Antibody Drug Conjugate (ADC) nel carcinoma mammario

Tossicità: diagnosi, prevenzione, gestione

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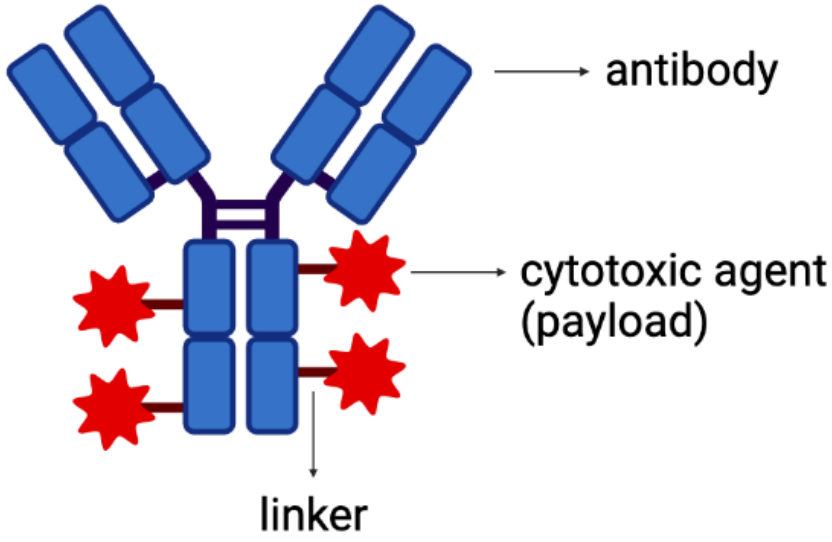
Disclosures

Travel support: Eli Lilly

ADC toxicities

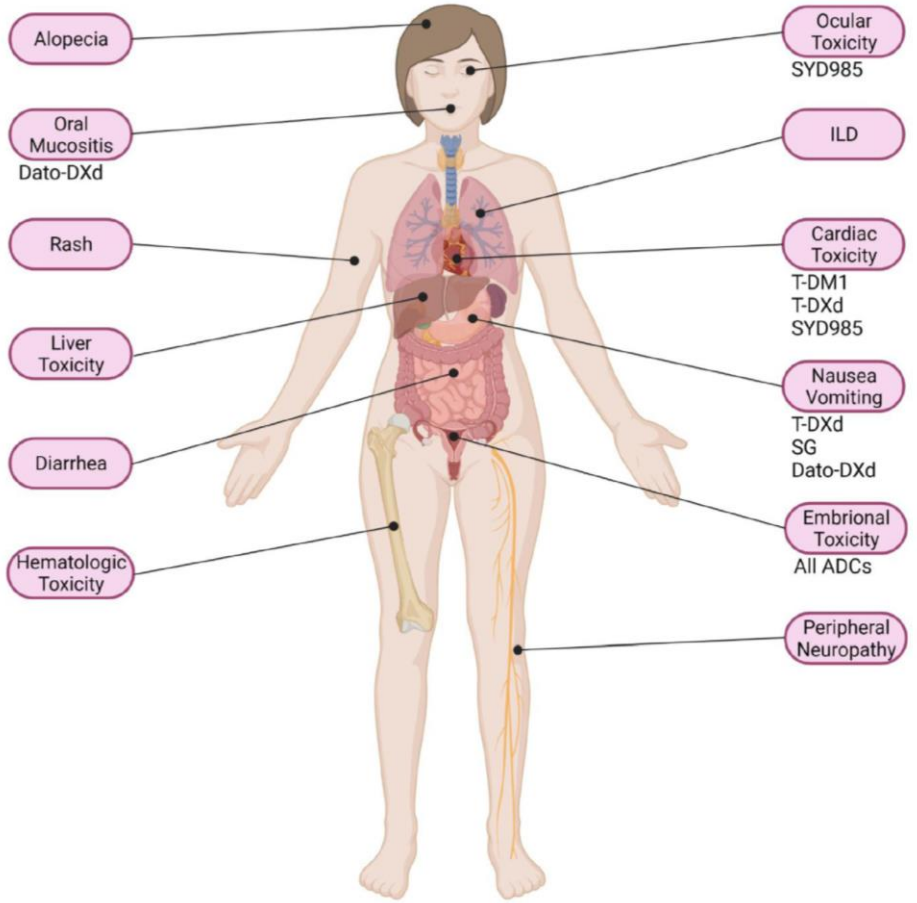
- Dose-limiting toxicities on normal tissues have represented a major obstacle to the use of cytostatic drugs
- ADCs were developed with the ultimate goal of improving the therapeutic index of conventional chemotherapies
- ADCs were designed for targeted delivery of cytotoxic molecules to cancer cells expressing a tumour-associated antigen targeted by the antibody component



