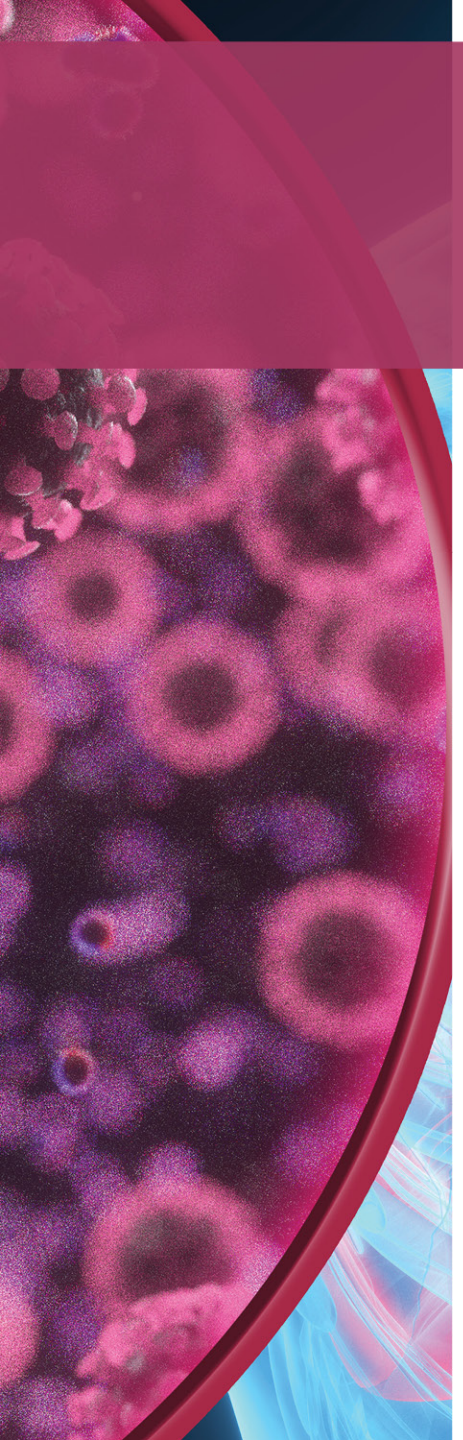
Frontline Treatment Approaches With Immune Checkpoint Inhibitors for Non-Small Cell Lung Cancer

Updates on Evolving Strategies

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



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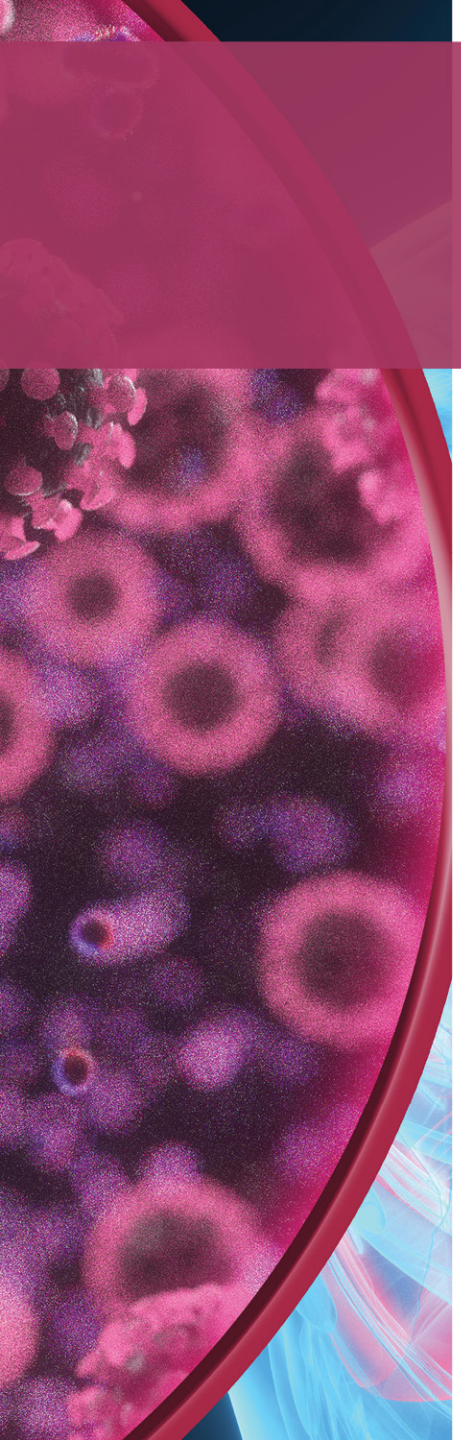

Disclosures

Dr. Segal has disclosed that she has no actual or potential conflicts of interest related to this program.

The clinical reviewer, **Lisa Holle, PharmD, BCOP, FHOPA**, has disclosed that she has no actual or potential conflicts of interest related to this program.

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Learning Objectives

- **Explain** key takeaways from recent clinical trials involving frontline treatments with immune checkpoint inhibitors (ICIs) for non-small cell lung cancer (NSCLC)
- **Discuss** emerging treatment strategies and ongoing research aimed at optimizing outcomes for NSCLC patients on ICIs in the frontline setting
- **Formulate** approaches for effective patient management, including drug-drug interactions and mitigating immune-related adverse events (irAEs) associated with ICIs in the frontline treatment of NSCLC

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- Lung Cancer Epidemiology
- Staging
- Histology and Genetics
- Stage I
- Stage II/III
- Adjuvant Treatment for Stage II/III NSCLC
- Neoadjuvant Treatment for Stage II/III NSCLC
- Management of Inoperable Stage III NSCLC
- Management of Select Immune-Related Adverse Events (irAEs)
- Management of Emerging Drug-Drug Interactions (DDIs)

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Incidence and Epidemiology

- Estimated 236,740 new cases of lung cancer in 2022
- 5-year relative survival of 22.9%
  - Survival rate for early-stage NSCLC has been increasing
  - Patients with stage I, II, III disease at high risk for recurrence and death

