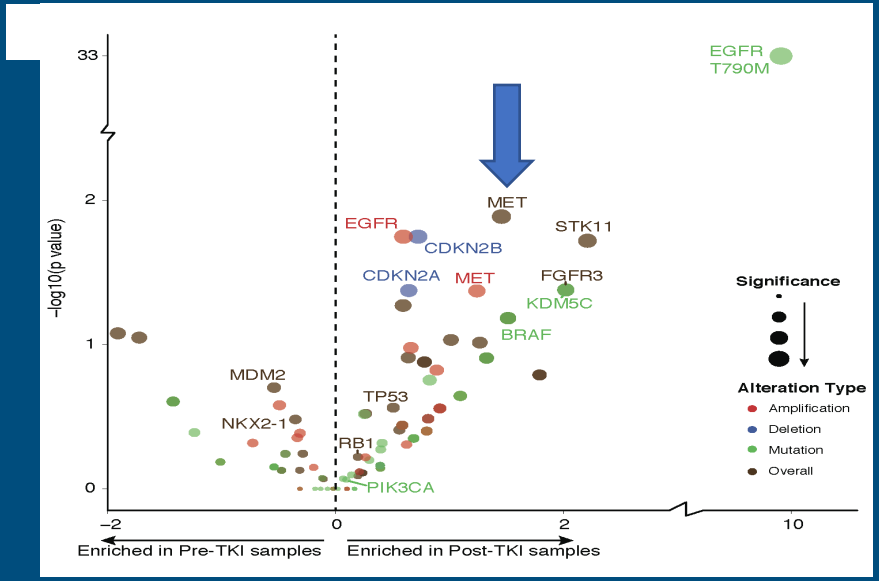
Osimertinib targets T790

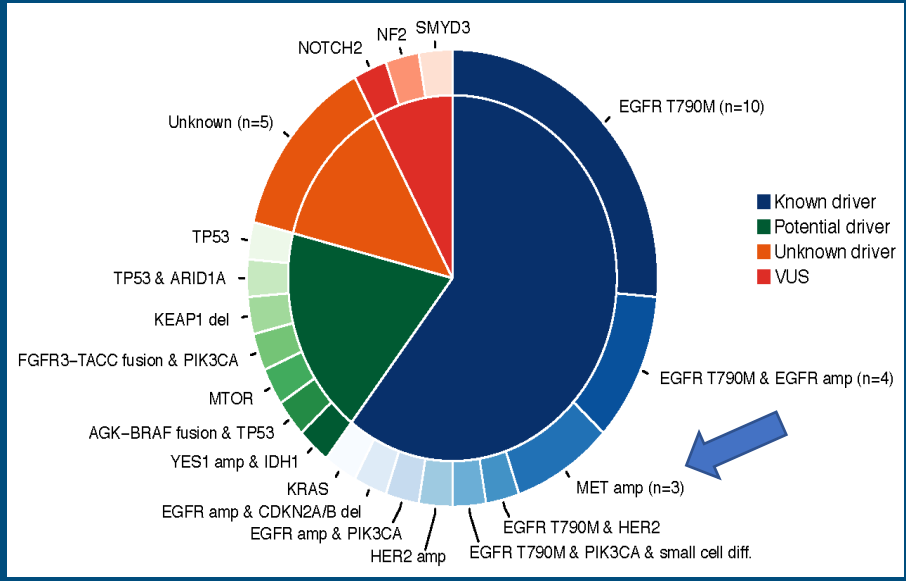




Soria et al, NEJM 2017

Acquired Resistance to 3rd Generation EGFR TKI





Helena Yu, CCR, 2018

Initial Therapy for Non-Squamous NSCLC EGFR Mutations

First Line

- Osimertinib

- Erlotinib
- Afatinib
- Gefitinib
- Dacomitinib

Progression

- T790 testing

Next Line

- Combination TKI?

Initial Therapy for Non-Squamous NSCLC
ALK Mutations- ~7% of lung cancers

- FDA-Approved ALK TKIs
  - 1st gen: crizotinib*
  - 2nd gen: ceritinib*, alectinib*, brigatinib**
  - 3rd gen: lorlatinib, ensartinib in randomized trials

***Approved first or later lines**

****Approved later lines**

Agents that do not cross the BBB

Brain mets are common at diagnosis and primary area of progression in ALK NSCLC

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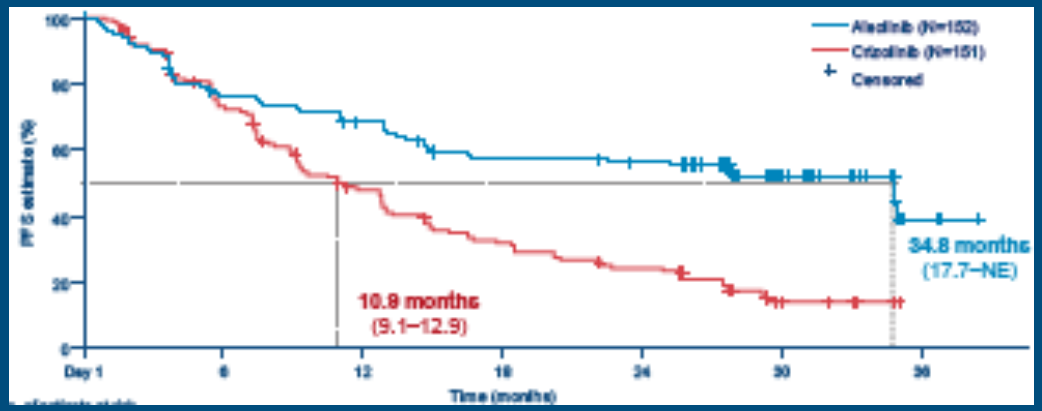
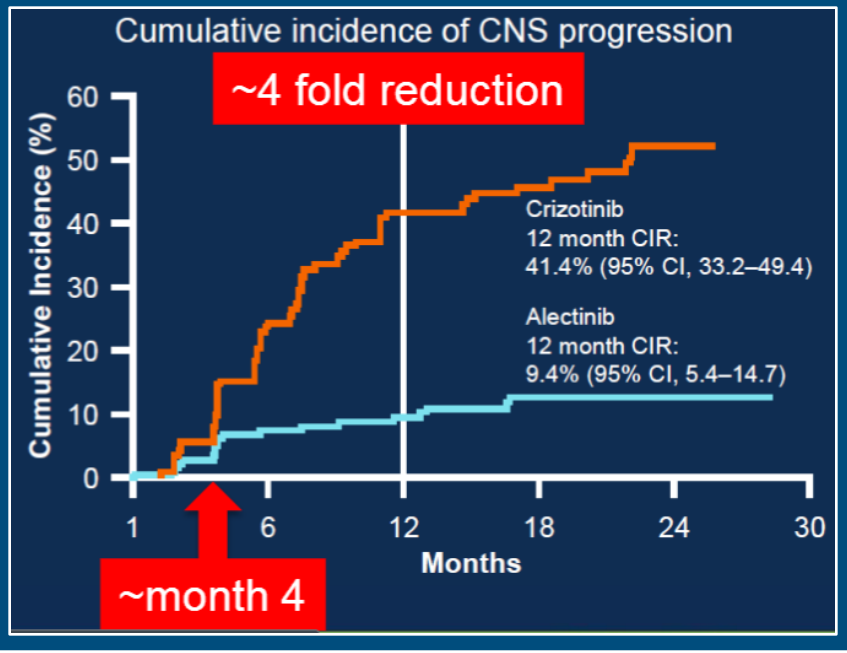
First Line ALEX Trial With Alectinib has mPFS of 35 mo and Marked Reduction in CNS Mets





Kwak, EL N Engl J Med 2010;363:1693-1703; Shaw AT Lancet Oncology 2011, 12:1004-12

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Initial Therapy for Non-Squamous NSCLC Other Mutations

ROS 1 Gene Rearrangement

- **Crizotinib-preferred***
- **Ceritinib***
- **Lorlatinib (ALK/ROS1)****
- **Entrectinib (ROS1/NTRK/ALK)****
- **Repotrectinib (ROS1/NTRK/ALK)****

BRAF V600E mutation

- Dabrafenib and trametinib*

***Approved first or later lines**

** In clinical trials

Drilon, A. Clin Cancer res. 2016. 22 (10); Lin et al WCLC Toronto 2018 OA02.02: Doebele et al WCLC Toronto 2018 OA02.01; Doebele et al WCLC Toronto 20Shaw AT. N Engl J Med. 2014 Nov 20;371(21):1963-71; Mazières J. J Clin Oncol. 2015 Mar 20;33(9):992-9; Goto K. Abstr #9022. ASCO 2016.;18 OA02.01; Ou et al WCLC Toronto 2018 OA02.03; Moro-Sibilot WCLC Toronto 2018 (AcSe trial).

