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UNC CANCER CARE

Lung Cancer Management in North Carolina: Updates for 2020

August 26, 2020

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Disclosures

Research funding to institution: AstraZeneca

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Learning Objectives

- **Recognize biomarkers for the selection of targeted therapy for non-small cell lung cancer**
- **Compare immune checkpoint inhibitor treatment options for metastatic non-small cell lung cancer**
- **Describe the role of immune checkpoint inhibitors in small cell lung cancer**

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Outline

- **Overview of molecular testing approaches**
- **Recent targeted therapy approvals for NSCLC**
  - Capmatinib
  - Selpercatinib
  - Emerging targets (KRAS, HER2)
- **Immunotherapy combinations**
- **Small cell lung cancer**
  - Role of immune checkpoint inhibitors
  - Lurbinectedin

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Case

- BT is a 70-year-old female non-smoker with a PMH of hypertension who presents to her PCP with left neck swelling for 2 weeks
- CT scan of the neck reveals supraclavicular lymphadenopathy
- CT scan of the chest demonstrates a dominant left upper lobe mass with mediastinal lymph node enlargement and bilateral lung nodules
- She is referred to interventional radiology and a core biopsy of the supraclavicular mass is performed
- Pathology: non-small cell carcinoma consistent with lung adenocarcinoma (CK-7, TTF-1 and Napsin positive)

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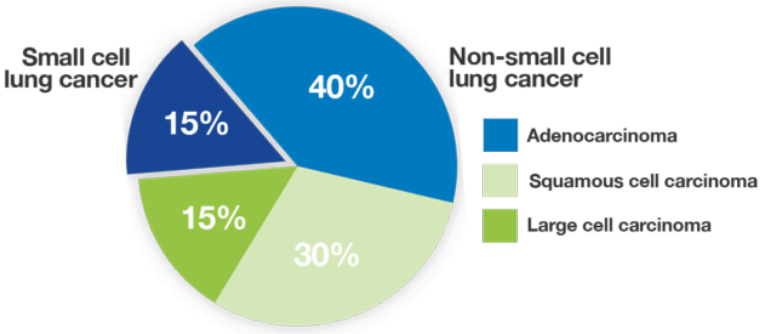
Lung Cancer: Histologic Subtypes



https://lcfamerica.org/lung-cancer-info/types-lung-cancer/

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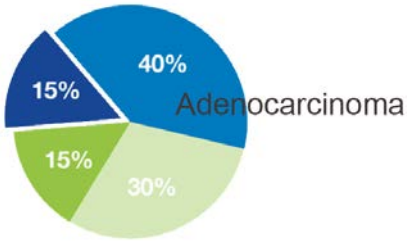
Genomic profiling methods



- Tissue-based:
  - Next Generation Sequencing (DNA or RNA)
  - Polymerase chain reaction (PCR)
  - Fluorescence in situ hybridization (FISH)
  - Immunohistochemistry (IHC)
- Blood-based ("liquid biopsy")

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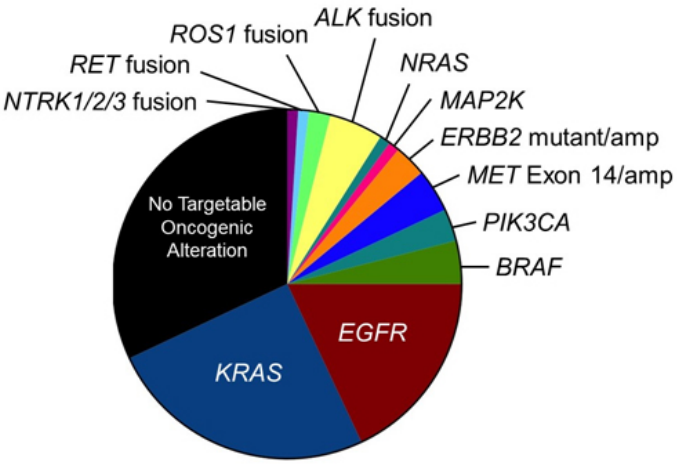
Distinct molecular subtypes



Janne P. ASCO, 2020

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Case

- Biopsy specimen is submitted for DNA-based next generation sequencing but there is insufficient material
- A “liquid biopsy” assay is performed
- A MET exon 14 deletion mutation is identified by cfDNA analysis
- Immunohistochemistry with the PD-L1 22C3 assay demonstrates a tumor proportion score (TPS) of 20%
- What therapy choices does this patient have?

