Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Cancer Immunotherapy in Practice: Is the Benefit Worth the Risk?

Marianne Davies, DNP, AOCNP, FAAN
Yale School of Nursing-Associate Professor
Thoracic Oncology Nurse Practitioner
Smilow Cancer Hospital
Yale Comprehensive Cancer Center

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Disclosures

Marianne Davies, DNP

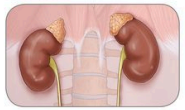
- I do not have any disclosures

Immune Related Adverse Events (IRAEs)

NEUROLOGIC
- Posterior Reversible Encephalopathy
- Neuropathy
- Guillian-Barre Syndrome
- Myelopathy
- Autoimmune Encephalitis
- Aseptic Meningitis
- Myasthenia gravis
- Transverse Myelitis
- Non-specific symptoms: headache, tremor, lethargy, memory disturbance, seizure

RESPIRATORY
- Cough/dyspnea
- Laryngitis
- Pneumonitis
- Bronchitis
- Pleuritis
- Sarcoid-like granulomatosis

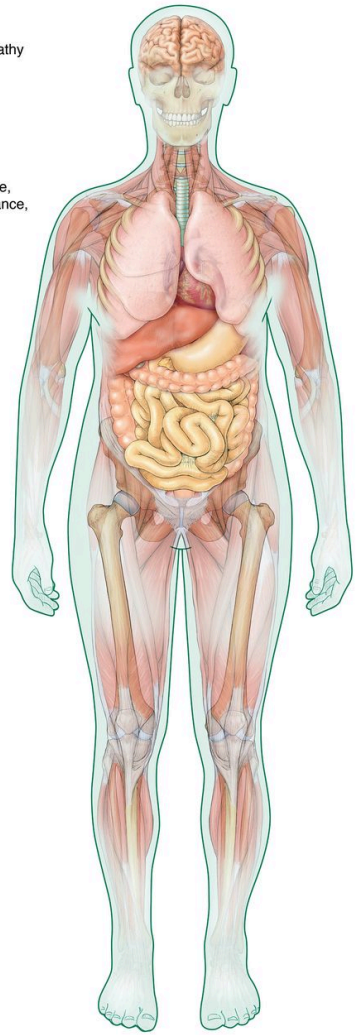
RENAL



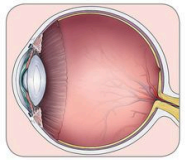
- Tubulointerstitial nephritis
- Acute renal failure
- Lupus nephritis
- Granulomatous lesions
- Thrombotic microangiopathy

HEMATOLOGIC
- Autoimmune hemolytic anemia
- Red cell aplasia
- Thombocytopenia
- Leukopenia/Neutropenia
- Acquired hemophilia
- Myelodysplasia

DERMATOLOGIC
- Rash/Pruritis
- Mucositis
- Psoriasis
- Vitiligo
- Bullous pemphigoid
- Steven-Johnson syndrome
- DRESS syndrome



OCULAR



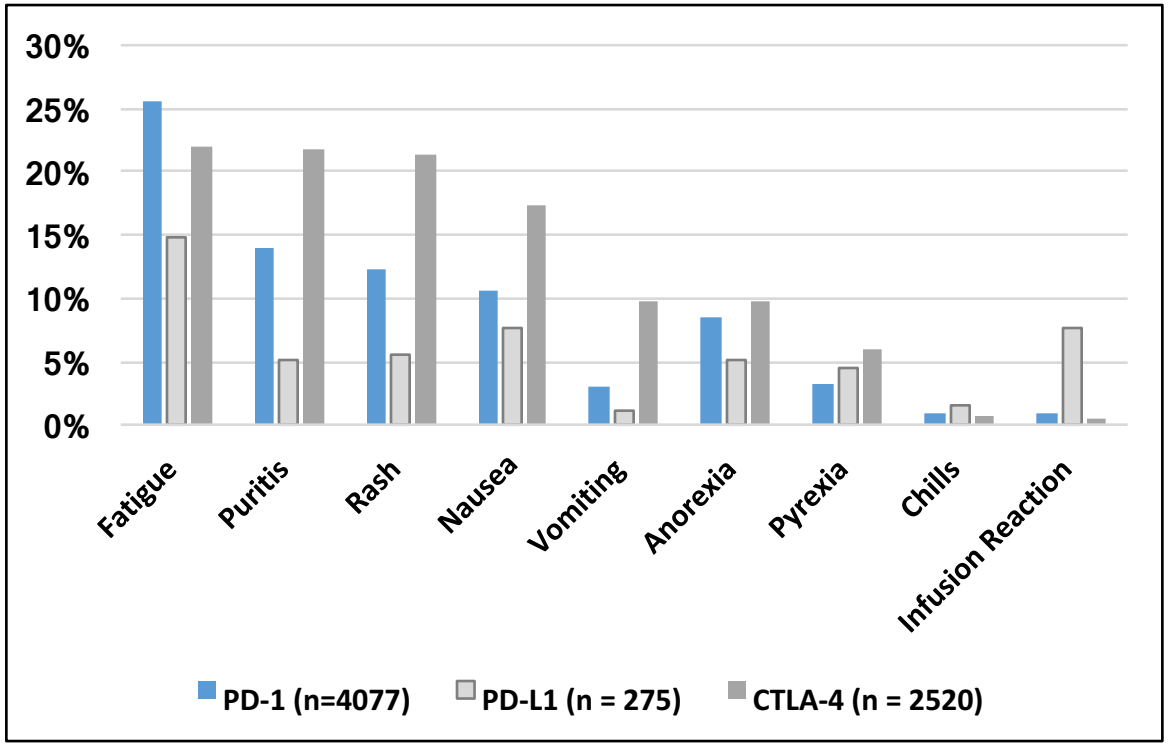
- Uveitis
- Conjunctivitis
- Scleritis, episcleritis
- Optic neuritis
- Blepharitis
- Retinitis
- Peripheral ulcerative keratitis
- Vogt-Koyanogi-Harada

CARDIOVASCULAR
- Myocarditis
- Pericarditis
- Pericardial effusion
- Arrhythmia
- Hypertension
- Congestive heart failure

ENDOCRINE
- Hyper or hypothyroidism
- Hypophysitis
- Adrenal insufficiency
- Diabetes

GASTROINTERSTINAL
- Diarrhea
- Gastritis
- Colitis
- Ileitis
- Pancreatitis
- Hepatitis

RHEUMATOLOGIC
- Arthralgias/Myalgias
- Inflammatory Polyarthritis
- PMR-like
- Psoriatic Arthritis
- Oligoarthritis
- Vasculitis
- Sicca Syndrome
- Sarcoidosis
- Inflammatory myositis
- Resorptive bone lesions and fractures



