Medication-related Pulmonary toxicity: focus on cancer drugs

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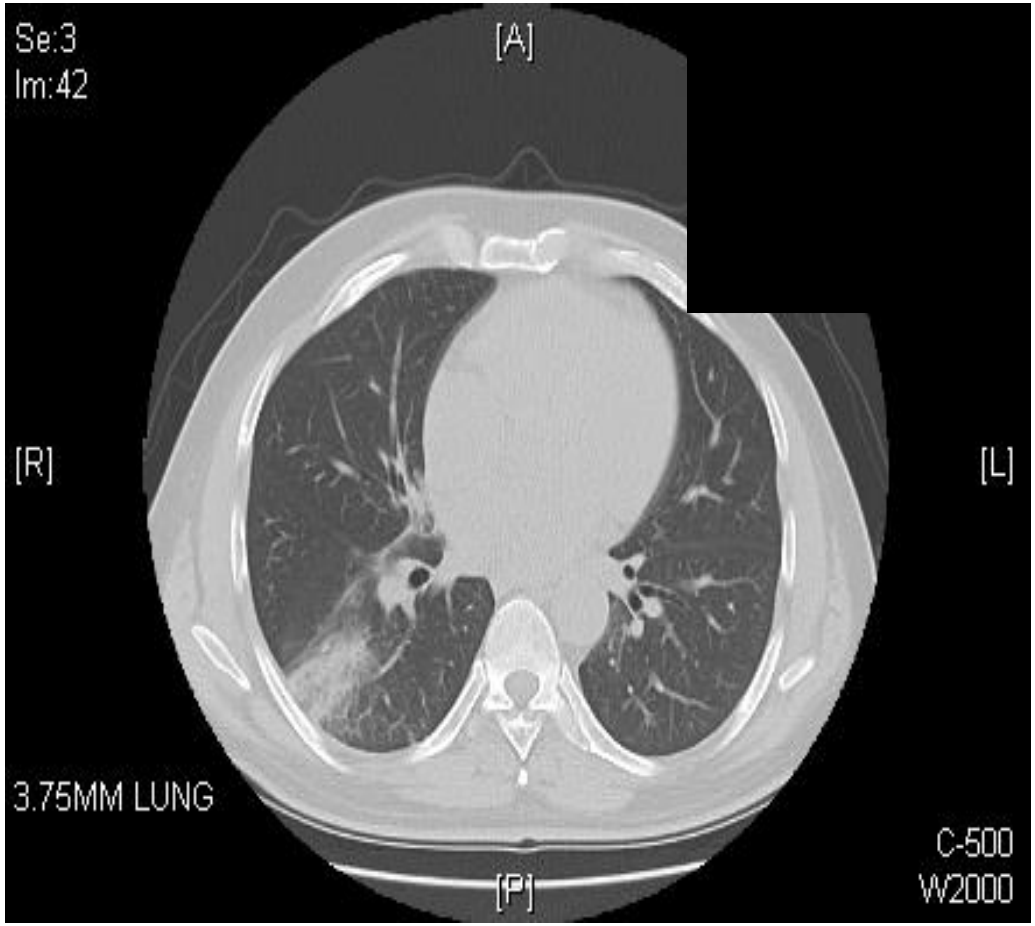
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Mass General Brigham

- 51 yo with metastatic carcinoid
- Waxing and waning consolidative opacities
- Offending agent:

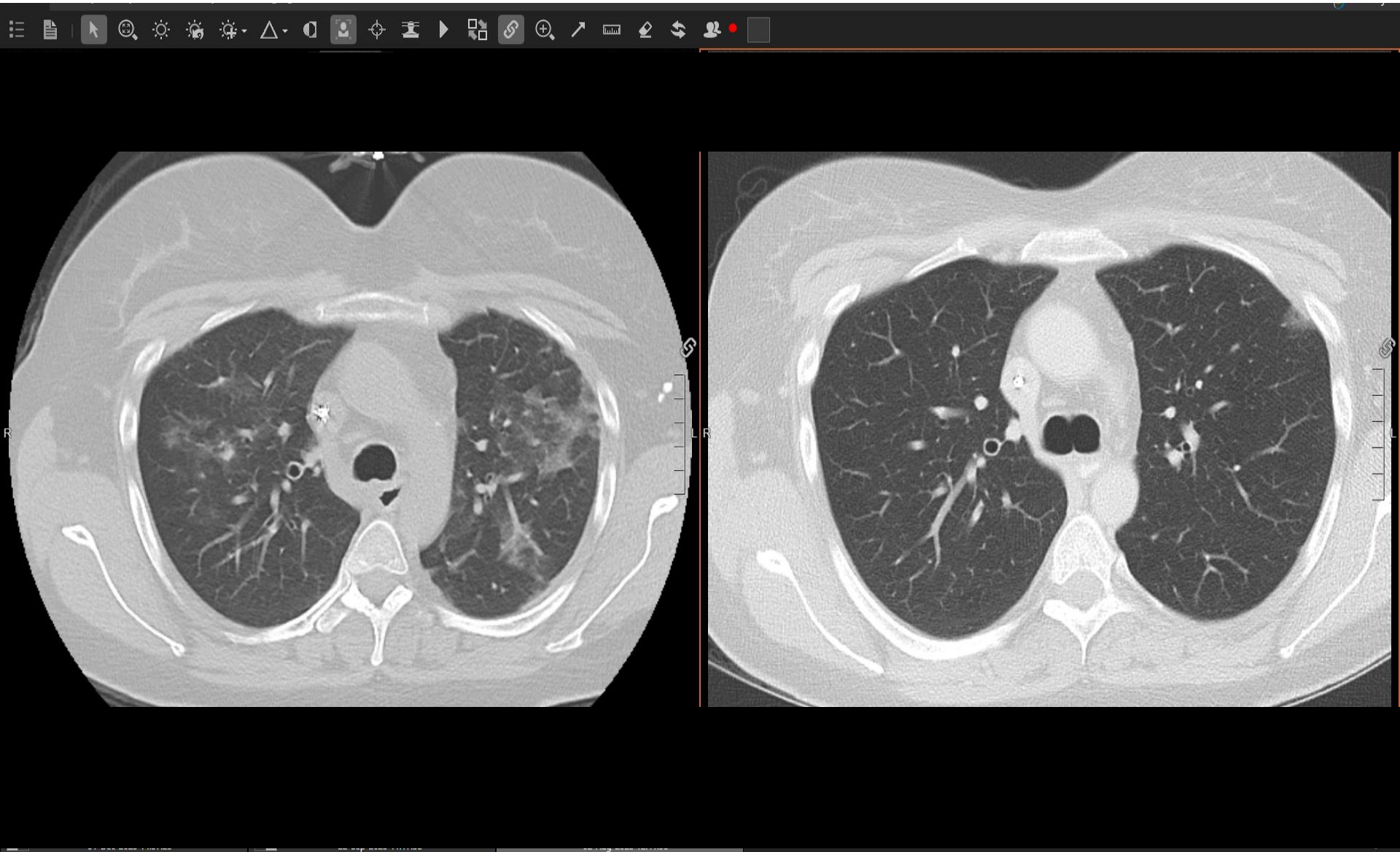
Everolimus



Pre and Post treatment with FOLFOXIRI (Fluorouracil, oxaliplatin, irinotecan)

December

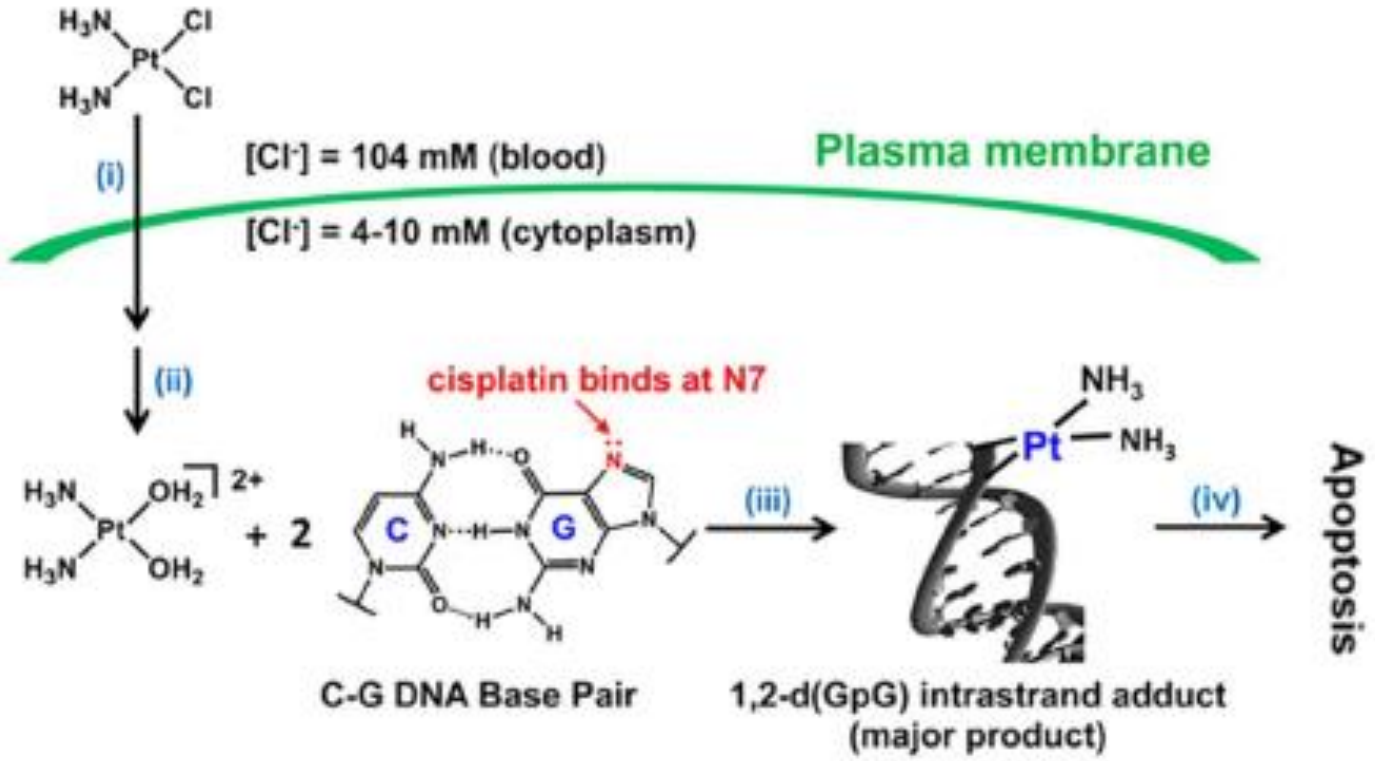
September



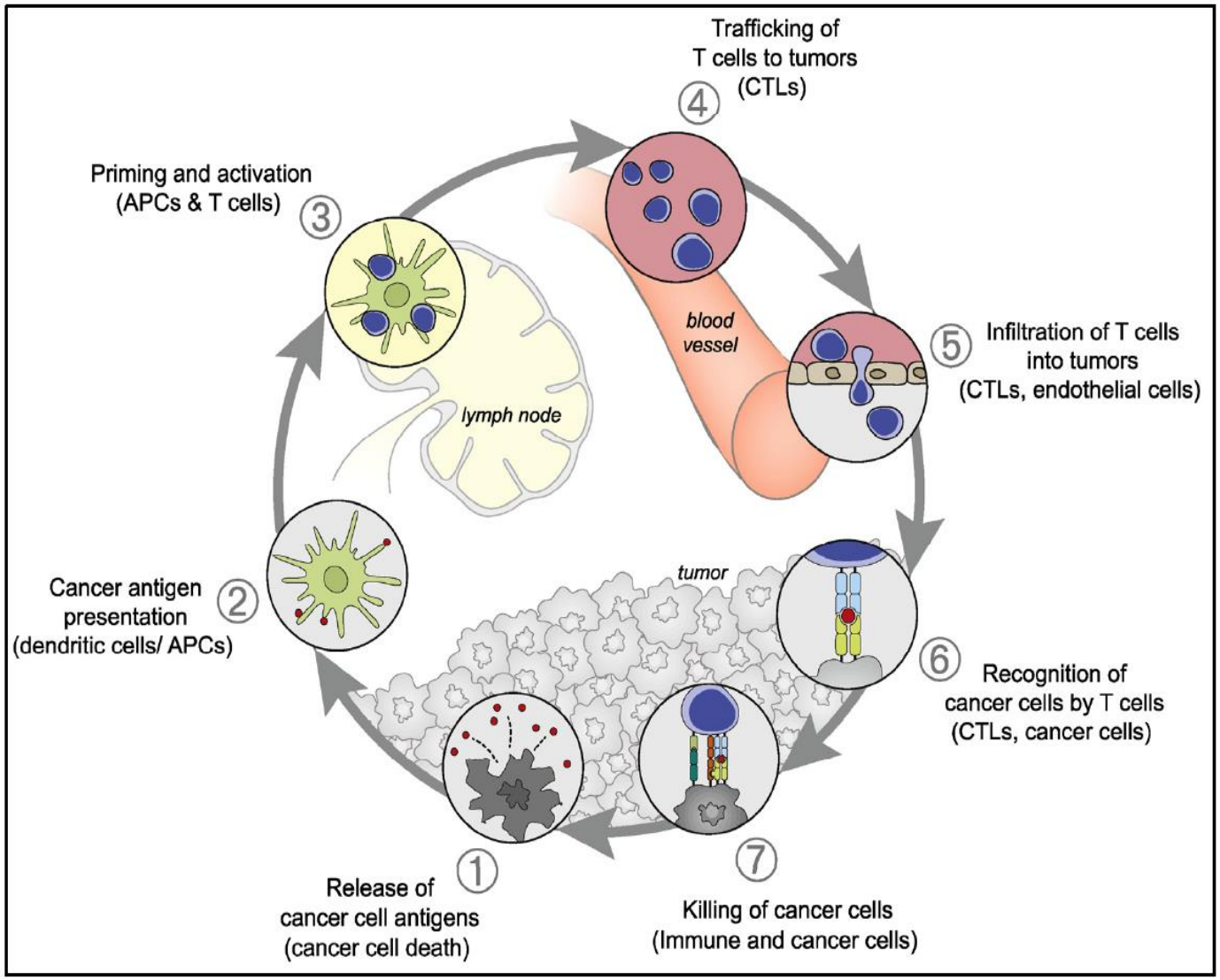
Fun facts about drug-induced ILD

- **3-5% of all cases of ILD**
- **Anti-neoplastic drugs 23-51% of drug-induced ILD**
  - **Next most common: anti-rheumatologics, amiodarone, antibiotics**
- **Bleomycin (6.8-21% with up to 48% mortality; dose-related) and mTOR inhibitors (everolimus) have the highest incidence.**
- **Targeted therapies are next most common (EGFR, cyclin-dependent kinase inhibitors (ie Palbociclib), poly (ADP-ribose) polymerase inhibitors (PARP; ie Olaparib).**
- **Immune checkpoint inhibitors 1-4%; higher when used in combination.**
- **New: Antibody-drug conjugates, ie trastuzumab-deruxtecan: 16% pneumonitis, 2.4% mortality in clinical trials but more recent, modified protocols: 10.5% pneumonitis and no mortality.**

