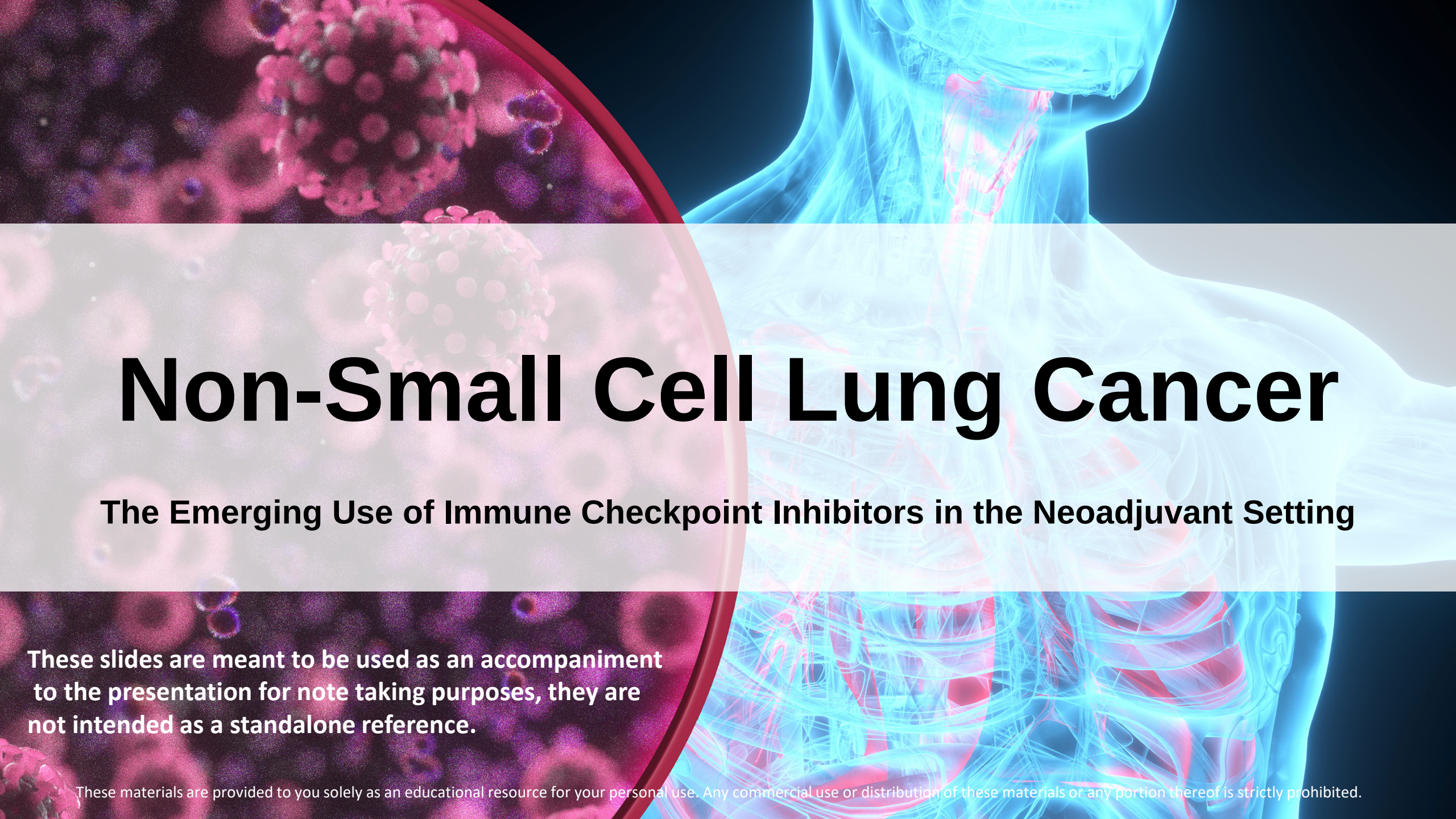
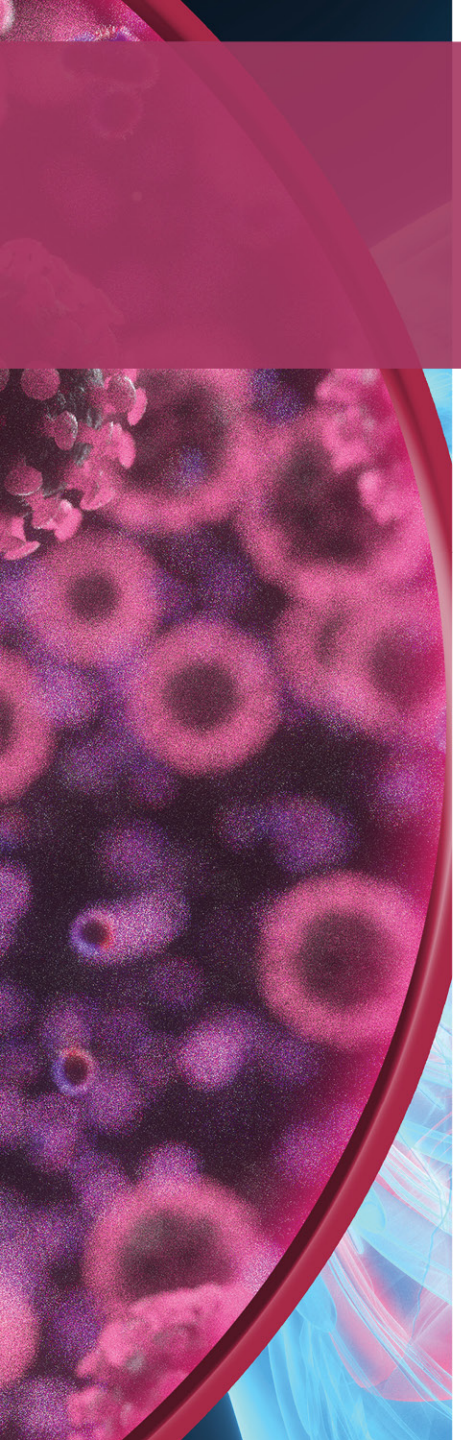


# Non-Small Cell Lung Cancer

## The Emerging Use of Immune Checkpoint Inhibitors in the Neoadjuvant Setting

**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.**



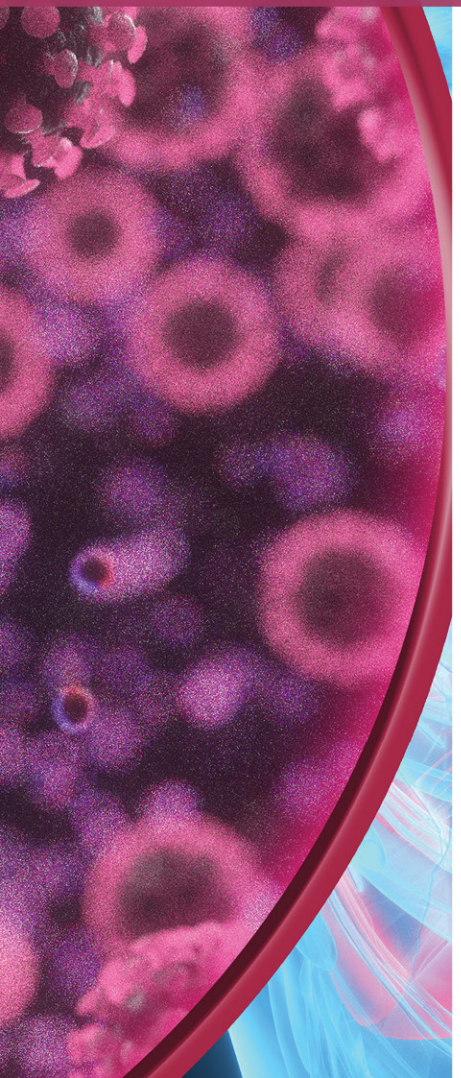
This educational activity is sponsored by Postgraduate Healthcare Education, LLC and is supported by an educational grant from Bristol Myers Squibb.

# Faculty

**Josiah D. Land, PharmD, BCOP**
Clinical Pharmacy Specialist
Thoracic Medical Oncology
Memorial Sloan Kettering Cancer Center
New York, NY

Originally from Lake Charles, Louisiana, Dr. Land received his BS in Biology from McNeese State University and PharmD from the University of Louisiana at Monroe. He completed a PGY1 Pharmacy Practice Residency at The University of Texas MD Anderson Cancer Center in Houston followed by a PGY2 Oncology Pharmacy Specialty Residency at Memorial Sloan Kettering Cancer Center in New York City. Dr. Land currently practices as a clinical pharmacy specialist for the Thoracic Medical Oncology Service at Memorial Sloan Kettering Cancer Center and is a Board-Certified Oncology Pharmacist (BCOP).

# Disclosures



**Dr. Land** has disclosed that he has served on an advisory board for Bristol Myers Squibb.

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

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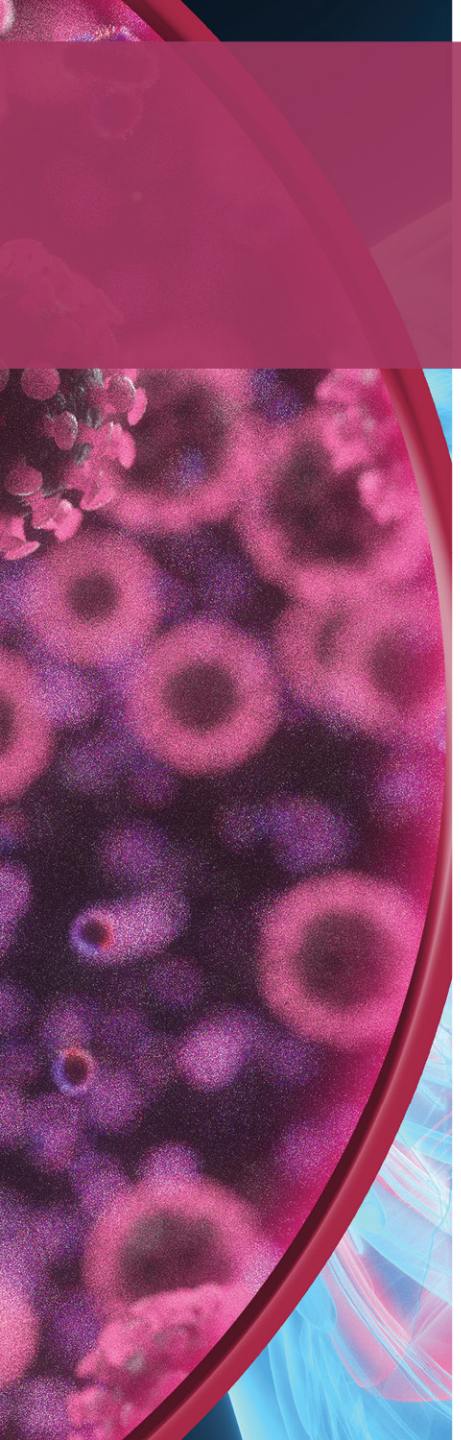

