First-Line Therapy for Metastatic Non–Small Cell Lung Cancer

State-of-the-Art Targeted Therapy and Immunotherapy Approaches

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Welcome and Introductions

Disclosures

Joshua Bauml, MD

- Research/Grant Support:
  - Merck, Incyte, Carevive Systems, Novartis, Bayer, Janssen, Astra Zeneca, Takeda, Amgen
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Christina Knepley, CRNP

- Nothing to disclose

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Product Disclosure

This activity may include discussion of agents that have not yet been approved by the U.S. Food and Drug Administration and investigational uses of approved products. Please consult prescribing information and practice guidelines for detail regarding safe and effective use of therapeutic agents.

Learning Objectives

At the conclusion of this continuing education activity, the oncology advanced practice provider will be better able to:

1. Use biomarkers to guide selection of first-line therapy for metastatic non–small cell lung cancer (mNSCLC)
2. Evaluate clinical data supporting first-line treatment of mNSCLC with targeted and immune checkpoint inhibitor (ICI) therapy
3. Devise first-line treatment plans for patients with mNSCLC in accordance with guidelines and best practices
4. Effectively manage adverse events associated with targeted and ICI therapy

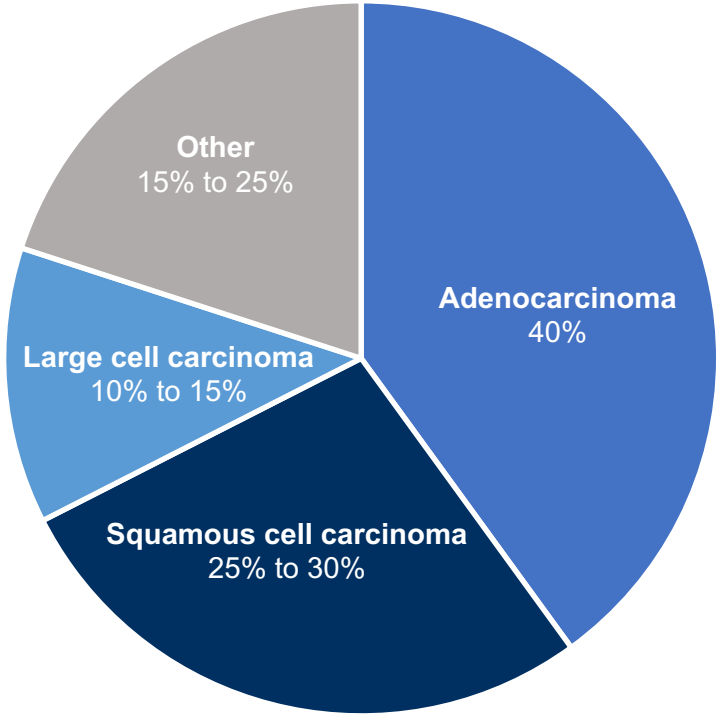
Epidemiology, Burden of Disease, and Unmet Needs

Histology

There are 2 main types of lung cancer:

- NSCLC (80% to 85%)
- Small cell lung cancer (10% to 15%)

NSCLC Subtypes

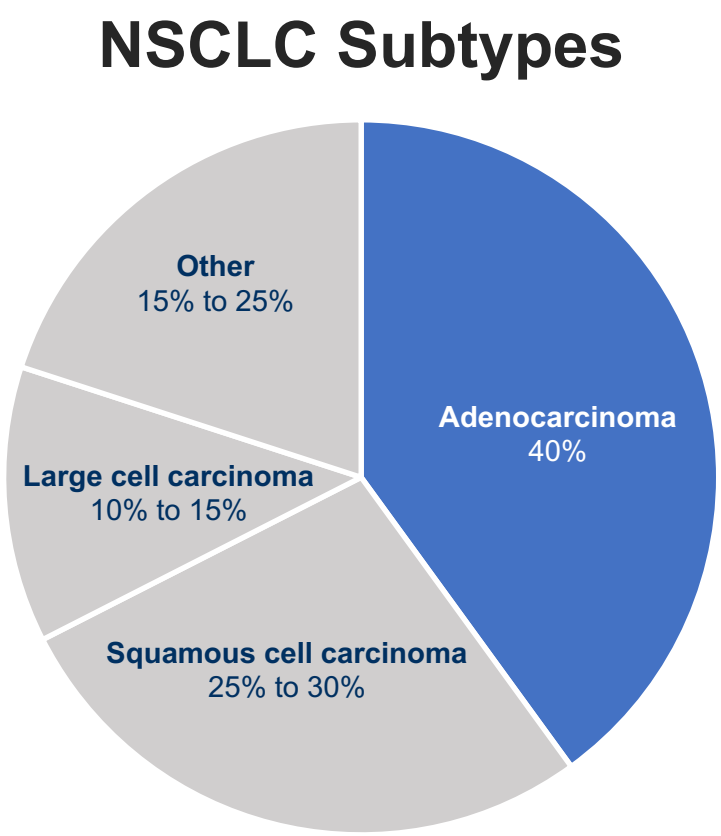


Reference: American Cancer Society. https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html. Updated May 16, 2016. Accessed September 16, 2019.

Histology: Adenocarcinoma

Adenocarcinoma

- Most common in current or former smokers, but also most common type of lung cancer in nonsmokers
- More common in women than men
- More likely to occur in younger people than other types of lung cancer
- Typically found in the outer parts of the lung
- May grow slower than other types of lung cancer and is more likely to be found before metastasis



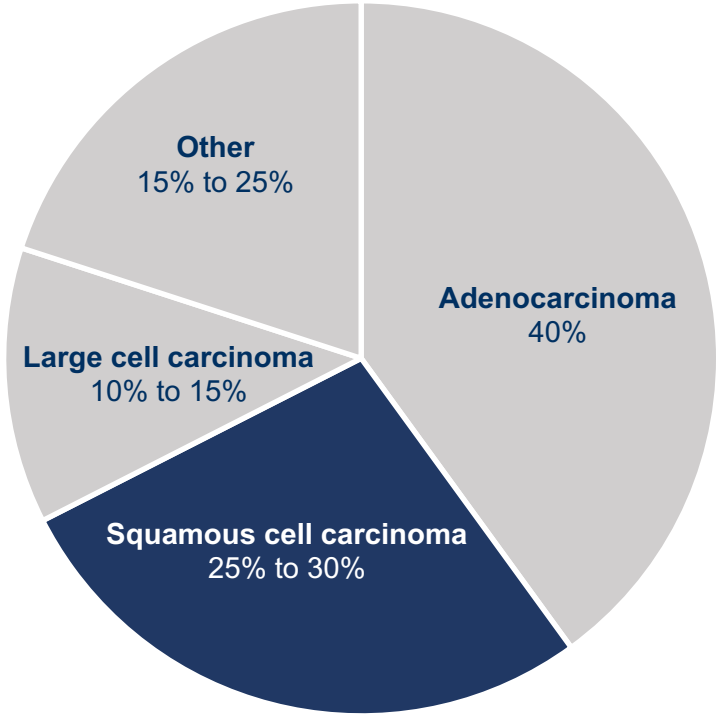
Reference: American Cancer Society. https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html. Updated May 16, 2016. Accessed September 16, 2019.

Histology: Squamous Cell Carcinoma

Squamous Cell Carcinoma

- Start in early versions of squamous cells (flat cells that line the inside of the airways in the lungs)
- Linked to history of smoking
- Often found in the central part of the lungs near the bronchi

NSCLC Subtypes



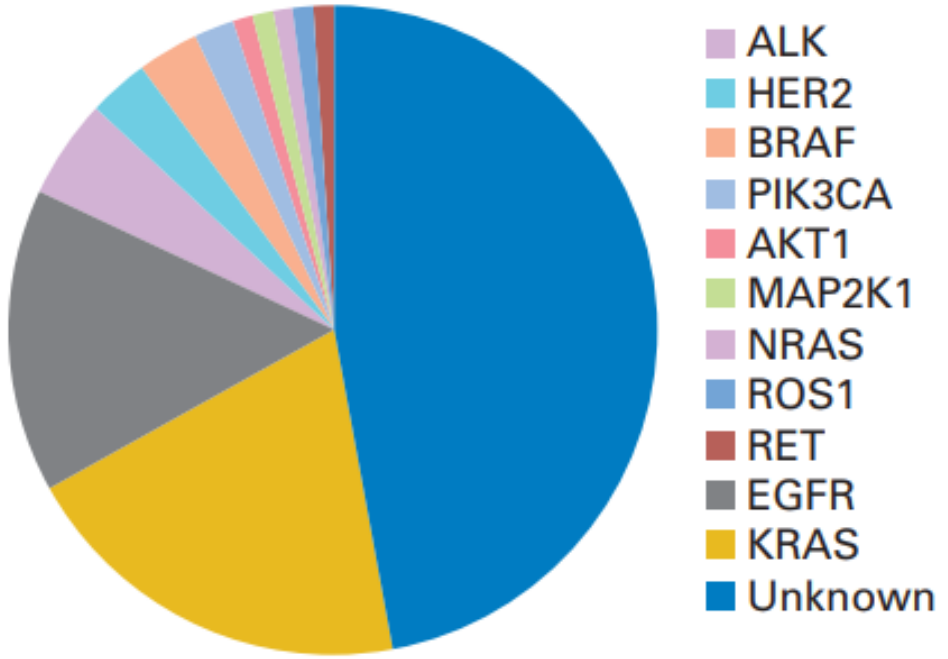
Reference: American Cancer Society. https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html. Updated May 16, 2016. Accessed September 16, 2019.

Biomarkers in NSCLC: Adenocarcinoma

National Comprehensive Cancer Network (NCCN) guidelines recommend molecular testing for the following biomarkers in advanced or metastatic adenocarcinoma, large cell carcinoma, or NSCLC not otherwise specified (NOS):[1]

- EGFR mutation testing (category 1)
- ALK testing (category 1)
- ROS1 testing (category 2A)
- BRAF testing (category 2A)
- PD-L1 testing (category 1)
- Broad molecular profiling to identify rare oncogenic drivers for which targeted therapies are available

Adenocarcinoma[2]



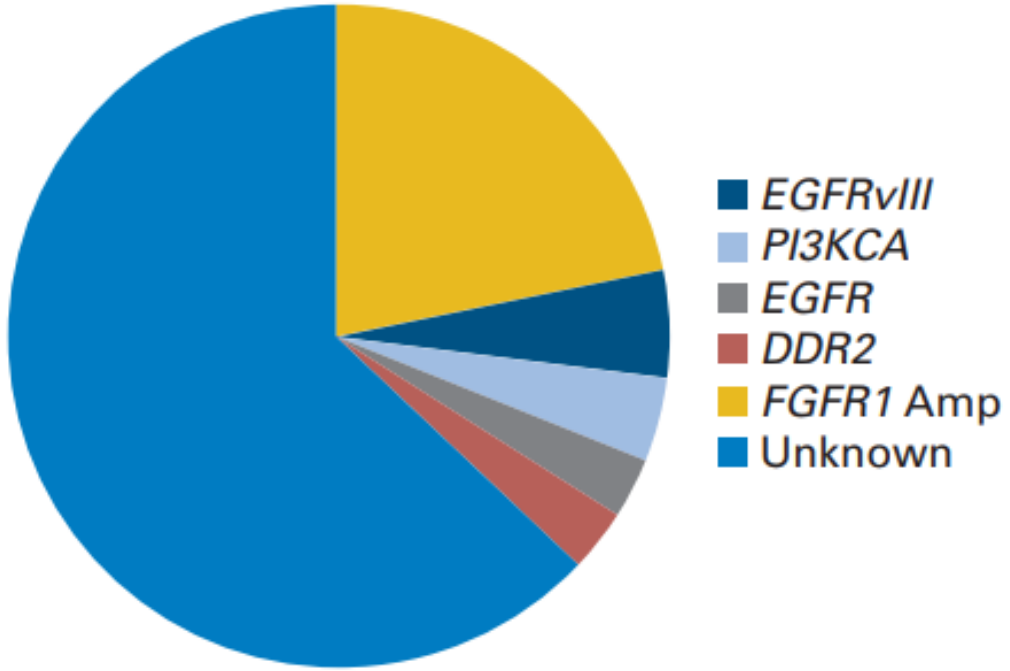
References: National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019. **2.** Li T, Kung H-J, Mack PC, Gandara DR. *J Clin Oncol.* 2013;31(8):1039-1049.

Biomarkers in NSCLC: Squamous Cell Carcinoma

NCCN guidelines recommend molecular testing for the following biomarkers in advanced or metastatic squamous cell carcinoma:[1]

- PD-L1 testing (category 1)
- Consider *EGFR* mutation testing and *ALK* testing in never smokers or small biopsy specimens or with mixed histology (category 2A)
- Consider *ROS1* and *BRAF* testing in small biopsy specimens or mixed histology (category 2A)
- Testing should be conducted as part of broad molecular profiling (category 2A)

Squamous Cell Carcinoma[2]



References: 1. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.
2. Li T, Kung H-J, Mack PC, Gandara DR. *J Clin Oncol.* 2013;31(8):1039-1049.

Liquid Biopsy

- Blood test to detect mutations from tumor cell DNA in the blood
- Can be done without an invasive procedure, and requires less time than traditional biopsy
- Valuable in cases in which tissue quantity is inadequate for mutation testing or in patients who refuse or are unable to undergo traditional biopsy

Reference: Kwapisz D. *Ann Transl Med.* 2017;5(3):46.

