ITP SECONDARY TO IMMUNOTHERAPY

Elisa Lucchini

UCO Ematologia – Trieste (Italy)

Disclosures of Elisa Lucchini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

ITP SECONDARY TO IMMUNOTHERAPY

IMMUNE CHECKPOINT INHIBITORS

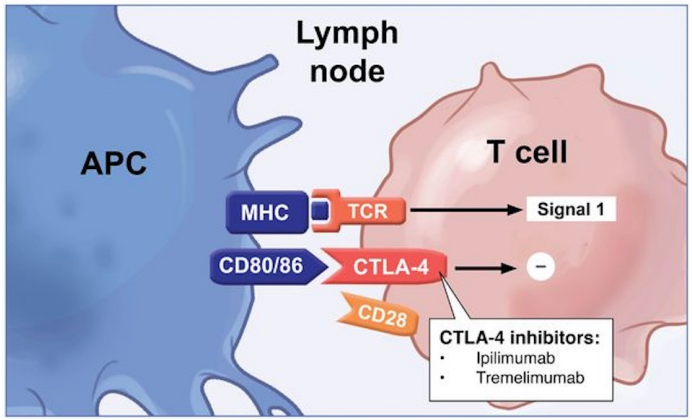
CAR-T CELLS

ALLOGENEIC STEM-CELL TRANSPLANTATION

MONOCLONAL ANTIBODIES

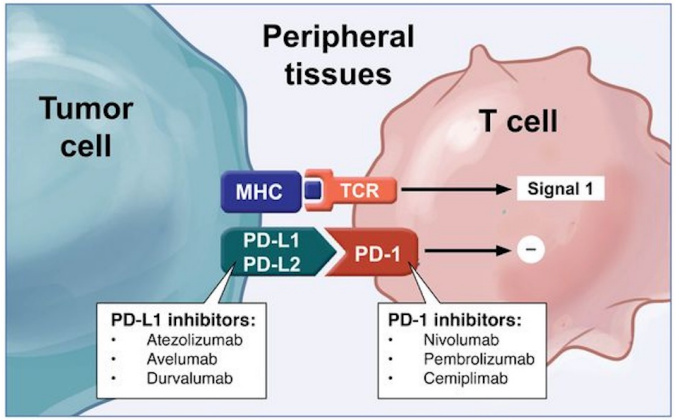
IMMUNE CHECKPOINT INHIBITORS

CTLA-4



- Expressed on activated T cells and T_{reg}cells
- Binds to CD80/86 on APCs: switch off of the APC

PD-1 / PD-L1



- PD-1 binding to PD-L1 on tumor cells induces a negative signal → anergy of effector cells
- PD-1 also expressed on B-cells, macrophages, NK cells

Kroll MH et al. Blood 2022

IMMUNE CHECKPOINT INHIBITORS

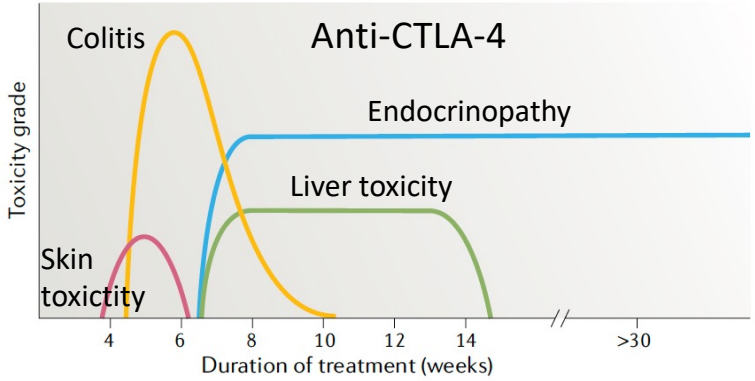
8 drugs, >14 FDA-approved indications for solid tumors and hematological malignancies

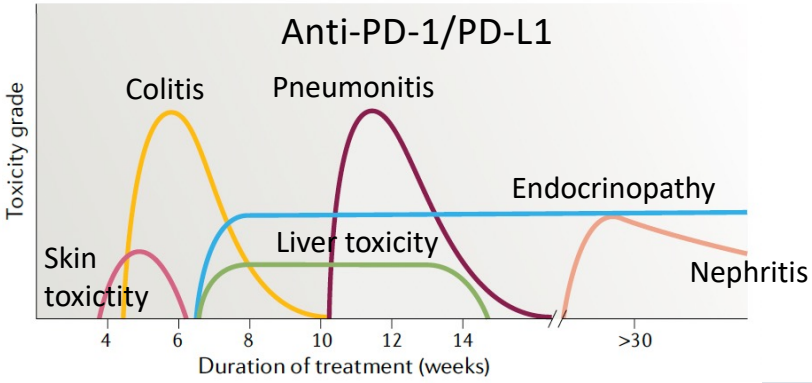
	Drug	FDA-approved indication
CTLA-4	Ipilimumab	Melanoma
	Tremelimumab	Non-small-cell lung cancer, hepatocellular carcinoma
PD-1	Nivolumab	Hodgkin lymphoma, melanoma, renal-cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma
	Pembrolizumab	Hodgkin lymphoma, primary mediastinal large-B cell lymphoma, melanoma, non-small and small-cell lung cancer, head and neck squamous cell cancer, urothelial carcinoma, colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular cancer, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma
	Cemiplimab	Urothelial carcinoma
PD-L1	Avelumab	Urothelial carcinoma, Merkel cell carcinoma, renal cell carcinoma
	Durvalumab	Urothelial carcinoma
	Atezolizumab	Urothelial carcinoma, non small-cell lung cancer, triple negative breast cancer

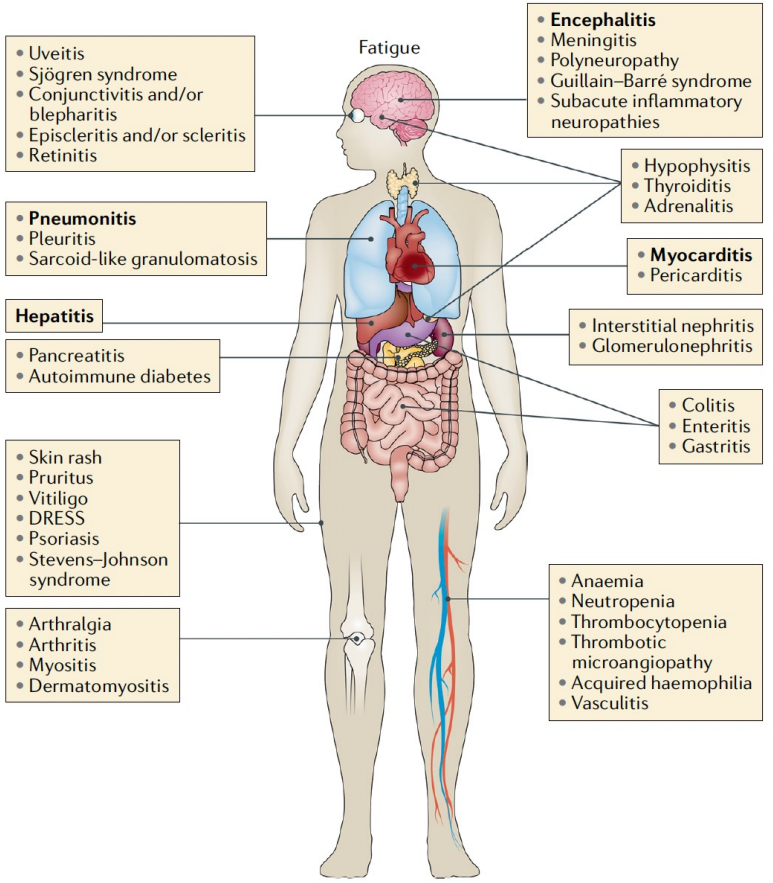
ICI TOXICITIES

Virtually all organs can be involved

- Dose-dependent for CTLA-4, non dose dependent for anti-PD-1/PD-L1
- Higher when used in combination







