National Comprehensive Cancer Network®

Treating Toxicities of Targeted and Immune-Based Therapies

Irene M. Kang, MD
City of Hope National Medical Center

Wafa Samara, PharmD
City of Hope National Medical Center

Kay T. Yeung, MD, PhD
UC San Diego Moores Cancer Center

National Comprehensive Cancer Network®

Treating Toxicities of Targeted and Immune-Based Therapies

Checkpoint Inhibitors

Kay T. Yeung, MD, PhD

UC San Diego Moores Cancer Center

SABCS 2025: Immunotherapy-related toxicity in breast cancer

10-minute roadmap

- What irAEs look like in breast cancer practice
- Predictive biomarkers emerging at SABCS 2025
- Toxicity monitoring / management strategies
- Special populations (age, race)

Prepared for discussion • January 2026

SABCS 2025 abstracts with new insights on immunotherapy-related toxicity in breast cancer

Predictive biomarkers (3)

- PD1-10 (Alpert, *et al.*): Immune age acceleration → higher risk of grade 3–4 irAEs (periop pembrolizumab)
- PS1-01-05 (Wolf, *et al.*): Pre-treatment immune signatures (ImPrint+) predict pneumonitis
- PS1-03-04 (Li, *et al.*): Genomic factors & TMB associate with thyroid irAEs (tislelizumab + chemo, TREND)

Toxicity monitoring & management (3)

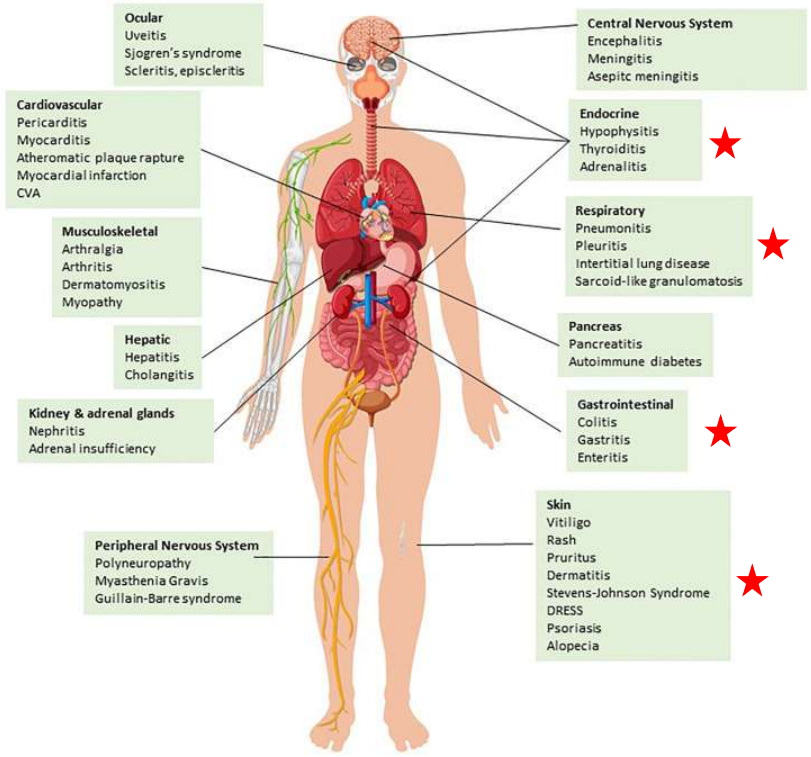
- PS1-01-09 (Kularni, *et al.*): Real-time HRCT monitoring workflow mitigates T-DXd + rilvegostomig ILD severity
- PS1-01-10 (Loirat, *et al.*): Chronic irAEs after neoadjuvant pembrolizumab (endocrine + cardiac signals)
- PS1-07-17 (El Fakih, *et al.*): Concurrent adjuvant RT + pembrolizumab safety in early TNBC (real-world)

Special populations (3)

- PS4-07-25 (Smith, *et al.*): Older adults (≥65) – high hospitalization/ discontinuation and irAE burden
- PS4-07-26 (Patel, *et al.*): CMF + pembrolizumab as feasible option in older/comorbid KEYNOTE-522–ineligible
- PS2-04-13 (Brock, *et al.*): KN522 treatment toxicity by race

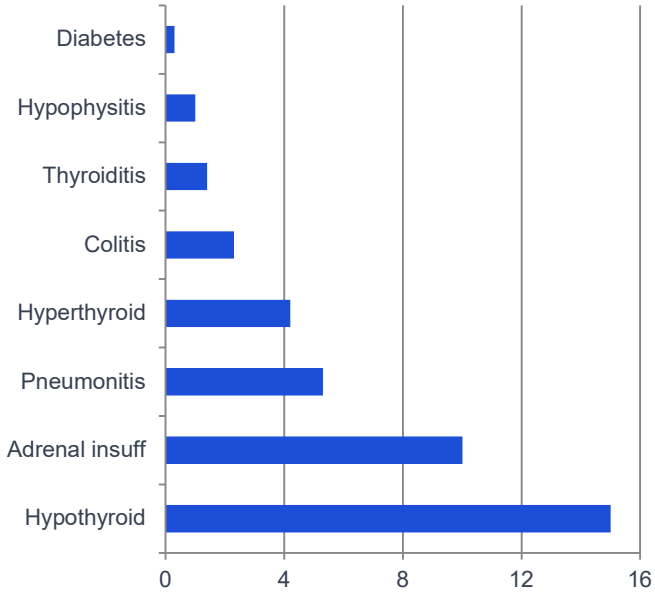
irAEs in breast cancer: typical organs & frequency

Breast cancer experience is dominated by endocrine, skin, GI and lung toxicities



Organ-system distribution of irAEs (Ibis et al., Frontiers in Immunology 2023).

Example incidence (I-SPY2 pooled IO arms, n=356)



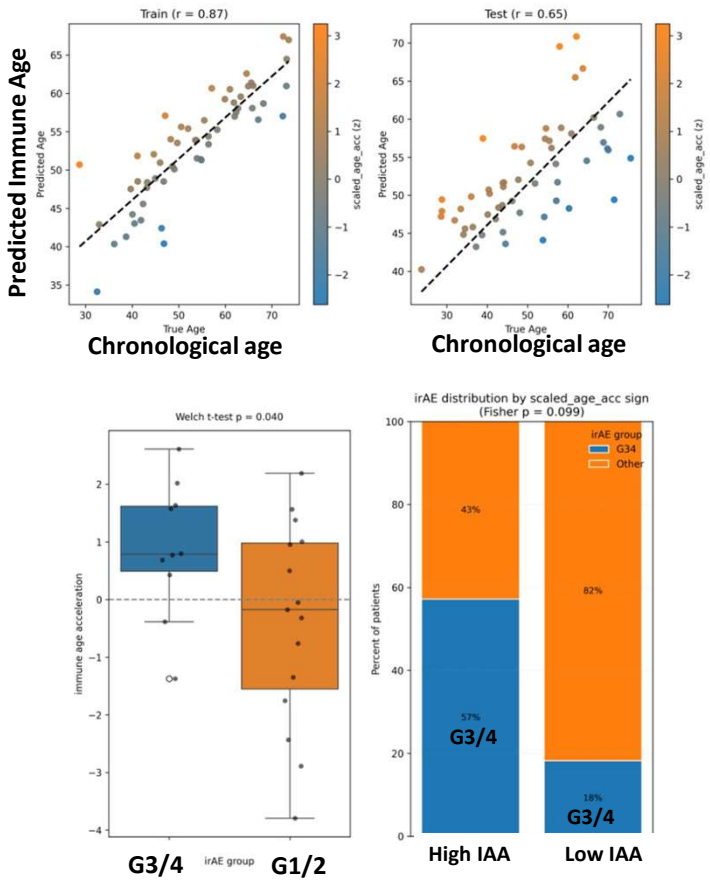
Note: regimen-/population-specific; chronic irAEs are increasingly recognized in curative TNBC.