ADC toxicities

- A meta-analysis of 169 trials including different tumor types reported an overall incidence of AEs of 91.2% (grade ≥3 for 46.1%)

- Different potential mechanisms:
  - *Off-target, off-tumor*, unrelated to the antigen targeted by the antibody, due to premature payload detachment
  - *On-target, off-tumor*, due to non-malignant tissues expressing the ADC target
  - Interactions of ADC's Fc domain with FcγRs on immune cells or other non-malignant cells



Zhu Y et al, Cancer 2023; D'Arienzo et al, eClinicalMedicine 2023

Nausea and vomiting

- T-DXd has the most emetogenic potential with (most common G3 AEs and most common cause of dose reduction)

Day 1		Day 2 – 3
DMX 12 mg PO/IV	*Ondansetron* - 16 – 24 mg OS - 8 – 16 mg IV	*Ondansetron* **OR** *DMX* 8 mg PO/IV - 16 mg OS - 8 – 16 mg IV
	Dolasetron 100 mg PO	*Dolasetron* 100 mg PO
	Granisetron - 2 mg PO - 0,01 mg/kg IV (MAX 1 mg)	*Granisetron* - 2 mg PO - 0,01 mg/kg IV (MAX 1 mg)
	Granisetron - 10 mg SQ (best) - 3,1 mg/24 h TD (24 – 48 h before infusion)	
	Palonosetron 0,25 mg IV (preferred in 2-drug regimen)	

Day 1			Day 2 – 3
DMX 12 mg PO/IV	*5-HT3 RA*	*Aprepitant* 125 mg PO	*Aprepitant* 80 mg PO +/- *DMX* 8 mg PO/IV
	5-HT3 RA	*Fosaprepitant* 150 mg IV	
	Palonosetron 0,5 mg OS	*Netupitant* 300 mg OS	
	Palonosetron 0,25 mg IV	*Fosnetupitant* 235 mg IV	

- HER3-DXd, Dato-DXd, and SG are moderate emetogenic agents

NAUSEA		
T-DXd	DB03	73%
	DB04	73%
SG	Ascent	57%
	Tropics02	55%
Dato-Dxd	TROPION-B	51%

VOMITING		
T-DXd	DB03	44%
	DB04	34%
SG	Ascent	29%
	Tropics02	19%
Dato-Dxd	TROPION-B	20%

Risk of first event of nausea and vomiting is higher in earlier cycles

D'Arienzo et al, eClinicalMedicine 2023

Diarrhea

- Diarrhea is a toxicity of topoisomerase I inhibitors (*off-target off-tumor* toxicity)
- Incidence of approximately 12-30% of any grade and about 1-3% of grade ≥3
- Early-onset diarrhea (cholinergic response): atropine administration (consider prevention)
- Late-onset diarrhea (gut mucositis, secretions, microbiota impairment): loperamide
- Soft diet with adequate fluid intake
- Dose reduction for ≥G3 events

DIARRHEA		
T-DXd	DB03	23.7%
	DB04	22.4%
SG	Ascent	59%
	Tropics02	57%
Dato-Dxd	TROPION-B	NR

≥G3 DIARRHEA		
T-DXd	DB03	<1%
	DB04	1.1%
SG	Ascent	10%
	Tropics02	9%
Dato-Dxd	TROPION-B	NR

Hematological toxicities

- Topoisomerase inhibiting payloads lead to DNA double-strand breaks and apoptosis of rapidly proliferating cells, including hematopoietic cell progenitors

- In case of neutropenia, G-CSF prophylaxis (for instance 2-3 days of a short acting growth factor) may be given

