Immune checkpoint inhibitors in solid tumours: Optimizing outcomes through multidisciplinary collaboration

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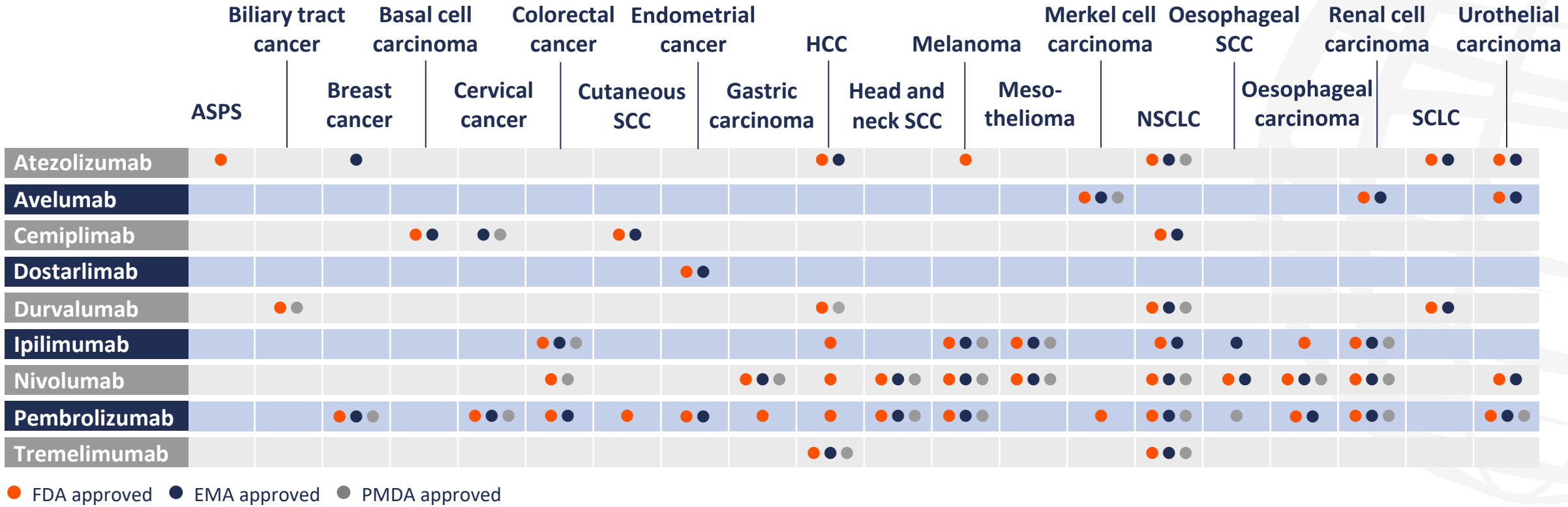
Treatment landscape for solid tumours

*Top-line overview of FDA-, EMA- and PMDA-approved immune checkpoint inhibitors**[1]



***ICIs approved as monotherapy and/or in combination with another ICI or chemotherapy depending on the indication – see individual prescribing information for full details.**

ASPS, alveolar soft part sarcoma; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PMDA, Pharmaceuticals and Medical Devices Agency; SCC, squamous cell carcinoma; SCLC, small-cell lung carcinoma.

1. Data for each immune checkpoint inhibitor from FDA prescribing information (www.accessdata.fda.gov/scripts/cder/daf/index.cfm), EMA summary of product characteristics (www.ema.europa.eu/en/medicines) and Japan PMDA (www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html), as applicable (accessed 9 May 2023).

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Pseudoprogression during immunotherapy

Pseudoprogression is an increase in the size of the primary tumour or the appearance of a new lesion, followed by tumour regression

Methods for differentiating pseudoprogression from true progression

Retrospective image analysis
Primary method for confirming pseudoprogression, but could result in premature cessation of effective treatment

Biomarkers
Potential association between pseudoprogression and a decrease or low level of ctDNA and IL-8

Biopsy
An effective method for confirming pseudoprogression but is invasive; liquid biopsy may be an effective alternative in the future

Medical imaging techniques
PET imaging may help to identify early and delayed pseudoprogression but further research is needed

ctDNA, circulating tumour DNA; IL, interleukin; PET, positron emission tomography.
Ma Y, et al. *Am J Cancer Res.* 2019;9:1546–53.