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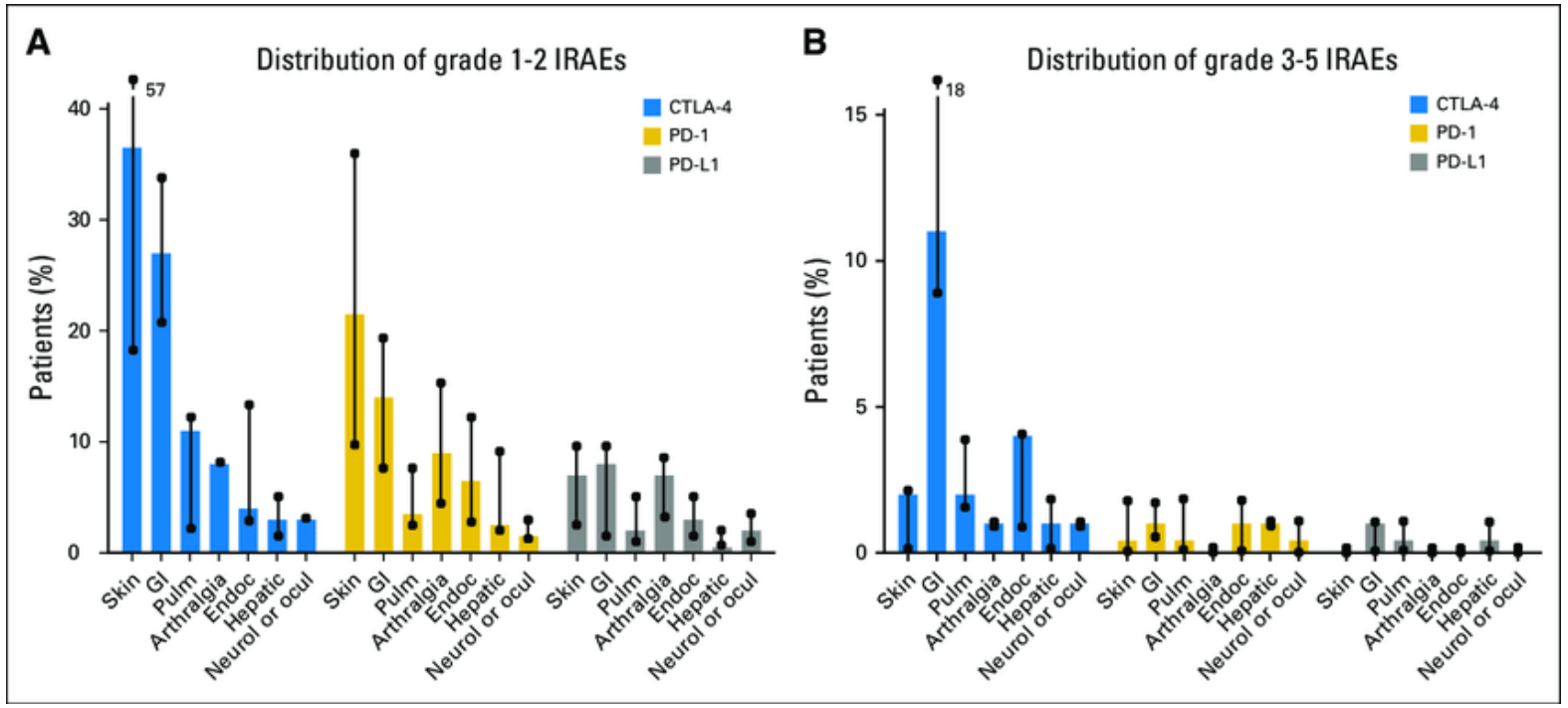
Shahin Jamal et al. J Rheumatol 2020;47:166-175

Frequency of irAEs with ICI Monotherapy



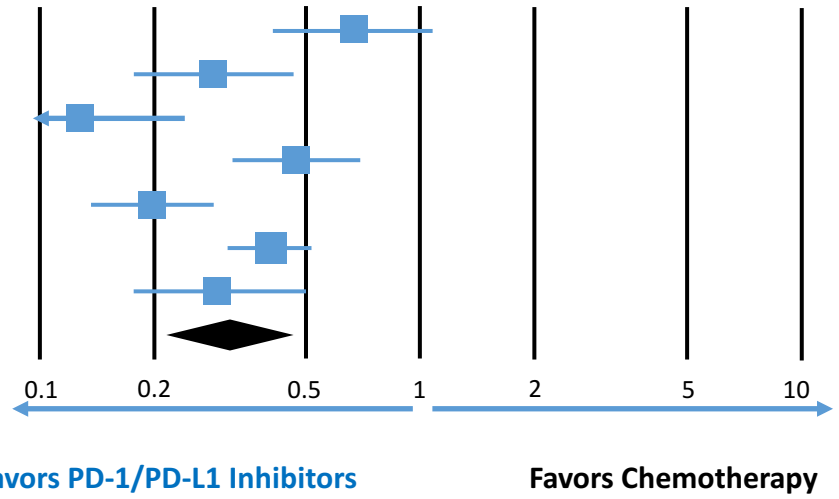
- **Onset**
  - Median onset is 5-12 weeks after initiation
    - Within days of first dose
    - After months of treatment
    - After discontinuation of therapy
- **Severity**
  - Incidence/severity higher in anti-CTLA-4 agents
  - High grade AE to one does not preclude safe administration to another class

Michot. Eur J Cancer. 2016;54:139.

Checkpoint Inhibitor vs Chemotherapy

Any High-Grade AE

Model	Study Name	Risk Ratio	Lower Limit	Upper Limit	*P*
	Robert 2014	0.663	0.411	1.071	.093
	Weber 2015	0.285	0.177	0.460	.000
	Brahmer 2015	0.125	0.065	0.239	.000
	Ribas 2015	0.468	0.322	0.680	.000
	Borghaei 2015	0.195	0.136	0.278	.000
	Herbst 2016	0.401	0.313	0.513	.000
	Fehrenbacher 2016	0.293	0.176	0.486	.000
Random		0.315	0.221	0.450	.000



- Lower total AEs[a] (67.6% vs 82.9%)
- Lower high-grade AEs[a] (11.4% vs 35.7%)
- Lower treatment discontinuation [a] (4.5% vs 11.1%)
- Lower treatment-related deaths (0.6% vs 1.4%)

[a] Statistically significant.

Nishijima TF et al. *Oncologist*. 2017;22:470-479.

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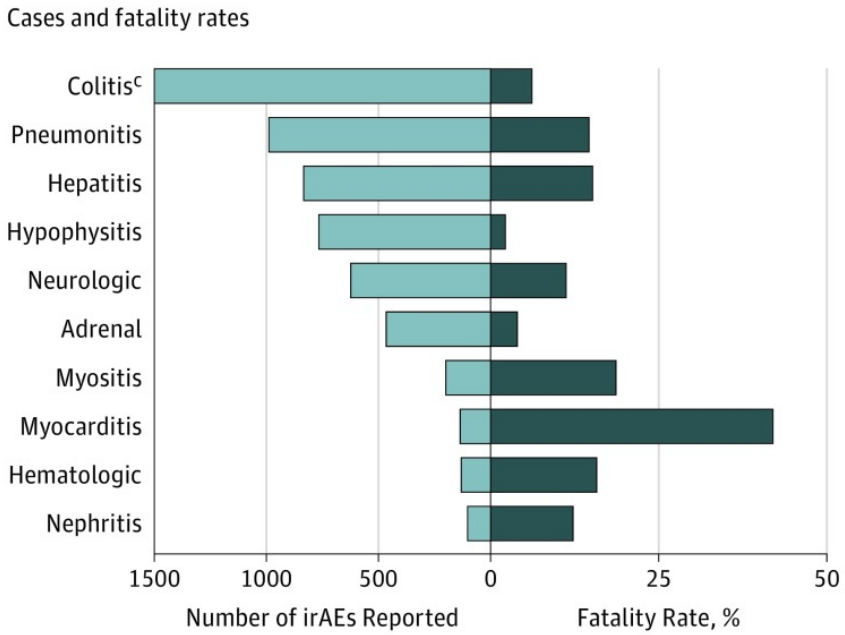
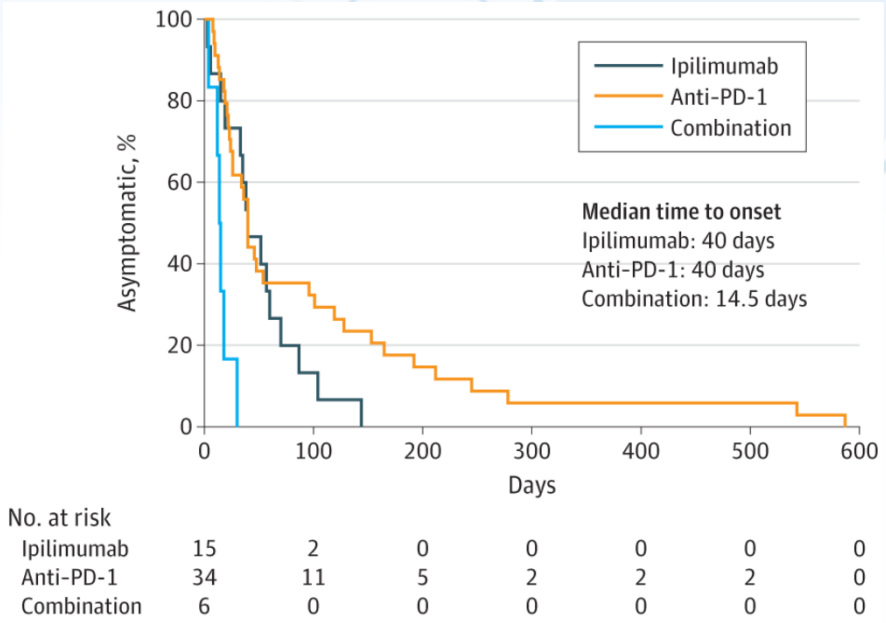
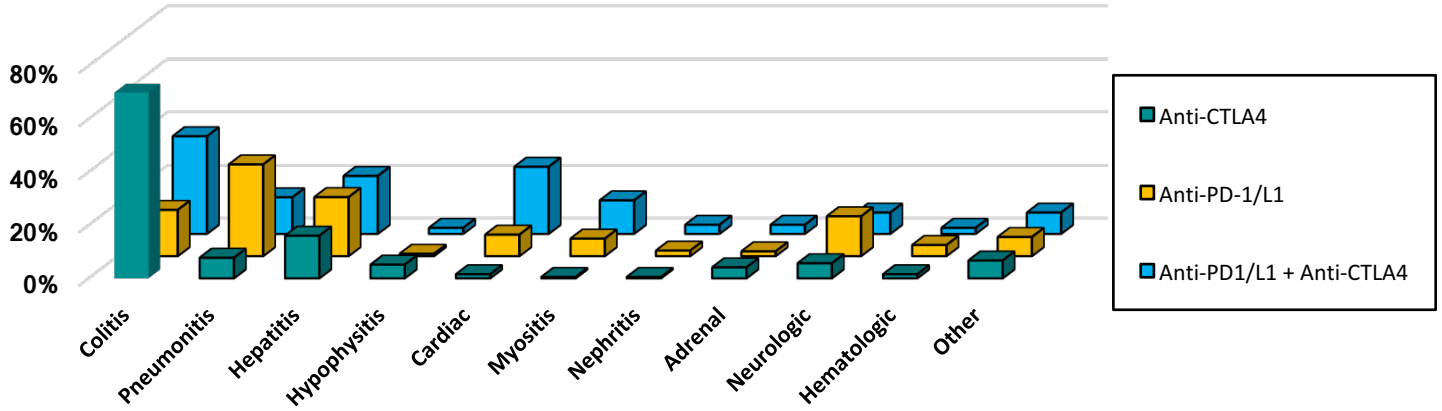
Fatal irAEs