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Concordance of blood and tissue-based testing

- Variable sensitivity (60-90%)
- High concordance with tissue testing for driver mutations
- Longitudinal analysis, resistance mechanisms
- Challenges:
  - Subclonal mutations
  - Clonal hematopoiesis of indeterminate potential (CHIP)
  - Identifying fusions

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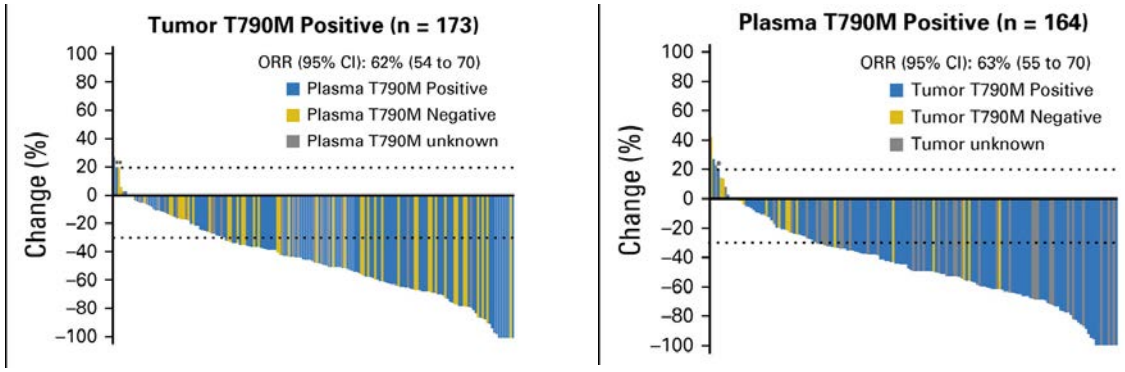
Treatment outcomes by plasma mutation analysis

Positive predictive value



Oxnard GR et al. *J Clin Oncol,* 2016.

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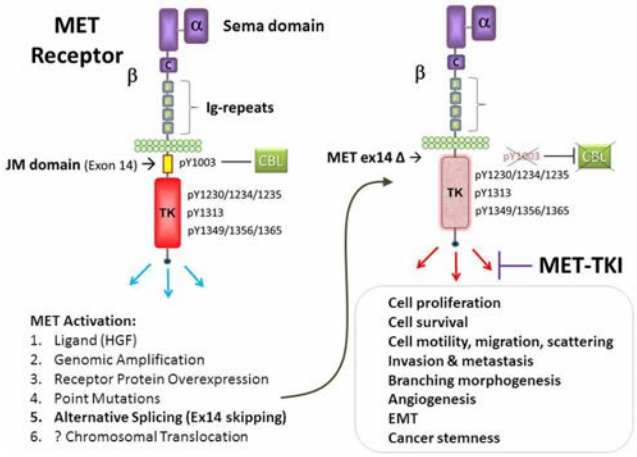
MET

- MET exon 14 skipping mutations occur in ~ 3-4% of patients with NSCLC
- Associated with poor response to chemotherapy and immunotherapy



Ma PC. *Cancer Discov*, 2015.

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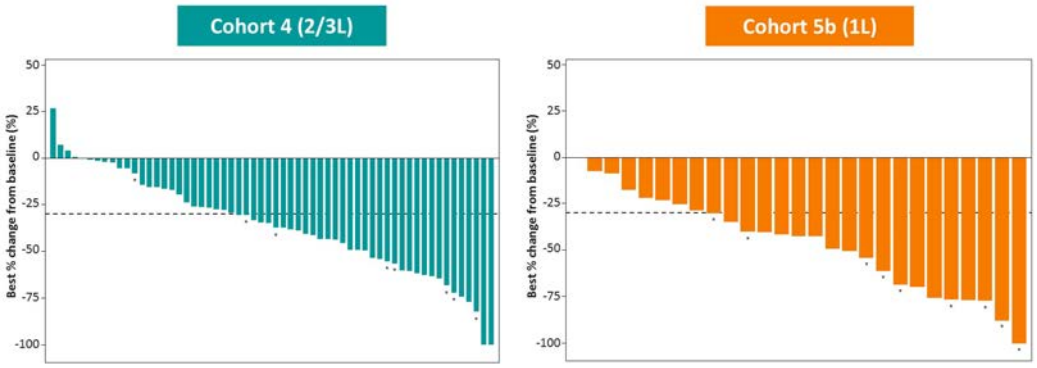
Capmatinib: Geometry Mono-1 Study