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Common immune-related adverse events (1/2)

Cutaneous irAEs

- Inflammatory dermatoses
- Bullous dermatoses
- Severe cutaneous adverse reactions

≤71.5% of patients

Time to onset 3–6 weeks after therapy initiation

Most common irAE

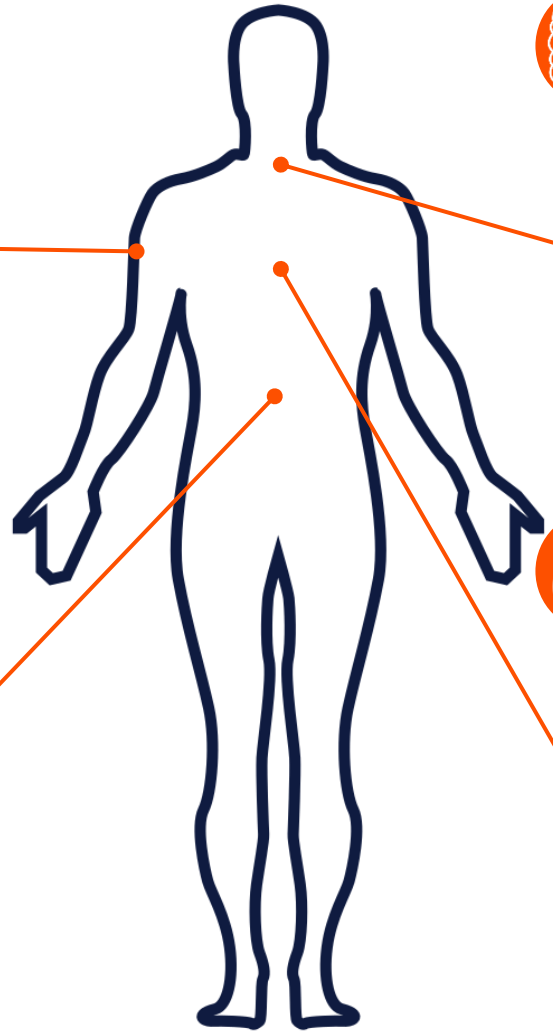
Gastrointestinal irAEs

- Colitis
- Gastritis
- Hepatitis
- Enterocolitis

Lower GI toxicities more common than upper GI toxicities

Colitis: **8–27%** of patients*
Diarrhoea: **≤54%** of patients*

Median time to onset 6 weeks after therapy initiation



Endocrine irAEs

Characterized by the gland/organ affected

- Primary hypothyroidism
- Hypophysitis
- Thyrotoxicosis
- Diabetes
- Primary adrenal insufficiency

Clinically significant endocrinopathy: **10%** of patients

Median time to onset 14.5 weeks after therapy initiation

Respiratory irAE

- Pneumonitis

10% of patients*

Median time to onset 34 weeks after therapy initiation

Uncommon but potentially serious

*In patients treated with combination therapy.
GI, gastrointestinal; irAE, immune-related adverse event.
Schneider BJ, et al. *J Clin Oncol.* 2021;9:4073–126.

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Common immune-related adverse events (2/2)

Haematologic irAEs

- Haemolytic anaemia
- Acquired TTP
- Haemolytic uraemic syndrome
- Aplastic anaemia
- Lymphopenia
- Immune thrombocytopenia
- Acquired haemophilia A

Haemolytic anaemia:
9.8% of patients

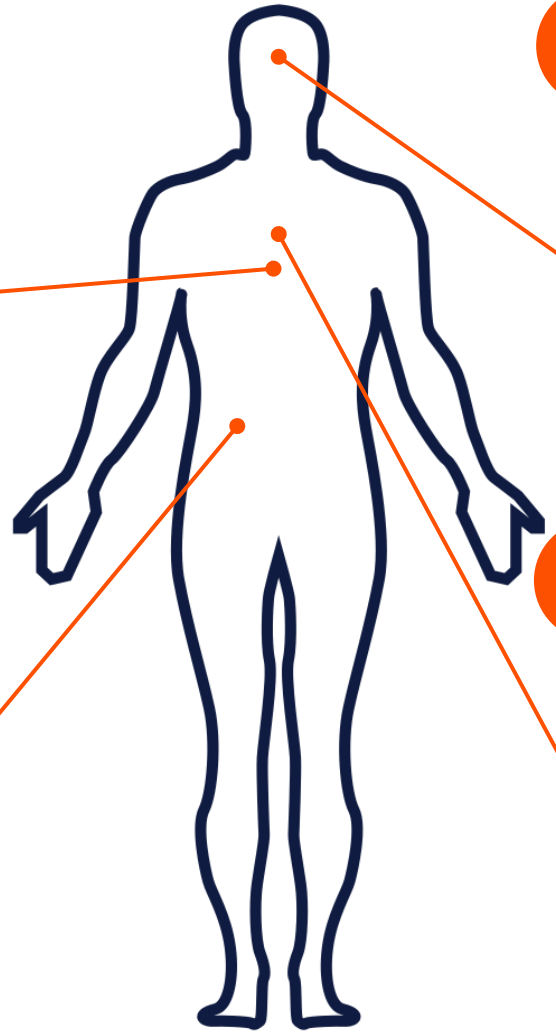
Median time to onset 5.7 weeks after therapy initiation