Testing Platforms

Overview	PCR	IHC	FISH	DNA NGS	RNA NGS

Biopsy samples are sent for pathologist review, which may include one or more of the following:

- Polymerase chain reaction (PCR)
- Immunohistochemistry (IHC)
- Fluorescent in situ hybridization (FISH)
- DNA next-generation sequencing (NGS)
- RNA NGS

References: 1. American Cancer Society. https://www.cancer.org/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/how-diagnosed.html. Updated May 16, 2019. Accessed September 16, 2019. **2.** National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.

Testing Platforms

Overview	**PCR**	IHC	FISH	DNA NGS	RNA NGS

- Molecular test to look for specific gene changes that can be treated with targeted drugs[1,2]
- Do not typically detect gene rearrangements (eg, *ROS1*, *ALK*)[2]
- May detect mutations in:[1,2]
  - *EGFR*
  - *ALK* (but unlikely to detect fusions with novel partners)
  - *ROS1* (but unlikely to detect fusions with novel partners)
  - *KRAS*
  - *BRAF*
  - *NTRK*

References: 1. American Cancer Society. https://www.cancer.org/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/how-diagnosed.html. Updated May 16, 2019. Accessed September 16, 2019. **2.** National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.

Testing Platforms

Overview | PCR | **IHC** | FISH | DNA NGS | RNA NGS

- Uses antibodies to test for antigens in a tissue sample[1]
- In NSCLC, used to evaluate expression of proteins targeted by current treatments[2]
- Proteins of relevance include:[2]
  - ALK
  - ROS1
  - PD-L1
  - BRAF V600E mutations

Reference: 1. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunohistochemistry. Accessed September 16, 2019. **2.** National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.

Testing Platforms

Overview	PCR	IHC	**FISH**	DNA NGS	RNA NGS

- Uses DNA probes that contain a fluorescent dye to label certain genes or areas of chromosomes[1]
- Requires technical expertise and experience[2]
- Regardless of fusion partner, can detect gene rearrangements in:[2,3]
  - *ALK*
  - *ROS1*

Reference: 1. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunohistochemistry. Accessed September 16, 2019. **2.** Shim HS, et al. *J Path Trans Med*. 2017;51:242-254. **3.** National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.

Testing Platforms

Overview	PCR	IHC	FISH	**DNA NGS**	RNA NGS

- Type of broad molecular profiling system that can detect panels of mutations, copy number variation, and gene rearrangements[1]
- Allows comprehensive mutational assessment using a small amount of sample material[2]
- Can detect mutations in:[1,2]

EGFR	*BRAF*	*MET*
KRAS	*HER2*	*ALK*
		ROS1

References: 1. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.
2. Coco S, et al. *Curr Drug Targets*. 2015;16(1):47-59.

Testing Platforms

Overview | NGS | IHC | FISH | DNA NGS | **RNA NGS**

- Utilizes NGS and/or polymerase chain reaction (PCR) to detect gene fusion abnormalities involving several genes, including:[1-3]
  - *ALK*
  - *ROS1*
  - *RET*
  - *NTRK1*
  - *FGFR*

Reference: 1. Vanderlaan PA, et al. *Lung Cancer*. 2014;84:39-44. **2.** Hiley CT, et al. *Lancet*. 2016;388:1002-1011. **3.** Shim HS, et al. *J Path Trans Med*. 2017;51:242-254.

Current Therapeutic Targets

PD-L1: Immunotherapy Overview

- Immune checkpoints are molecules on immune cells that need to be activated (or deactivated) to start an immune response[1]
- Some cancer cells utilize these checkpoints to avoid attacks by the immune system[1]
- In NSCLC, agents are available to target programmed death-ligand 1 (PD-L1) and its receptor, PD-1[2]

References: 1. American Cancer Society. https://www.cancer.org/cancer/non-small-cell-lung-cancer/treating/immunotherapy.html. Updated April 18, 2019. Accessed September 17, 2019. **2.** Sui H, Ma N, Wang Y, et al. *J Immunol Res*. 2018;2018:6984948.

EGFR: Overview

- EGFR is a receptor tyrosine kinase[1]
- Normally, EGFR participates in cell signaling pathways that control cell division and survival[1]
- When mutated in cancer cells, EGFR is present in higher-than-normal levels and causes cells to divide more rapidly[1]
- Most patients with *EGFR* mutations are nonsmokers or former light smokers with adenocarcinoma histology[2]
- Sensitizing mutations occur in ~10-15% of Caucasian patients with NSCLC and up to 20-30% of Asian patients[3]

References: 1. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/egfr. Accessed September 5, 2019. **2.** National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019. **3.** Choughule A, et al. *Indian J Cancer.* 2013;50(2):107-111.

EGFR: Mutations

- Most commonly found mutations include:
  - Exon 19 deletion (~45% of patients)
  - Point mutation in exon 21 (L858R, ~40% of patients)
- Less common mutations (~10%) include:
  - Exon 19 insertions (L861Q, G719X, S768I)
- These sensitizing mutations result in inactivation of the tyrosine kinase domain and are associated with sensitivity to small molecule EGFR tyrosine kinase inhibitors (TKIs)
- **Patients with tumors that do NOT have sensitizing *EGFR* mutations should NOT be treated with EGFR TKIs in any line of therapy**

Reference: National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.

EGFR: TKIs Overview

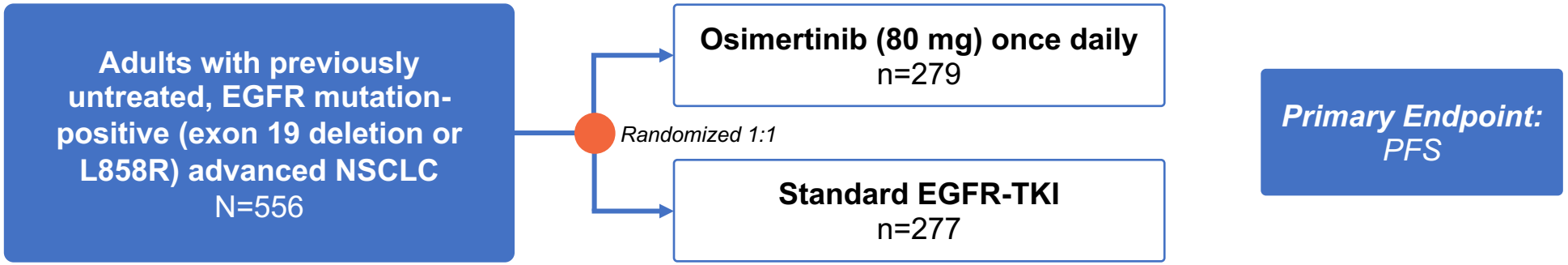
EGFR inhibitors target excess EGFR, which is a protein on the surface of cells that normally helps the cells grow and divide, on the surface of NSCLC cells.[1]

Agent	Brand Name	Approval in NSCLC	Indication in NSCLC
Gefitinib[2,3]	Iressa	2003	• *First-line treatment:* metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutation
Erlotinib[4,5]	Tarceva	2004	• *First-line, maintenance, or second-line or greater treatment:* metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutation
Afatinib[6,7]	Gilotrif	2013	• *First-line treatment:* metastatic NSCLC with nonresistant EGFR mutations • *Second-line treatment:* metastatic squamous NSCLC progressing after platinum-based chemotherapy
Osimertinib[10,11]	Tagrisso	2018	• *First-line treatment:* metastatic NSCLC with exon 19 deletion or exon 21 (L858R) mutation • *Second-line treatment:* metastatic EGFR T790M mutation-positive NSCLC progressing on or after EGFR tyrosine kinase inhibitor therapy
Dacomitinib[12,13]	Vizimpro	2018	• *First-line treatment:* metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation

Osimertinib: FLAURA Trial

Overview | Efficacy | Safety

The April 2018 approval of osimeritinib was based on the FLAURA multicenter, international, randomized, double-blind, active-controlled trial[1,2]

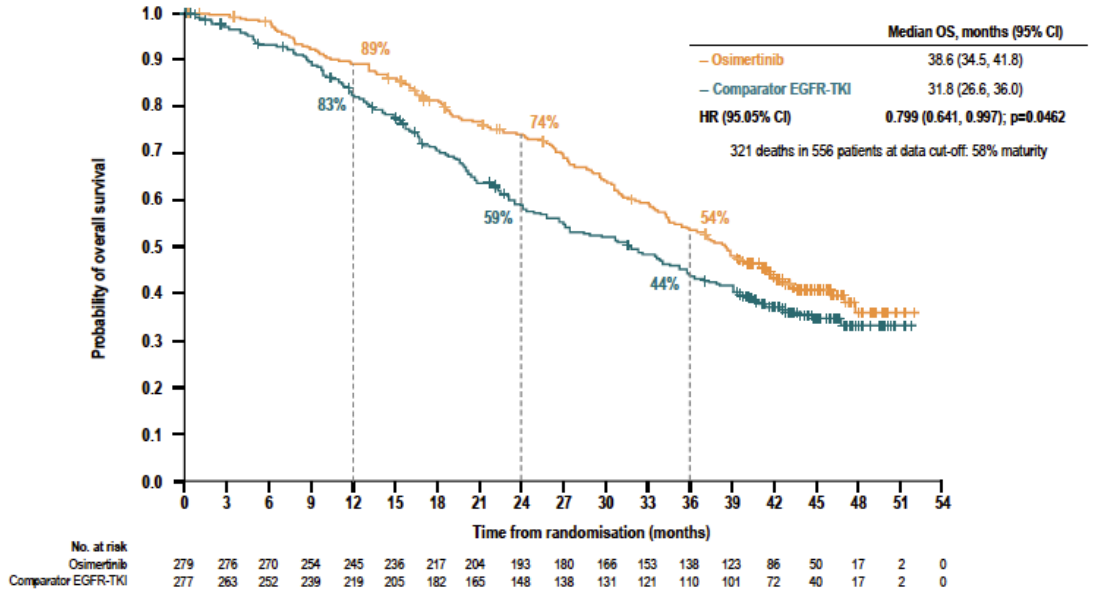


References: 1. U.S. Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-first-line-treatment-metastatic-nsclc-most-common-egfr-mutations. Published April 19, 2018. Accessed September 16, 2019. **2.** Soria J, et al. *N Engl J Med.* 2018;378:113-125.

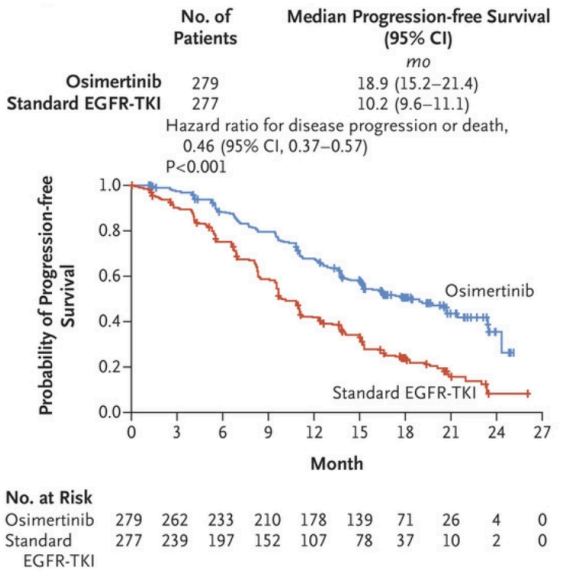
Osimertinib: FLAURA Trial

Overview | **Efficacy** | Safety

Overall Survival[1]



Progression-Free Survival[2]



Reference: 1. Ramalingam SS. Abstract LBA5_PR. Presented at ESMO Congress 2019. Barcelona, Spain. **2.** Soria J, et al. *N Engl J Med.* 2018;378:113-125.

Osimertinib: FLAURA Trial

Overview | Efficacy | **Safety**

- Serious AEs were reported in 22% of the osimertinib group and 25% of the standard EGFR-TKI group
- Fatal AEs occurred less often in the osimertinib group (2% vs 5%)
- AEs leading to permanent discontinuation occurred in 14% and 18% of patients

Reference: Soria J, et al. *N Engl J Med.* 2018;378:113-125.

Osimertinib: FLAURA Trial

Overview | Efficacy | **Safety**

Any Grade Adverse Events (≥20% in any group)

	Osimertinib N=279				EGFR-TKI N=277			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	34 (12%)	144 (52%)	83 (30%)	6 (2%)	22 (8%)	125 (45%)	103 (37%)	11 (4%)
Rash or acne	134 (48%)	24 (9%)	3 (1%)	0	110 (40%)	87 (31%)	19 (7%)	0
Diarrhea	120 (43%)	35 (13%)	6 (2%)	0	116 (42%)	35 (13%)	6 (2%)	0
Dry Skin	87 (31%)	12 (4%)	1 (<1%)	0	76 (27%)	21 (8%)	3 (1%)	0
Paronychia	52 (19%)	44 (16%)	1 (<1%)	0	55 (20%)	34 (12%)	2 (1%)	0
Stomatitis	65 (23%)	13 (5%)	1 (<1%)	1 (<1%)	47 (17%)	8 (3%)	1 (<1%)	0
Decreased appetite	27 (10%)	22 (8%)	7 (3%)	0	25 (9%)	22 (8%)	5 (2%)	0
Aspartate aminotransferase elevation	18 (6%)	6 (2%)	2 (1%)	0	38 (14%)	18 (6%)	12 (4%)	0
Alanine aminotransferase elevation	11 (4%)	6 (2%)	1 (<1%)	0	31 (11%)	19 (7%)	21 (8%)	4 (1%)

No severe rash was observed*

Reference: Soria J, et al. *N Engl J Med.* 2018;378:113-125.