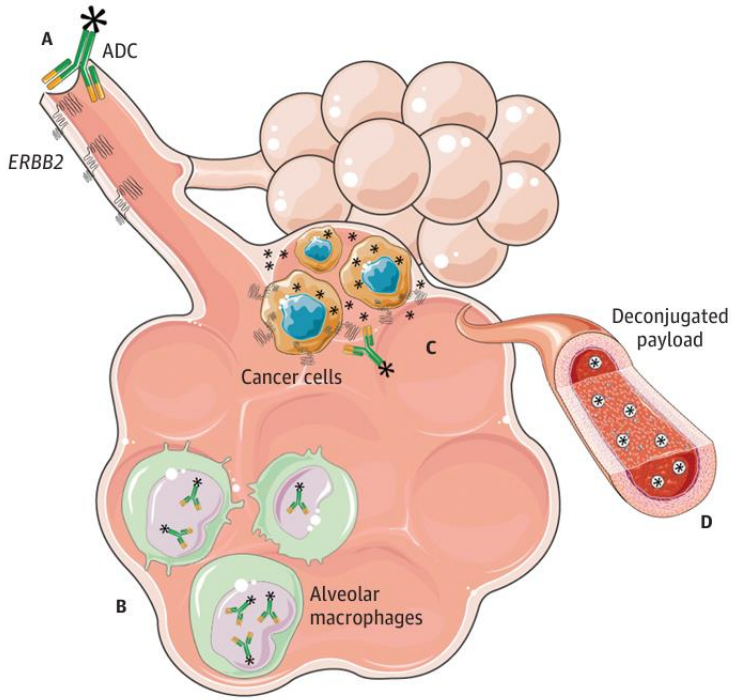
Neutropenia Severity	Occurrence	Dose Modification
Grade 4 neutropenia ≥7 days OR Grade 3 febrile neutropenia (ie ANC<1000/mm^3 and fever ≥38.5°C) OR At time of scheduled treatment, grade 3-4 neutropenia that delays dosing by 2-3 weeks for recovery to ≤grade 1	First	Administer granulocyte-colony stimulating factor (GCSF)
	Second	25% dose reduction
	Third	50% dose reduction
	Fourth	Discontinue treatment

NEUTROPENIA		
T-DXd	DB03	42.8%
	DB04	33.2%
SG	Ascent	63%
	Tropics02	70%
Dato-Dxd	TROPION-B	11%

FEBRILE NEUTROPENIA		
T-DXd	DB03	<1%
	DB04	<1%
SG	Ascent	6%
	Tropics02	5%
Dato-Dxd	TROPION-B	1%

ILD

- Interstitial lung disease (ILD) is a life-threatening side effect associated to T-DXd
- The most common TEAE associated with treatment discontinuation of T-DXd (8.2% in DESTINY-Breast03)
- ILD is a large, heterogeneous group of lung disorders that manifests as inflammation and/or fibrosis mainly in the interstitium of the lungs



ILD		
T-DXd	DB03	10.5%
	DB04	12.1%
SG	Ascent	0%
	Tropics02	0%
Dato-Dxd	TROPION-B	3%

≥G3 ILD		
T-DXd	DB03	0.8%
	DB04	1.3%
SG	Ascent	0%
	Tropics02	0%
Dato-Dxd	TROPION-B	1%

Tarantino P et al, JAMA Oncol 2021

ILD - pooled analysis

	N = 1150
Age, median (range), years	60.0 (20-96)
≥ 65 years, n (%)	396 (34.4)
Female, n (%)	755 (65.7)
Japanese, n (%)	506 (44.0)
ECOG PS, n (%)	
0	583 (50.7)
1 / 2	565 (49.1) / 2 (0.2)
Tumor type, n (%)[a]	
Breast cancer	510 (44.3)
Gastric cancer	294 (25.6)
Lung cancer	203 (17.7)
Colorectal cancer	107 (9.3)
Other	34 (3.0)
Lung comorbidities, n (%)[b]	81 (7.0)