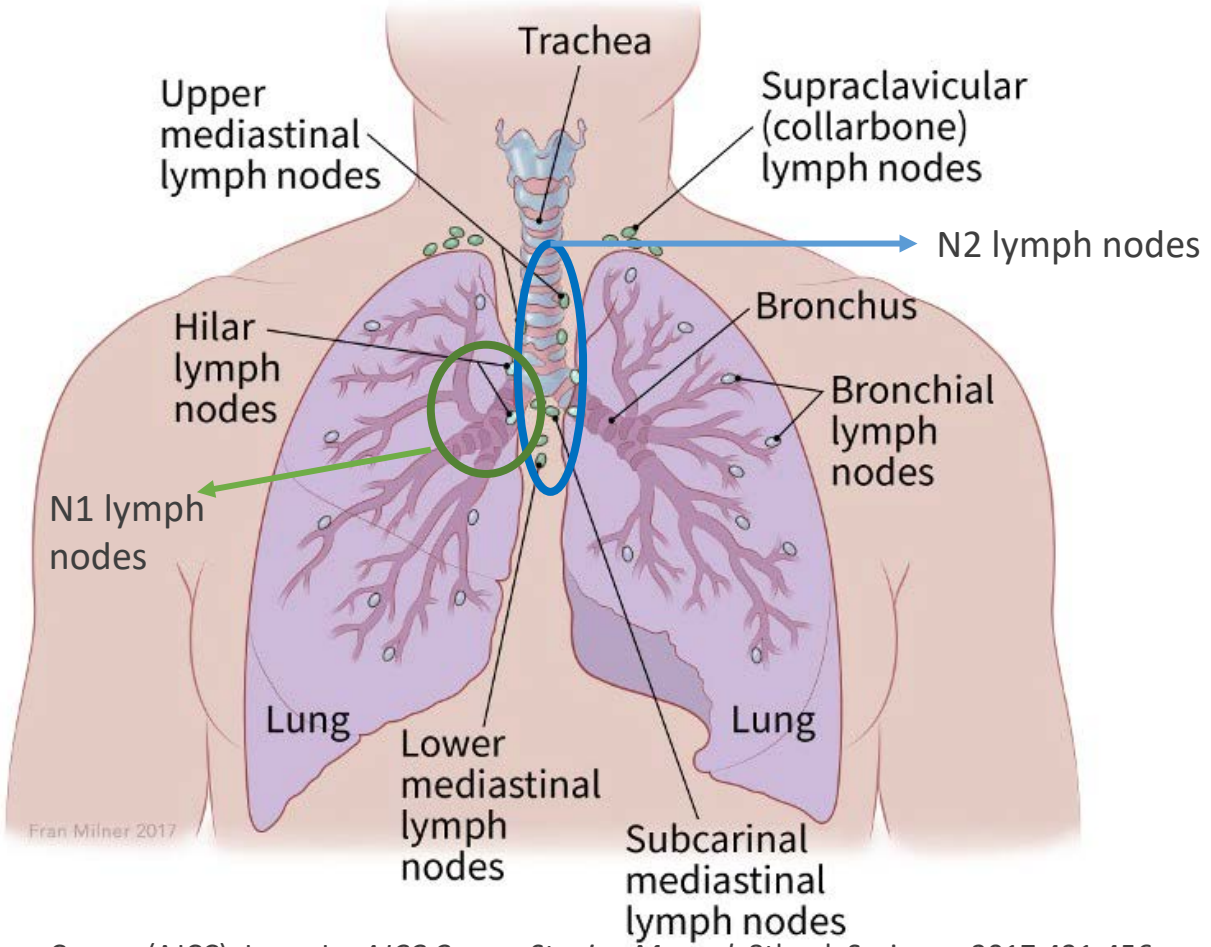
Lung Cancer: Incidence and Survival

Stage	Frequency of Diagnosis (%)	5-Year Survival (%)
Localized	19	61.2
Regional	22	33.5
Distant	55	7
Unknown	4	9.9

Cancer stat facts: lung and bronchus cancer. SEER17 2012-2018. All races, both sexes by SEER Summary Stage. Accessed February 18, 2023. https://seer.cancer.gov/statfacts/html/lungb.html

NSCLC Staging

NSCLC: Stages and Definitions (AJCC V8)	
Stage Number	**Definition**
I	• Minimally invasive, usually limited to primary lesion • No nodal involvement • Differences between stages IA-1B depend on size
II	• Larger tumor size • N1 nodal involvement • Tumor may have spread to lymph nodes (eg, hilar lymph nodes)
III	• Larger tumor (>5 cm), has grown into pleura • N2 nodal involvement • May have spread to other lymph nodes on other sides of the body
IV	• Distant metastatic disease



American Joint Committee on Cancer (AJCC). Lung. In: *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017:431-456.

Image: Respiratory lymph nodes. © 2017 The American Cancer Society. Used with permission.

Pathology of Lung Cancers

- Non-small cell lung cancer (NSCLC) histology: 80% to 85% of all lung cancers
  - Adenocarcinoma: ≈ 40% of NSCLC, most common type in nonsmokers
  - Squamous cell carcinoma: 25% to 30% of NSCLC
  - Large cell carcinoma: 10% to 15% of NSCLC

- Small cell lung cancer (SCLC) histology: 10% to 15% of all lung cancers
  - Classic small cell carcinoma
  - Large cell neuroendocrine cancer
  - Combined small cell carcinoma
  - Typical carcinoid
  - Atypical carcinoid

Govindan R, et al. *J Clin Oncol*. 2006;24(28):4539-4544; Wahbah M, et al. *Ann Diagn Pathol*. 2007;11(2):89-96.

Determining Treatment for New Diagnosis of NSCLC

- Assess patient performance status
- Molecular and biomarker testing
  - Molecular profiling for oncogenic driver variants/sensitizing mutations such as *EGFR*, *BRAF*, *ALK, MET, ROS1, RET, METex14, NTRK1/2/3*
  - Immunohistochemistry (IHC) analysis testing for programmed death-ligand 1 (PD-L1) expression
- PD-L1 expression may be used as a biomarker to predict antitumor response and correlates to response rates up to 30%; may be imprecise
  - Shortcomings
    - Availability of assays to measure PD-L1
    - Variability of PD-L1 expression

Garinet S, et al. *J Clin Med*. 2018;7(6):144; Baumgart M. *Am J Hematol Oncol*. 2015;11(6):10-13; Davis AA, Patel VG. *J Immunother Cancer*. 2019;7(1):278; Sideway P. *Nat Rev Clin Oncol.* 2019;16(6):337.

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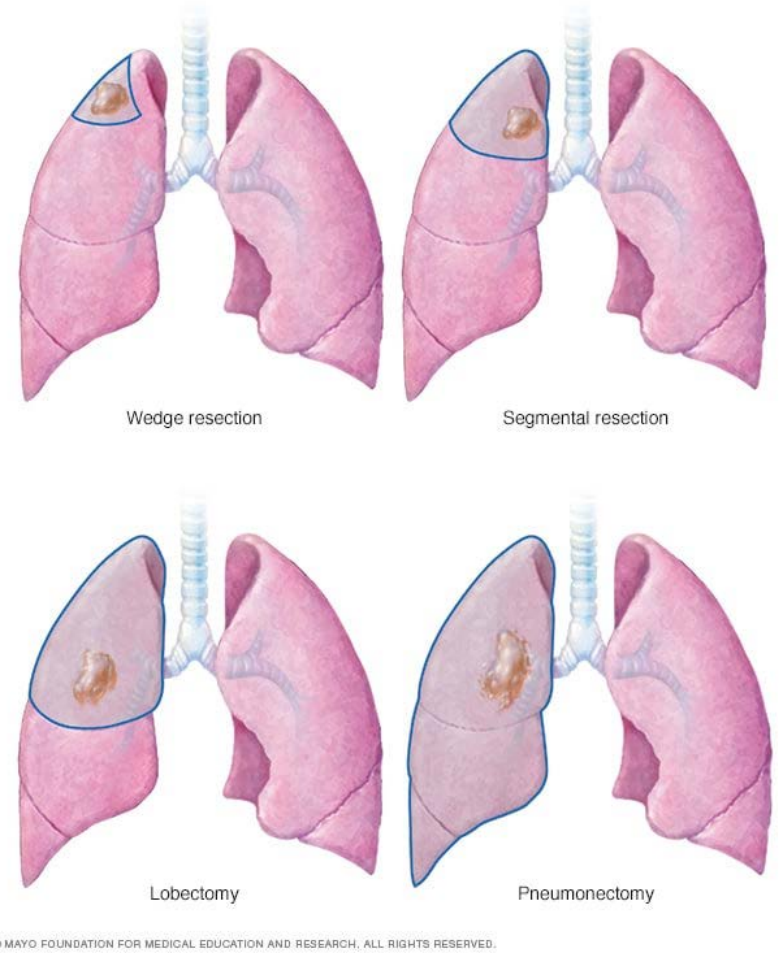
Approach to Stage I NSCLC

Patients With Surgically Resectable Disease

- Segmentectomy, wedge resection, lobectomy, or pneumonectomy with lymph node sampling