Initial Therapy for Non-Squamous NSCLC Other Mutations

MET exon 14 skipped 3%

- **Crizotinib- approved**
- **Tepotinib****
- **Telisotuzumab****

RET

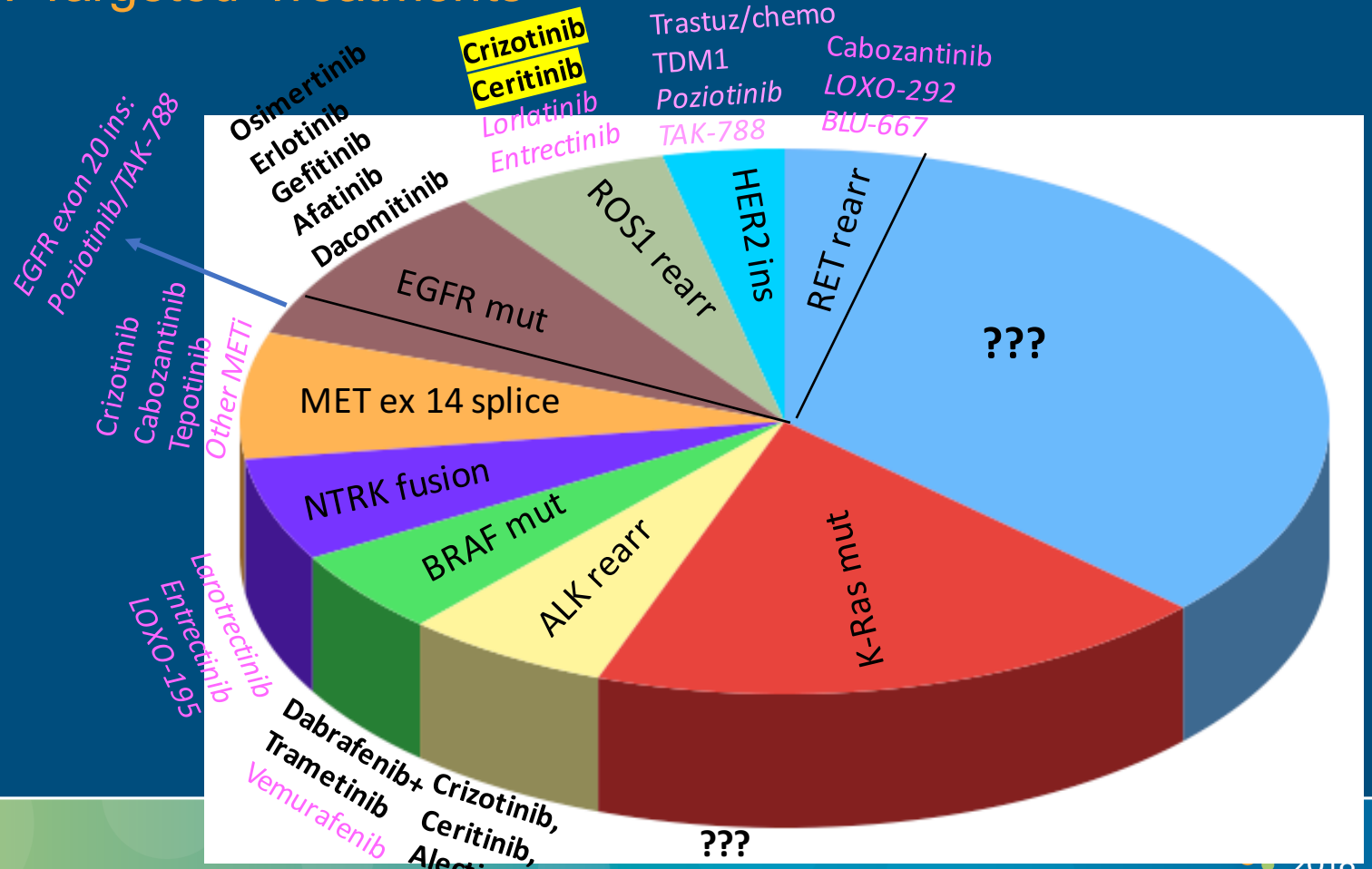
- BLU-667**
- LOXO-292**

Other Targets Include:
- HER2 (ERBB2)
- NTRK (TRK fusions)

** In clinical trials

Drilon WCLC Toronto 2018 (PROFILE1001; Felip WCLC Toronto 2018 OA12.01; Proc AACR, Chicago 14-18 April 2018; Oxnard WCLC Toronto 2018 OA12.07; Strickler JCO 2018 ; Moro-Sibilot WCLC Toronto 2018 (AcSetiral)

NSCLC: Targeted Treatments



BOLD = FDA approved

Regular = Consider off label

Italics = promising emerging therapies

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J Neal 2018

NCCN Guidelines

Adenocarcinoma	Squamous Cell Carcinoma
• Pembrolizumab (if 50%) • (Carboplatin or cisplatin) + pemetrexed + pembrolizumab • Carboplatin + paclitaxel + bevacizumab + atezolizumab • Chemo doublet +/- bevacizumab if ICPI ineligible	• Pembrolizumab • (Carboplatin or cisplatin) + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab • Chemo doublet

Second-Line Therapy

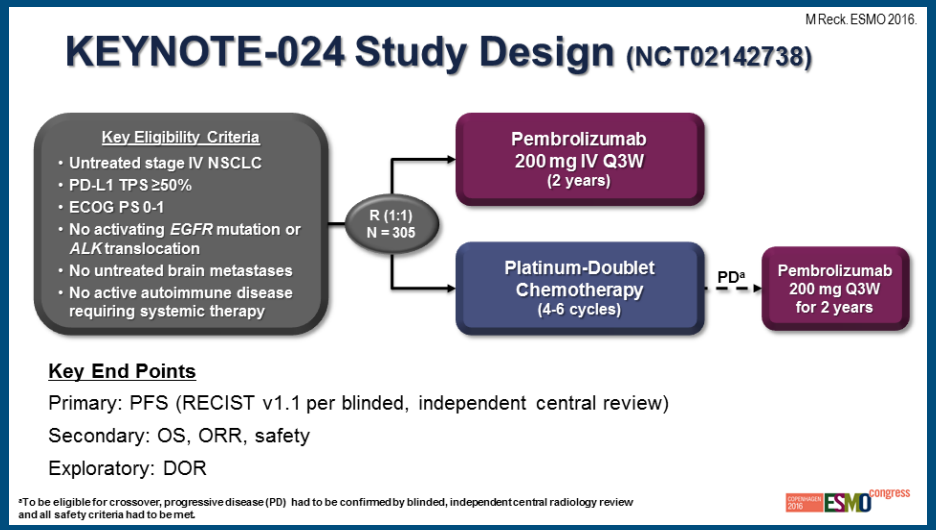
Adenocarcinoma

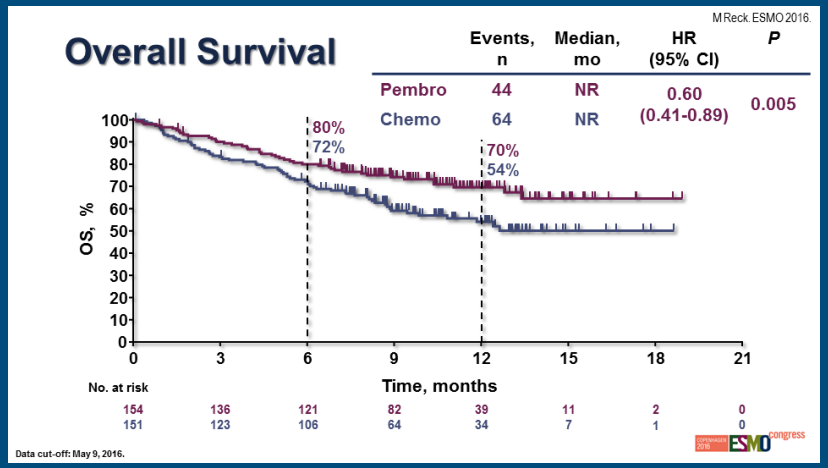
- Systemic immune checkpoint inhibitors
- Other systemic therapy
  - Docetaxel or pemetrexed or gemcitabine
  - Ramucirumab & docetaxel
  - +/- Bevacizumab

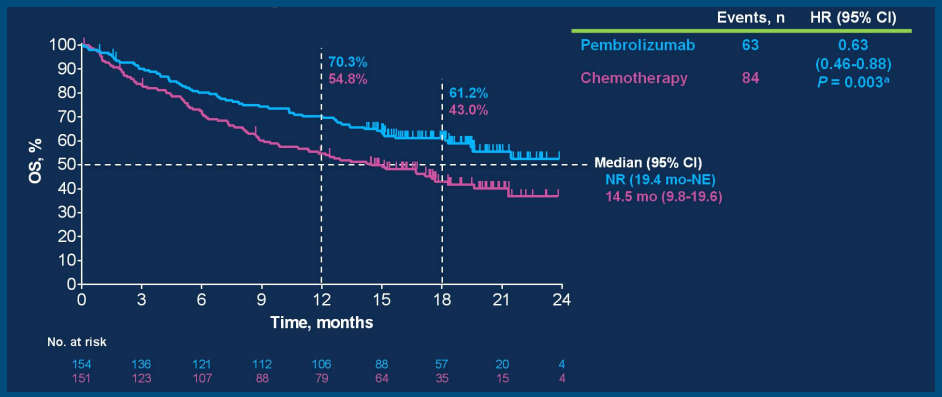
Squamous Cell

- Systemic immune checkpoint inhibitors
- Other systemic therapy
  - Docetaxel or gemcitabine
  - Ramucirumab and docetaxel