- Chemotherapy Fatalities: 1.4%
- ICB Fatality rates vary: 0.25%-1.1%

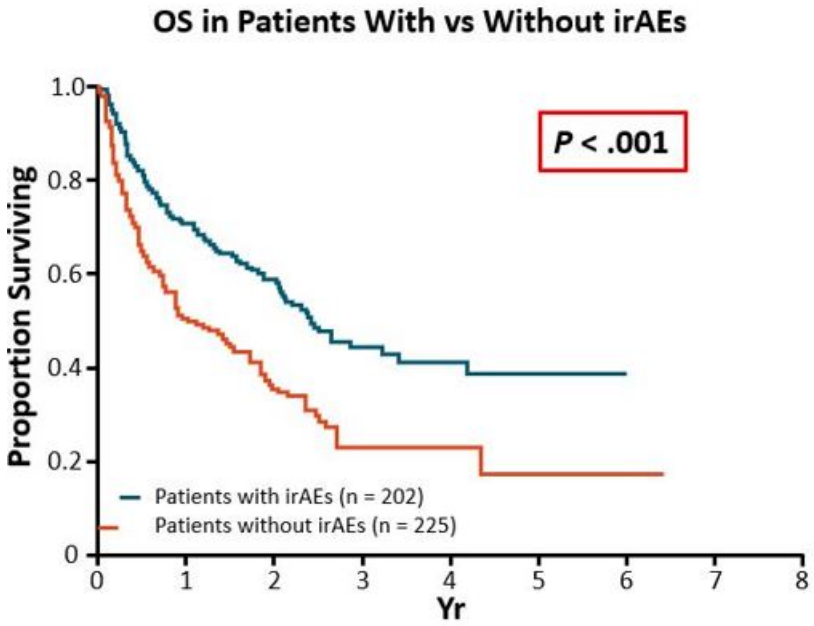


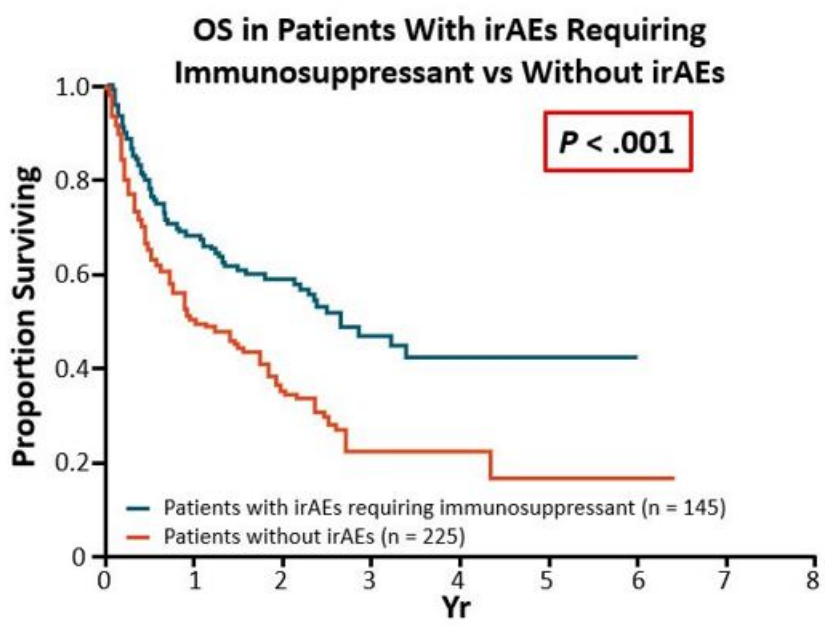




Wang et al. 2018. JAMA Oncol. ; Nishijima et al. 2017. The Oncologist

Immune Related Adverse Events
A Prognostic Biomarker?