Predictive biomarkers: Host & tumor immune features may help stratify pneumonitis and high-grade irAE risk

PD1-10 (Alpert, et al.)
Immune Age Acceleration (IAA)

- Serum inflammatory proteomics → "immune age" outperformed chronological age in capturing baseline inflammation.
- Levels of 92 inflammatory proteins in serum using Olink® panel
- In TNBC perioperative pembrolizumab cohort (n=33), higher baseline IAA associated with grade 3–4 irAEs
  - 57% in high IAA group (n=14)
  - 18% in low IAA (n=11)

→ Hypothesis generating: host-centric risk score may guide treatment surveillance intensity



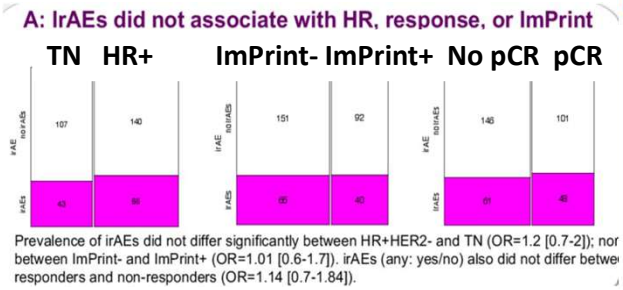
Orange = high IAA
Blue = low IAA

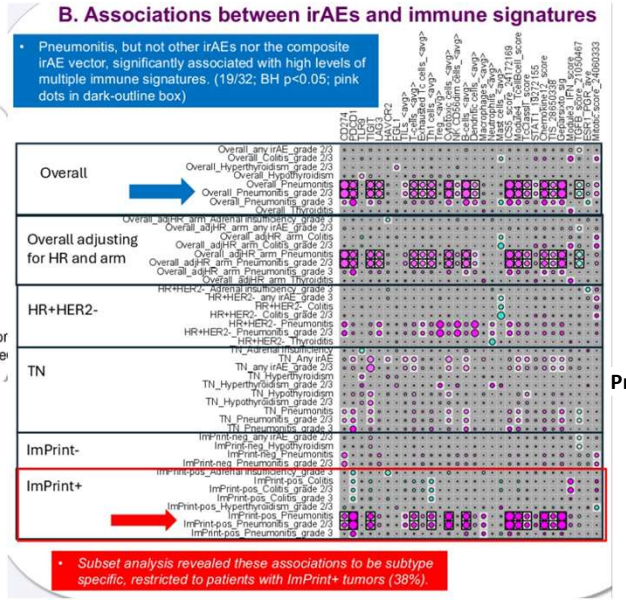
Predictive biomarkers: Host & tumor immune features may help stratify pneumonitis and high-grade irAE risk

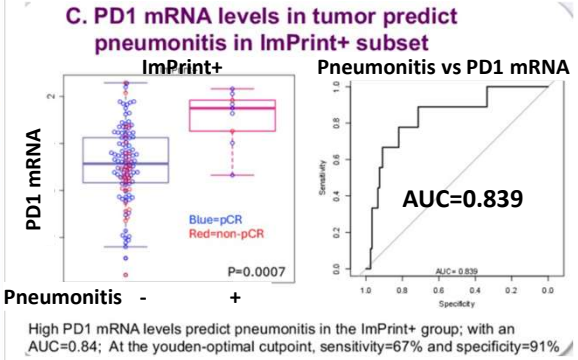
PS1-01-05 (Wolf, et al.) — Pre-treatment immune signatures predict pneumonitis (I-SPY2 pooled IO arms)

- Across 5 IO arms (n=356), irAE prevalence ranged from 19-44% by IO arms with highest prevalence in dual-IO arms
- irAEs did not associate with HR status, treatment response, or ImPrint (immune predictive) biomarker
- Pneumonitis (5.3%)—but not other irAEs—associated with multiple immune signatures
- Signals restricted to ImPrint+ tumors where PD-1 (PDCD1) mRNA predicted pneumonitis (**AUC 0.84**; specificity 91%).

→ **Candidate tumor + host immune context model pneumonitis risk; needs prospective validation**





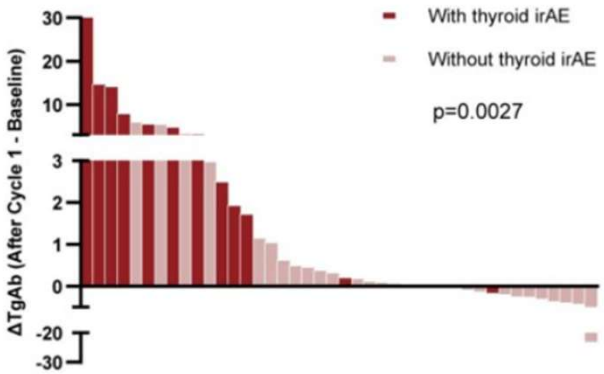


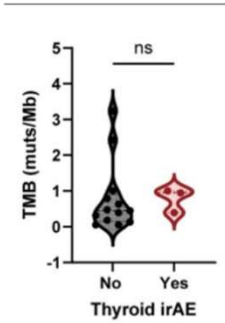
Predictive biomarkers: Host & tumor immune features may help stratify pneumonitis and high-grade irAE risk

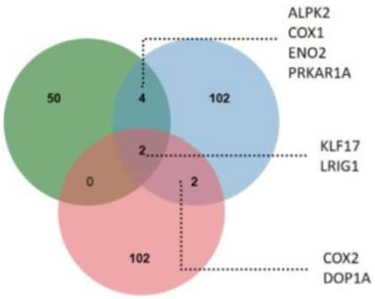
PS1-03-04 (Li et al.) — Thyroid irAEs with tislelizumab + chemotherapy (TREND trial)

- TREND trial: phase II neoadjuvant tislelizumab (Q3w x 8 cycles) + chemotherapy (nab-paclitaxel Q1w x 12 + EC Q3w x 4), n=52
- Thyroid irAEs occurred in 28% (mostly grade 1–2)
- Baseline TMB did not correlate with thyroid irAEs
- Clinical predictors: baseline TgAb+ and lower baseline FT3
- Certain mutations (e.g., KLF17, LRIG1) may be associated with thyroid toxicity risk

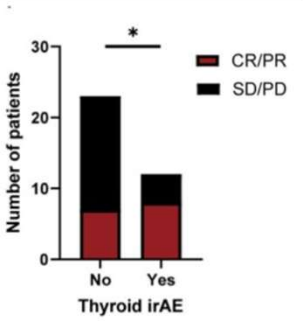
→ **Hypothesis generating: baseline thyroid labs/antibodies may be a practical stratifier; tumor genomics possible but more difficult**







Whole exome sequencing



Toxicity monitoring & management

Three pragmatic studies: chronic irAEs, ILD workflows, and RT + ICI safety

PS1-01-10 (Loirat D, et al.)
Chronic irAEs

- Real-world KEYNOTE-522 regimen (n=203): chronic irAEs in 36.5%.
- Endocrine dominated (79% of chronic irAEs):
  - hypothyroid 62%
  - corticotropic insuff 45% (no recovery).
- Cardiac myocarditis reported in 4.9%; managed with steroids.

→ Implication for survivorship planning + endocrine/cardiac follow-up.

PS1-01-09 (Kularni T, et al.)
Proactive ILD monitoring

- I-SPY2.2: T-DXd + rilvegostomig, intensive safety workflow.
- ILD incidence 15.7% in first 51 pts; all detected by HRCT q6w. 50% were asymptomatic.
- PFTs/6MWT did not add early detection and were dropped.

→ In IO+ADC settings, protocolized HRCT may catch

PS1-07-17 (El Fakih A, et al.)
RT + pembrolizumab safety

- Institut Curie retrospective (n=89): adjuvant RT with vs without concurrent pembrolizumab.
- No grade ≥3 toxicities
- **More grade 1 radiodermatitis with RT+Pembro** (83% vs 44%).
- 2 cases grade 1 pulmonary toxicity in RT+P; no cardiac toxicity signal (mean heart dose ~1.8 Gy).

→ Supports feasibility with RT + pembro while awaiting long-term toxicity assessment.

Toxicity monitoring & management

chronic irAEs

PS1-01-10 (Loirat D, et al.)
Chronic irAEs

- Real-world KEYNOTE-522 regimen (n=203)
- Median age 49
- Chronic irAEs (≥12 months) in 36.5%
- Endocrine dominated (79%):
  - hypothyroid 62%
  - corticotropic insuff 45% (none recovered).
- Cardiac myocarditis reported in 4.9% (n=10); managed with steroids + cardio meds
- No immune-tox deaths

→ Implication: survivorship planning + endocrine/cardiac follow-up.

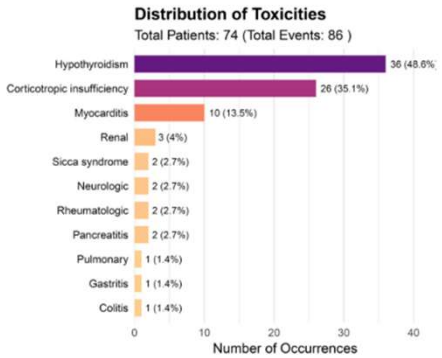
RESULTS

Characteristic	N = 203
Median age (range)	49 (22–74) years
Germline BRCA1/2 mutation	30 (14.8%)
Histology	187 (92.1%) invasive carcinoma of no special type
Pathological complete response (pCR)	142 (70%)
Autoimmune disease history	6 (3%)
Tumor size	T1–2: 150 (74%); T3–4: 52 (26%)
Nodal status	N0: 80 (40%); N+: 122 (60%)
Neoadjuvant pembrolizumab	203 (100%, at least one dose)
Adjuvant pembrolizumab	120 (59%, at least one dose)
Did not receive adjuvant treatment	83 (41%)
Median number of pembrolizumab cycles	10 (range 1–17)

Table 1. Study population and main characteristics

- **Ten patients (4.9%) experienced multiple chronic irAEs**
- **No deaths related to immune-mediated toxicity were observed**

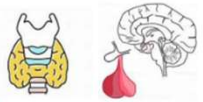
Chronic irAEs occurred in 36.5% of patients (n = 74)



- **Endocrine**: 79% (hypothyroidism 62%, corticotropic insufficiency 45%; 7% had both)
- **Cardiac**: 4.9% (n = 10; all myocarditis)
- **Sicca syndrome**: 1.0% (n = 2) characterized by dryness of the eyes and mouth due to reduced tear and saliva production, often linked to autoimmune disorders such as Sjögren's syndrome.