Initial Therapy for NSCLC
No Driver Mutations







M Reck ESMO 2016

Note: TPS ≥50%

Updated analysis
Brahmer, J. J Clin Oncol 35. 2017 (suppl. Abst. 9000)

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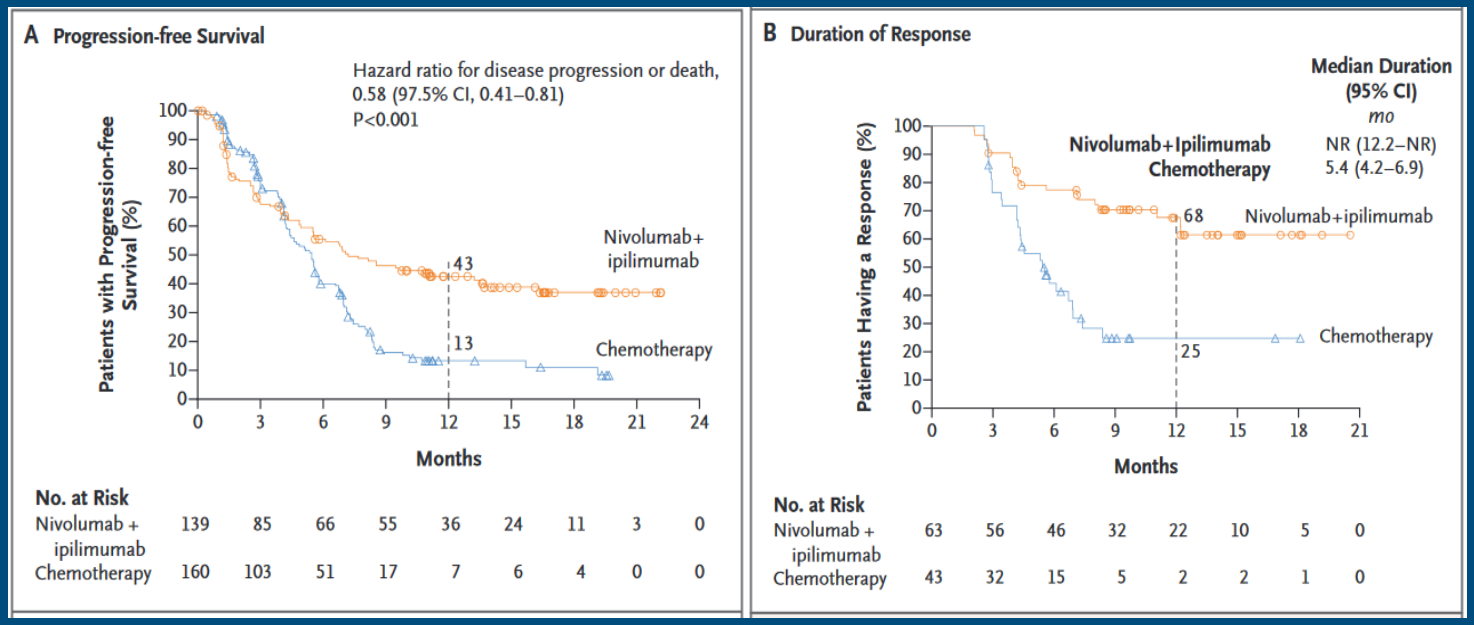
Combination Immune Checkpoint Therapy



Hellman, et al N Engl J Med 2018

Approved and Emerging Checkpoint Inhibitors

DRUG	TARGET	DOSE	INDICATIONS
Ipilimumab	Anti-CTLA-4	Met Mel: 1-3 mg/kg IV over 90 min, every 3 weeks x 4 Adj Mel: 10 mg/kg/IV every 3 weeks x 4, then 10 mg/kg every 12 weeks up to 3 years.	Melanoma: adults & pediatrics, unresectable, metastatic; adjuvant; Renal Cell-in Combo with Nivolumab
Tremelimumab	Anti-CTLA-4	Orphan Drug Destination	Mesothelioma
Nivolumab	Anti-PD-1	240 mg IV over 60 min, every 2 weeks	Melanoma, Renal Cell, **NSCLC**, Hodgkin Lymphoma, SCCH&N, Urothelial, Microsatellite Instability-high or mismatch repair deficient solid tumor, Hepatocellular
		480 mg IV over 60 min, every 4 weeks	
		Combination with ipilimumab	Melanoma; MSI-H/dMMR-CRC
Pembrolizumab	Anti-PD-1	200 mg IV over 30 min, every 3 weeks	Melanoma, **NSCLC *,** SCCH&N, Hodgkin's Lymphoma, Urothelial, Microsatellite instability or mismatch repair deficient solid tumor, Colorectal, Gastric; Thymic *Considerations for PD-L1 testing
		200 mg IV in combination with chemotherapy every 3 weeks	**NSCLC**
Atezolizumab	Anti-PD-L1	1200 mg IV over 60/30 min, every 3 weeks	**NSCLC**, Urothelial
Durvalumab	Anti-PD-L1	10 mg/kg IV over 60 min, every 2 weeks	Urothelial, **Stage III NSCLC adjuvant**
Avelumab	Anti-PD-L1	10 mg/kg IV over 60 min, every 2 weeks.	Merkel cell, Urothelial

Management of Toxicities of Targeted Therapies in NSCLC

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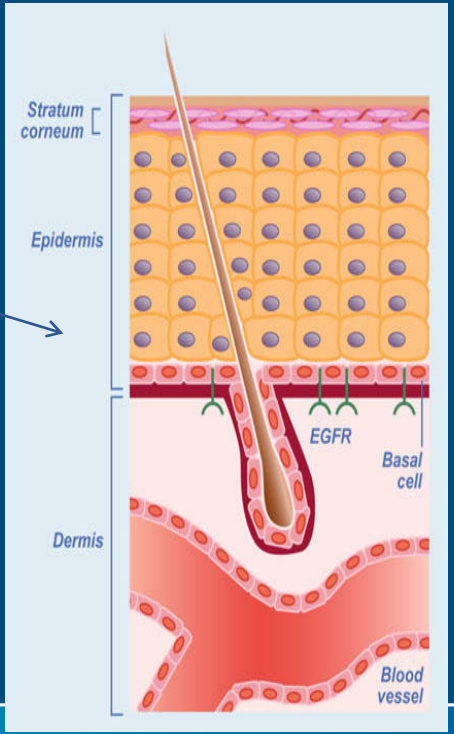
EGFR Inhibitor Rash

- Most common "toxicity" associated with EGFR inhibitors
- Tends to appear on the face and chest but can be seen on any part of the body
- Can range from mild to severe
- Often described as a "papulopustular eruption"

Why Does EGFR Inhibitor Rash Occur?

- The epidermis relies on EGF
- The keratinocytes located in the basal layers of the epidermis express elevated level of EGF
- Inhibition of EGF will result in negative effects on cell growth in this layer of the epidermis
- This results in thinning, which decreases ability of skin to hold in moisture
- The damage also causes recruitment of the immune system response and thus, a pustular eruption



Adapted from Lacouture, 2006

Incidence and Severity of Rash

Agent	All Rash Incidence	Grade 3/4 Incidence
Cetuximab	89% (70% in FLEX trial)	12% (10% in FLEX trial)
Erlotinib	First Line: 85% Second Line: 75%	First Line: 14% Second Line: 9%
Panitumumab	89%	12%
Gefitinib	First Line: 66%	First Line: 3%
Afatinib	First Line EGFR: 90% Squamous NSCLC: 70%	First Line: 16% Squamous NSCLC: 7%
Osimertinib	41%	0.5%
Dacomitinib	78%	21%

Pirker et al, 2009; Gatzemeier et al, 2008. Mok, T, et al 2009. Data from package inserts 10/21/2016; 10/2018

Meta-Analysis of EGFR Rash and Clinical Benefit

Liu and colleagues (2013) reviewed 33 studies of EGFR TKIs that reported rash and clinical benefit

- Rash was a significant predictor of clinical benefit for NSCLC patients receiving EGFR inhibitor therapy
- Rash predicted ORR, longer PFS, and longer OS

Liu HB, et al. *PLoS One*. 2013;8(1):e55128.

Strategies to Prevent Dermatologic Toxicities: Preemptive

STEPP trial in panitumumab-containing regimens in 95 metastatic colorectal patients:

- Showed significant improvement in EGFR rash and quality of life (QOL) with preemptive doxycycline and topical hydrocortisone cream
- Skin toxicities of ≥ grade 2 were reduced by more than 50% at 6 weeks in the preemptive arm

Lacouture ME, et al. *J Clin Oncol*. 2010;28:1351-1357.