ALK/ROS1 Overview

- The *ALK* gene encodes a protein called anaplastic lymphoma kinase, which is involved in cell growth[1]
  - Most patients with *ALK* rearrangements are light or never-smokers with adenocarcinoma histology[2]
- ROS1 encodes a receptor tyrosine kinase involved in cell growth and signaling similar to ALK[1,2]
  - *ROS1* rearrangements occur more frequently in patients who are negative for *EGFR*, *KRAS*, and *ALK* gene rearrangements[2]
- *ALK* and ROS1 translocations may increase the growth of cancer cells[1]
- The NCCN recommends that all patients with metastatic nonsquamous NSCLC be tested for *ALK* rearrangements[2]
  - Testing may be considered in other patients with small biopsy specimens or mixed histology or those who are light or never-smokers[2]
  - *ROS1* testing is recommended in patients with metastatic nonsquamous NSCLC and can be considered in some patients with metastatic squamous cell carcinoma[2]

References: 1. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/alk-gene. Accessed September 17, 2019. **2.** National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019.

ALK: TKIs Overview

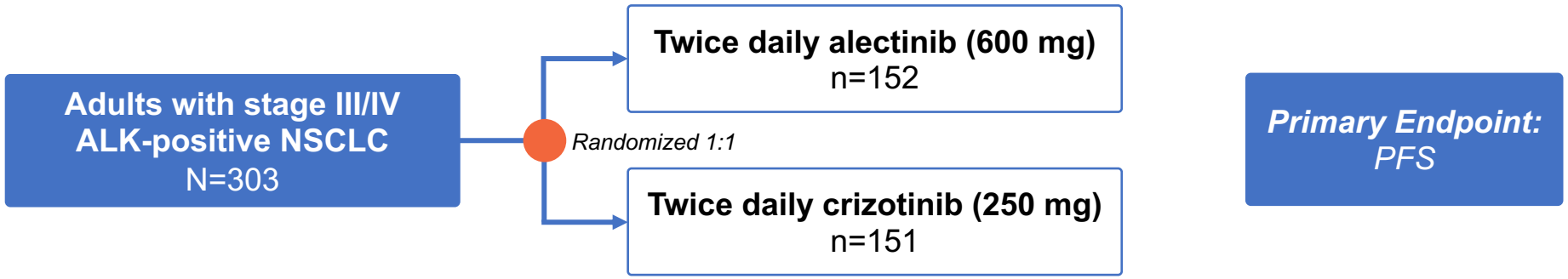
Normally, ALK is expressed rarely in adults. However, a genetic rearrangement that gives rise to an ALK fusion protein, most commonly with EML4 in NSCLC, results in activation of the ALK kinase domain, which helps malignant cells grow and spread.[1-2] ROS1 is similar to ALK, and gene rearrangements with ROS1-rearranged NSCLC may sometimes be treated with the same agents as with ALK.[3]

Agent	Brand Name	Approval in NSCLC	Target Activity	Indication in NSCLC
Ceritinib[4,5]	Zykadia	2014	ALK, ROS1	*First-line treatment:* metastatic ALK-1–positive NSCLC
Alectinib[6,7]	Alecensa	2015	ALK	*First-line treatment:* metastatic ALK-1–positive NSCLC
Crizotinib[8,9]	Xalkori	2016	ALK, ROS1	*First-line treatment:* metastatic ALK- or ROS1-positive NSCLC
Brigatinib[10,11]	Alunbrig	2017	ALK, ROS1	*Second-line treatment:* metastatic ALK-positive NSCLC in patients who have progressed on or are intolerant to crizotinib
Lorlatinib[12,13]	Lorbrena	2018	ALK, ROS1	*Second- and third-line treatment:* metastatic ALK-positive NSCLC for patients whose disease has progressed on crizotinib and at least 1 other ALK inhibitor for metastatic disease or alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease
Entrectinib[14,15]	Rozlytrek	2019	ROS1, ALK	*First-line treatment:* metastatic ROS1-positive NSCLC

Alectinib: ALEX Study

Overview | Efficacy | Safety

- The November 2017 approval of alectinib was based on ALEX, a randomized, multicenter, open-label, active-controlled trial[1]
  - Updated efficacy and safety data published in 2019[2]

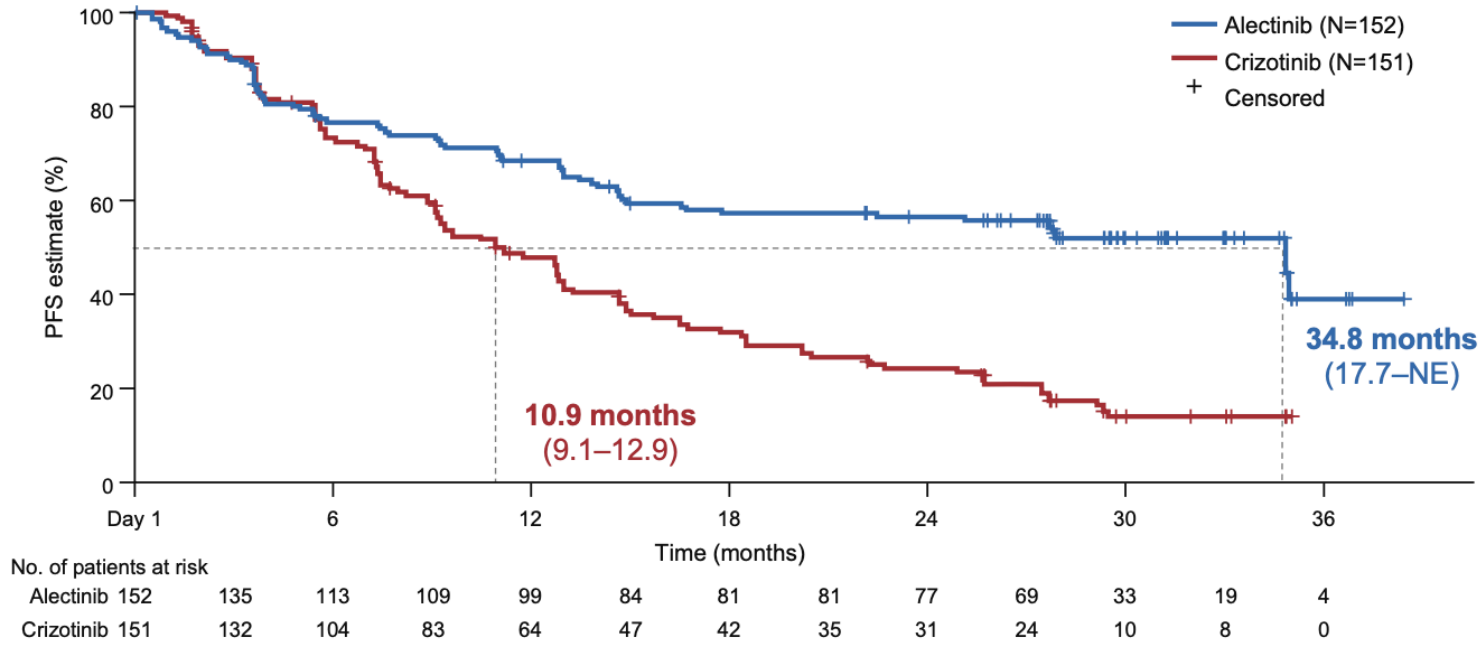


References: 1. U.S. Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/alectinib-approved-alk-positive-metastatic-non-small-cell-lung-cancer-nsclc. Updated November 7, 2017. Accessed September 17, 2019. **2.** Camidge DR, et al. *J Thorac Oncol*. 2019;14(7):1233-1243.

Alectinib: ALEX

Overview | **Efficacy** | Safety

Progression-Free Survival



Reference: Camidge DR, et al. *J Thorac Oncol*. 2019;14(7):1233-1243.

Alectinib: ALEX

Overview | Efficacy | **Safety**

AE Summary

AE	Alectinib (n=152)	Crizotinib (n=151)
All-grade AEs	147 (97.7%)	147 (97.4%)
Serious AEs	46 (30.3)	46 (30.5%)
Grade 3-5 AEs	68 (44.7%)	77 (51.0%)
Fatal AEs	6 (3.9%)	7 (4.6%)
AEs leading to treatment discontinuation	20 (13.2%)	20 (13.2%)
AEs leading to dose reduction	25 (16.4%)	31 (20.5%)
AEs leading to dose interruption	34 (22.4%)	38 (25.2%)

Most Common AEs (≥20% in any arm)

AE	Alectinib (n=152)	Crizotinib (n=151)
Anemia	34 (22.4%)	11 (7.3%)
Peripheral edema	28 (18.4%)	48 (31.8%)
ALT level increased	26 (17.1%)	50 (33.1%)
AST level increased	24 (15.8%)	40 (26.5%)
Nausea	24 (15.8%)	75 (49.7%)
Diarrhea	20 (13.2%)	70 (46.4%)
Vomiting	14 (9.2%)	62 (41.1%)

Reference: Camidge DR, et al. *J Thorac Oncol*. 2019;14(7):1233-1243.

BRAF and NRTK: TKIs Overview

Target	Agent	Brand Name	Approval in NSCLC	Indication in NSCLC
BRAF	Dabrafenib + trametinib[1-3]	Tafinlar + Mekinist	2017	*First-line treatment:* as combination therapy for metastatic NSCLC with BRAF V600E mutation
NRTK	Larotrectinib[4]	Vitrakvi	2018 (for solid tumors as shown in the indication column)	*First-line treatment or later:* adult and pediatric patients with solid tumors that: • Have a *NRTK* gene fusion without a known acquired resistance mutation, • Are metastatic or where surgical resection is likely to result in severe morbidity, and • Have no satisfactory alternative treatments or that have progressed following treatment
	Entrectinib[5,6]	Rozlytrek	2019	*First-line treatment:* metastatic ROS1-positive NSCLC *First-line treatment or later*: adult and pediatric patients with solid tumors that: • Have a *NRTK* gene fusion without a known acquired resistance mutation, • Are metastatic or where surgical resection is likely to result in severe morbidity, and • Have either progressed following treatment or have no satisfactory alternative therapy

References: 1. Tafinlar [package insert]. July 2019. **2.** Mekinist [package insert]. July 2019. **3.** U.S. Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-dabrafenib-and-trametinib-combination-metastatic-nsclc-braf-v600e. June 22, 2017. Accessed September 17, 2019. **4.** Vitrakvi [package insert]. July 2019. **5.** U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-third-oncology-drug-targets-key-genetic-driver-cancer-rather-specific-type-tumor. August 15, 2019. Accessed September 17, 2019. **6.** Rozlytrek [package insert]. August 2019.

Emerging Targets

Genetic Alteration	Available Targeted Agents with Activity in Lung Cancer[1]	Other Agents (not FDA-approved)
High-level *MET* amplification or *MET* exon 14 skipping mutation	Crizotinib	Tepotinib[2]
RET rearrangements	Cabozantinib Vandetanib	Pralsetinib[3] Selpercatinib[4]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine	TAK-788[5]
Tumor mutational burden (TMB)	Nivolumab + ipilimumab Nivolumab	n/a

Reference: National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated August 30, 2019. Accessed September 16, 2019. **2.** Paik P, et al. *Ann Oncol.* 2019;30(suppl_2):ii38-ii68. **3.** ESMO. https://www.esmo.org/Oncology-News/BLU-667-in-RET-driven-NSCLC-and-Thyroid-Cancer. Updated June 21, 2019. Accessed September 17, 2019. **4.** Drilon A, et al. IASCLC 2019 World Converence on Lung Cancer. Presentation. **5.** Chandrashekhar LP. https://www.targetedonc.com/publications/targeted-therapy-news/2018/september-2018/targeted-treatments-emerge-for-her2-mutations-in-lung-cancer. Published September 20, 2018. Accessed September 29, 2019.