Management

- ✓ corticosteroids and standard cardioprotective therapies;
- ✓ No patient required second-line immunosuppression



- ✓ Long-term hormone replacement therapy was administered to all patients, with levothyroxine for hypothyroidism and hydrocortisone for corticotropic insufficiency resulting from immunotherapy.
- ✓ No cases of functional recovery observed.

Loirat D, Matte P, Hacini I, et al. Chronic Immune-Related Adverse Events after neoadjuvant pembrolizumab in early-stage triple-negative breast cancer: A Real-World cohort analysis. SABCS 2025. Poster Session 1. PS1-01-10

Toxicity monitoring & management

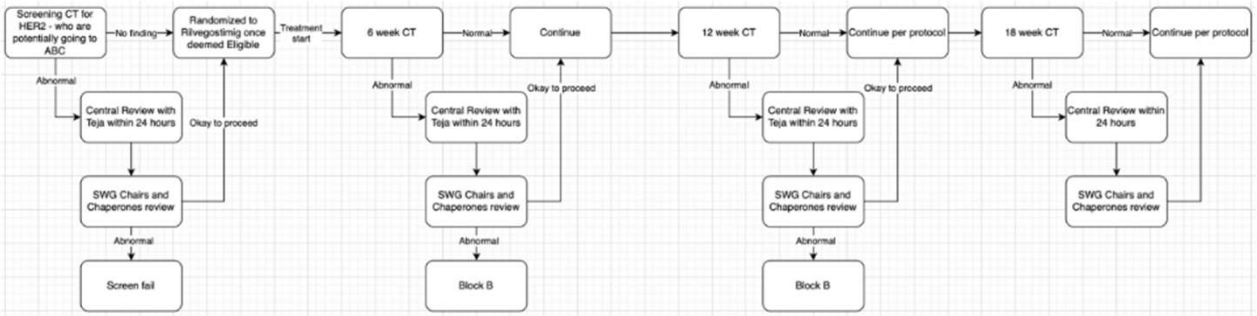
ILD workflows

PS1-01-09 (Kularni T, et al.)
Proactive ILD monitoring

- I-SPY2.2: T-DXd + rilvegostomig, intensive safety workflow.
- ILD incidence 15.7% in first 51 pts; all detected by HRCT q6w. 50% were asymptomatic.
- PFTs/6MWT did not add early detection and were dropped.

→ In IO+ADC settings, protocolized HRCT may catch

Figure 1:Real-time study workflow



Real-time study workflow in a study of combination of trastuzumab deruxtecan and rilvegostomig administered every 3 weeks in the I-SPY2.2 phase 2 platform trial. CT scans were considered abnormal if new ground-glass opacities, nodules, infiltrates, or fibrotic changes were present. Per protocol, a diagnosis of pneumonitis (any grade) prompted transition to Block B upon confirmation of resolution of CT findings and symptoms. HRCT: High resolution computed tomography; PFTs: Pulmonary Function Test; 6MWT: Six-minute Walk test

Toxicity monitoring & management

Concurrent RT + ICI safety

PS1-07-17 (El Fakih A, et al.)
RT + pembrolizumab safety

- Institut Curie retrospective (n=89): adjuvant RT with vs without concurrent pembrolizumab.
- No grade ≥3 toxicities
- **More grade 1 radiodermatitis with RT + pembrolizumab** (83% vs 44%).
- 2 cases grade 1 pulmonary toxicity in RT + pembrolizumab; no cardiac toxicity signal (mean heart dose ~1.8 Gy).

→ Supports feasibility with RT + pembrolizumab while awaiting long-term toxicity assessment.

Toxicity (CTCAE v5. graded)	Total (n=89)	%	Concurrent RT-pembrolizumab (n=48)	%	Pembrolizumab withheld (n=41)	%	p-value
Early radiation-induced toxicity							
Radiodermatitis							
grade 0	28	31.5 %	8	16.7 %	20	48.8 %	<0.001
grade 1	58	65.2 %	40	83.3 %	18	43.9 %	
grade 2	3	3.4 %	0	0 %	3	7.3 %	
Esophagitis							
grade 0	84	94.4 %	47	97.9 %	37	90.2 %	0.265
grade 1	4	4.5 %	1	2.1 %	3	7.3 %	
grade 2	1	1.1 %	0	0 %	1	2.4 %	
Oedema							
grade 0	82	92.1 %	43	89.6 %	39	95.1 %	0.567
grade 1	7	7.9 %	5	10.4 %	2	4.9 %	
Xerodermia							
grade 0	86	96.6 %	47	97.9 %	39	95.1 %	0.89
grade 1	3	3.4 %	1	2.1 %	2	4.9 %	
Pruritis							
grade 0	86	96.6 %	46	95.8 %	40	97.6 %	0.236
grade 1	2	2.2 %	2	4.2 %	0	0 %	
grade 2	1	1.1 %	0	0 %	1	2.4 %	
Tracheitis							
grade 0	87	97.8 %	46	95.8 %	41	100 %	0.546
grade 1	2	2.2 %	2	4.2 %	0	0 %	
Pain							
grade 0	87	97.8 %	47	97.9 %	40	97.6 %	1
grade 1	2	2.2 %	1	2.1 %	1	2.4 %	
Late radiation-induced toxicity							
Oedema							
grade 0	88	98.9 %	47	97.9 %	41	100 %	1
grade 1	1	1.1 %	1	2.1 %	0	0 %	
Lung fibrosis							
grade 0	87	97.8 %	46	95.8 %	41	100 %	0.546
grade 1	2	2.2 %	2	4.2 %	0	0 %	

Special Populations: Older patients

PS4-07-25 (Smith, et al.)
Older adults (≥65)

- n=85 (median age 70) treated with pembrolizumab-containing neoadjuvant regimens.
- 50% did not have anthracycline
- pCR 43%
- Hospitalization 41%; early discontinuation 41%; irAEs 39% (about half required steroids).
- 3 treatment-attributed deaths (incl. pneumonitis) reported.
- Age >70: higher odds of irAE and lower relative dose intensity.

PS4-07-26 (Patel, et al.)
KEYNOTE-522–ineligible

- Retrospective analysis
- CMF + pembrolizumab (n=10) for comorbid/PS-limited pts.
- Median age 81
- 60% with >/= 1 comorbidities
- ECOG 0-2 (median=1)
- Low acute toxicity: 1 grade 3 colitis → pembrolizumab stop + hospitalization; otherwise minimal TRAE-driven stops.
- pCR 56% among 9 with surgery info (1 has not gone to surgery)

→ alternative chemotherapy backbones may widen access for the very old/ high comorbid pts

Special populations: Race

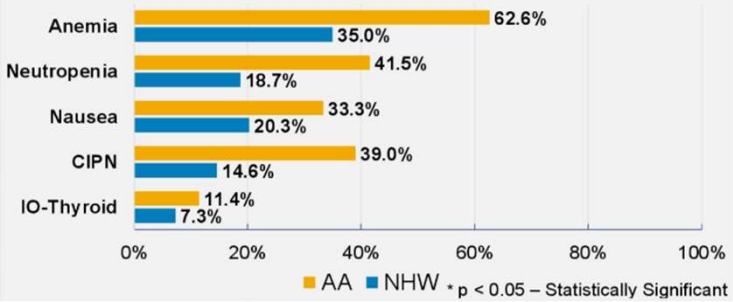
PS2-04-13 (Brock, et al.)
AA/Back vs NHW

- Retrospective study on toxicity by race in early-stage TNBC treated with KN522
- n=124 (AA/Black n=80; NHW n=44), median age 56.5.
- AA pts had higher chemotherapy-related toxicities (anemia, G3/4 neutropenia, CIPN) and more treatment modifications (chemotherapy + pembrolizumab), numerically.
- **No statistically significant difference** in overall irAE rates between AA vs NHW (signal driven more by chemotherapy toxicity than immune toxicity)
- **Similar pCR** 52% by race
- **36-mo OS lower in AA** (89.7%) vs NHW (97.3%)

123 of 135 patients were analyzed after receiving at least 12 weeks of the recommended treatment.

Table 1: Baseline Characteristics	Total N=123 (100%)	AA N=80 (65.0%)	NHW N=43 (34.9%)	P-value
Age at diagnosis, Median (Q1-Q3)	56 (42-66)	59 (49-68)	50 (38-63)	**0.013***
BMI, Median (Q1-Q3)	30.6 (25.4-35.4)	32.2 (26.4-35.9)	27.7 (23.5-33.6)	**0.007***
Marital status, n (%)				
Single	45 (36.9)	33 (41.8)	12 (27.9)	
Married	51 (41.8)	24 (30.4)	27 (62.8)	**0.002***
Widow/ Divorced/Separated	26 (21.3)	22 (27.8)	4 (9.3)	
Comorbidities, N(%)				
Anxiety	19 (15.5)	6 (7.5)	13 (30.2)	**<0.001***
Hypertension	59 (47.9)	46 (57.5)	13 (30.2)	**0.004***
Thyroid disorder	16 (13.0)	6 (7.5)	10 (23.3)	**0.013***
Cancer Stage, N(%)				
Stage 1	17 (13.8)	11 (13.7)	6 (13.9)	
Stage 2	66 (56.7)	39 (48.7)	27 (62.8)	0.250
Stage 3	40 (32.5)	30 (37.5)	10 (23.3)	

Figure 1: Select Adverse Events



Take-home Points

- **Prediction is moving toward host/tumor context** (proteomic "immune age," immune signatures for pneumonitis), but for now its best use is to **identify who needs intensified monitoring**
- **Systems-level management works:** centralized/structured monitoring pathways (e.g., HRCT-led ILD workflows) can reduce severity while keeping patients on effective therapy—implementation matters as much as biology.
- **Chronic irAEs are common (~1/3) after curative-intent pembrolizumab in early TNBC and are often *permanent* (endocrine), with a non-trivial myocarditis signal** → counsel early; build survivorship follow-up.