Cisplatin targets DNA



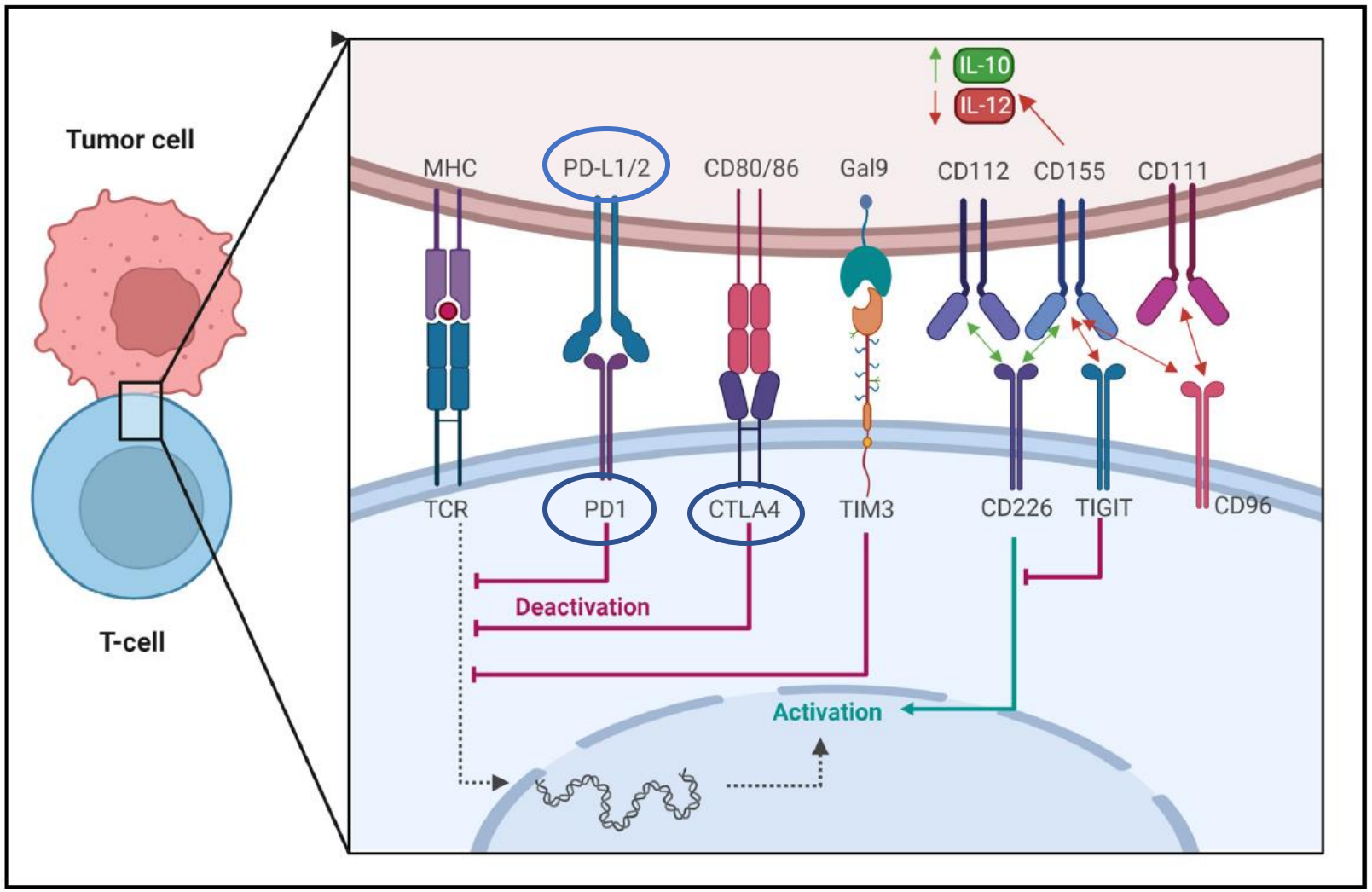
Cancer immunity cycle



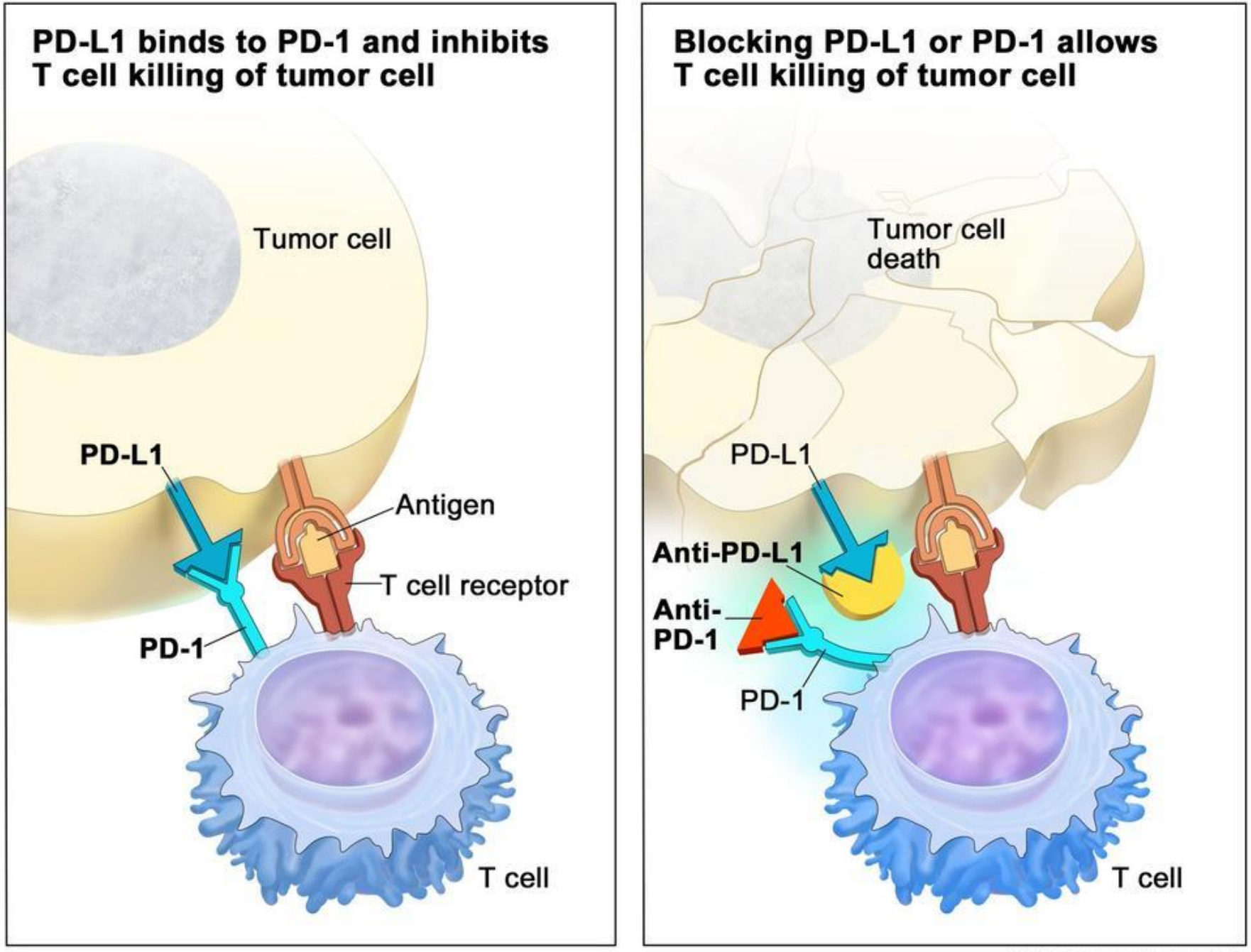
Dendritic cells may be the link between the innate and adaptive immune systems

Cancers 2023;15:2721.https://doi.org/10.3390/cancers15102721

Immune checkpoints between tumor and T-cells

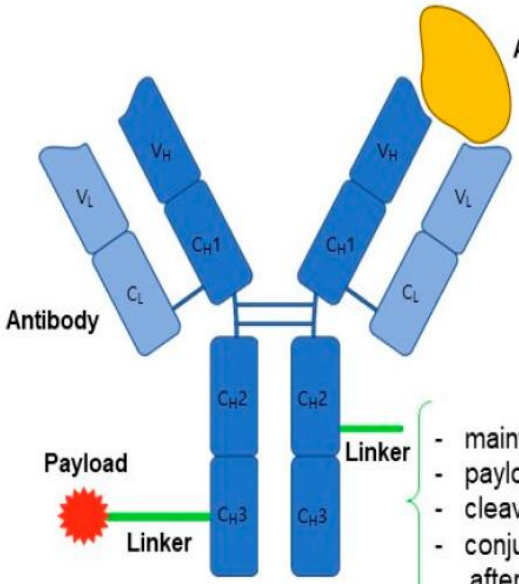


Cancers 2023;15:2721.https://doi.org/10.3390/cancers15102721



Cancers 2023;15:2721.https://doi.org/10.3390/cancers15102721

Antibody-drug conjugates



Antibody
- selective recognition of antigens
- low immunogenicity
- long plasma half-life
- monoclonal antibodies are commonly used

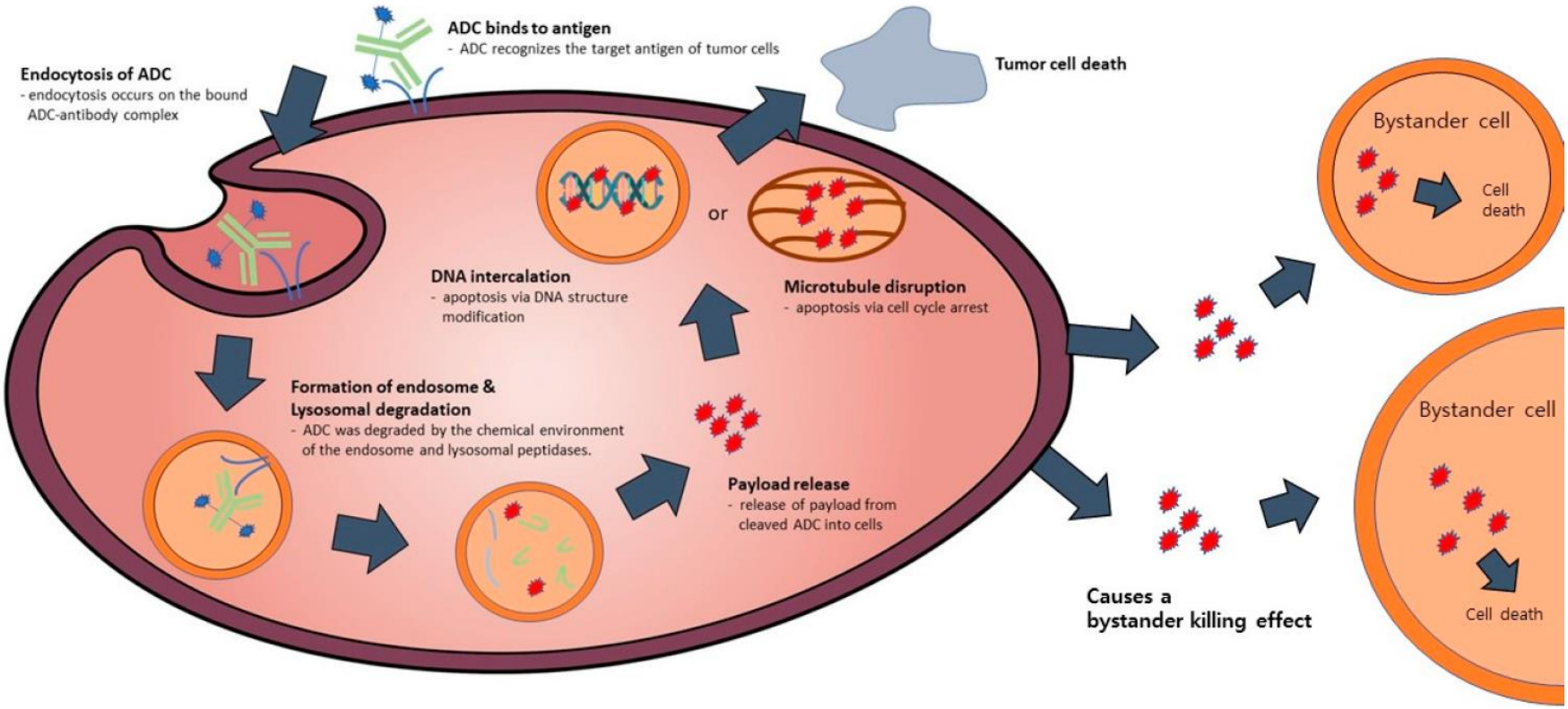
Payload
- induction of apoptosis of tumor cells
- concentration in nM or pM
- bind to microtubules or DNA

Antigen
- predominantly expressed on tumor cells
- rare or few in normal tissue
- on the surface of tumor cells

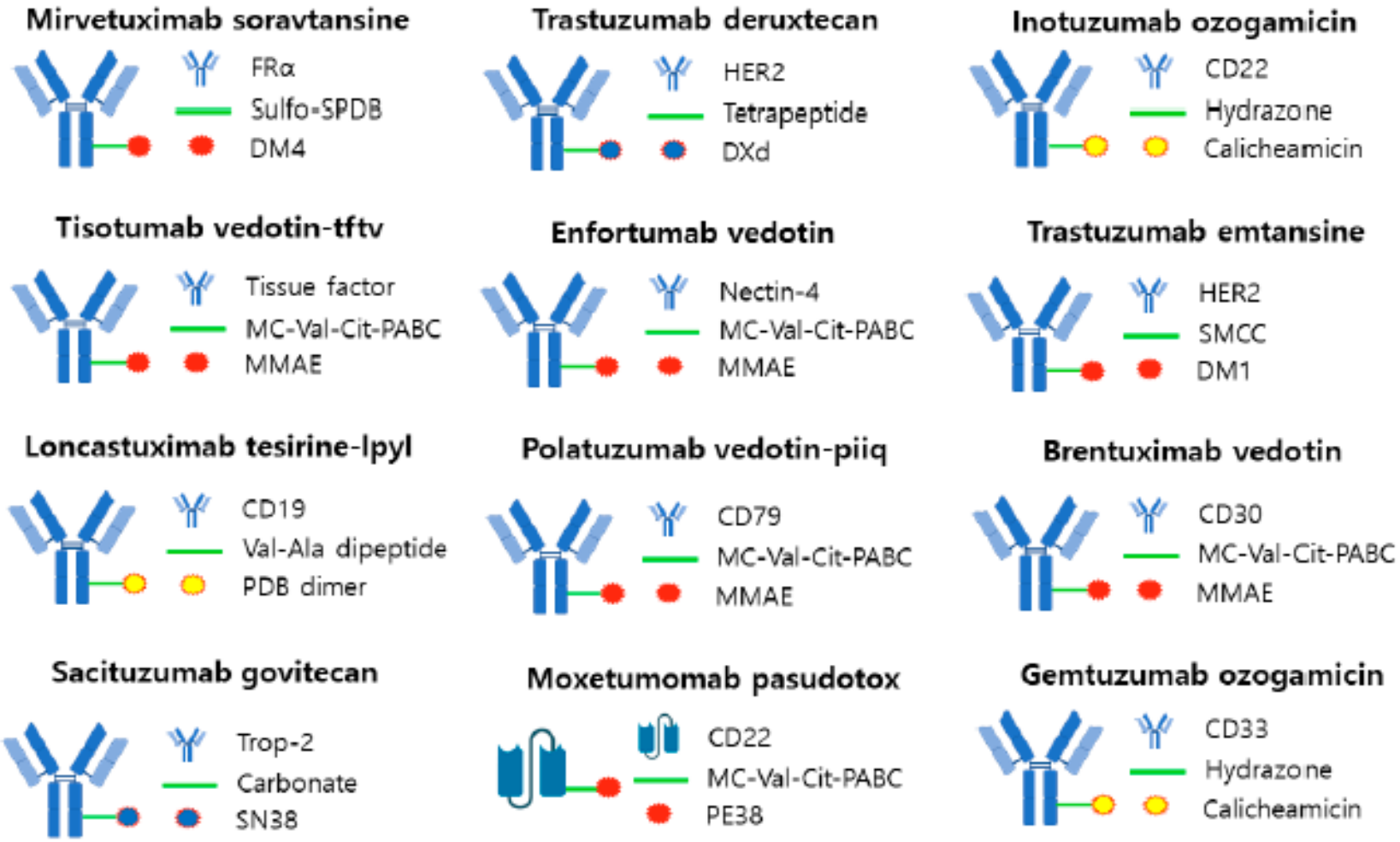
Linker
- maintain bonds in the blood
- payload release after internalization
- cleavable or non-cleavable linker
- conjugation to the antibody surface or conjugation after artificial modification