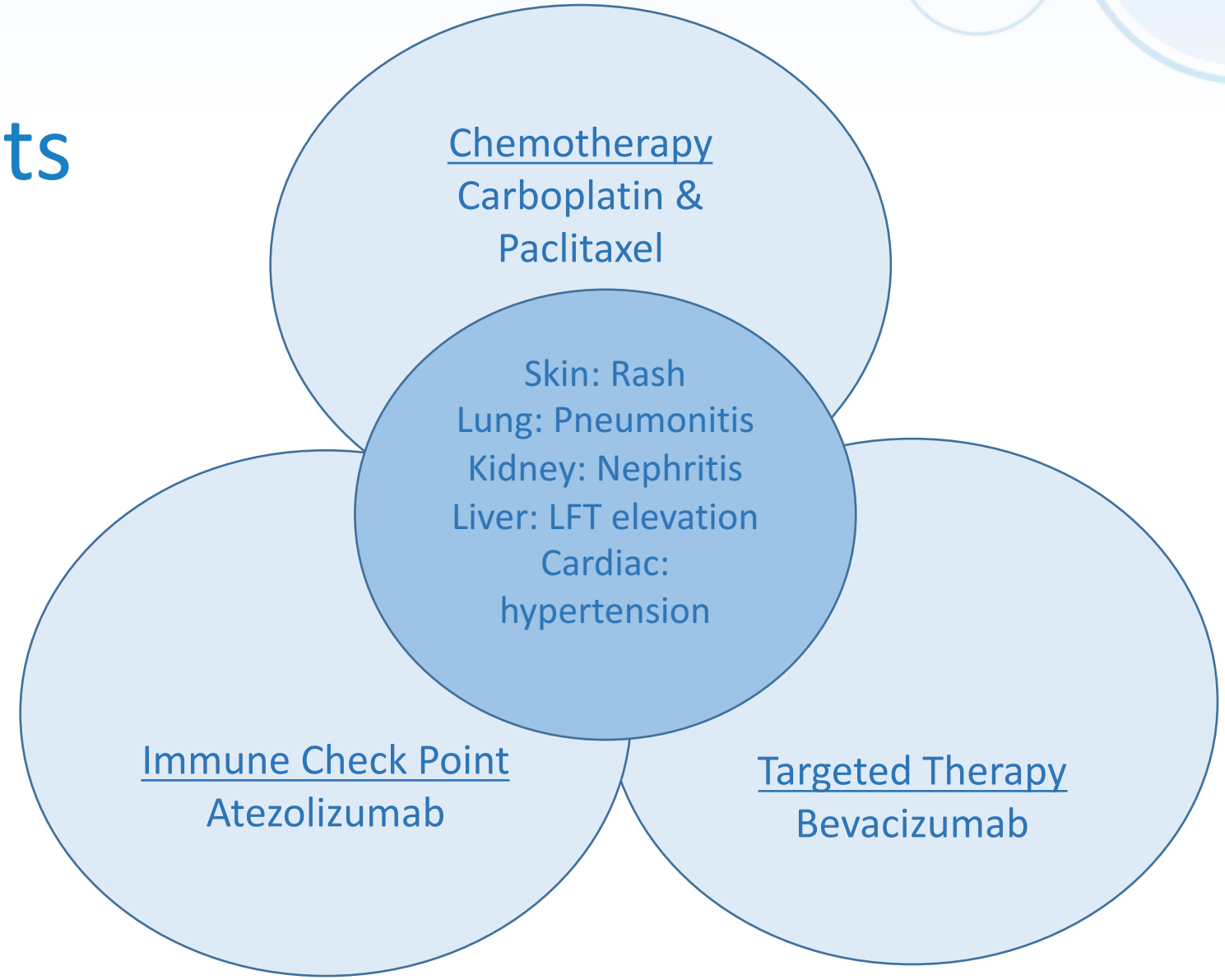




- Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Abu-Sbeih. J Immunother Pres Oncol. 2018; 1:7

Overlapping Adverse Effects



Preparation & Prevention

Prior to Start of Therapy

Providers
- Understanding of immune toxicity spectrum
- Identification of IO champions within organization

Patient Assessment
- Evaluate for autoimmune risks
  - Autoimmune diagnosis
  - Prior organ transplantation
    - ➢ Risk of graft loss
- Medication reconciliation, including OTC and herbal
  - Immunosuppressants, immune-stimulants, immune-modulating
  - Antibiotic Use

Patient Preparation
- Manage expectations about biomarker testing and treatment candidacy
- Adequate birth control during & for at least 5 months after ICPI
- Vaccinations prior to start of therapy
  - Inactivated or killed preparations while on ICPI
  - Live vaccine use not recommended

Preparation & Prevention

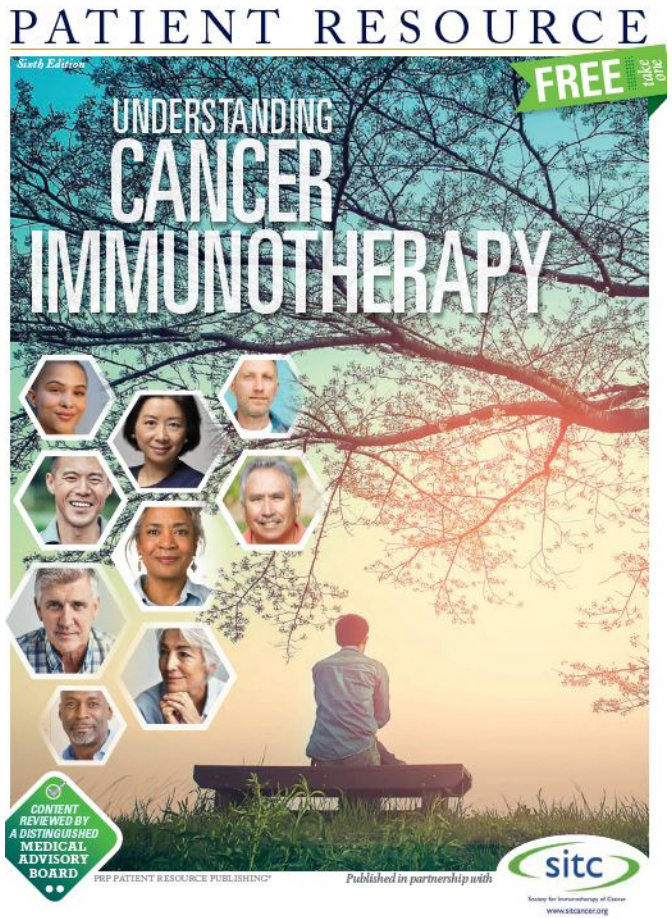
EDUCATION

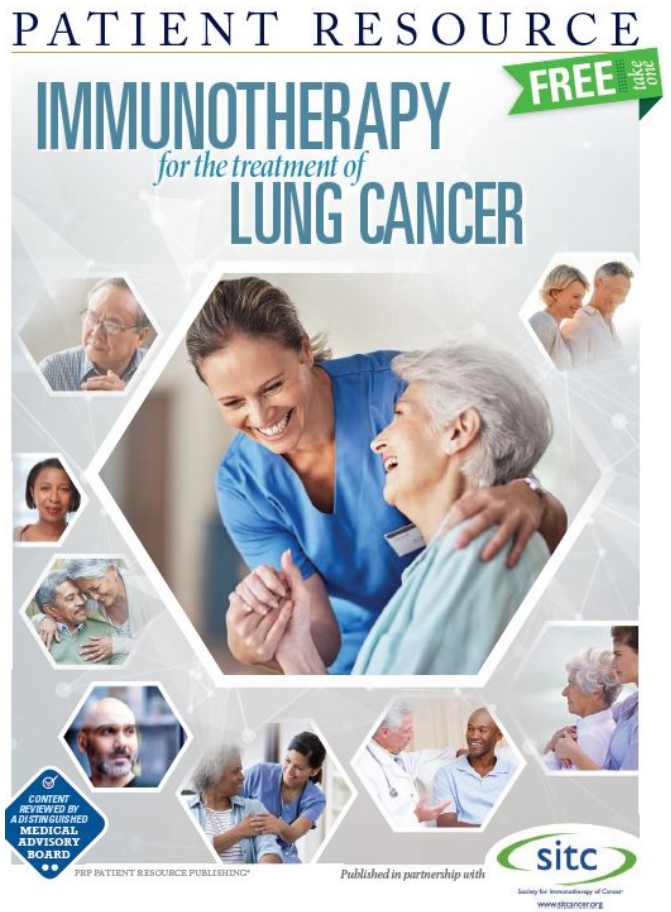
- How the Immune System works
- Role of Immune Checkpoint Inhibitors
- Expectations of treatment response
- Mechanism of IRAEs

- Potential adverse events (IRAEs)
  - Onset & presentation
- Management of IRAEs
  - Telephone Triage
- Implications of IRAEs