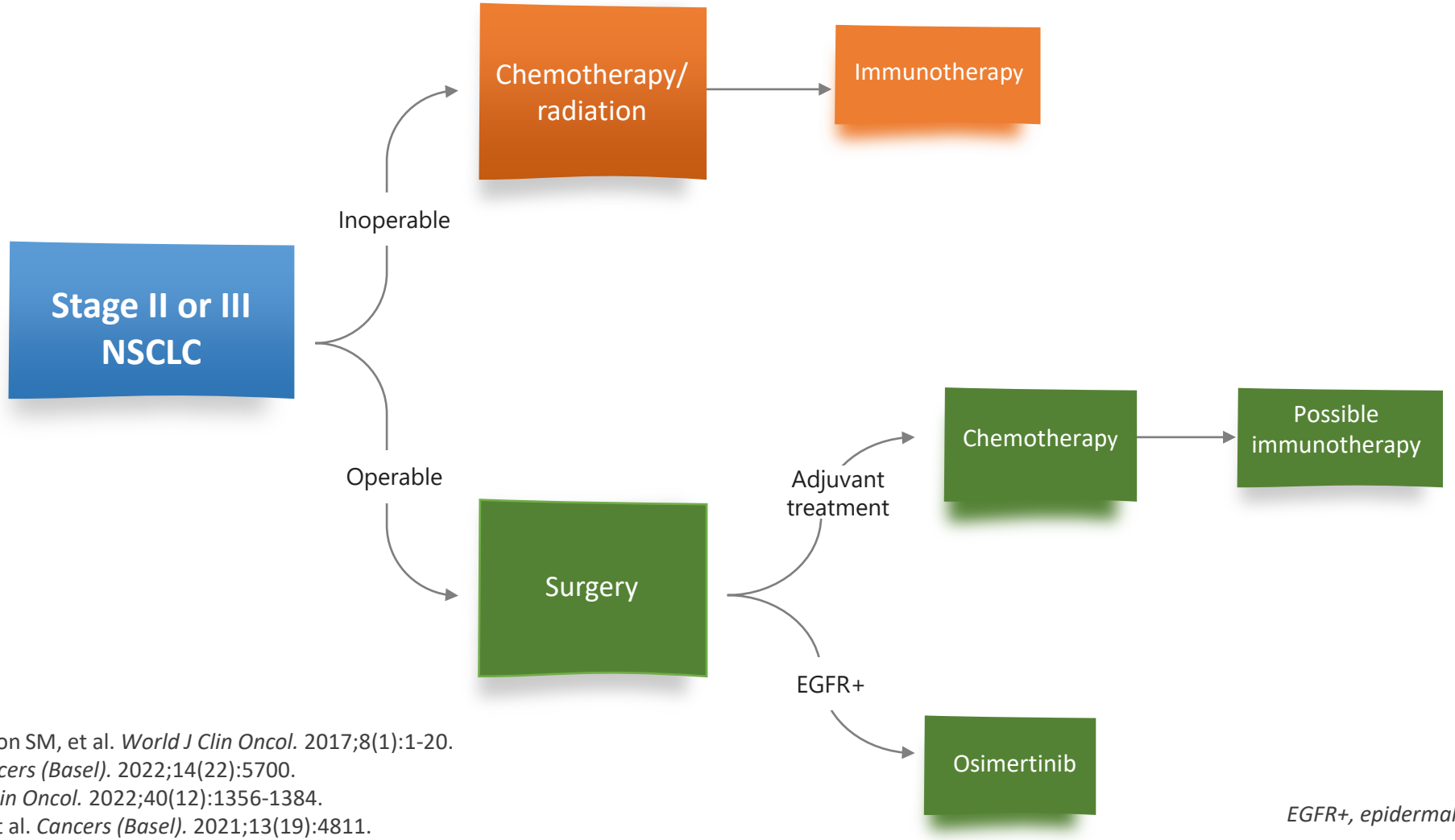
Patients With Inoperable Disease

- Radiation



Lackey A, Donington JS. *Semin Intervention Radiol*. 2013;30(2):133-140; Choi JI. *Transl Lung Cancer Res.* 2019;8(1):32-47.
Image: Mayo Clinic. Lung cancer surgery. Accessed February 18, 2023. https://www.mayoclinic.org/diseases-conditions/lung-cancer/multimedia/lung-cancer-surgery/img-20006167

Approach to the Treatment of Stage II/III NSCLC



Adapted from: Yoon SM, et al. *World J Clin Oncol.* 2017;8(1):1-20.
Ferro A, et al. *Cancers (Basel).* 2022;14(22):5700.
Daly ME, et al. *J Clin Oncol.* 2022;40(12):1356-1384.
Mielgo-Rubio X, et al. *Cancers (Basel).* 2021;13(19):4811.

EGFR+, epidermal growth factor receptor positive.

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Adjuvant Chemotherapy

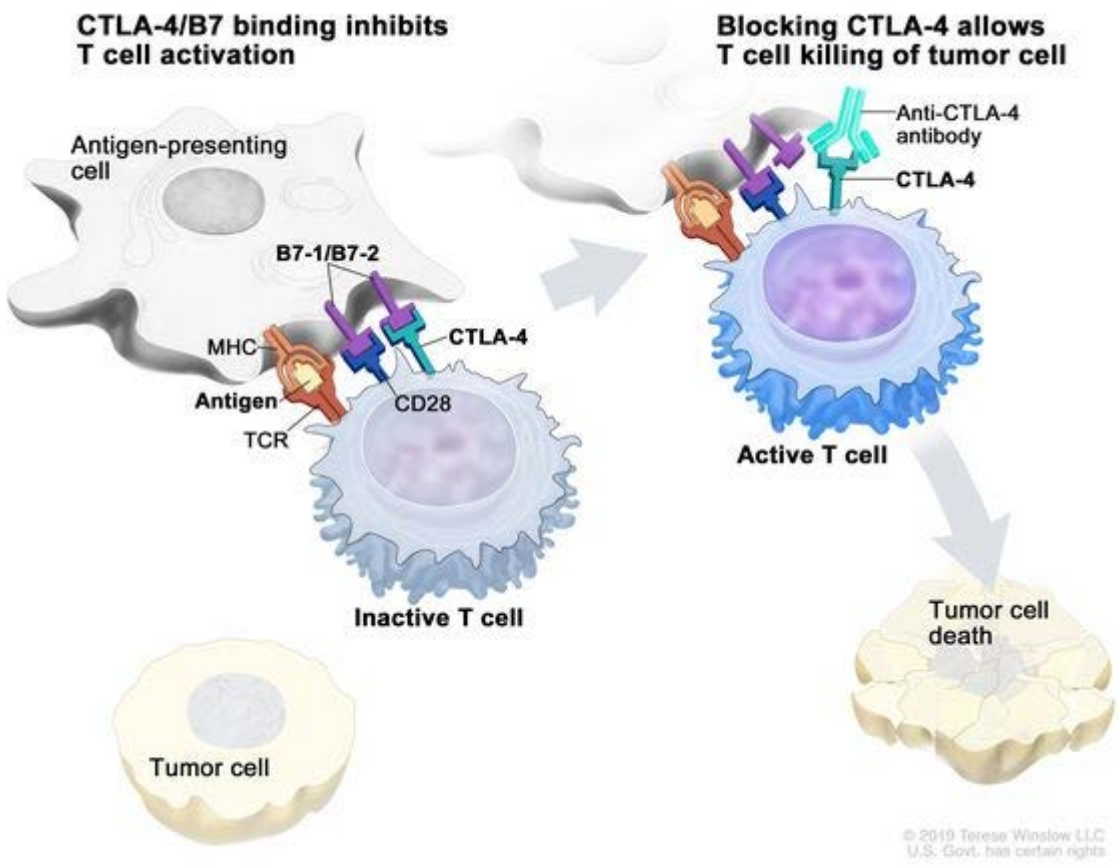
- Pooled patient data from 5 studies of adjuvant cisplatin-based doublet chemotherapy following completely-resected patients after 1995 (N = 4584)
  - Regimens included: cisplatin + vinorelbine, cisplatin + etoposide, or cisplatin + vinca alkaloid
- 5-year absolute benefit of 5.4% from chemotherapy
  - 5.8% benefit in disease-free survival
- Benefit varied by stage
- Chemotherapy effect was higher in patients with better performance statuses

Category	Hazard Ratio (95% CI)
Stage	
IA	1.40 (0.95-2.06)
IB	0.93 (0.78-1.10)
II	**0.83 (0.73-0.95)**
III	**0.83 (0.72-0.94)**
Regimen	
Cisplatin + vinorelbine	0.8 (0.7-1.07)
Cisplatin + etoposide or vinca alkaloids	0.92 (0.8-1.07)
Cisplatin + other	0.97 (0.84-1.13)

Pignon J, et al. *J Clin Oncol*. 2008;26(21):3552-3559.

Immune Checkpoints and Cancer

- Immune homeostasis critical to survival
- Uncontrolled immune response can cause inflammation and autoimmune disease
- To prevent this, the immune system relies on checkpoints:
  - **Programmed cell death-protein 1 (PD-1 or PD-L1)**
    - Regulates T-cell activity within tissues and tumors
    - Examples: atezolizumab, pembrolizumab, nivolumab
  - **Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4)**
    - Blocks signals initiated by T-cells and CD28
    - Examples: ipilimumab, tremelimumab
- Immune checkpoints help regulate immune homeostasis, chronic infections, and tumor antigens
  - Can be dysregulated by tumors, leading to immune resistance



Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264; NCCN Guidelines for Non-Small Cell Lung Cancer. v2.2023.

Image: *NCI Dictionary of Cancer Terms*. National Cancer Institute. Accessed February 18, 2023. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/ctla-4

IMpower010: Adjuvant Atezolizumab in Stage IB-IIIA NSCLC

Completely resected stage IB- IIIA NSCLC
- Stage IB tumors ≥4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis (N = 1280)

→ Adjuvant chemotherapy* for 1-4 cycles (N = 1269)

*Cisplatin + pemetrexed, gemcitabine, docetaxel, or vinorelbine

→ Atezolizumab 1200 mg Q3W for 16 cycles (N = 507)

→ Best supportive care (BSC) (N = 498)

→ *Survival follow-up*

No crossover allowed

Stratification Factors
- Patient sex
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 TPS

Primary Endpoints
- Investigator-assessed DFS tested hierarchically
  - PD-L1 TC ≥1% stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key Secondary Endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% stage II-IIIA population
- 3- and 5-year DFS in all 3 populations

DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cells; TPS, tumor proportion score.