Antibodies 2023;12:72. https://doi.org/10.3390/antib12040072

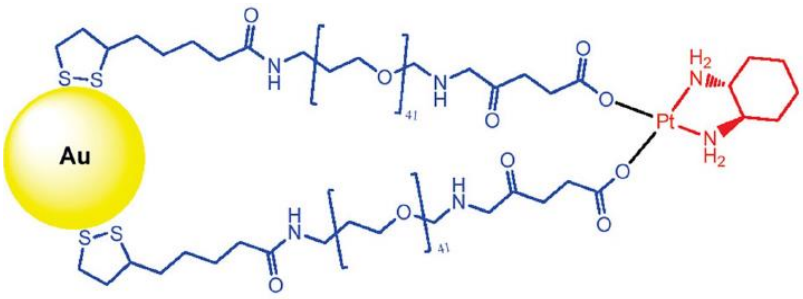
Antibody-drug conjugates

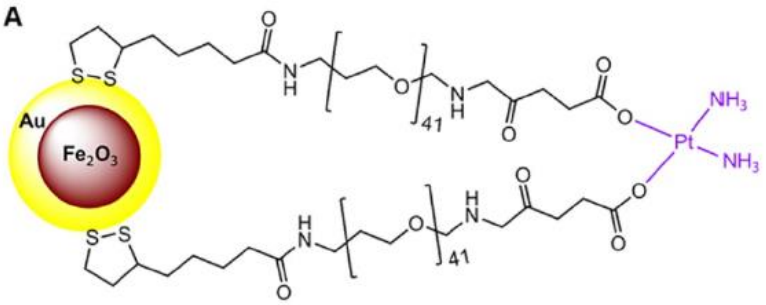


FDA-approved ADC's

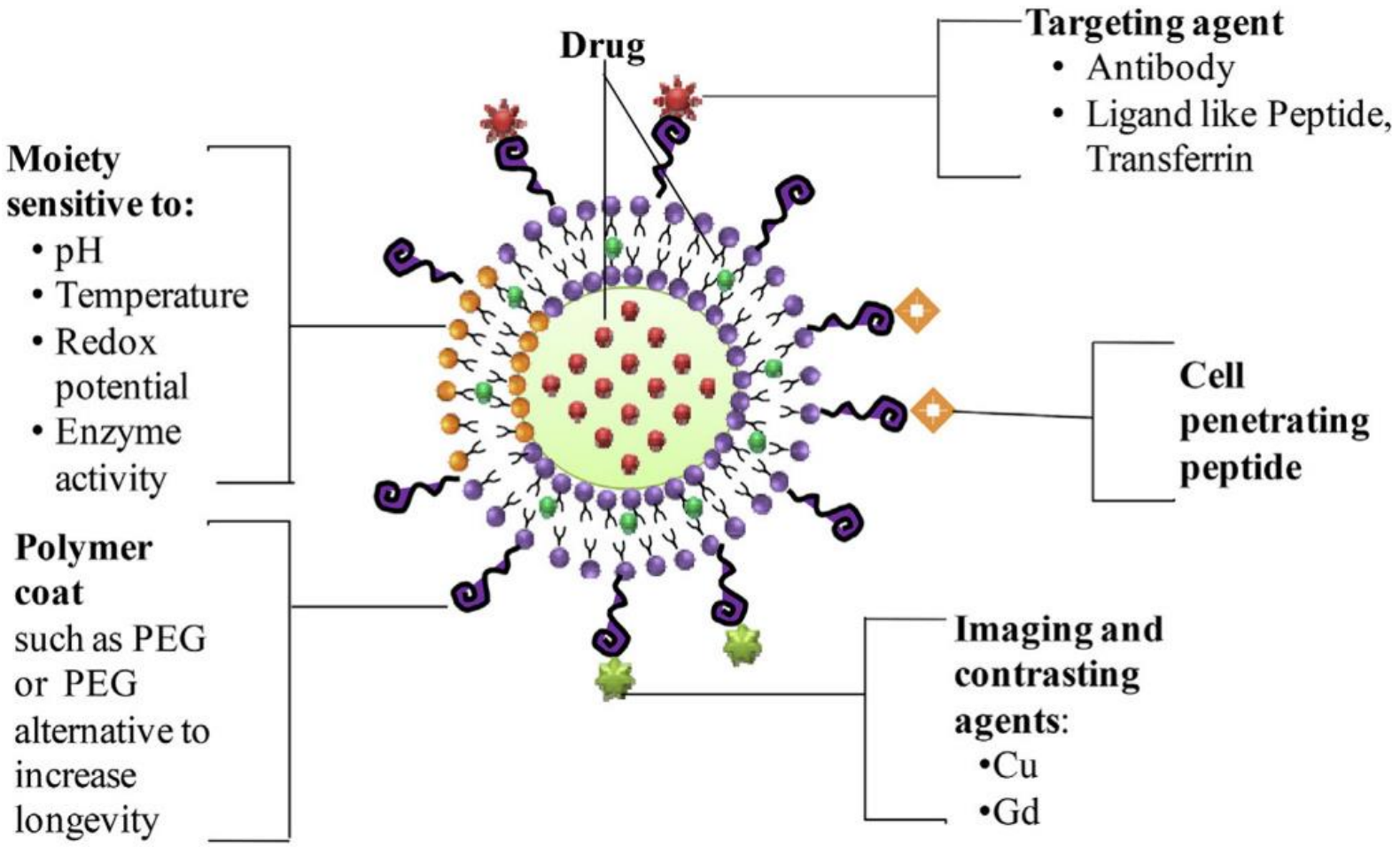


Nanoparticles

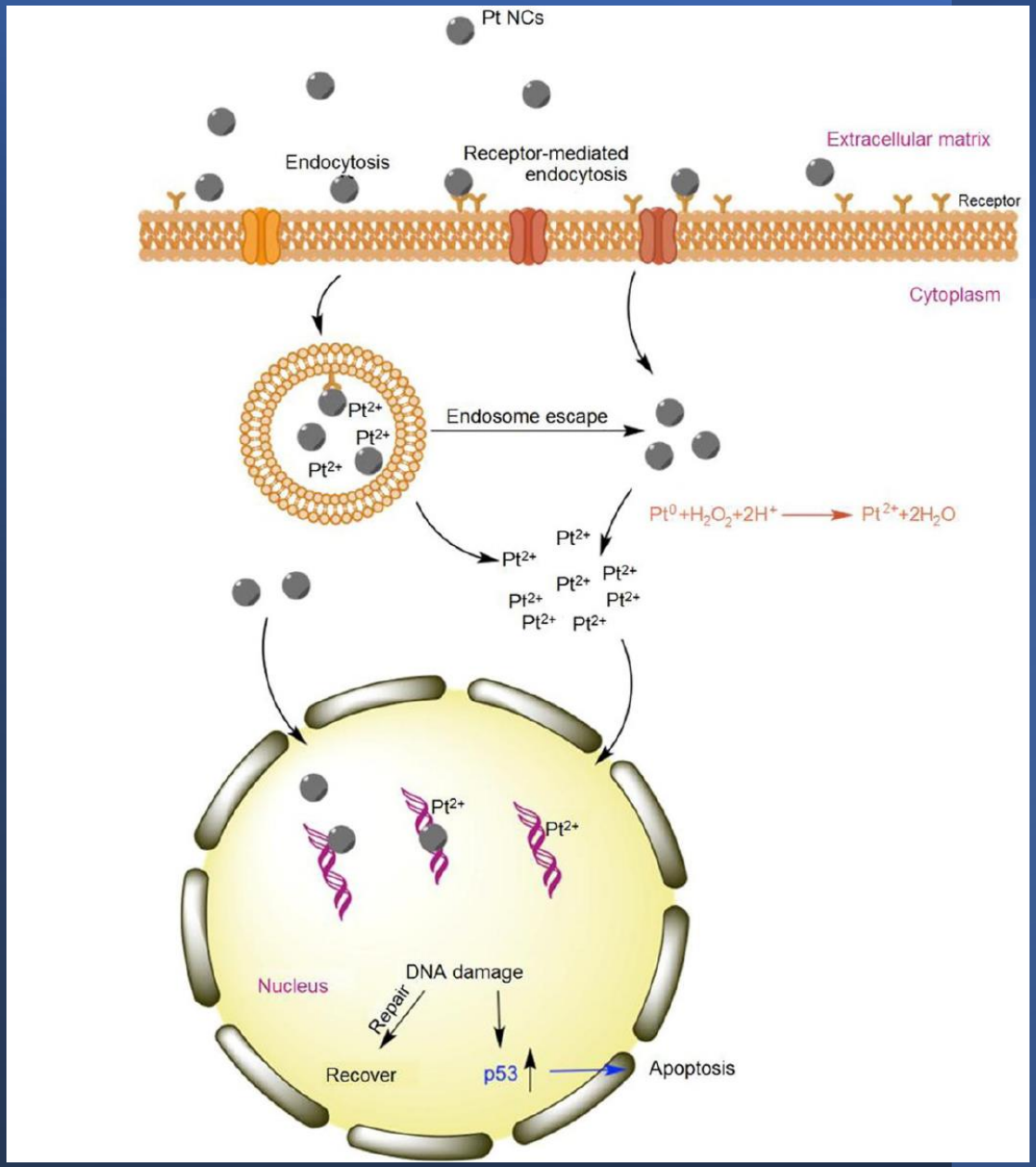




Liposomes



Life Sciences 2024;353:122899.


Pt NCs
Extracellular matrix
Endocytosis
Receptor-mediated endocytosis
Receptor
Cytoplasm
Endosome escape
Pt^{2+}
$Pt^{0}+H_2O_2+2H^+ \rightarrow Pt^{2+}+2H_2O$
Nucleus
DNA damage
Repair
Recover
p53
Apoptosis

Types of Nanoparticles	Properties	Applications	Toxicity	Modification	Safety Considerations
Gold	High surface-to-volume ratio and distinctive optical properties	Noninvasive imaging with chemicals, targeting/imaging moieties, and therapeutic drugs	Toxicity depends on size, shape, and surface modifications.	Nanoconjugates for targeted molecular imaging with decreased systemic toxicity.	Reduced toxicity at specific areas and reduced systemic toxicity.
Iron Oxide	Used to target tumors using surface ligands.	Targeted tumor imaging and drug delivery vehicle	Non-targeted and antibody size constraints	Ligands/antibodies for tumor targeting, adjusted to improve tumor site accumulation.	Improved cancer diagnosis tool effective medicine administration using tailored strategy.
Silica	Size and shape control, functionalization for different applications	Implant in surgery, medication administration, imaging agents, sensitive to changes in pH and temperature.	Misconception about perfect safety.	Mesoporous structures for drug storage, functionalization with imaging agents, and thermoresponsive polymers for controlled drug release.	Generally safe but needs careful assessment for specific uses.
Carbon Nanotubes	High aspect ratio and surface chemical functions	Drug delivery, photoacoustic imaging, fluorescence imaging, and photothermal treatment	Concerns about biocompatibility and toxicity	Surface functionalization for biocompatibility, drug and nucleic acid loading, and precision-targeting ligands	Addresses biocompatibility and toxicological problems for clinical usage.
Quantum Dots	Large surface area for drug conjugation, unique optical characteristics.	tumor detection, medication administration, fluorescence imaging, and photothermal treatment.	Potential toxicity concerns	Coatings for safety, conjugation with therapeutic compounds, targetability	Effective at lower doses, fewer side effects with a tailored approach.
Liposomes	Encapsulate hydrophilic and hydrophobic substances.	Drug delivery, encapsulating chemotherapy, diagnostic imaging, and targeted treatment	Possible immunological responses	Surface-modified with ligands, antibodies, or peptides for targeting and encapsulating of imaging agents	High biocompatibility, low toxicity, useful for targeted medication administration.

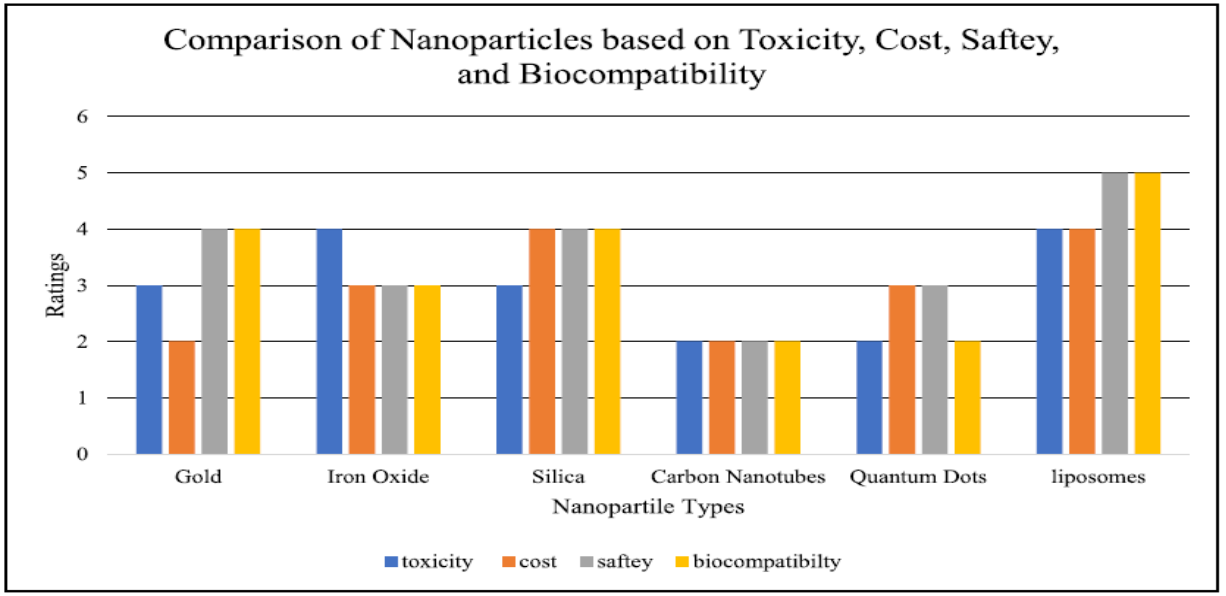


Fig. 8. Comparative analysis of nanoparticles: based on toxicity, cost, safety, and biocompatibility (Ratings on a scale from 1 to 5) **[Original figure created by the authors]**

Mechanism of lung toxicities

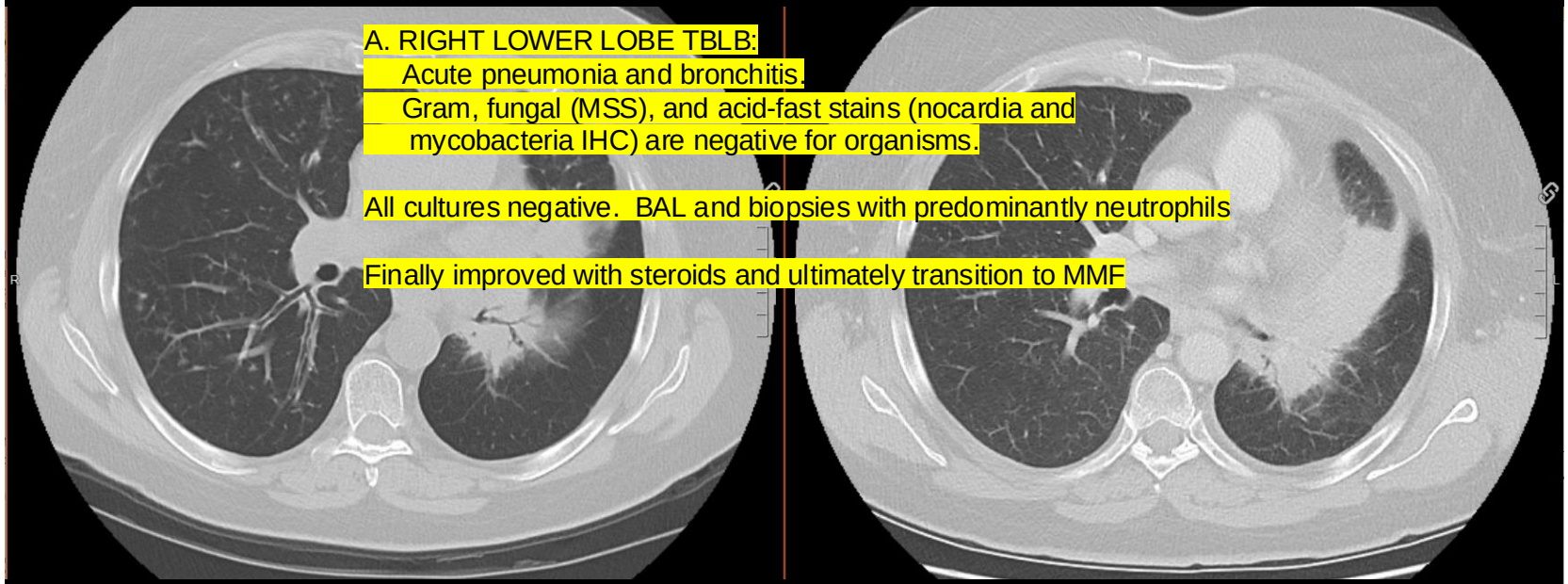
- **Immunologic: direct haptogen modification or antibody-antigen immune complex deposition followed by inflammation**
- **Direct toxic effect on endothelium and epithelium (seen with bleomycin—neutrophilia, and methotrexate—lymphocytic alveolitis). HER-2 receptors on bronchial and bronchiolar epithelium, for example, may serve as a target forT-DXd but target independent uptake**
- **Release of toxic reactive oxygen species (seen with bleomycin, amiodarone, nitrofurantoin)**
- **Endothelial permeability**
- **“Bystander” effect (ADC’s)**

Clinical presentation

- Typically presents days to months after drug administration

- Majority within first 2 months for ICIs and initial 12 months with ADCs.

Small cell carcinoma, treated with radiation, chemotherapy, and nivolumab. P/w productive cough.



A. RIGHT LOWER LOBE TBLB:
Acute pneumonia and bronchitis.
Gram, fungal (MSS), and acid-fast stains (nocardia and mycobacteria IHC) are negative for organisms.