Renal irAEs

- Nephritis
- Acute kidney injury

Acute kidney injury:
4.5% of patients*

Median time to onset 14 weeks after therapy initiation



Neurologic irAEs

- Myasthenia gravis or myasthenic syndrome
- Aseptic meningitis
- Encephalitis
- Guillain–Barré-like syndrome
- Variety of other peripheral neuropathy phenotypes and demyelinating disorders

12.0% of patients*

Median time to onset 4 weeks after therapy initiation

Cardiovascular irAEs

- Myocarditis
- Pericarditis
- Arrhythmias
- Vasculitis
- Venous thromboembolism
- Impaired ventricular function with heart failure

<0.3% of patients*

Median time to onset 6 weeks after therapy initiation

High mortality risk

*In patients treated with combination therapy.
irAE, immune-related adverse event; TTP, thrombotic thrombocytopenic purpura.
Schneider BJ, et al. *J Clin Oncol.* 2021;9:4073–126.

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Common immune-related adverse events

Associations by class

Monotherapy

PD-1	PD-L1	CTLA-4
Cemiplimab Nivolumab Pembrolizumab	Atezolizumab Avelumab Durvalumab	Ipilimumab

Most common irAEs relative to CTLA-4

- Rheumatic
- Auto-immune
- Musculoskeletal
- Thyroid
- Pulmonary
- Infusion-related reactions
- Oral mucositis
- Myasthenia gravis

Generally **greater incidence** of irAEs and of **higher severity** compared with PD-1/PD-L1

Most common relative to PD-1/PD-L1

- GI-associated
- Hypophysitis fatigue
- Ophthalmologic
- Dermatologic

Combination therapy

ICI + ICI

Most common irAEs

- GI-associated
- Hepatic
- Endocrine (thyroid)
- Fatigue
- Nausea
- Rash

ICI + VEGF

Most common irAEs

- Negative cardiac effects
- Transaminitis/hepatic
- GI-associated

ICI + CT

- Lower overall risk of high-grade AEs relative to CT alone, except for neuropathy

ICI + EGFR

Most common irAEs

- Pulmonary
- Hepatic

AE, adverse event; CT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte antigen-4; EGFR, epidermal growth factor receptor; GI, gastrointestinal; ICI, immune checkpoint inhibitor; irAE, immune-related AE; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1; VEGF, vascular endothelial growth factor.

Olsen TA, et al. *Front Endocrinol.* 2022;13:779915.

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Case study

Presentation

61-year-old male

Metastatic head and neck cancer

Treatment

Durvalumab within a clinical trial commenced April 2022

Surveillance

CT chest:
Good partial response on CT scan July 2022

Follow-up

Discontinued due to liver and haematologic toxicity in August 2022 after six cycles

CT, computerized tomography.

Overall summary of irAE management strategies*

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Supportive care/treatment as needed			
Continue ICI with close monitoring†	Temporarily discontinue ICI		Permanently discontinue ICI‡
Corticosteroids normally not required	Low-dose corticosteroids • If no improvements in 2–3 days, increase dose	High-dose corticosteroids • If no improvement in 2–3 days, use additional/alternative immunosuppressants, e.g. mycophenolate mofetil, infliximab	
	Consult relevant disease specialists		
	Gradually taper corticosteroid dose over at least 4–6 weeks once symptoms improve to grade ≤1		Consider hospitalization
	Restart ICI therapy when symptoms improve	Consider restarting ICI therapy when symptoms improve • Discontinue if symptoms continue for 4–6 weeks	

*Guidelines for treatment recommendations for each specific irAE should be consulted; †For some neurologic, haematologic or cardiac irAEs, ICI therapy should be discontinued at any grade until the nature of the irAE is defined; ‡Therapy with ICI can continue if the grade 4 irAE is an endocrinopathy that can be controlled with hormone replacement.
ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.
Medina P, et al. *J Pharm Pract.* 2020;33:338–49.