Considerations: Language, Culture, Literacy, Timing, Access

Patient Education Resources





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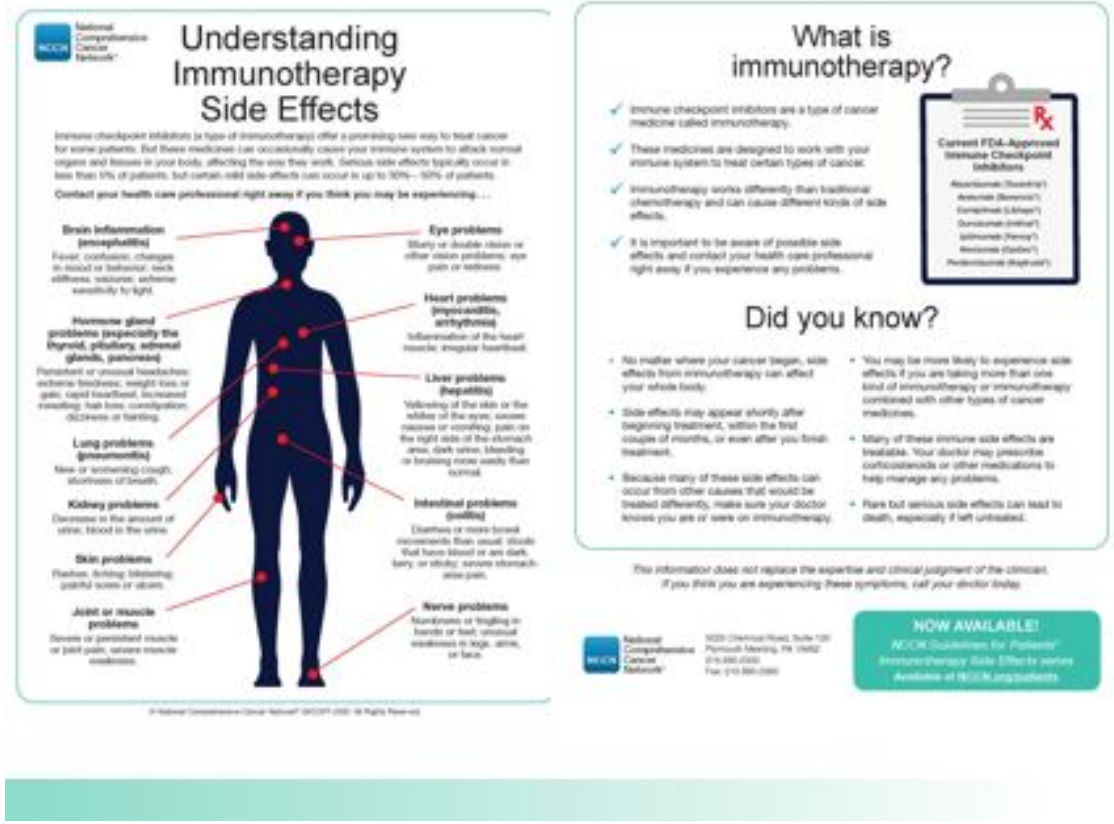
Patient Education Resources

American Society of Clinical Oncology

National Comprehensive Cancer Network



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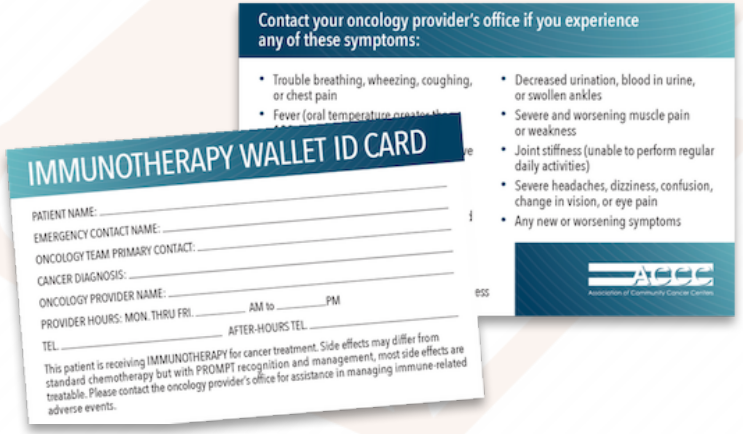
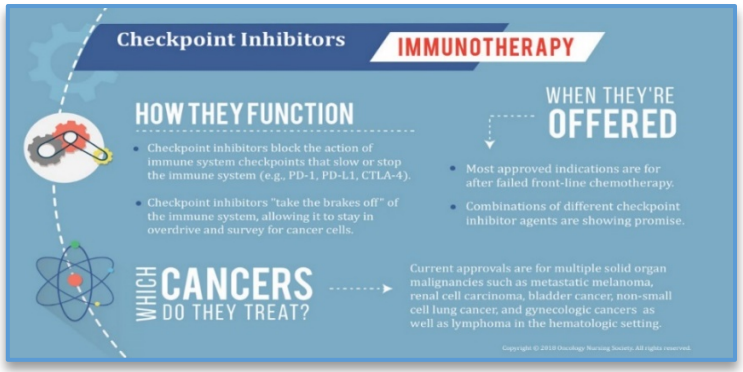
Patient Education Resources

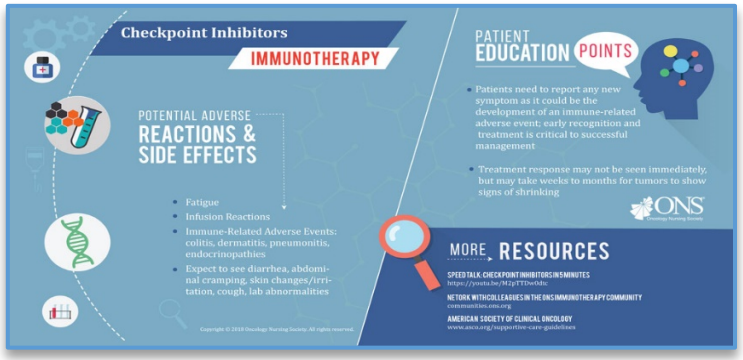
AIM with Immunotherapy Immuno-Oncology Essentials

ACCC



Oncology Nursing Society





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Patient Education Resources

Cancer Support Community

LUNGEVITY

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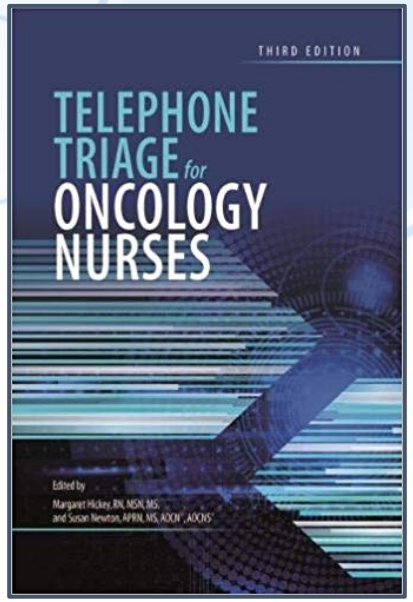
Telephone Triage: Guidelines



- Provides tool to distinguish which patients can be treated at home and which ones need to come into the clinic
- **All staff must be educated in the use and updates of the Telephone Triage guidelines**
- Early identification of symptoms will minimize severity of AEs and keep patients on beneficial therapy for a longer period of time

Patient calls with complaint of diarrhea	RN returns call; triage questions	Additional IO-specific symptom questions
• Secretary notifies clinic practice nurse	• When did it start? • How many episodes? • Any recent sick contacts? • Is the patient able to drink fluids?	• Any associated abdominal pain, cramping, nausea, or vomiting? • Any blood or mucous in the stool?

If mild (increase of <4 stools/day >baseline) and not interfering with ADLs, **patient may hydrate by mouth and take an antidiarrheal agent**

If moderate or severe, not able to maintain fluid intake or associated with any other symptoms, **patient should come into the clinic for evaluation**

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Telephone Triage: Challenges

Variable onset of irAEs

25% of ED visits by patients treated with ICPI are due to irAEs[1]

- **CMS implications**

By 2020, hospital penalties for cancer hospitals for patient visits to ED or hospitalizations due to chemotherapy; rules for ICPI likely to follow

- **Patient considerations**

- ❑ Is the patient a reliable and accurate "historian"?
- ❑ How reliable is the patient to follow telephone instructions? Comprehension of "sense of urgency"?
- ❑ Language barriers, cognitive deficits, alcohol and drug use, comorbidities?
- ❑ How far does the patient live from the clinic? Is there available transportation?
- ❑ What support or resources does the patient have to follow guidelines?