All cultures negative. BAL and biopsies with predominantly neutrophils

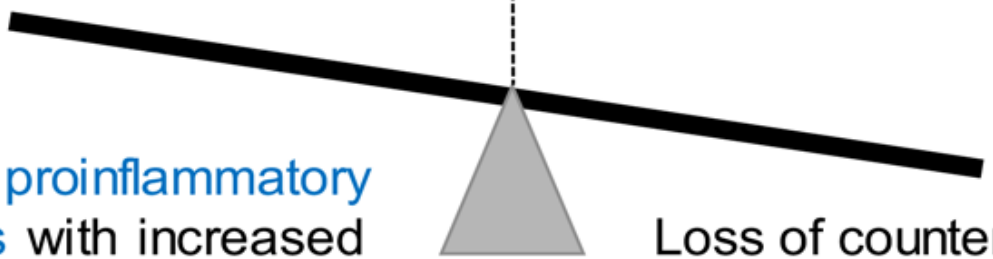
Finally improved with steroids and ultimately transition to MMF

The Journal of Clinical Investigation CLINICAL MEDICINE

The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis

Karthik Suresh,[1] Jarushka Naidoo,[2,3] Qiong Zhong,[1] Ye Xiong,[1] Jennifer Mammen,[4] Marcia Villegas de Flores,[5] Laura Cappelli,[5] Aanika Balaji,[2] Tsvi Palmer,[1] Patrick M. Forde,[2,3] Valsamo Anagnostou,[2,3] David S. Ettinger,[2] Kristen A. Marrone,[2,3] Ronan J. Kelly,[2,3] Christine L. Hann,[2,3] Benjamin Levy,[2,3] Josephine L. Feliciano,[2,3] Cheng-Ting Lin,[6] David Feller-Kopman,[1] Andrew D. Lerner,[1] Hans Lee,[1] Majid Shafiq,[1] Lonny Yarmus,[1] Evan J. Lipson,[3,4] Mark Soloski,[5] Julie R. Brahmer,[2,3] Sonye K. Danoff,[1] and Franco D'Alessio[1]

T cells	Increased Tcm (expressing CD62L) and TNF-α^{hi}, IFN-γ^{hi} $CD8^+$ cells	Decreased PD-1/CTLA-4 expression in Tregs
Myeloid cells	Increased $CD11b^{hi}$, IL-$1\beta^{hi}$ populations	Decreased IL-$1RA^{hi}$ cell populations



Increase in proinflammatory cell subsets with increased expression of endothelial adhesion markers

Loss of counter-regulatory suppressive cell phenotypes

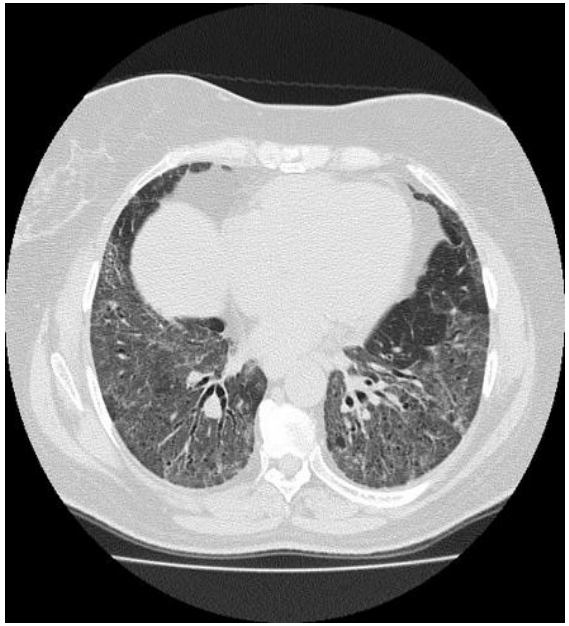
J Clin Invest. 2019;129(10):4305-4315.

“Pneumonitis”

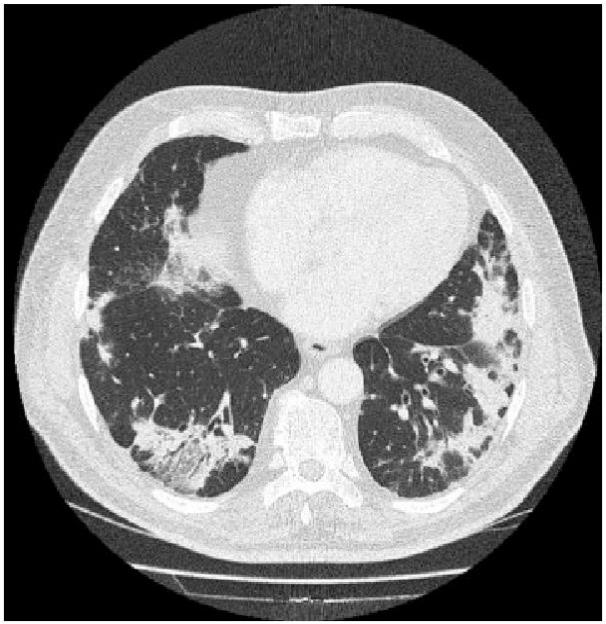
- Not a specific entity
- Non-infectious inflammation of the lungs
- Spectrum of pathologic findings affecting the interstitium and alveoli including (but not limited to):

  - Cellular (non-specific) interstitial pneumonitis
  - Organizing pneumonia
  - Diffuse alveolar damage

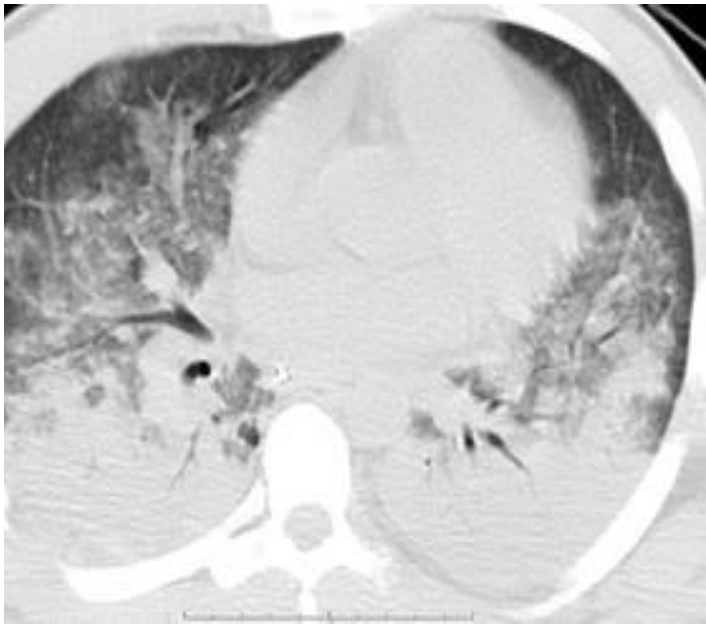
Cellular interstitial pneumonitis
"non-specific interstitial pneumonitis"

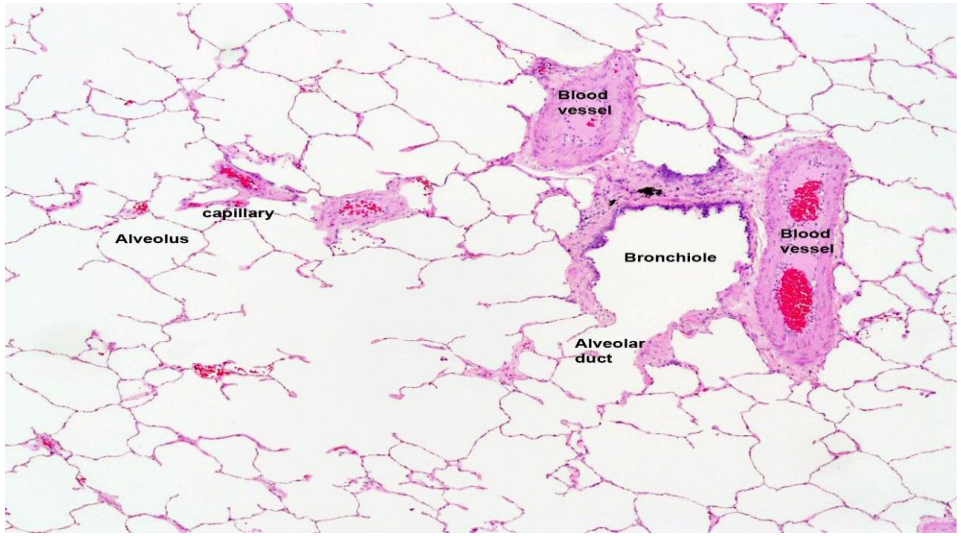


Organizing pneumonia



Diffuse alveolar damage





Cellular interstitial pneumonitis
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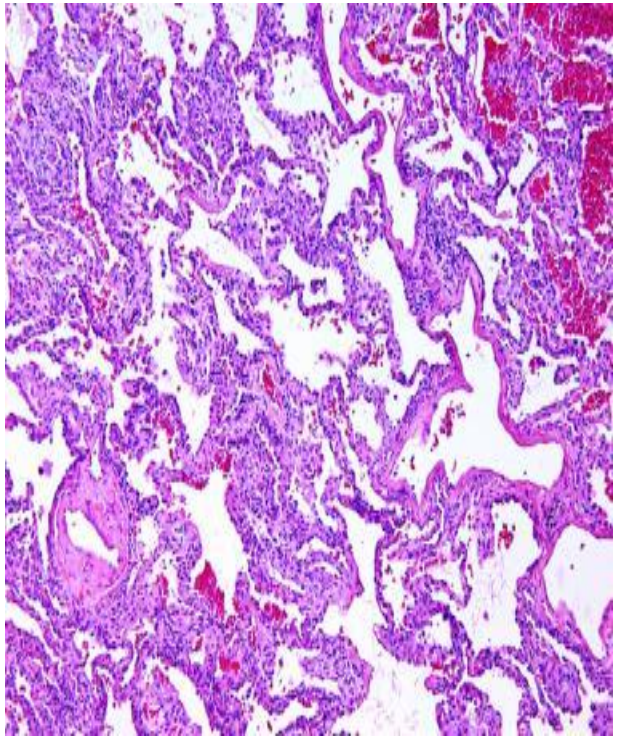
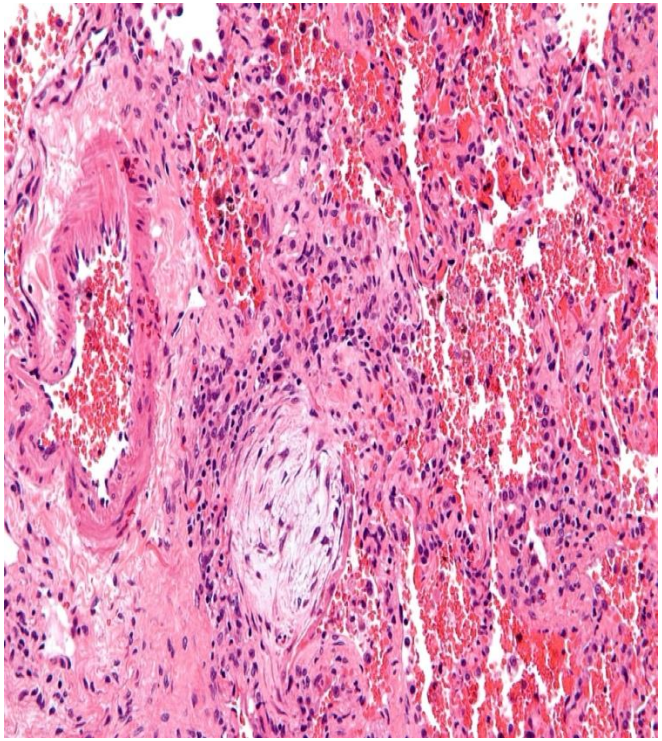
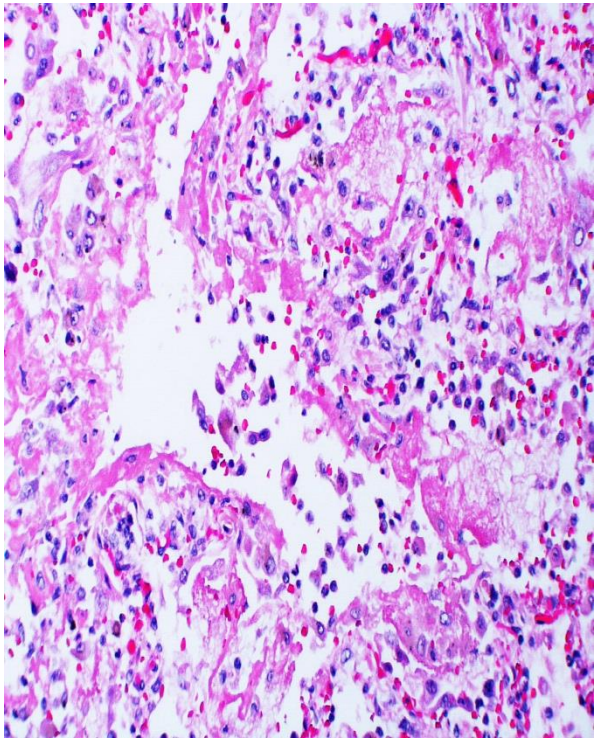


Organizing pneumonia



Diffuse alveolar damage



Presentation of ici pneumonitis

- More common: dyspnea and cough
- Less common: fever (12%) and chest pain (7%)
- Additional irAE in 58%: rash, colitis most common
- Radiographic findings:
  - 45% bilateral
  - Majority “ground glass” and/or consolidation
  - Majority (86%) away from tumor; minority are “peri-tumoral”.

Naidoo et al., JCO, 2017
Suresh et al., *JTO*, 2018

Suggested criteria for diagnosis of "ici" pneumonitis

- **Clinical**
  - History of checkpoint blockade treatment
  - Symptoms and/or radiographic evidence
  - Resistance to antibiotic treatment; absence of microorganism in BAL or sputum
  - "Exclusion of other possibilities"

- **Radiographic**
  - CT findings of interstitial pneumonia:
    - Organizing pneumonia-like pattern
    - Ground glass opacities
    - "Sarcoid-like" pattern