Suggestions for Prevention

- Moisturizers: creams without dyes or fragrances (e.g., Eucerin, Aveeno, Sarna Ultra, Neutrogena)
  - SPF 15 or higher with zinc recommended
- Protective clothing
- Either erlotinib or afatinib, taken on an empty stomach
- Geftinib, osimertinib, dacomitinib can be taken with or without food
- Avoid very hot showers, try lukewarm water
- Generally avoid direct sunlight and extreme temperatures

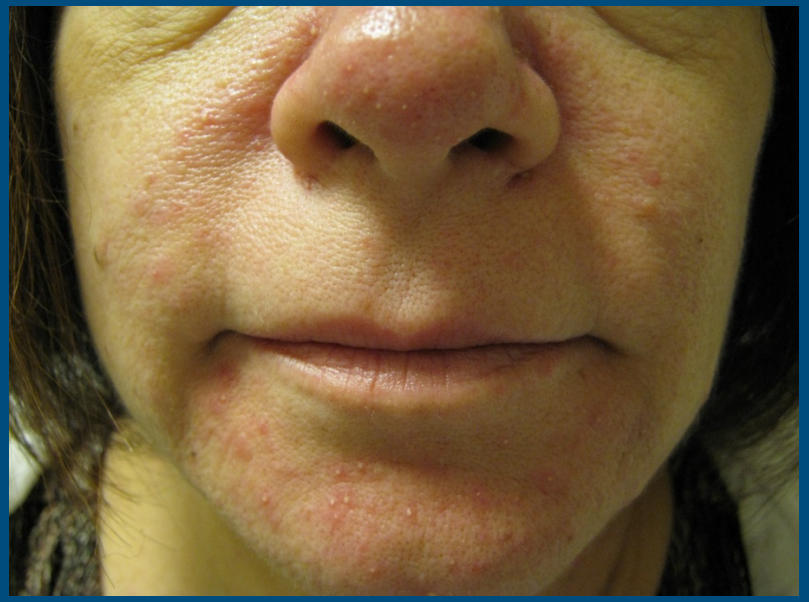
MASCC Recommendations for Treatment

	Recommended	Not Recommended	Level of Evidence	Recommendation Grade	Comments
Topical	Alclometasone 0.05% cream Fluocinonide 0.05% cream twice daily Clindamycin 1%	Vitamin K1 cream	IV	C	
Systemic	Doxycycline 100 mg twice daily Minocycline 100 mg daily Isotretinoin at low doses 20–30 mg/d	Acitretin	IV	C	Photosensitizing agents

Lacouture ME, et al. *Support Care Cancer*. 2011;19:1079-1095.

Mild to Moderate EGFRI Rash

- Patient develops grade 1 rash on chin and cheeks
- Continue erlotinib
- Prescribe topical clindamycin lotion 1%
- Encourage to moisturize
- Rash tends to be less in active smokers taking erlotinib[a]



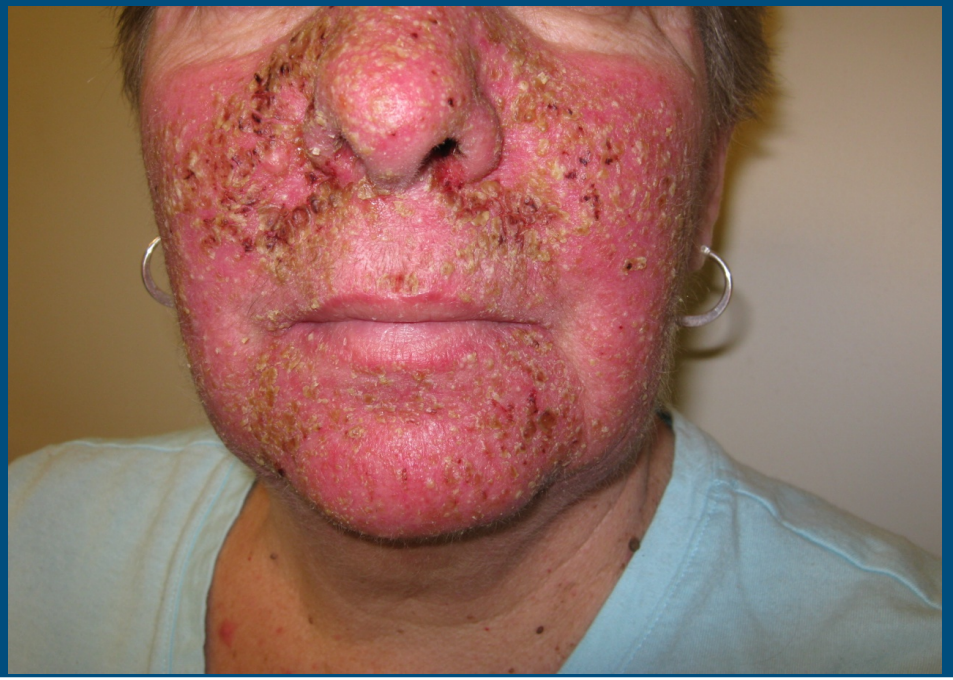
[a]Hamilton et al, 2006.

EGFR Rash Grade 3 to Grade 1 or 2

Treated with oral doxycycline and topicals

Grade 3/4 EGFR Rash

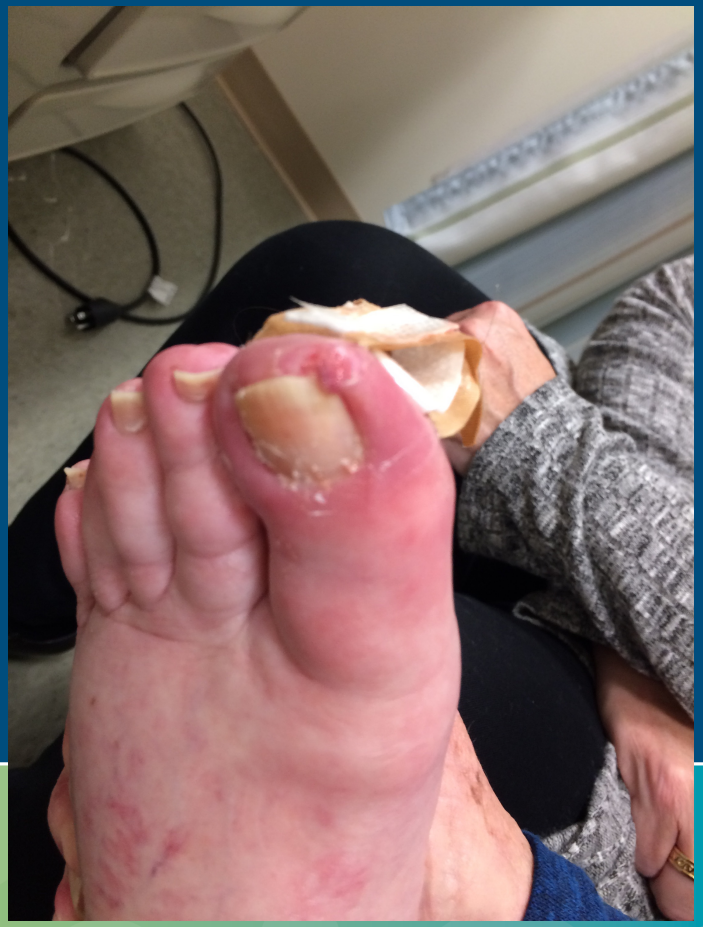
- Patient develops a grade 3 rash with significant erythema
- Recommendation is to hold afatinib and treat with oral doxycycline (100 mg bid) and topical hydrocortisone cream
- Restart agent at 30 mg
- Be sure the patient is using sunscreen

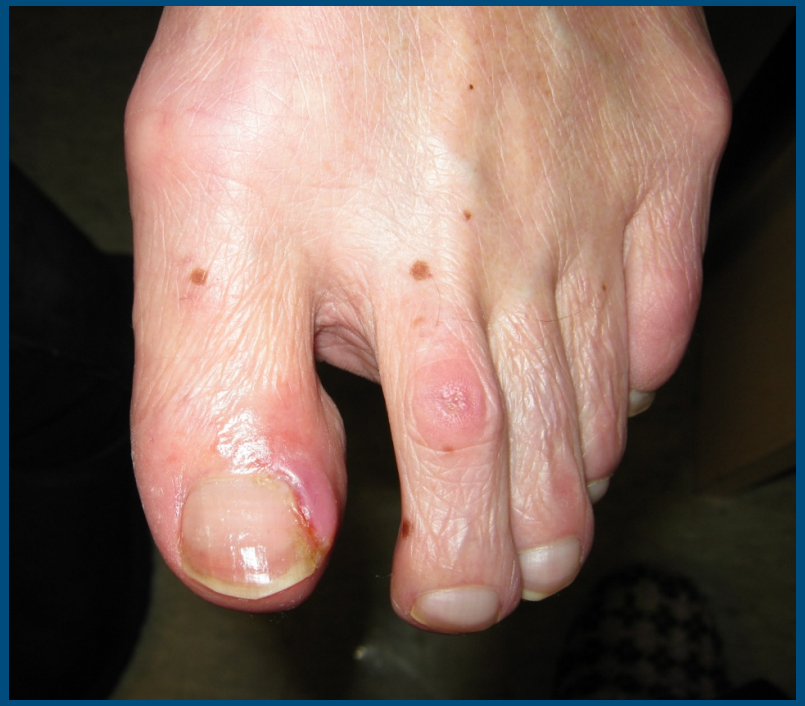


Trichomegaly

- If curling out, trim carefully
- If curling in, consult ophthalmology
- Can develop blepharitis, conjunctivitis

Paronychia With EGFRIs





Paronychia With EGFR Inhibitors

- Diluted vinegar soaks
- Mostly inflammatory but still important to culture bacterial component to guide systemic therapy
- Topical steroids or cauterization with silver nitrate sticks may be used for inflammation
- For difficult cases, consult dermatologist or podiatrist for consideration of nail avulsion