Felip E, et al. *Lancet.* 2021;398(10308):1344-1357.

IMpower010: Results

IMpower010 Results for All-Randomized Stage II-IIIA and ITT Populations (Primary Endpoint) *Median follow-up: 32.8 months (range 0.1-57.5)*		
Endpoint	**Atezolizumab (N = 248)**	**BSC (N = 228)**
Median DFS (95% CI), months	NR (36.1, NE)	35.3 months (29.0, NE)
Stratified HR (95%, CI)	0.66 (0.50, 0.88)	
P-value	0.004	

BSC, best supportive care; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; NR, not reached.

Safety Summary for IMpower010 in the Safety Evaluable Population		
Grade	**Atezolizumab (N = 495)**	**BSC (N = 495)**
Adverse event, N (%)		
Any grade	459 (93)	350 (71)
Grade 3-4	108 (22)	57 (12)
Serious	87 (18)	42 (8)
Grade 5	8 (2)	3 (1)
Led to dose interruption of atezolizumab	142 (29)	–
Led to discontinuation of atezolizumab	90 (18)	–
Immune-related adverse events, N (%)		
Any grade	256 (52)	47 (9)
Grade 3-4	39 (8)	3 (1)
Required corticosteroids	60 (12)	4 (1)
Led to discontinuation	52 (11)	0

Felip E, et al. *Lancet.* 2021;398(10308):1344-1357.

PEARLS/KEYNOTE-091: Adjuvant Pembrolizumab in Stage IB-IIIA NSCLC

Eligible for Registration
- Confirmed stage IB tumors ≥4 cm, II, or IIIA NSCLC per AJCC v7
- Complete surgical resection
- Provision of tumor tissue for PD-L1 analysis

PD-L1 Testing

Eligible for Randomization
- No evidence of disease
- ECOG PS 0-1
- Adjuvant chemotherapy
  - Considered for stage IB
  - Recommended for stage II and IIIA
  - Limited to ≤4 cycles

R
1:1

Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 year) (N = 590)

Placebo Q3W for ≤18 administrations (~1 year) (N = 587)

Stratification Factors
- Stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Geographic region
- Received adjuvant chemotherapy (Yes vs No)

Dual Endpoints
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary Endpoints
- DFS in PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% population
- Lung cancer-specific survival in the overall population
- Safety

AJCC, American Joint Committee on Cancer; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; PD-L1, programmed death-ligand 1; R: randomization; TPS, tumor proportion score.

O'Brien M, et al. *Lancet Oncol.* 2022;23(10):1274-1286.

PEARLS/KEYNOTE-091: Results

PEARLS/KEYNOTE-091 Results, DFS for the Overall Population (Primary Endpoint)		
Endpoint	**Pembrolizumab (N = 590)**	**Placebo (N = 587)**
Median DFS* (95% CI), months	53.6 months (39.2, NR)	42.0 months (31.3, NR)
Stratified HR (95%, CI)	0.76 (0.63, 0.91)	
P-value	0.0014	

*For patients with a TPS score of ≥50% (N = 168 in pembrolizumab arm vs 165 in placebo), DFS was NR in either group.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NR, not reached; TPS, tumor proportion score.

Select Key Safety Results for PEARLS/KEYNOTE-091 in the Safety Evaluable Population

Adverse Event	Pembrolizumab (N = 580)				Placebo (N =581)			
Grade N (%)	**1-2**	**3**	**4**	**5**	**1-2**	**3**	**4**	**5**
Any	358 (62)	166 (29)	21 (4)	11 (2)	379 (65)	130 (22)	14 (2)	6 (1)
Pruritus	124 (21)	1 (<1)	0	0	72 (12)	2 (<1)	0	0
Hypothyroidism	119 (21)	1 (<1)	0	0	27 (5)	0	0	0
Arthralgia	104 (18)	4 (1)	0	0	74 (13)	1 (<1)	0	0
Diarrhea	99 (17)	7 (1)	0	0	81 (14)	2 (<1)	0	0
Fatigue	95 (16)	1 (<1)	0	0	86 (15)	3 (1)	0	0
Increased ALT	42 (7)	4 (1)	0	0	31 (5)	3 (1)	0	0
Increase AST	39 (7)	2 (<1)	0	0	28 (5)	4 (1)	0	0
Maculopapular rash	40 (7)	3 (1)	0	0	20 (3)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

O'Brien M, et al. *Lancet Oncol.* 2022;23(10):1274-1286.

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Neoadjuvant Treatment for Early-Stage NSCLC

TREATMENT TIMELINES

Neoadjuvant therapy → **Surgery**

Attacks cancer cells throughout the body

Attacks residual disease

Surgery → **Adjuvant therapy**

Neoadjuvant Treatment

- Opportunity to eradicate micrometastases
- Can start systemic treatment faster with better treatment adherence
- Assess therapeutic response on surgical resection
- Reduce tumor burden before surgery (“downstage”)
- Can eliminate/reduce risk of tumor cells being released into the body during surgery

Adjuvant Treatment

- Proceed to surgery faster
- No risk of presurgery complications from systemic therapy
- Potentially longer treatment durations, which may allow for better disease control
- Flexible timing of treatment after surgery, allowing for patients to recover
- Can eliminate microscopic cancer cells remaining after surgery

Desai A, et al. *JAMA Oncol.* 2022;8(9):1364.

CheckMate 816: Neoadjuvant Nivolumab + Platinum Chemotherapy

Patients with newly diagnosed, resectable stage IB tumors (≥4 cm) to IIIA NSCLC via AJCC v7
- No sensitizing *EGFR* or *ALK* mutations
- ECOG PS 0 or 1

(N = 358)

→ Nivolumab 360 mg Q3W + Chemotherapy* Q3W (3 cycles) (N = 179)

→ Chemotherapy Q3W (3 cycles) (N = 179)

→ Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± radiation → Follow-up

Chemotherapy regimens: cisplatin/vinorelbine, docetaxel/cisplatin, gemcitabine/cisplatin, pemetrexed/cisplatin, paclitaxel/carboplatin, carboplatin/pemetrexed.

Stratification Factors
- Stage (IB/II vs IIIA)
- Sex
- PD-L1 TPS (≥1% and <1%)

Primary Endpoints
- Pathologic complete response (pCR)
- Event-free survival (EFS)

Key Exploratory Endpoints
- Overall response rate (ORR)
- Feasibility of surgery, peri- and post-operative, surgery-related adverse events

- **EFS:** time from randomization to 1) any progression of disease precluding surgery, 2) recurrence of disease after surgery, 3) progression of disease without surgery, 4) death due to any cause
- There was a third arm that evaluated ipilimumab + nivolumab, but it was closed early based on external data

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

Forde P, et al. *N Engl J Med.* 2022;386(21):1973-1985.

CheckMate 816: Results

CheckMate 816 Results: EFS and pCR *Median follow-up: 21 months (range 0.1–42 months)*		
Endpoint	**Nivolumab + Chemotherapy (N = 179)**	**Chemotherapy (N = 179)**
Median EFS (95% CI), months	31.6 months (30.2, NR)	20.8 months (14, 26.7)
Stratified HR for EFS (95%, CI)	0.63 (0.43, 0.91)	
P-value	0.005	
pCR	24%	2%
OR for pCR (99%, CI)	13.94 (3.49-55.75)	
P-value	<0.001	

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NR, not reached; OR, odds ratio; pCR, pathologic complete response.