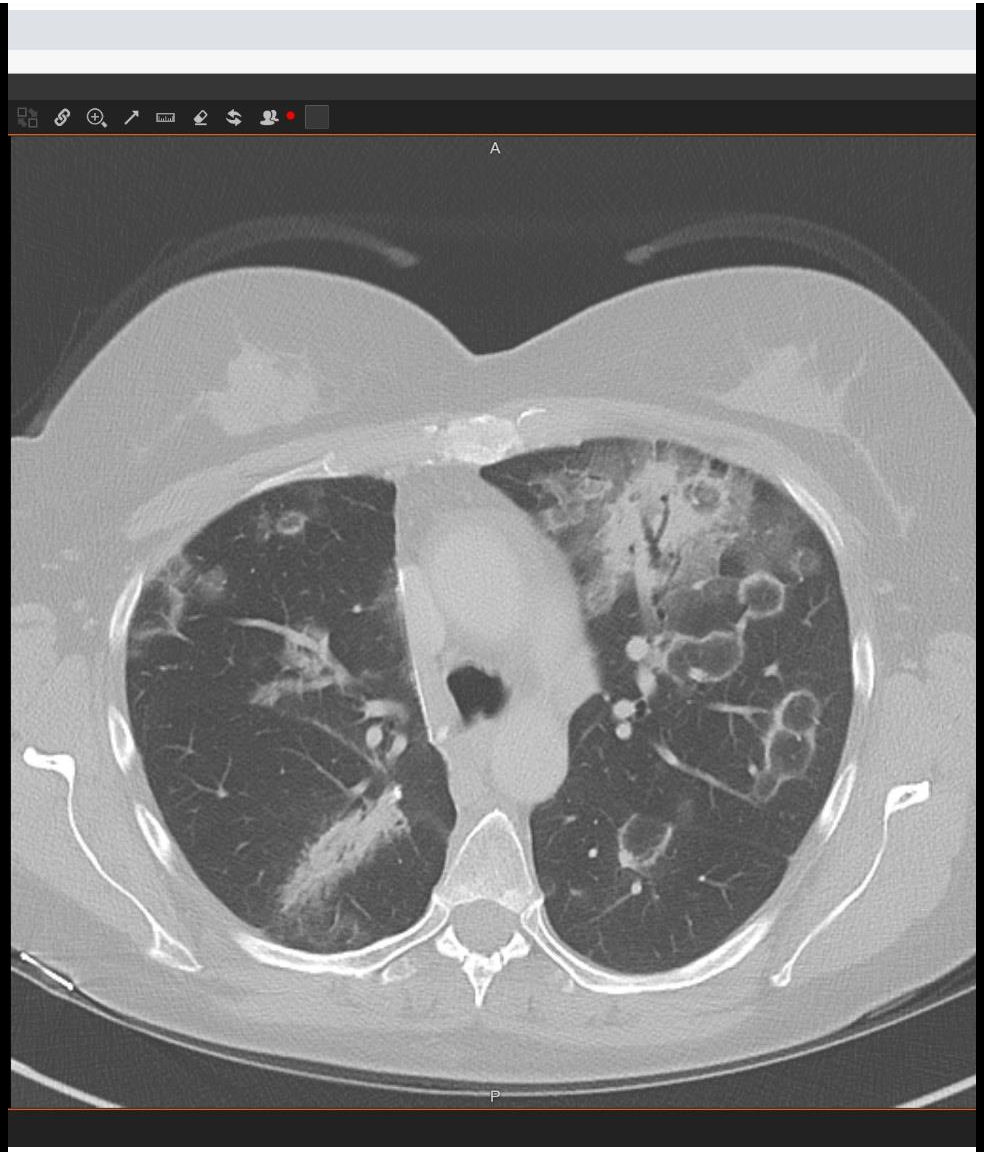
Porcu et al. Cancers 2019;11:305

Grading for severity

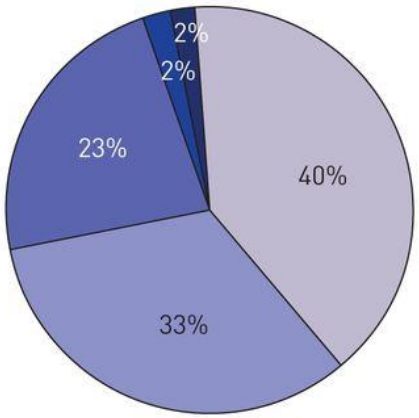
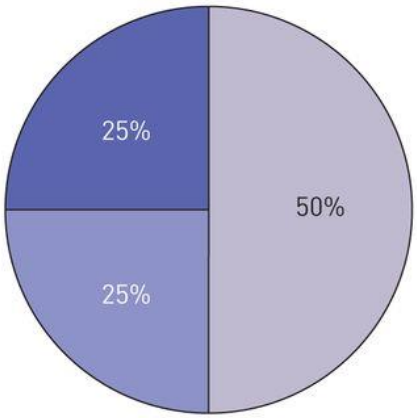
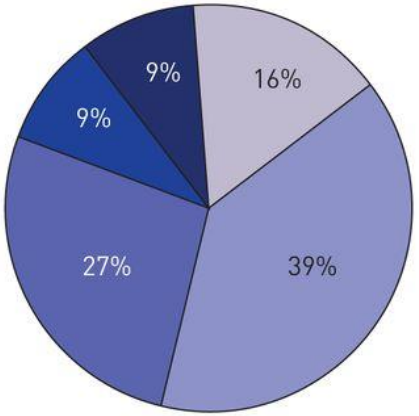
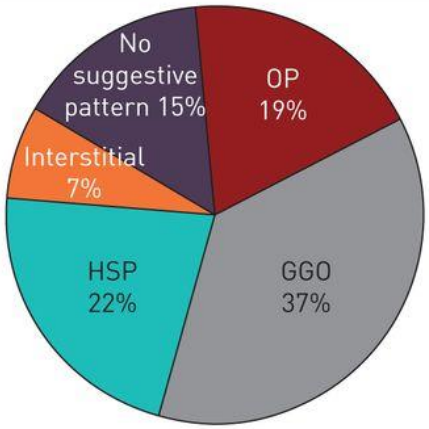
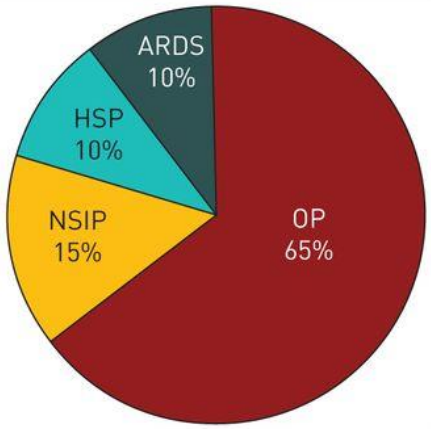
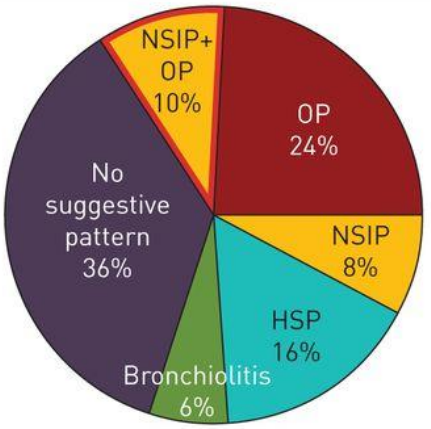
Common Terminology Criteria for Adverse Events (CTCAE) Grading System				
Grade		General Criteria	Criteria for Pneumonitis	Criteria for Pulmunary Fibrosis
1	Mild	Asymptomatic or mild symptoms that do not require intervention	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Radiologic pulmonary fibrosis <25% of lung volume associated with hypoxia
2	Moderate	It requires minimal, local or non invasive intervention	Symptomatic; medical intervention indicated; limiting instrumental activity of daily living (ADL)	Evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25–50% associated with hypoxia
3	Severe or medically significant but not immediately life-threatening	It requires hospitalization or prolongation of hospitalization	Severe symptoms; limiting self care activity of daily living (ADL); oxygen indicated	Severe hypoxia; evidence of right-sided heart failure; radiographic pulmonary fibrosis > 50–75%
4	Life-threatening consequences	It requires urgent intervention	Life-threatening respiratory compromise; urgent intervention indicated (i.e., tracheotomy or intubation)	Life-threatening consequences (i.e., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing
5	Death	Death related to adverse event (AE)	Death	Death

Porcu et al. Cancers 2019;11:305

Radiology



ICI pneumonitis

Study	Naidoo *et al.* [7]	Nishino *et al.* [8]	Delaunay *et al.* [6]
ILD severity grade# Grade 1 Grade 2 Grade 3 Grade 4 Grade 5			
Radiology patterns			

European Respiratory Review 2019 28: 190012; **DOI:** 10.1183/16000617.0012-2019

Radiologic features of pneumonitis associated with nivolumab in non-small-cell lung cancer and malignant melanoma

Tomohisa Baba*,[1], Fumikazu Sakai[2], Terufumi Kato[3], Masahiko Kusumoto[4], Hirotsugu Kenmotsu[5], Hiroaki Sugiura[6], Junya Tominaga[7], Katsunori Oikado[8], Masafumi Sata[9], Masahiro Endo[5], Noriyo Yanagawa[10], Shinichi Sasaki[11], Tae Iwasawa[1], Yoshinobu Saito[12], Yutaka Fujiwara[13], Yuichiro Ohe[4], Naoya Yamazaki[4], Takahiko Sakamoto[14], Takashi Koshiba[14] & Kazuyoshi Kuwano[15]

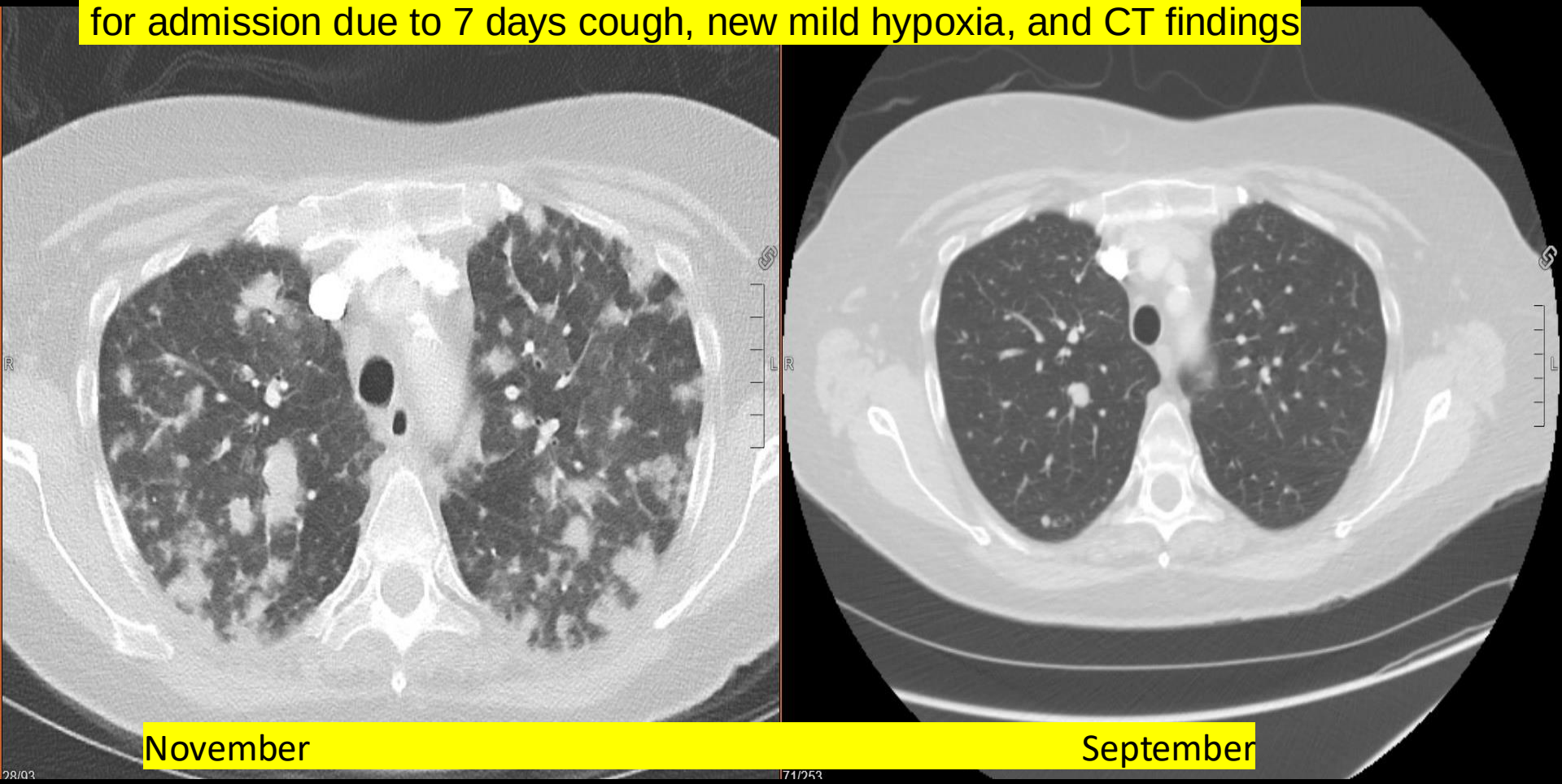
Future Oncol. (2019) 15(16), 1911–1920

90% lung cancer
42% prior radiation
24/144 deaths
Time to onset of ILD: 47 days

CT findings at onset of nivolumab-associated ILD	Total	PTI	Non-PTI	
Ground glass opacity	141 (97.9)	23 (100)	118 (97.5)	
Consolidation	84 (58.3)	12 (52.2)	72 (59.5)	
Reticulation	34 (23.6)	5 (21.7)	29 (24.0)	
Traction bronchiectasis	23 (16.0)	4 (17.4)	19 (15.7)	
Pleural effusion	39 (27.1)	9 (39.1)	30 (24.8)	
Distribution				
– Bilateral	83 (57.6)	15 (65.2)	68 (56.2)	
– Contralateral to the tumor	28 (19.4)	3 (13.0)	25 (20.7)	
– Ipsilateral to the tumor	23 (16.0)	5 (21.7)	18 (14.9)	
– Not applicable[†]	10 (6.9)	0 (0)	10 (8.3)	
Overall pattern of ILD				
AIP/DAD-like pattern	19 (13.2)	1 (4.3)	18 (14.9)	N.S. (0.5073) [X]
HP-like pattern	35 (24.3)	5 (21.7)	30 (24.8)	
COP-like pattern	68 (47.2)	12 (52.2)	56 (46.3)	
NSIP-like pattern	12 (8.3)	2 (8.7)	10 (8.3)	
Others	10 (6.9)	3 (13.0)	7 (5.8)	

Peritumoral vs non-peritumoral

RCC with metastases to lungs s/p 1 dose of ipi/nivo presenting for admission due to 7 days cough, new mild hypoxia, and CT findings



November

September

Risk factors for ici pneumonitis

- ECOG > or = 2
- Smoking > 50 pk-yr
- Autoimmune diseases
- **Interstitial lung disease**
- Pre-existing other lung disease
- Thoracic RT
- PD-1 inhibitor
- Combination therapies
- Lung metastases

Lung cancer (squamous > adeno) > melanoma

Differential Diagnosis

- Infection
  - Bacterial (typical and atypical)
  - Viral
  - Opportunistic infections (PJP)
- Aspiration pneumonitis
- Radiation-induced lung injury
- Other drug toxicity
- Cardiogenic pulmonary edema
- Cancer

Diagnosis:

Uncertainty Is Always Present

- **Bronchoscopy**
  - No findings specific to drug-induced lung disease
  - Main role is to exclude infection or recurrent malignancy
- **Biopsy**
  - No pathognomonic findings
    - Virtually all histopathologic patterns of lung injury have been described
  - Exclude other processes when they cannot be excluded by less invasive means
- **Rechallenge**
  - Can be confirmatory but may be risky

Incidence

Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy

Table 1. Patients Who Received Anti–PD-1/PD-L1 Therapy in Two Institutions: Complete Patient Database

	MSKCC, No. (%)	MIA, No. (%)
No. of patients	578	337
Single agent *v* combination		
Monotherapy	441 (76)	275 (82)
Combination	137 (24)	62 (18)
PD-1 *v* PD-L1		
PD-1	405 (70)	337 (100)
PD-L1	173 (30)	0
Primary cancer type		
Non–small-cell lung carcinoma	209	0
Metastatic melanoma	195	337
Renal cell carcinoma	24	0
Hematologic malignancy	35	0
Bladder carcinoma	30	0
Pancreatic carcinoma	18	0
Breast carcinoma	14	0
Head and neck squamous carcinoma	10	0
Sarcoma	7	0
Colorectal carcinoma	6	0
Gastroesophageal carcinoma	12	0
Ovarian carcinoma	7	0
Hepatocellular carcinoma	4	0
Prostate carcinoma	3	0
Anal carcinoma	2	0
Small-cell lung carcinoma	2	0
Pneumonitis		
No	551 (95)	321 (95)
Yes	27 (5)	16 (5)

- 2 centers over 2.5 years
- Combination vs Monotherapy **10% vs 3% P < .001**
- No difference between PD-1 and PD-L1
- NSCLC (3.6%) vs Melanoma (3.3%)
- Pneumonitis occurred irrespective of line of therapy in which immunotherapy was received

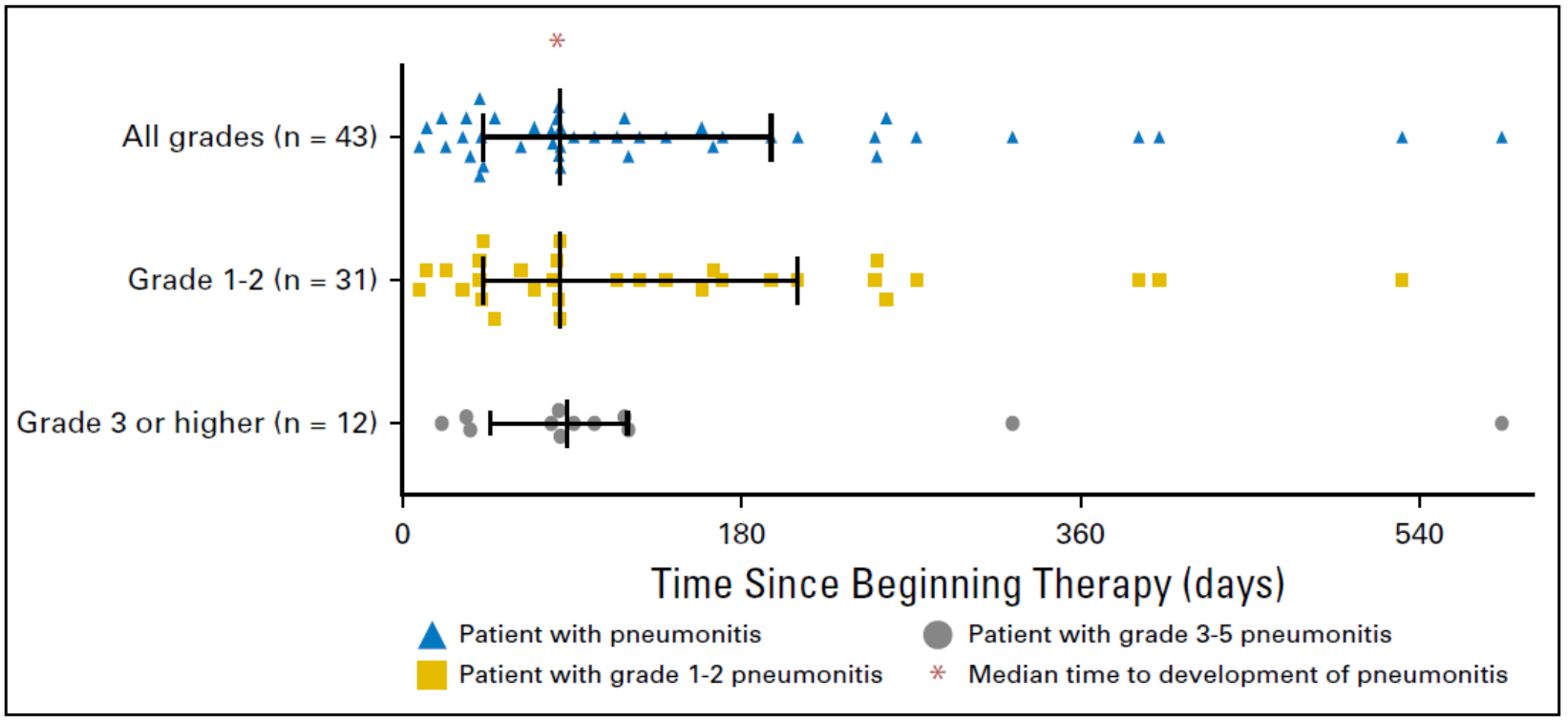
Naidoo, et al. J Clin Oncology 2017;35

VOLUME 35 · NUMBER 7 · MARCH 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