Martins F et al. Nat Rev.2019

HEMATOLOGICAL TOXICITIES

Poorly described: infrequent occurrence, lack of recognition, ICI often given in association with chemotherapy

- **Anemia**. All grade: 9.8%; grade 3-5: 5%
- **Thrombocytopenia**. All grade: 2.84%; grade 3-5: 1.83%
- Neutropenia. All grade: 1.07%; grade 3-5: 0.94%
- Aplastic anemia
- Acquired hemophilia A
- aTTP

Data from systematic review and meta-analysis from 47 studies and 9324 patients[1]

1.Petrelli F et al. Eur J Cancer.2018;103:7-16

HEMATOLOGICAL TOXICITIES

Michot JM et al.[1]	Martin M et al.[2]	Haddad TC et al[3]
Case reports from literature	French pharmacovigilance database	Single-center retrospective
63 patients with grade ≥2 hematological toxicity	68 cases with ICI-related grade ≥2 cytopenia	1038 patients Incidence of grade ≥3 thrombocytopenia
29% ITP 19% Pancytopenia or aplastic anemia 17% Neutropenia 16% Auto immune hemolitic anemia 11% Hemophagocytic syndrome 8% Pure red cell aplasia	**50% ITP** 25% AIHA 13% Autoimmune neutropenia 8% Pure red cell aplasia 3%Aplastic anemia	8.6% thrombocytopenia (any cause) 1.7% ITP
Median time to onset: 10 weeks	Median time to onset: 2 months	Median time to onset: 72.5 days

1.Michot JM et al. Eur J Cancer,2019:122:72-90; 2. Martin M et al. Cancers 2022,14,5030. 3.Haddad TC et al. Cancer Immunol Immunother;2022;71:1157-1165

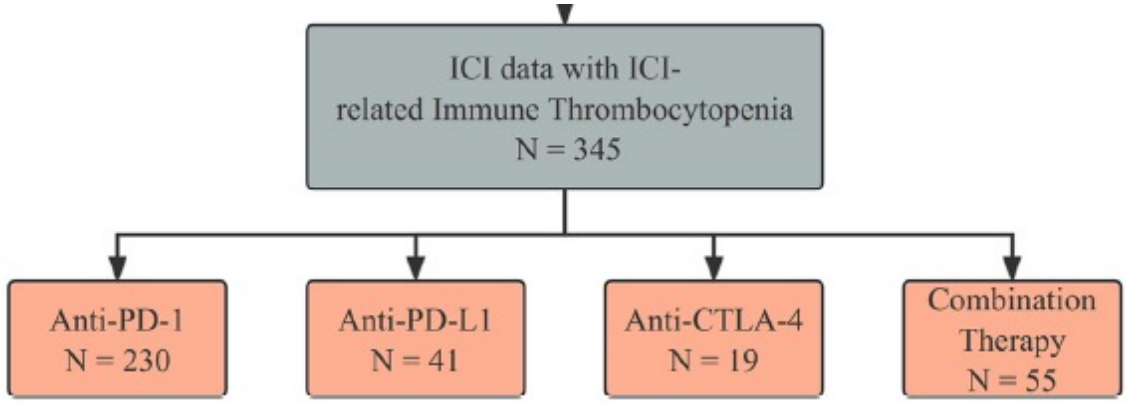
HEMATOLOGICAL TOXICITIES

Association of thrombocytopenia with immune checkpoint inhibitors: a large-scale pharmacovigilance analysis based on the data from FDA adverse event reporting system database

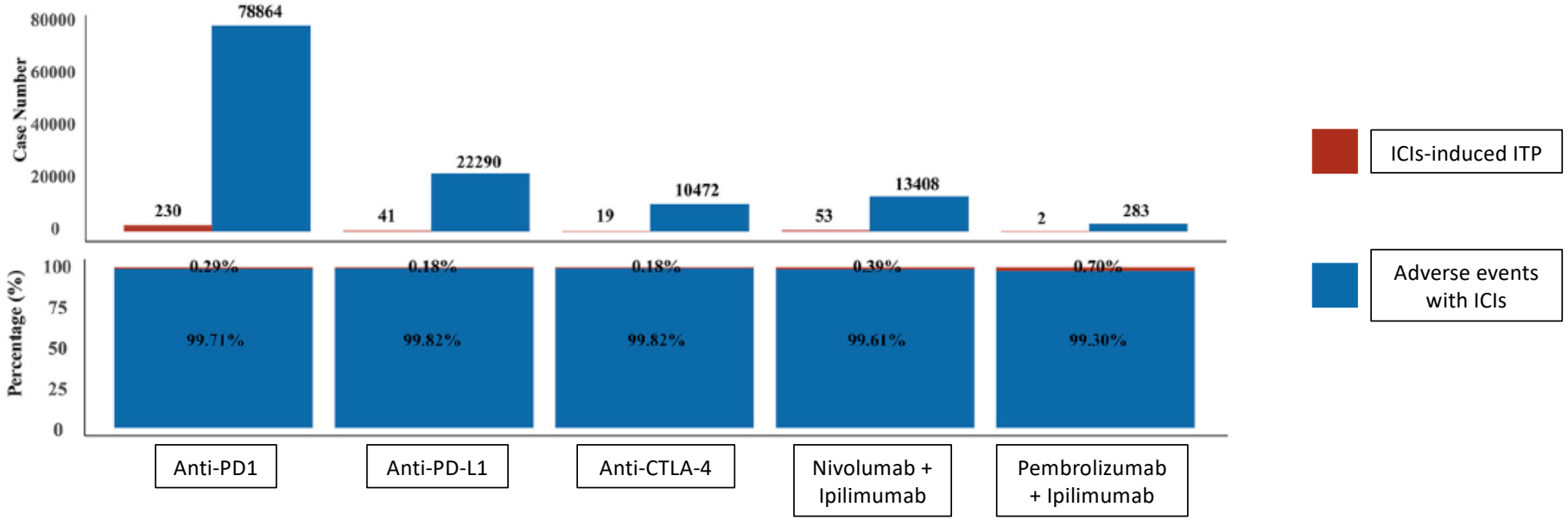
Geliang Liu[1,2,3], Shuxian Zhang[1,3], Zhuang Mo[1,4], Tai Huang[1,3], Qi Yu[1,3], Xuechun Lu[1,5,3]* and Peifeng He[1,6]*

frontiers | Frontiers in Pharmacology

- FDA Adverse Event Reporting System (FAERS) database
- From 01/2012 to 12/2022
- «immune thrombocytopenia»
- Age ≥ 18 years