Managing IRAEs

Detection

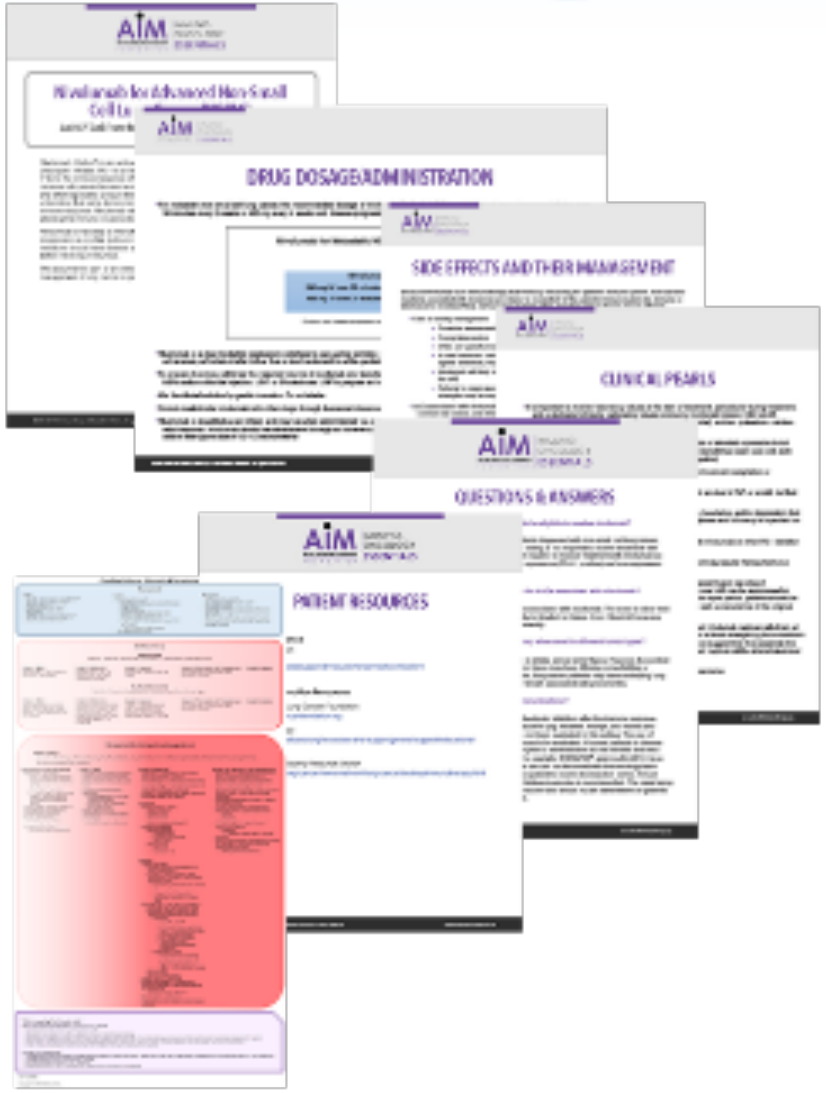
Interventions

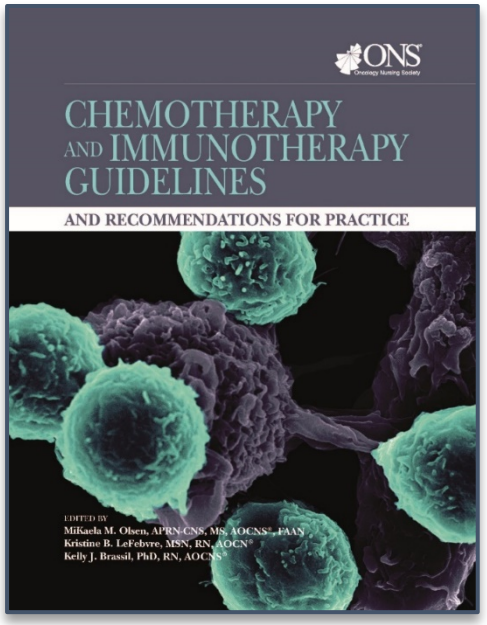
- Regular monitoring
- Telephone triage
- Use of Toxicity Management Guidelines
- Rule out other causes
- Assess and monitor kinetics of toxicity
- Determine need for hospitalization vs ambulatory care

Patient Education

- Therapy requires close communication
- Report any new signs or symptoms that develop
- Report if seen by any other healthcare provider or admitted to the hospital

Clinical Practice Guidelines





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Algorithm for Management of IRAEs

Questions: Continue ICPI, Suspend, Discontinue
Use of Steroids & Referral to specialists

- **Grade 1: asymptomatic to mild symptoms**
  - Observation
  - Supportive Care
  - Intervention not needed
- **Grade 2: moderate symptoms**
  - Local or noninvasive intervention indicated
  - Withhold drug, consider redose if toxicity resolves to grade ≤ 1
  - Low-dose corticosteroids likely needed
    - 0.5 to 1.0 mg methylprednisolone
  - May be able to continue treatment
- **Grade 3: medically significant but not immediately life-threatening**
  - Stop immunotherapy immediately
  - Hospitalization indicated
  - High-dose steroids indicated
    - 1.0-2.0 mg methylprednisolone
  - Slow steroid taper over ≥ 1 mo once toxicity resolves to grade ≤ 1
- **Grade 4: life-threatening consequences**
  - Urgent intervention
  - Permanently discontinue ICI therapy

Additional Immunosuppressants: infliximab, mycophenolate, IVIG

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Dermatologic IRAE:
macules, papules, pustules

Education & Assessment

What Patient Should Report?	What to Assess	Rule out other causes
• Dry Skin • Pruritis • Rash • Skin peeling • Blistering • Oral lesions • Anal, genitourinary, vaginal lesions • Impact on ADLs	• Total body exam (including mucosa) • Distribution of rash • Presence of peeling or blistering • Prior history of dermatologic autoimmune disease (eczema, psoriasis, scleroderma)	• Other drug reaction • Chemotherapy • Cellulitis • Contact dermatitis • Sun Exposure • Radiation Recall • Infection • Bullous dermatitis • DRESS/DIHS • Stevens-Johnson Syndrome/ Toxic epidermal necrolysis

Supportive Care: Gentle skin care, non-steroidal moisturizers or emollients; sun protective measures; Oral antihistamines for pruritus

GRADING

1	• Mild <10% BSA • With/out other symptoms (pruritis, burning, tightness)
2	• Moderate 10-30% BSA • With/out other symptoms • Limit IADLS
3	• Severe >30% BSA • Limiting self-care ADLs
4	• Potentially Life-Threatening • Papules/pustules, sloughing; superinfection

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***DRESS: drug rash with eosinophilia and systemic symptoms**
DIHR: drug induced hypersensitivity reaction

Gastrointestinal IRAE: diarrhea, colitis

Education & Assessment

What Patient Should Report?	What to Assess	Rule out other causes
• Increase in stool frequency • Increase in ostomy output • Blood or mucous in stool • Abdominal cramping/pain • Urgency, incontinence	• Calculate freq. & volume of diarrhea • History of opioid constipation • Stool cultures • Stool lactoferrin +/or calprotectin if available	• Dietary intolerance • Infectious etiology • Other drug cause (bowel regimen; antibiotics)

Supportive Care: Bland BRAT diet, Hydration, anti-spasmotic, anti-diarrheal; discontinue laxatives or stool softeners

GRADING

1
- < 4 stools > base
- Mild increase in ostomy output
- Asymptomatic

2
- 4-6 stools > baseline
- Limiting ADLs
- Abdominal cramps/pain

3
- > 7 stools > baseline
- Limiting self-care ADLs
- Severe abdominal pain; peritoneal signs

4
- Life-threatening
- Hemodynamic collapse

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Pulmonary IRAE: pneumonitis

Education & Assessment

What Patient Should Report?	What to Assess	Rule out other causes
• Increase or new onset dyspnea, cough, wheezing, chest pain, fever, increased oxygen requirements	• Oxygen saturation at rest and ambulation • Resp rate • Breath sounds • Nasal swab • Sputum culture • CXR • CTA	• Infection • Disease progression • Pulmonary embolism • Pleural effusion • Pulmonary fibrosis post Radiation Therapy

Supportive Care: Smoking cessation; vaccinations (influenza, pneumococcal)

GRADING

1
- <25% lung, confined to one lobe
- Asymptomatic
- Diagnostic observation

2
- 25-50% of lung
- Symptomatic: sob, cough, chest pain
- Limiting IADLs

3
- > 50% of lung
- Severe symptoms
- Limiting self-care ADLs
- Oxygen indicated

4
- Life-threatening
- Respiratory compromise

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Hepatic IRAE: transaminitis, hepatitis