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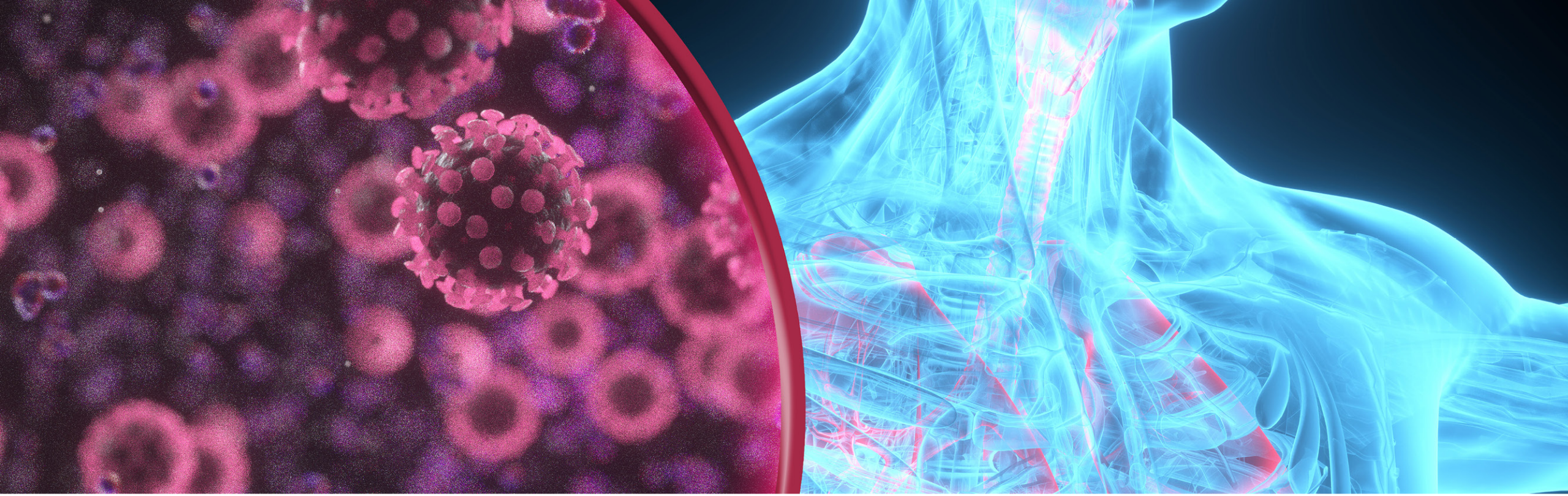
**Type of Activity:** Application

# Learning Objectives

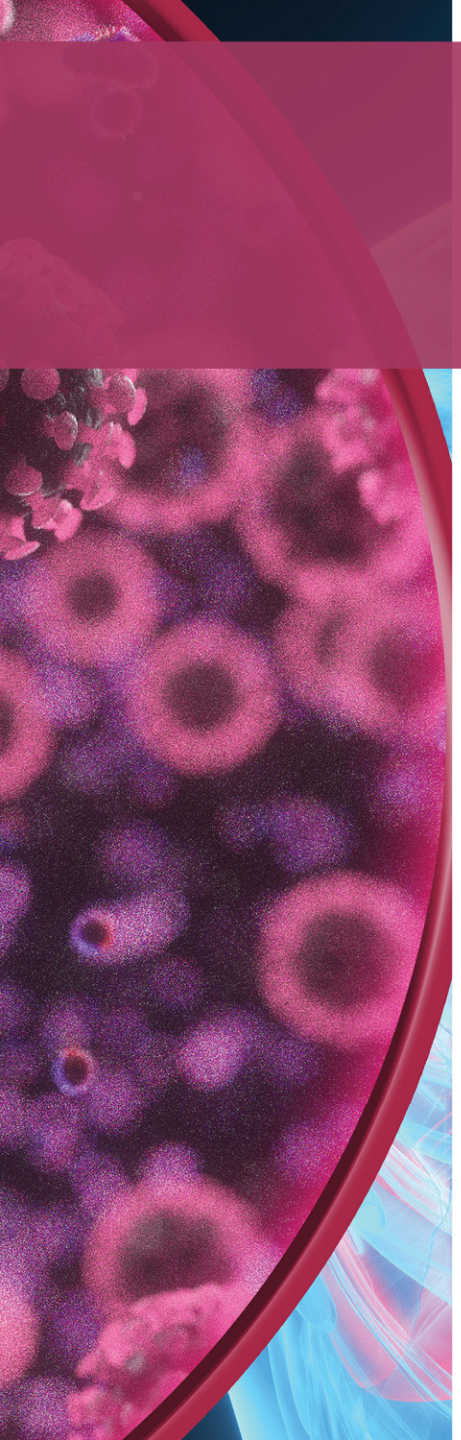
- **Identify** potential predictive biomarkers and surrogate endpoints of neoadjuvant immunotherapy for non-small cell lung cancer (NSCLC)
- **Discuss** emerging clinical trial data and the rationale for using neoadjuvant immune checkpoint inhibitors for treatment of early-stage NSCLC
- **Formulate** approaches for mitigation of common toxicities associated with neoadjuvant immunotherapy for NSCLC



# Neoadjuvant Therapy for Early-Stage NSCLC

## Historical Perspectives

# Lung Cancer



## Leading cause of cancer mortality in the US and worldwide

- 235,760 cases in 2021
- 131,880 deaths in 2021
- 84% of cases = **non-small cell lung cancer** (**NSCLC)**

## 5-year survival = 19% for all patients

- Local disease = 61%
- Regional disease = 35%
- Advanced/metastatic = 6%

Ahren et al. *J Immunother Cancer*. 2021;9(6):e002248.
Cancer stat facts: lung and bronchus cancer. NCI/SEER. Accessed March 7, 2022. www.seer.cancer.gov

# NSCLC: Staging

## Staging Review

- **Resectable disease**
- **Role for perioperative systemic therapy**
  - Neoadjuvant vs adjuvant as a strategy to reduce the risk of **recurrence**

The goal of resectable NSCLC is **CURE**

| T/M | Subgroup | N0 | N1 | N2 | N3 |
|---|---|---|---|---|---|
| **T1** | T1a | **IA1** | **IIB** | **IIIA** | IIIB |
| | T1b | **IA2** | **IIB** | **IIIA** | IIIB |
| | T1c | **IA3** | **IIB** | **IIIA** | IIIB |
| **T2** | T2a | **IB*** | **IIB** | **IIIA** | IIIB |
| | T2b | **IIA** | **IIB** | **IIIA** | IIIB |
| **T3** | T3 | **IIB** | **IIIA** | IIIB | IIIC |
| **T4** | T4 | **IIIA** | **IIIA** | IIIB | IIIC |
| **M1** | M1a | IVA | IVA | IVA | IVA |
| | M1b | IVA | IVA | IVA | IVA |
| | M1c | IVB | IVB | IVB | IVB |

TMN, tumor-node-metastasis cancer staging system.
*consider high-risk features

Detterbeck. *J Thorac Cardiovasc Surg.* 2018;155(1):356.
NCCN Clinical Practice Guidelines in Oncology. NSCLC, v3.2022.

# Perioperative Chemotherapy for Resectable Disease: NCCN Recommendations

## Surgery followed by chemotherapy (adjuvant)

- Not recommended for IA disease
- Consider for high-risk, margin-negative IB disease
- Fastest time to surgery
- Recommended for patients with completely resected stages IB-IIIA
  - Cisplatin/pemetrexed = preferred regimen for nonsquamous histology
  - Cisplatin/gemcitabine and cisplatin/docetaxel = preferred regimens for squamous histology

## Preoperative chemotherapy followed by surgery (neoadjuvant)

- Delivery of chemotherapy can be complex in postsurgical setting
  - Patient comorbidity or incomplete/lengthy postsurgical recovery
- Provides early opportunity to eliminate micrometastatic disease
- Benefit similar to adjuvant chemotherapy
- Response criteria considerations—can provide early indication of response
  - Pathologic complete response (pCR) vs major pathologic response (MPR)

NCCN Clinical Practice Guidelines in Oncology. NSCLC, v3.2022.

# Historical Adjuvant Trials

| Study | No. Pts in CT Arm (N) | Median Age, Y | Stage: % | Adjuvant CT Regimen(s) | 5-Y OS (CT vs control) | HR for OS (95% CI) | CT-Related Death, % |
|---|---|---|---|---|---|---|---|
| IALT | 932 (1867) | 59 | I/II/III: 36/25/40 | Cisplatin/vindesine, cisplatin/ vinblastine, cisplatin/vinorelbine, or cisplatin/etoposide | 44.5 vs 40.4 | 0.86 (0.76-0.98) | 0.8 |
| JBR.10 | 242 (482) | 61 | IB/IIA/IIB: 45/13/42 | Cisplatin/vinorelbine | 69 vs 54 | 0.69 (0.52-0.91) | 0.8 |
| ANITA | 407 (840) | 59 | IB/II/IIIA: 36/22/41 | Cisplatin/vinorelbine | 62/52/42 vs 64/39/26 | 0.80 (0.66-0.96) | 2.0 |
| CALGB 9633 | 173 (344) | 61 | IB: 100 | Carboplatin/paclitaxel | 60 vs 58 | 0.83 (0.64-1.08) | 0 |

Arriagada et al. *N Engl J Med*. 2004;350(4):351.
Winton et al. *N Engl J Med*. 2005;352(25):2589.
Douillard et al. *Lancet Oncol*. 2006;7(9):719.
Strauss. *J Clin Oncol*. 2008;26(31):5043.

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; Pts, patients; OS, overall survival.

# Historical Neoadjuvant Trials

| Study | Size (N) | Stage | CT Regimen(s) | ORR, % | pCR, % | Complete Resection (Induction CT vs Surgery Alone) | Median OS (Induction CT vs Surgery Alone) |
|---|---|---|---|---|---|---|---|
| NATCH | 413 | IB-IIIA | Carboplatin + paclitaxel | 53.3 | 10.5 | NR | NR |
| SWOG 9900 | 354 | IB-IIIA | Carboplatin + paclitaxel | 41 | 9 | 93% vs 84% | 62 mo vs 41 mo (HR 0.79, 95% CI, 0.60-1.06; *P* = .11) |
| Gilligan et al (2007) | 519 | IB-IIIA | Platinum-based | 49 | 4 | 82% vs 80% | 54 mo vs 55 mo (HR 2.01, 95% CI, 0.80-1.31; *P* = .86) |
| Scagliotti et al (2010) | 270 | IB-IIIA | Cisplatin + gemcitabine | 35.4 | 4 | 88% vs 84% | 93 mo vs 57 mo (HR 0.63, 95% CI, 0.43-0.92; *P* = .02) |
| Depierre et al (2002) | 355 | IB-IIIA | Cisplatin + ifosfamide | 64 | 11 | 92% vs 86% | 37 mo (95% CI, 26.7-48.3) vs 26 mo (95% CI, 19.8-33.6); *P* = .15<br>HR 0.78 (95% CI, 0.60-1.02) |

CT, chemotherapy; NR, not reported; ORR, overall response rate; pCR, pathologic complete response.