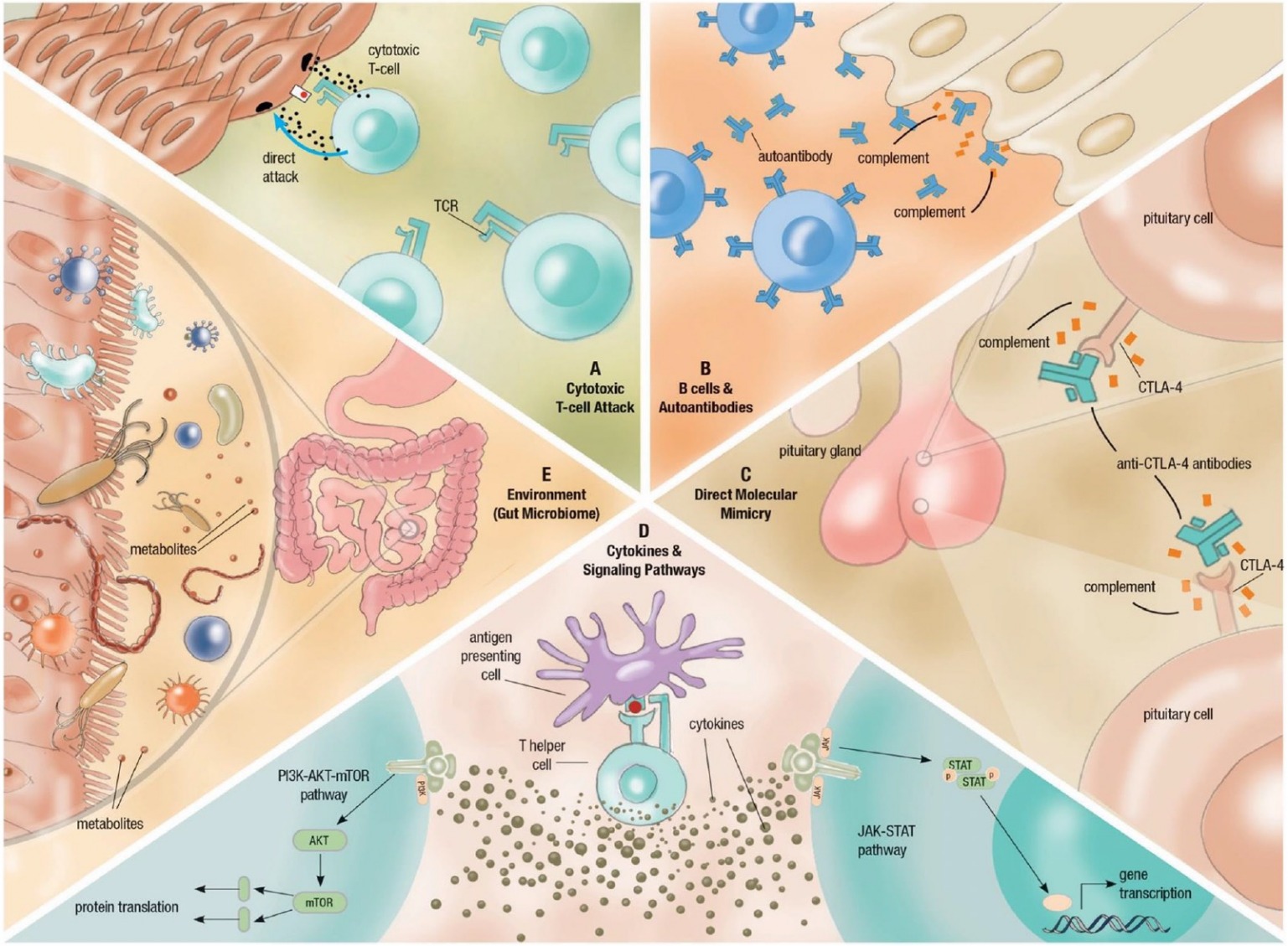
HEMATOLOGICAL TOXICITIES



- ICIs – induced ITP occurs steadly under all drugs, and increases significantly with combination therapy
- Median time to ITP onset: 42 days (IQR 17-135)
- No differences in treatment onset according to monotherapy vs combination therapy (p=0.89), nor different monotherapy drugs used (p=0.95), nor among different cancer origins (p=0.54)

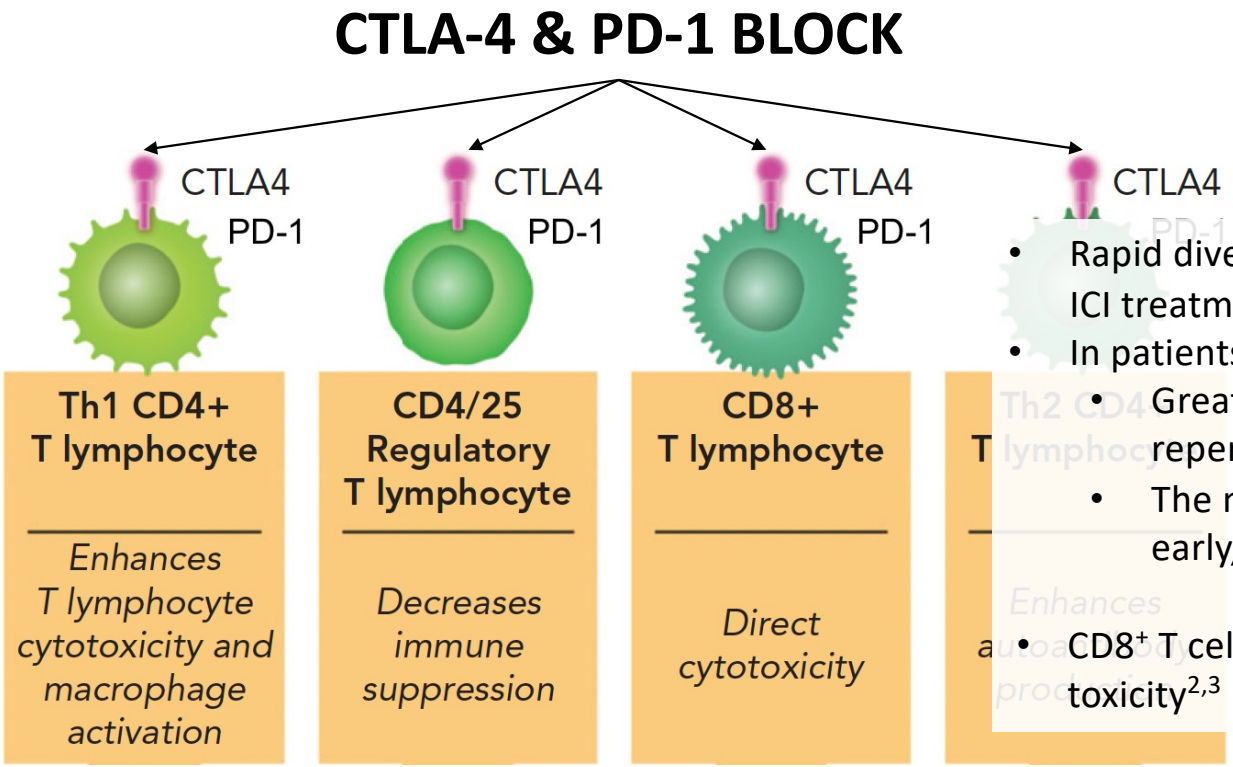
Liu G et al. Frontiers in Pharmacology 2024

PATHOGENESIS



Martins F et al. Nat Rev.2019

T-CELLS



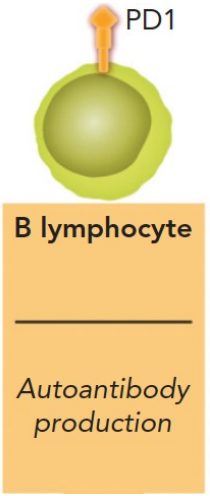
- Rapid diversification and clonal expansion of T cells after ICI treatment[1]
- In patients who develop irAEs[1]:
  - Greater diversification of $CD4^+$ and $CD8^+$ T-cell repertoire
    - The most relevant changes in T-cell repertoire occur early, at 2 weeks
- $CD8^+$ T cell clonal expansion as a marker predictive of ICI toxicity[2,3]

Kroll MH et al. Blood.2022;139:3594-3604

1.Oh DJ et al. Cancer Res;2017;77:1322-1330; 2.Subudhi SK et al. PNAS;2016:11919-24; 3.Lee DJ et al. Curr Cardiol Rep;2021;23:98.