Tumor shrinkage per BIRC

Deep responses observed in a majority of patients across both cohorts



*patients still on-treatment

Wolf J et al. ASCO Annual Meeting, 2019

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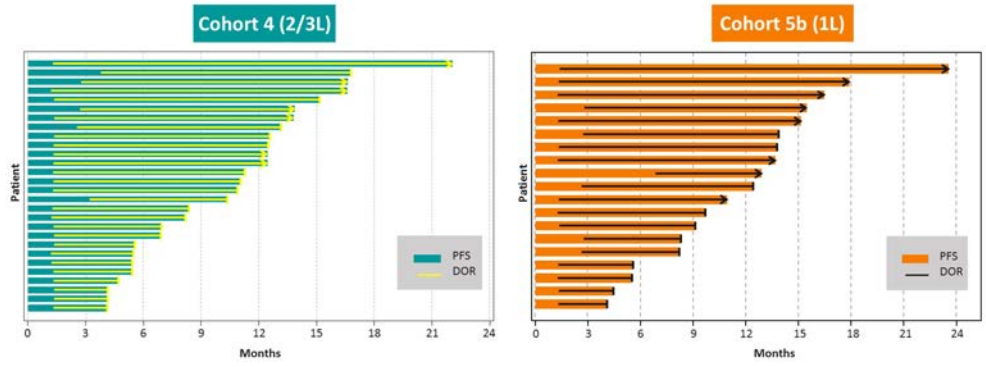
Capmatinib: Duration of response

Swimmer plots for responders

Rapid and durable responses across both cohorts

Majority of patients had onset of response within the first 7 weeks of treatment: 82.1% in Cohort 4 and 68.4% in Cohort 5b



Wolf J et al. ASCO Annual Meeting, 2019

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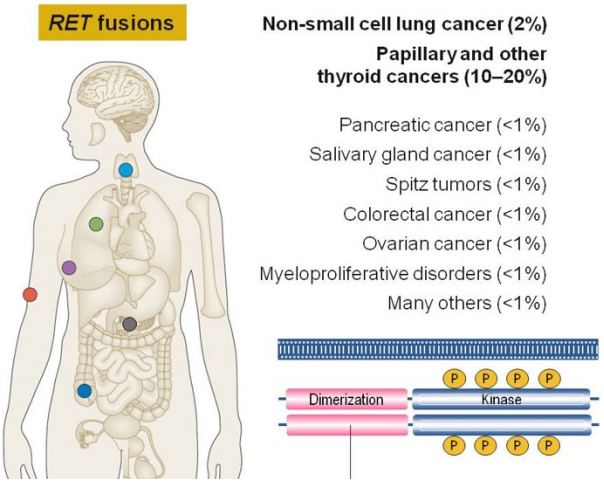
RET fusions

- Receptor tyrosine kinase activated by fusions or point mutations
- Common fusion partners in NSCLC: *KIF-5B, CCDC6*



Drilon A. et al. ASCO, 2018.

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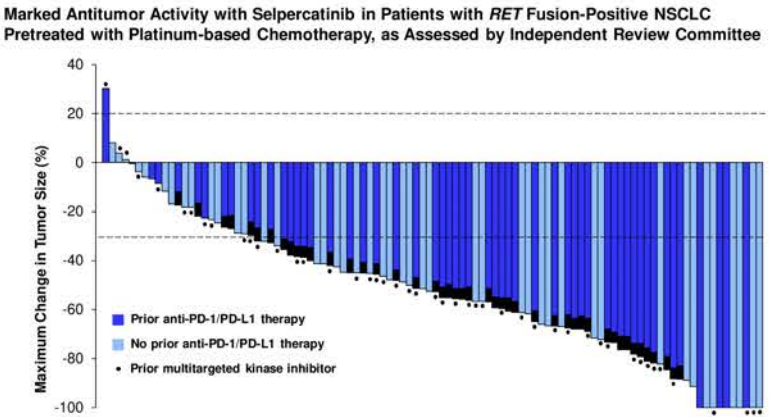
Selpercatinib for RET fusion-positive NSCLC



- Prior platinum doublet
  - ORR 64%
  - Intracranial ORR 91%
  - mDOR 18 months
- Treatment naïve:
  - ORR 85%
  - mDOR NR
- Intracranial activity

Goto K et al. ASCO, 2020.