Education & Assessment

What Patient Should Report?	What to Assess	Rule out other causes
• Abdominal pain • Nausea, emesis • Yellowing of skin • Bleeding or bruising • Drowsiness • Fatigue • Change in stool culture • Ascites • Excessive skin itching	• Liver function tests: Total bilirubin, AST, ALT, Alk Phos • Electrolytes • Viral panel: hepatitis	• Hepatotoxic drugs: acetaminophen, supplements • Concurrent Chemotherapy • ETOH use • Infection • Reactivation of viral hepatitis • Disease progression

Supportive Care: Limit hepatotoxic drugs and alcohol use
Infliximab CONTRAINDICATED due to potential hepatotoxic effects

GRADING

1	• AST/ALT: > ULN-3.0 x ULN • T Bili: > ULN-1.5xULN
2	• AST/ALT: >3.0-5.0 x ULN • Tbili: >1.5-3.0xULN
3	• AST/ALT: >5.0-20.0x ULN • Tbili: >3.0-10.0xULN
4	• AST/ALT: > 20x ULN • T Bili: > 10 x ULN

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Renal IRAE: nephritis

Education & Assessment

What Patient Should Report?	What to Assess	Rule out other causes
• Vague nausea • Decreased urine output • Blood in urine • Ankle swelling	• Serum creatinine • Electrolytes • Urinalysis • Urine protein/creatinine ratio • Urine lytes & osmo	• Other nephrotoxic drugs: antibiotics, NSAIDS, PPIs • Concurrent Chemo • Contrast dye • Dehydration • Pre/post renal causes • Infection

Supportive Care: Hydration; Limit nephrotoxic drugs and use of contrast dye

GRADING

1	• Creatinine >ULN-1.5 x ULN
2	• Creatinine >1.5- 3.0 x baseline; > 1.5-3.0 x ULN
3	• Creatinine >3.0 baseline; >3.0- 6.0 x ULN
4	• Creatinine > 6.0 ULN • Life-Threatening • Dialysis indicated

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Endocrine Toxicities: Thyroid

Presentation

Fatigue, sluggishness, anorexia, weight loss/gain, irritability, mood change,
palpitations, feeling hot/cold, visual disturbances, headaches, change in sexual drive.

Assessment

Close laboratory monitoring
Monitor TSH & free T4 every 4-6 weeks

- Rule out other causes: infection, brain metastases, primary vs secondary AE

.

SURGICAL Considerations

- Anesthesia complications from untreated hypothyroidism ->delayed emergence, hypothermia, bradycardia, low cardiac output and impaired hypoxic and hypercapnic respiratory drive.
- In severe cases, myxedema coma. Hypoventilation, profound hypotension, bradycardia, severe hypothermia & electrolyte abnormalities.
- If suspicion, 200-400 µg IV levothyroxine (T4) followed by 100 µg day or 10-24 µg triiodothyronine (T3) every 8 hours (caution with cardiac patients).

- Untreated hyperthyroidism -> risk of thyroid storm intraoperatively. Tachycardia, fever, cardiovascular collapse.
- Tx: IV beta-blockers and hydration
- If sub-clinical, initiate beta-blocker with methimazole or propylthiouracil several weeks before surgery

Treatment: Thyroid Dysfunction

Levothyroxine: adjust levels to maintain free T4 level at mid-range
Typically: 1.6 mcg/kg/day
Educate patients that hormone replacement in likely lifetime

Asymptomatic Hypothyroidism	Clinical Hypothyroidism	Thyrotoxicosis
• TSH btw 4-10; T4 norm: continue ICPI • TSH >10; T4 norm: continue; consider levothyroxine • TSH low; T4 low/norm: consider central hypothyroidism	• Monitor TSH and T4 every 4-6 weeks • Levothyroxine replacement • Consider endocrine consultation • Exclude concomitant adrenal insufficiency	• Continue ICPI • Propranolol for palpitations • Repeat TFTs in 4-6 weeks.

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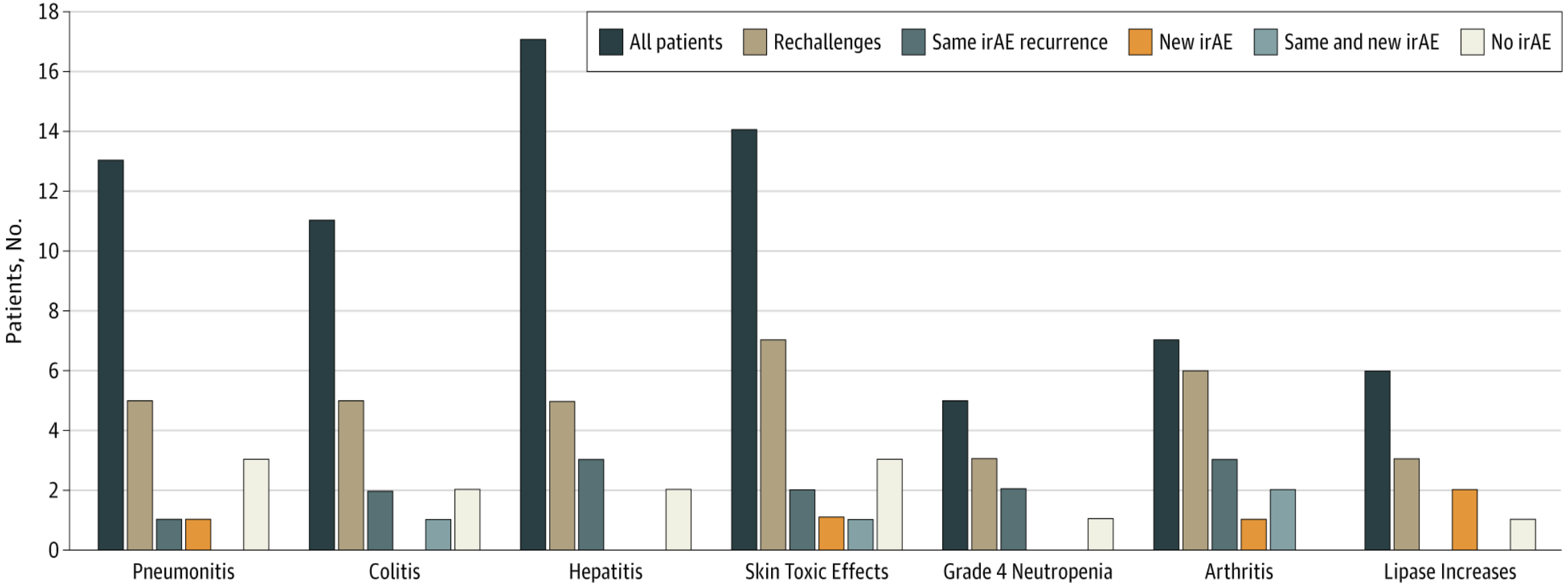
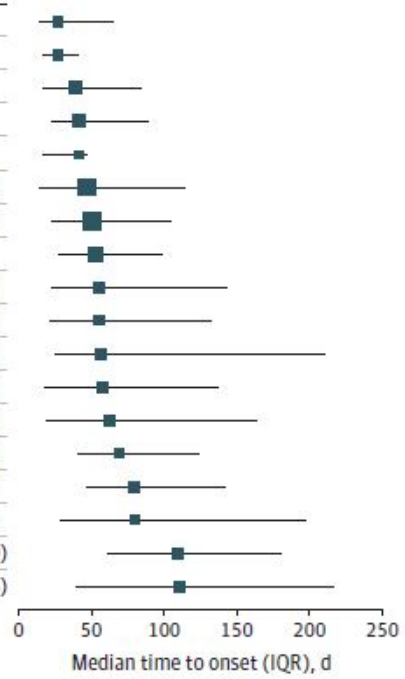
Patient Outcomes after Anti-PD-1 or Anti-PD-L1 Rechallenge following irAEs