Toxicities of PI3K & AKT Inhibitors

Wafa Samara, Pharm.D.
Vice President and Chief Pharmacy Officer
Enterprise Pharmacy Services, City of Hope

Available PI3K Inhibitors

Endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative advanced or metastatic breast cancer

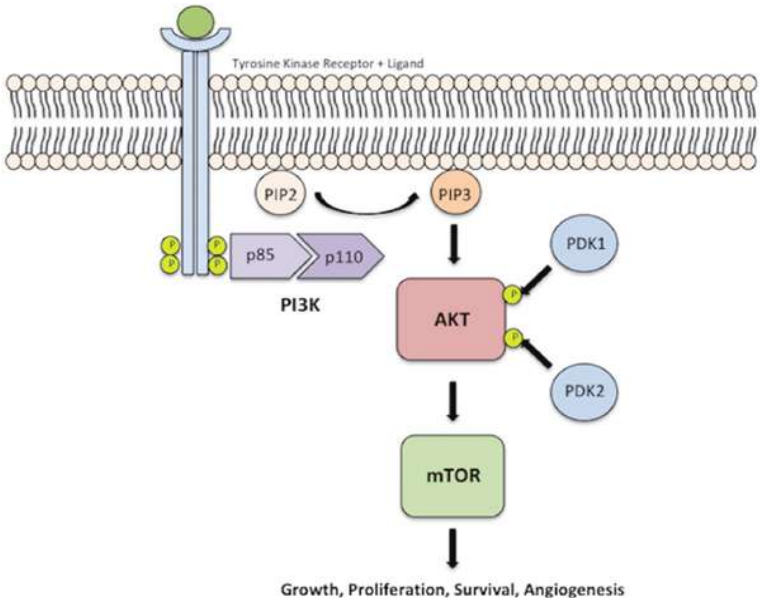
- Alpelisib
- Inavolisib

Available AKT Inhibitors

Endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative advanced or metastatic breast cancer

- Capivasertib

PI3K/AKT Mechanism of Action



- PI3K/AKT/mTOR pathway promotes cell survival and growth
- Pathway implicated in oncogenesis

1. Adimonye A., et al. *Oncotarget*. 2018.

Toxicities of PI3K/AKT Inhibitors

Breast Cancer PI3K/AKT Warnings/Precautions
• Hyperglycemia
• Rash/cutaneous reactions (alpelisib, capivasertib)
• Severe diarrhea
• Embryo-fetal toxicity
• Stomatitis (inavolisib)

Labeled warnings and management may vary based on product

1. Alpelisib [package insert].Revised January 2024. Accessed February 2, 2026.
2. Inavolisib. [package insert]. Revised December 2025. Accessed February 2, 2026.
3. Capivasertib. [package insert]. Revised November 2025. Accessed February 2, 2026.

Toxicities of PI3K & AKT Inhibitors

	Alpelisib SOLAR-1	Inavolisib INAVO120	Capivasertib CAPItello-291
Hyperglycemia	**Any grade: 64%** • **Grade ≥3: 37%**	Any grade: 48% • Grade ≥3: 4%	Any grade: 16% • Grade ≥3: 2%
Rash/cutaneous reactions	**Any grade: 54%** • **Grade ≥3: 20%**	Any grade: 25% • Grade ≥3: 0%	Any grade: 38% • Grade ≥3: 12%
Stomatitis/mucosal inflammation	Any grade: 18% • Grade ≥3: 2%	**Any grade: 51%** • **Grade ≥3: 6%**	Any grade: 15% • Grade ≥3: 2%
Diarrhea	Any grade: 58% • Grade ≥3: 7%	Any grade: 48% • Grade ≥3: 4%	**Any grade: 72%** • **Grade ≥3: 9%**

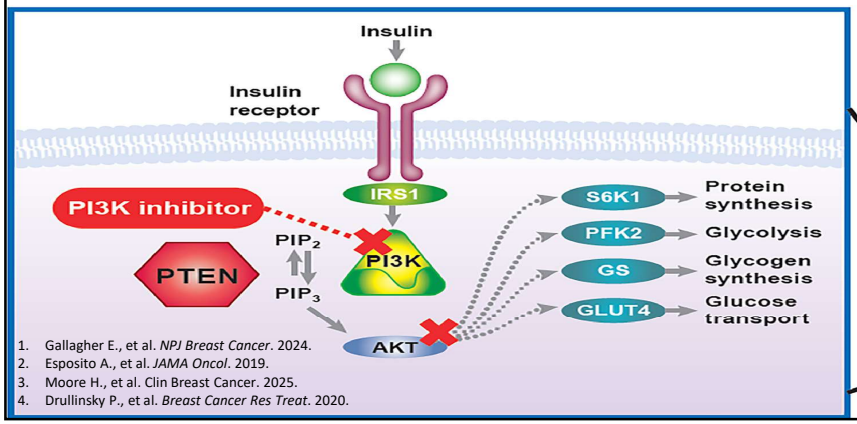
1. André F., et al. *N Engl J Med*. 2019.
2. Turner NC., et al. *N Engl J Med*. 2024.
3. Turner NC., et al. *N Engl J Med*. 2023.

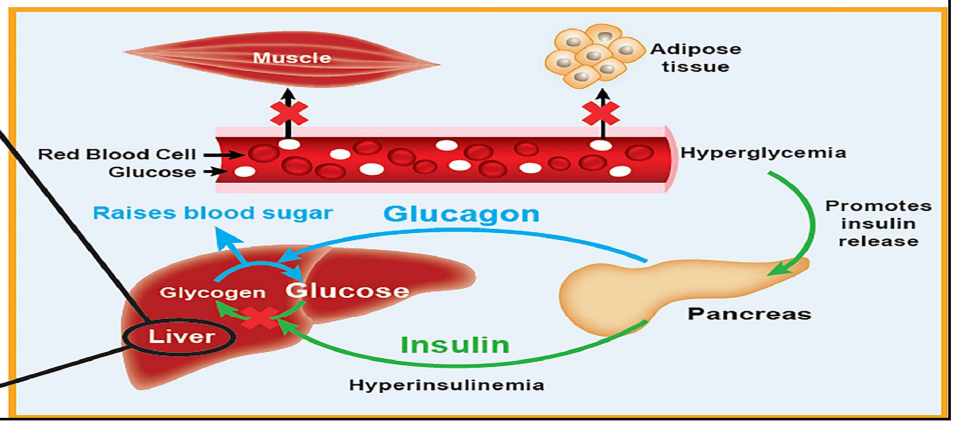
PI3K/AKT-Associated Hyperglycemia

Mechanism:

- Insulin activates the PI3K pathway to lower blood glucose (BG)
  - PI3K pathway stimulates glucose uptake in muscle and adipose tissue
  - PI3K suppresses hepatic glucose production
- PI3K inhibitors block these pathways → increased blood glucose
- AKT inhibitors act further downstream in the pathway and are therefore associated with less hyperglycemia. The difference likely because PI3K-α acts upstream in insulin signaling and more strongly regulates hepatic glucose production

- **Onset:** typically occurs within first month of treatment
- **Risk Factors:**
  - ≥70 years old
  - Body mass index (BMI) ≥ 30 kg/m2
  - Baseline HbA1c of 5.7–6.4% or fasting glucose levels between 100-125 mg/dL
  - Pre-existing type 2 diabetes mellitus





1. Gallagher E., et al. *NPJ Breast Cancer*. 2024.
2. Esposito A., et al. *JAMA Oncol*. 2019.
3. Moore H., et al. Clin Breast Cancer. 2025.
4. Drullinsky P., et al. *Breast Cancer Res Treat*. 2020.

PI3K/AKT-Associated Hyperglycemia Management

- **Metformin** is the preferred first-line anti-hyperglycemic agent
- It is recommended to initiate prophylactic metformin in patients with baseline HbA1c of 5.7-6.4%
- Diet: limit carbohydrate to 60-130g/day with regular exercise
- Endocrinology evaluation for patients with risk factors or pre-existing diabetes

BG Monitoring:

- Frequency of BG monitoring is should be based on baseline risk of hyperglycemia
- More frequent monitoring for those at higher risk

Recommended Alternatives to Metformin

- **Thiazolidinediones (TZDs)**
- **Sodium glucose co-transporter 2 inhibitors (SGLT2i)**
- **Dipeptidyl peptidase-4 inhibitors (DPP4i)**

1. Gallagher E., et al. *NPJ Breast Cancer*. 2024.
2. Esposito A., et al. *JAMA Oncol*. 2019.
3. Moore H., et al. *Clin Breast Cancer*. 2025.