Summary

- For patients with molecularly targetable lesions, use a targeted therapy
- Resistance remains a major issue
- Multiple lines of therapy now available for many mutations
  - Consider clinical trials
- Chemotherapy still active for these diseases

AE Recognition (Case Studies)

Slides Courtesy of Beth Sandy, MSN, CRNP, OCN

AE Recognition for Therapies Without an Identified Molecular Target

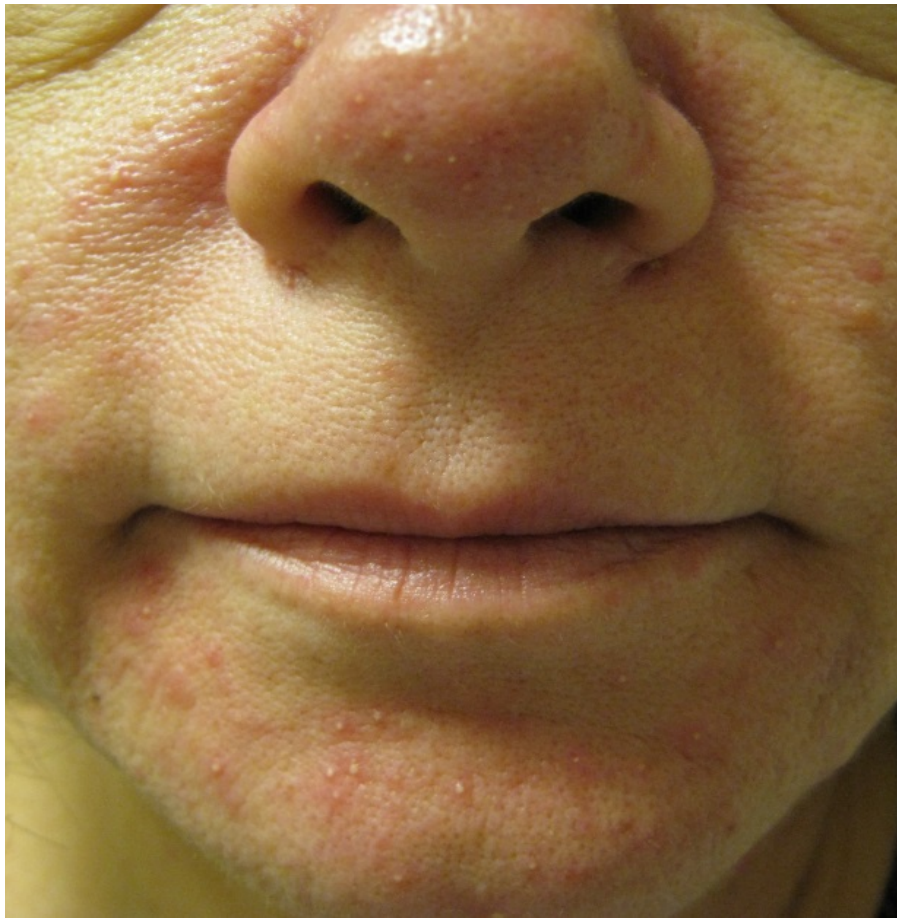
- Patient education and engagement is critical!
- *Symptom recognition*
  - *Patient diary*
  - *Telephone triage*
  - *Agent-specific checklists*
  - *Patient education*
- imAEs include pneumonitis, colitis, dermatitis, hepatitis, nephritis, and endocrinopathy

Case Study Patient 1

- 56-year-old female with exon 19 deletion and brain mets
- She recently started osimertinib 80 mg daily
- The patient calls in reporting a new rash on her face and chest that looks like “teenage acne” that started 2 days ago

Rash: General Recommendations

- Moisturize
- Sun protection
- Avoid hot water while washing dishes and showering



Rash: Grading and Management

Grade	Description	Management
1	Papules and/or pustules covering < 10% BSA	Moisturize with thick cream
2	Papules and/or pustules covering 10-30% BSA, can be associated with pruritus or tenderness	Topical clindamycin gel for pustules and topical steroid for erythema and may add oral antibiotics
3-4	Papules and or pustules covering > 30% BSA with moderate or severe symptoms	Hold drug and may need to reduce dose, higher steroid cream and oral antibiotics

Case Study Patient 1

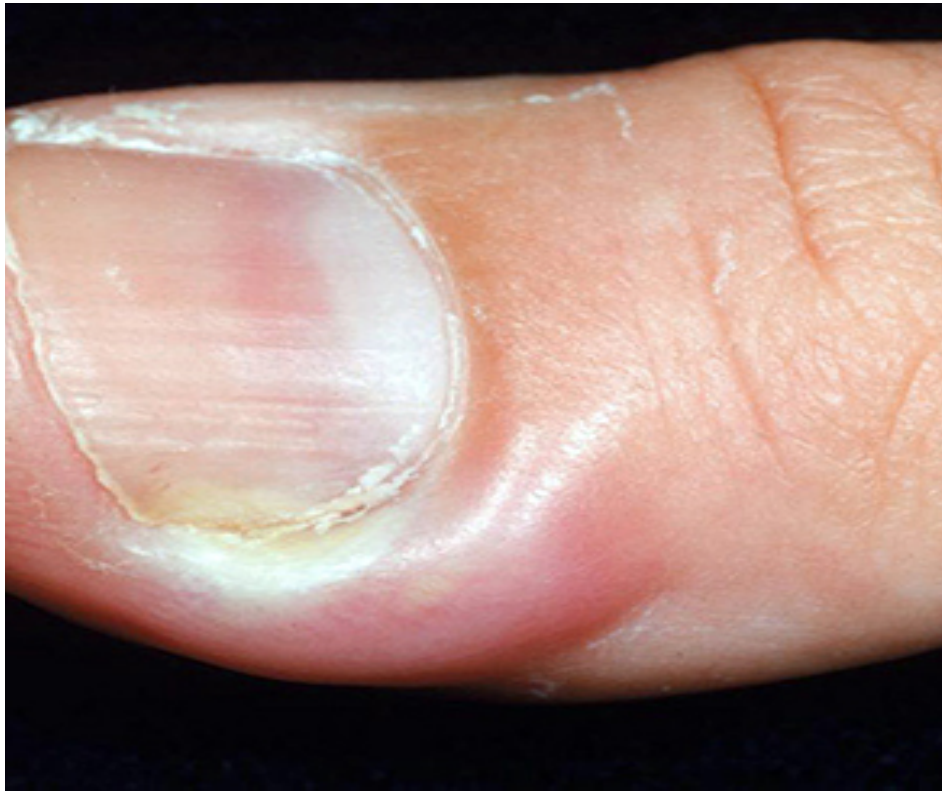
- Any additional symptoms to ask about?
  - Pruritus, tenderness
- What is the likely cause of the rash?
  - Inhibition of EGFR
- Grade of rash and treatment?
  - Grade 2
  - Topical clindamycin for pustular lesions and topical steroid cream for erythema

Case Study Patient 1

- The patient calls back after using the topical clindamycin and steroid cream, with minimal improvement for 2 days
- She now has tenderness in some areas and it spread to her chest
- She also reports her fingernails are hurting, “split fingertips,” and a very itchy scalp
- She also states she has noticed worsening diarrhea over the last week

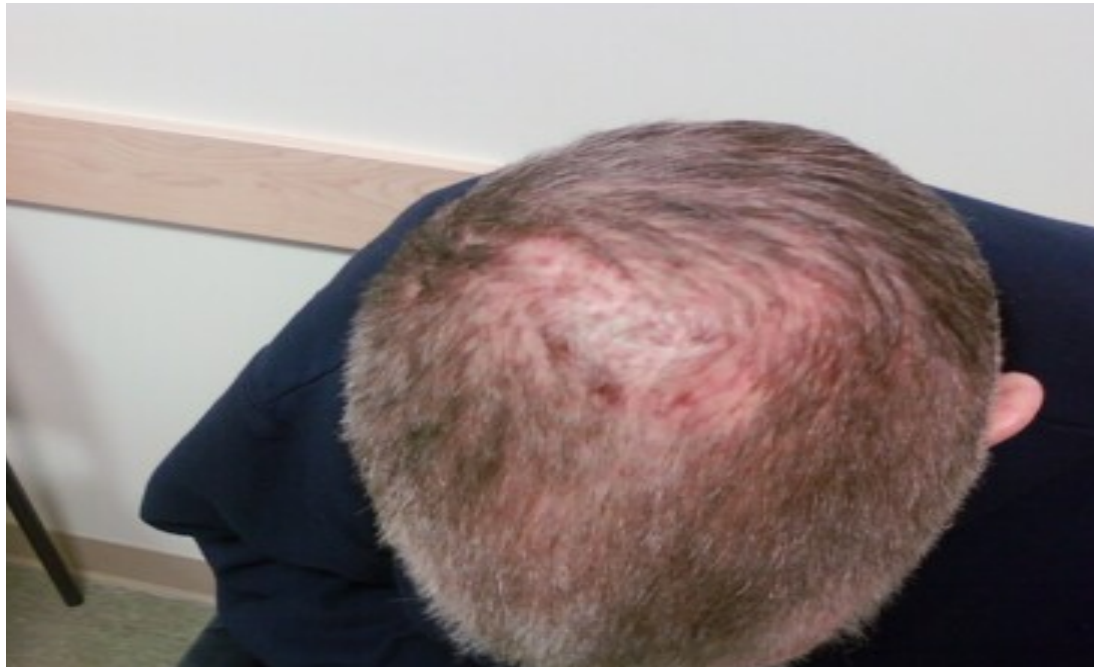
Paronychia

- Patient education: trimmed nails
- Water vinegar soaks: equal parts water and vinegar, 3-4x daily
- Topical steroids or antibiotics
- Systemic antibiotics



Scalp Rash

- Moisturizing shampoos with selenium, dandruff brands
- Topical solutions either shampoo form or liquid solution that is applied and leave in: fluocinolone shampoo or solutions



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

Fissures

- Wear gloves and minimal exposure to hot water
- Thick moisturizer, liquid glues to seal cracks
- Steroid tapes

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

Diarrhea: Grading and Management

- Well managed with over-the-counter antidiarrheals or prescription if needed
- Adequate hydration is important!

Grade	Description	Management
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Oral hydration and OTC antidiarrheal medication
2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Oral hydration, bring in for IVFs if needed, add prescription antidiarrheals
3	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Hold treatment. Okay to restart when the symptom is grade 2 or less within 3 weeks, normally at reduced dose
4	Life-threatening consequences; urgent intervention indicated	

Case Study Patient 1

- Patient started on oral doxycycline 100 mg BID, dandruff shampoo, and begins to apply superglue to finger splits
- She begins Imodium as needed
- She returns to clinic reporting feeling well
- Her scan shows a PR to therapy

Case Study Patient 2

- 39-year-old female with *ALK*-translocated NSCLC
- She recently started lorlatinib after progressing on alectinib
- She is also taking atorvastatin
- She reports SOB

Pneumonitis

- Class effect of TKIs
  - Rare, but can be fatal if not identified
  - If confirmed, cannot get that drug ever again!
- Usually acute onset SOB, must be worked up by CT chest with contrast
  - Need to rule out other causes of SOB in lung cancer patients
  - **An important side note:** Brigatinib in particular is associated with a specific pulmonary event that is NOT pneumonitis

An Exception to the Rule: Brigatinib Pulmonary Event

Severity	Description	Management
Mild or moderate	**Grade 1:** asymptomatic, clinic or diagnostic observation only	• Continue escalation with brigatinib • Reassure and reassess frequently • Dose-escalated as tolerated after resolution
	Grade 2: Symptomatic, medical intervention needed	
Severe in an otherwise healthy patient	**Grade 3:** severe symptoms, limiting self-care and requiring supplemental O_2	• Supportive care with O_2 supplementation (± corticosteroids) • Continue brigatinib therapy at same dose if possible (reassess frequently) • Dose escalate to 180 mg if tolerated after resolution • Consider home O_2 monitoring • If tolerable, hold dosing, allow resolution with supportive care, and consider rechallenge with step-up dosing
Severe in a patient with significant comorbidities or poor support system	**Grade 3:** severe symptoms, limiting self-care and requiring supplemental O_2	• Hold drug and utilize supportive care with O_2 supplementation (± corticosteroids) (with respiratory support for grade 4) • Reassure, frequently reassess, and once resolved consider rechallenge with brigatinib using 3-day 30-mg, 3-day 60-mg, 3-day 90-mg shallow step-up dosing (± prophylactic supportive care) • Dose-escalate to 180 mg after 3 days at a dose of 90 mg as tolerated
Very severe	**Grade 4:** life-threatening, urgent intervention indicated (eg, intubation, BiPAP)	
Proactive plan: If there is concern regarding baseline compromised respiratory function in an individual patient when administration of brigatinib is initiated, consider proactive use of a shallow step--up dosing regimen from the start.		

Reference: Camidge DR, et al. *J Thorac Oncol*. 2019;14(7):1547-155.

Back to the Case Study…

Case Study Patient 2

- CT with contrast shows no evidence of pneumonitis
- SOB resolves, and she is feeling well on therapy
- She is noted to have elevated LDL at toxicity visit

Hypercholesterolemia

- Unique toxicity seen with lorlatinib
- Monitor labs and hold treatment grade 3 or higher
- Okay to restart grade 2 or less at lower dose
- Many patients need a concurrent statin agent

Summary

- Patient education and engagement is critical!
- imAEs include pneumonitis, colitis, dermatitis, hepatitis, nephritis, and endocrinopathy
  - Brigatinib is associated with a specific pulmonary event that is NOT pneumonitis
  - Hypercholesterolemia is a unique toxicity seen with lorlatinib