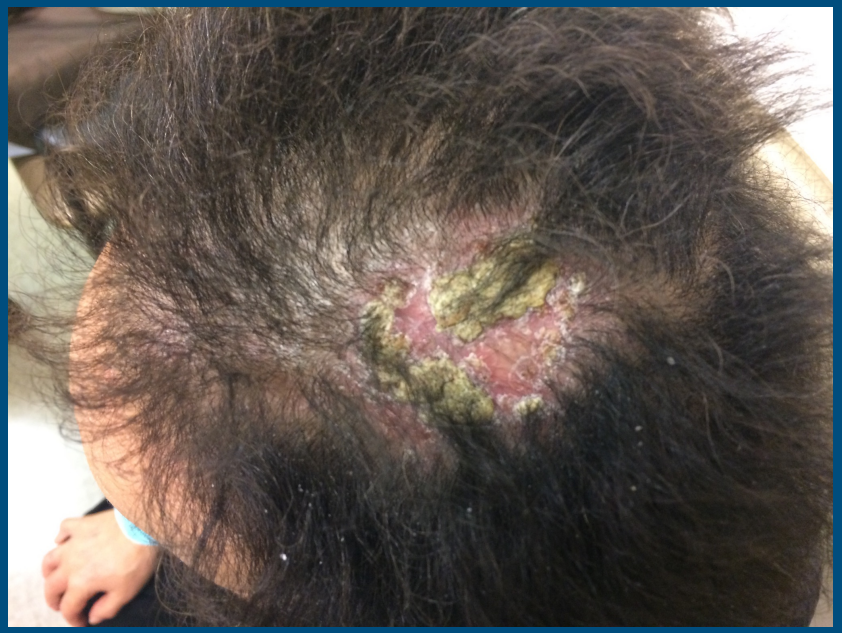
Fissures/Cracking

- Moisturize with thick cream
- Protect the areas
- Glue together with agent of choice
  - Liquid bandages
  - Superglue, etc.

Lacouture et al, 2011

EGFRI: Scalp Rash

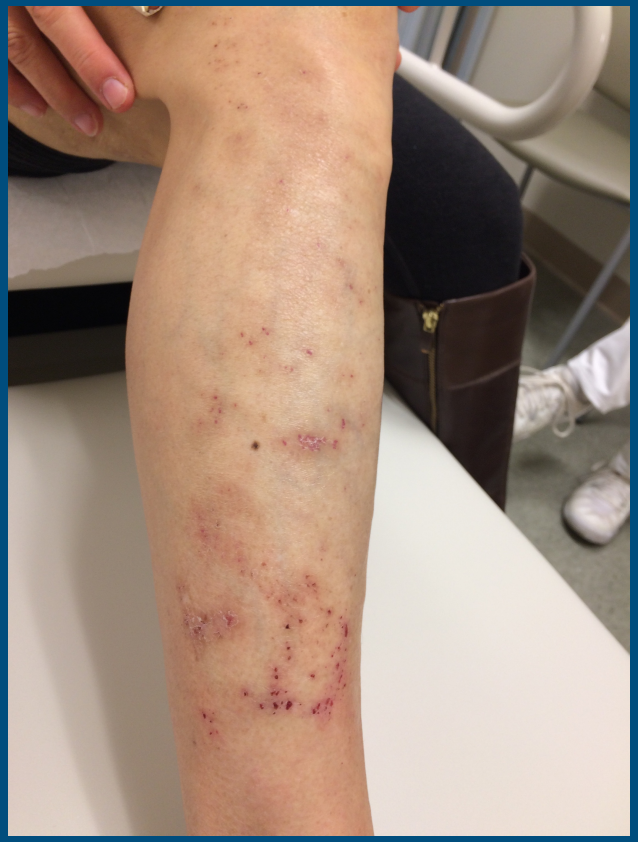
- Systemic rash management
- Selenium-based shampoos
- Fluocinonide solution/shampoo



Lacouture et al, 2011

EGFRI: Pruritus and Xerosis

- Antihistamines
  - Topical or orals
- Moisturize
- Aprepitant?
- Pregabalin?



Lacouture et al, 2011; Santiti, D. 2012; Ehrchen, J et al. 2008 *JAAD* 58(2)

Diarrhea in EGFRIs in NSCLC

Agent	All Diarrhea Incidence	Grade 3/4 Incidence
Erlotinib	First Line: 62%	First Line: 5%
Gefitinib	First Line: 29%	First Line: 3%
Afatinib	First Line EGFR: 96% Squamous NSCLC: 75%	First Line: 15% Squamous NSCLC: 10.8%
Osimertinib	58%	2.2%
Dacomitinib	86%	11%

Info taken from PIs

Management Diarrhea From EGFRIs

- Loperamide
- Diphenoxylate/atropine
- Hydration and electrolyte repletion
- Dose reductions

EGFR-I Considerations

- Side effects vary from drug to drug
- Dacomitinib: most recent approval, superiority over gefitinib first-line setting
- Osimertinib appears the least toxic
  - Better PFS in head to head study vs gefitinib/erlotinib
- Afatinib has data from post-hoc analysis:
  - 40 mg was equal to 30 mg in both pharmacokinetic data and PFS

Yang, J.C-H. et al, *Annals of Oncology*. 2016; Mok, TS, et al. *JCO* 2018; Soria JC, et al, *NEJM*. 2018

Toxicity Management of ALK/ROS1 Inhibitors in NSCLC

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Crizotinib (twice a day dosing)

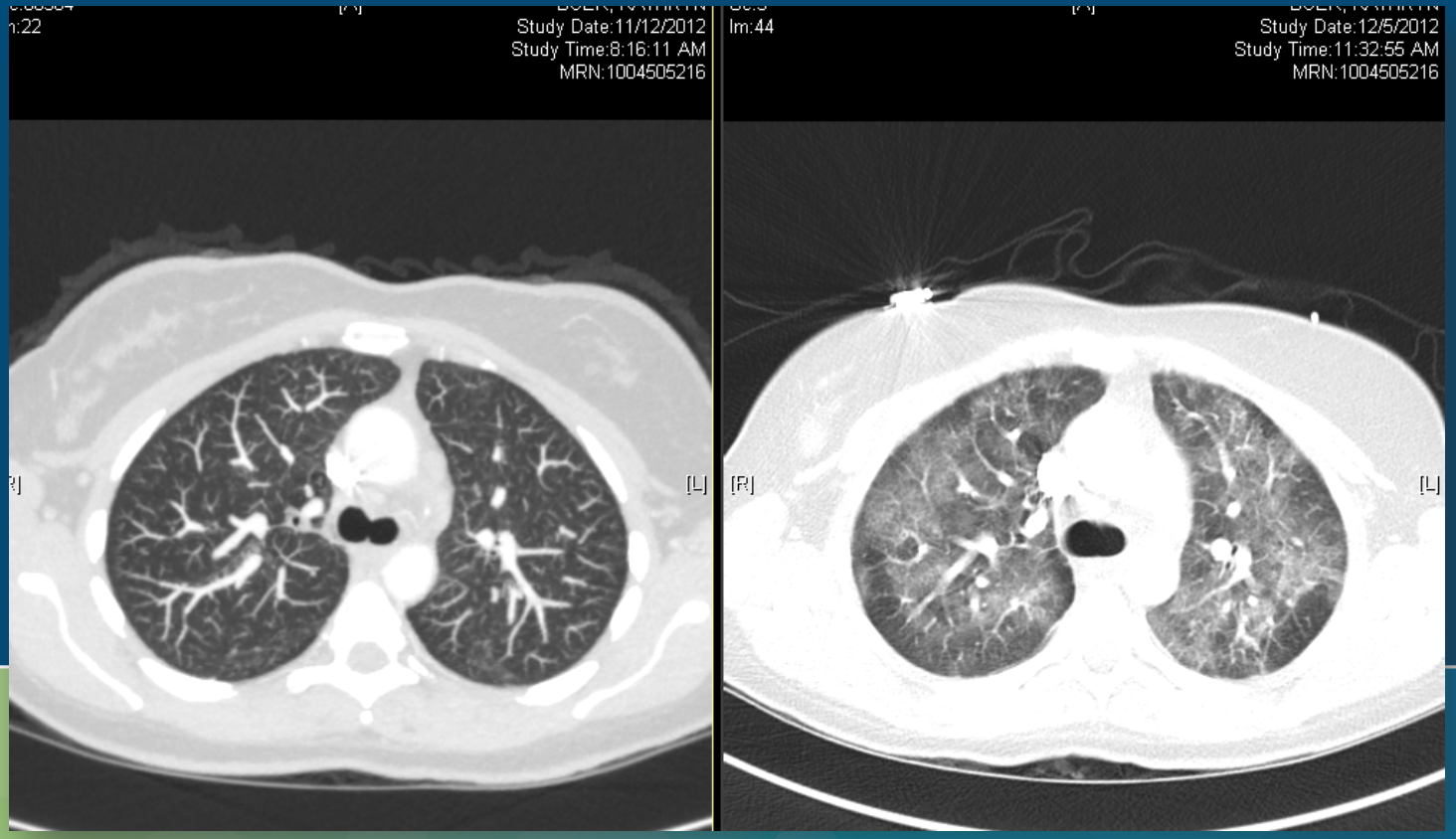
Warnings:

- Hepatoxicity
- ILD/pneumonitis (2.9%)
- QT prolongation
- Bradycardia
- Severe vision loss (0.2%)
- Embryo-fetal toxicity

Common Toxicities:

- Visual changes 71%
  - Light and dark accommodation
  - Recommend no driving at night in beginning
- Vomiting 46%
- Diarrhea 61%
- Edema 49%

Case of Pneumonitis 2 weeks after starting crizotinib for ALK + NSCLC



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Ceritinib 750 mg daily (initially), now 450 mg daily (150-mg capsules)

Warnings:

- Severe/persistent GI toxicity
- Hepatotoxicity
- ILD (4%)
- QT interval prolongation
- Hyperglycemia
- Bradycardia
- Pancreatitis
- Embryofetal toxicity

Common Adverse Events:

- Diarrhea 86%, 6% grade 3/4
- Nausea 80%
- Vomiting 60%
- Fatigue 52%

*Data to support 450mg daily with food similar PK as 750mg on empty stomach with less GI toxicity.