Felip et al. *J Clin Oncol*. 2010;28(19):3138. Pisters et al. *J Clin Oncol*. 2010;28(11):1843. Gilligan et al. *Lancet*. 2007;369(9577):1929. Scagliotti et al. *J Clin Oncol*. 2012;30:172. Depierre et al. *J Clin Oncol*. 2002;20(1):247. Chen and Kewei. *Curr Oncol*. 2021;28(5):4129.

# Historical Neoadjuvant Trials: Data from 3 Meta-Analyses

| Study | No. of Trials (Pts) | Stage | CT Regimen(s) | Outcomes |
|---|---|---|---|---|
| Berghmans et al (2005) | 6 (590) | I-III | Cisplatin-based | Overall HR 0.66 (95% CI, 0.48-0.93)<br>Stage III HR 0.65 (95% CI, 0.41-1.04) |
| Burdett et al (2006) | 12 (988) | I-III | Platinum-based | HR 0.82 (95% CI, 0.69-0.97; *P* = .02)<br>OS of 20% at 5 years |
| Song et al (2010) | 13 (3224) | I-III | Platinum-based | Overall HR 0.84 (95% CI, 0.77-0.92; *P* = .0001)<br>Stage III HR 0.84 (95% CI, 0.75-0.95; *P* = .005) |

**Conclusion:** Neoadjuvant CT added to surgery significantly improves OS in operable patients, including patients with stage III disease

Berghmans et al. *Lung* Cancer. 2005;49(1):13.
Burdett et al. *J Thorac Oncol*. 2006;1(7):611.
Song et al. *J Thorac Oncol.* 2010;5(4):510.

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; Pts, patients; OS, overall survival.

# Pathologic Complete Response

## Pathologic Complete Response (pCR)

- Absence of residual viable tumor cells on histopathologic examination after neoadjuvant chemotherapy
- Associated with improved survival
- Uncommon

- Median frequency in neoadjuvant trials: 4% (range 0-16%)
- Rareness of pCR can limit conclusions on its relation to survival
- Although pCR is related to increased survival, meaningful survival data requires trials with large sample sizes
- Need for more effective therapies in neoadjuvant setting

Pataer et al. *J Thorac Oncol*. 2020;16(5):1289.
Hellmann et al. *Lancet Oncol*. 2014;15(1):e42.

# Major Pathologic Response

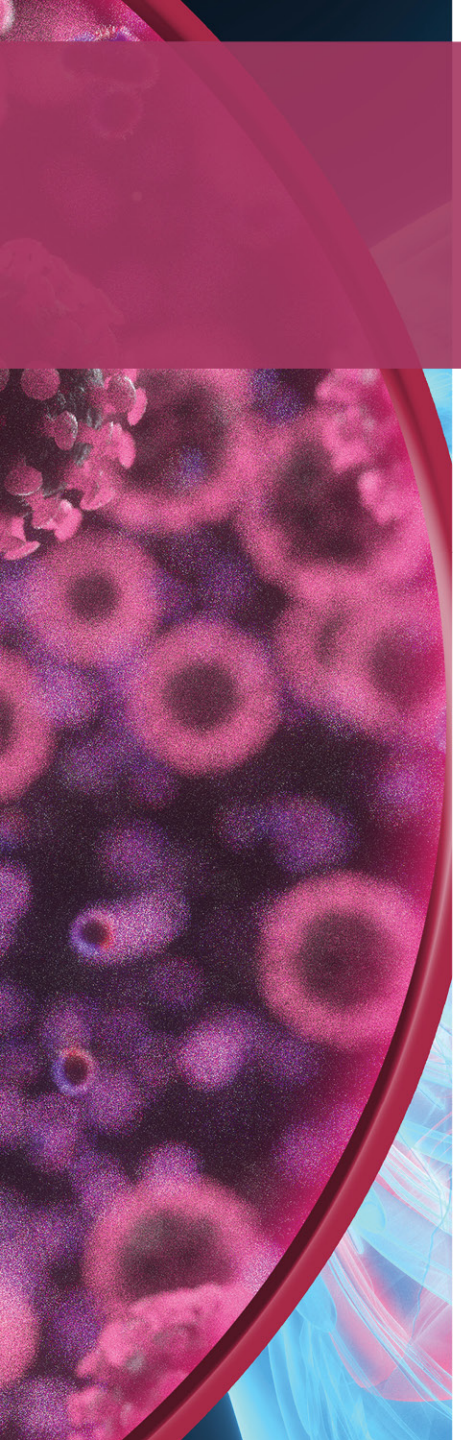
## Major Pathologic Response (MPR)

- Residual viable tumor ≤10%
- A potential surrogate endpoint for survival as pCR can have limited utility
- Pataer et al (n = 192) showed improved survival in resected lung cancers treated with neoadjuvant CT in those meeting the definition of MPR

| Percentage of Residual Viable Tumor Following Neoadjuvant CT | HR for Death |
|---|---|
| 1-10% | 1.00 |
| 11-30% | 2.51 (95% CI, 0.91-6.96) |
| 31-50% | 3.39 (95% CI, 1.40-8.22) |
| 51-70% | 4.57 (95% CI, 1.98-10.52) |
| 71-100% | 4.78 (95% CI, 2.06-11.11) |

Pataer et al. *J Thorac Oncol*. 2020;16(5):1289.
Hellmann et al. *Lancet Oncol*. 2014;15(1):e42.

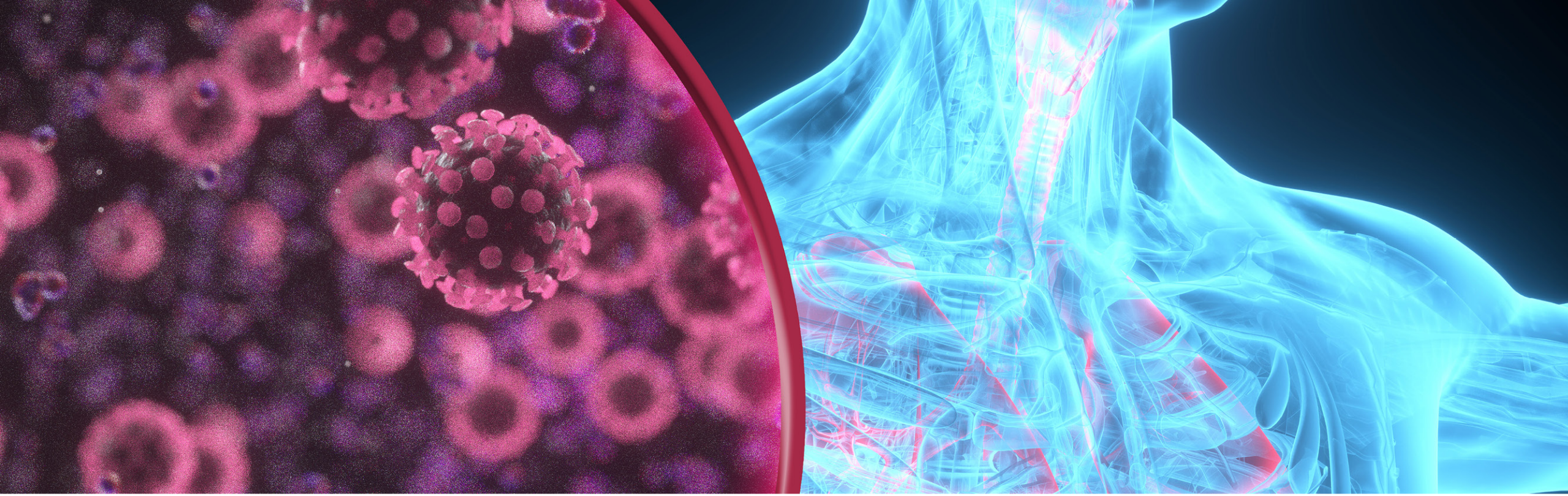
# Perioperative Chemotherapy for Early-Stage NSCLC: Recent Progress



- The addition of **immune checkpoint inhibition (ICI)** improves outcomes in early-stage NSCLC
  - **PACIFIC** trial—consolidation durvalumab significantly improved OS at 5 years post-CCRT for locally advanced, unresectable stage III NSCLC
  - **IMpower010**—adjuvant atezolizumab improved DFS in stage IB-IIIA (primarily II-IIIA) NSCLC following surgery and adjuvant chemotherapy in tumors with PD-L1 ≥1%
- Is there a role for ICI in the **neoadjuvant space**?

CCRT, concurrent chemoradiotherapy; DFS, disease-free survival; PD-L1, programmed death-ligand 1.