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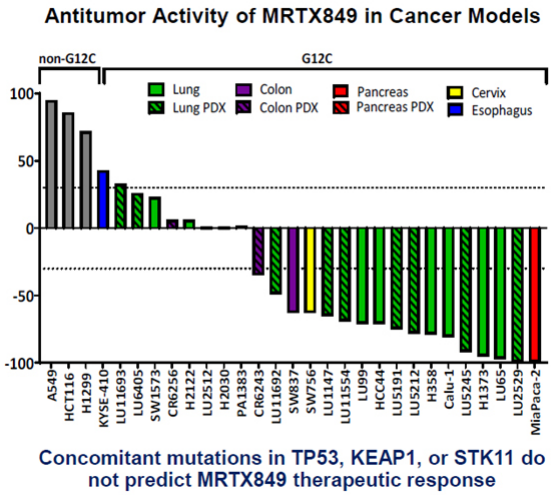
KRAS G12C Inhibitors: Drugging the undruggable

- **Multiple agents in clinical trials:**
- Irreversibly bind KRASG12C in inactive, GDP-bound state
- Orally bioavailable
  - AMG 510
  - MRTX849
- Phase II/Combination trials underway



Concomitant mutations in TP53, KEAP1, or STK11 do not predict MRTX849 therapeutic response

Janne P et al. AACR-NCI-EORTC, 2019.

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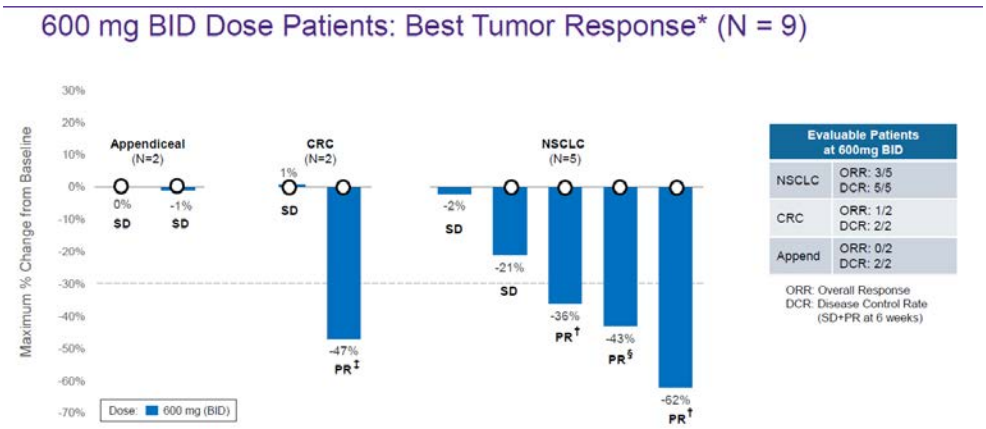
MRTX849: Phase I/II Trial



Janne P et al. AACR-NCI-EORTC, 2019.

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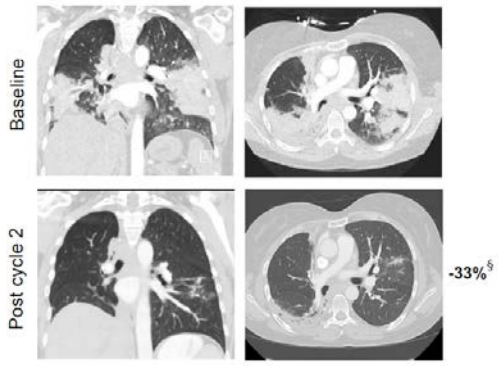
MRTX849: Case Study in NSCLC



§ This patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)

Demographics

45 year old female with metastatic lung adenocarcinoma, former smoker

Molecular Characteristics

- *KRAS* G12C mutation (c.34G>T)
- *KEAP1* (K97M)
- *STK11* (E223*)

Treatment History

- Carboplatin/pemetrexed/pembrolizumab
- Docetaxel
- Investigational treatment with binimetinib plus palbociclib
- Best response on prior regimens is SD

Best Response

PR: 33% reduction at first scan. A 43% reduction was observed at the second scan, after the data cut-off. The patient remains on study.