*Cho BC, et al. J Thorac Oncol;2017

Alectinib 600 mg daily (150-mg capsules)

Warnings:

- Hepatotoxicity
- ILD: 0.4%
- Bradycardia
- Severe myalgia/Elevated CPK
- Embryo-fetal toxicity

Common Adverse Events:

- Fatigue 41%
- Constipation 34%
- Edema 30%
- Myalgia 29% (1-4% severe)
  - Check CPK's

Brigatinib: 180 mg daily

Warnings

- ILD 9.1%, this is why there is a run-in of 90mg for 7 days, then 180mg daily
- HTN
- Bradycardia
- Visual disturbance: not the same as crizotinib
- CPK elevation, pancreatic enzyme elevation, hyperglyemia
- Embryo-Fetal toxicity

Common Adverse Events

- Nausea/Diarrhea
  - Grade 3/4 0.9%, 0%
- Fatigue
- Cough
- Headache

ALK Conclusions

- Alectinib superior to crizotinib in first-line setting
- Toxicities significant vary from drug to drug

Toxicity Management of BRAF Inhibitors in NSCLC

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BRAF Inhibitors: Dabrafenib + Trametinib

- Very rare V600E + NSCLC, 1% or less
- 3.2% of patients developed cutaneous squamous cell ca in the first month of being on drug (higher risk when giving dabrafenib alone, 11%)
- 1.1% of patients developed non-cutaneous malignancies, thought to be due to RAS activation

- Pyrexia/Fever- 55% (5% grade 3)
  - Grade 2 102.3-104.0
  - If 104 or complicated fever, hold and dose reduce
- Hemorrhage: 2.2%
- Cardiomyopathy: ECHO at baseline recommended
- Uveitis, hyperglycemia, embryo-fetal, G6P deficiency
- Rash: Severe only 0.7%
- GI: Nausea/vomiting

Other Toxicities of Targeted Agents

Toxicity	Agents	Considerations
Diarrhea	EGFRIs & ALKIs	Loperamide; diphenoxylate/atropine; hydration and electrolyte replacement; dose reduction
ILD/Pneumonitis	EGFRI's, ALKI's	CTA; Consider discontinuation
Cardiotoxicity (cardiomyopathy, QT prolongation, bradycardia)	EGFRI (osimertinib); ALKIs, BRAFI	ECHO; Consider dose reduction
Hepatoxicities	EGFRI's, ALKI's	Monitor LFTs; Consider dose reduce
Visual Changes	ALKI's; BRAFI	Recommend no driving at night
Edema	Crizotinib, alectinib	May need diuretics
Hyperglycemia	Ceritinib; BRAFI	Monitor blood glucose levels regularly
Myalgias	ALKIs	Monitor CPK
Pyrexia/Fever	BRAFI's	Temp > 104, hold and dose reduce

Conclusions

- Several targeted therapies approved in NSCLC
- Different toxicity profiles
- More to come!
- Most toxicities can be predicted and manageable

Management of Toxicities of Immune Checkpoint Inhibitors

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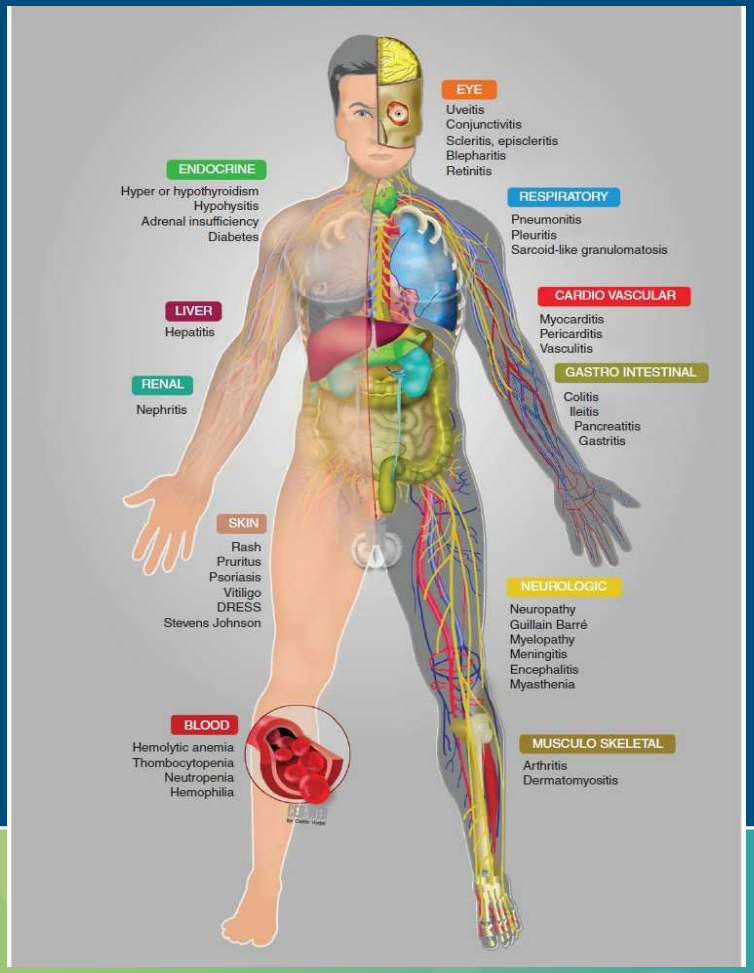
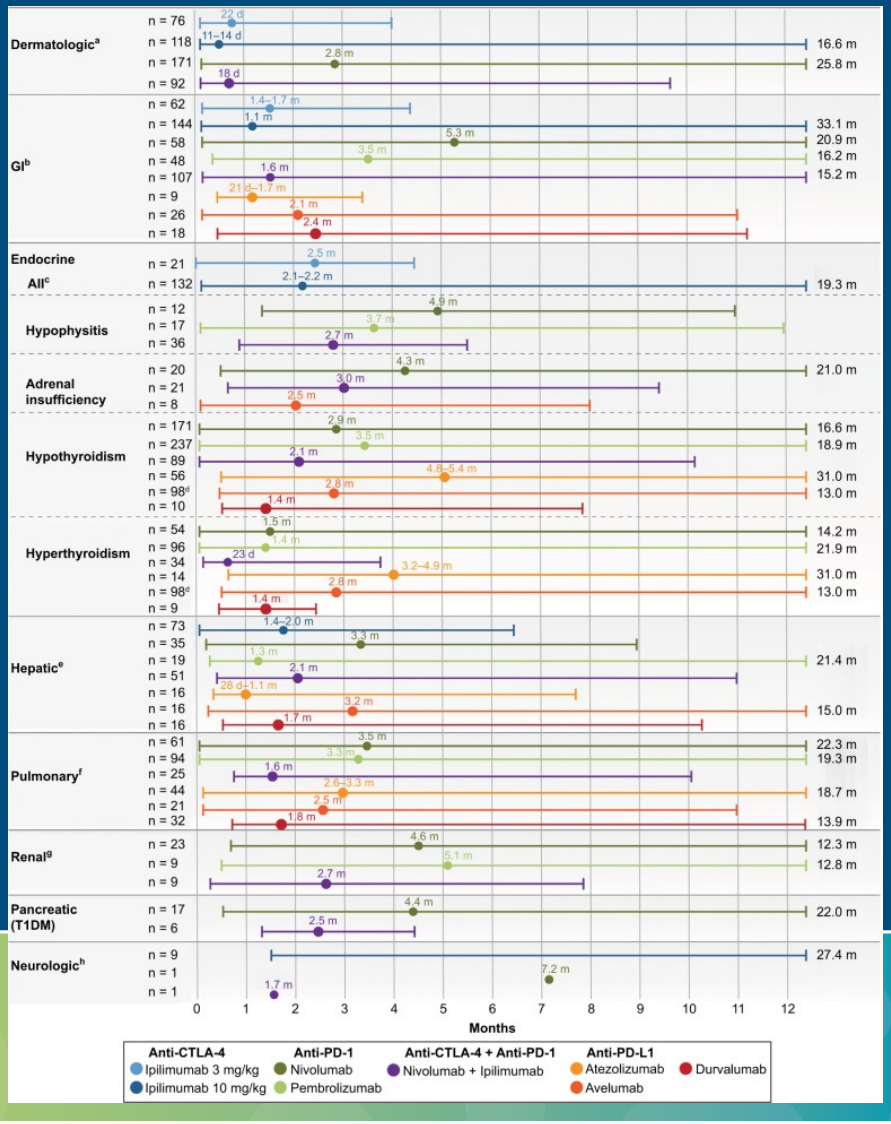
Immune-Related Adverse Events (IRAEs)