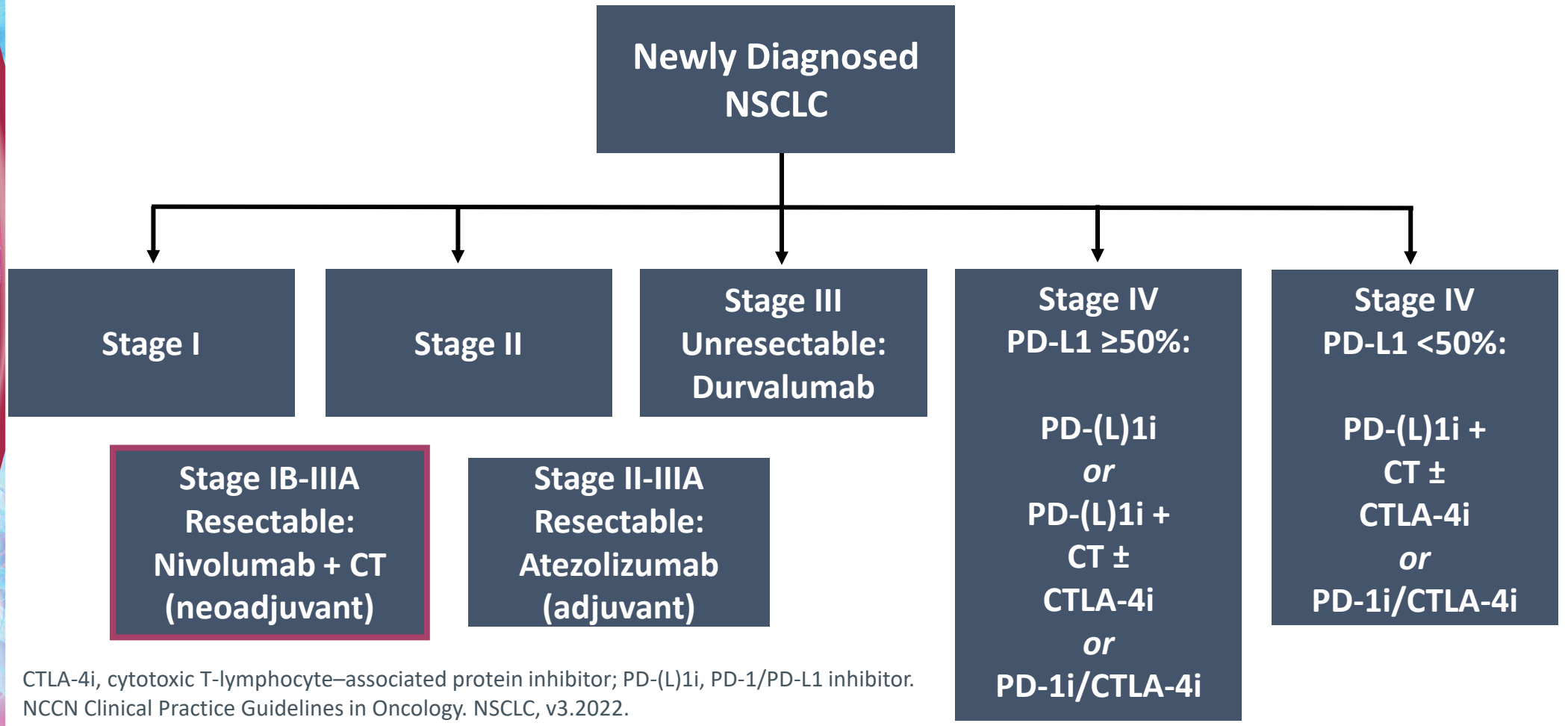
Antonia et al. *N Engl J Med*. 2018;379(24):2342.
Antonia et al. *N Engl J Med*. 2017;377(20):1919.
Felip et al. *Lancet*. 2021;398:1344.



# Neoadjuvant Therapy for Early-Stage NSCLC

## Role of Immune Checkpoint Inhibition

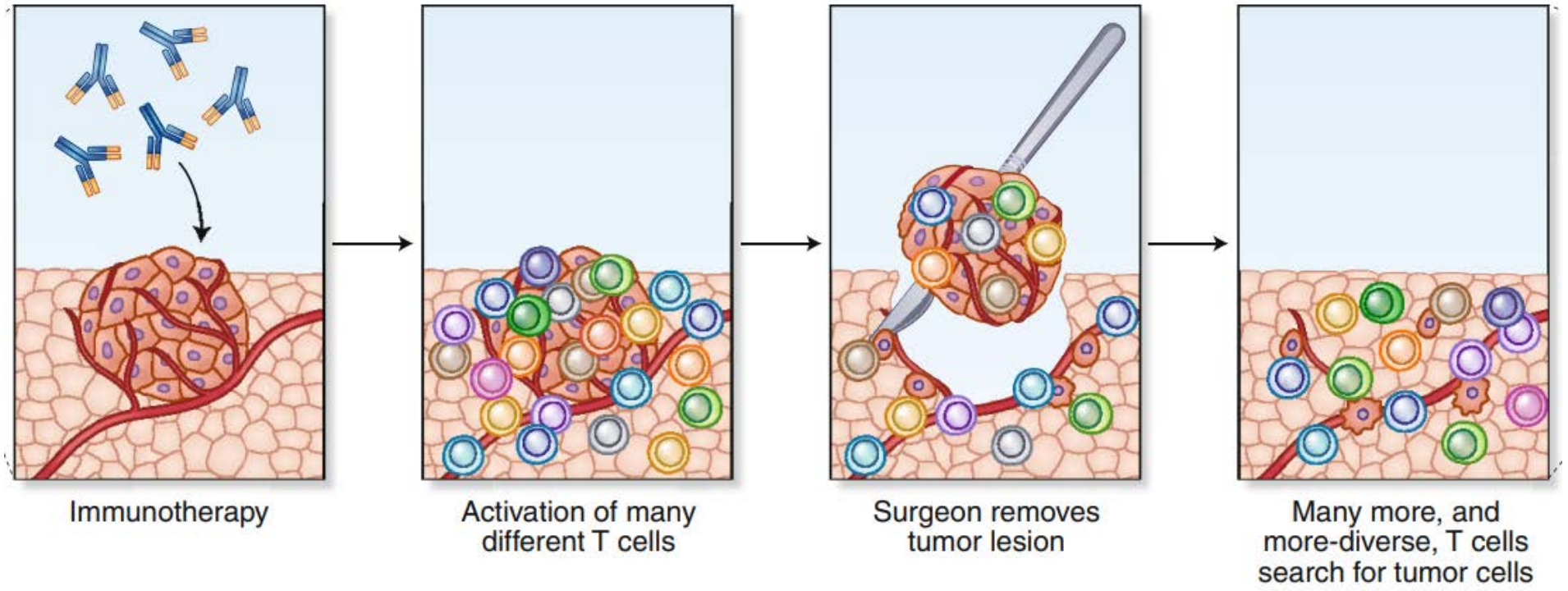
# Overview of ICI in NSCLC




CTLA-4i, cytotoxic T-lymphocyte–associated protein inhibitor; PD-(L)1i, PD-1/PD-L1 inhibitor.

NCCN Clinical Practice Guidelines in Oncology. NSCLC, v3.2022.

# Rationale for Neoadjuvant Immunotherapy




Versluis et al. *Nat Med*. 2020;26(4):475.

# ICI Biomarkers of Interest

Historically, response rates with ICI therapy in NSCLC were around 20%—identification of biomarkers necessary to predict efficacy

## Programmed death-ligand 1 (PD-L1)

- Heterogeneous biomarker
- Historically assessed in ICI trials for predictive role
- Utility as a biomarker varies from trial to trial—cutoff values from clinical trials may dictate therapy

## Tumor mutation burden (TMB)

- Number of mutations per DNA megabases
- High TMB creates neoantigens/increases tumor immunogenicity
- Identified as a potential predictive biomarker based on efficacy in cancers with high TMB

Grellier et al. *Transl Lung Cancer Res*. 2018;7(6):4639.

# Current Phase 2 Data: Neoadjuvant ICI in NSCLC

| Study | N | Stages | Neoadjuvant Regimen | All Stages, % | | |
|---|---|---|---|---|---|---|
| | | | | MPR | pCR | ORR |
| CheckMate 159 | 20 | I-IIIA | Nivolumab x 2 | 45 | 10 | 10 |
| LCMC3 | 90 | IB-IIIB | Atezolizumab x 2 | 19 | 5 | 7 |
| NEOSTAR<br>▪ Arm A<br>▪ Arm B | 44 | I-IIIA | <br>Nivolumab x 3<br>Nivolumab/ipilimumab x 3 | <br>19<br>44 | <br>10<br>38 | <br>22<br>19 |
| Gao et al | 40 | IB-IIIA | Sintilimab x 2 | 37.5 | 7.5 | 20 |
| NADIM | 46 | IIIA | Nivolumab + carboplatin/paclitaxcel x 3 | 85 | 61 | 74 |
| Shu et al | 14 | IB-IIIA | Atezolizumab + carboplatin/nab-paclitaxcel x 2 | 63.6 | 27.3 | 57 |
| SAKK 16/14 | 55 | IIIA | Cisplatin/docetaxel x 3, then durvalumab x 2 | 60 | 18 | 58 |

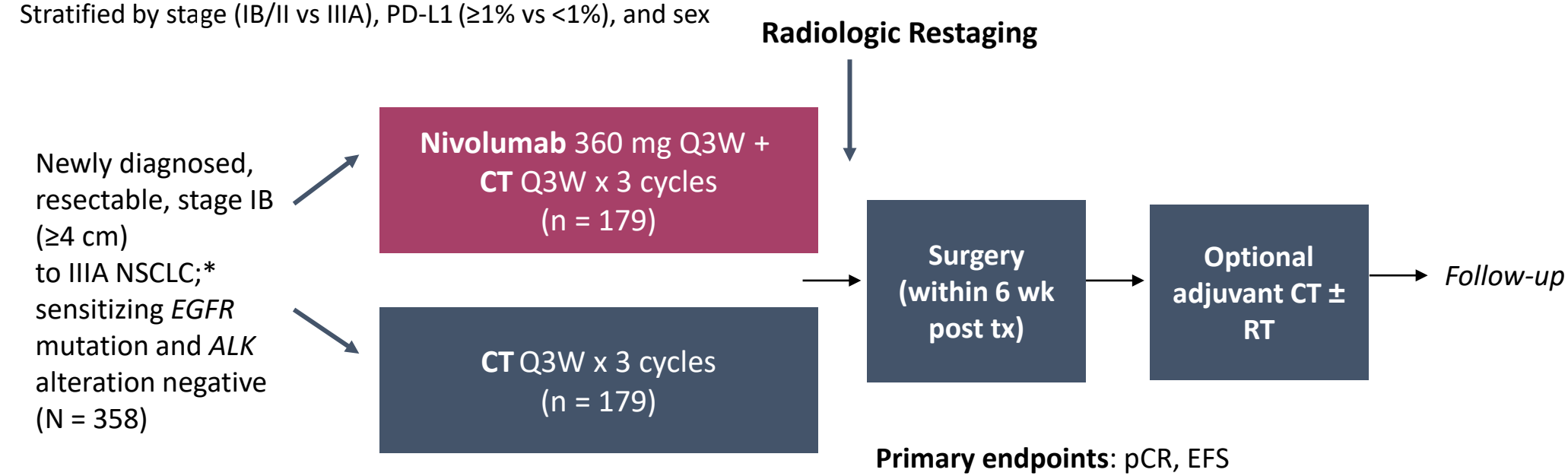
MPR, major pathologic response; ORR, overall response rate; pCR, pathologic complete response.

Adapted from Palmero et al. *Transl Lung Cancer Res.* 2021;10(1):539.

# CheckMate 816: Neoadjuvant Nivolumab + Platinum Chemotherapy for Resectable Stage IB-IIIA NSCLC

**Randomized, open-label, phase 3 trial**

Stratified by stage (IB/II vs IIIA), PD-L1 (≥1% vs <1%), and sex




**Primary endpoints**: pCR, EFS

- pCR = 0% viable tumor in lung/lymph nodes

**Key secondary endpoints:** OS, MPR, time-to-death or distant metastasis, potential predictive biomarkers (PD-L1, TMB)

*Per AJCC 7th ed cancer staging manual.
AJCC, American Joint Committee on Cancer; EFS, event-free survival; RT, radiotherapy; tx, treatment.
Forde et al. AACR 2021. Abstract CT003.