FDA-Approved Therapies Without Identified Molecular Targets

KEYNOTE 024

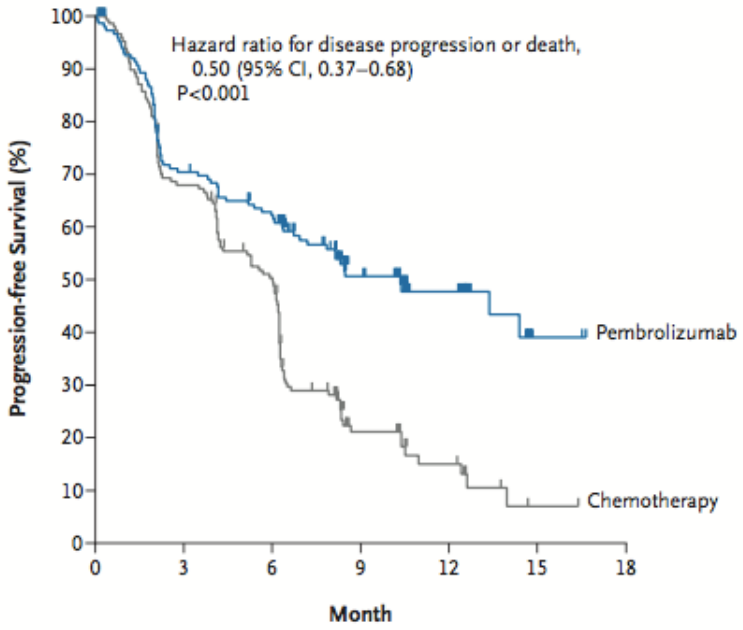
Pembrolizumab vs Platinum Doublet

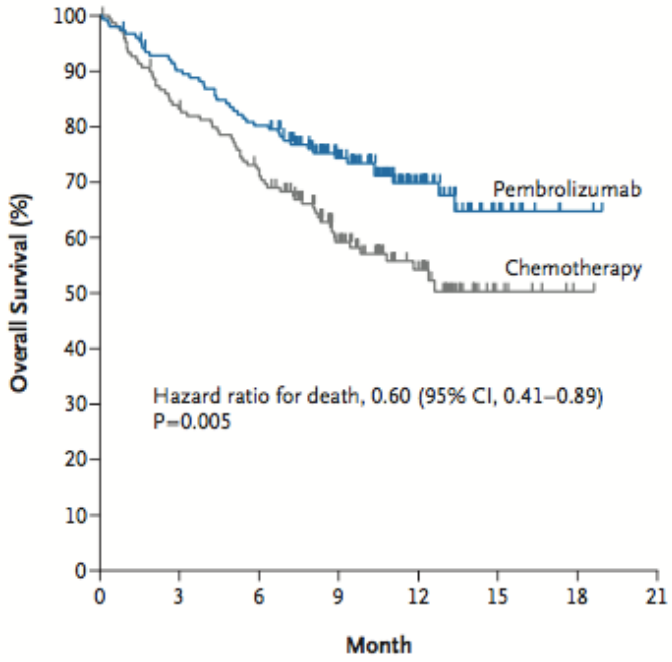
Eligibility
- Stage IIIB/IV, untreated NSCLC
- PD-L1 >50%
- No EGFR or ALK
- PS 0-1

Pembrolizumab 200 mg every 3 weeks

Platinum doublet*

*Bevacizumab was not included
*Maintenance was not required





In patients with advanced NSCLC and PD-L1 expression on ≥50% of tumor cells, pembrolizumab was associated with:
- Significantly longer PFS and OS
- Fewer adverse events

Reference: Reck M, et al. *N Engl J Med*. 2016;375(19):1823-1833.

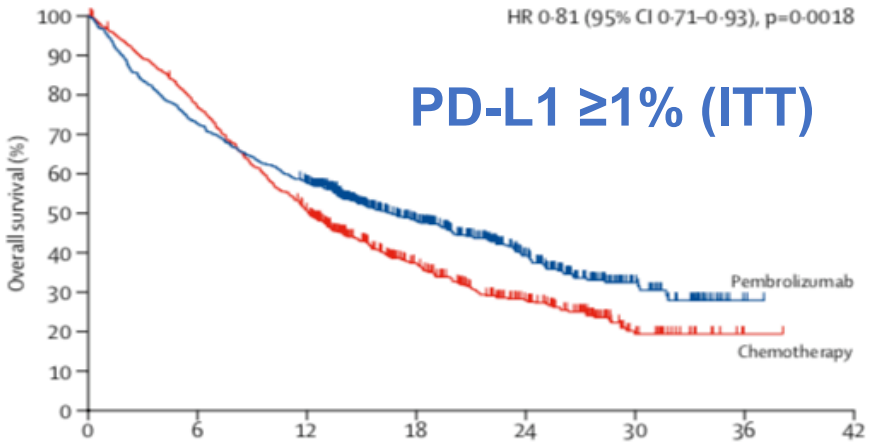
KEYNOTE 042

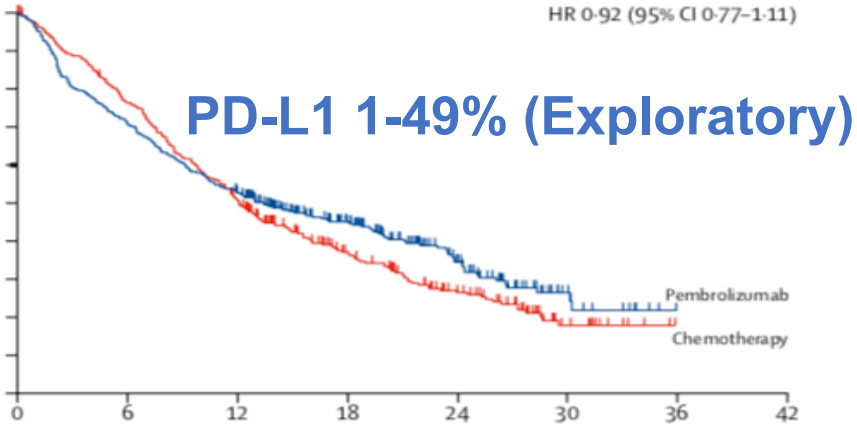
Pembrolizumab vs Platinum Doublet

Eligibility Criteria
- Stage IIIB/IV, untreated NSCLC
- PD-L1 >1%
- No EGFR or ALK
- PS 0-1

Pembrolizumab 200 mg
Every 3 weeks

Carboplatin/paclitaxel
or
Carboplatin/pemetrexed



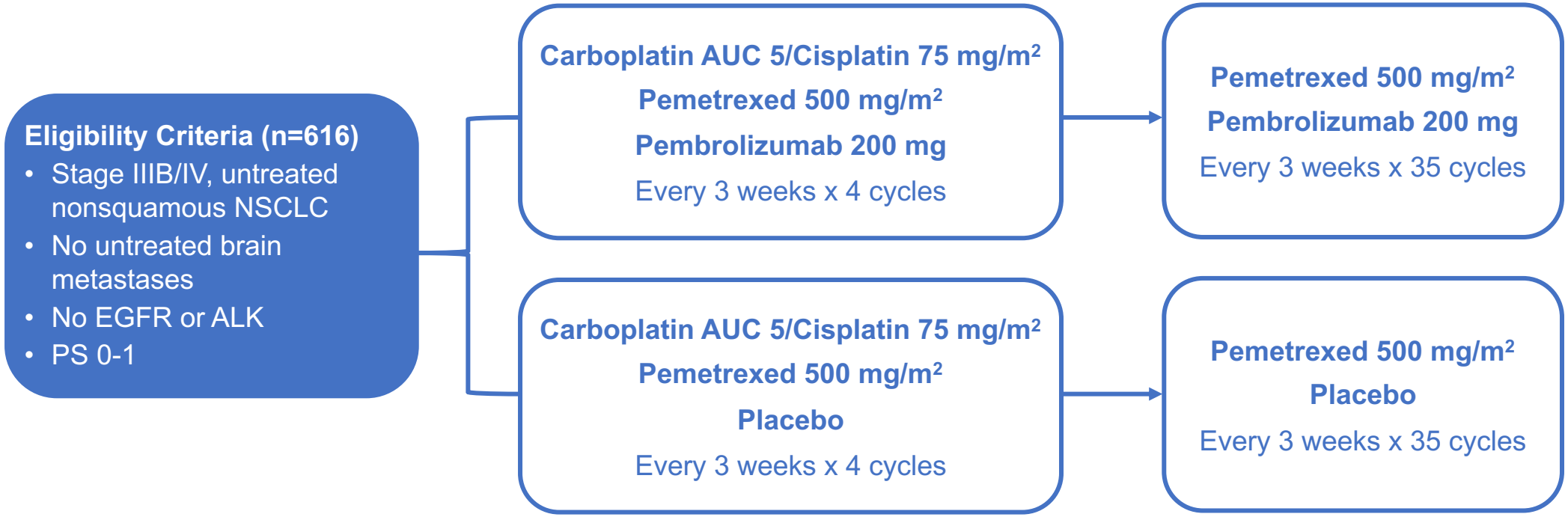


Pembrolizumab monotherapy can be used as first-line therapy in patients with locally advanced or metastatic NSCLC *without* sensitizing EGFR or ALK alterations and with low PD-L1 TPS.

Reference: Mok TSK, et al. *Lancet*. 2019;393(10183):1819-1830.

KEYNOTE 189

Carboplatin/Pemetrexed ± Pembrolizumab

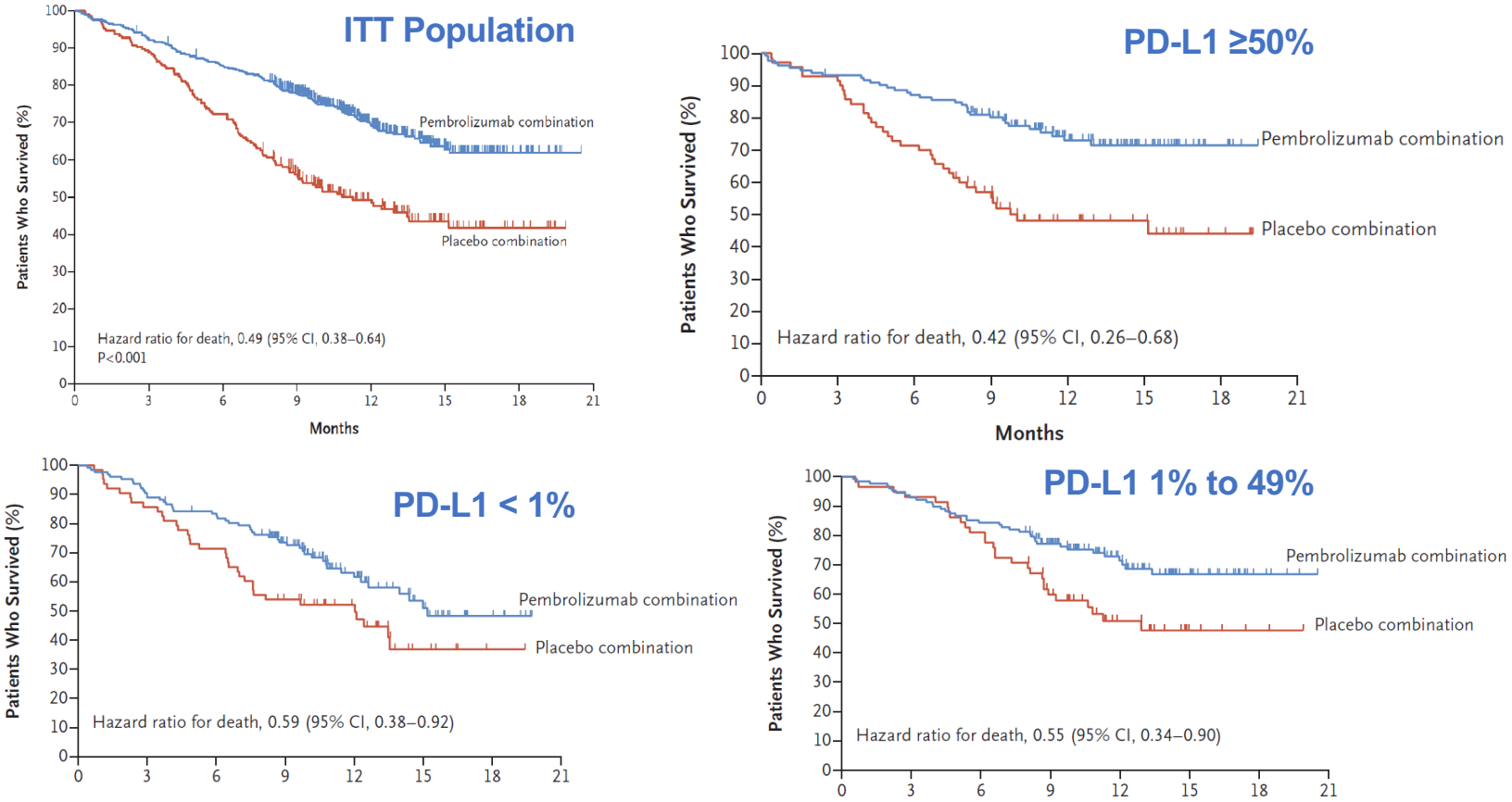


Reference: Gandhi L, et al. *N Engl J Med.* 2018;378(22):2078-2092.

KEYNOTE 189

Carboplatin/Pemetrexed ± Pembrolizumab

Overall Survival



Significantly longer median OS with addition of pembrolizumab (69.2% vs 49.4% at 12 months) (*P*<0.001) in the ITT population

Reference: Gandhi L, et al. *N Engl J Med.* 2018;378(22):2078-2092.