- Immune checkpoint inhibitors promote T-cell activity
- Activation of the immune system cannot be confined to antitumor effects
- Amplification of immune system can lead to unrestrained T-cells attack on healthy tissue: “auto-immunity”
- Rule out all causes of adverse events;
  - If no other cause, assume irAE
- Immune related adverse events (IrAEs)
  - Inflammation (-”itis” or “-opathy”)



Patterns of IRAEs

- Onset
  - Median onset is 5-12 weeks after initiation
    - Within days of first dose
    - After months of treatment
    - After discontinuation of therapy
- Organs affected
  - May affect one or many organs
  - Concurrently or sequentially
- Severity
  - Incidence/severity higher in anti-CTLA-4 agents
  - High grade AE to one class does not preclude safe administration to another class
- Dose & combination
  - Suggested dose dependency
  - Cumulative effect with anti-CTLA-4 agents
  - Not evident with anti-PD-1/PD-L1 agents
  - Increased in combination with other ICPI, targeted agents, chemotherapy and radiation therapy

Davies, M. & Duffield, E. (2017). Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *ImmunoTargets and Therapy*. 6:51-71

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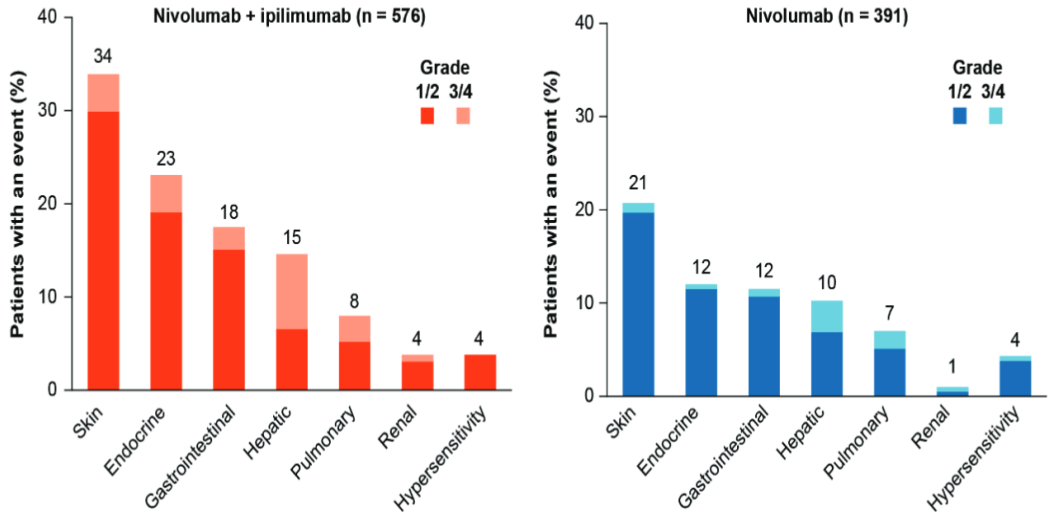
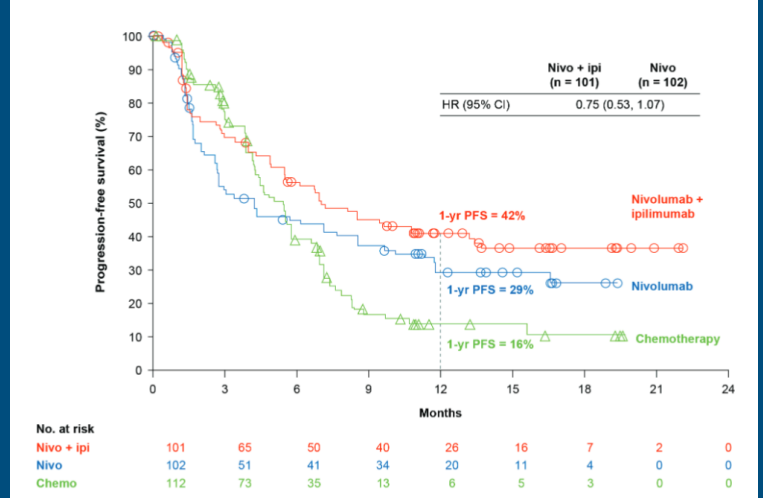
Figure S7. Treatment-Related Select Adverse Events[a] by Category With Nivolumab Plus Ipilimumab



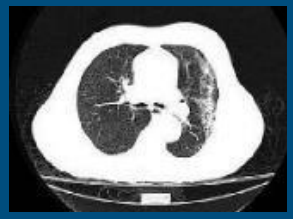
[a]Select adverse events are those with potential immunologic etiology that require frequent monitoring/intervention

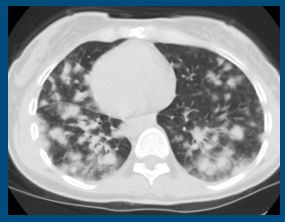
Figure S6. Progression-free Survival With Nivolumab Plus Ipilimumab Versus Nivolumab Monotherapy and Chemotherapy[a] in Patients With TMB ≥10 Mutations/Mb and ≥1% Tumor PD-L1 Expression



[a]HR (95% CI) = 0.62 (0.44, 0.88) for nivolumab + ipilimumab versus chemotherapy

Pulmonary: Pneumonitis





Prevent-Anticipate-Evaluate	Detect-Monitor-Grade	Treatment-Management
Prevent: smoking cessation, vaccinations	Physical Exam: Respiratory rate, heart rate, oxygen saturation at rest & walk	Grade 1: <25% of lung on CT; Asymptomatic; Continue Tx; Close imaging
Risk: prior chest irradiation, COPD		
Presentation: Dyspnea, shortness of breath at rest, dry cough, wheezing, tachypnea, tachycardia, chest pain, hypoxia, Increased oxygen requirements	Diagnostic Imaging: Computerized tomography scan • Interstitial fibrosis • Alveolar infiltrates • Diffuse ground glass opacities • Lobular nodularity with air trapping Pulmonary Function Tests Arterial Blood Gases (if hypoxic)	Grade 2: 25-50%; HOLD ICPI; infectious w/u; Consider empiric antibiotics; Methylprednisolone/prednisone 1-2 mg/kg/day; if no improvement in 48-72 hours, treat at grade 3
	Laboratory: infectious work up (nasal swab for viral pathogens; sputum culture; blood cultures)	Grade 3-4: > 50%; Permanent discontinue ICPI; Infectious w/u; Pulmonary & infectious disease consult; methylprednisolone 1-2 mg/kg/day; if no improvement in 48-72 hours, escalate
R/O: pulmonary embolism, pleural effusion, pneumonia, disease progression, resp. failure	Other: Pulmonary & infectious disease consult; consider bronchoscopy with bronchoalveolar lavage	Refractory: Inflicimab 5 mg/kg IV, second dose in 14 days if needed; Mycophenolate mofetil 1-1.5 g BID, then taper; IVIG 0.4 g/kg/day x 5 days

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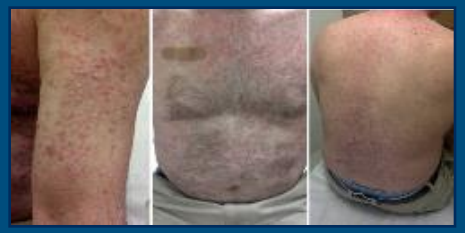
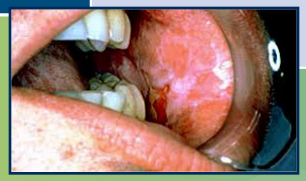
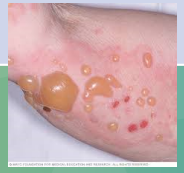
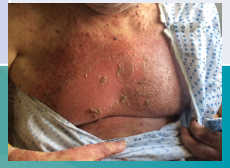
Dermatologic Toxicities

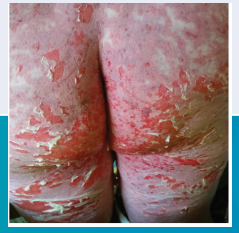


Prevent-Anticipate-Evaluate	Detect-Monitor-Grade	Treatment-Management
Prevent: Sun screen, moisturizer, sunglasses	Physical Exam: dry flaky skin, blisters, eosinophilic infiltrates, lichenoid deposits, vitiligo, alopecia; Assess mucous membranes	Grade 1: <10% BSA with no symptoms; Continue ICPI; Moderate potency topical steroids, oral antihistamines
Risk: Psoriasis, eczema		
Presentation: pruritic, urticaria, maculopapular rash, peeling of skin, blisters, toxic epidermal necrolysis, Steven Johnson Syndrome,	Diagnostic Imaging: no standard	Grade 2: Moderate: 10-30% BSA; Consider holding ICPI; High potency topical steroids +/or prednisone 0.5-1.0 mg/kg/day;
	Laboratory:	Grade 3-4: :>30% BSA; Hold ICPI; High potency topical steroids; Prednisone 0.5-1.0 mg/kg/day (increase dose if no improvement); Urgent dermatology
R/O: cellulitis, contact dermatitis, allergies, sun exposure, radiation recall, other drug reaction, psoriasis/eczema flare	Other: Dermatology consult, consider biopsy	Other: Topical emollients; Urgent Dermatology and Permanent discontinuation of ICPI with bullous, SJS, TEN