CheckMate 816: Adverse Events				
Adverse Event	**Nivolumab + Chemotherapy (N = 176)**		**Chemotherapy Alone (N = 176)**	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Adverse events of any cause, N (%)				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to treatment discontinuation	18 (10.2)	10 (5.7)	20 (11.4)	7 (4)
Serious	30 (17)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events, N (%)				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to treatment discontinuation	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death	0	--	3 (1.7)	--

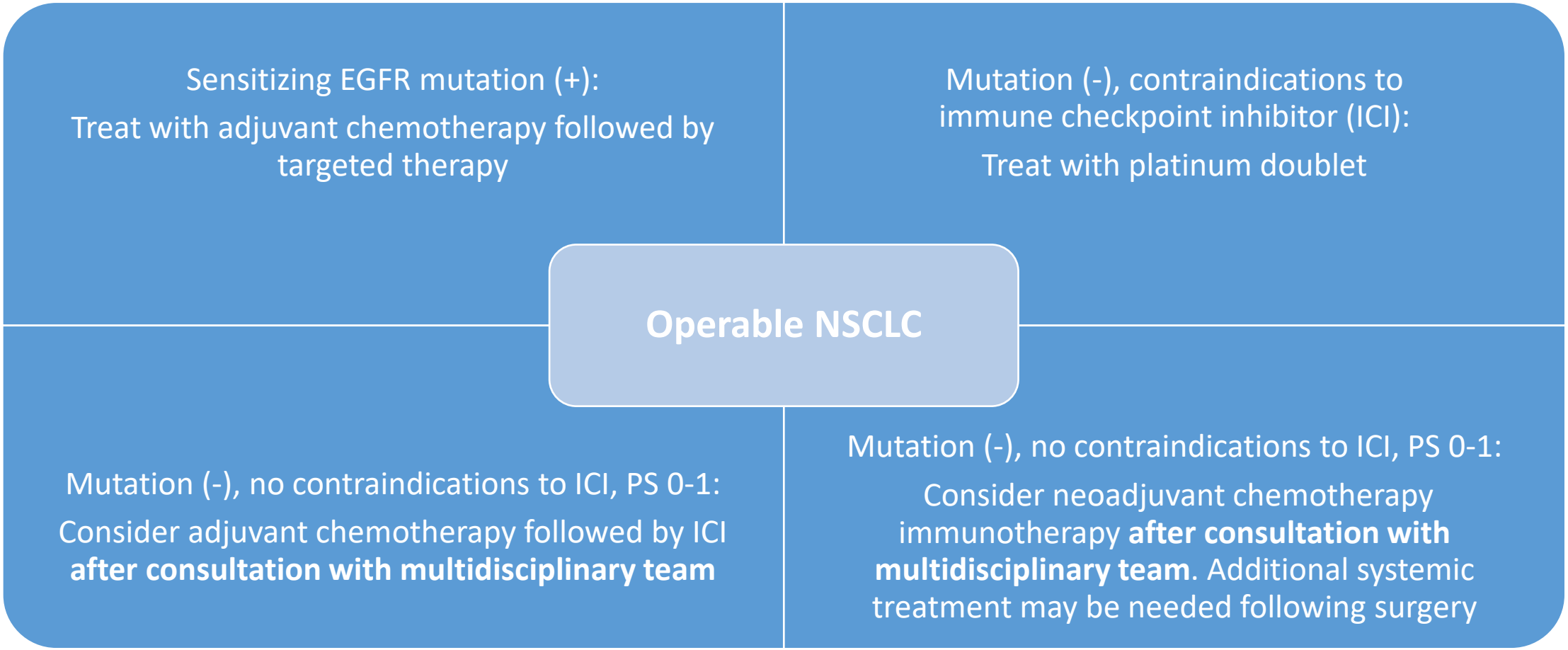
Forde P, et al. *N Engl J Med.* 2022;386(21):1973-1985.

Practice-Related Questions as a Result of CheckMate 816

- Who should receive neoadjuvant treatment versus adjuvant treatment?
- Is pCR predictive of EFS?
- Can EFS be used as a surrogate endpoint for OS?
- 20% of patients in CheckMate 816 received adjuvant treatment, is that necessary?
- Who should get adjuvant therapy? How do we determine eligibility?
- Patients with sensitizing mutations were excluded. How do we ensure our patients get biomarker testing prior to treatment?
- Using this type of regimen requires multidisciplinary input, is this feasible in all centers?

Lovly CM. *N Engl J Med.* 2022;386(21):2050-2051.

Putting the Picture Together: Operable NSCLC



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Treatment Strategies for Locally Advanced Disease in Inoperable Patients

- Which patients?
  - Patients with unresectable disease
    - Larger tumors, multiple tumors, and/or nodal involvement
  - Patients who are not surgical candidates

- Primary treatment
  - Chemotherapy (platinum-based agent) + concurrent radiation
    - Rationale: Better regional and systemic disease control
    - Median PFS benefit: 8 months; 20% of patients are alive at 5 years
    - Induction chemotherapy can be considered if patient's tumor does not fit in radiation field

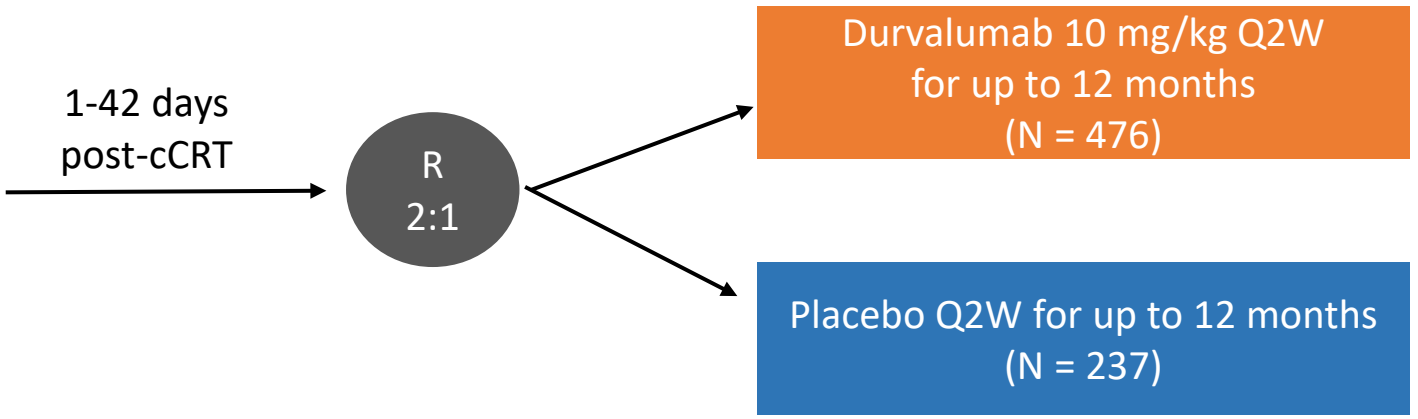
PFS, progression-free survival.

Costa GJ, et al. *Ann Transl Med*. 2018;6(suppl 1):S65; Johnson DH. *Chest.* 2000;117(4 suppl 1):123S-126S.

PACIFIC: Consolidation Durvalumab After Concurrent Chemoradiation (cCRT)

Unresectable III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- ECOG PS 0-1
- If available, tumor tissue for PD-L1 analysis

(N = 713)



Primary Endpoints
- PFS
- OS

Key Secondary Endpoints
- ORR
- DoR
- TTDM
- Safety
- PROs

DoR: duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PROs: patient reported outcomes; TTDM, time-to-death or disease progression.

Antonia SJ, et al. *N Engl J Med*. 2018;379(24):2342-2350; Spigel DR, et al. *J Clin Oncol.* 2022;40(12):1301-1311.

PACIFIC: Results (5-Year Follow-up)

PACIFIC Trial: 5-Year Survival OS and PFS Survival Outcome (Primary Endpoints)
Median follow-up: 34.2 months (range 0.2–74.7 months)

Endpoint	Durvalumab (N = 473)	Placebo (N = 236)
OS	47.5 months	29.1 months
Stratified HR for OS (95%, CI)	0.72 (0.59, 0.89)	
PFS	16.9 months	5.6 months
Stratified HR for PFS (95%, CI)	0.55 (0.45, 0.68)	
Estimated 5-year OS survival rates	42.9% (38.2, 47.4)	33.4% (27.3, 39.6)
Estimated 5-year PFS survival rate	33.1% (28, 38.2)	19% (13.6, 25.2)

CI, confidence interval; OS, overall survival; HR, hazard ratio; PFS, progression-free survival.

PACIFIC Select Safety Events (Based on original trial by Antonia et al)

Adverse Event	Durvalumab (N = 475)		Placebo (N = 234)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause, N (%)				
All	460 (96.8)	145 (30.5)	222 (94.9)	61 (26.1)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Radiation pneumonitis	96 (20.2)	7 (1.5)	37 (15.8)	1 (0.4)
Diarrhea	88 (18.5)	3 (0.6)	46 (19.7)	3 (1.3)
Pneumonia	63 (13.3)	21 (4.4)	18 (7.7)	9 (3.8)
Pneumonitis	60 (12.6)	9 (1.9)	18 (7.7)	4 (1.7)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Rash	58 (12.2)	1 (0.2)	12 (5.1)	0

Spigel DR, et al. *J Clin Oncol.* 2022;40(12):1301-1311.
Antonia SJ, et al. *N Engl J Med*. 2018;379(24):2342-2350.