Marked clinical improvement within 2 weeks, including complete resolution of baseline cough and oxygen dependency.

Janne P et al. AACR-NCI-EORTC, 2019.

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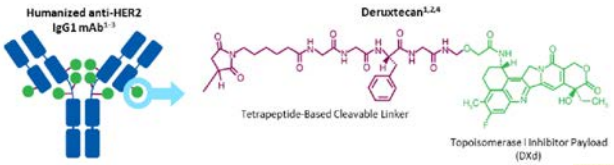
HER2 activating mutations



- HER2-activating mutations in 1-3% of NSCLC
- Trastuzumab deruxtecan is a HER2-antibody drug conjugate

DESTINY-Lung01 HER2-Mutated NSCLC

Efficacy Results

	Patients (N = 42)
Confirmed ORR by ICR	**61.9% (n = 26)** (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
Not evaluable	4.8% (n = 2)
Disease control rate	90.5% (95% CI, 77.4%-97.3%)
Duration of response, median	Not reached (95% CI, 5.3 months-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 months)

Smith EF et al. ASCO, 2020

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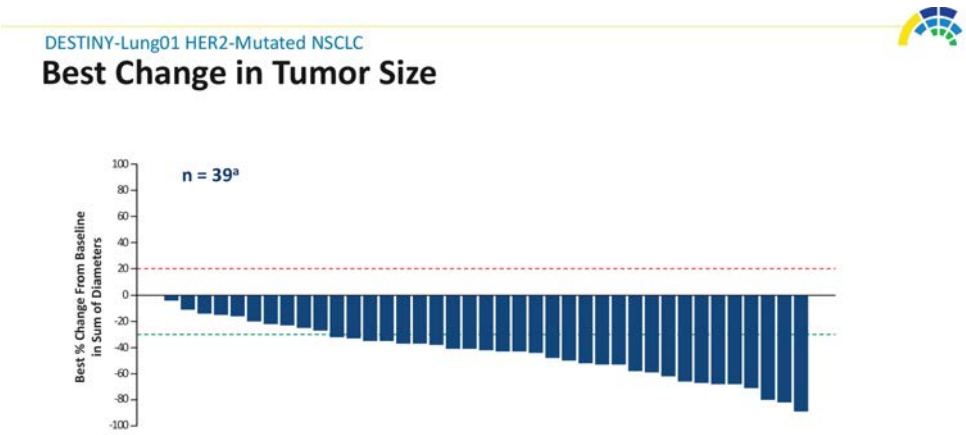
DESTINY-Lung 01



Smith EF et al. ASCO, 2020

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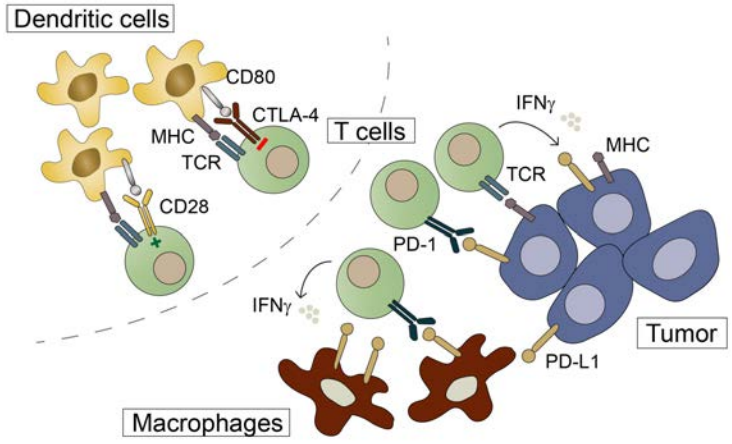
Immunotherapy: Mechanism of Action



Patel, SA and Weiss JM. *Clin Chest Med*, 2020.