KEYNOTE 189

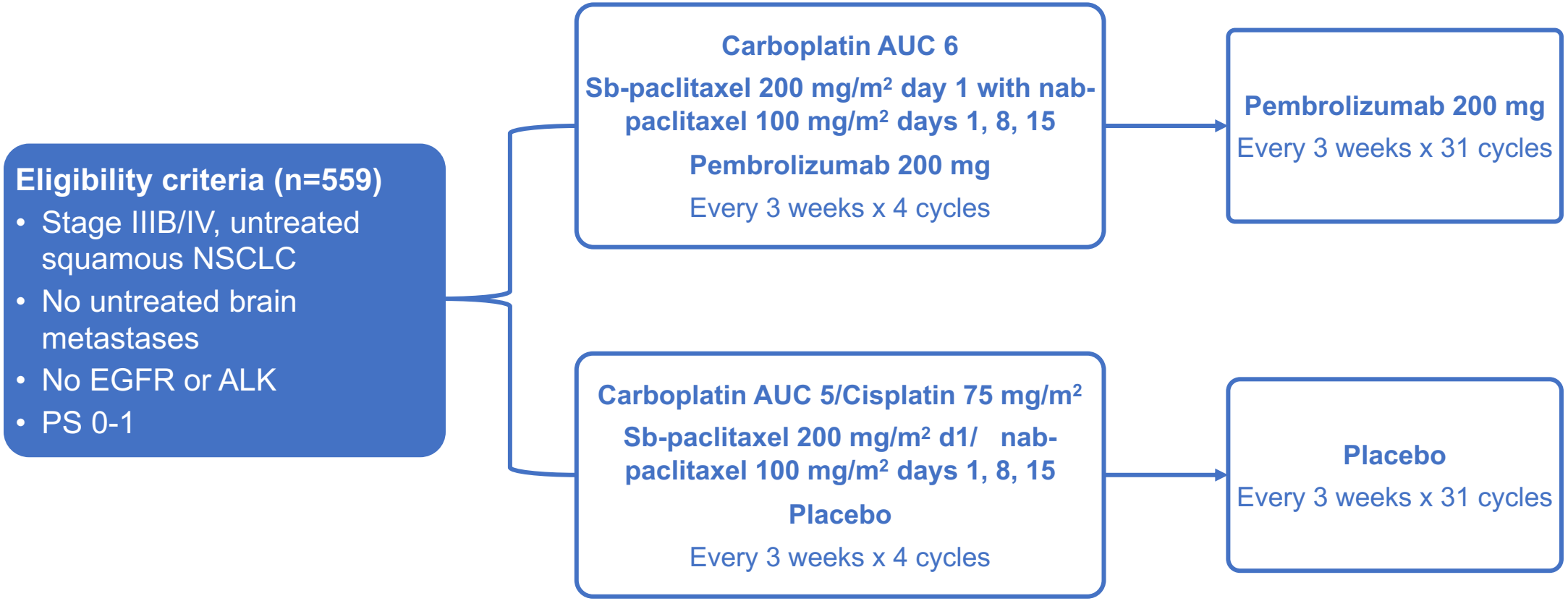
Carboplatin/Pemetrexed ± Pembrolizumab

Adverse Event, n (%)	Triplet (n = 405)	Platinum Doublet (n = 202)
Any cause	404 (99.8)	200 (99.0)
▪ Grade 3-5	202 (67.2)	133 (65.8)
▪ Resulting in death	27 (6.7)	12 (5.9)
▪ Resulting in discontinuation of all treatment	56 (13.8)	16 (7.9)
▪ Resulting in discontinuation of any treatment	112 (27.7)	30 (14.9)
Immune mediated	92 (22.7)	24 (11.9)
▪ Grade 3-5	36 (8.9)	9 (4.5)
▪ Resulting in death	3 (0.7)	0

Reference: Gandhi L, et al. *N Engl J Med.* 2018;378(22):2078-2092.

KEYNOTE 407

Carboplatin/Taxane ± Pembrolizumab

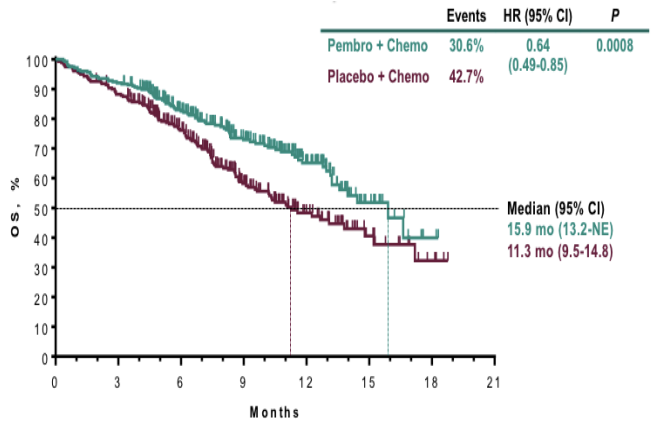


Reference: Paz-Ares L, et al. *N Engl J Med.* 2018;379(21):2040-2051.

KEYNOTE 407

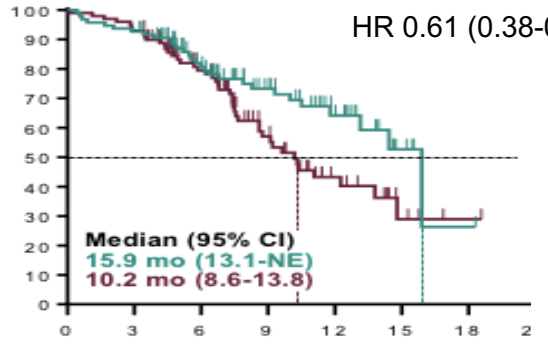
Carboplatin/Taxane ± Pembrolizumab

Overall Survival



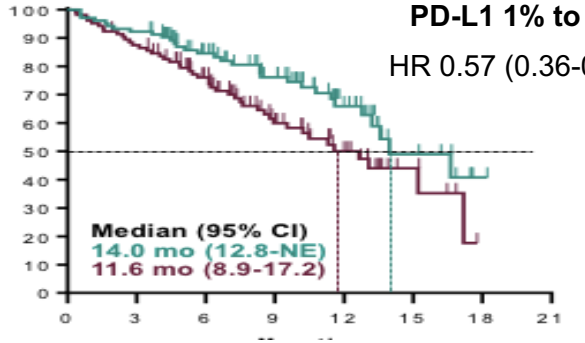
PD-L1 <1%

HR 0.61 (0.38-0.98)



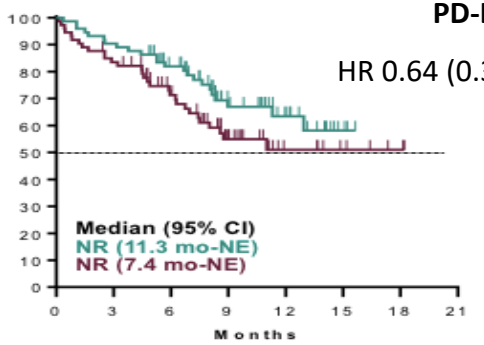
PD-L1 1% to 49%

HR 0.57 (0.36-0.90)



PD-L1 ≥50%

HR 0.64 (0.37-1.10)



Addition of pembrolizumab to chemotherapy with carboplatin + paclitaxel or nab-paclitaxel resulted in significantly longer median OS (15.9 vs 11.3 months) in the ITT population.

Reference: Paz-Ares L, et al. *N Engl J Med.* 2018;379(21):2040-2051.

KEYNOTE 407

Carboplatin/Taxane ± Pembrolizumab

- Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group
- Discontinuation of treatment because of adverse events was more frequent in the pembrolizumab-combination group than in the placebo-combination group (13.3% vs. 6.4%)
- No new safety signals identified

Table 3. Adverse Events of Interest in the As-Treated Population.*

Event	Pembrolizumab Combination (N=278)		Placebo Combination (N=280)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	80 (28.8)	30 (10.8)	24 (8.6)	9 (3.2)
Hypothyroidism	22 (7.9)	1 (0.4)	5 (1.8)	0
Hyperthyroidism	20 (7.2)	1 (0.4)	2 (0.7)	0
Pneumonitis	18 (6.5)	7 (2.5)†	6 (2.1)	3 (1.1)†
Infusion reaction	8 (2.9)	4 (1.4)	6 (2.1)	1 (0.4)
Colitis	7 (2.5)	6 (2.2)	4 (1.4)	3 (1.1)
Hepatitis	5 (1.8)	5 (1.8)	0	0
Severe skin reaction	5 (1.8)	3 (1.1)	1 (0.4)	1 (0.4)
Hypophysitis	3 (1.1)	2 (0.7)	0	0
Thyroiditis	3 (1.1)	1 (0.4)	0	0
Nephritis	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)

* The adverse events of interest are infusion reactions and events with an immune-related cause; they are considered regardless of whether the investigator attributed the event to a trial regimen or considered the event to be immune-related. The events are listed in descending order of frequency in the pembrolizumab-combination group. In addition to the specific preferred terms that are listed, related terms were also included. The as-treated population included all patients who underwent randomization and received at least one dose of the assigned combination treatment.

† Data include 1 patient (0.4%) in each trial group who had grade 5 pneumonitis.

Reference: Paz-Ares L, et al. *N Engl J Med.* 2018;379(21):2040-2051.

IMPOWER 150

First-Line Atezolizumab

Eligibility (n=1202)

- Stage IV, recurrent or metastatic untreated Squamous NSCLC
- Any PD-L1 immunohistochemistry status
- EGFR or ALK
- PS 0-1
- No untreated CNS metastases

ABCP

Atezolizumab 1200 mg (administered until loss of benefit)
Paclitaxel 200 mg/m² day 1
Carboplatin AUC 6
Bevacizumab 15 mg/kg day 1
Every 3 weeks x 4-6 cycles

ACP

Atezolizumab 1200 mg (administered until loss of benefit)
Paclitaxel 200 mg/m² day 1
Carboplatin AUC 6
Every 3 weeks x 4-6 cycles

BCP

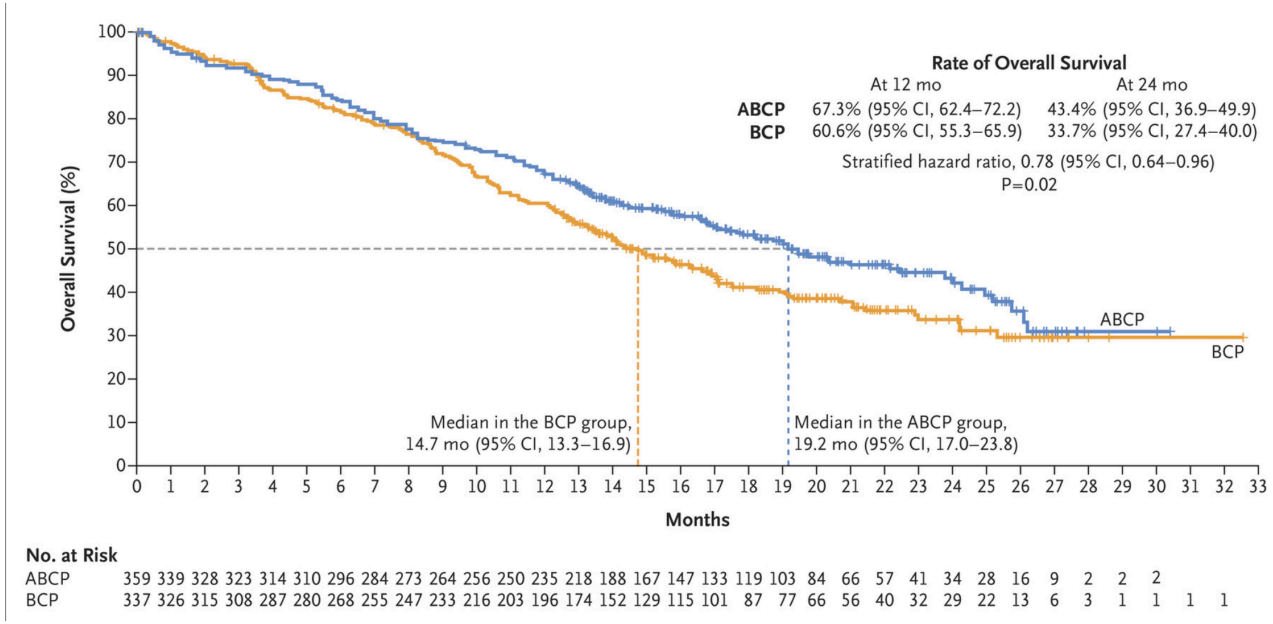
Paclitaxel 200 mg/m² day 1
Carboplatin AUC 6
Bevacizumab 15 mg/kg day 1
Every 3 weeks x 4-6 cycles

Maintenance therapy with atezolizumab, bevacizumab, or both

Reference: Socinski MA, et al. *N Engl J Med.* 2018;378(24):2288-2301.

IMPOWER 150

First-Line Atezolizumab



- The ABCP group had improved OS (19.2 vs 14.7 months) regardless of PD-L1 expression and EGFR or ALK genetic alteration status
  - Later subgroup analyses indicated that the advantage holds when patients have baseline liver metastases
  - However, EGFR-sensitizing mutations may not have a significant survival advantage with atezolizumab

Reference: Socinski MA, et al. *N Engl J Med.* 2018;378(24):2288-2301.