Rash/Cutaneous Reactions Management

Onset: typically occurs within first 2 months of treatment

Management Strategies:

- Consider prophylactic non-sedating (H1) antihistamines for patients starting PI3K therapy

Initial management for rash:

- Non-sedating (H1) antihistamines
  - Doses may be escalated based on response
- Topical steroids (Class I-III)
  - Selection based on affected body part and affected BSA
- Oral corticosteroids is recommended in patients with rash affecting ≥ 10% BSA
- Consider consult to a dermatologist

Recommended Non-Sedating Antihistamines

- **Cetirizine 10 mg**
- **Levocetirizine 5 mg**
- **Loratadine 10 mg**
- **Fexofenadine 180 mg**

Recommended Topical Steroids

- **Fluocinonide 0.1%**
- **Triamcinolone acetonide 0.5%**
- **Betamethasone dipropionate 0.05%**

1. Gallagher E., et al. *NPJ Breast Cancer*. 2024.
2. Esposito A., et al. *JAMA Oncol*. 2019.

Stomatitis/Mucosal Inflammation Management

Onset: typically occurs within first month of treatment

Management:

- Corticosteroid-containing mouthwash for prophylaxis or treatment
  - Dexamethasone 0.5mg/5mL oral rinse: swish and spit 10mL four times daily
  - Avoid alcohol, hydrogen peroxide, iodine, or thyme containing products and harsh mouth washes (e.g., Listerine)

Supportive care:

- Dietary modifications
  - Avoid crunchy, spicy, acidic, and hot food/drinks
- Topical steroids (Class II-VI)
  - Selection based on severity

Recommended Topical Steroids

- **Triamcinolone acetonide 0.05-0.5%**
- **Fluocinolone acetonide 0.025-0.05%**
- **Clobetasol propionate 0.025%**

1. Turner NC., et al. *N Engl J Med*. 2024.
2. Inavolisib Safety Guide. Published 2025.
3. NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities (Version 1.2026).

Diarrhea Management

- **Onset**: typically occurs within first month of treatment

Management:

- Antidiarrheal treatment (loperamide, diphenoxylate/atropine)

Supportive care:

- Dietary modifications
    - Discontinue lactose-containing products and eat small meals
- Hydration
    - Encourage adequate hydration with salt-containing liquids such as broths or sports drinks
- Electrolyte supplementation

1. Inavolisib. [package insert]. Revised December 2025. Accessed February 2, 2026.
2. NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities (Version 1.2026).
3. NCCN Guidelines for Palliative Care (Version 1.2026).

Dose Adjustments for Toxicities of PI3K & AKT Inhibitors

CTCAE v5.0	Hyperglycemia	Rash/Cutaneous Reaction	Stomatitis/Mucosal Inflammation	Diarrhea
Grade 1	**No dosage adjustment** • Consider initiating oral anti-hyperglycemic medication • Consider endocrinology consultation	**No dosage adjustment** • Initiate topical corticosteroid treatment • Consider addition of oral antihistamine	**No dosage adjustment** • Initiate corticosteroid-containing mouthwash (e.g., dexamethasone oral rinse)	**No dosage adjustment** • Initiate antidiarrheal medications (e.g., loperamide) • Supportive care (diet, hydration, and electrolyte supplementation)
Grade 2	**Hold treatment** until FPG ≤ 160mg/dL, then **resume at same dose** ***Alpelisib: no hold required** • Initiate or intensify oral anti-hyperglycemic medication • If prolonged FPG > 160mg/dL (>21-28 days), consider resuming at one lower dose level	**Hold treatment** until recovery to grade ≤ 1, then **resume at same dose** • Initiate or intensify topical corticosteroid and oral antihistamine treatment • Consider low dose systemic corticosteroid treatment	**Hold treatment** until recovery to grade ≤ 1, then **resume at same dose** • Initiate or intensify appropriate treatment • If recurrence or prolonged recovery (>28 days), may resume at one lower dose level	**Hold treatment** until recovery to grade ≤ 1, then **resume at same dose** • Initiate or intensify appropriate treatment • If recurrence or prolonged recovery (>28 days), may resume at one lower dose level
Grade 3	**Hold treatment** until recovery to grade ≤ 1, then **resume at one lower dose level** • Initiate or intensify diabetic medications and treat any electrolyte abnormalities • Consider rescue insulin for 1-2 days • If FPG > 500, consider permanent discontinuation	**Hold treatment** until recovery to grade ≤ 1, then **resume at one lower dose level** • If recurrence, consider permanent discontinuation	**Hold treatment** until recovery to grade ≤ 1, then **resume at one lower dose level**. • If prolonged recovery (>28 days), consider permanent discontinuation	**Hold treatment** until recovery to grade ≤ 1, then **resume at same or one lower dose level**. • If prolonged recovery (>28 days), consider permanent discontinuation
Grade 4	Permanently discontinue treatment			

CTCAE: Common Terminology Criteria for Adverse Events; **FPG**: fasting plasma glucose

*For specific dose adjustment, please refer to medication package information

CITY OF HOPE

1. Alpelisib [package insert].Revised January 2024. Accessed February 2, 2026.
2. Inavolisib. [package insert]. Revised December 2025. Accessed February 2, 2026.
3. Capivasertib. [package insert]. Revised November 2025. Accessed February 2, 2026.
4. Esposito A., et al. *JAMA Oncol*. 2019.

References

1. Gallagher EJ, Moore H, Lacouture ME, et al. Managing hyperglycemia and rash associated with alpelisib: expert consensus recommendations using the Delphi technique. *NPJ Breast Cancer*. 2024;10(1):12. Published 2024 Jan 31. doi:10.1038/s41523-024-00613-x

2. Adimonye A, Stankiewicz E, Kudahetti S, et al. Analysis of the PI3K-AKT-mTOR pathway in penile cancer: evaluation of a therapeutically targetable pathway. Oncotarget. 2018;9(22):16074-16086. Published 2018 Mar 23. doi:10.18632/oncotarget.24688

3. Drullinsky, P.R., Hurvitz, S.A. Mechanistic basis for PI3K inhibitor antitumor activity and adverse reactions in advanced breast cancer. Breast Cancer Res Treat 181, 233–248 (2020).

4. Esposito A, Viale G, Curigliano G. Safety, Tolerability, and Management of Toxic Effects of Phosphatidylinositol 3-Kinase Inhibitor Treatment in Patients With Cancer: A Review. *JAMA Oncol*. 2019;5(9):1347-1354. doi:10.1001/jamaoncol.2019.0034

5. Moore HN, Goncalves MD, Johnston AM, et al. Effective Strategies for the Prevention and Mitigation of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia: Optimizing Patient Care. *Clin Breast Cancer*. 2025;25(1):1-11. doi:10.1016/j.clbc.2024.09.017

6. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2019;380(20):1929-1940. doi:10.1056/NEJMoa1813904

7. Turner NC, Im SA, Saura C, et al. Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer. *N Engl J Med*. 2024;391(17):1584-1596. doi:10.1056/NEJMoa2404625

8. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2023;388(22):2058-2070. doi:10.1056/NEJMoa2214131

9. Inavolisib Safety Guide. Published 2025. Accessed January 14, 2026. https://bit.ly/4tfyS1G.

10. Alpelisib [package insert].Revised January 2024. Accessed February 2, 2026.

11. Inavolisib. [package insert]. Revised December 2025. Accessed February 2, 2026.

12. Capivasertib. [package insert]. Revised November 2025. Accessed February 2, 2026.

13. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Management of Immune Checkpoint Inhibitor-Related Toxicities (Version 1.2026) © National Comprehensive Cancer Network, Inc. Available at www.NCCN.org/guidelines.

14. NCCN Guidelines® for Palliative Care (Version 1.2026). © National Comprehensive Cancer Network, Inc. Available at www.NCCN.org/guidelines.