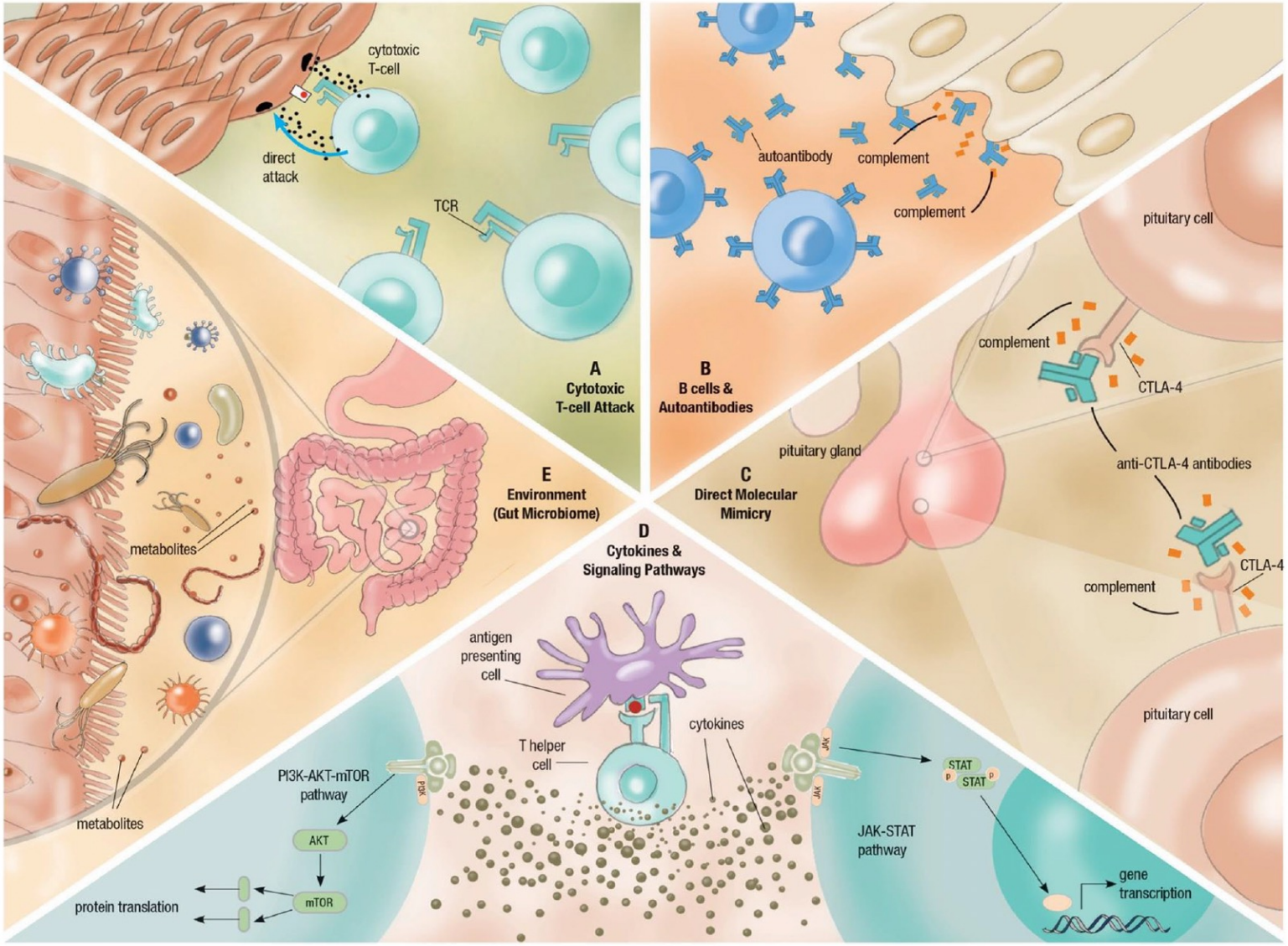
B-CELLS

- Peripheral accumulation of activated B-cells[1]
- B-cell expansion both in a T-cell dependent manner and T-cell-independent (B cells express PD-1)[2]
- Expansion of self-reactive antibody repertoire → anti-thyroid, anti-acetylcholine receptor, anti-transglutaminase[2-4]
- Regulatory B cells express PD-1/PD-L1: impaired immune surveillance upon checkpoint blockade[5]



1.Das R et al. J Clin Invest. 2018;128:715-20; 2.De Moel EC et al. Cancer Immunol Res. 2019;6-11; 3.Becquart O et al. J Immunother 2019;309-12; 4.Alsaadi D et al. J Immunother Cancer, 2019;7:203; 5.Sun X et al. QJM;2019:1-6; 6. Kroll MH et al. Blood.2022;139:3594-3604

PATHOGENESIS



Martins F et al. Nat Rev.2019

ITP POST-ICI MANAGEMENT

ASCO GUIDELINES

Grading	Management
G1: Platelet count 75 to < 100/μL	Continue ICPi with close clinical follow-up and laboratory evaluation.
G2: Platelet count 50 to < 75/μL	Hold ICPi but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to G1. Administer prednisone 1 mg/kg per day (dosage range, 0.5-2 mg/kg per day) orally for 4 weeks followed by taper over 4-6 weeks to the lowest effective dose. IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.
G3: Platelet count 25 to < 50/μL	As per G2. Hematology consult. Consider as alternative to prednisone or dexamethasone 40 mg daily for 4 days. If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. If previous treatment with corticosteroids and/or IVIG has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression. (*From American Society of Hematology guideline on ITP*[189]*—consult for further details)*
G4: Platelet count < 25/μL	

Schneider BJ et al. JCO 2021

ITP SECONDARY TO IMMUNOTHERAPY

IMMUNE CHECKPOINT INHIBITORS

CAR-T CELLS

ALLOGENEIC STEM-CELL TRANSPLANTATION

MONOCLONAL ANTIBODIES

ALLOGENEIC STEM-CELL TRANSPLANTATION

Immune mediated cytopenias after allo-SCT occur more often in patients with full donor chimerism → consequence of a donor reaction against the donor's hematopoietic system → AUTOIMMUNE[1]

Incidence of autoimmune cytopenia[2]:

- Hemolytic anemia: 1-5%
- Thrombocytopenia: 0.5-2%
- Neutropenia: <2%

May occur weeks, months or years after transplant

Risk factors[3,4]:

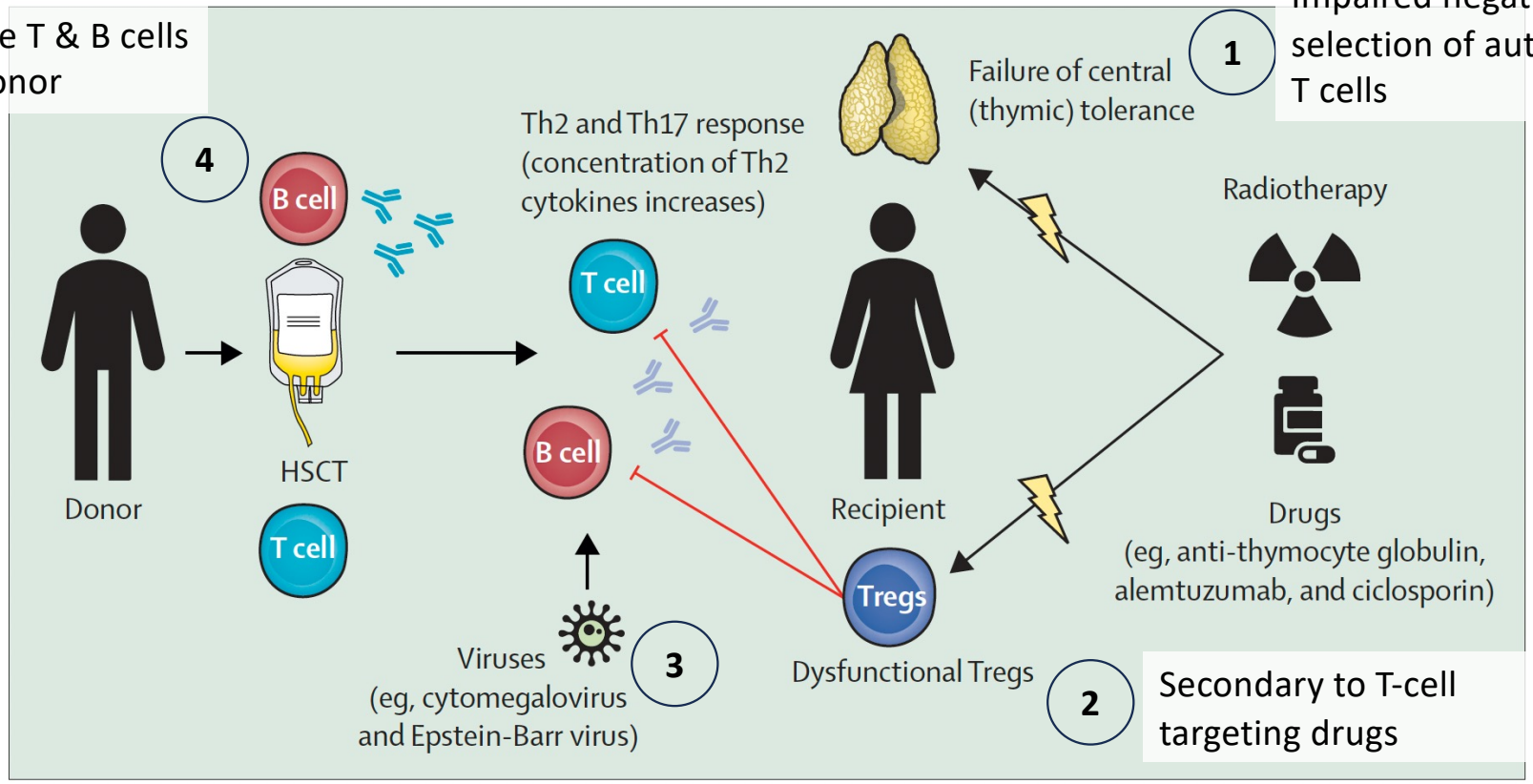
- Age < 15 yrs
- Non-malignant primary disease
- Haploidentical or unrelated donor
- Cord blood and PBSC as stem cell source
- Absence of TBI
- Presence of chronic GVHD