IMPOWER 150

First-Line Atezolizumab

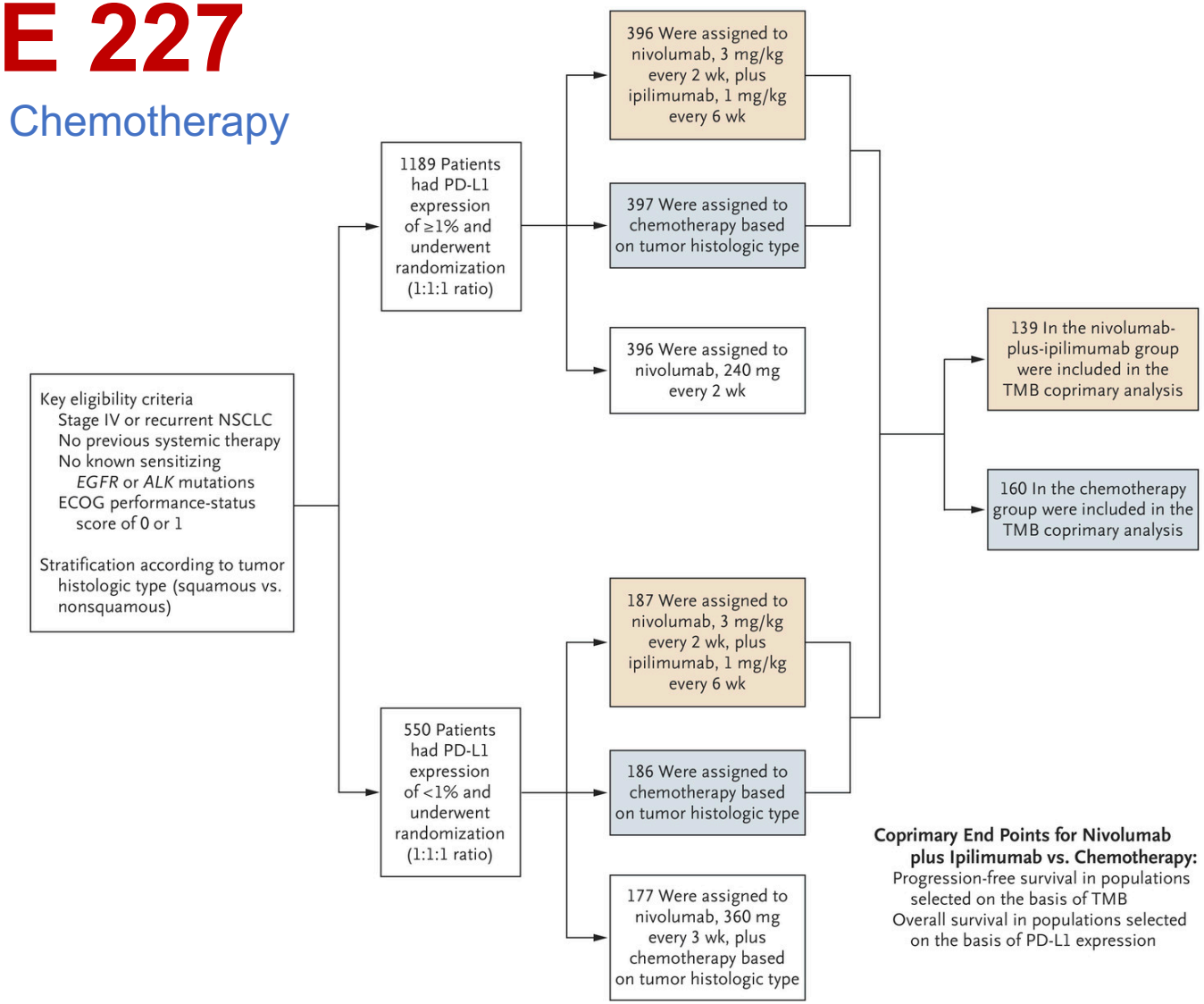
AE	ABCP (n=393)	BCP (n=394)
Treatment-related AE	141 (35.9%)	179 (45.4%)
Grade 1-2 treatment-related AEs with incidence of ≥15% in any group		
Alopecia	183 (46.6%)	173 (43.9%)
Peripheral neuropathy	141 (35.9%)	113 (28.7%)
Nausea	119 (30.3%)	101 (25.6%)
Fatigue	88 (22.4%)	79 (20.1%)
Anemia	70 (17.8%)	71 (18.0%)
Decreased appetite	77 (19.6%)	56 (14.2%)
Diarrhea	70 (17.8%)	58 (14.7%)
Arthralgia	63 (16.0%)	55 (14.0%)
Constipation	65 (16.5%)	45 (11.4%)
Epistaxis	50 (12.7%)	68 (17.3%)

Safety profile of ABCP was consistent with previously reported safety risks of the individual medicines

Reference: Socinski MA, et al. *N Engl J Med.* 2018;378(24):2288-2301.

CHECKMATE 227

Nivolumab + Ipilimumab vs Chemotherapy

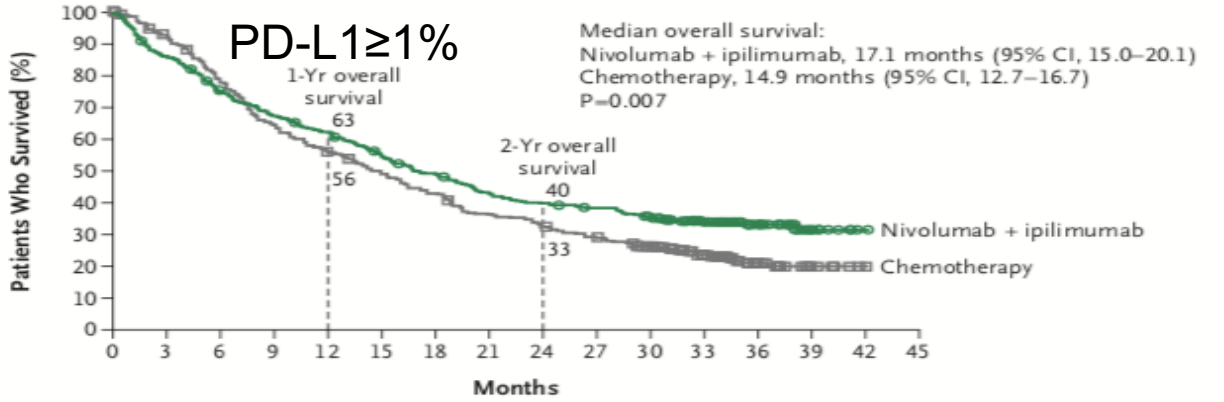


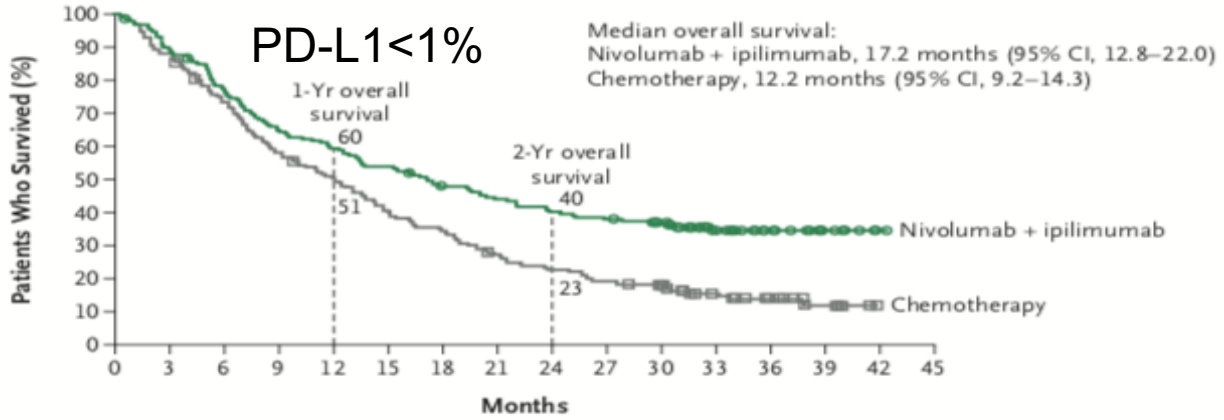
Reference: Hellman MD, et al. *N Engl J Med.* 2018;378(22):2093-2104.

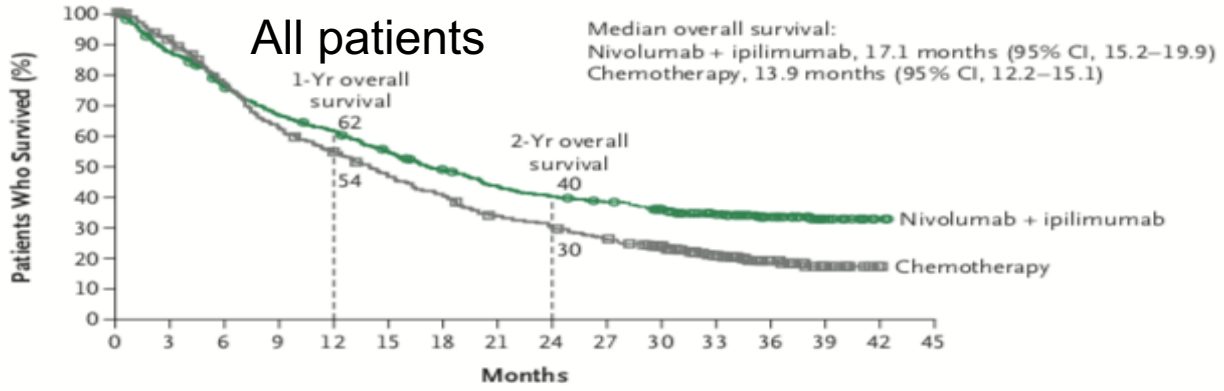
CHECKMATE 227

Nivolumab + Ipilimumab vs Chemotherapy

	Nivolumab + Ipilimumab	Chemotherapy
PD-L1 ≥1% Median OS (95% CI) HR (97.72% CI) *P* value	n=396 17.1 (15.0-20.1) months 0.79 (0.65-0.96) *P*=0.007	n=397 14.9 (12.7-26.7) months - -
PD-L1 <1% Median OS (95% CI) HR (95% CI)	n=187 17.2 (12.8-22.0) months 0.62 (0.48-0.78)	n=186 12.2 (9.2-14.3) months -
All Pts Median OS 95% CI HR	n=583 17.1 (15.2-19.9) months 0.73 (0.64-0.84)	n=583 13.9 (12.2-15.1) months -







Reference: Hellman MD, et al. *N Engl J Med.* 2019

CHECKMATE 227

Nivolumab + Ipilimumab vs Chemotherapy

Adverse Event	Nivolumab plus Ipilimumab (N=576)		Chemotherapy (N=570)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	number of patients (percent)			
Treatment-related adverse events				
All events	442 (76.7)	189 (32.8)	467 (81.9)	205 (36.0)
Reported in ≥15% of patients				
Diarrhea	98 (17.0)	10 (1.7)	55 (9.6)	4 (0.7)
Rash	98 (17.0)	9 (1.6)	30 (5.3)	0
Fatigue	83 (14.4)	10 (1.7)	108 (18.9)	8 (1.4)
Decreased appetite	76 (13.2)	4 (0.7)	112 (19.6)	7 (1.2)
Nausea	57 (9.9)	3 (0.5)	206 (36.1)	12 (2.1)
Anemia	22 (3.8)	8 (1.4)	188 (33.0)	66 (11.6)
Neutropenia	1 (0.2)	0	98 (17.2)	54 (9.5)
Treatment-related serious adverse events	141 (24.5)	106 (18.4)	79 (13.9)	61 (10.7)
Treatment-related adverse events leading to discontinuation†	104 (18.1)	71 (12.3)	52 (9.1)	28 (4.9)
Treatment-related death‡	8 (1.4)	—	6 (1.1)	—

Reference: Hellman MD, et al. *N Engl J Med.* 2018;378(22):2093-2104.

Summary

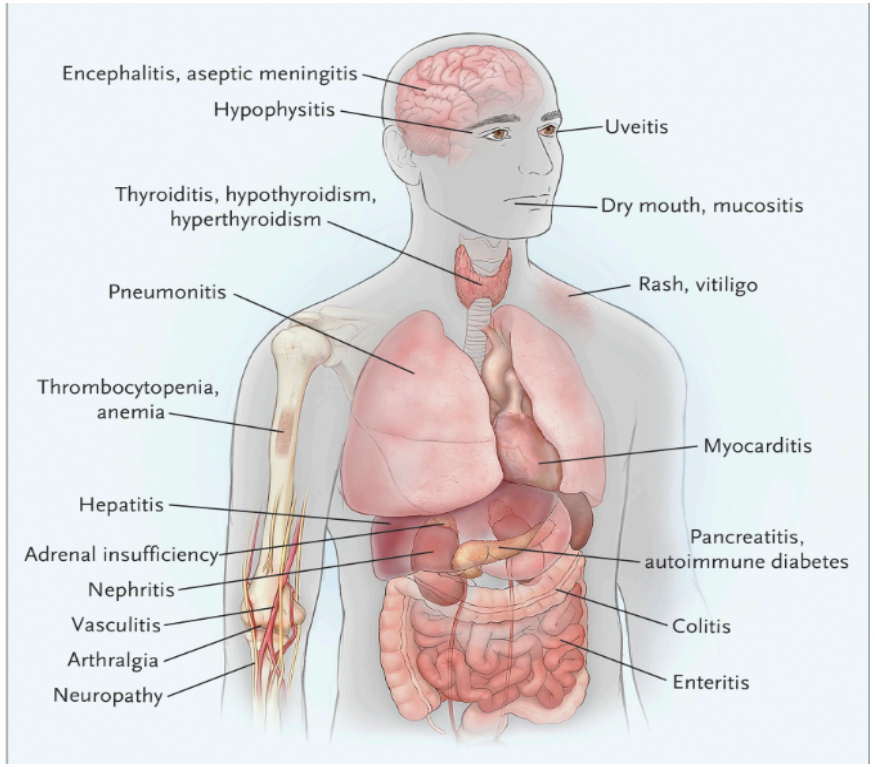
- ICI immunotherapy may be effective in patients with metastatic NSCLC without other actionable mutations
  - Pembrolizumab
  - Nivolumab
  - Atezolizumab
  - Durvalumab
- Must be aware of imAEs

AE Recognition (Case Studies)

Slides Courtesy of Beth Sandy, MSN, CRNP, OCN

Immunotherapy Toxicity Is Real!

- We are not as concerned about traditional chemotherapy side effects
  - This gets a bit confused when given concurrent with chemotherapy
- "Any word that ends in '–itis' can happen"



Reference: Postow MA, et al. *N Engl J Med.* 2018;378(2):158-168.