# CheckMate 816: Baseline Characteristics

| Characteristic | Nivolumab + CT (n = 179) | CT (n = 179) |
|---|---|---|
| Median age, y (range) | 64 (41-82) | 65 (34-84) |
| Female, % | 28 | 29 |
| Region, % | | |
| ▪ North America | 23 | 28 |
| ▪ Europe | 23 | 14 |
| ▪ Asia | 48 | 51 |
| Stage, % | | |
| ▪ IB-II | 36 | 35 |
| ▪ IIIA | 63 | 64 |
| Histology, % | | |
| ▪ Squamous | 49 | 53 |
| ▪ Nonsquamous | 51 | 47 |
| Smoking status, % | | |
| ▪ Current/former | 89 | 88 |
| ▪ Never | 11 | 11 |

| Characteristic | Nivolumab + CT (n = 179) | CT (n = 179) |
|---|---|---|
| Tumor PD-L1 expression, % | | |
| ▪ Not evaluable | 7 | 7 |
| ▪ <1% | 44 | 43 |
| ▪ ≥1% | 50 | 50 |
| ▪ 1-49% | 28 | 26 |
| ▪ ≥50% | 21 | 24 |
| TMB, % | | |
| ▪ Not evaluable/ not reported | 51 | 50 |
| ▪ <12.3 mut/Mb | 27 | 30 |
| ▪ ≥12.3 mut/Mb | 22 | 21 |

mut/Mb, mutations per megabase; TMB, tumor mutation burden.

Forde et al. AACR 2021. Abstract CT003.

# CheckMate 816: Treatment and Surgery Outcomes

| Patients, n (%) | Nivolumab + CT (n = 179) | CT (n = 179) |
|---|---|---|
| **Received neoadjuvant treatment** | 176 (98) | 176 (98) |
| **Reason off neoadjuvant treatment** | | |
| • Completed (3 cycles) | 165 (94) | 149 (85) |
| • Study drug toxicity | 10 (6) | 12 (7) |
| • Disease progression | 1 (1) | 2 (1) |
| • Other | 0 | 13 (7) |
| **Patients with definitive surgery** | 149 (83) | 135 (75) |
| **Type of surgery** | | |
| • Lobectomy | 115 (77) | 82 (61) |
| • Pneumonectomy | 25 (17) | 34 (25) |
| • Other | 29 (19) | 35 (26) |
| **R0 resection** (negative margins) | 124 (83) | 105 (78) |

R0, resection for cure or complete remission.

Forde et al. AACR 2021. Abstract CT003.

# CheckMate 816: Other Outcomes Nivolumab + CT vs CT Alone

- Definitive Surgery Rate: 83.2% vs 75.4%
- Overall Response Rate: 53.6% vs 37.4%
- Radiographic Downstaging: 30.7% vs 23.5%
- Grade 3/4 Treatment-Related AE Rate: 33.5% vs 36.9%

AE, adverse event.

Spicer et al. ASCO 2021. Abstract 8503. NCT02998528.

# CheckMate 816 Primary Endpoint: pCR Rate Nivolumab + CT vs CT Alone

## Intent-to-Treat (ITT) Population

- **24% vs 2.2%**, OR 13.94 (99% CI, 3.49-55.75); *P* < .0001

## Key Subgroups

- Stage IB/II: **26% vs 5%**
- IIIA: **23% vs 1%**
- PD-L1: **<1%** (17% vs 3%) and **≥1%** (33% vs 2%)
- TMB: **Low** (22% vs 2%) and **High** (31% vs 3%)
- MPR: **36.9% vs 8.9%**, OR 5.7 (95% CI, 3.16-10.26)

Forde et al. AACR 2021. Abstract CT003.
Spicer et al. ASCO 2021. Abstract 8503. NCT02998528.

# CheckMate 816 Primary Endpoint: EFS Nivolumab + CT vs CT Alone

## Median Event-Free Survival (EFS), months

- **31.6 vs 20.8**, HR* 0.63 (97.38% CI, 0.43-0.91); *P* = .005

## Median EFS: Key Subgroups, months

- Stage:
  - **IB/II**: NR vs HR (95% CI), 0.87 (0.48-1.56)
  - **IIIA**: 31.6 vs 15.7 HR (95% CI), 0.54 (0.37-0.80)
- TMB:
  - **Low** 30.5 vs 26.7 HR (95% CI), 0.86 (0.47-1.57)
  - **High** NR vs 22.4 HR (95% CI), 0.69 (0.33-1.46)
- PD-L1:
  - **<1%** 25.1 vs 18.4 HR (95% CI), 0.85 (0.54-1.32)
  - **≥1%** NR vs 21.1 HR (95% CI), 0.41 (0.24-0.70)
  - **1-49%** NR vs 26.7 HR (95% CI), 0.58 (0.30-1.12)
  - **≥50%** NR vs 19.6 HR (95% CI), 0.24 (0.10-0.61)

HR, hazard ratio; NR, not reached.

*HR for disease progression, disease recurrence, or death.

Forde et al. *N Engl J Med*. 2022 April 11. Online ahead of print. doi:10.1056/NEJMoa2202170

# CheckMate 816: EFS/OS Data

**Median EFS, months by pCR status** (exploratory)

- Nivolumab + CT
  - **pCR vs no pCR**: NR vs 26.6, HR 0.13 (0.05-0.37)
- CT only
  - **pCR vs no pCR**: NR vs 18.4, HR not computed

**Overall Survival, months** (interim analysis)

- Nivolumab + CT: NR
- CT only: NR

**HR (99.67% CI), 0.57 (0.30-1.07); *P* = .0079**
*Significance boundary for OS (0.0033) not met at time of interim analysis*

Forde et al. *N Engl J Med*. 2022 April 11. Online ahead of print. doi:10.1056/NEJMoa2202170

# CheckMate 816: Safety

| Adverse Event (AE), % | Nivolumab + CT* (n = 176) | | CT (n = 176) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Any AE | 93 | 41 | 97 | 44 |
| Treatment-related AE | 82 | 34 | 89 | 37 |
| Any AE leading to d/c | 10 | 6 | 11 | 4 |
| Treatment-related AE leading to d/c | 10 | 6 | 10 | 3 |
| Any serious AE | 17 | 11 | 14 | 10 |
| Treatment-related serious AE | 12 | 8 | 10 | 8 |
| Surgery-related AEs | 42 | 11 | 47 | 15 |
| Treatment-related deaths (n) | 0 | | 3 | |

*irAEs in Nivolumab + CT arm: rash, hyperthyroidism, hypothyroidism, diabetes, hypophysitis, adrenal insufficiency, pneumonitis, hypersensitivity/IRR.

d/c, discontinuation; irAE, immune-related adverse events; IRR, infusion-related reaction.

Forde et al. AACR 2021. Abstract CT003.

# CheckMate 816: Summary

CheckMate 816 showed a statistically significant improvement in the primary endpoints of pCR and EFS

- pCR and EFS benefit consistent across most subgroups
  - MPR and ORR also improved
- Circulating tumor DNA (ctDNA) clearance more frequent with nivolumab + CT vs CT
- OS data maturing, although promising at interim analysis

Tolerable safety profile with addition of nivolumab without adversely affecting feasibility of surgery

On March 4, 2022, the FDA approved nivolumab + CT for adult patients with resectable NSCLC in the neoadjuvant setting

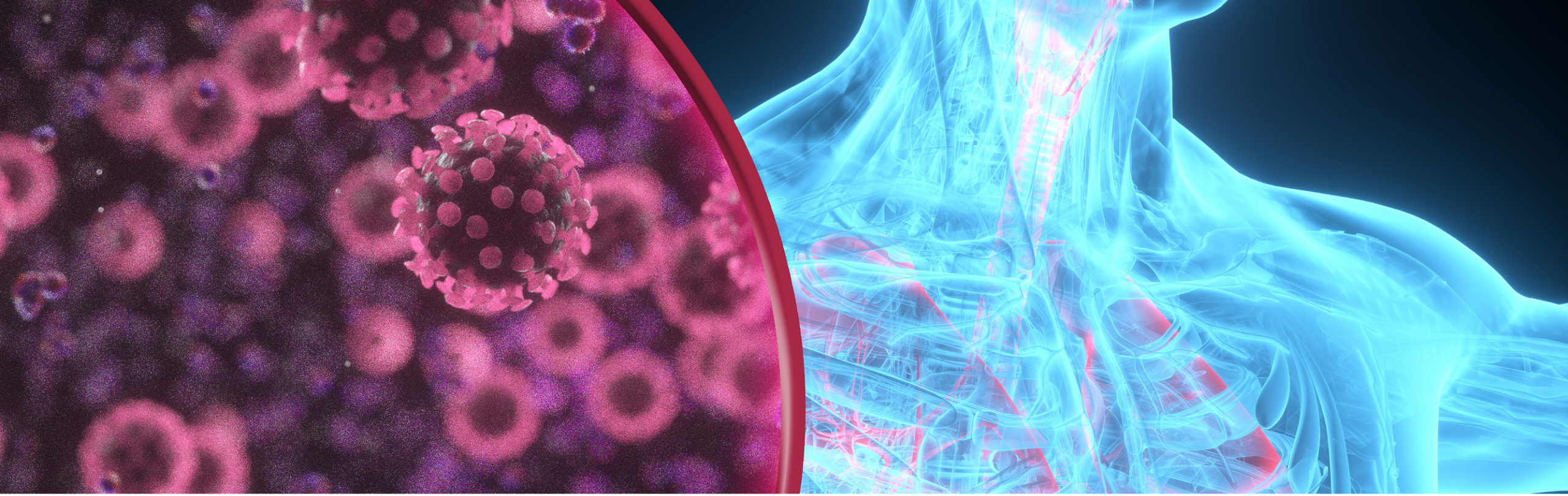
Forde et al. AACR 2021. Abstract CT003. Forde PM et al. *N Engl J Med*. 2022 April 11. Online ahead of print. doi:10.1056/NEJMoa2202170.
FDA. March 4, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-nivolumab-and-platinum-doublet-chemotherapy-early-stage-non-small-cell-lung

# Ongoing Phase 3 Trials of Neoadjuvant CT + ICI in Early-Stage NSCLC

| Study Title (Planned Accrual) | Disease Stage (TNM Edition) | CT Regimen | Neoadjuvant ICI | Adjuvant IO Treatment | Primary Endpoint(s) |
|---|---|---|---|---|---|
| KEYNOTE-671 (N = 786) | II-IIIB (8th) | ≥4 cycles of cis/gem or pemetrexed | Pembrolizumab or placebo | 13 x 3-wk cycles of pembrolizumab or placebo | EFS, OS |
| IMpower030 (N = 451) | II-IIIB (8th) | 4 cycles of carbo/pemetrexed, carbo/nab-pac, cis/pemetrexed, or cis/gem | Atezolizumab or placebo | 16 x 3-wk cycles of atezolizumab or BSC | EFS |
| AEGEAN (N = 800) | IIA-IIIB (8th) | 4 cycles of carbo/pac, carbo/pemetrexed, cis/gem, or cis/pemetrexed | Durvalumab or placebo | 12 x 4-wk cycles of durvalumab or placebo | pCR, EFS |
| CheckMate 77T (N = 452) | IIA-IIIB (8th) | ≥4 cycles carbo/pac, cis/doc, carbo/pemetrexed, cis/pemetrexed | Nivolumab or placebo | Nivolumab or placebo for 1 y | EFS |

IO, immunotherapy; BSC, best supportive care.