1. Baur K et al. Lancet hematol 2021; 8:e229-239; 2. Faraci M et al. Blood Bone Marrow Transplant, 2014;20:272-78;
3.Michniacki TF et al. Curr Oncol Rep 2019; 21:87; 4.Neunert CE et al. Pediatr Blood Cancer 2019;66:e27569

PATHOGENESIS

Impaired immune reconstitution + failure/loss of self-tolerance

Transfer of autoreactive T & B cells from the donor



Baur K et al. Lancet hematol 2021; 8:e229-239;

DIFFERENTIAL DIAGNOSIS

Post (allo) transplant ITP remains a diagnosis of exclusion
Differential diagnosis

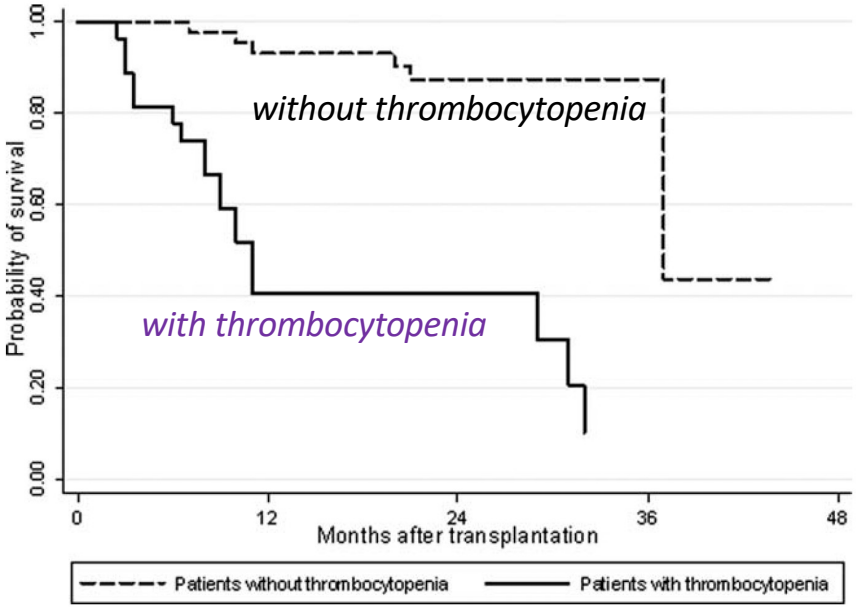
ACUTE	DELAYED
Chemotherapy	Recurrence of underlying malignancy
Graft failure	Graft failure
GVHD	Drugs
Infections	Viral infections (CMV, HHV6, EBV)
	GVHD
	ITP
	Microangiopathy

Immature platelet fraction (IPF), TPO and antiplatelet antibodies
may be useful for differential diagnosis

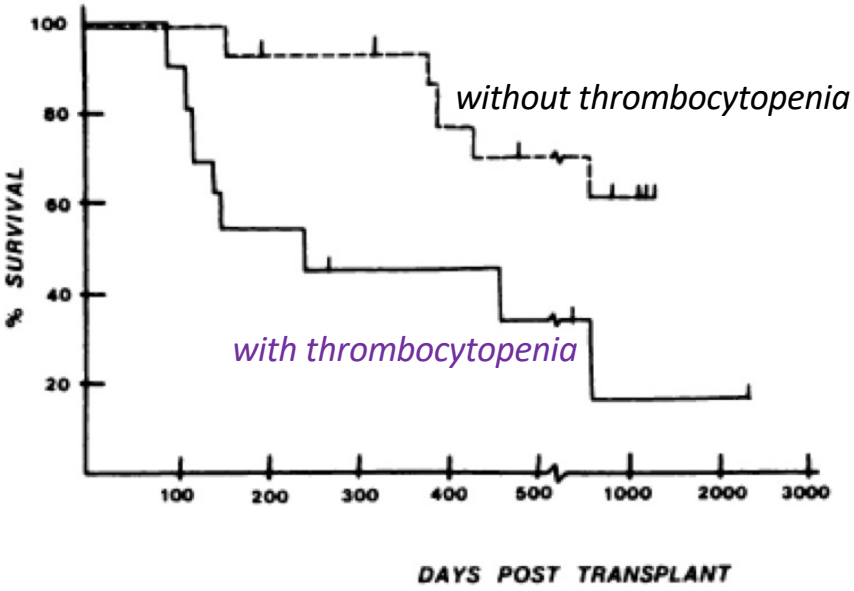
ALLOGENEIC STEM-CELL TRANSPLANTATION

Late-onset thrombocytopenia is observed in 20-40% of patients and represents a negative prognostic factor for survival, especially when it is related to cGVHD[1,2,3]

All allo-transplanted patients[2]



cGVHD patients[3]



1. Bruno B et al. Biol Blood Marrow Transplant 2001;7:154-162. 2.Zaja F et al. AJH 2011. 3.Lewis R et al. Blood, 1985:368-374

TREATMENT

Thrombopoietin Receptor Agonists for Severe Thrombocytopenia after Allogeneic Stem Cell Transplantation: Experience of the Spanish Group of Hematopoietic Stem Cell Transplant

86 patients with persistent thrombocytopenia after allo-SCT

Median plt count	14 (1-57)
Eltrombopag Romiplostim	51 (59%) 35 (41%)
Median time between alloSCT and TPO-RA	127 days (27-1177)

ORR (plt > $50x10^9$/L)	72%
Median time to response	66 days (2-247)
Median duration of TPO-RA	62 days (7-700)

81% discontinued TPO-RA maintaining the remission

Bento L et al. Biol Blood Marrow Transplant. 2019:1825-1831

TREATMENT

TPO-RAs FOR THE TREATMENT OF POST-ALLOTRANSPLANT THROMBOCYTOPENIA

	N° of patients	Plt > 50x10^9	Treatment start after SCT	Median time to platelet recovery	Tapering and discontinuation
Eltrombopag	12[1]	72%	5.6 months	54 days (14-195)	67%
	13[2]	66%	81 (36-300)	33 days (11-68)	NA
	36[3]	63.9%	66 (28-180)	15 days (4-104)	NA

	N° of patients	Plt > 50x10^9	Treatment start after SCT	Median time to platelet recovery	Tapering and discontinuation
Romi	24[4*]	75%	85 days (42-259)	45 days (21-77)	NA

* Phase I/II prospective study

1.Tanaka T et al. Biol Blood Marrow Transplant 2016; 3. Yuan C et al. Biol Blood Marrow ransplant, 2019. 4. Gunes EK et al. Leukemia research 2024. 5.Peffault de Latour R et al. Blood 2020