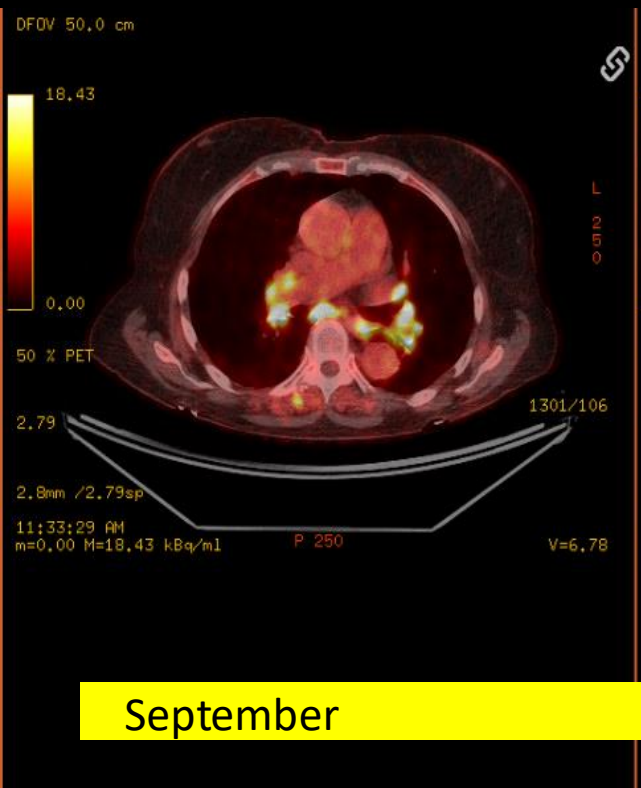
ORIGINAL REPORT

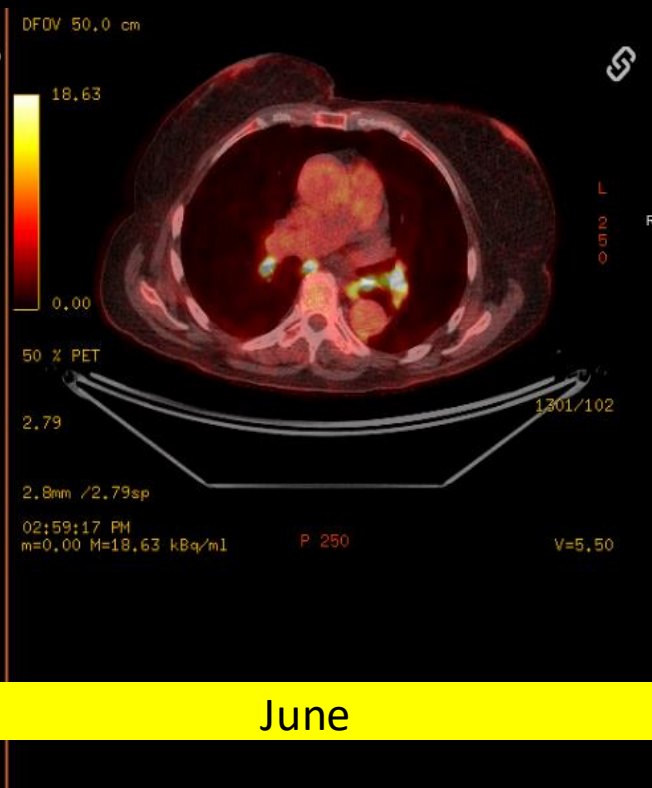
Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy

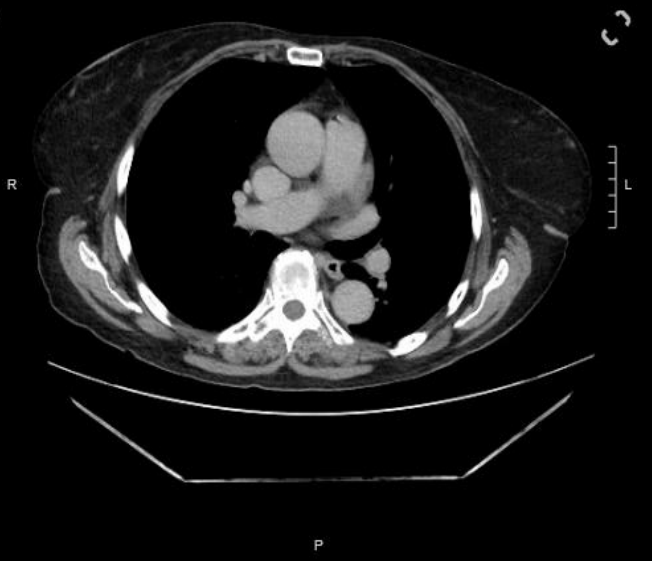


Median time to onset 2.8 M (range 9 days to 19.2M)
Onset earlier with combination therapy then monotherapy (2.7 vs 4.6 month)
More then 50% patients with pneumonitis experienced other organ itox.

Endometrial cancer treated with chemo and radiotherapys completing in mid March.
Began pembrolizumab April







September June April: no nodes

JAMA Oncology | Original Investigation

Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials

A Systematic Review and Meta-analysis

Yucai Wang, MD, PhD; Shouhao Zhou, PhD; Fang Yang, MD, PhD; Xinyue Qi, MS; Xin Wang, MD; Xiaoxiang Guan, MD, PhD; Chan Shen, PhD; Narjust Duma, MD; Jesus Vera Aguilera, MC; Ashish Chintakuntlawar, MD; Katharine A. Price, MD; Julian R. Molina, MD, PhD; Lance C. Pagliaro, MD; Thorvardur R. Halfdanarson, MD; Axel Grothey, MD; Svetomir N. Markovic, MD, PhD; Grzegorz S. Nowakowski, MD; Stephen M. Ansell, MD, PhD; Michael L. Wang, MD

39/82 deaths

Table. Causes of 82 Treatment-Related Deaths in Clinical Trials of PD-1 and PD-L1 Inhibitors

Cause of Death	No. (%)[a]
Respiratory (n = 39)	
Pneumonitis	23 (28.0)
Radiation pneumonitis	2 (2.4)
Pneumonia	5 (6.1)
Respiratory failure	5 (6.1)
Respiratory distress	2 (2.4)
Exertional dyspnea	1 (1.2)
Pulmonary hypertension	1 (1.2)

JAMA Oncol. 2019;5(7):1008-1019.

Impact of Radiation

Relationship Between Prior Radiotherapy and Checkpoint-Inhibitor Pneumonitis in Patients With Advanced Non–Small-Cell Lung Cancer

Khinh Ranh Voong,[1] Sarah Z. Hazell,[1] Wei Fu,[4] Chen Hu,[4] Cheng Ting Lin,[5] Kai Ding,[1] Karthik Suresh,[6] Jonathan Hayman,[6] Russell K. Hales,[1] Salem Alfaifi,[1] Kristen A. Marrone,[2,3] Benjamin Levy,[2] Christine L. Hann,[2] David S. Ettinger,[2] Josephine L. Feliciano,[2] Valerie Peterson,[2] Ronan J. Kelly,[2] Julie R. Brahmer,[2,3] Patrick M. Forde,[2,3] Jarushka Naidoo[2,3]

188 patients treated for NSCLC

The time from receipt of ICI to development of pneumonitis did not differ between those who had radiation and those who did not.

Of those who developed pneumonitis and had prior chest RT, it was much more likely that they were treated for curative intent then palliative.

Clinical Lung Cancer, Vol. 20, No. 4, e470-9 © 2019

Figure 1 Relationship of Immune-Related Pneumonitis Timing and Chest Radiation

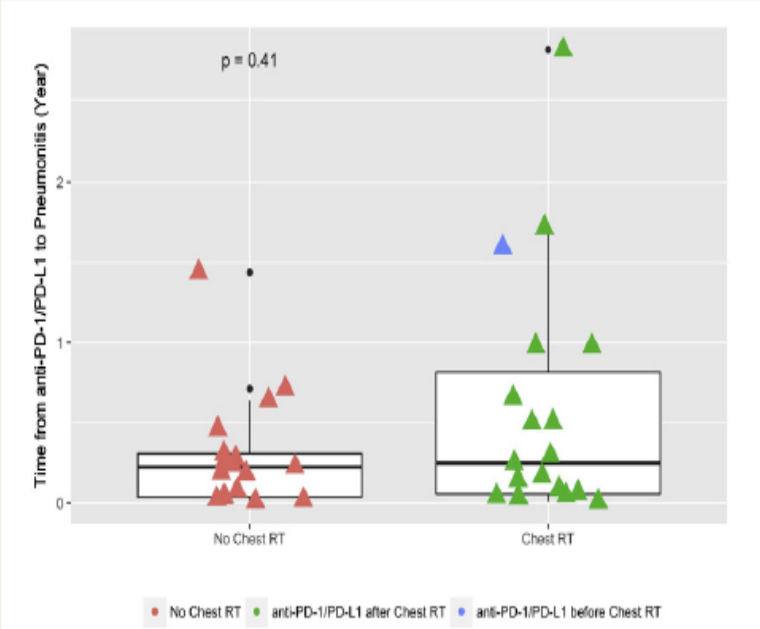
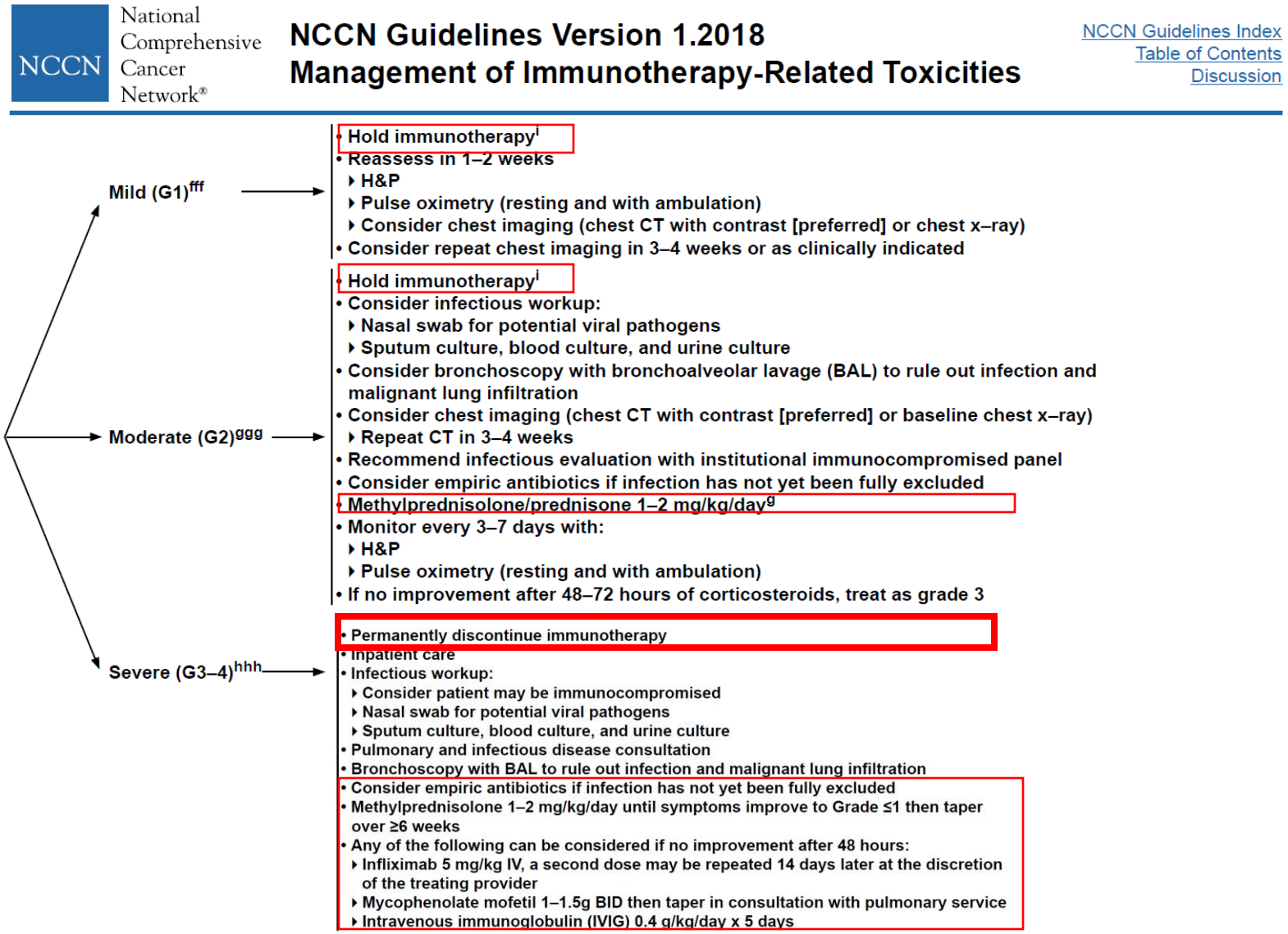


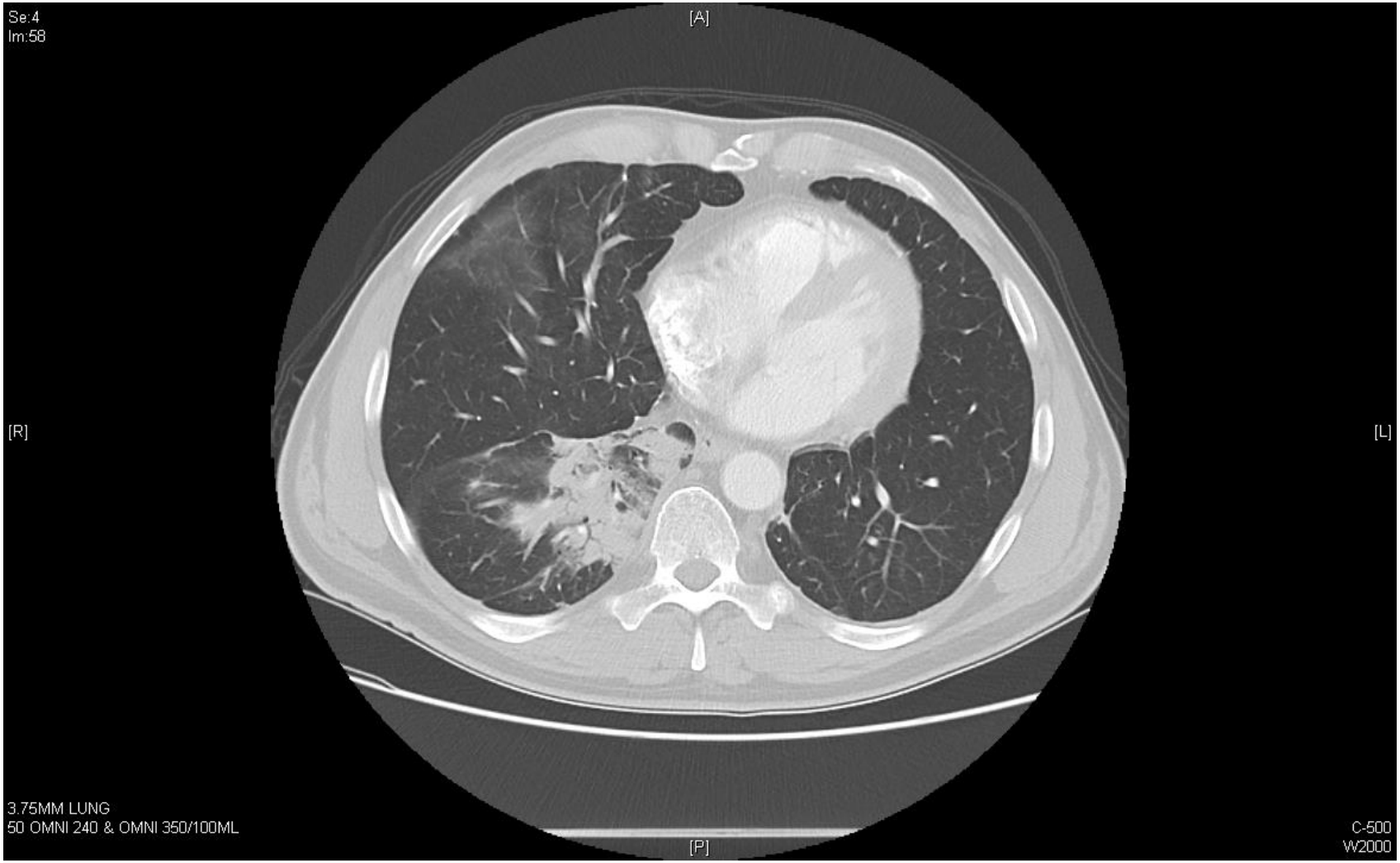
Table 3 IR Pneumonitis and IR Pneumonitis Radiographic Features in Relation to RT Fields

Characteristic	Value
IR Pneumonitis (CTCAE grade)	n (%)
All grades	36 (100)
Grade 2	14 (38.9)
Grade 3	14 (38.9)
Grade 4	2 (5.6)
Grade 5	5 (13.9)
Unknown	1 (2.8)
IR Pneumonitis Radiographic Features With Overlaid Chest RT Plans	**N = 13**
Chest RT Indication	
Palliative intent (20-30 Gy)	2 (15)
Curative intent (52.5-66 Gy)	11 (85)
Predominant IR Pneumonitis Feature	
Moderate to marked GGO	7 (54)
Minimal to mild GGO	3 (23)
Organizing pneumonia	2 (15)
Centrilobular tree-in-bud nodularity	1 (8)
Predominant Location of IR Pneumonitis Feature in Relation to Chest-RT Dose Regions[a]	
High-dose RT	0
Intermediate-dose RT	1 (8)
Low-dose RT	5 (38)
Outside RT dose fall-off region	7 (58)

Management



Asymptomatic:
To treat or not to treat?



What if steroid-refractory?