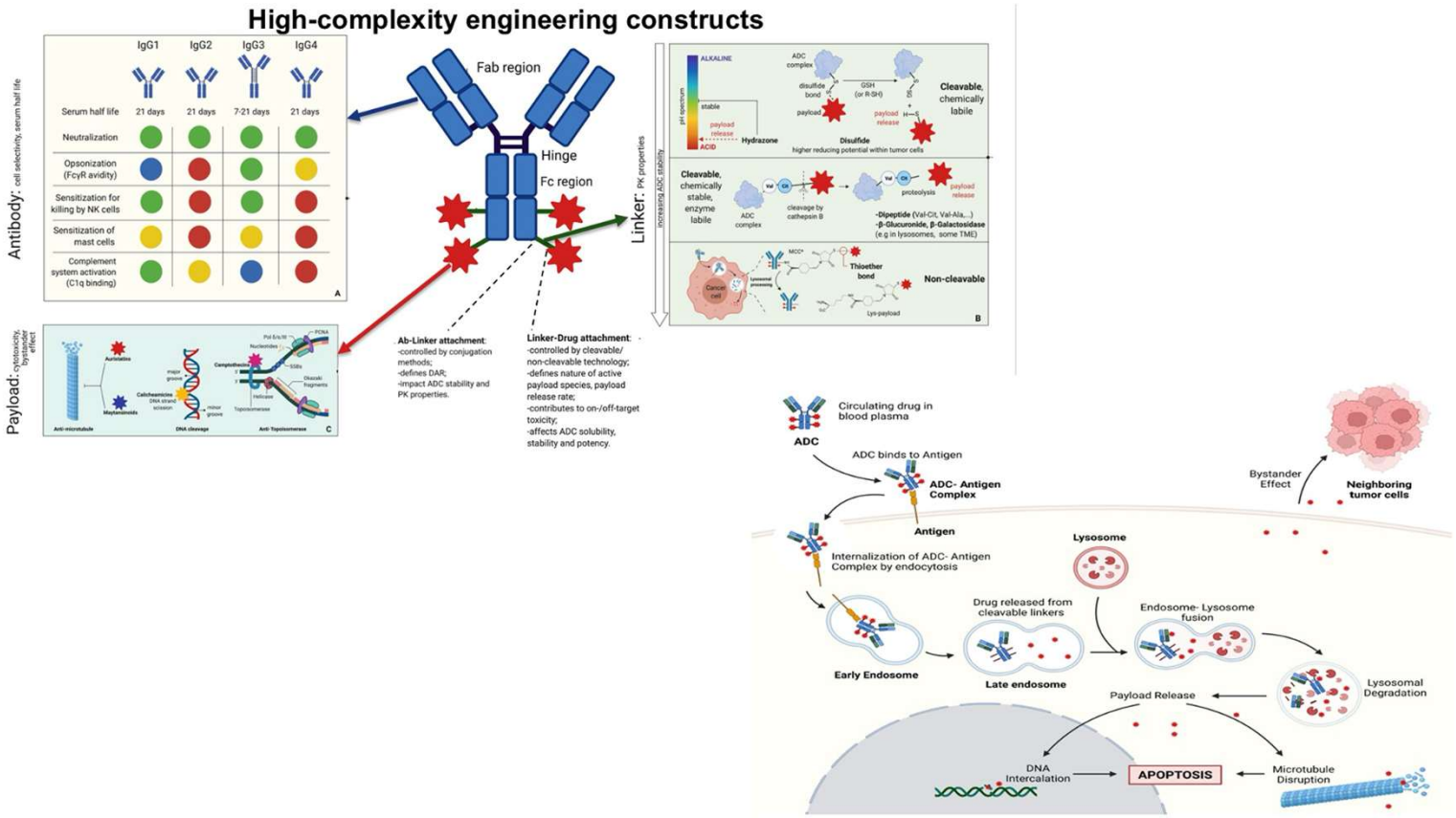
15. National Cancer Institute. Common Terminology Criteria for Adverse Events, Version 5.0.

NCCN 2026 Breast Cancer Congress

Treating Toxicities of Antibody Drug Conjugates

Irene Kang, MD

Medical Director of Women's Health Oncology
Assistant Professor of Medical Oncology and Therapeutics Research
City of Hope Orange County



Larose et al. Cancer Drug Resist. 2025.

Antibody Drug Conjugates in Advanced Breast Cancer

	Trastuzumab deruxtecan[1,2]	Datopotamab deruxtecan[4,5]	Sacituzumab govitecan[1,7]
Target antigen	HER2	TROP-2	TROP-2
Indication	HER2+ mBC; HER2-low and HER2-ultralow mBC	Unresectable or metastatic, HR+, HER2-BC (HER2-ultralow, HER2-low, IHC 0)	Unresectable locally advanced or mTNBC; Unresectable locally advanced or metastatic HR+, HER2- BC (HER2-ultralow, HER2-low, IHC 0)
Type of mAb	Humanized IgG1	Humanized IgG1	Humanized IgG1
Payload	Topoisomerase I inhibitor[a]	Topoisomerase I inhibitor[a]	Topoisomerase I inhibitor (SN-38)[b]
Approx. DAR	8:1	4:1	7.6:1
Linker cleavage	Yes (protease-cleavable)	Yes (protease-cleavable)	Yes (hydrolysable)
Median half-life	5.5 days	4.8 days	23.4 hours
Bystander effect	Yes[3]	Yes[6]	Yes[8]
Dosing	IV q3w	IV q3w	IV Day 1, 8 of 3-wk cycle

a Exatecan derivative. b Irinotecan derivative.9
BC, breast cancer; DAR, drug-to-antibody ratio; Dato-DXd, datopotamab deruxtecan; DM1, mertansine; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IC, investigator's choice of treatment; ICC, investigator's choice of chemotherapy; IgG, immunoglobulin G; IV, intravenous; mAb, monoclonal antibody; mBC, metastatic breast cancer; mTNBC, metastatic triple negative breast cancer; q3w, every 3 weeks; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; TNBC, triple-negative breast cancer; TROP-2, trophoblast cell surface antigen-2; TB; TROPION-Breast; tx, treatment.

Ref: Matsuda Y, et al. *Chem Pharm Bull.* 2021; Enhertu. Package insert. Daiichi Sankyo, Inc.; 2025. Okajima D, et al. *Mol Cancer Ther.* 2021
Datroway. Package insert. Daiichi Sankyo, Inc.; 2025. Trodelvy. Package insert. Gilead Sciences, Inc.; 2024

Trastuzumab deruxtecan (T-DXd)

CITY OF HOPE

Trastuzumab deruxtecan

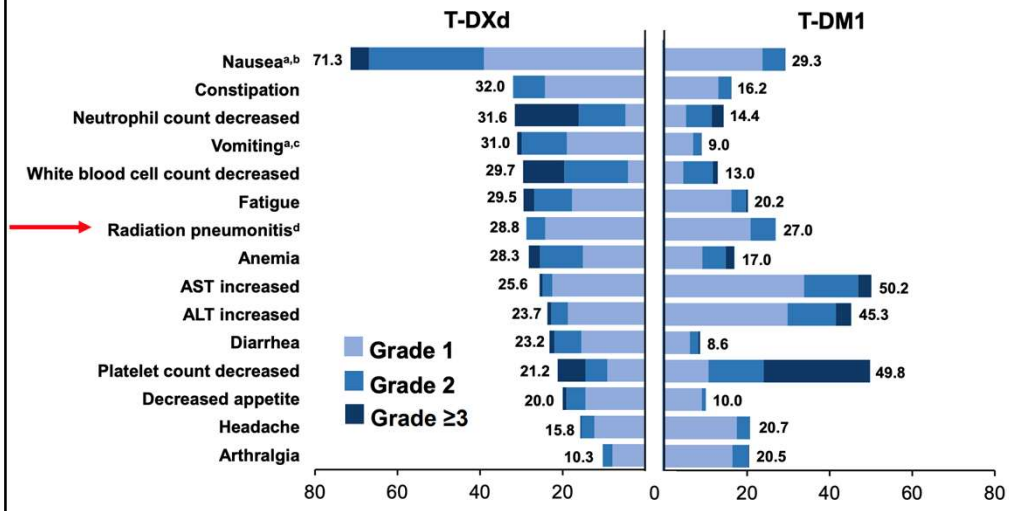
Disease State	Indication (registration trials)
HER2+	Metastatic: First line and later (DB-09, DB-03) Post-Neoadjuvant High-Risk (DB-05)
HR+ HER2- (low and Ultra-low)	Metastatic: First line chemotherapy (DB-06)
HR+ and HR- HER2 (low)	Metastatic: later line chemotherapy (DB-04)

DB= Destiny-Breast

Interim Analysis of DESTINY-Breast05 : Safety

	T-DXd (n=806)	T-DM1 (n=801)
Grade ≥3 TEAEs, n (%)	408 (50.6)	416 (51.9)
Serious TEAEs	140 (17.4)	109 (13.6)
TEAEs associated with discontinuation	144 (17.9)	103 (12.9)
TEAEs associated with drug interruptions	400 (49.6)	329 (41.1)
TEAEs associated with deaths*	3 (0.4)	5 (0.6)
Treatment-related deaths	2 (0.2)	1 (0.1)
Median treatment duration (months)	9.8	9.7
Patients completed 14 cycles (%)	72.3	76.3
ILD (adjudicated), n (%)	77(9.6)	13 (1.6)
grade ≥3 ILD	9 (1.1)	0 (0)
grade 5 ILD	2 (0.3%)	0 (0)
LV dysfunction	23 (2.9)	14 (1.7)

Treatment-Emergent Adverse Events (TEAEs) in ≥20% of Patients



Safety Overview		T-DXd (n=806)[a]	T-DM1 (n=801)[a]
Overall TEAEs	Any grade	802 (99.5)	788 (98.4)
	Grade ≥3	408 (50.6)	416 (51.9)
	Serious	140 (17.4)	109 (13.6)
	Associated with drug d/c	144 (17.9)	103 (12.9)
	Associated with deaths	3 (0.4)	5 (0.6)
Adjudicated Drug-related ILD[b]	Any grade	77 (9.6)	13 (1.6)
	Grade 1	16 (2.0)	8 (1.0)
	Grade 2	52 (6.5)	5 (0.6)
	Grade 3	7 (0.9)	0
	Grade ≥4	2 (0.2)[c]	0
LV Dysfunction	Any grade	23 (2.9)	14 (1.7)
	Grade 1	1 (0.1)	0
	Grade 2	20 (2.5)	11 (1.4)
	Grade 3	2 (0.2)	3 (0.4)
	Grade ≥4	0	0

[a] Prophylactic antiemetics were recommended but not mandatory. [b] In the T-DXd and T-DM1 arms: 39.1% and 23.7% grade 1, 27.8% and 5.5% grade 2, and 4.5% and 0.1% grade 3 events, respectively. [c] In the T-DXd and T-DM1 arms: 19.0% and 6.9% grade 1, 10.9% and 2.0% grade 2, and 1.1% and 0.1% grade 3 events, respectively. [d] In the T-DXd and T-DM1 arms: 24.2% and 20.8% grade 1 and 4.6% and 6.1% grade 2 events, Geyer CE, et al. ESMO 2025. Abstract LBA1.