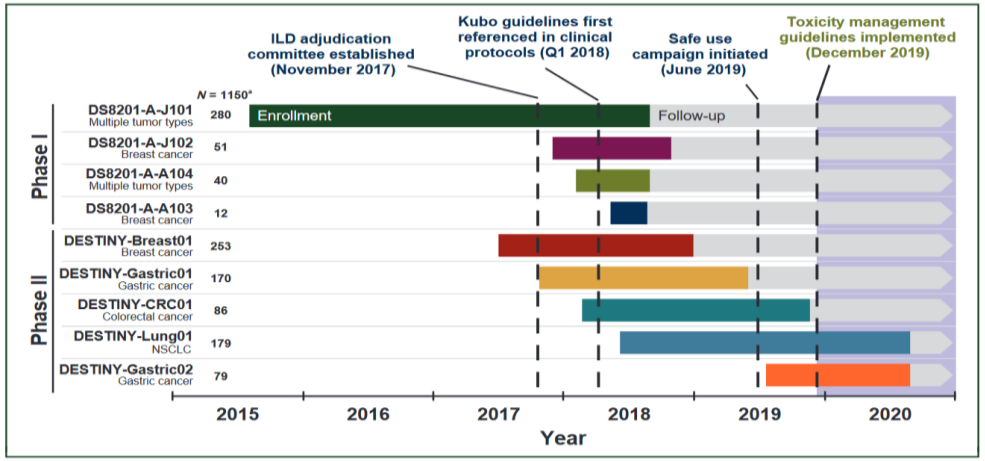


Table 3. Adjudicated drug-related ILD/pneumonitis by tumor type and grade[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All patients (*N* = 1150)	48 (4.2)	89 (7.7)	14 (1.2)	1 (0.1)	25 (2.2)	177 (15.4)
Breast cancer (*n* = 510)	32 (6.3)	51 (10.0)	7 (1.4)	0	15 (2.9)	105 (20.6)
HER2-positive breast cancer treated with T-DXd 5.4 mg/kg q3w (*n* = 245)[b]	9 (3.7)	22 (9.0)	2 (0.8)	0	7 (2.9)	40 (16.3)
Gastric cancer (*n* = 294)	5 (1.7)	15 (5.1)	3 (1.0)	1 (0.3)	1 (0.3)	25 (8.5)
Lung cancer (*n* = 203)[c]	7 (3.4)	16 (7.9)	2 (1.0)	0	6 (3.0)	31 (15.3)
Colorectal cancer (*n* = 107)	0	5 (4.7)	1 (0.9)	0	3 (2.8)	9 (8.4)
Other cancer (*n* = 34)	4 (11.8)	2 (5.9)	1 (2.9)	0	0	7 (20.6)

Overall incidence of ILD/pneumonitis in T-DXd-treated patients was 15.4%

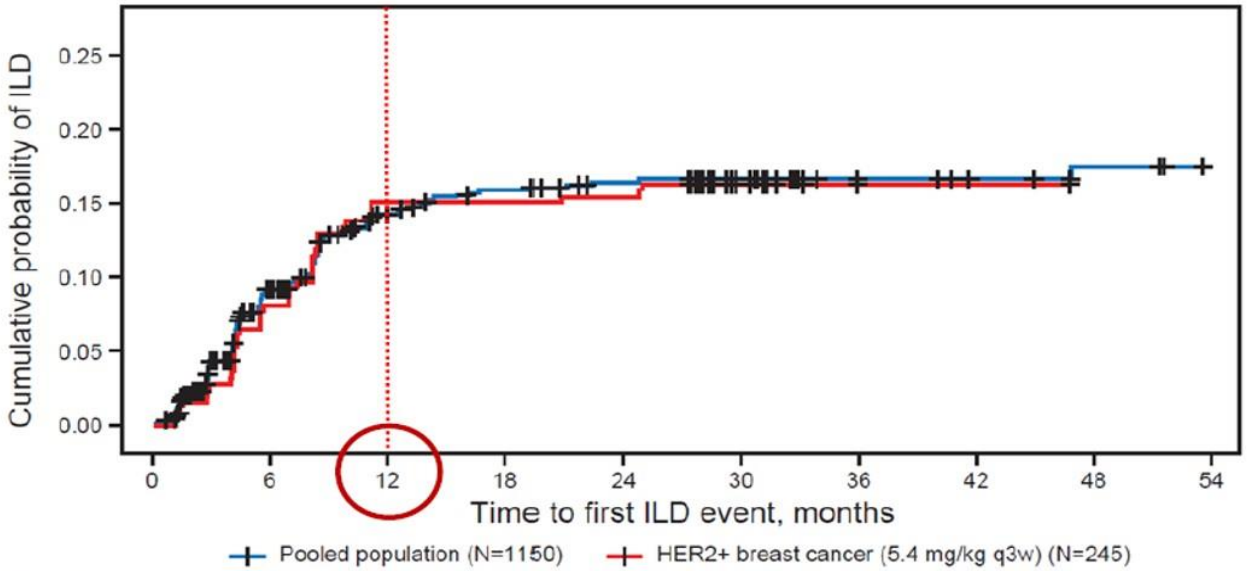
137 of 177 patients with ILD/pneumonitis (77%) had grade 1 or 2 events