- Recommendations based on consensus, not data
- If grade 3 or higher, use IV corticosteroids. If no response in 48 hr, “steroid-refractory”.
- Consider additional immunosuppression:
  - Infliximab
  - Mycophenolate mofetil
  - Cyclophosphamide
  - IVIG
  - Tocilizumab
- **Also, consider the differential diagnosis!**

Steroid-refractory pneumonitis (failure of improvement after 2-14 d of hi-dose steroid)

Table 1 Baseline characteristics of patients with steroid-refractory or -resistant pneumonitis

	No (%)
No of patients	26
Median age, years (range)	67 (52–79)
Female sex	9 (34.6)
BMI, median (range)	26.1 (21.3—38.5)
Smoking status	
Former	22 (84.6)
Never	4 (15.4)
Pulmonary history*	
No	19 (73.1)
Yes	7 (26.9)
Primary malignancy	
NSCLC	8 (30.8)
Malignant melanoma	4 (15.4)
Renal cell carcinoma	4 (15.4)
Sarcoma	2 (7.7)
Head and neck squamous cell cancer	2 (7.7)
Bladder carcinoma	1 (3.8)
Colorectal carcinoma	1 (3.8)
Esophageal squamous cell cancer	1 (3.8)
Multiple myeloma	1 (3.8)
Prostate cancer	1 (3.8)
SCLC	1 (3.8)
Line of therapy	
1	9 (34.6)
2	9 (34.6)
≥3	8 (30.8)
Prior chest radiation	
No	17 (65.4)
Yes	9 (34.6)
Causative checkpoint inhibitor agent	
PD1	16 (61.5)
PDL1	3 (11.5)
CTLA4	1 (3.8)
Combination	6 (23.1)

Table 2 Management and outcomes

	No (%)
CTCAE grade	
2	11 (42.3)
3	13 (50.0)
4	2 (7.7)
Refractory/resistant	
Steroid refractory	12 (46.2)
Steroid resistant	14 (53.8)
Maximum steroid dose, prednisone equivalent	
Range (median)	30–1250 mg (100 mg)
≥60 mg*	21 (80.7)
Additional immune modulator	
TNF antagonist	21 (80.8)
Mycophenolate mofetil	9 (34.6)
Cyclophosphamide	1 (3.8)
>1	5 (19.2)
Response to additional immune modulator	
Durable improvement	10 (38.5)
Transient improvement	13 (50.0)
No improvement	3 (11.5)
Outcomes	
Mortality due to pneumonitis	6 (23.1)
Mortality due to infection	3 (11.5)

J Immunother Cancer 2021;9;e001884

Chronic Pneumonitis

- Pneumonitis that persists or worsens with steroid tapering, and requires ≥12 weeks of immunosuppression, after ICI
- A retrospective review of 299 patients with NSCLC and melanoma treated with ICI therapy, detected an overall incidence of 2% (6/299) (Naidoo et al., 2020).
- Most commonly have an organizing pneumonia-like appearance on CT chest.
- Additional therapies used included infliximab (1/6) and mycophenolate mofetil (2/6), with variable outcome.

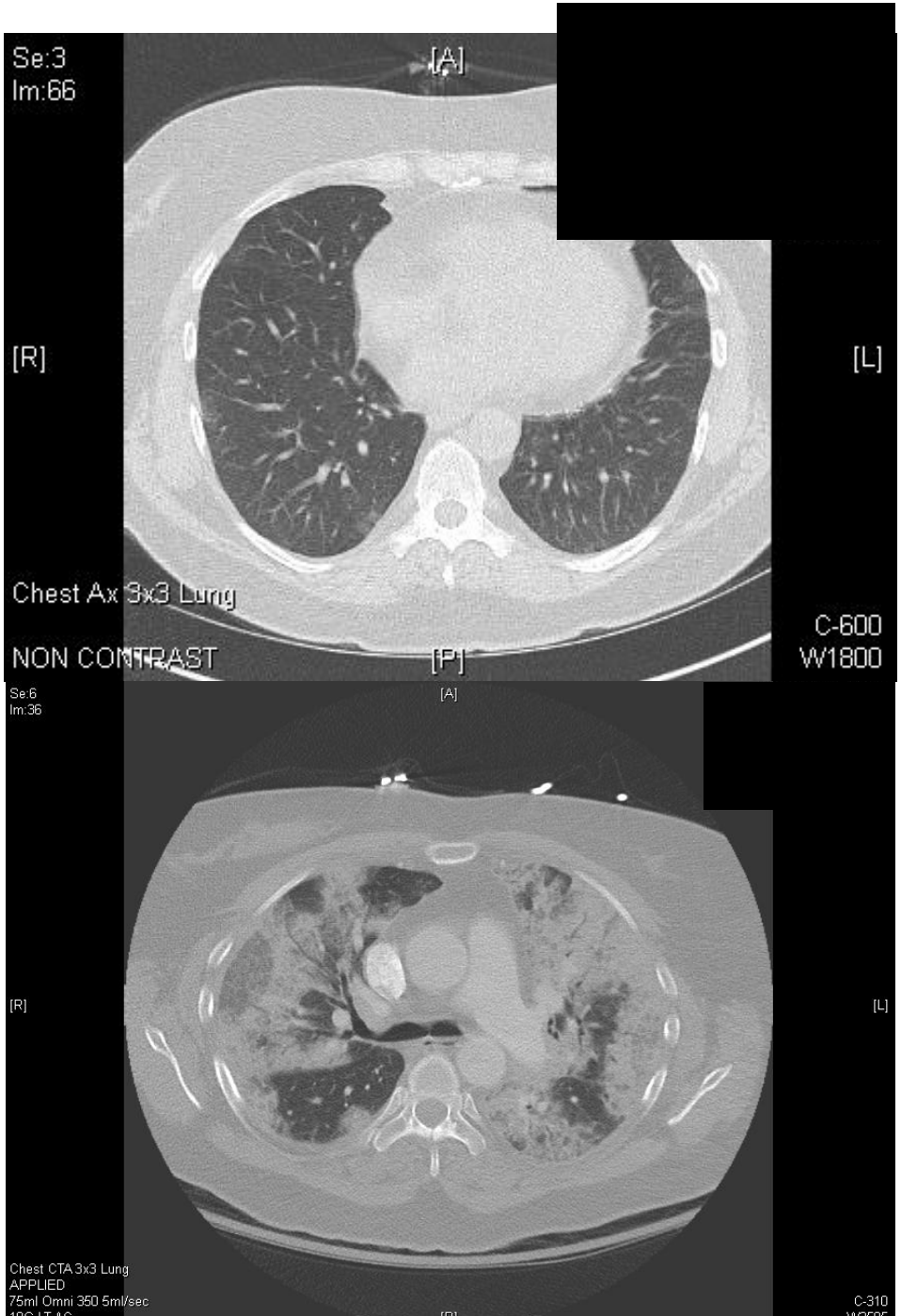
Recurrent Pneumonitis

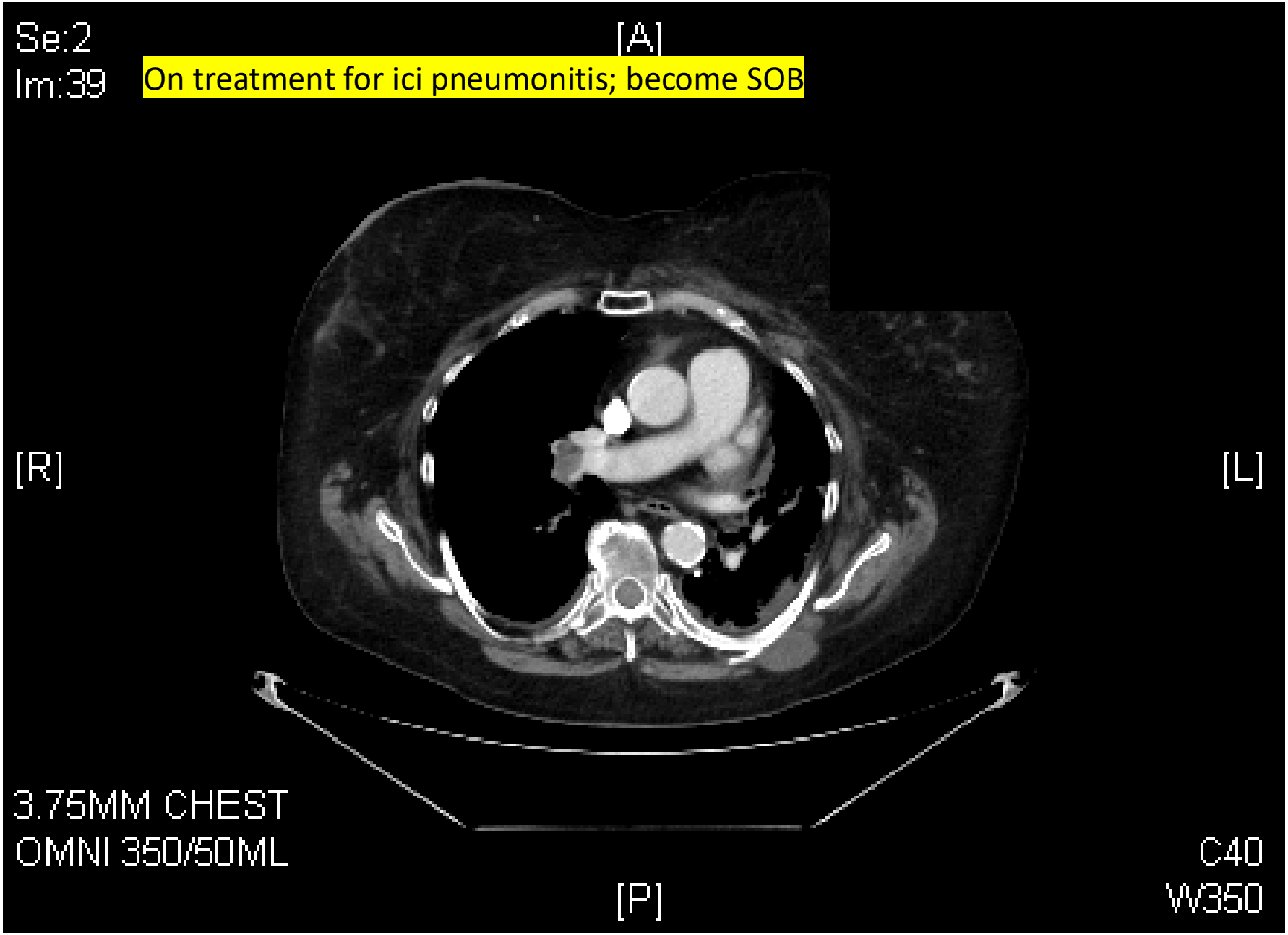
Recurrent CIP is defined as an additional episode of pneumonitis after complete clinical and radiological resolution of previous episode and can occur on re-introduction of ICI therapy (provoked) or despite complete discontinuation of ICI therapy (unprovoked).

In a single-center retrospective review, ICI pneumonitis recurred in 6/19 ICI pneumonitis cases (Asher et al., 2019).

Beware!

- Patient with breast cancer treated with pembrolizumab
- Developed asymptomatic findings.
- Admitted in respiratory failure 2 months later.
- Given pulse dose steroids
- Diagnosis:
  - Legionella pneumonia




Se:2
Im:39
On treatment for ici pneumonitis; become SOB
[A]
[R]
[L]
[P]
3.75MM CHEST
OMNI 350/50ML
C40
W350

Questions and Challenges

Is CIP associated with efficacy of immune checkpoint blockade ?

JAMA Oncology | Brief Report

Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non–Small Cell Lung Cancer

Koji Haratani, MD; Hidetoshi Hayashi, MD, PhD; Yasutaka Chiba, PhD; Keita Kudo, MD, PhD; Kimio Yonesaka, MD, PhD; Ryoji Kato, MD; Hiroyasu Kaneda, MD, PhD; Yoshikazu Hasegawa, MD, PhD; Kaoru Tanaka, MD, PhD; Masayuki Takeda, MD, PhD; Kazuhiko Nakagawa, MD, PhD

March 2018

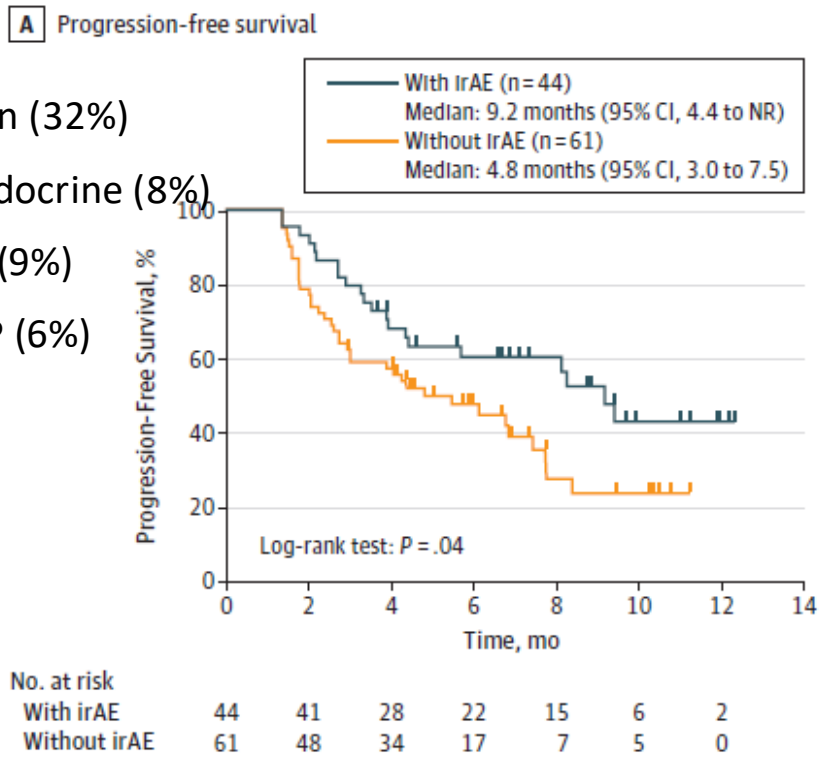
irAE 69/134 (51%)

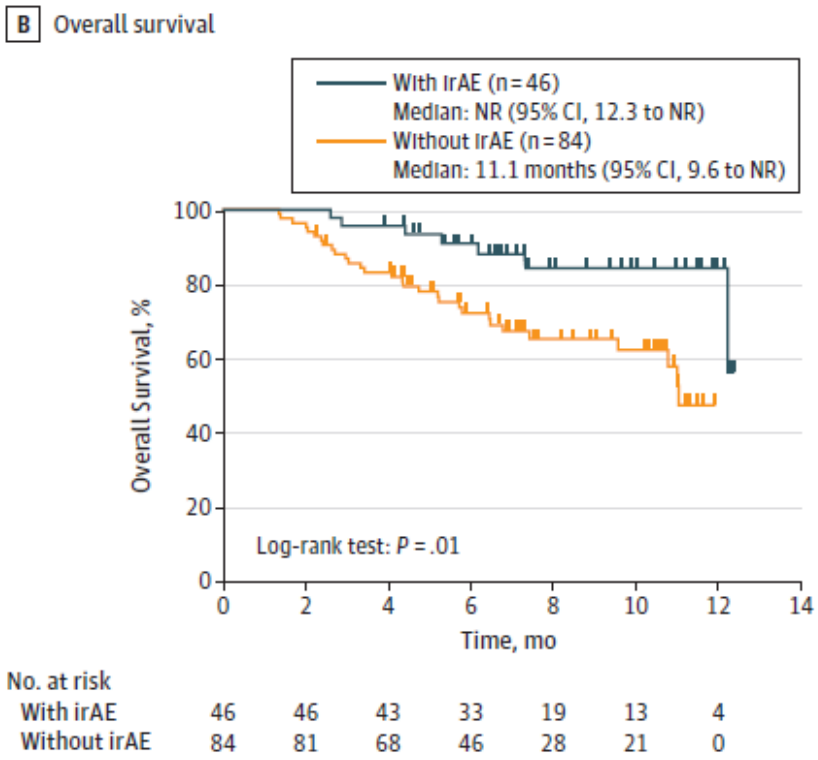
Skin (32%)

Endocrine (8%)

GI (9%)

CIP (6%)





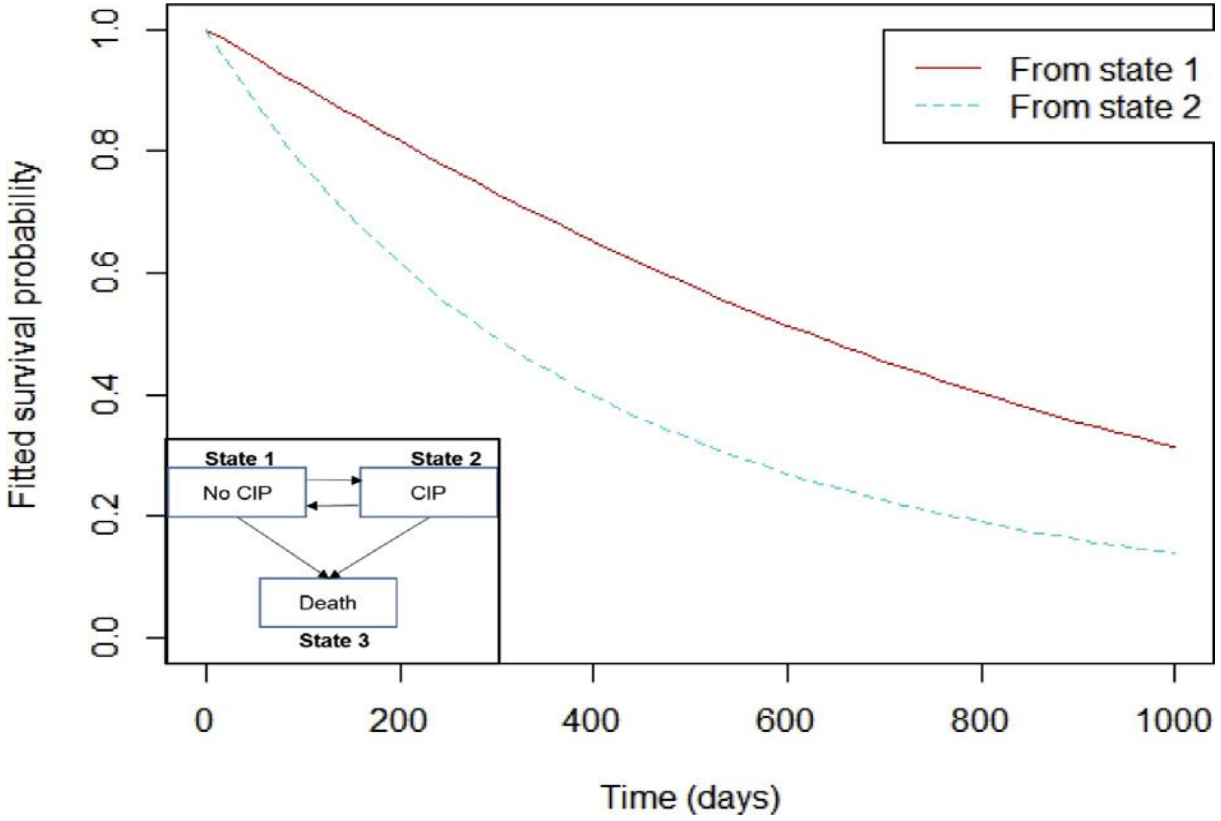
Impact of Checkpoint Inhibitor Pneumonitis on Survival in NSCLC Patients Receiving Immune Checkpoint Immunotherapy

Karthik Suresh, MD,[a,*] Kevin J. Psoter, PhD,[b] Khinh Ranh Voong, MD,[c]
Bairavi Shankar, MD,[d] Patrick M. Forde, MD,[d,e] David S. Ettinger, MD,[d]
Kristen A. Marrone, MD,[d,e] Ronan J. Kelly, MD,[d,e] Christine L. Hann, MD,[d,e]
Benjamin Levy, MD,[d,e] Josephine L. Feliciano, MD,[d,e] Julie R. Brahmer, MD,[d]
David Feller-Kopman, MD,[a] Andrew D. Lerner, MD,[a] Hans Lee, MD,[a]
Lonny Yarmus, DO,[a] Russell K. Hales, MD,[c] Franco D'Alessio, MD,[a]
Sonye K. Danoff, MD, PhD,[a] Jarushka Naidoo, MBBCh[d,e]

Retrospective
38/204 (19%) pneumonitis

CIP was associated with decreased survival.