Select Ongoing Phase II and III Trials

Study Title (Planned Accrual)	Status	Disease Stage	Chemotherapy Backbone (max 4 cycles)	Neoadjuvant Intervention	Adjuvant Treatment	Primary Endpoint(s)
IMpower030 (N = 450)	Active, not recruiting	II, IIIA, IIIB	Carboplatin, nab-paclitaxel, carboplatin/pemetrexed, cisplatin/pemetrexed, or cisplatin/gemcitabine	Atezolizumab or placebo	Atezolizumab or placebo Q3W x 16 cycles	EFS
KEYNOTE-671 (N = 786)	Active, not recruiting	II, IIIA, IIIB	Cisplatin/gemcitabine or cisplatin/pemetrexed	Pembrolizumab or placebo	Pembrolizumab or placebo Q3W x 13 cycles	EFS, OS
AEGEAN (N = 825)	Active, not recruiting	II, IIIA, IIIB	Carboplatin/paclitaxel, carboplatin/pemetrexed, cisplatin/gemcitabine, or cisplatin/pemetrexed	durvalumab or placebo	Durvalumab or placebo Q4W x 12 cycles	pCR, EFS
NADIM-II (N = 90)	Active, not recruiting	IIIA, IIIB	Paclitaxel/carboplatin	nivolumab or placebo	nivolumab Q4W x 6 cycles	pCR

EFS, event-free survival; pCR, pathologic complete response.

Impower030. NCT0456063. Accessed February 21, 2023. https://clinicaltrials.gov/ct2/show/NCT03456063
KEYNOTE-671. NCT03425643. Accessed February 21, 2023. https://clinicaltrials.gov/ct2/show/NCT03425643
AEGEAN. NCT03800134. Accessed February 21, 2023. https://clinicaltrials.gov/ct2/show/NCT03800134
NADIM II. NCT03838159. Accessed February 21, 2023. https://clinicaltrials.gov/ct2/show/NCT03838159

Session Overview

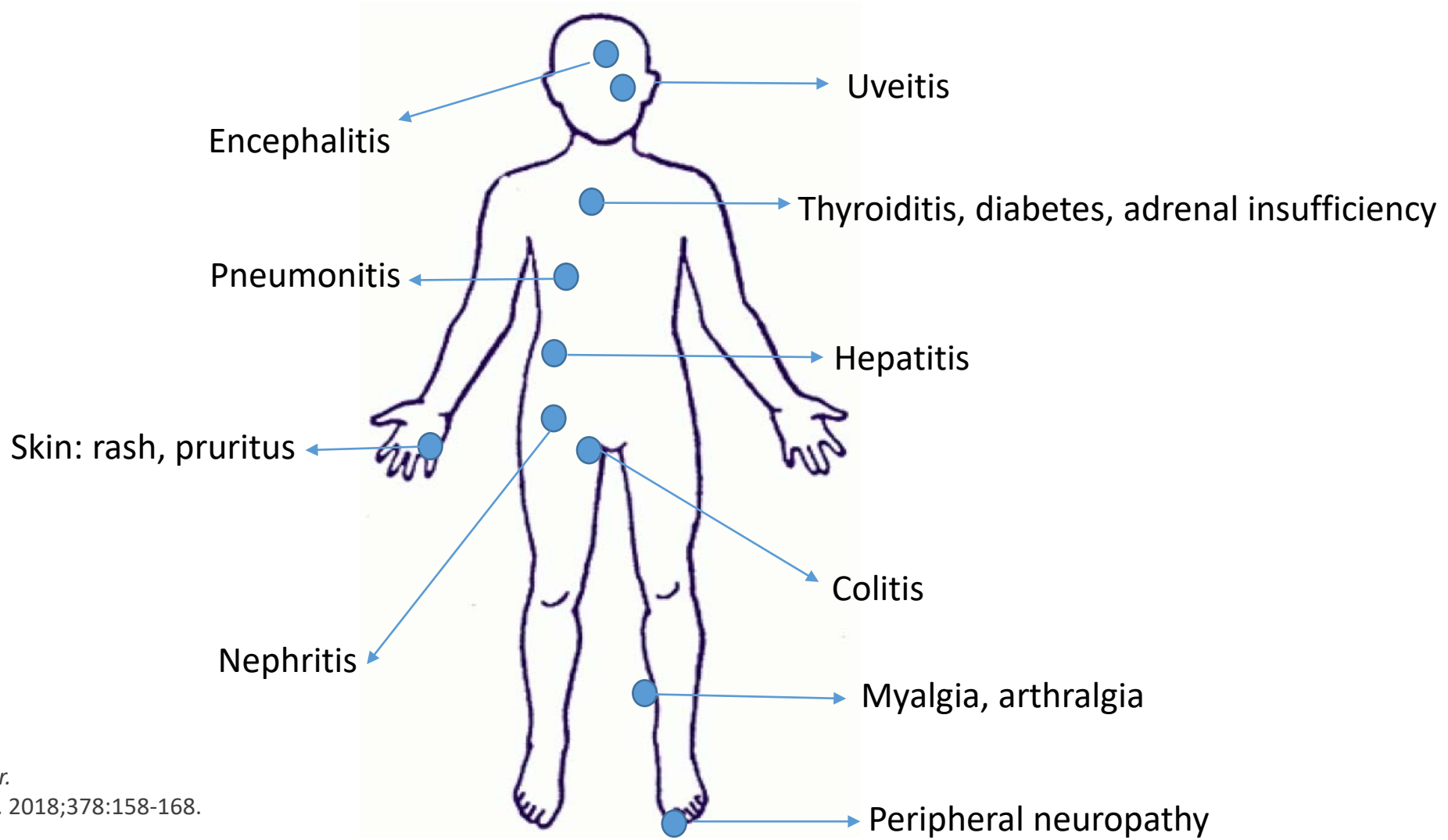
- Lung Cancer Epidemiology
- Staging
- Histology and Genetics
- Stage I
- Stage II/III
- Adjuvant Treatment for Stage II/III NSCLC
- Neoadjuvant Treatment for Stage II/III NSCLC
- Management of Inoperable Stage III NSCLC
- **Management of Select irAEs**
- **Management of Emerging DDIs**

Immune-Related Adverse Events (irAEs)

- Adverse effects associated with oncology immunotherapies
  - CTLA-4 inhibitors: increased grade 3 adverse effects
    - 20% incidence overall
    - Associated with colitis
  - PD-1/PD-L1 inhibitors: 10% to 13% incidence of irAEs
    - Associated with thyroiditis and pneumonitis
- Mechanism: removal of activation of autoreactive T cells, increased inflammatory cytokines, or generation of autoreactive antibodies

Kennedy LC, et al. *J Natl Compr Canc Netw*. 2019;17(6):750-757; Medina PJ, Adams VR. *Pharmacotherapy*. 2016;36(3):317-334; Postow MA, et al. *N Engl J Med*. 2018;378(2):158-168.

ICI Impact on Organ Systems



ICI, immune checkpoint inhibitor.