ITP SECONDARY TO IMMUNOTHERAPY

IMMUNE CHECKPOINT INHIBITORS

CAR-T CELLS

ALLOGENEIC STEM-CELL TRANSPLANTATION

MONOCLONAL ANTIBODIES

ALEMTUZUMAB – anti-CD52

Anti-CD52 antibody expressed on the surface of T and B cells

Hammersmith hospital experience

Alemtuzumab used as induction treatment for kidney transplantation (170 patients/year)

40 patients (2.7%) developed an autoimmune cytopenia from January 2010 to March 2018:

- 28 ITP
- 7 AIHA
- 5 Evans

Median age at diagnosis: 52 yrs (21 – 76)

100% on immunosuppressive treatment with Tacrolimus (70% monotherapy)

Comorbidities: 65% cardiovascular; 40% diabetes

ALEMTUZUMAB

Median time between Alemtuzumab and diagnosis: 33.5 months (6-109), with a peak between 10 and 20 months

ITP n=28

ORR after first-line: 62%

67.7% required 2 or more lines of therapy

Response rate to TPO-RAs: 75%

Response rate to Rituximab: 92%

50% of responders achieved SROT

AIHA n=7

ORR after first-line: 67%

62.5% required 2 or more lines of therapy

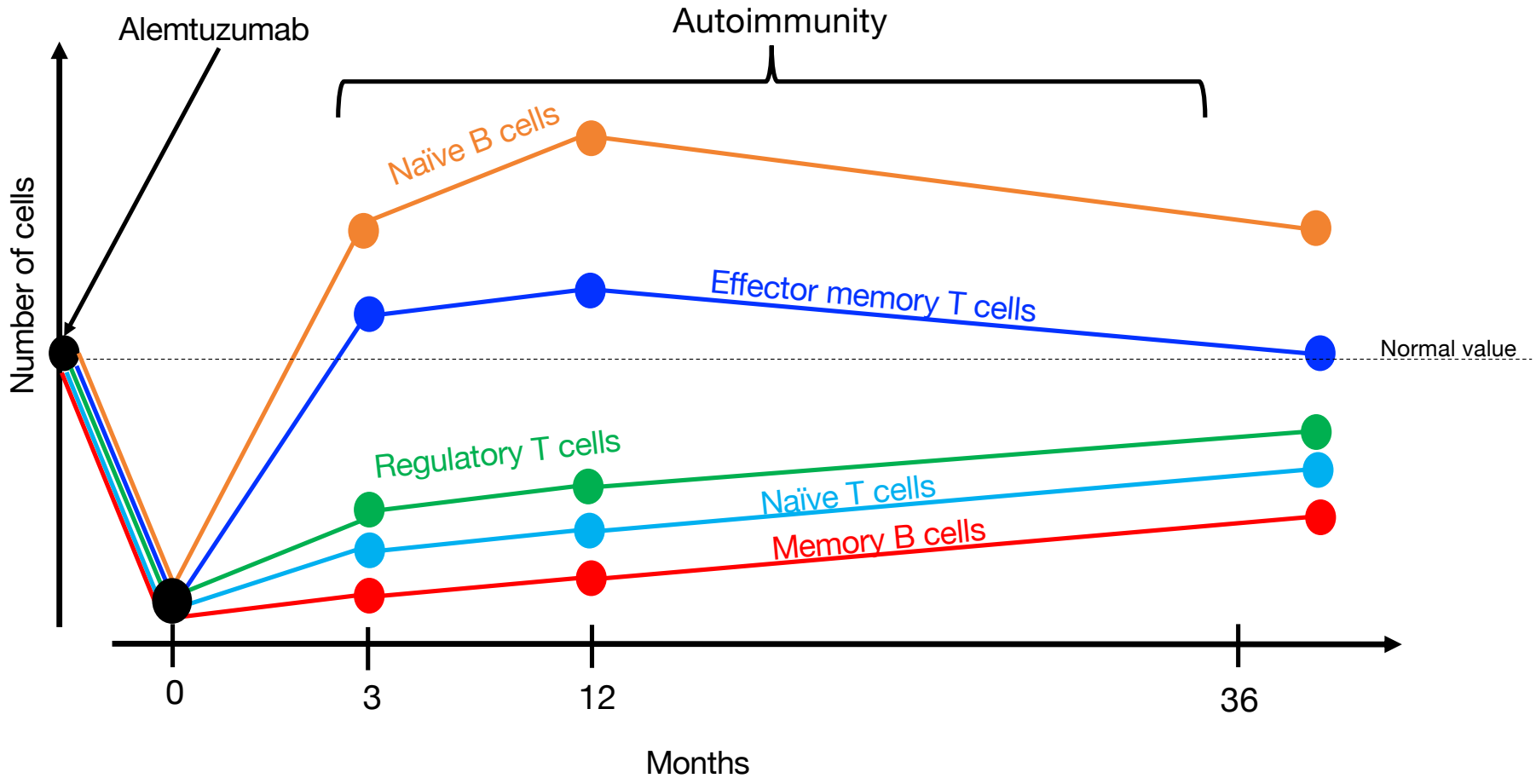
Second-line therapy: rituximab in 100%

87.5% of patients experienced ≥1 AE.

More common Aes: cardiovascular (52.5%) and infections (62.5%).

Unpublished data

ALEMTUZUMAB



Coles AJ et al. Lancet 1999;354:1691-5

ITP SECONDARY TO IMMUNOTHERAPY

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CAR-T CELLS

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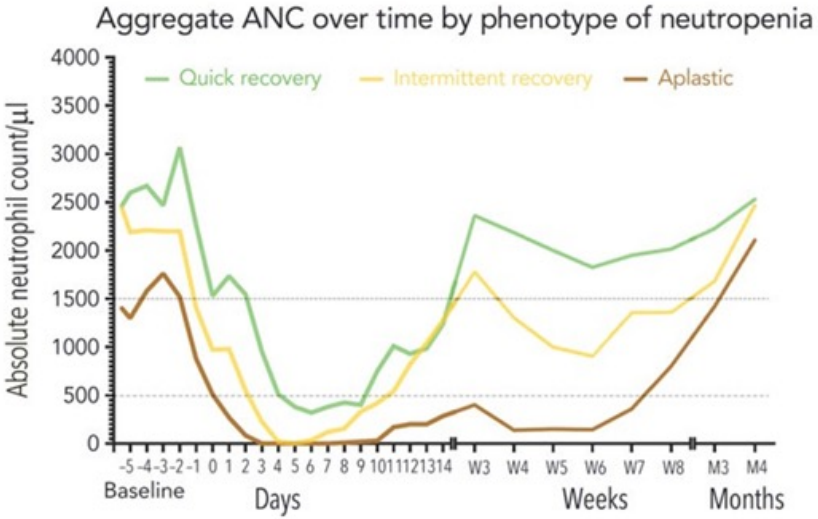
MONOCLONAL ANTIBODIES

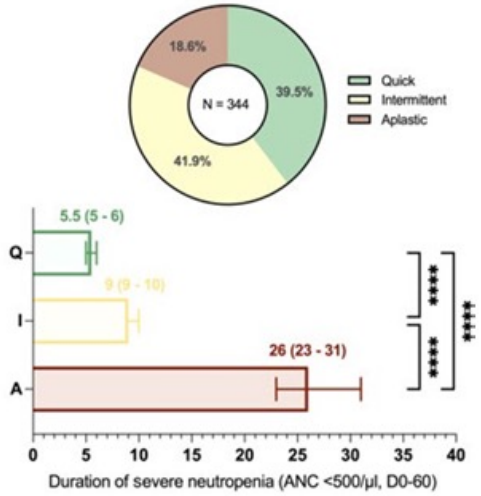
CAR-T CELLS

Immune effector cell-associated hematotoxicity (ICAHT): the most common non canonical CAR-T toxicity

Grade 3-4	Initial	Persistent*
Anemia	30-70%	5-17%
Thrombocytopenia	20-60%	21-29%
Neutropenia	30-60%	30-38%