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Biomarkers: Immunotherapy

- **PD-L1 Immunohistochemistry (IHC)**
  - IHC is fast and readily available
  - Tumor proportion score (TPS): percentage of tumor cells showing positive staining
  - Concordance between antibodies and samples
- **Tumor mutational burden (TMB)**

Tsao, MS et al. *J Thorac Oncol,* 2018

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Immunotherapy agents

PD-1 antibodies:	**PD-L1 antibodies**:	**CTLA-4 antibodies**:
Pembrolizumab	Atezolizumab	Ipilimumab
Nivolumab	Durvalumab	Tremelimumab
Cemiplimab	Avelumab	

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Combination approaches for first line treatment

Non-squamous:	**Squamous**:
• Carboplatin + pemetrexed + pembrolizumab	• Carboplatin + paclitaxel + pembrolizumab
• Carboplatin + paclitaxel + atezolizumab + bevacizumab	• Carboplatin + nab-paclitaxel + pembrolizumab
• Nivolumab + ipilimumab (PD-L1 > 1%)	• Nivolumab + ipilimumab (PD-L1 > 1%)
• Nivolumab + ipilimumab + pemetrexed + platinum	• Nivolumab + ipilimumab + paclitaxel + carboplatin

NCCN Guidelines v6.2020

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Nivolumab + Ipilimumab

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Hellmann MD et al. *N Engl J Med*, 2019

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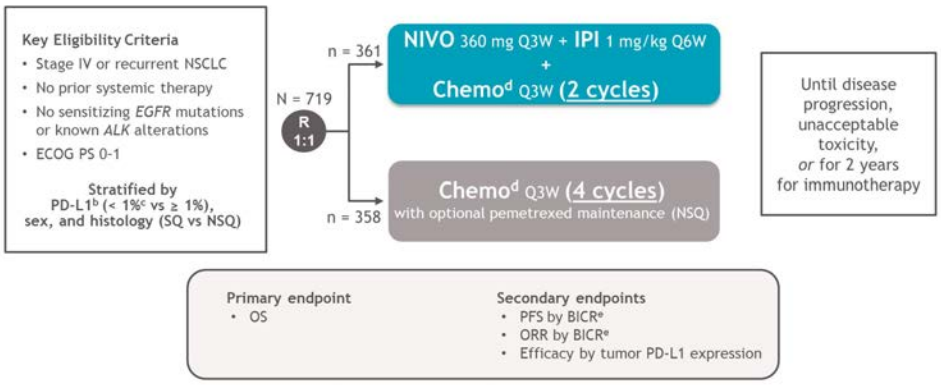
Nivolumab + Ipilimumab + chemotherapy

CheckMate 9LA study design[a]



Reck M et al. ASCO, 2020

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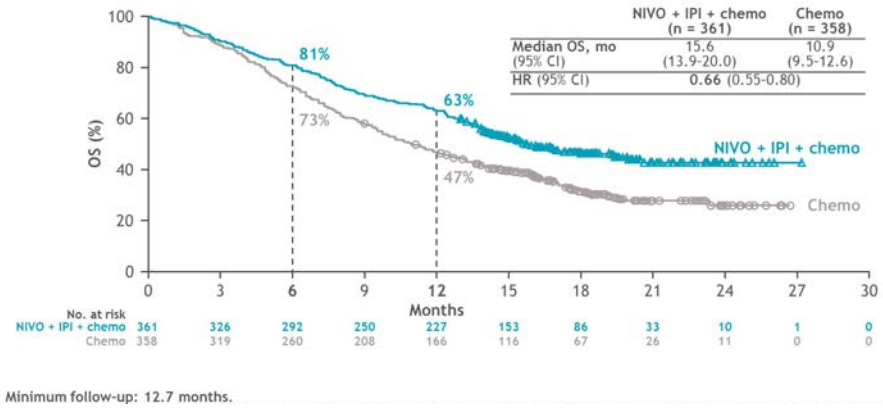
Checkmate 9LA

Primary endpoint (updated): Overall survival[a]



Minimum follow-up: 12.7 months.

Reck M et al. ASCO, 2020

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Multiple first-line options: how to choose?