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

Pharmacist Involvement: irAE Management

- Early recognition
- Assess irAE severity: Common Terminology Criteria for Adverse Events (CTCAE)
- Consult specialists for complex management
- Use available guideline recommendations for management
  - National Comprehensive Cancer Network (NCCN)
  - European Society for Medical Oncology (ESMO)
  - American Society of Clinical Oncology (ASCO)
  - Prescribing information (PI)
- Educate patients on potential adverse effects

Puzanov I, et al. *J Immunother Cancer*. 2017;5(1):95; Medina PJ, et al. *J Pharm Pract*. 2020;33(3):338-349.

irAE Management: General Overview

Grade	Management of irAE	Concomitant Treatment With ICI	Management of Persistent or Refractory irAE
1	Monitor	Continue	N/A
2	Begin systemic steroids*	Consider holding, if holding resume when < grade 1	Systemic steroids
3	Systemic steroids with prolonged taper >4 weeks	Hold or discontinue	Additional immunosuppression (eg, infliximab), d/c ICI
4	Systemic steroids with prolonged taper >4 weeks	Discontinue (except for endocrine irAE)	Add additional immunosuppression

***Immunosuppressive Systemic Steroid Regimens:**

- Methylprednisolone (IV) or prednisone (PO) 0.5 to 1 mg/kg/day
- Methylprednisolone (IV) or prednisone (PO) 1 to 2 mg/kg/day

Kennedy LC, et al. *J Natl Compr Canc Netw*. 2019;17(6):750-757; Postow MA, et al. *N Engl J Med*. 2018;378(2):158-168; Medina P, et al. *J Pharm Pract*. 2020;33(3):338-349; Schneider B, et al. *J Clin Oncol.* 2021;39(36):4073-4126.

irAE Management: Prevention and Management of AEs Related to Steroids

ASCO Guideline Recommendations

Pretreatment Considerations

- Baseline workup to include viral HBV and HCV. Consider testing for latent/active TB
- Patients with preexisting comorbid conditions (diabetes, HTN, HF, cataract, glaucoma, infection, or osteoporosis) should have condition managed before starting corticosteroids
- Ideal steroid dosing and duration is individualized by patient, ICI, and type of irAE
- Lowest dose of steroids should be used for shortest duration of time

Prevention of Opportunistic Infection

- Prophylaxis for opportunistic infection with PJP may be considered in those receiving prednisone equivalent of ≥20 mg/d for 4 or more weeks or >30 mg for 3 weeks or more
- Prophylactic fluconazole with prolonged steroid use (>12 weeks) remain unclear; refer to institutional guidelines
- Prophylaxis against herpes zoster reactivation may be offered to patients who have had zoster before and will be receiving corticosteroids

Monitoring for Adverse Effects

- Routinely ask and assess patient for adverse effects
- GI prophylaxis with PPI or H2 antagonist
- To limit bone loss, patients should receive adequate calcium, diarrhea, vitamin D, and weight-bearing exercises. Use bone-modifying agents in patients on steroids for >3 months

H2, histamine-2; HBV, hepatitis B virus; HCV, hepatitis C virus; HF, heart failure; HTN, hypertension; PJP, Pneumocystis jirovecii *pneumonia ; PPI, proton pump inhibitor; TB, tuberculosis.*

Schneider B, et al. *J Clin Oncol.* 2021;39(36):4073-4126.

Background: Pneumonitis

- Rare and potentially life-threatening
  - 3 patients (2%) died on a phase 1 trial of nivolumab in NSCLC
  - 1 patient (0.2%) died during a phase 1 trial of pembrolizumab in NSCLC
- Incidence
  - ~3% in trials evaluating monotherapy
    - Incidence is higher in PD-1/PD-L1 than CTLA-4
  - ~5-10% in trials using combination therapy
  - Higher incidence in NSCLC than other tumor types
- Grade 3-4 pneumonitis (hypoxia or respiratory compromise) is uncommon
  - One of few irAEs associated with drug-related deaths

Gettinger SN, et al. *J Clin Oncol.* 2015;33(18):2004-2012; Garon EB, et al. *N Engl J Med.* 2015;372(21):2018-2028; Chuzi S, et al. *Cancer Manag Res.* 2017;9:207-213.

Management of irAEs: Pneumonitis

Background & Symptoms

- Incidence <10%
  - Median onset: 3 months
  - Higher incidence in NSCLC
- Dyspnea
- Cough
- R/O Infection or PE

Mild (Grade 1)

- Consider holding ICI
- Reassess in 1-2 weeks
  - H&P
  - Pulse oximetry (resting and with ambulation)
- Consider repeat chest CT scan in 3-4 weeks or as clinically indicated

Moderate (Grade 2)

- Hold ICI
- Consider pulmonary consultation
- Prednisone 1-2 mg/kg orally daily
- Monitor every 3 to 7 days, if no improvement, treat as grade 3

Severe (Grade 3-4)

- Discontinue ICI
- Inpatient admission required
- Methylprednisolone 1-2 mg/kg/day, taper over 6+wk
- No improvement over 48 h: consider infliximab, IVIg, or mycophenolate

CT, computed tomography; H&P, history and physical exam; IVIg, intravenous immunoglobulin; PE, pulmonary embolism; R/O, rule out.

Brahmer JE, et al. *J Clin Oncol*. 2018;36(17):1714-1768; Schneider B, et al. *J Clin Oncol*. 2021;39(36):4073-4126.

Management of irAEs: Colitis

Background & Symptoms

- Incidence 0.3-16%
  - Median onset: 4-10 weeks
  - CTLA-4 > PD-1/L1
- Abdominal pain
- Diarrhea
- Black, tarry stools
- Blood or mucus in stools
- R/O infection, medication

Mild (Grade 1)

- Consider holding ICI
- Loperamide or diphenoxylate/ atropine for 2-3 days
- Hydration
- Monitor. If persistent, check lactoferrin; if positive, treat as grade 2. If negative, add mesalamine and/or cholestyramine

Moderate (Grade 2)

- Hold ICI
- Prednisone 1-2 mg/kg/day
- No response in 2-3 days, continue steroids, add infliximab or vedolizumab within 2 weeks

Severe (Grade 3-4)

- Discontinue ICI
- Consider inpatient management
- IV methylprednisolone 1-2 mg/kg/day
- No response in 2 days, continue steroids, add infliximab or vedolizumab within 2 weeks

Brahmer JE, et al. *J Clin Oncol*. 2018;36(17):1714-1768; Schneider B, et al. *J Clin Oncol*. 2021;39(36):4073-4126.

Steroid-Refractory irAEs

- Patients with steroid-refractory irAEs require quick management and possibility inpatient care
- Some agents may be used in combination, depending on irAE type and severity
- No preferred agent; doses and duration of therapy variable

Select Agents Used for Refractory irAEs		
Abatacept	Etanercept	Plasmapheresis
Adalimumab	Hydroxychloroquine	Rituximab
Alemtuzumab	Infliximab	Sulfasalazine
Anti-thymocyte globulin (ATG)	IVIg	Tocilizumab
Azathioprine	Leflunomide	Tofacitinib
Cyclophosphamide	Methotrexate	TNF-α inhibitors
Cyclosporine	Mycophenolate	Ustekinumab
Dupilumab	Omalizumab	Vedolizumab

Martins F, et al. *Lancet Oncol*. 2019;20(1):e56-e64; NCCN Guidelines for Management of Immunotherapy-Related Toxicities. v1.2022; Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-1768; Puzanov I, et al. *J Immunother Cancer*. 2017;5(1):95.

DDIs and ICIs: Background

- Traditionally, concomitant medications alter efficacy and worsen toxicity through pharmacodynamic (PD) and pharmacokinetic (PK) interactions
- ICIs have a predictable PK profile that is minimally influenced by concomitant medications
- Drug-drug interactions (DDIs) are emerging in the literature
  - Which medications?
    - Medications that have immunomodulatory effects
    - Medications that impact the gut microbiome
  - Does timing matter?
    - Evidence suggests that medications that exert these effects prior to ICI administration may interact with the PD properties of the ICI

Hussain N, et al. *Hum Vaccin Immunother.* 2021;17(1):55-61; Cortellini A, et al. *J Immunother Cancer.* 2020;8(2):e001361.

DDIs: Corticosteroids

- Corticosteroids are commonly prescribed in oncology
  - Cancer-related symptoms
  - Treatment-related adverse effects (corticosteroid treatment is first-line therapy for irAEs)
  - Anticancer effects
  - Oncologic emergencies
  - Underlying comorbidities
- Mechanism of interaction
  - Anti-inflammatory effects via inhibition of interleukin-1 and -6 (IL-1 and IL-6)
    - Leads to impairment of CD28 costimulatory pathway, which causes diminished T-cell function
  - May also alter the microbiome
- Significance of corticosteroids on OS and PFS
  - Challenging to understand
  - Patients on >10 mg of prednisone equivalent daily are excluded from clinical trials
- Timing and duration consideration

Cortellini A, et al. *J Immunother Cancer.* 2020;8(2):e001361; Goodman RS, et al. *Clin Cancer Res.* 2023 Feb 3:OF1-OF8. https://doi.org/10.1158/1078-0432.CCR-22-3181