Powell CA et al. ESMO Open 2022

ILD - pooled analysis

The risk of all-grade ILD/pneumonitis decreased after 12 months, as the cumulative probability of adjudicated drug-related ILD/pneumonitis began to plateau at this point

- Among 177 patients who had ILD/pneumonitis, 154 patients (87%) had a first ILD/pneumonitis event within 12 months of treatment
- 24.1% of patients remained on treatment > 12 months



No. at risk (events)										
Pooled population	1150 (0)	547 (101)	262 (154)	142 (170)	84 (174)	35 (176)	13 (176)	7 (176)	4 (177)	0 (177)
HER2+ breast cancer	245 (0)	170 (20)	95 (37)	66 (37)	45 (38)	11 (40)	2 (40)	1 (40)	0 (40)	0 (40)
ILD rate										
Pooled population	0	9.2%	14.3%	16.0%	16.4%	16.6%	16.6%	16.6%	17.5%	17.5%
HER2+ breast cancer	0	8.2%	15.1%	15.1%	15.5%	16.3%	16.3%	16.3%	16.3%	16.3%

Months (range)	Pooled Analysis
Median treatment duration	5.8 (0.7-56.3)
Median time to adjudicated ILD/pneumonitis onset	5.4 (< 0.1-46.8)

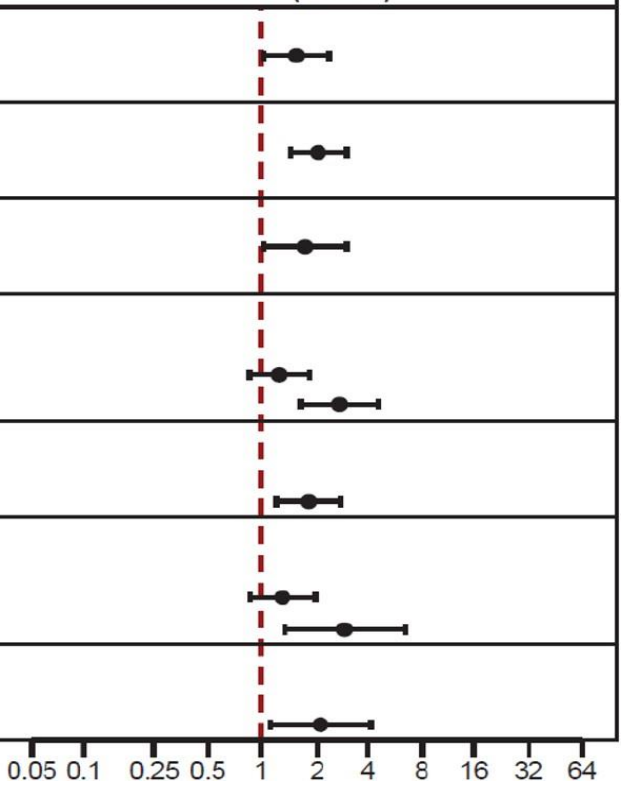
Data cutoff: December 21, 2020

Treatment discontinuations due to reasons other than ILD/pneumonitis were included as competing events.

Powell CA, et al. Pooled Analysis of Drug-Related Interstitial Lung Disease and/or Pneumonitis in 9 Trastuzumab Deruxtecan Monotherapy Studies. ESMO Open. 2022;7(4).