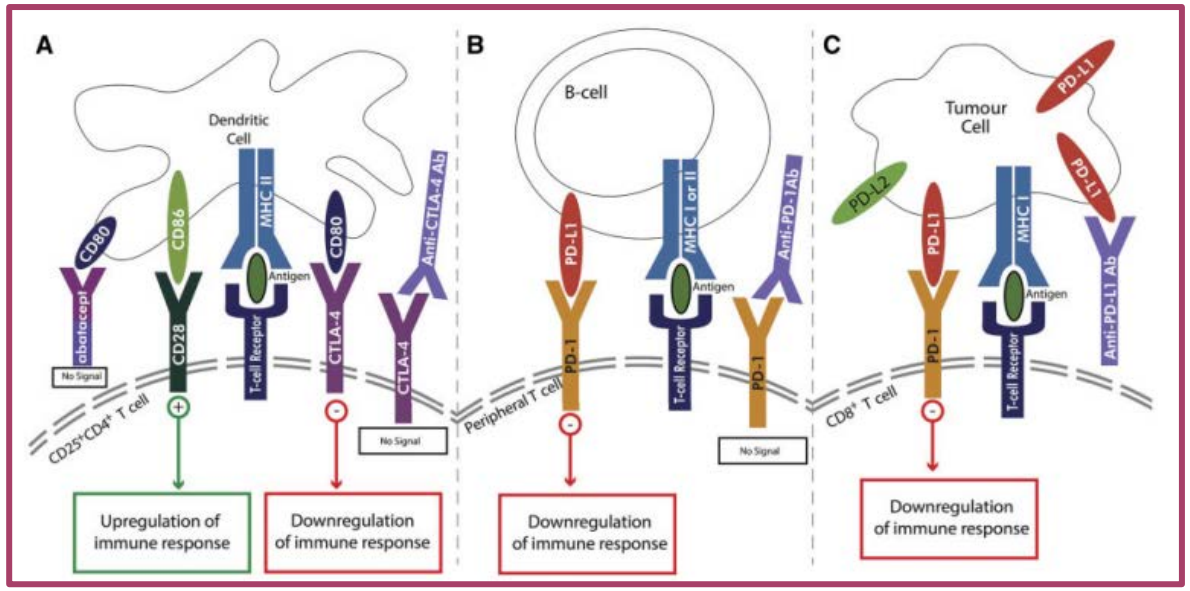
NCT03425643. NCT03456063. NCT03800134. Heymach et al. *J Thorac Oncol*. 2019;14:S625. Abstract P1.18-02. NCT04025879. Gray et al. FLASCO Spring Session 2021. Poster.



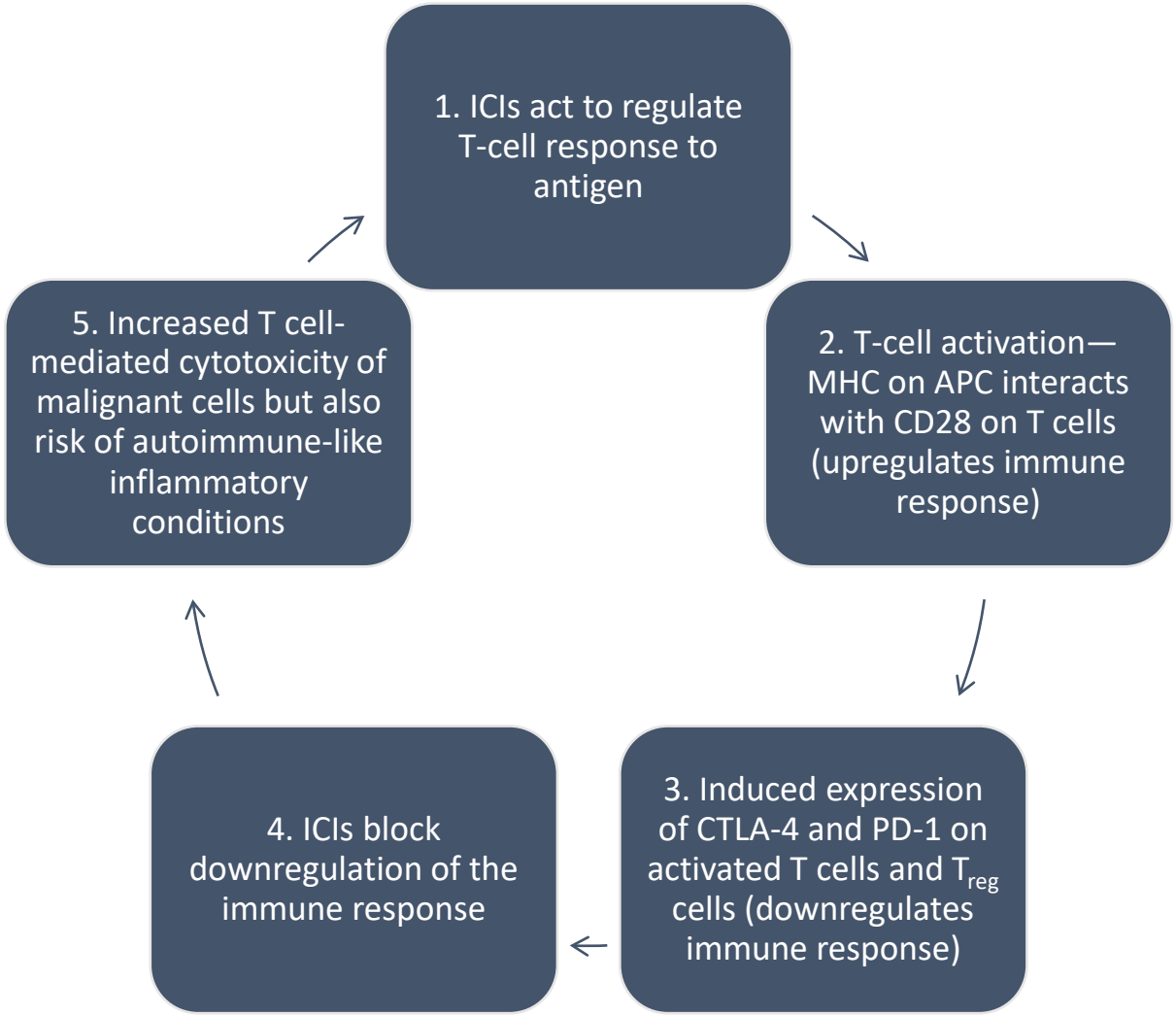
# Neoadjuvant Therapy for Early-Stage NSCLC

## Managing Immune-Related Adverse Events

# Immune-Related Adverse Events (irAEs)



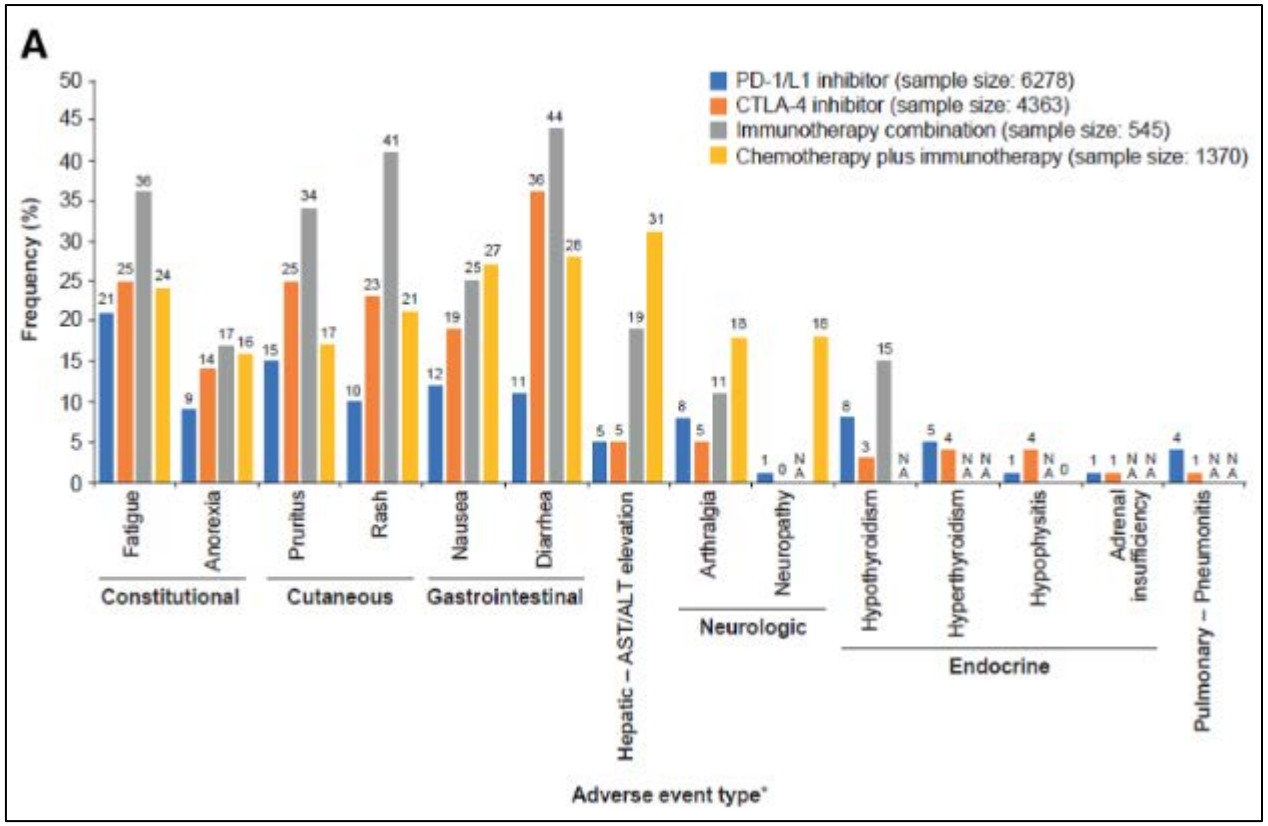

- irAEs are a consequence of enhanced T-cell activation by inhibition of CTLA-4 and/or PD-1