*after day +28





3 distinct patterns of ICAHT:
- Quick (25%)
- Intermittent (biphasic) (50%)
- Aplastic (25%)

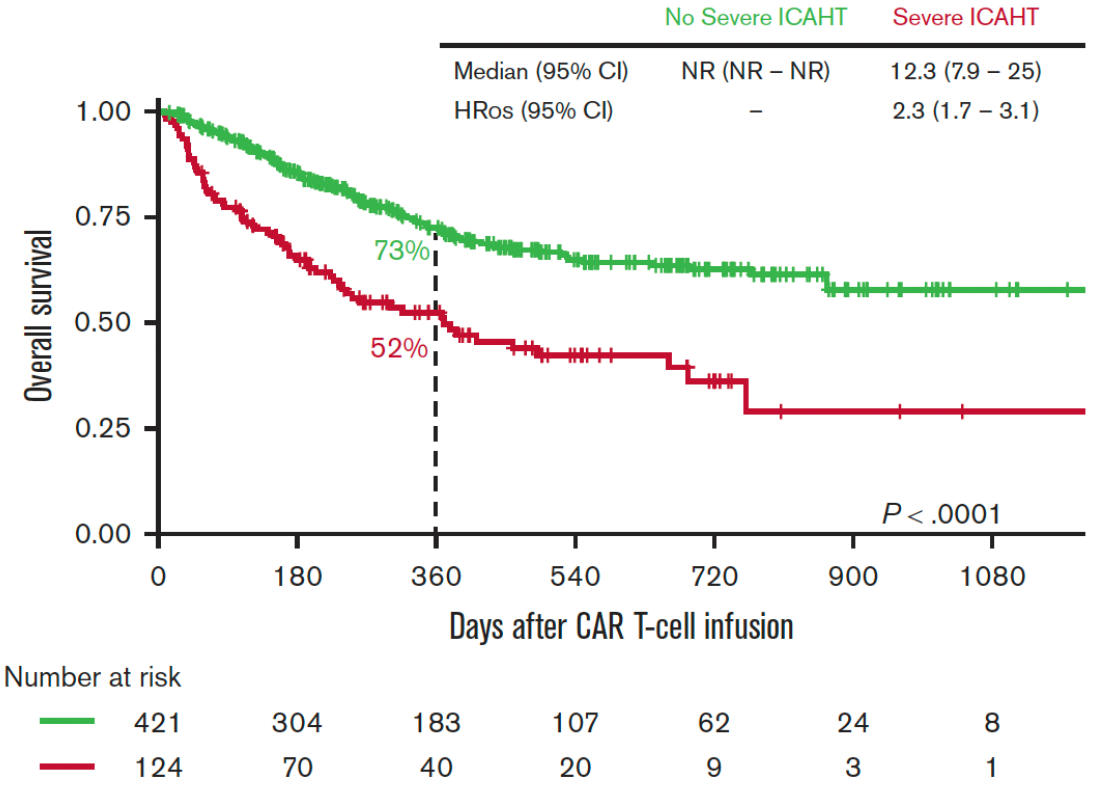
Rejeski et al. Blood 2021; ASH 2023 (Educational)

CAR-T CELLS

Cytopenias increase morbidity and mortality post-CART

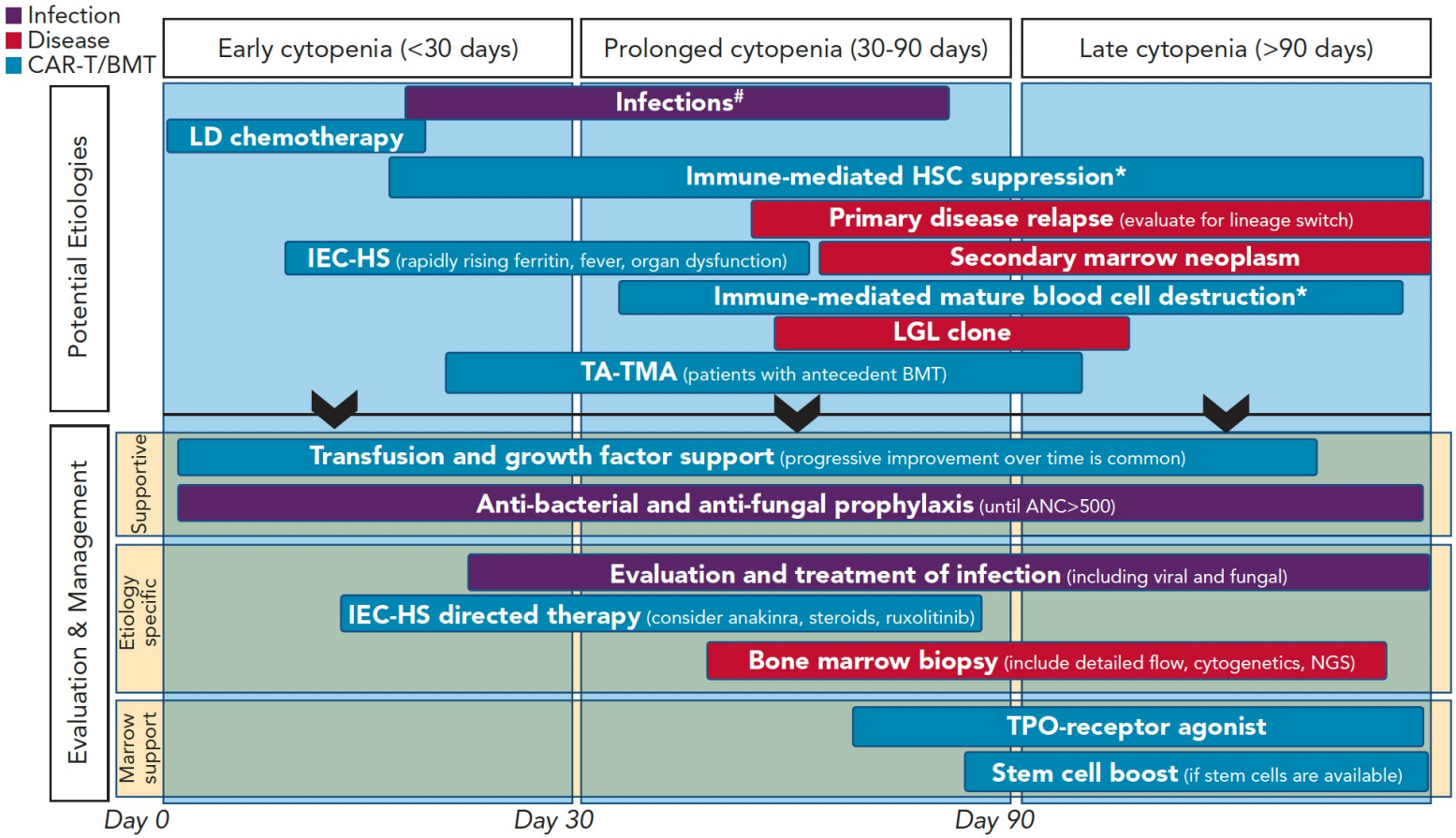
Severe (grade ≥3) ICAHT:

- Associated with a higher rate of severe infections
- Increased non-relapse mortality
- Inferior survival