ILD - pooled analysis

Potential risk factor	Patients, *n* (*N* = 1150)	Hazard ratio[a] (95% CI)
Age group		
<65 years	754	1.56 (1.02-2.38)
≥65 years	396	Ref
Country		
Japan	506	2.08 (1.45-2.98)
Non-Japan	644	Ref
Lung comorbidities[b]		
Yes	81	1.75 (1.03-2.98)
No	1069	Ref
Baseline renal function[c,d]		
Normal	470	Ref
Mild decrease	458	1.24 (0.83-1.84)
Moderate/severe decrease	196	2.73 (1.65-4.52)
Time since disease diagnosis[c]		
0 to ≤4 years	624	Ref
>4 years	403	1.82 (1.20-2.75)
Dose		
5.4 mg/kg q3w	315	Ref
6.4 mg/kg q3w	808	1.30 (0.85-1.99)
>6.4 mg/kg q3w	27	2.92 (1.32-6.42)
Baseline SpO_2[c]		
≥95%	1080	Ref
<95%	57	2.14 (1.11-4.13)



Lung metastases / lymphangitic carcinomatosis at baseline and prior chest / lung radiotherapy were not associated with ILD / pneumonitis in this analysis

Numerically similar rates of adjudicated drug-related ILD/ pneumonitis in patients with or without prior ICI use

b) Includes asthma, chronic obstructive pulmonary disease, prior interstitial lung disease/pneumonitis, pulmonary fibrosis, pulmonary emphysema, and radiation pneumonitis

Powell CA et al. ESMO Open 2022

ILD

In more recent trials (e.g. DESTINY-Breast03) lower rates of ILD have been observed with G4 or G5 events

Probably due to:

- less heavily pretreated study population
- updated guidance for ILD/pneumonitis monitoring and management

Large real world data reported lower rates of ILD (5.4%)

DESTINY-Breast01

Interstitial Lung Disease, n (%)	August 2019 DCO T-DXd 5.4 mg/kg (N = 184)	June 2020 DCO T-DXd 5.4 mg/kg (N = 184)	March 2021 DCO T-DXd 5.4 mg/kg (N = 184)
Grade 1	5 (2.7)	6 (3.3)	7 (3.8)
Grade 2	15 (8.2)	16 (8.7)	16 (8.7)
Grade 3	1 (0.5)	1 (0.5)	1 (0.5)
Grade 4	0	0	0
Grade 5	4 (2.2)	5 (2.7)	5 (2.7)
Any grade/total	25 (13.6)	28 (15.2)	29 (15.8)

DESTINY-Breast03

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

Modi et al, SABCS 2020; Modi et al, NEJM 2020; Cortes et al, ESMO 2021; Cortes et al, NEJM 2022; Fountzilas E et al, EBCC 2024

ILD - management

Monitor for suspected ILD/P

- Interrupt T-DXd if ILD/P is suspected
- Rule out ILD/P if radiographic changes consistent with ILD/P or if acute onset of new or worsening pulmonary symptoms develop

Confirm ILD/P by evaluation

- High-resolution CT, pulmonologist consultation, blood culture and CBC, bronchoscopy or BAL, PFTs and pulse oximetry, arterial blood gases, PK analysis of blood sample (as clinically indicated and feasible)[a]
- **All ILD/P events regardless of severity or seriousness should be followed until resolution including after drug discontinuation**

Manage ILD/P

Grade 1

- **Interrupt T-DXd**
- T-DXd can be resumed if the ILD/P resolves to grade 0
  - If resolved in ≤28 days from onset, maintain dose
  - If resolved in >28 days from onset, reduce dose by 1 level[b]

- **Discontinue T-DXd** if ILD/P occurs beyond day 22 and has not resolved within 49 days from the last infusion

- Monitor and closely follow-up in 2-7 days for onset of clinical symptoms and pulse oximetry
- Consider:
  - Follow-up imaging in 1-2 weeks, or as clinically indicated
  - Starting systemic glucocorticoids (e.g. ≥0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks

If diagnostic observations worsen despite initiation of corticosteroids, then follow grade 2 guidelines.