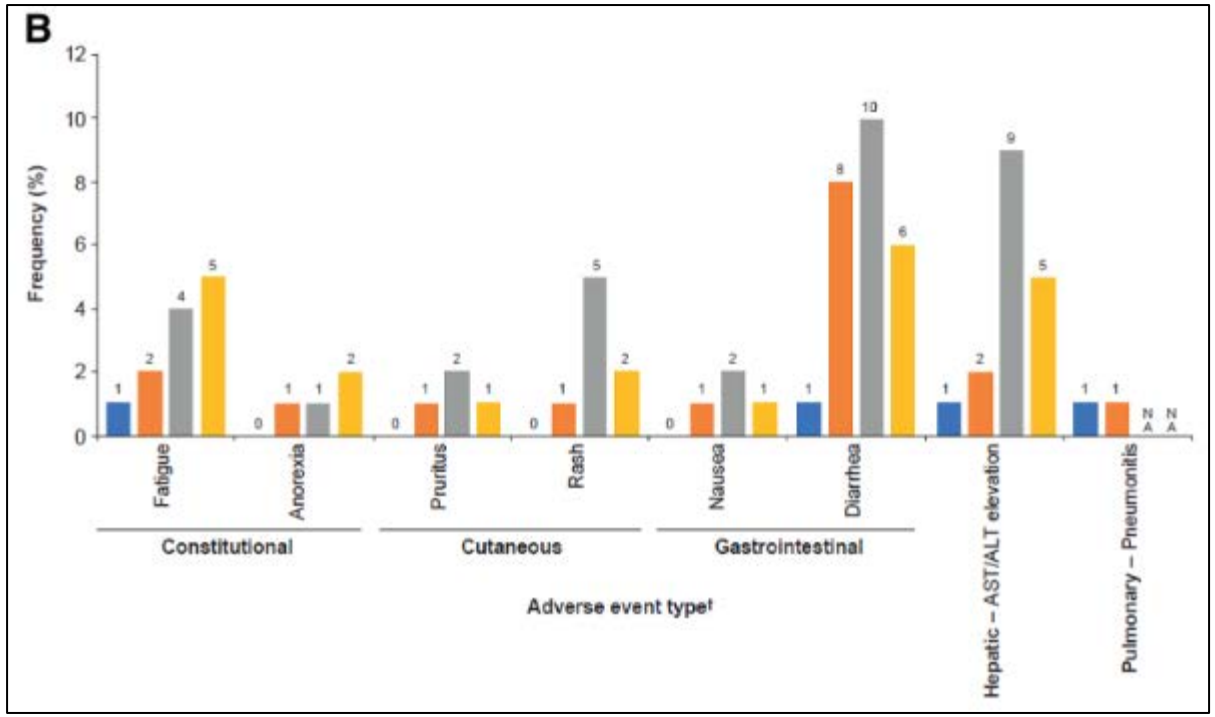



APC, antigen-presenting cell; CD28, cluster of differentiation 28; MHC, major histocompatibility complex; $T_{reg}$ cells, regulatory T cells.

Weinmann and Pisetsky. *Rheumatology (Oxford)*. 2019;58(suppl 7):vii59.

# Frequency of irAEs




**A:** Any grade irAE

**B:** Grade 3/4 irAE

Zubiri et al. *Oncologist*. 2020;25(3):e398.

# Types of irAEs

### Dermatologic
- Rash
- Pruritus
- Stevens-Johnson syndrome/ Toxic epidermal necrolysis

### Gastrointestinal
- Diarrhea/colitis

### Ocular
- Uveitis
- Dry eyes
- Optic neuropathy

### Hepatic
- Hepatitis
- Transaminitis

### Renal
- Nephritis
- Increased serum creatinine (SCr)

### Pancreatic
- Acute pancreatitis
- Increased amylase/lipase

### Central Nervous System
- Neuropathy
- Encephalopathy
- Guillain-Barré syndrome
- Myasthenia gravis

### Endocrine
- Hyper/hypothyroidism
- Adrenal insufficiency
- Type 1 diabetes mellitus
- Hypophysitis

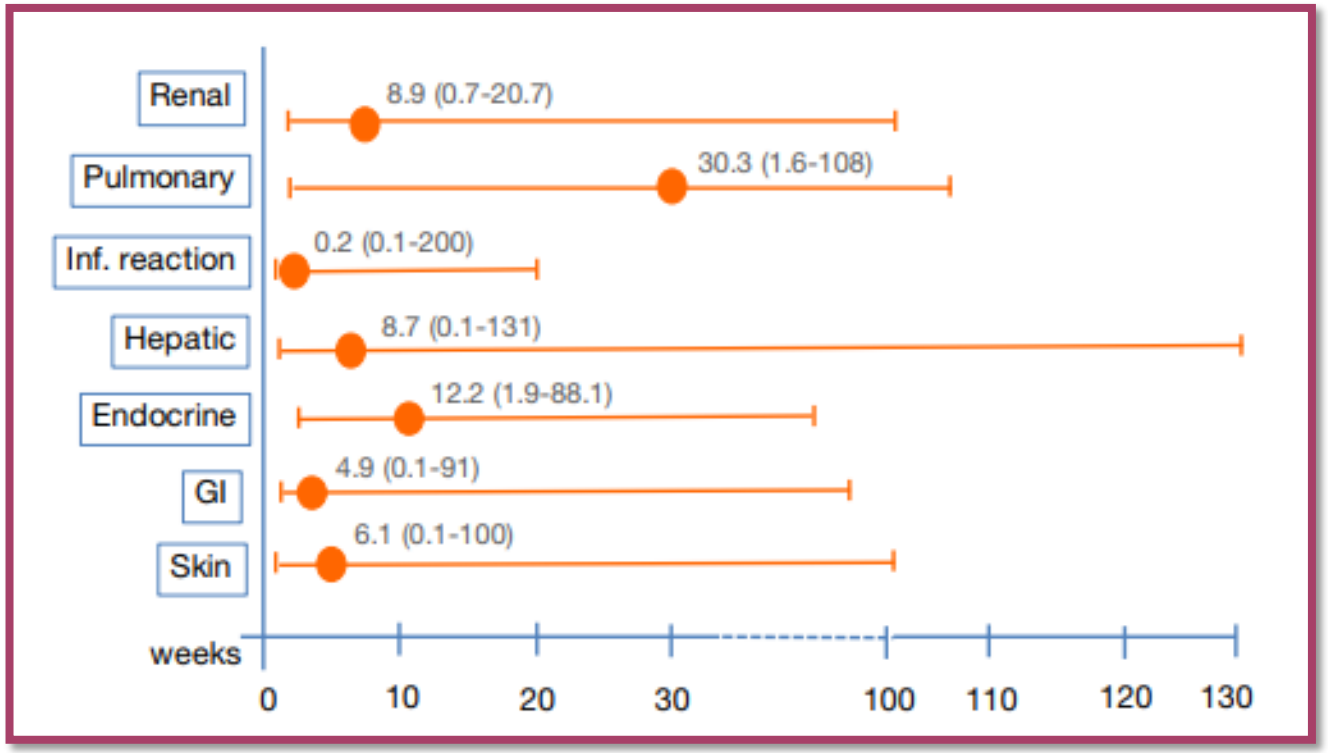
### Cardiac
- Myocarditis/pericarditis
- Cardiomyopathy
- Cardiac arrest

### Pulmonary
- Pneumonitis

### Musculoskeletal
- Myalgias/myositis
- Arthritis

NCCN Guidelines. Management of Immunotherapy-Related Toxicities, v1.2022.

# Time to Onset of irAEs

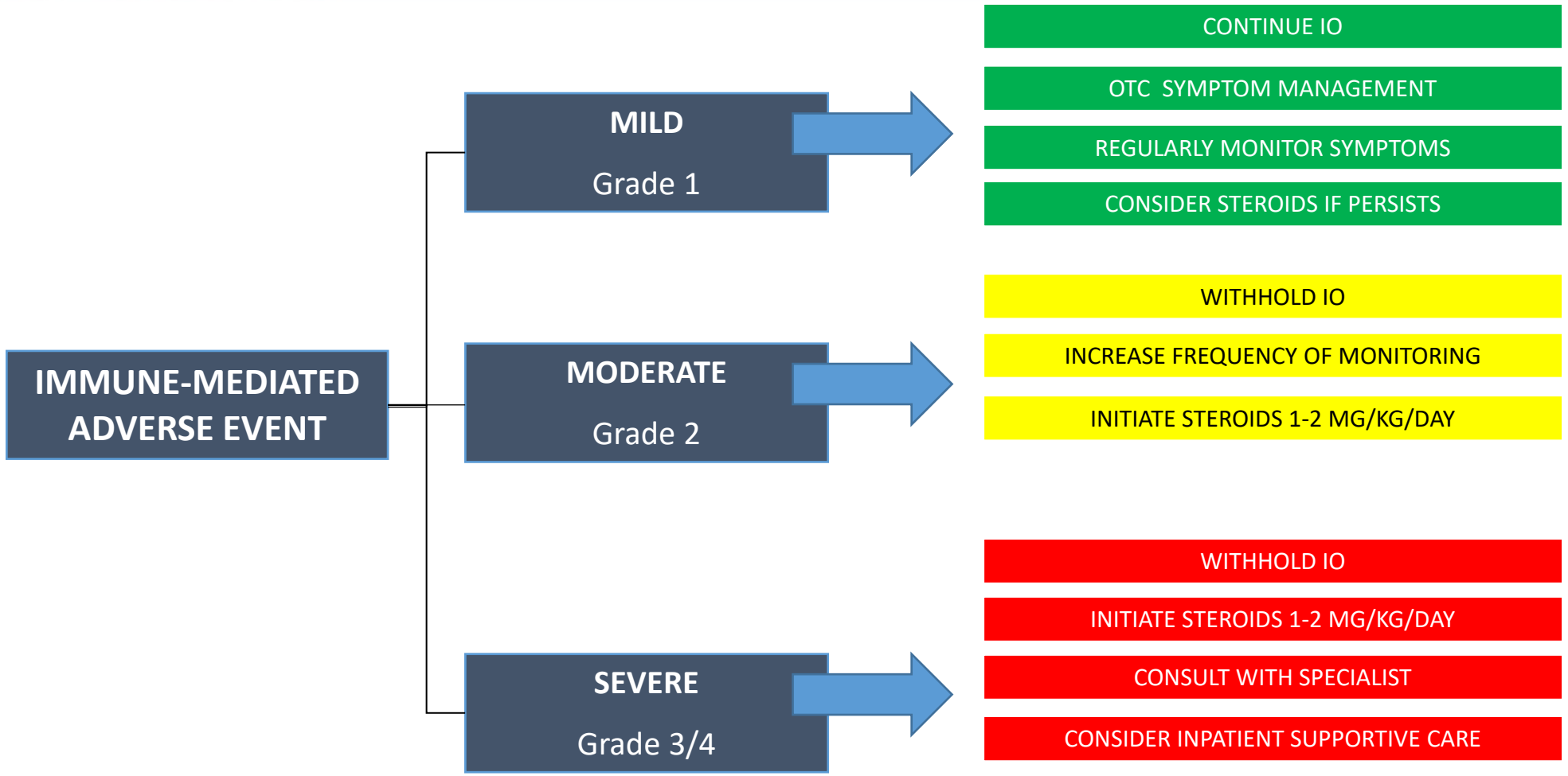



Median time to onset of irAE for different toxicities with anti-PD-1 therapy in NSCLC

Circles = medians, bars = ranges.