Case Study Patient 1

- 65-year-old male with stage IV NSCLC with PD-L1 90% has been on pembrolizumab for 9 months
- He presents for his routine treatment with increased SOB and changes in his baseline cough
- He reports that sometimes his SOB is so severe that he has to stop to catch his breath
- Vital signs
  - BP 132/88
  - HR 92
  - Pulse ox 90% (does not require oxygen), baseline 95-100%

Case Study Patient 1

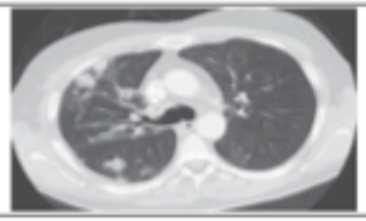
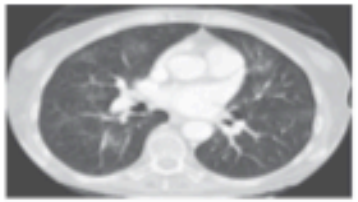
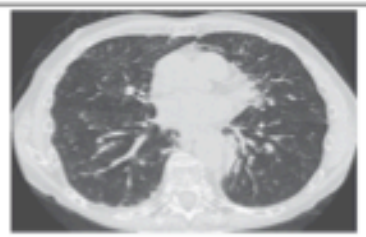
- Should any testing be ordered?
  - CT chest with IV contrast
  - Resting and walking pulse ox
- CT scan results shows diffuse ground glass opacities in both lungs
- Walking pulse ox 85%, quickly returns to 90% after stopping

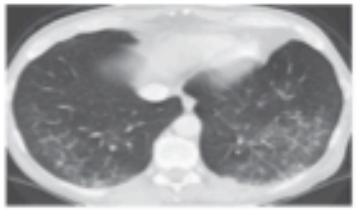
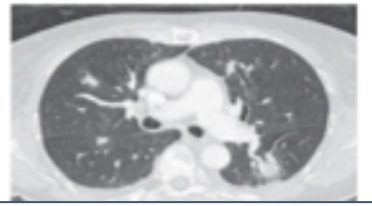
Pneumonitis

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; oxygen indicated.
4	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)
5	Death

Reference: US Department of Health and Human Services. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Published November 27, 2017. Accessed September 29, 2019.

The Many Faces of Pneumonitis

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases

Radiologic Subtypes	Representative Image	Description
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Reference: Naidoo J, et al. *J Clin Oncol.* 2017;35(7):709-717.

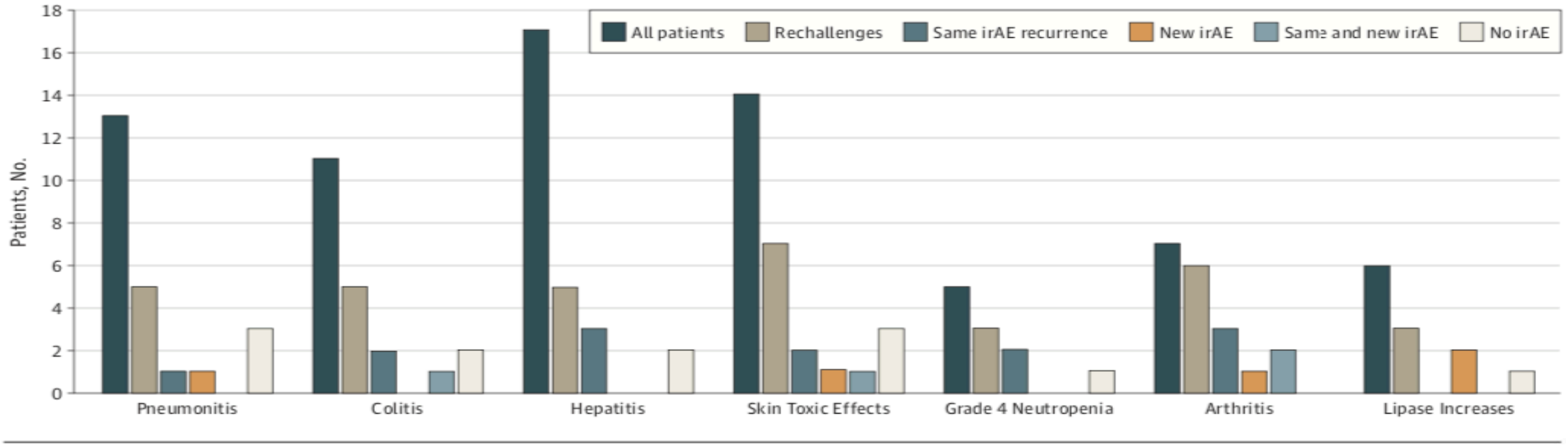
Management

Grade	Treatment
1	• Increased monitoring • If evidence of progression, treat at higher grade
2	• Immunotherapy should be withheld and steroids (eg, prednisone 1 mg/kg daily) administered • If symptoms improve to ≤ grade 2, start slow steroid taper over >1 month • If symptoms do not improve, or worsen, treat as grade 3-4
3/4	• Permanently discontinue immunotherapy (except endocrinopathies and skin toxicity) • Initiate methylprednisolone IV, 2 mg/kg/day; consider hospitalization and ICU care • Taper steroids over >2 months • If persistent with steroids, consider alternative immunosuppressive agents (infliximab at 5 mg/kg) • Consider drug rechallenge on a case-by-case basis after discussions weighing risk/benefit with the patient and only if symptoms and imaging abnormalities resolve • Permanently discontinue for grade 4

Case Study Patient 1

- He is started on prednisone 1 mg/kg daily and feels better almost immediately
- He is tapered off steroids over 4 weeks
- He asks, “Can I go back on pembrolizumab?”

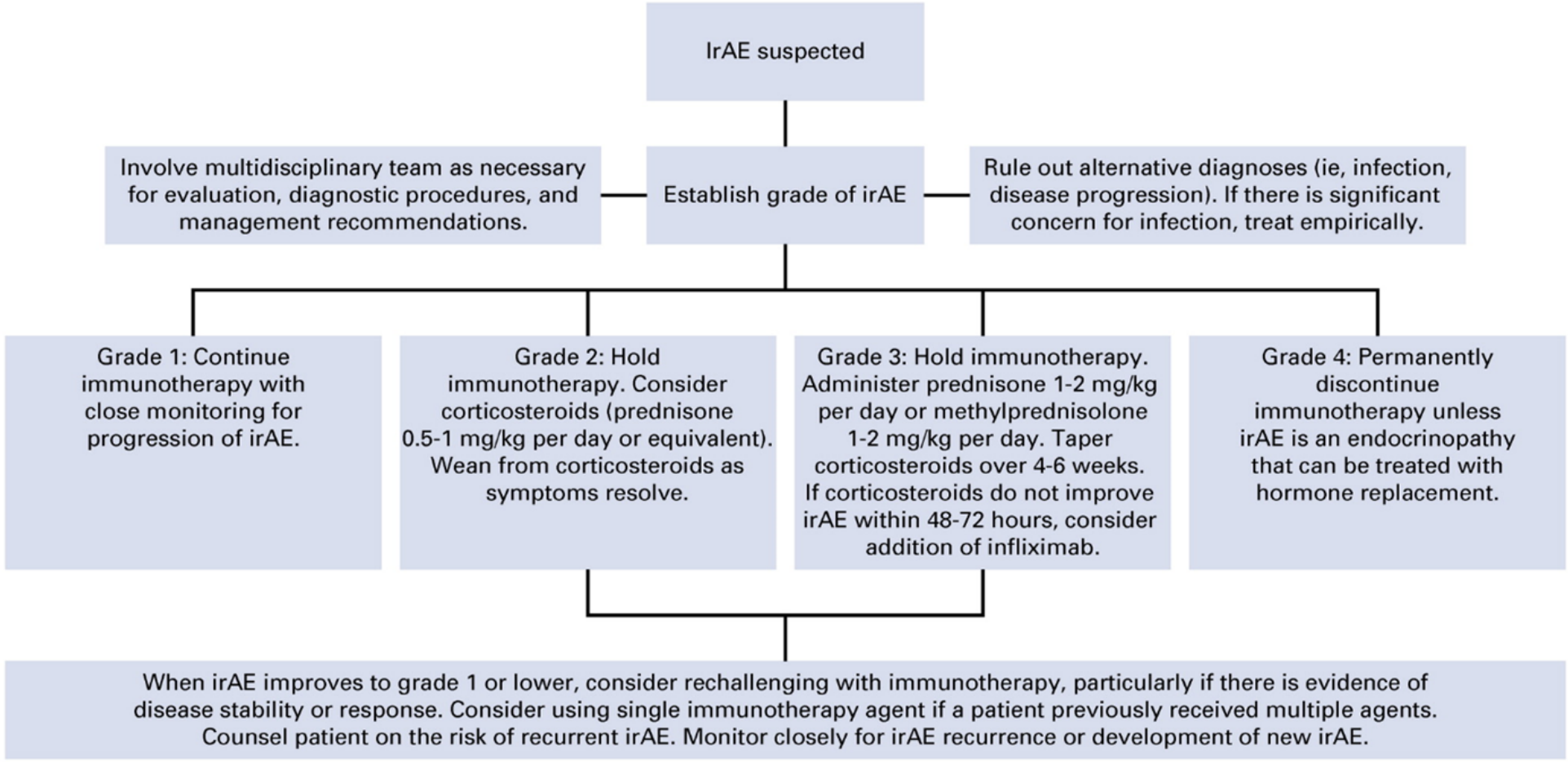
Treatment Rechallenge



- For most cases, rechallenge after steroids is reasonable (particularly pneumonitis)
- I generally do not rechallenge with grade 4 AEs

Reference: Simonaggio A, et al. *JAMA Oncol.* 2019. doi:10.1001/jamaoncol.2019.1022.

Severity-Guided Management of imAEs



Reference: Nakajima, E.C., Lipson, E.J., Brahmer, J.R. JCO. 2019; 30(37):2714-2718

Case Study Patient 2

- 56-year-old female with stage IIIA NSCLC
- Recently treated with concurrent chemoradiation
- She has been on consolidative durvalumab for 9 weeks
- She reports baseline 2-3 bowel movements daily
- She presented in clinic with abdominal pain, increase in bowel movements (now 4-5 bowel movements) with some blood and mucus

Colitis

A disorder characterized by colon inflammation

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Abdominal pain; mucus or blood in stool
3	Severe abdominal pain; peritoneal signs
4	Life-threatening with death consequences; urgent intervention indicated

Reference: US Department of Health and Human Services. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Published November 27, 2017. Accessed September 29, 2019.

Management

Grade	Treatment
1	• Supportive treatment, increased monitoring; if worsening, treat as grade 2 or as 3/4
2	• Delay treatment, consider glucocorticosteroids at 0.5–1 mg/kg daily if symptoms persist more than 5-7 days. If worsening, treat as grade 3/4 • May resume immunotherapy if toxicity returns to grade 1 or less after steroids tapered over a month
3/4	• Permanently discontinue immunotherapy (except endocrinopathies and skin toxicity) • Initiate glucocorticosteroids at 1–2 mg/kg daily; consider hospitalization • Taper steroids over at least a month • If persistent with steroids, consider alternative immunosuppressive agents (infliximab at 5 mg/kg)

Reference: Boutros C, et al. *Nat Rev Clin Oncol.* 2016;13(8):473-486.

Case Study Patient 2

- What is her likely diagnosis?
  - Colitis
- What grade?
  - Grade 2, increased bowel movements along with abdominal pain and blood/mucus in stool
- How would you manage?
  - Hold treatment, start prednisone 1 mg/kg daily

Case Study Patient 2

- Her symptoms are improving. Would you order CT scan?
  - Okay to hold off on CT abdomen/pelvis if symptoms are improving
  - If not improving, have scan done
- What would be the management if symptoms do not improve and the patient is unable to tolerate hydration?
  - Inpatient admission for IV fluids, steroids, and GI consult
  - Consult with research team since she is research patient

Summary: General Rules of imAEs

- Communication is critical
- For endocrine imAEs steroids are not usually indicated
  - Adrenal insufficiency is an exception, but different MOA
- For nearly all others, treatment is high-dose steroids
  - 1 mg/kg/day prednisone equivalent
  - Treat until symptoms improve, taper over 4-6 weeks
- Patients may be resistant to taking steroids
  - Untreated imAEs are associated with BAD outcomes
- If ineffective, low threshold for consultation of relevant specialty
  - Panhypopituitarism: I always consult endocrine
  - Bullous rashes: I always consult dermatology (to be seen same day!)
  - Myocarditis: I always consult cardiology

Conclusions and Assessment

Summary of Key Points (PEARLs)

- For patients with molecularly targetable lesions, use a targeted therapy
  - Resistance remains a major issue
  - Chemotherapy still active for these diseases
- ICI immunotherapy (eg, pembrolizumab, nivolumab, atezolizumab, durvalumab) may be effective in patients with metastatic NSCLC without other actionable mutations
- Patient education and engagement is critical to manage imAEs
  - imAEs include pneumonitis, colitis, dermatitis, hepatitis, nephritis, and endocrinopathy
  - Brigatinib is associated with a specific pulmonary event that is NOT pneumonitis
  - Hypercholesterolemia is a unique toxicity seen with lorlatinib
  - Management depends on type of imAE and patient characteristics
    - Referral to appropriate specialty may be needed

Questions

First-Line Therapy for Metastatic Non–Small Cell Lung Cancer

State-of-the-Art Targeted Therapy and Immunotherapy Approaches

Thank you for joining us!

Please complete your evaluations.