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Gastrointestinal Toxicities: Diarrhea, Colitis

Prevent-Anticipate-Evaluate	Detect-Monitor-Grade	Treatment-Management
Prevent: Dietary modification; hydration	Physical Exam: Abdominal exam;	Grade 1: < 4 stools over base; Consider holding ICPI; loperamide; hydration
Risk:: irritable bowel disease; Crohn's		
Presentation: Abdominal cramps, spasm, increased stool frequency, volume, blood or mucous in bowel	Diagnostic Imaging: Abdominal CT with contrast;	Grade 2: Moderate; Hold ICPI; IV methylprednisolone (1 mg/kg/day); if no response in 2-3 days, increase to 2 mg/kg/day; consider infliximab;
	Laboratory: Stool: culture, C.difficile, Ova & parasite; consider lactoferrin/calprotectin	Grade 3: Hold ICPI, consider resuming if resolution of toxicity. Grade 4:Permanent discontinuation; Consider inpatient care; Both: IV methylprednisolone 2 mg/kg/day; if no response in 2 days, consider infliximab; if refractory-consider vedolizumab
R/O: infectious etiology or underlying autoimmune process	Other: GI consultation: may need colonoscopy +/- endoscopy (EGD) with biopsy	Supportive care, hydration

Endocrine Toxicities: Thyroid

<table>
<tr><th>Anticipate</th><th>Detect-Monitor</th><th colspan="3">Treatment-Management</th></tr>
<tr><td rowspan="4">Presentation: fatigue, sluggishness, anorexia, weight loss/gain, irritability, palpitations</td><td rowspan="2">Physical Exam: heart rate,</td><td rowspan="3">Asymptomatic Hypothyroid subclinical</td><td>TSH 4 to < 10; Patient asymptomatic; Normal T4</td><td>Continue ICPI; Monitor TFTS</td></tr>
<tr><td rowspan="3">Diagnostic Imaging: rarely thyroid ultrasound to r/o other cause</td><td>TSH >10; Normal Free T4</td><td>Continue ICPI; Consider levothyroxine 1.6 mcgt/kg/day</td></tr>
<tr><td>Normal or low TSH; low free T4</td><td>Consider Central Hypothyroidism</td></tr>
<tr><td>Primary Hypothyroid</td><td colspan="2">Continue ICPI; Consider endocrine consult; Thyroid hormone replacement; Exclude adrenal insufficiency (AM cortisol level)</td></tr>
<tr><td rowspan="2">R/O: Other endocrinopathies; underlying disease progression</td><td>Laboratory: TSH, free T4; every 4 to 6 weeks;</td><td rowspan="2">Central Hypothyroid</td><td rowspan="2">Evaluate ACTH, cortisol (AM), FSH, LH, TSH, free T4; Estradiol-women; Testosterone-men; Consider MRI brain-pituitary</td><td rowspan="2">Continue ICPI
Treat at hypophysitis</td></tr>
<tr><td>Other: Endocrinology Consult</td></tr>
</table>

Endocrine Toxicities: Adrenal and Pituitary

Anticipate	Detect-Monitor	Treatment-Management		
Presentation: fatigue, headache, irritability, visual disturbances.	Physical Exam: Neurologic; Cardiac focused	Primary Adrenal Insufficiency	Continue ICPI; Consider endocrine consult; Thyroid hormone replacement; Exclude adrenal insufficiency (AM cortisol level)	HOLD ICPI *Start corticosteroid before other hormone replacement to avoid adrenal crisis; Hydrocortisone 20/10 or prednisone 7.5 to 10 am and 5 mg pm AND Fludrocortisone 0.1 mg QOD and titrate Supportive care
	Diagnostic Imaging: MRI of the brain with pituitary/sellar cuts			
R/O: Other endocrinopathies; underlying disease progression	Laboratory: TSH, free T4; every 4 to 6 weeks; ACTH, FSH; Morning Cortisol, cosyntropin stimulation test < 3 µg/dL			
	Other: Endocrinology Consult	Hypophysitis	Evaluate ACTH, cortisol (AM), FSH, LH, TSH, free T4; Estradiol-women; Testosterone-men;	HOLD ICPI until symptoms resolve; methylprednisolone 1-2 mg/kg/day; Hormone replacement as indicated; patient education for stress doses of hydrocortisone

Presentation and Management of IRAEs

System	Signs & Symptoms	Evaluation	Additional Management
Hepatic	Nausea, vague abdominal discomfort, RUQ pain, dehydration, jaundice, bleeding, bruising, dark skin, drowsiness.	Liver enzymes (AST, ALT, ALK, total and direct bilirubin; Liver ultrasound, GI consult r/o viral syndrome	Hold hepatotoxic drugs Mycophenolate 2 mg/kg/d, if refractory NO Infliximab
Renal, Nephritis	Elevated serum creatinine, vague nausea, emesis; Decreased urine output; Blood in urine, Ankle swelling	Serum creatinine, urinalysis; Nephrology consult; Renal ultrasound; Biopsy	Limit nephrotoxic drugs, ABX, NSAIDS, contrast dye; Identify high risk patients (CRF); Hydration
Cardiac	Chest pain, SOB, tachycardia, arrhythmias, VTE, fluid retention, pericarditis, myocarditis, effusion, vasculitis	EKG, echocardiogram, CXR, Cardiology Consult	Blood pressure support Heart rate regulation
Neurologic	Unusual weakness, numbness, Peripheral neuropathy, autonomic neuropathy, alt. gait, Memory difficulties, Seizures, aseptic meningitis, Myasthenia Gravis, Guillain Barre; Encephalitis, transverse myelitis	Neurology consult MRI of brain to r/o CVA, brain met MRI spine; LP Rule out infection	Permanent discontinuation; rehab services; IVIG
Ocular	Dry scratchy eyes, vision changes, redness, inflammation, pain. Iritis, Uveitis, Blepharitis, episcleritis, conjunctivitis	Rule out infection, Ophthalmology consult	Lubricating eyedrops Topical corticosteroid eyedrops Decrease local irritants; contact lens, eye makeup
Musculo-skeletal	Inflammatory arthritis, myositis, polymyalgia-like syndrome,	Rheumatologic tests-autoimmune panel (ANA, RF, anti-CCP, ESR,CK, CRP), imaging, EMG	NSAIDS, corticosteroid joint injections, DMARD, methotrexate; PT/OT
Hematologic	Autoimmune hemolytic anemia, acquired TTP, hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia, acquired hemophilia		

Immune related adverse event list is not all inclusive

Refractory IRAEs

- If no improvement or progression, additional immunosuppressant treatment may be needed
  - Infliximab 5 mg/kg, TNF inhibitor (except if contraindicated)
    - Risk of HBV/HCV & TB reactivation
    - Avoid in hepatitis
  - Mycophenolate mofetil 1 g twice daily
  - Cyclosporine
  - Intravenous immunoglobulin (IVIG)
  - Tacrolimus

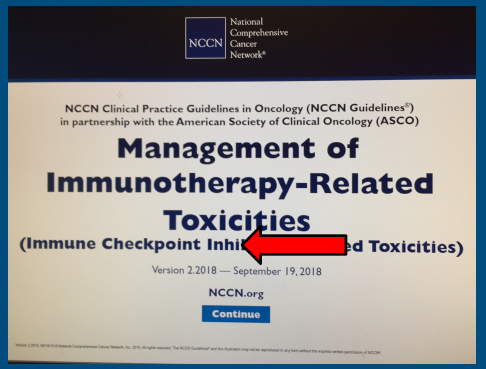
Guiding Principles of Immunosuppression for IrAEs

- Corticosteroids are the mainstay treatment
- Use of corticosteroids has NOT been shown to reduce anti-tumor efficacy
- Longer steroid tapers > 4 weeks may be necessary
- Prophylaxis against *Pneumocystis jiroveci* pneumonia (PJP) +/- fungal infections (e.g., fluconazole) can be considered if prednisone >20 or more for more than 4 weeks
- Proton pump inhibitor or H2 blockers for gastritis
- Long term use: prevention of osteoporosis

- Anti-TNFα agents (e.g., infliximab) are effective
  - Risk of hepatitis B reactivation
  - Risk of TB activation
  - Used if severe IrAEs not responsive to corticosteroids
- Patients with pre-existing autoimmune conditions or organ transplant may be at high risk for development of IrAEs

Resources

- **AIM with Immunotherapy**
- National Comprehensive Cancer Network (NCCN) Teaching/monitoring tool
  - https://www.nccn.org/immunotherapy-tool/pdf/NCCN_Immunotherapy_Teaching_Monitoring_Tool.pdf
- **Society for Immunotherapy in Cancer (SITC)**
- Association of Community Cancer Centers (ACCC)
- American Society of Clinical Oncologists (ASCO)
- Oncology Nursing Society



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THANK YOU

QUESTIONS?

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