Remon et al. *J Thorac Dis*. 2018;10(suppl 13):S1516.

# irAE Management Algorithm




**FOR ALL-GRADE EVENTS**

- Evaluate for alternative etiology
- Consider corticosteroids in the absence of clear alternative etiology, even for low-grade events, to prevent progression to higher-grade events

IO, immunotherapy; OTC, over-the-counter.

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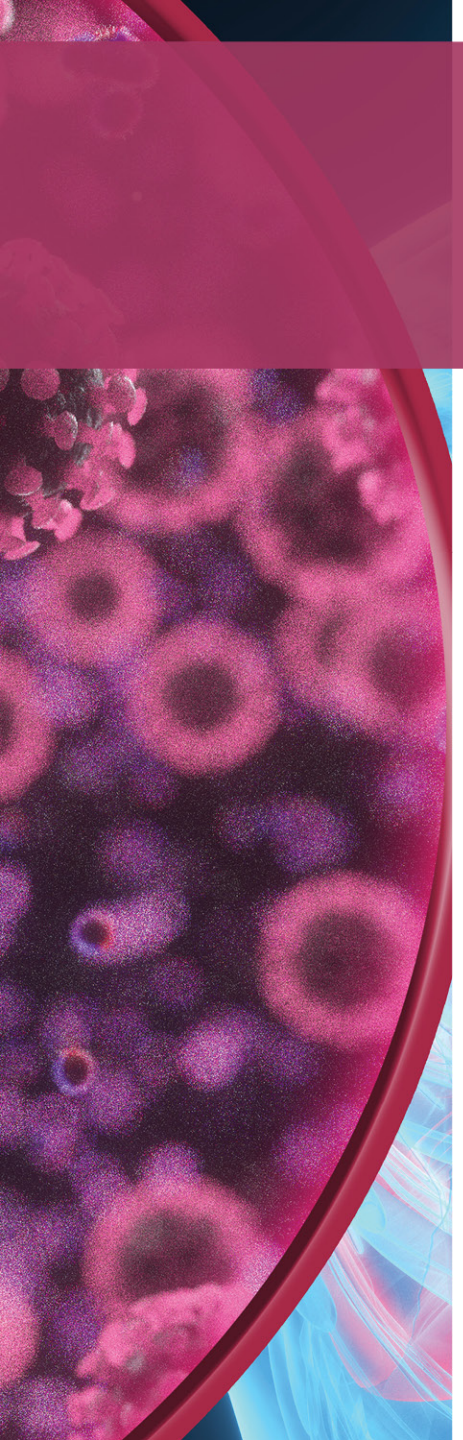
# Agents Used to Treat irAEs



## Corticosteroids

- Topical
- Oral
- Intravenous (IV)

## Anti-TNF Agents

- Infliximab

## Anti-IL-6 Agents

- Tocilizumab

## Other Immunosuppressants

- Mycophenolate mofetil
- Cyclosporine
- IV immunoglobulin (IVIG)
- Cyclophosphamide
- Rituximab
- Methotrexate/azathioprine
- Antithymocyte globulin (ATG)
- Vedolizumab

IL-6, interleukin-6; TNF, tumor necrosis factor.

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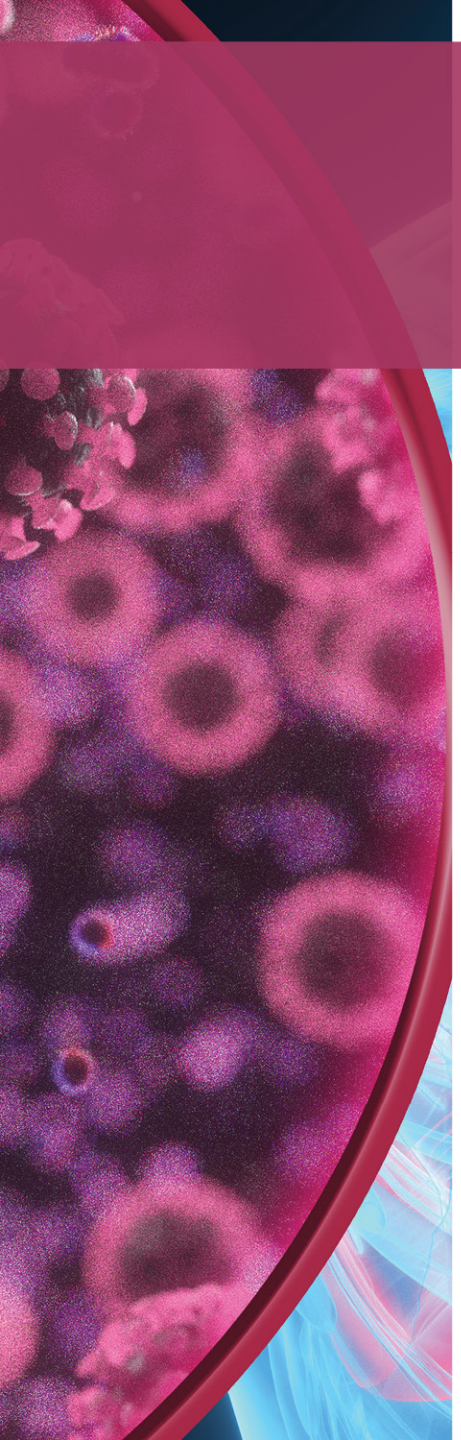
# Supportive Care Considerations With Corticosteroids



- Consider consult with appropriate specialty service
- Begin taper once irAE has resolved to appropriate grade
- Tapers are patient specific but should generally occur over 4-6 weeks
- Patient should contact oncologist if any symptoms worsen during taper
- Prophylaxis Considerations
  - H2RA/PPI
  - PJP
  - Antifungal
  - Vitamin D/calcium

H2RA, histamine-2 receptor antagonist; PJP, *Pneumocystis jirovecii* pneumonia; PPI, proton pump inhibitor.

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# Select Steroid-Refractory irAEs

| irAE | Potential Intervention(s) |
|---|---|
| Pneumonitis | Infliximab 5 mg/kg IV (consider second dose at Day 14)<br>Mycophenolate mofetil 1-1.5 g Q12H<br>IVIG |
| Colitis | Infliximab 5 mg/kg IV at Week 0, 2, and 6<br>Vedolizumab 300 mg IV at Week 0, 2, and 6 |
| Hepatitis | Mycophenolate mofetil 0.5-1 g Q12H<br>**Do not use infliximab** |

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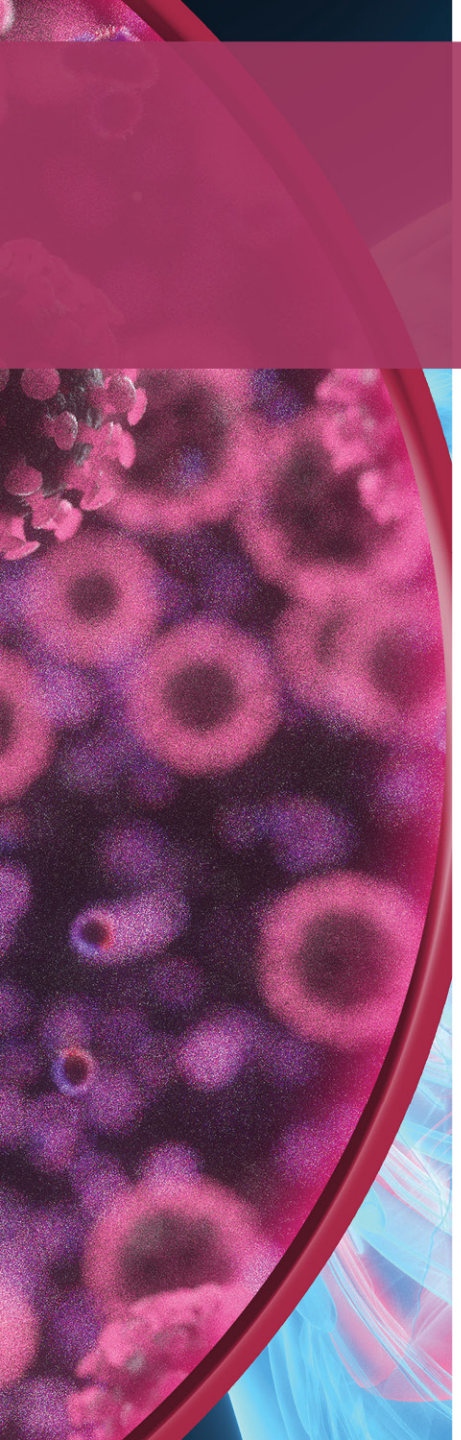
# Prior to Starting ICI Therapy



Educate patient on ICI mechanism → Document underlying medical conditions (including any history of autoimmune conditions) → Assess patient ability to monitor/report irAEs

Educate patient about signs/symptoms and onset timing of ICI toxicity →

Patient should notify oncology team with any:

- Severe fatigue, headache, rash, cough, shortness of breath, chest pain, abdominal bloating, changes in bowel patterns, weight loss, vision change, severe muscle weakness/joint pain, mood change

NCCN Guidelines. Management of Immunotherapy-Related Toxicities, v1.2022.

# Conclusion

Perioperative chemotherapy historically improves outcomes in resectable NSCLC, particularly with respect to risk of recurrence and survival

The emerging role of immunotherapy in the resectable NSCLC space provides an opportunity to improve both pCR and MPR rates, which may translate to significant improvements in EFS

Nivolumab + chemotherapy is a newly FDA-approved option for neoadjuvant treatment of resectable stage IB-IIIA NSCLC

Pharmacists can play a vital role in educating, monitoring, and managing patients at risk for or who experience an irAE

# Questions & Answers