We suggest considering steroids for selected grade 1 cases that show extensive lung involvement or in patients at increased risk for progression of ILD/P

Grade 2 (symptomatic)

Permanently discontinue T-DXd

- Promptly start systemic glucocorticoids (e.g. ≥1 mg/kg/day prednisone or equivalent) for ≥14 days until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks
- Monitor symptoms closely
- Re-image as clinically indicated
- If worsening or no improvement in clinical or diagnostic observations in 5 days:
  - Consider increasing dose of glucocorticoids (e.g. 2 mg/kg/day prednisone or equivalent), and administration may be switched to i.v. (e.g. methylprednisolone)
  - Reconsider additional workup for alternative etiologies as described above
  - Escalate care as clinically indicated

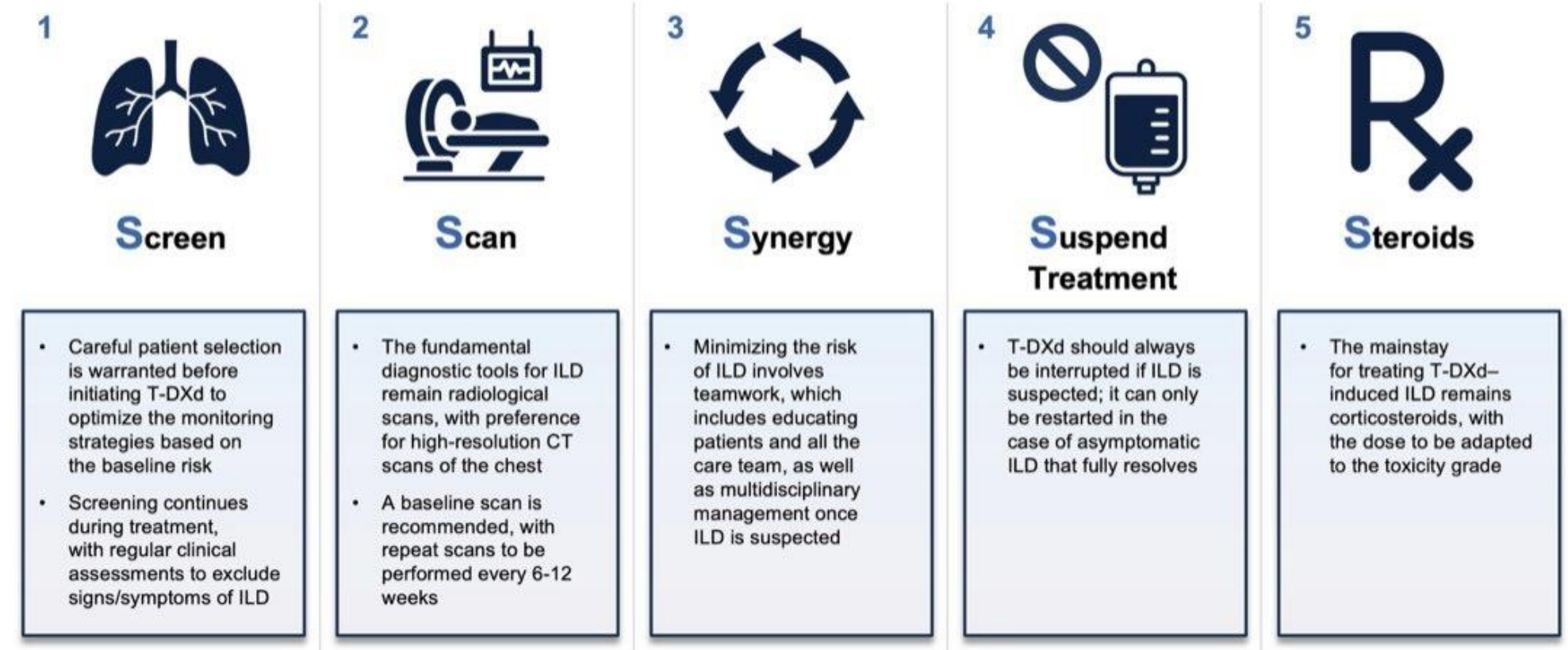
Grade 3 or 4

Permanently discontinue T-DXd

- Hospitalization required
- Promptly start empirical high-dose methylprednisolone i.v. treatment (e.g. 500-1000 mg/day for 3 days), followed by ≥1.0 mg/kg/day of prednisone (or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks
- Re-image as clinically indicated
- If still no improvement within 3-5 days:
  - Reconsider additional workup for alternative etiologies as described above
  - Consider other immunosuppressants (e.g. infliximab or mycophenolate mofetil) and/or treat per local practice