? Impact on other organ systems, relationship with steroid use



Journal of Thoracic Oncology Vol. 14 No. 3: 494-502

Questions and Challenges

Is CIP associated with efficacy of immune checkpoint blockade ?

Is it safe to re-challenge?

Safety of retreatment with immunotherapy after immune-related toxicity in patients with lung cancers treated with anti-PD(L)-1 therapy.

Fernando Costa Santini, Hira Rizvi, Olivia Wilkins, Martine van Voorthuysen, Elizabeth Panora, Darragh Halpenny, …

- 71/482 patients with irAE necessitating treatment delay at least one week
- 39 patients re-challenged
- Overall, 10/39 had same irAE, 9/39 had a new one.
- 20/39 had no subsequent irAE
- Recurrent or new irAE was 33% (2/6) in those with pneumonitis

Journal of Clinical Oncology 2017;35:9012.

- **JAMA Oncology** Original Investigation September 1, 2019
- **Evaluation of Readministration of Immune Checkpoint Inhibitors After Immune-Related Adverse Events in Patients With Cancer**
- **Audrey Simonaggio**, MD; Jean Marie Michot, MD; Anne Laure Voisin, MD; Jérome Le Pavec, MD, PhD; Michael Collins, MD; Audrey Lallart, MD; Geoffray Cengizalp, MD; Aurore Vozy, MD; Ariane Laparra, MD; Andréa Varga, MD; Antoine Hollebecque, MD; Stéphane Champiat, MD, PhD; Aurélien Marabelle, MD, PhD; Christophe Massard, MD, PhD; Olivier Lambotte, MD, PhD

- 93 patients, 16% lung cancer
- Initial irAE 13 (14%) pneumonitis
- 40 patients re-challenged
- Same or different irAE in 22 (55%)
- Second irAE's were not more severe then the first

Rechallenge: summary

If patients have developed grade 1 CIP which completely resolves, guidelines would recommend that the patient may safely restart ICI upon clinical +/- radiographic resolution of CIP.

If a patient develops grade 2-3 CIP which completely resolves, patients may recommence ICI at the discretion of their treating oncologist with close monitoring, and knowledge that there is increased risk of re-emergent CIP on reinstitution of ICIs (Naidoo et al, JCO 2016).

In patients with severe (grade 3+ CIP) which does not completely resolve, ICI should be permanently discontinued.

Questions and Challenges

Is CIP associated with efficacy of immune checkpoint blockade ?

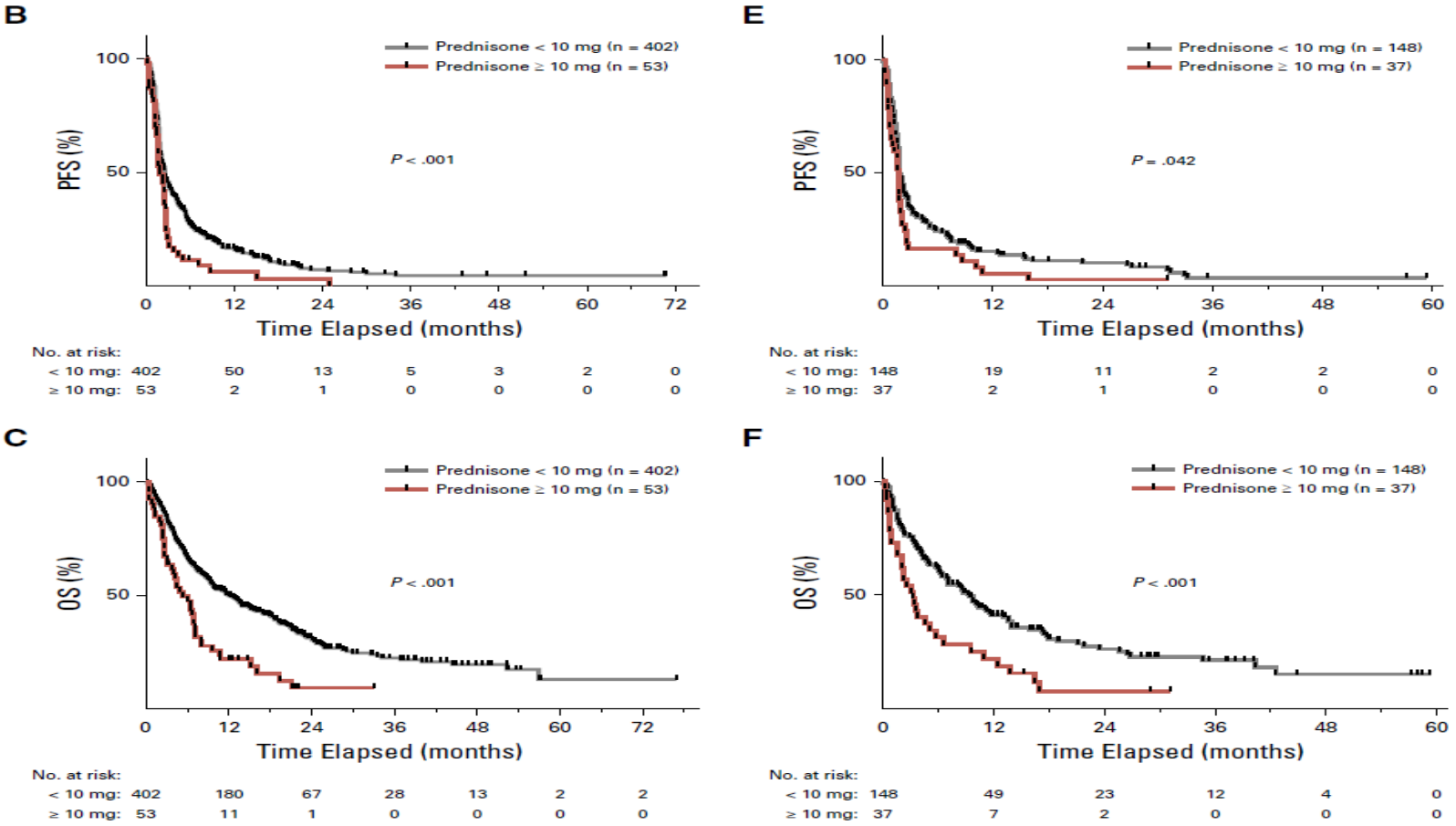
Is it safe to re-challenge?

Is treatment with steroids associated with worse cancer-related outcome?

Can you treat patients with ICI if they have co-existing interstitial lung disease, airway disease, etc?

Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer

Kathryn C. Arbour, Laura Mezquita, Niamh Long, Hira Rizvi, Edouard Auclin, Andy Ni, Gala Martínez-Bernal, Roberto Ferrara, W. Victoria Lai, Lizza E.L. Hendriks, Joshua K. Sabari, Caroline Caramella, Andrew J. Plodkowski, Darragh Halpenny, Jamie E. Chaft, David Planchard, Gregory J. Riely, Benjamin Besse, and Matthew D. Hellmann



J Clin Oncol 36:2872-2878.

Is CIP associated with efficacy of immune checkpoint blockade ?

Is it safe to re-challenge?

Is treatment with steroids associated with worse cancer-related outcome?

Can you safely treat patients with ICI if they have co-existing interstitial lung disease, airway disease, etc?

Outcomes of Patients With Interstitial Lung Disease Receiving Programmed Cell Death 1 Inhibitors: A Retrospective Case Series

Ioana A. Dobre,[1] Angela J. Frank,[2] Kristin M. D'Silva,[3] David C. Christiani,[2,4] Daniel Okin,[2] Amita Sharma,[5,#] Sydney B. Montesi[2,#]

Table 1 Baseline Demographic and Clinical Characteristics at the Time of Initiation of Immune Checkpoint Inhibitor Therapy.

Characteristic	Patients with ILD ($N = 41$)
Age, years (mean ± SD)	75 ± 9
Male sex (N, %)	33 (80.5)
Current or former smoker (N, %)	37 (90.2)
Comorbidities (N, %)	
COPD / emphysema	11 (26.8)
Asthma	5 (12.2)
OSA	2 (4.9)
GERD	7 (17.1)
Autoimmune disease[a]	3 (7.3)

Table 2 Cancer and Cancer Treatment Characteristics.

Characteristic	Patients with ILD ($N = 41$), Number (%)
Primary cancer type	
Lung	30 (73.2)
Head & neck	5 (12.2)
Skin	2 (4.9)
Gastrointestinal	2 (4.9)
Renal	1 (2.4)
Hematologic	1 (2.4)
Immunotherapy type	
Nivolumab	26 (63.4)
Pembrolizumab	15 (36.6)
Concurrent treatment with CTLA-4 inhibitors	1 (2.4)
Duration of immunotherapy	
≤2 months	19 (46.3)
2–4 months	5 (12.2)
4–6 months	3 (7.3)
6–12 months	7 (17.1)
≥12 months	7 (17.1)
Radiation therapy involving the thorax	
Before immunotherapy	18 (43.9)
During follow-up	1 (2.4)
Total	19 (46.3)

Table 3 ILD Characteristics Before the Initiation of Immunotherapy.

Characteristic	Patients With ILD ($N = 41$), Number (%)
Radiologic ILD pattern	
UIP	12 (29.3)
Probable UIP	9 (21.9)
Indeterminate for UIP	12 (29.3)
Alternative diagnosis (total)	8 (19.5)
HP	4 (9.8)
OP	3 (7.3)
RB/OP	1 (2.4)
RA-ILD[a]	1 (2.4)
IPAF	0 (0.0)
Prior diagnosis of ILD at the of ICI initiation	8 (19.5)
Receiving antifibrotic therapy[b]	0 (0.0)
Supplemental O_2 requirement	4 (9.8)

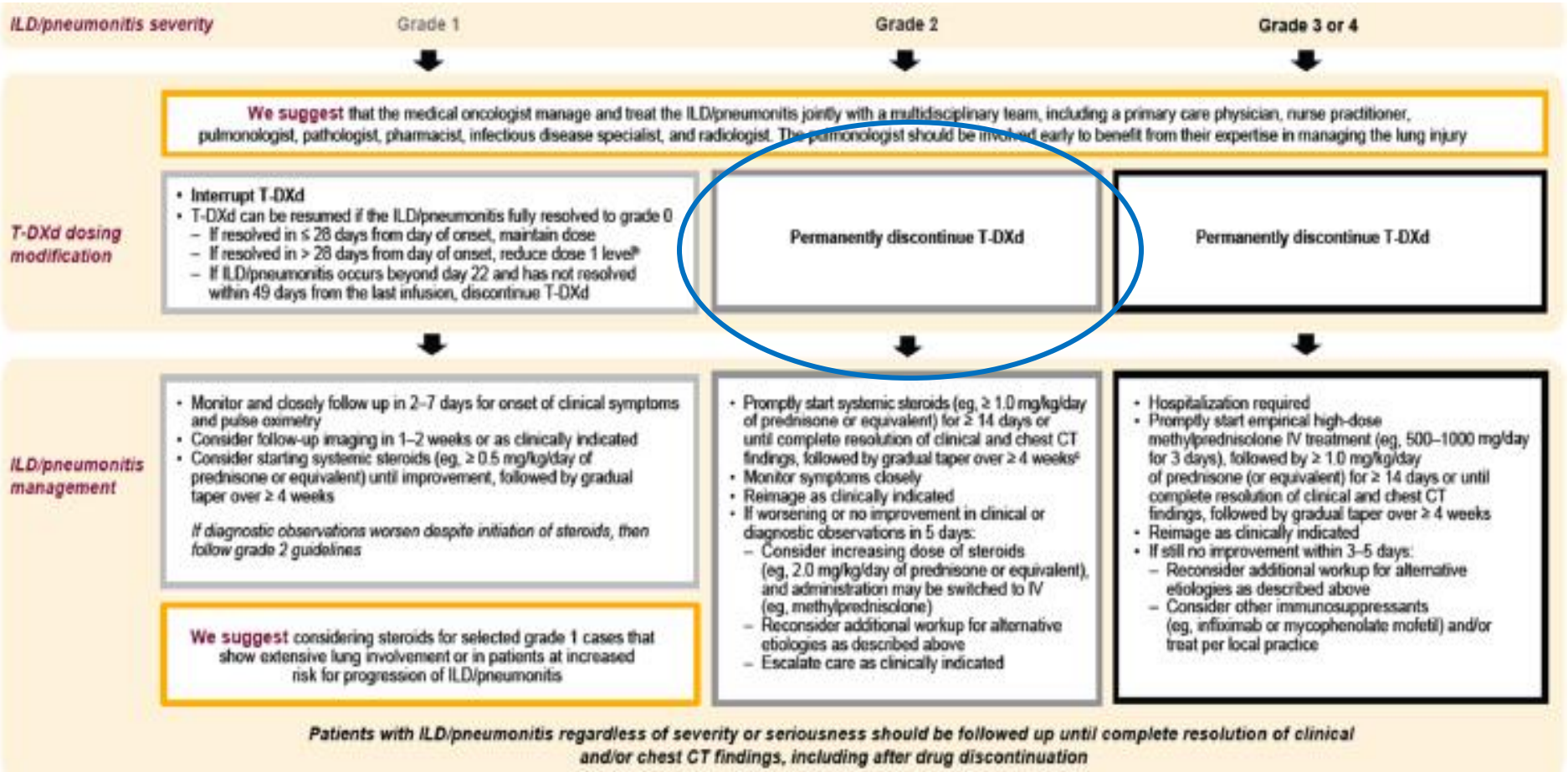
Table 5 Clinical Outcomes of Interest During the 1-Year Follow-up Period.

Outcome	Patients With ILD ($n = 41$), Number (%)
Mortality	
Alive	17 (41.5)
Deaths	23 (56.1)
Death related to cancer	16 (39.0)
Death owing to respiratory failure secondary to ILD or pneumonitis	3 (7.3)
Death owing to other causes not related to ILD or cancer[a]	4 (9.8)
Lost to follow-up	1 (2.4)
Hospital admission owing to respiratory cause	11 (26.8)
Owing to underlying ILD or drug-induced pneumonitis	3 (7.3)
Related to other cause[b]	8 (19.5)
Drug-induced pneumonitis	
Attributable to immunotherapy	3 (7.3)
Attributable to chemotherapy[c]	1 (2.4)

Patients with ILD

- In this small retrospective series:
- Conclusions:
  - Patients with ILD who received PD-1 inhibitors were more likely to die from cancer or non-ILD cause then from ILD or drug-induced pneumonitis

Special consideration for ADC



Key Take-Home Points

- Medication related lung toxicity:
  - Potentially serious/fatal
  - Usually responds to holding the medication and starting steroids
  - Consider if safe to re-challenge
  - Multi-disciplinary Toxicity Team; at least 50% will have other organ toxicities if experiencing ICI pneumonitis
  - Consider and re-consider the differential diagnosis.

gweinhouse@bwh.harvard.edu