- **Patient considerations:**
  - Performance status
  - Preferences (avoid chemotherapy)
  - Co-morbidities (neuropathy, cytopenias, etc)
- **Disease considerations:**
  - PD-L1 status
  - Distribution of metastases (liver), histology
  - Symptom burden and need for response

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Case 2

- BB is a 58-year-old male with a 60 pack-year smoking history presenting with facial, arm swelling and cough
- A chest x-ray demonstrates increased soft tissue in the mediastinum
- Chest CT demonstrates a mediastinal mass with compression of the SVC and hypodensities in the liver
- Biopsy of a liver lesion demonstrates small cell carcinoma
- Should this patient be treated with immune checkpoint blockade?

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Small cell lung cancer

- **Limited stage vs Extensive Stage (ES-SCLC)**
- IMpower 133

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Horn L et al. *NEJM,* 2018

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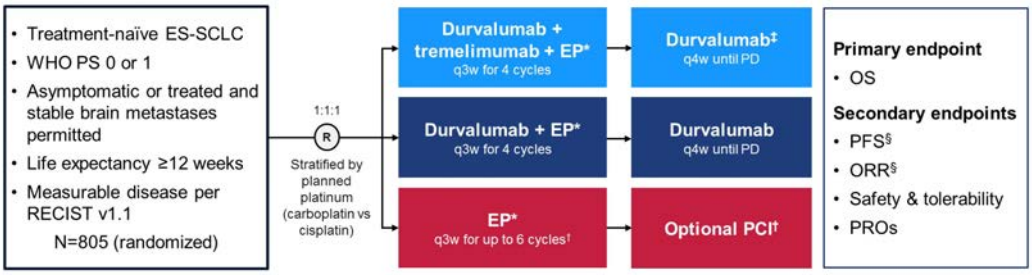
ES-SCLC

CASPIAN Study Design

Phase 3, global, randomized, open-label, active-controlled, multicenter study



Paz-Ares L *et. al*, ASCO, 2020.

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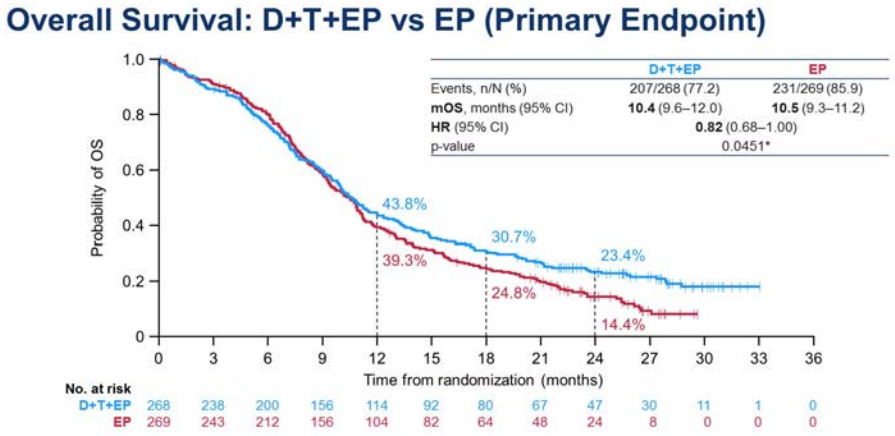
Durvalumab+Tremelimumab+EP



Paz-Ares L *et. al*, ASCO, 2020.

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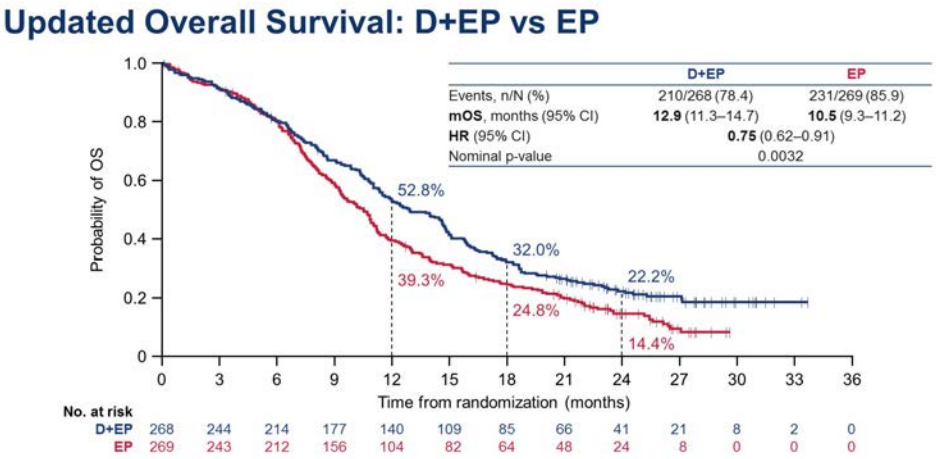
Durvalumab+EP



Paz-Ares L *et. al*, ASCO, 2020.