Rugo et al, ESMO Open 2022

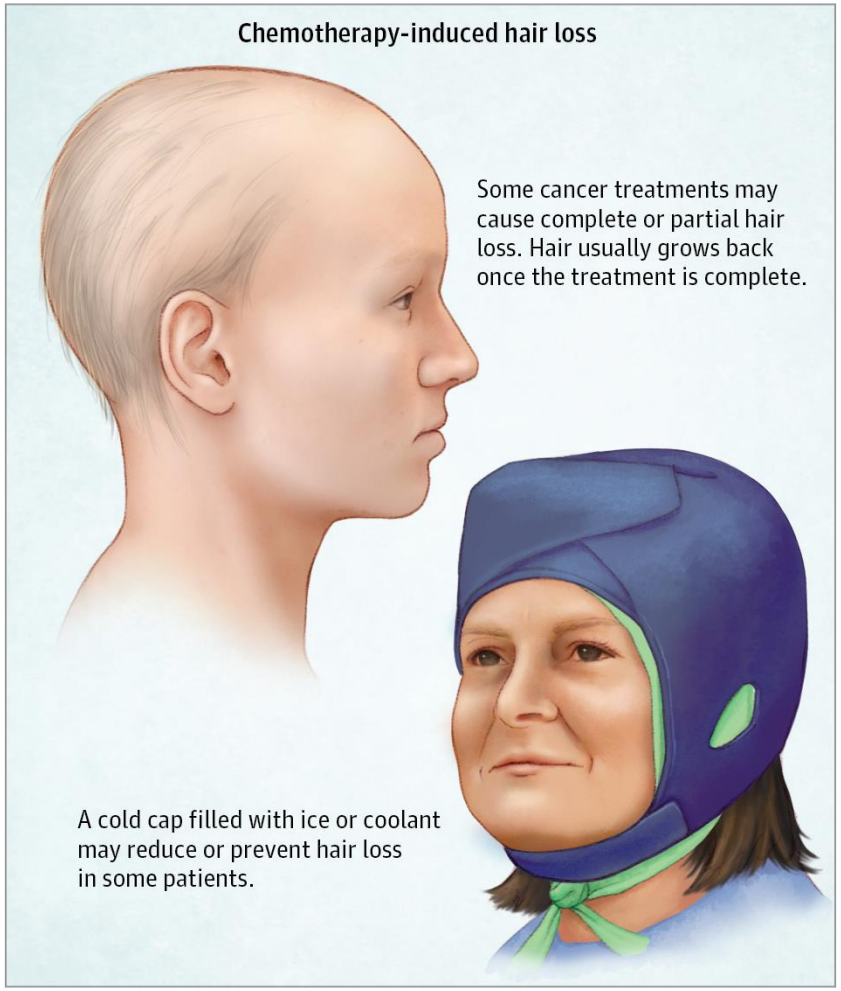
ILD - five "S" Rules



Tarantino et al, JCO Onc Prac 2023

Alopecia

ALOPECIA		
T-DXd	DB03	36.2%
	DB04	37.7%
SG	Ascent	46%
	Tropics02	46%
Dato-Dxd	TROPION-B	36%



West et al, JAMA Oncol 2017

Conclusions…

- Despite being designed with the rationale of expanding the therapeutic indices of conventional chemotherapies, ADCs can cause a number of distinct toxicities
- An increased understanding of these events and the optimization of diagnostic and management are critical to maximize treatment duration and benefit
- Prophylaxis for nausea and vomiting and proactive management of ILD/pneumonitis are especially important to improve safety of T-DXd and reduce risk of drug discontinuation

…and future challenges

- ADCs in the early setting
- Sequential use of different ADCs
- Combination therapies (i.e. immunotherapy, PARPi)

Thank you for your attention

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