Corticosteroids and ICIs: Select Clinical Studies

Reference	Study Design (N)	Cancer Type	ICI Type	Steroid Prescription and Window	Early Steroid Users (N)	Clinical Findings in Early Steroid Users
Arbor et al	Retrospective multicenter (640)	NSCLC	Anti-PD-1/PD-L1	• 10-20 mg of prednisone for palliative indications • Within 30 days or on the day	14% (90)	Baseline corticosteroids of ≥10 mg: decreased OS (5.4 vs 12.1 months, *P* <.001) and PFS (1.9 vs 2.6 months, *P* <.001)
Scott et al	Retrospective (210)	NSCLC	Anti-PD-1/PD-L1	>10 mg prednisone	12% (25)	Decreased OS (4.3 vs 11 mo, *P* = .006)
Ricciuti et al	Retrospective (650)	NSCLC	CTLA-4 ± anti-PD-1/PD-L1	2 cohorts: • ≥10 mg prednisone • <10 mg prednisone At time of ICI within 24 h	14.3% (93)	≥10 mg cohort: decreased OS (4.9 vs 11.2 mo, *P* <.001) and PFS (2.0 vs 3.4, *P* = .01) <10 mg cohort: **No significant difference on survival outcomes**
Fuca et al	Retrospective (151)	NSCLC	Anti-PD1	>10 mg prednisone at time of ICI within 1 mo	23% (35)	Decreased OS (4.86 vs 15 mo, *P* <.001) and PFS (1.98 vs 3/94, *P* = .003)
Maslov et al	Retrospective (247)	Metastatic cancer	CTLA-4 ± anti-PD-1/PD-L1	Corticosteroid use around timing of ICI. Patients in 2 cohorts: • ≥2 mo after starting ICI • <2 mo after starting ICI	52% (129)	Steroid use ≥2 mo after starting ICI had longer PFS (HR 0.30, *P* <.001), and OS (HR 0.34, *P* <.0001) than those who received steroids <2 mo after starting ICI

Adapted from: Hussain N,et al. *Hum Vaccin Immunother*. 2021;17(1):55-61; Goodman RS, et al. *Clin Cancer Res.* 2023 Feb 3:OF1-OF8. https://doi.org/10.1158/1078-0432.CCR-22-3181

Key Takeaways: Corticosteroids

- Low dose of corticosteroids may not compromise antitumor efficacy
- Steroids should be avoided or decreased prior to initiation with an ICI
- If corticosteroids cannot be avoided, consider corticosteroid-sparing approaches, delaying corticosteroid exposure, or if possible, short delays of ICI to facilitate a corticosteroid taper if appropriate
- Clinical trials to watch: NCT03656627 and NCT03816345, which are evaluating use of nivolumab in autoimmune diseases

Factors That Influence ICI Efficacy

Timing

- Baseline and early corticosteroid use can interact with the PD of ICI

Dose

- Higher doses of corticosteroid associated with poor survival outcomes

Cancer-related symptoms

- Corticosteroid use for cachexia and other cancer-related symptoms associated with poorer outcomes

Goodman RS, et al. *Clin Cancer Res.* 2023 Feb 3:OF1-OF8. https://doi.org/10.1158/1078-0432.CCR-22-3181

Emerging DDIs: PPIs

- Selective inhibitors of H+/K+ ATPase and are widely used for GERD and peptic ulcer treatment
  - Commonly prescribed for oncology to manage GI symptoms and prevent erosion of the gastric mucosal lining caused by cancer treatments
- PPIs potential to cause immune-suppression is multifaceted
  - Can cause changes to gut microbiome diversity
  - Changes to gastric pH
  - Delay in gastric emptying
  - Immune-suppression by reducing expression of adhesion molecules on inflammatory cells

GERD, gastroesophageal reflex disease; GI, gastrointestinal; H+/K+, gastric hydrogen potassium; PPIs, proton pump inhibitors.

Hussain N, et al. *Hum Vaccin Immunother*. 2021;17(1):55-61; Chalabi M, et al. *Ann Oncol*. 2020;31(4):525-531.

PPIs and ICIs: Select Clinical Studies

Reference	Study Design (N)	Cancer Type	ICI Type	Endpoint	Findings
Chalabi et al	Retrospective review (169) • Pooled analysis of OAK and POPLAR trials	NSCLC	Atezolizumab	OS, PFS	PPI associated with shorter OS (9.6 vs 14.5 months, HR 1.45, 95% CI 1.2-1.75; *P* = .01) PPI associated with shorter PFS (1.9 vs 2.8 months, HR 1.30, 95% CI 1.10-1.53; *P* = .001)
Hopkins et al	Retrospective review (1225) • Pooled analysis of IMpower150	NSCLC	Atezolizumab	OS, PFS	PPI associated with worse OS (HR 1.53, 95% CI 1.21-1.95; *P* <.001) PPI associated with worse PFS (HR 1.34, 95% CI 1.12-1.61; *P* = .002)
Chen et al	Meta-analysis (7383)	Various	CTLA-4 ± Anti-PD-1/PD-L1	OS, PFS	PPIs associated with worse OS and PFS. OS HR 1.31 (95% CI, 1.19-1.44; *P* <.001) PFS HR 1.30 (95% CI, 1.17-1.46; *P* <.001)
Baek et al	Retrospective review (2963)	NSCLC	Anti-PD-1/ PD-L1	OS	PPI associated with worse OS and a 28% increased risk of mortality compared to nonuse (HR 1.28; 95% CI 1.13-1.46)

Chalabi M, et al. *Ann Oncol*. 2020;31(4):525-531; Hopkins AM, et al. *Br J Cancer*. 2022;126(1):42-47; Chen BQ, et al. *Ther Adv Med Oncol.* 2022;14:17588359221111703. doi: 10.1177/17588359221111703; Baek YH, et al. *Int J Cancer.* 2022;150(8):1291-1300.

Emerging DDIs: Antibiotics

- Mechanism of interaction
  - Broad-spectrum antibiotics can cause long-standing disruption to gut microbiome
- Antibiotic impact on survival
  - Data suggests that patients treated with antibiotics have worse survival outcomes
    - Shorter OS, PFS, and ORR
  - Duration of antibiotics and influence on outcomes also not clear
    - Interpreting data is challenging
    - Patient-specific factors (eg, performance status, comorbid conditions) are not considered

Araji G, et al. *J Immunother Precis Oncol.* 2022;5(1):13-25.

Antibiotics and ICIs: Select Clinical Data

Reference	Study Design (N)	Cancer Type	ICI Type	Antibiotic Window pre-ICI	Clinical Findings in Antibiotic Users
Ahmed et al	Retrospective (60)	Multiple	Anti-PD-L1/PD-1 ± chemotherapy	- 14 days and +14 days	Lower response rates in antibiotic users (29.4%) versus nonusers (62.8*%)
Tinsley et al	Retrospective (291)	NSCLC, melanoma, RCC	Anti-PD-1/PD-L1	-14 days and +42 days	Decreased OS (10.4 vs 21.7 mo, *P* = .002) and PFS (3.1 vs 6.3 mo, *P* = .003)
Ruiz-Patino et al	Retrospective (140)	NSCLC	Anti-PD-L1/PD-1 ± chemotherapy	-30 days and during ICI	Decreased OS when antibiotics started prior to treatment (20.3 vs 40.6 mo, *P* <.05) Decreased OS when antibiotics used during treatment (24.7 vs 40.6 mo, *P* <.05) No change in PFS, no changes in RR
Pinato et al	Prospective multicenter (196)	Multiple	Anti-PD-L1/PD-1	-30 days and during ICI	Decreased OS (2 vs 26 mo, *P* <.01)
Kaderbahi et al	Retrospective (74)	NSCLC	Anti-PD-L1/PD-1	-90 days	No changes in PFS (*P* = .72), no change in RR (*P* = .75)
Kim et al	Retrospective (234)	NSCLC (131), others (103)	Anti-PD-1/PD-L1, Anti-CTLA-4	-60 days	Decreased OS (5 vs 17 mo, *P* <.001) and PFS (2 vs 4 mo, *P* <.001)

RCC, renal cell carcinoma; RR, response rate.

Adapted from: Araji G, et al. *J Immunother Precis Oncol.* 2022;5(1):13-25.

Key Takeaways

- Immunotherapy has produced strong and robust clinical outcomes in patients with early- or advanced-stage NSCLC
- Whether to choose concurrent chemoradiation followed by ICI, adjuvant ICI, or neoadjuvant treatment is made on a case-by-case basis
- Organ-related irAE is a diagnosis of exclusion and that diagnosis can be challenging
- Pharmacists play a key role in the management of irAEs through therapy selection and education
- DDIs with irAEs continues to emerge. Mechanism of interaction may be related to alterations in the gut microbiome or medications that have an immunomodulatory effect

Questions & Answers