Simonaggio et al. JAMA Oncol 2019; 5 (9):1310-1317

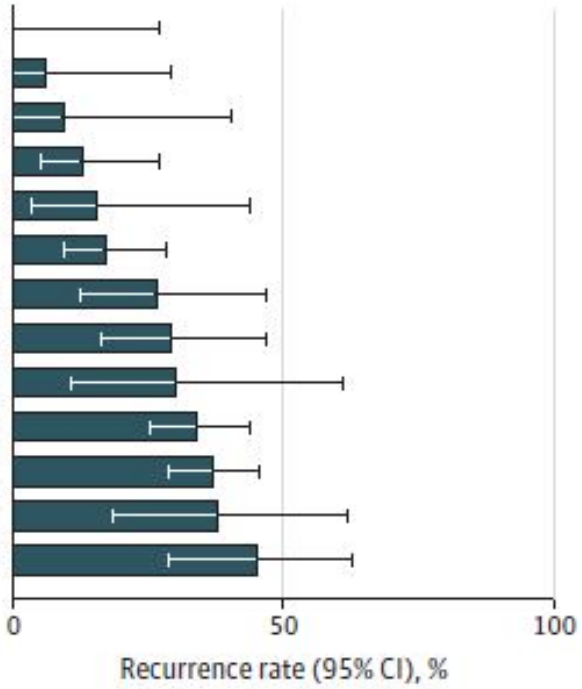
Rechallenge After IRAEs

Adverse drug reaction	No. of cases with available time-to-onset data	Median time to irAE onset (IQR), d
Myocarditis	129	28 (16-65)
Myositis	190	28 (18-41)
Neurologic	434	40 (18-85)
Hepatitis	642	42 (23-89)
Vasculitis	13	42 (18-48)
Pneumonitis	2484	48 (16-114)
Colitis	2293	51 (24-105)
Thyroiditis	1227	54 (28-99)
Hematologic	114	56 (24-143)
Uveitis	105	56 (23-133)
Skin	198	57 (26-210)
Mucositis	173	59 (19-137)
Arthritis	445	63 (20-164)
Nephritis	68	70 (42-124)
Hypophysitis	370	80 (48-142)
Pancreatitis	129	81 (30-197)
Adrenal	421	110 (62-180)
Diabetes	216	112 (40-216)



Squares represent the median and whiskers represent the interquartile range (IQR) of time to immune-related adverse event (irAE) onset. Square size is log-proportional to the number of cases.

Adverse drug reaction	No. of cases	Recurrence rate (95% CI), %
Diabetes	13	0 (0-27)
Neurologic	17	6 (0-29)
Uveitis	11	9 (0-40)
Adrenal	40	12 (5-27)
Pancreatitis	13	15 (3-43)
Thyroiditis	60	17 (9-28)
Hypophysitis	23	26 (12-47)
Hepatitis	31	29 (16-47)
Hematologic	10	30 (10-61)
Pneumonitis	101	34 (25-43)
Colitis	123	37 (29-45)
Skin	16	38 (18-61)
Arthritis	29	45 (28-62)



#LearnACI

Dooadile C. JAMA Oncol. 2020;6(6):865-871. doi:10.1001/jamaoncol.2020.0726

Multidisciplinary Strategies to Reduce Acute Care

(Handley, 2018)

Strategy	Example Interventions (order of complexity)
Enhance access and care coordination	• Reliable mechanisms for patient to contact the care team • Improved and standardized care transitions • Patient Navigation programs • **Automated Hovering**
Standardized clinical pathways for symptom management	• Outpatient symptom management and telephone triage • Supportive care • ED symptom pathways
Develop urgent care tactics	• Flexible scheduling and embedded urgent care • Cancer providers embedded in ED • Dedicated acute care treatment clinics • Dedicated cancer ED

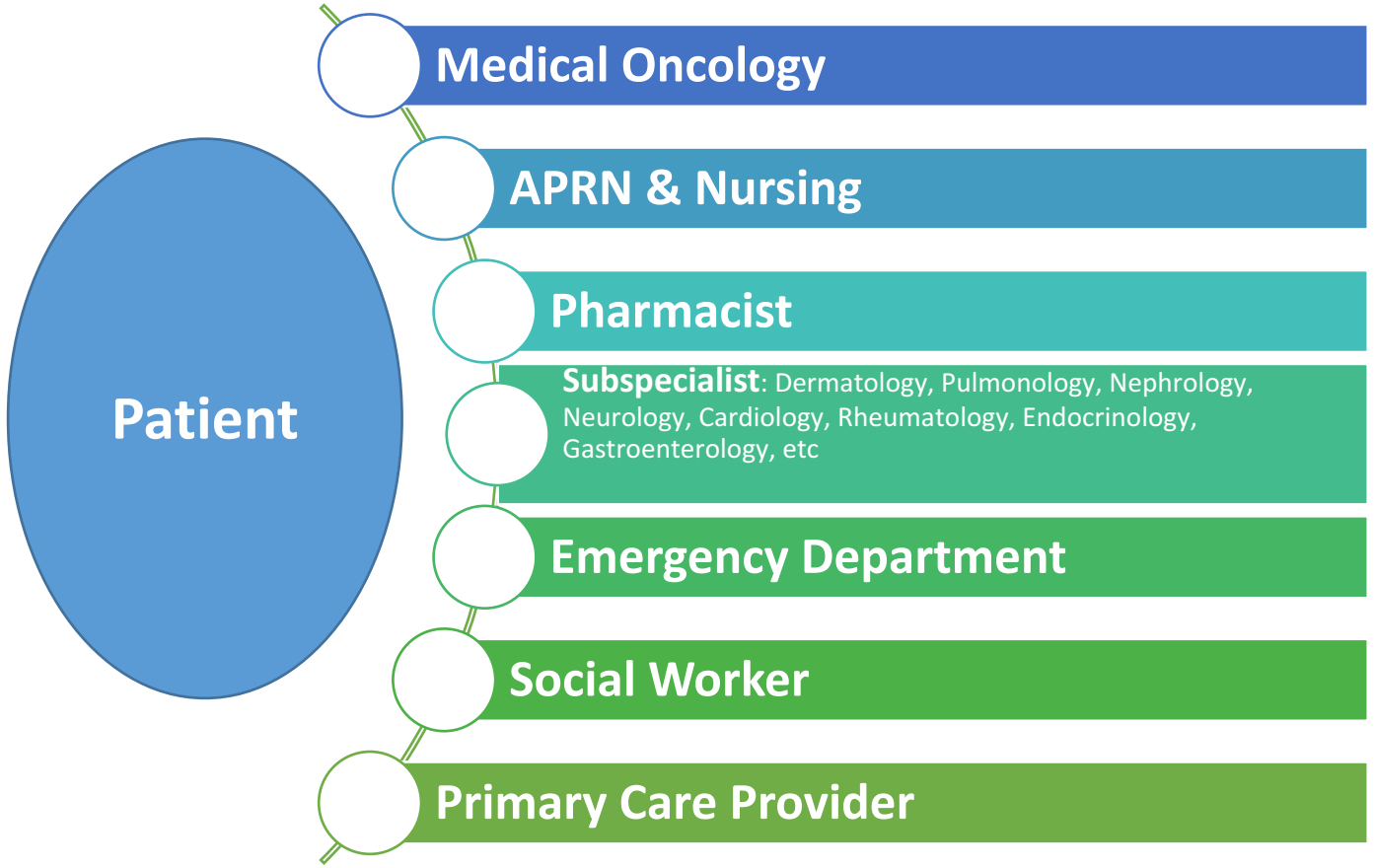
BEST PRACTICE MODELS

Immune Toxicity Clinics	• Specialized clinics to treat patient's with emergent IMAEs staffed by specialists with expertise
Immune Tumor Boards	• Virtual, Scheduled or Reactive • Identification of appropriate patients • Discussion of toxicities • Discussions of predictive biomarkers.
Immune Toxicity Service	• Inpatient Consult Service • Round on patients admitted with IMAEs • Educate inpatient services

M. Davies, DNP. April 2019

Multidisciplinary Patient Care

- Team-wide and interdisciplinary communication, collaboration and coordination of care is essential.
  - Discuss potential for IRAEs with the entire healthcare team and educate colleagues.



Questions?