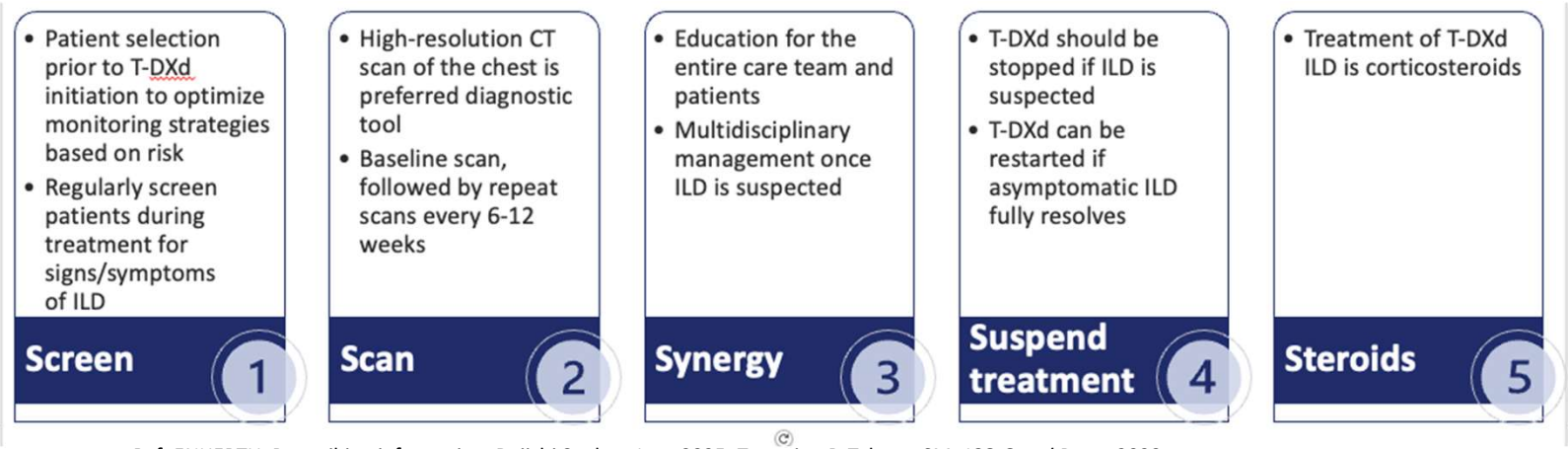
T-DXd AE management

- Nausea: NCCN Guidelines for Antiemesis (highly emetogenic category)
  - 5-HT3 antagonist (Palonosetron)
  - Dexamethasone
  - NK1 antagonist (Aprepitant)
  - and/or Olanzapine
- Fatigue: NCCN Guidelines Cancer-Related Fatigue
  - Physical activity, massage, CBT, educational therapies (Category 1)

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Antiemesis (Version 2.2025).; NCCN Guidelines® for Cancer-Related Fatigue (Version 1.2026).

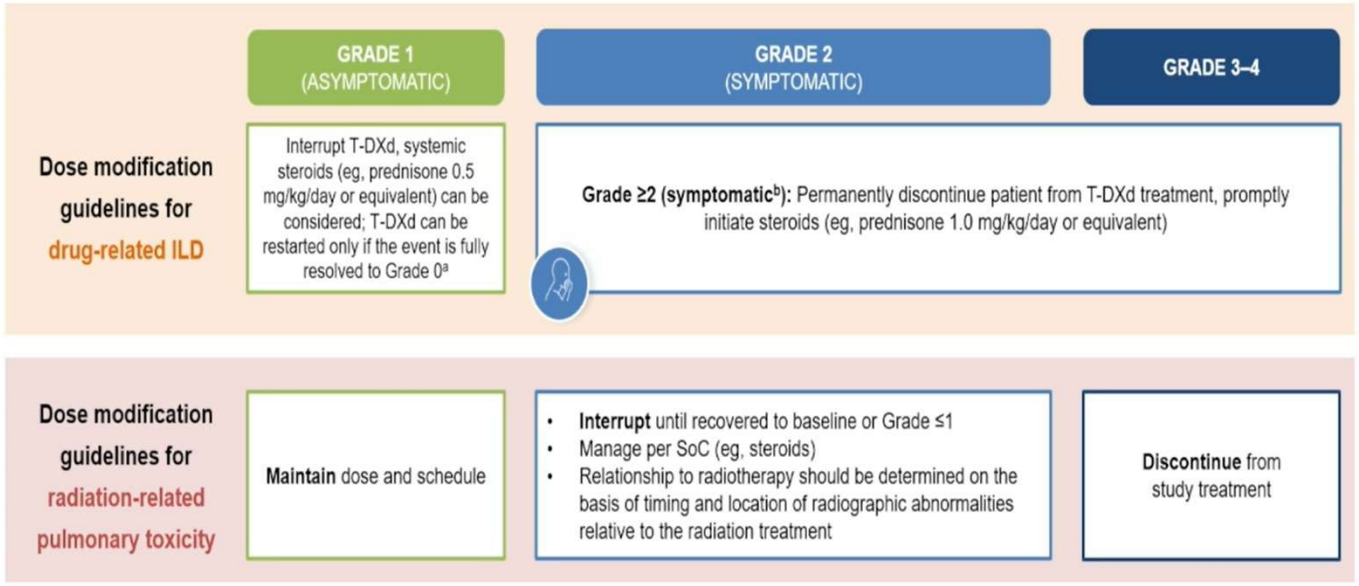
T-DXd and ILD

- 12% all patients (majority grade 1 or 2); <1% fatality
- CT scan: HRCT scan every 9-12 weeks. More frequently for those with respiratory symptoms
  Postneoadjuvant high risk (DB-05): baseline; after radiation (if sequential) and prior to cycles 3, 7, and 11 and at 40 days follow up
- 5 S's



Ref: ENHERTU. Prescribing information. Daiichi Sankyo, Inc.; 2025; Tarantino P, Tolaney SM. *JCO Oncol Pract*. 2023; Rugo et al. *JCO Oncol Pract* 2023; Loibl et al. NEJM 2025

Management for ILD in DB-05 (adjuvant T-DXd)



ILD, interstitial lung disease; SoC, standard of care; T-DXd, trastuzumab deruxtecan.
[a]If resolved in ≤28 days from day of onset, maintain dose. If resolved in >28 days from day of onset, reduce dose 1 level. However, if the event grade 1 ILD/pneumonitis has not resolved within 126 days from the last infusion, T-DXd should be discontinued. [b]Develops an acute onset of new/worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever.
Clinical Study Protocol. DESTINY-Breast05. Protocol DS8201-A-U305. Version 3.0, 22 Nov 2020.

DESTINY-Breast05

Loibl et al. RF6-01 SABCS 2025

Trop-2 targeted Antibody-drug conjugates (ADC's)