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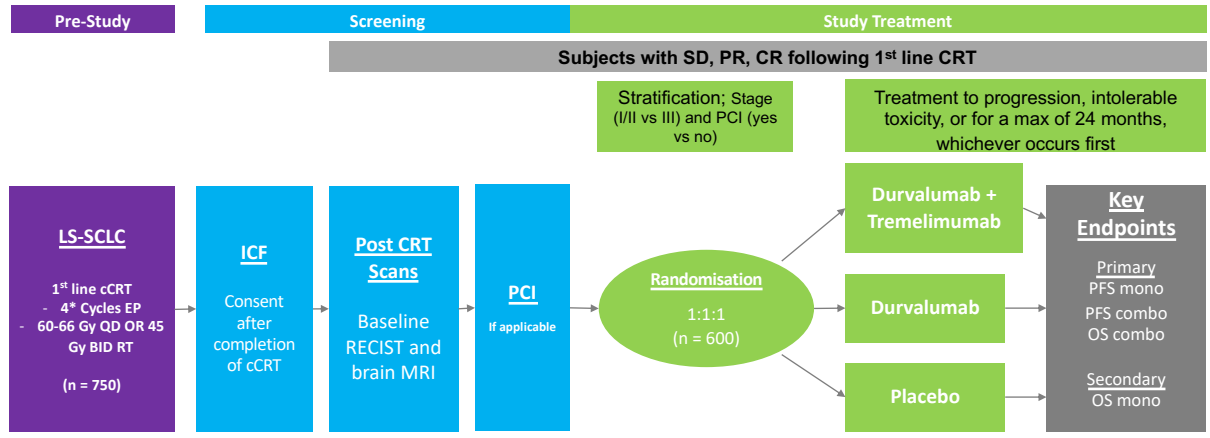
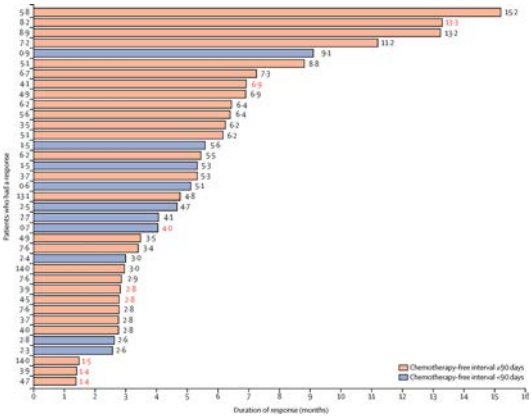
ADRIATIC: LS-SCLC



Lurbinectedin

- A selective inhibitor of oncogenic transcription → apoptosis



- Chemotherapy-free interval < 90 days
  - 22% PR + 29% Stable disease
  - mDOR: 4.7 months
- Chemotherapy-free interval ≥ 90 days
  - 45% PR + 37% Stable disease
  - mDOR 6.2 months

Trigo J et al. *Lancet Oncol*, 2020.

Lurbinectedin: Toxicity Profile

- **Common treatment-related AEs**
- Anemia
- Leukopenia
- Neutropenia
- Thrombocytopenia
- LFT abnormalities
- Fatigue
- Nausea/vomiting
- Diarrhea

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Summary

- Genomic profiling of lung adenocarcinomas is important for treatment selection
- Recent targeted therapy approvals include capmatinib and selpercatinib
- Novel KRAS, HER2 targeting agents are on the horizon
- Review of recent chemotherapy and immunotherapy combinations approvals
- PD-L1 antibodies are standard of care for first line extensive stage SCLC
- Lurbinectedin is a novel agent for ES-SCLC

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