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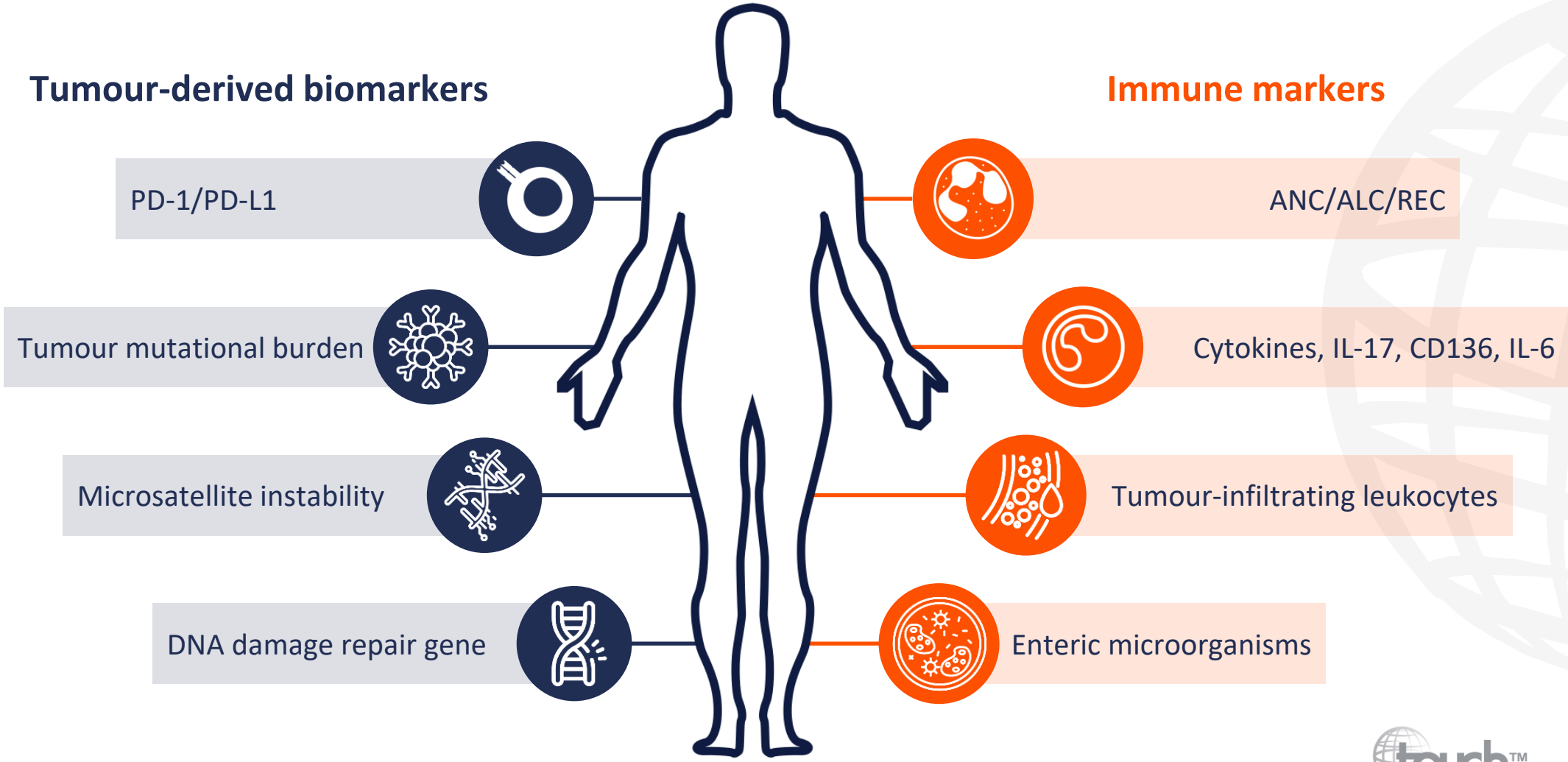
Biomarkers for immune checkpoint inhibitors



ALC, absolute lymphocyte counts; ANC, absolute neutrophil counts; CD, cluster of differentiation; IL, interleukin; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; REC, relative eosinophil counts.

Li N, et al. *Biomed Pharmacother.* 2022;147:112470.

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