Rejeski et al. Blood Advances 2023

CAR-T CELLS



Jain T et al. Blood 2023

Safety and efficacy of eltrombopag in patients with post-CAR T cytopenias

European Journal of Haematology

42 patients, 24 DLBCL, 18 MM, with persistent cytopenia after day +21

Eltrombopag up to 150 mg/day

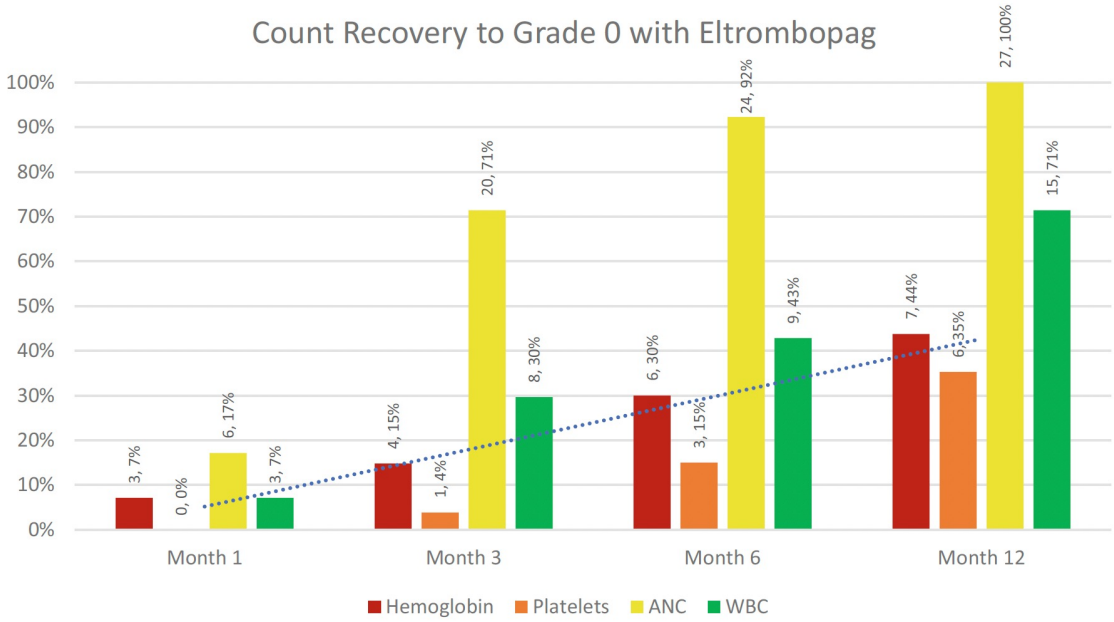
Median time to eltrombopag initiation: 33 days (28-50)
Median duration on treatment: 63 days (32-172)

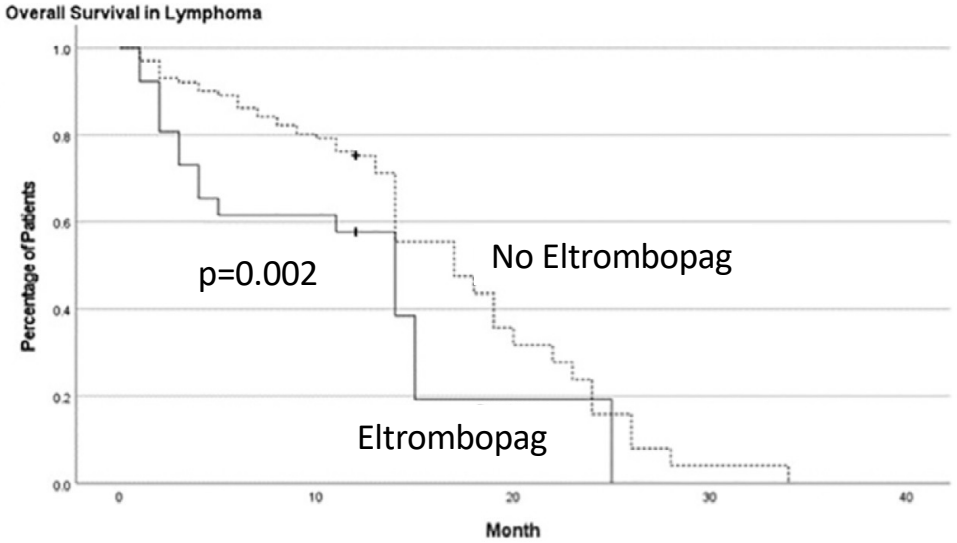
More likely to have cytopenia at lymphodepletion
More likely to have received bridging therapy
More likely to have developed CRS

Wesson W et al. Eur J Haematol 2024;112-538-546

Safety and efficacy of eltrombopag in patients with post-CAR T cytopenias

European Journal of Haematology





Wesson W et al. Eur J Haematol 2024;112-538-546

CAR-T CELLS

Use of Eltrombopag to Improve Thrombocytopenia and Tranfusion Requirement in Anti-CD19 CAR-T Cell-Treated Patients

Journal of Clinical Medicine

38 patients, 34 DLBCL, 3 ALL, 1 FL with plt transfusion dependance at day +30 or beyond

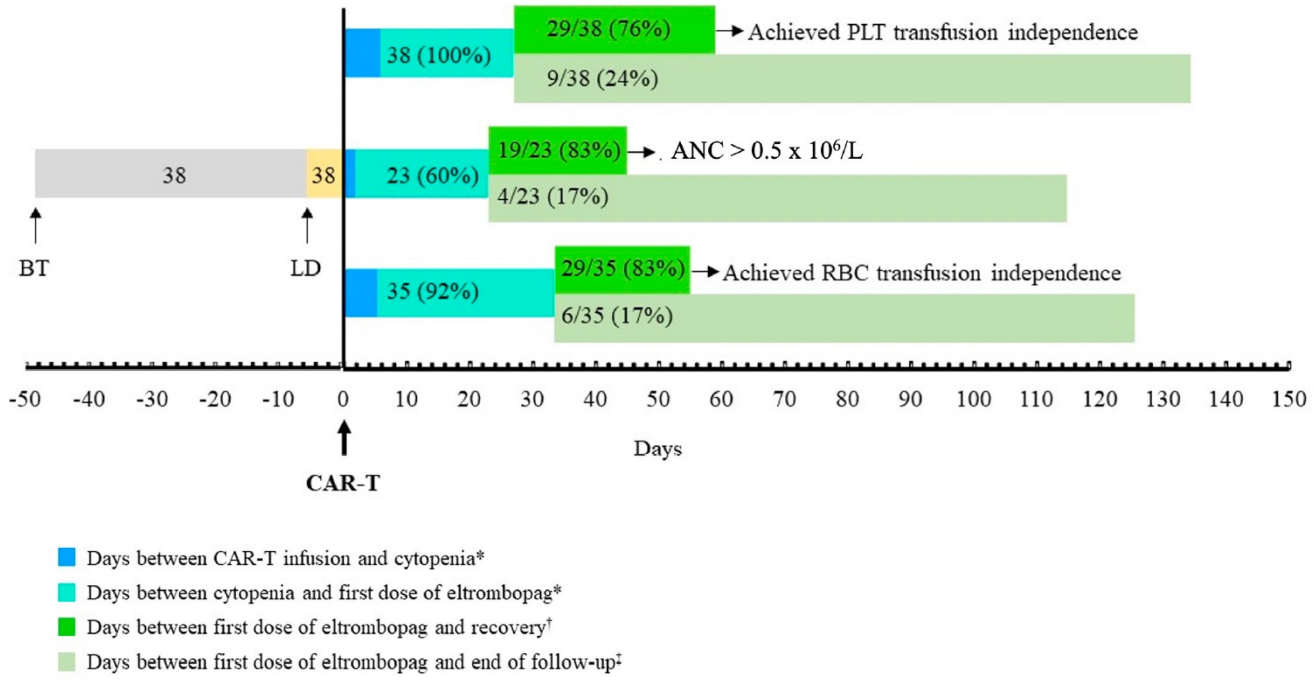
Eltrombopag up to 150 mg/day

Median time to eltrombopag initiation: 21 days (7.5-55)
Median duration on treatment: 68 days (48-154)

Mingot-Castellano ME et al- J Clin Med 2024

Use of Eltrombopag to Improve Thrombocytopenia and Tranfusion Requirement in Anti-CD19 CAR-T Cell-Treated Patients

Journal of Clinical Medicine



Plt count >20x10^9: 76.3%
Time (from Elt start): 32 days (14-38)

Plt count >50x10^9: 68.4%
Time (from Elt start): 33 days (19-57)

Mingot-Castellano ME et al- J Clin Med 2024

THANK YOU!

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UNIVERSITÀ DEGLI STUDI DI TRIESTE