Sacituzumab govitecan
Datopotamab deruxtecan

CITY OF HOPE

Trop-2 ADC Indications

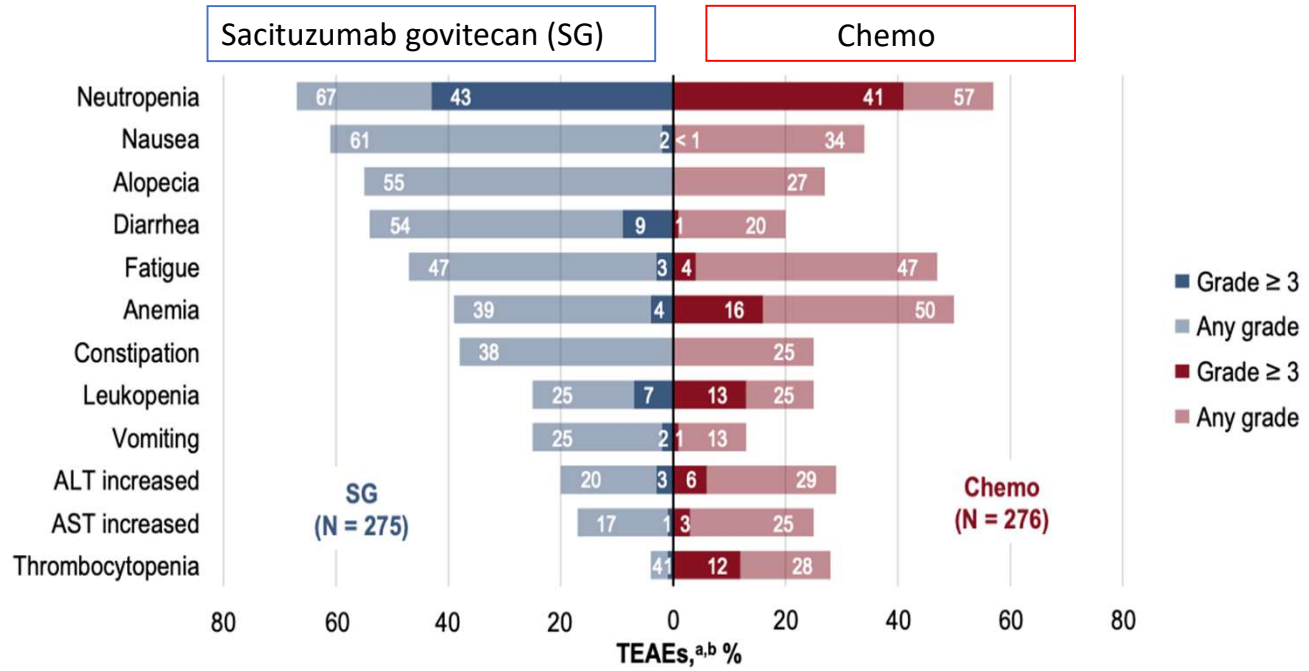
	Sacituzumab govitecan	Datopotamab deruxtecan
Metastatic HR+HER2- after endocrine therapy	2 prior lines chemotherapy: TROPiCS-02	Second line or later: TROPION-Breast01
Metastatic TNBC PD-L1+	First line: ASCENT-04	
Metastatic TNBC PD-L1- or ICI ineligible	First line: ASCENT-03 Later line: ASCENT	First line: TROPION-Breast02

TROP2 ADC Toxicity Profile in 1L TNBC

	Sacituzumab govitecan (Cortés, ESMO 2025)		Datopotamab deruxtecan (Dent, ESMO 2025)	
	TEAEs		TRAEs	
Adverse Event	Any grade (%)	Grade ≥3 (%)	Any grade (%)	Grade ≥3 (%)
Any AE[a]	99	66	93	33
Neutropenia	67	43	12	3
Anemia	39	4	15	2
Nausea	61	2	45	<1
Vomiting	25	2	20	1
Diarrhea	54	9	-	-
Fatigue	47	3	32	3
Alopecia	55	N/A	41	N/A
Oral mucositis/stomatitis	-	-	60	8
Any ocular surface toxicity	-	-	47	7
Dry eye	-	-	24	1
Keratitis	-	-	13	2
Conjunctivitis	-	-	7	<1
ILD/pneumonitis	-	-	3	<1*

Garrido-Castro ESMO 2025

ASCENT-03: Most Common AE's (≥20% in any group)



Data cutoff date: April 2, 2025.

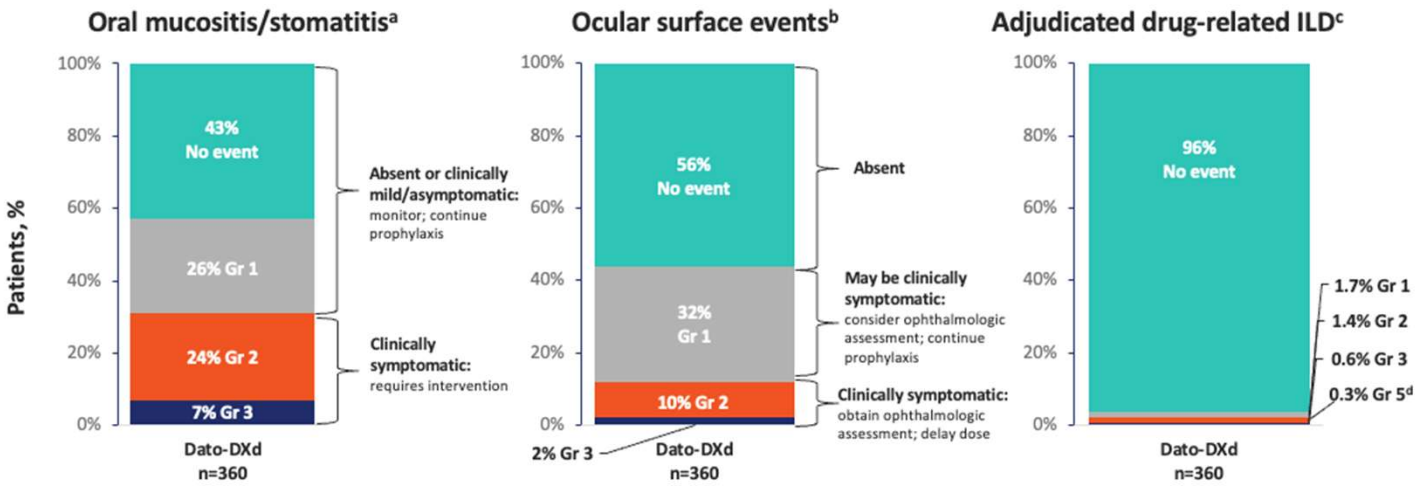
[a] TEAEs were included if they occurred in ≥20% of patients in either group. [b] Combined preferred terms of neutropenia includes neutrophil count decreased, fatigue includes asthenia, anemia includes hemoglobin decreased and red blood cell count decreased, leukopenia includes white blood cell count decreased, and thrombocytopenia includes platelet count decreased.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; chemo, chemotherapy; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.
Cortés J, et al. Presented at: 2025 European Society for Medical Oncology (ESMO); October 17-21, 2025; Berlin Germany.

Sacituzumab govitecan

- **Nausea**
  - High emetogenic risk
  - Premedicate: Dexamethasone + 5-HT3 receptor antagonist or NK1 receptor antagonist
- **Other premedications**:
  - History of infusion reaction: antipyretic, H1/H2 blockers, corticosteroid
  - History of cholinergic reaction: Atropine
- **Neutropenia:**
  - Intermediate risk by NCCN Guidelines
  - Primary prophylaxis for patients with risk factors
    - Prior chemotherapy or neutropenia, older patients, organ dysfunction, poor PFS

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Antiemesis (Version 2.2025).; NCCN Guidelines® Hematopoietic Growth Favtors (V3.2026).
© 2026 National Comprehensive Cancer Network, Inc. Available at www.NCCN.org/guidelines. Trodelvy. Prescribing information. Gilead Sciences Inc; 2025

Datopotamab-DXd (Dato-DXd) AEs of special interest



- Mucositis/stomatitis events 86% resolved/resolving
- Ocular surface events were mostly dry eye; 86% gr 3 events resolved/resolving
- Adjudicated drug-related ILD <4% of patients

Pistilli B. et al. ESMO 2025

Prevention and management of toxicities with datopotamab-deruxtecan

LUNG PROBLEMS

- Monitor for cough or shortness of breath

EYE PROBLEMS

- Baseline optometry/ ophthalmologic exam
- Do not wear contact lenses
- Preservative-free lubricating eye drops 4x per day

MOUTH ULCERS & SORES

- Steroid mouthwash 4x per day
- Ice chips (consider)

NAUSEA & VOMITING

- High emetic risk
- Olanzapine
- NK1 receptor antagonist
- 5-HT3 receptor antagonist
- Dexamethasone

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Antiemesis (Version 2.2025).;.

Clinical Cases

CITY OF HOPE

Case 1

- 45-year-old woman with metastatic HER2+ breast cancer receives trastuzumab deruxtecan + pertuzumab for first line therapy.
  - How often do you plan to monitor for ILD and with what imaging modality?
  - Can you differentiate between infectious findings and drug-induced ILD?

Case 2

- 72-year-old female with HR+ HER2- (ultralow) metastatic invasive lobular carcinoma involving the bones only.
- She initiated treatment in 2019 with letrozole and ribociclib and progressed 6 years later in 2025 with new lesions in the bone, lymph nodes and pulmonary nodules.
- Initial tumor NGS testing revealed a PIK3CA mutation.
  ctDNA testing at progression demonstrated PIK3CA mutation and was negative for ESR1
- She is started on fulvestrant + capivasertib.
- Her A1c is 5.5 and she is on amlodipine for hypertension only.
- Do you initiate any prophylactic measures?

Case 2 Continued

- 4 weeks into starting fulvestrant + capivasertib she develops a pruritic macular papular rash on her trunk, arms, legs.
- How would you manage this rash?
- The rash resolves in 3 weeks: would you resume capivasertib and if so, at what dose?
- What kind of prophylaxis would you pursue once resuming capivasertib?

Case 3

- A 35-year-old woman with cT2N1 triple negative breast cancer of the left breast is on weekly paclitaxel, carboplatin and pembrolizumab with plan to continue to doxorubicin, cyclophosphamide and pembrolizumab after 4 cycles.
- On her C1D15 her AST/ALT are elevated to 125 and 145 respectively (>3x ULN). Bilirubin is normal.
- For her Grade 2 elevation of AST/ALT how would you manage her care?

National Comprehensive Cancer Network®

NCCN Member Institutions

Who We Are

An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To define and advance quality, effective, equitable, and accessible cancer care and prevention so all people can live better lives

Our Vision

Access to high-quality, high-value, patient-centered cancer care for all people globally

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal