GIORNATE EMATOLOGICHE VICENTINE

X edizione

12-13 Ottobre 2023
Palazzo Bonin Longare - Vicenza

Emostasi, complemento e danno endoteliale nel TMO: una interazione complessa

Alessandro Rambaldi

Professor of Hematology, Department of Oncology and Hematology, University of Milan and Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Piazza OMS, 1 - 24127 Bergamo

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Travel support
Omeros			✔			✔	✔
Amgen			✔			✔	
Pfizer						✔	
Jazz						✔	
Incyte						✔	
Abbvie							✔
Kite-Gilead							✔
Novartis						✔	
Celgene-BMS							✓
Astellas						✓	
Roche							✓

Case study: a 67-year-old patient with high risk MDS

January 2018:

- Female, Caucasian, 67-years-old MDS patient with isolated del(5q).
- Treatment: lenalidomide.

December 2019:

- RCMD with complex karyotype.

August 2020:

- alloHSCT due to high-risk disease
- IPSS-R: 5.5 (high risk)

Donor:

HLA aploidentical donor: son (44 old); AB0 match: patient B-, donor B+.

Conditioning (reduced intensity regimen):

Thiotepa; Busulfan; Fludarabine

GvHD prophylaxis:

Post-transplant Cyclophosphamide, CSA and MMF.

Day +39:

- Cutaneous aGvHD stage III (overall grade II)
- Steroid therapy (methylpred 2 mg/kg) with good response (on day +46 acute cutaneous GvHD stage I, grade I) and subsequent tapering of steroid therapy.

Day +74:

- Sudden thrombocytopenia and anemia;
- Elevated LDH.

Case study: a 67-year-old patient with high risk MDS

- 3 schistocytes/HPF;
- LDH 495 U/L (ULN 246 U/L);
- Negative Coombs test;
- Platelets 12.000/mmc;
- Hb 7.9 g/dl;
- Haptoglobin 0,23 g/l (LLN 0,4 g/l);
- Proteinuria 0,27 g/L ;
- Protein/creatinine ratio 400 mg/g;
- Reticulocyte: 129.8 x 10^9/L;
- Circulating endothelial cells: 35/ml;
- Normal coagulation tests;
- Normal ADAMTS13 activity,
- No anti ADAMTS13 Ab.
- Cyclosporine blood level: 276 ng/ml

What's the diagnosis?

aGvHD

Cyclosporine toxicity

SOS/VOD

TA-TMA

Agenda

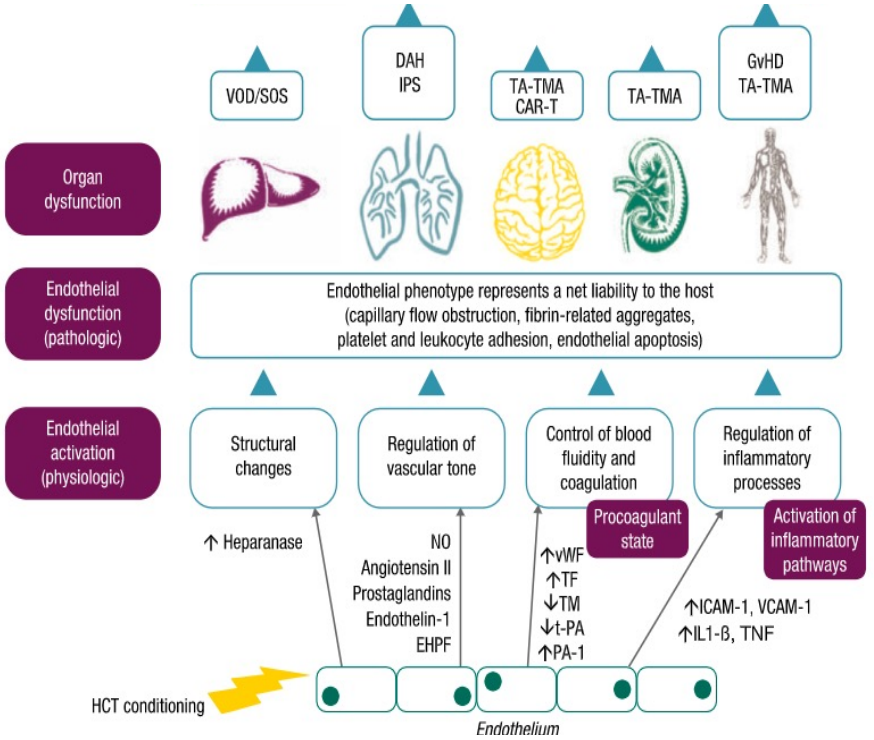
- Introduction to TA-TMA
- One disease, many diagnostic criteria**: the International Harmonization Effort**
- A new biomarker: focus on **C5b-9**
- TA-TMA therapy: from supportive care to complement inhibition
- **Narsoplimab**, from clinical trial to real-life data: a new standard of care?
- **Concomitant GvHD and TA-TMA**: a case report
- What's next: **prospective evaluation of C5b-9** in patients with TA-TMA treated with Narsoplimab

Introduction to TA-TMA: from complement activation to organ damage

Introduction to HSCT-TMA
The Spectrum of Transplant-Associated Endothelial Injury

Endothelial injury syndromes
post-HSCT complications characterized by endothelial injury as a common pathophysiology and include:[1]

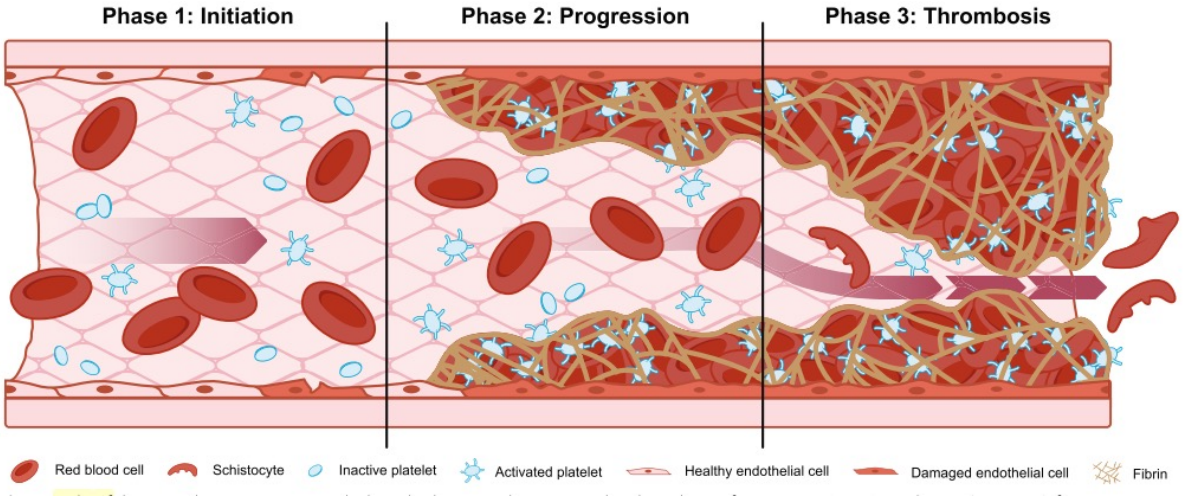
- **Thrombotic microangiopathy (TMA)**
- GvHD
- Hepatic veno-occlusive disease (VOD)
- Idiopathic pneumonia syndrome (IPS)
- Diffuse alveolar hemorrhage (DAH)
- Capillary leak syndrome (CLS)



[1] Gavriilaki. Exp Hematol Oncol. 2021 Dec 19;10(1):57.

Figure: Hildebrandt; Br J Haematol . 2020 Aug;190(4):508-519

Pathophysiology of HSCT-TMA: Endothelial Injury Pathways



Endothelial injury causes[1]

Immunosuppressive agents, acute GVHD, infection, cytotoxic agents or radiation

Complement activation including lectin pathway[1]

Altered carbohydrate and acetylated ligand patterns on injured ECs; microvascular damage

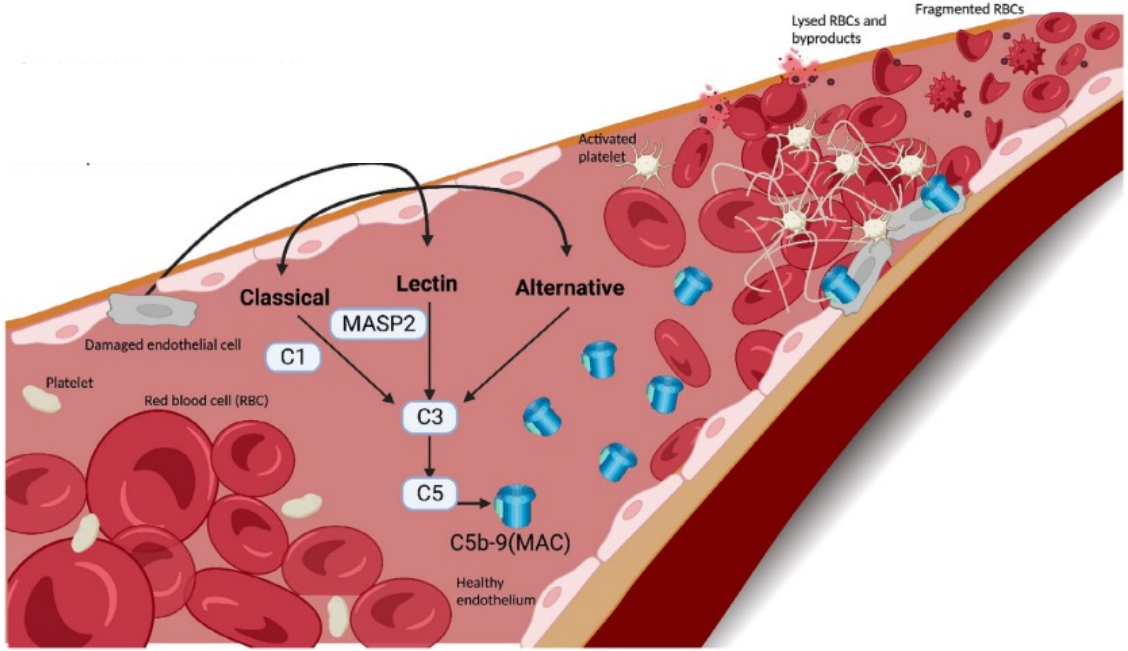
Thrombosis[1]

Platelet aggregation, microthrombi formation, thrombocytopenia, hemolysis and organ damage

[1] Gavriilaki E. et al. Exp Hematol Oncol. 2021 Dec 19;10(1):57.

The Role of the Complement System in HSCT-TMA

- Endothelial injury activates the complement system
- Three complement activation pathways (**classical**, **lectin**, and **alternative)** eliminate or clear infection, or damaged host cells; however, dysregulation can cause excessive complement activation and organ damage
- Terminal complement activation can be measured by elevated levels of **sC5b-9 i**n blood



Gavriilaki. Exp Hematol Oncol. 2021 Dec 19;10(1):57.

Figure: Jodele S, et Al.. Am J Hematol. 2023 Feb 6.

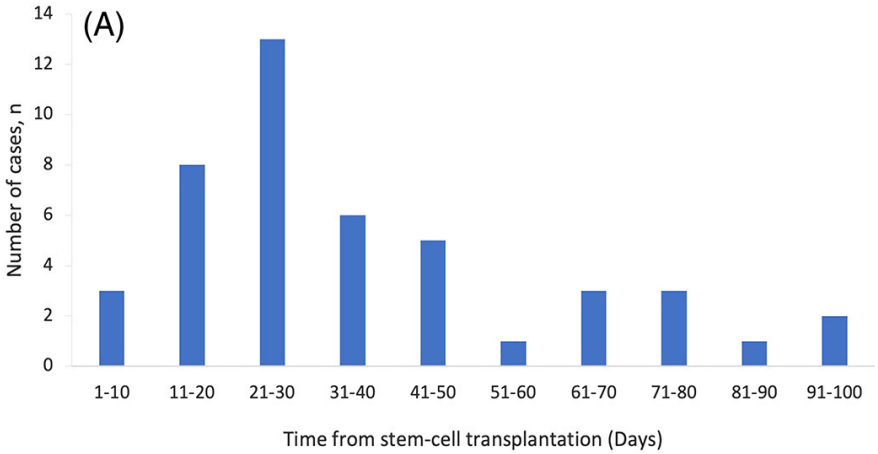
Epidemiology of HSCT-TMA
Incidence by Transplant Type and Patient's Age

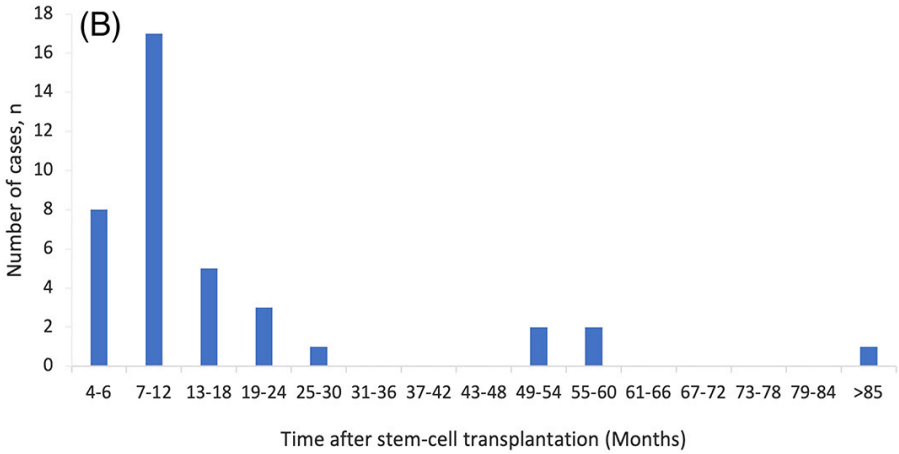
Type of Transplant	Incidence in Children	Incidence in Adults
Allogeneic HSCT	19% to 30% [2]	4% to 68% [1]
Autologous HSCT	10% [2]	Not well studied

[1]: Gavriilaki. Exp Hematol Oncol. 2021 Dec 19;10(1):57.
[2] Dandoy, Blood Adv. 2021 Jan 12;5(1):1-11

HSCT-TMA: time of onset

TA-TMA is most often described as an early event in allo-HSCT with a time of onset between 32 and 86 days, although a recent study by Heybeli et al. [1] documented a bimodal distribution of TA-TMA, with a first peak at day 27 and a second peak around day 200.





[1] Heybeli, C. et al. Am. J. Hematol. 2020, 95, 1170–1179.

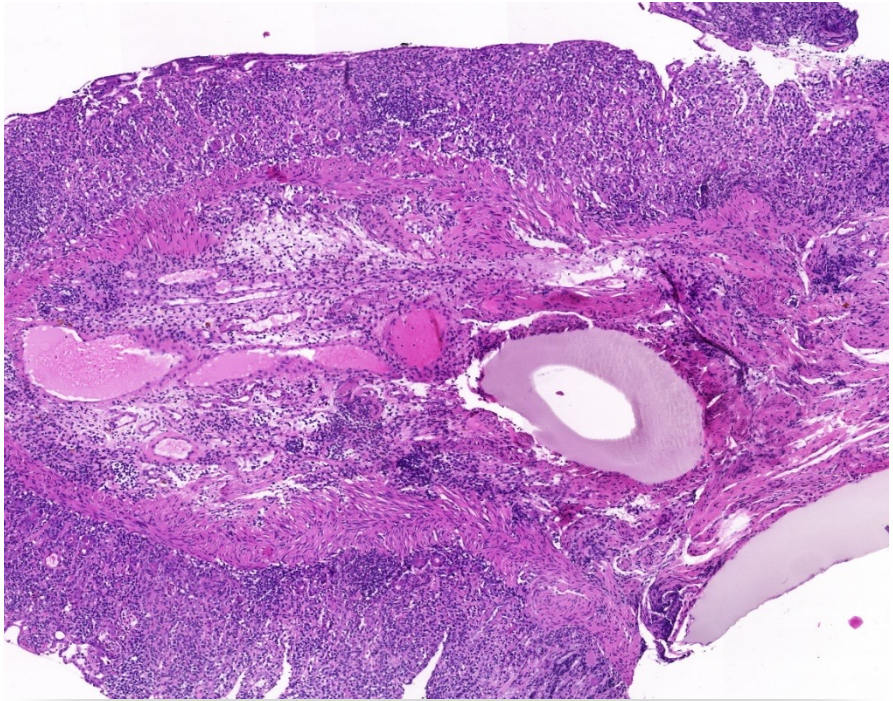
Multi-Organ Injury in HSCT-TMA
Common Manifestations by Organ System

Organ	Manifestations
Renal	≥50% reduction in GFR from pre-HCT conditioning value calculated by serum creatinine or increase in serum creatinine≥2 times baseline
Pulmonary	Any need for positive-pressure ventilation for >24 hours in the absence of definite etiology (i.e adenovirus pneumoniae, fluid overload or severe sepsis), diffuse alveolar hemorrhage
Cardiovascular	Pulmonary hypertension diagnosed by a cardiologist using cardiac catheterization, or pulmonary hypertension diagnostic criteria on echocardiography
Serositis	Clinically significant serositis (pleural or pericardial effusions or ascites) requiring medical therapy (i.e diuretics) or dreinage in the absence of other causes (eg, VOD/SOS, congestive heart failure)
Central Nervous System	Confusion, altered mental status, seizures with or without imaging evidence of posterior reversible encephalopathy syndrome (PRES)
GI	GU bleeding and/or intestinal strictures requiring medical or surgical interventions.

Schoettler ML. Transplant Cell Ther. 2023 Mar;29(3):151-163

HSCT-TMA: the role of Histologic Tissue Evaluation

- GvHD often **co-exist** with TA-TMA and both conditions may require simultaneous therapy.
- TA-TMA and GvHD are known **to trigger one another** which could explain the overlap in their clinical picture.
- The most challenging **differential** is between intestinal TA-TMA and intestinal GvHD.
- Tissue biopsies are useful but **not mandatory** for diagnosis.



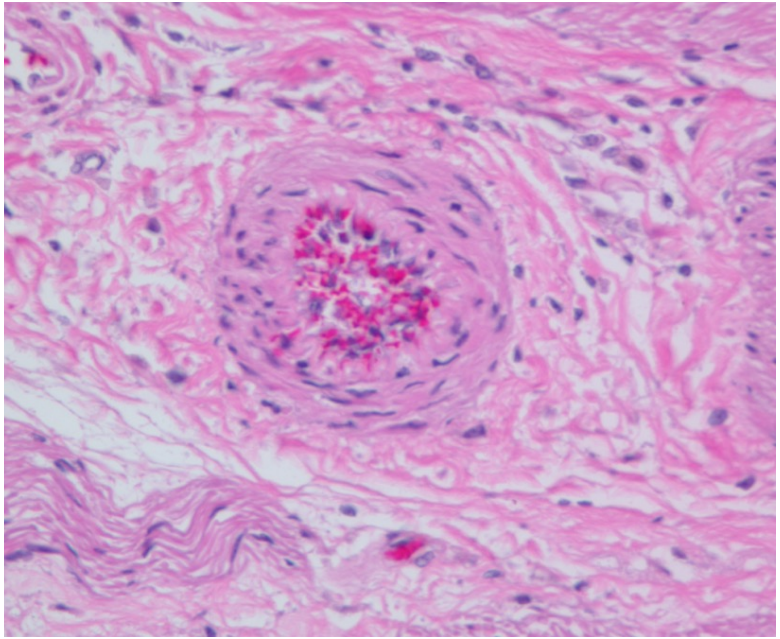
Jodele S. Am J Hematol. 2023 Feb 6.

By courtesy of Dr A. Gianatti, Pathology Unit of Papa Giovanni XXIII Hospital, Bergamo (Italy)

HSCT-TMA: the role of Histologic Tissue Evaluation

- Loss of glands
- Mucosal hemorrhages
- Intraluminal schistocytes
- Intraluminal fibrin (debris)
- Intraluminal microthrombi
- Endothelial cell swelling
- Endothelial cell denudation
- Total mucosal denudation

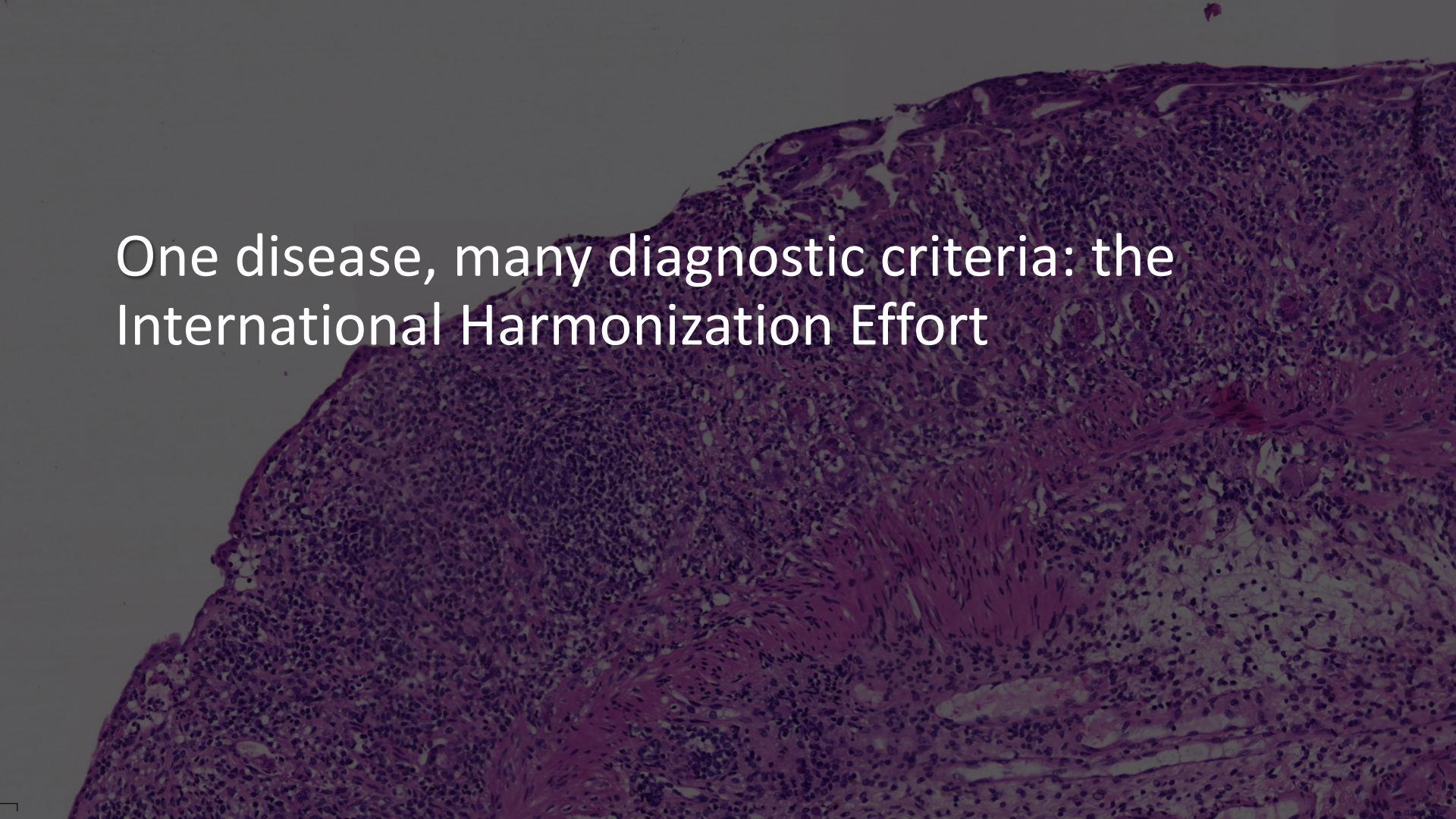
Microangiopathy in Mesenteric Vessel



El-Bietar J. Biol Blood Marrow Transplant. 2015;21:1994–2001

Warren M. Arch Pathol Lab Med. 2017;141(11):1558-1566

One disease, many diagnostic criteria: the International Harmonization Effort



The diagnosis of HSCT-TMA: historical Lack of Consensus on Diagnostic Criteria

Parameter	*CTN 2005*[8]	*IWG 2007*[9]	*Overall TMA, Cho* et al.[7]	*TMA by Jodele* et al.[5]
Schistocytes	⩾2/HPF	>4%	⩾2/HPF	Present
Serum LDH	Elevated	Sudden or persistent elevation	Elevated	Elevated
Renal and/or neurological dysfunction	Serum creatinine 2× baseline or 50% dec'd creatinine clearance	NA	NA	Proteinuria ⩾30 mg/dL or hypertension
Direct and indirect Coombs test	Negative	NA	Negative	NA
Thrombocytopenia	NA	*De novo* prolonged or progressive	*De novo* prolonged or progressive	*De novo*
Anemia	NA	Decreased Hb or increased transfusion requirements	Decreased Hb	Decreased Hb or increased transfusion requirements
Serum haptoglobin	NA	Decreased	Decreased	NA
Terminal complement activation	NA	NA	NA	Elevated sC5b-9

Abbreviations: CTN = Blood and Marrow Transplant Clinical Trials Network; Hb = hemoglobin; HPF = high-power field; IWG = European LeukemiaNet International Working Group; LDH = lactate dehydrogenase; NA = not applicable; TA-TMA = transplantation-associated thrombotic microangiopathy.

8. Ho VT. Et al. Biol Blood Marrow Transplant. 2005;11(8):571-575; 9. Ruutu T. et al. Haematologica. 2007;92(1):95-100
7. Cho BS. Et al. Transplantation. 2010;90(8):918-926; 5. Jodele S. et al. Blood. 2014;124(4):645-653.

The diagnosis of HSCT-TMA: International Effort to Establish Harmonization Criteria

Problem:

the lack of harmonization of diagnostic/prognostic markers for HSCT-TMA makes it difficult to compare the results of interventional trials or conduct multi-institutional studies

Solution:

convene an expert panel of nominated representatives from 4 organizations:

- American Society for Transplantation and Cellular Therapy
- Center for International Bone Marrow Transplant Research
- Asia-Pacific Blood and Marrow Transplantation
- European Society for Blood and Marrow Transplantation

Schoettler ML. Transplant Cell Ther. 2023 Mar;29(3):151-163

Harmonization Criteria for the diagnosis of HSCT-TMA

HSCT-TMA can be diagnosed using clinical and laboratory criteria ***or*** tissue biopsy of kidney or gastrointestinal tissue; **however, biopsy is not required.**

≥ 4 of the following 7 consensus diagnostic criteria must occur twice within 14 days:

- **Anemia** (failure to achieve transfusion independence despite neutrophil engraftment, hemoglobin decline by 1 g/dL, or new-onset transfusion dependence). DAT negativity.
- **Thrombocytopenia** (failure to achieve platelet engraftment, higher-than-expected transfusion needs, refractoriness to platelet transfusions, or 50% reduction in baseline platelet count after full platelet engraftment)
- **Elevated LDH** (≥ ULN)
- **Schistocytes** (present)
- **Hypertension (**Children: > 99th percentile for age, Adults: Systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg)
- **Elevated sC5b-9** (≥ ULN)
- **Proteinuria** (rUPCR ≥ 1 mg/mg)

Schoettler ML. Transplant Cell Ther. 2023 Mar;29(3):151-163

Harmonization Criteria to define high-risk HSCT-TMA

Patients with any of the following features should be stratified as having **high-risk HSCT-TMA**:

- Elevated sC5b-9
- Peak LDH > 2 times the ULN
- rUPCR ≥ 1 mg/mg
- Multiorgan dysfunction
- Concurrent grade II-IV acute GvHD
- Infection (bacterial or viral)

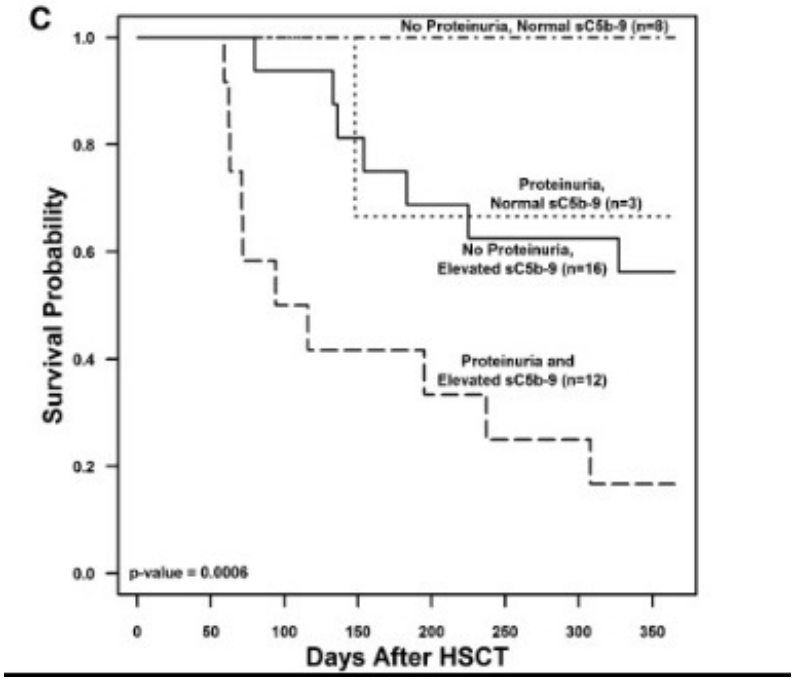
Schoettler ML. Transplant Cell Ther. 2023 Mar;29(3):151-163

A new biomarker: focus on C5b-9

Terminal Complement Activation Is an Indicator of Reduced Survival

- **Proteinuria** (≥ 30 mg/dl or urine protein to creatinine ratio ≥ 2 mg/mg) and elevated markers of complement activation (**sC5b-9**) at TMA diagnosis are associated with poor outcome [1].

- **Increased organ injury** also associated with sC5b-9 levels [2].

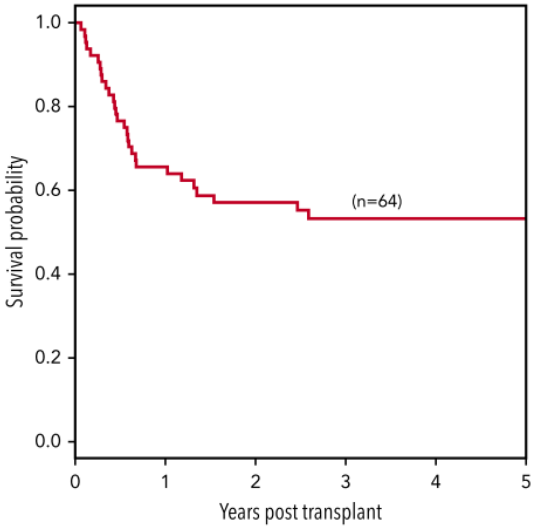


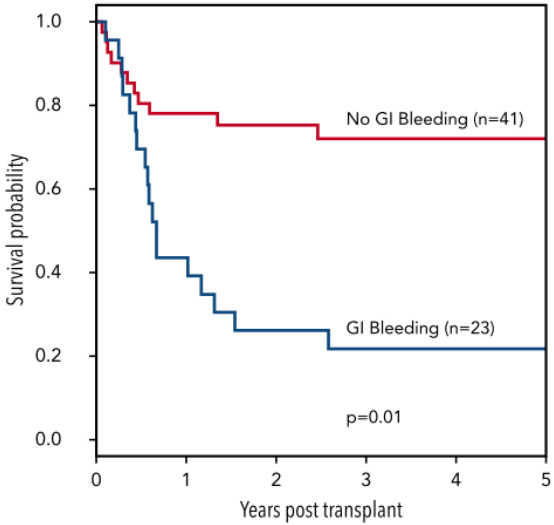
[1] Jodele S. Blood. 2014 Jul 24;124(4):645-53. [2] Jodele S. Transplant Cell Ther. 2022;28(7):392.e1-392.e9

sC5b-9 Levels Predict Response to Complement Blocker Therapy

- Subjects with a higher sC5b-9 at HSCT-TMA diagnosis were **less likely to respond** to eculizumab treatment [1]

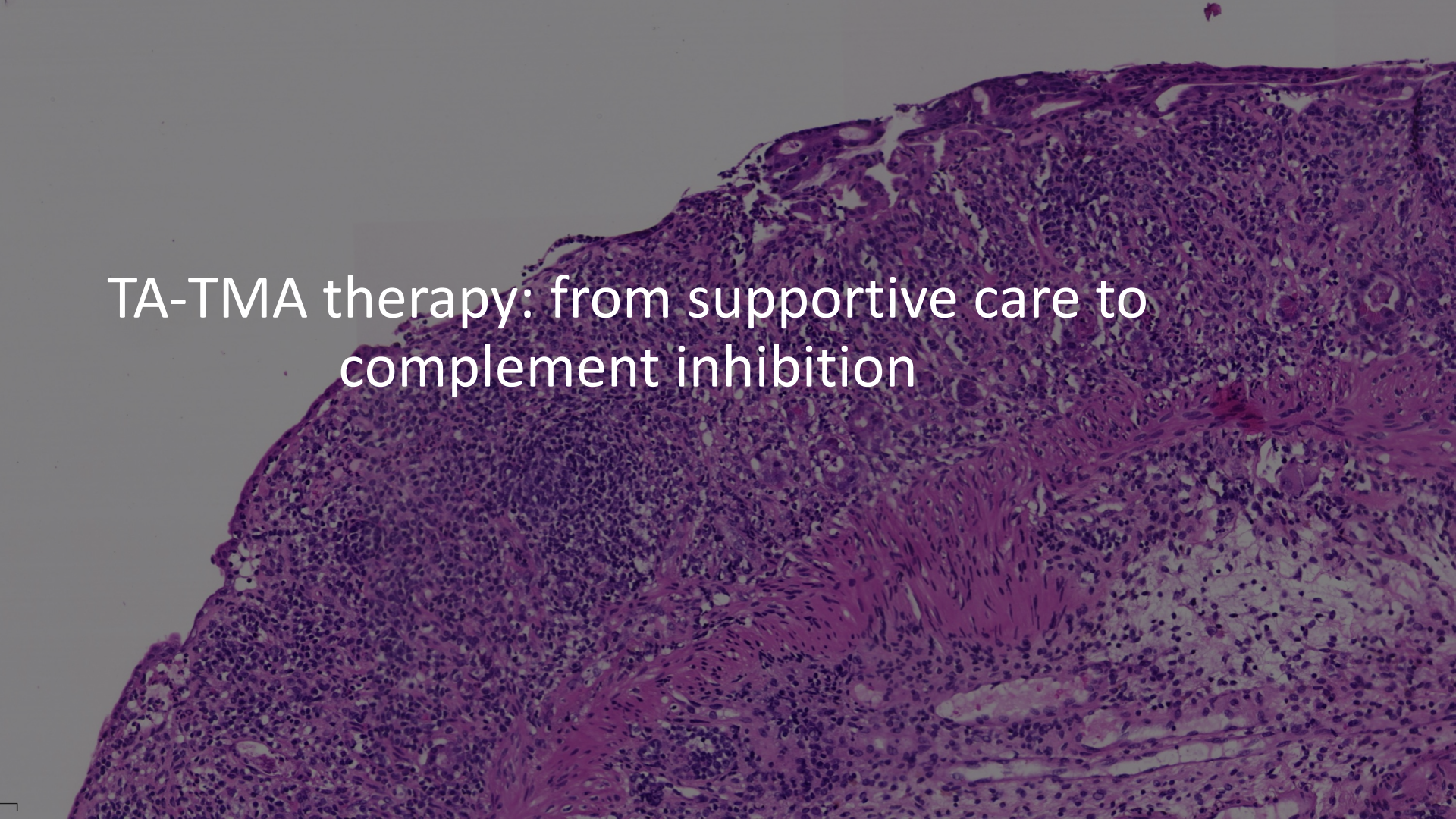
- Subjects with a higher sC5b-9 at HSCT-TMA diagnosis **required more eculizumab doses for treatment** (*P* = .0004) [1]



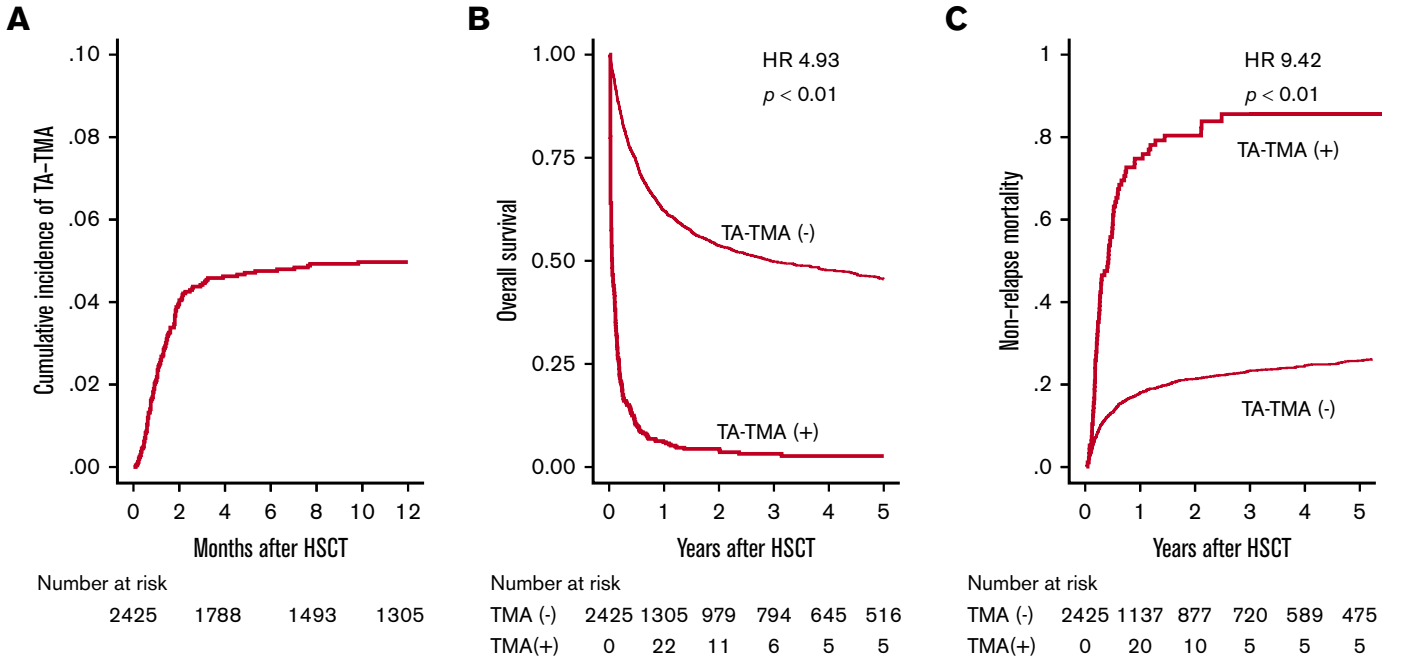


[1] Jodele S. Blood. 2020;135(13):1049-1057.

TA-TMA therapy: from supportive care to complement inhibition



The natural history of HSCT-TMA: the Kyoto Stem Cell Transplantation Group (KSCTG)

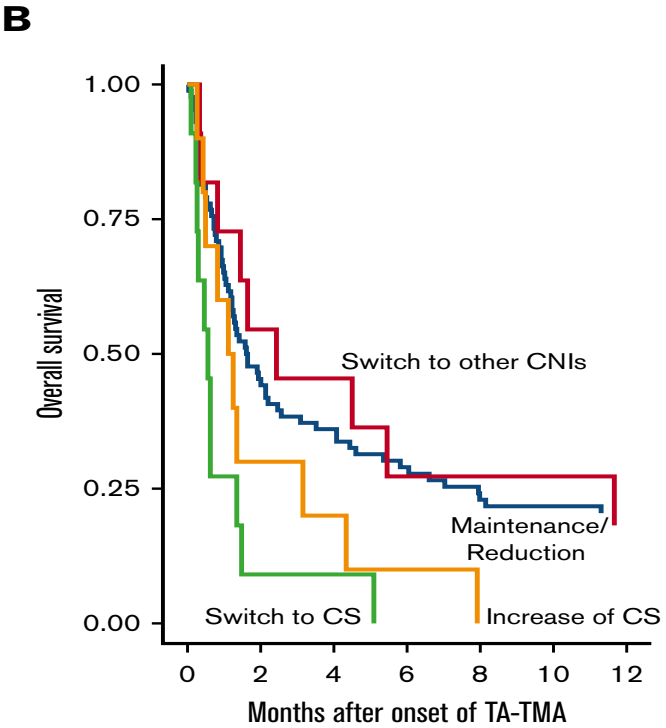


Blood advances 14 july 2020 volume 4, number 13, 3169-3179

Should we withdraw CNIs as a therapeutic intervention for HSCT-TMA?

Key Points

- aGVHD and VOD/SOS syndrome were associated with a higher incidence of TA-TMA, performance status, and HLA mismatch.
- CNI maintenance or reduction induced a better outcome, whereas replacement with steroids and plasma infusion/exchange were not recommended.



Blood advances 14 july 2020 volume 4, number 13, 3169-3179

Should we withdraw CNIs as a therapeutic intervention for HSCT-TMA?

- In a large, single-center, retrospective study [1] discontinuation of CNIs failed to improve survival, no matter the type of GvHD prophylaxis
- This may be attributed to a subsequent development or exacerbation of GvHD

Standard practice at our center

- Avoid inappropriate high blood levels of CNIs
- Continue GvHD prophylaxis with CNIs unless severe nephrotoxicity develops

[1] Li, A. et al. Biol Blood Marrow Transpl. 2019, 25, 570–576.

Complement Inhibitors for Management of HSCT-TMA
Overview of Agents Under Investigation

Agent	Mechanism	Class	Status	Clinical Trials (Patient Ages)
Eculizumab[a,b]	C5 inhibition	mAb	• Phase 2 ongoing • **FDA approved for PNH, aHUS, gMG, and NMOSD**	NCT03518203 (pediatric/adult)
Narsoplimab[c]	MASP-2 inhibition	mAb	• Phase 2 complete • **Currently pursuing FDA approval for HSCT-TMA**	NCT02222545 (adult)
Ravulizumab[d-f]	C5 inhibition	mAb	• Phase 3 ongoing • **FDA approved for PNH, aHUS, and gMG**	NCT04543591 (adolescent/adult) NCT04557735 (pediatric)
Nomacopan[g]	C5 and LTB4 inhibition	Recombinant protein	• Phase 3 ongoing	NCT04784455 (pediatric)
Pegcetacoplan[h-i]	C3 inhibition	PEGylated recombinant protein	• Phase 2 ongoing • **FDA approved for PNH**	NCT05148299 (adult)

aHUS, atypical hemolytic uremic syndrome; gMG, generalized myasthenia gravis; LTB4, leukotriene B4; mAb, monoclonal antibody; MASP-2, mannan-binding lectin-associated serine protease 2; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal hemoglobinuria. a. NCT03518203; b. Eculizumab [PI]. Approved 2007; Revised Nov 2020; c. NCT02222545; d. NCT04543591; e. NCT04557735; f. Ravulizumab-cwvz [PI]. Approved 2018; Revised April 2022; g. NCT04784455; h.NCT05148299; i. Pegcetacoplan [PI]. Approved May 2021.

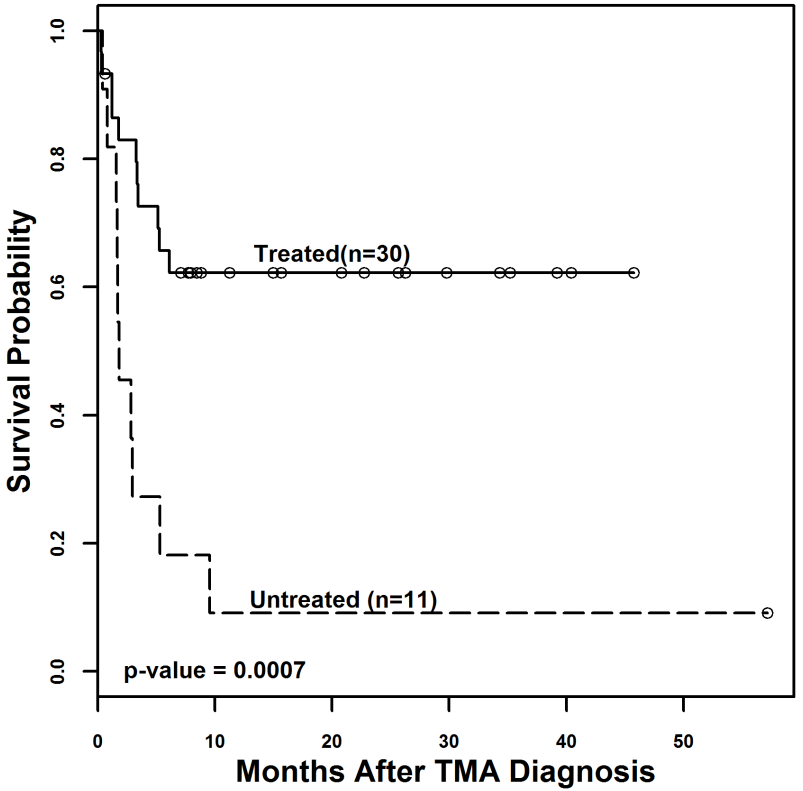
Eculizumab

Anti-C5 monoclonal antibody

- Inhibits cleavage of C5 to C5a and C5b
- Blocks C5b-9 from forming on the surface of endothelial cells

Clinical development

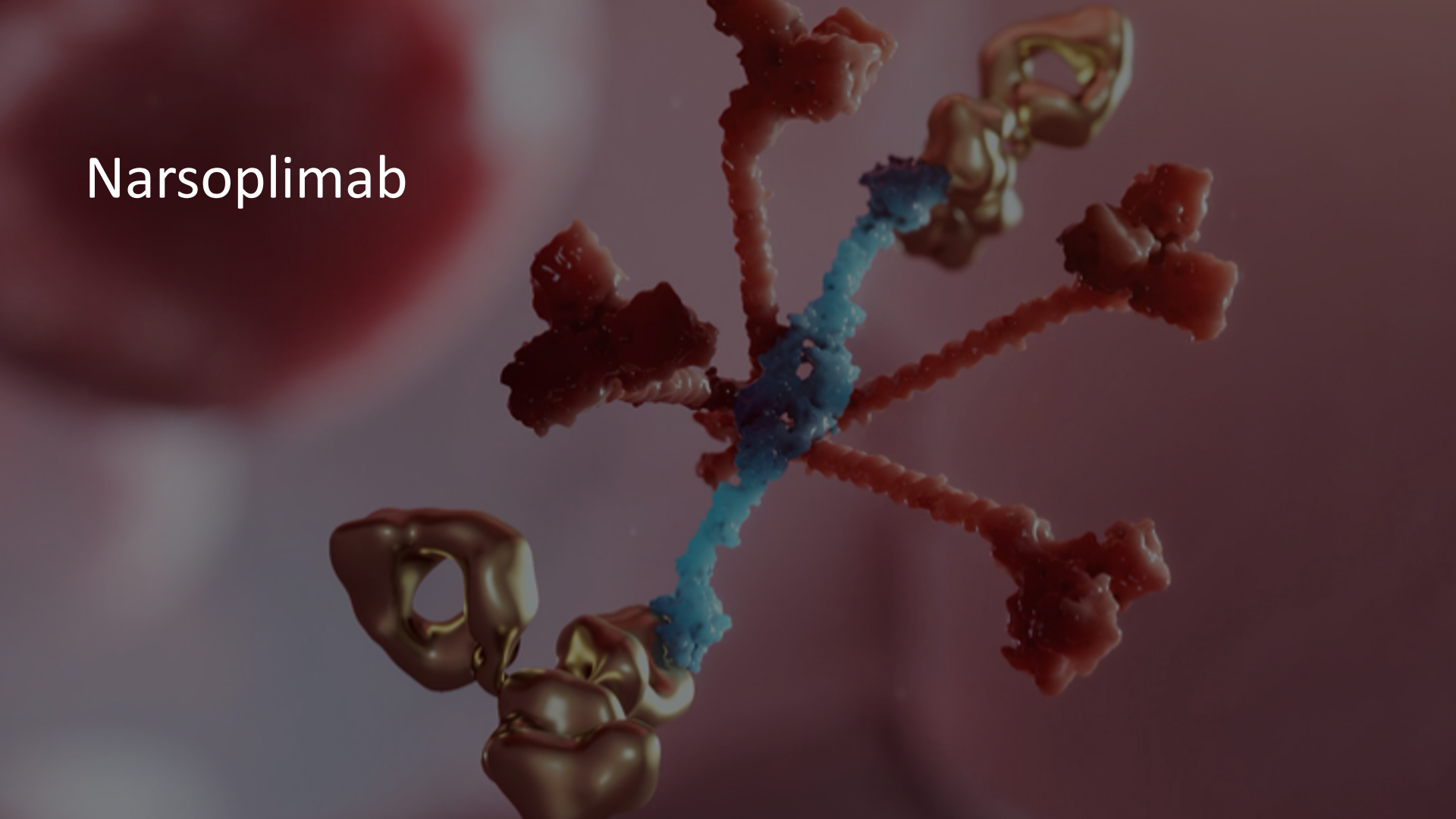
- Currently approved by FDA for PNH, aHUS, gMG, and NMOSD
- Approved by EMA (but not yet available in most EU countries)
- Phase 2 trial in HSCT-TMA is ongoing [2]
- Higher risk of **infections**



Survival of Pediatric Patients With Post-Allogeneic HSCT-TMA *Comparing Outcomes After Eculizumab With Historical Controls [1]*

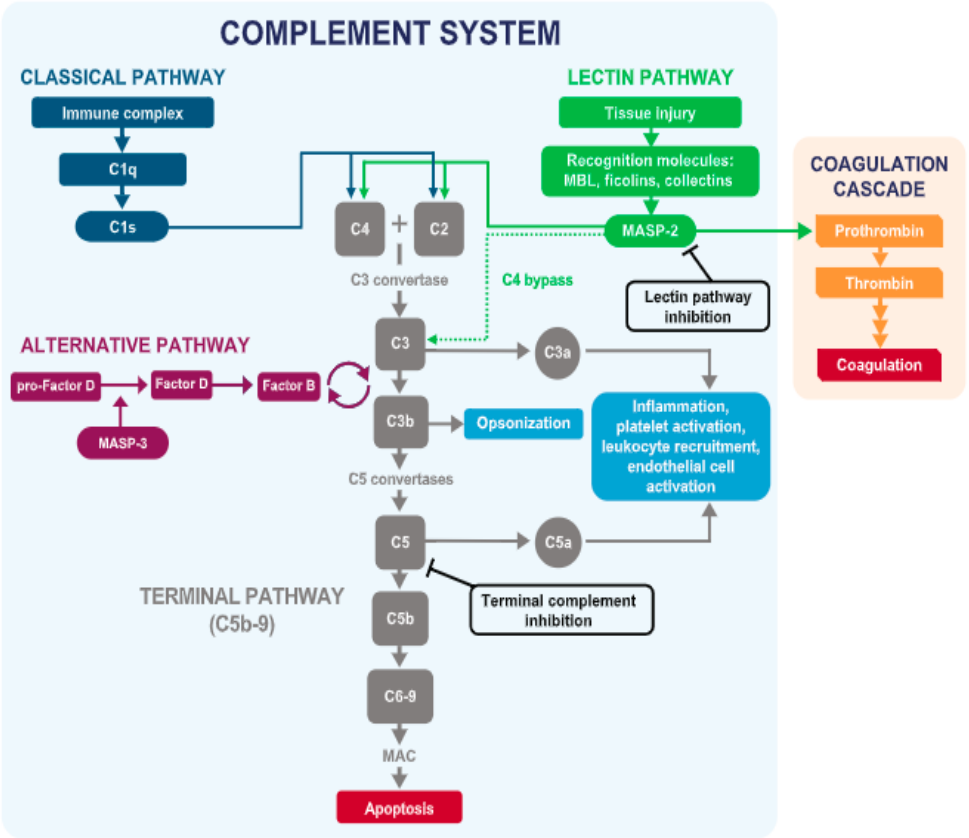
[1]Jodele S. et Al. *Blood*. 2020;135(13):1049-1057
[2] NCT03518203

Narsoplimab



Narsoplimab

- Is a fully human monoclonal antibody
- Binds to MASP-2, the effector enzyme of the lectin pathway of complement
- Leaves intact the effector function of the adaptive immune response, important for fighting infection
- Blocks MASP-2-mediated coagulation (conversion of prothrombin to thrombin and activation of Factor XII to XIIa) and activation of kallikrein
- **The only agent that targets MASP-2 and blocks the lectin pathway**



Gavriilaki E *et al. Exp Hematol Oncol*. 2021;10:57.

A Phase 2 Trial with Narsoplimab for high-risk HSCT-TMA

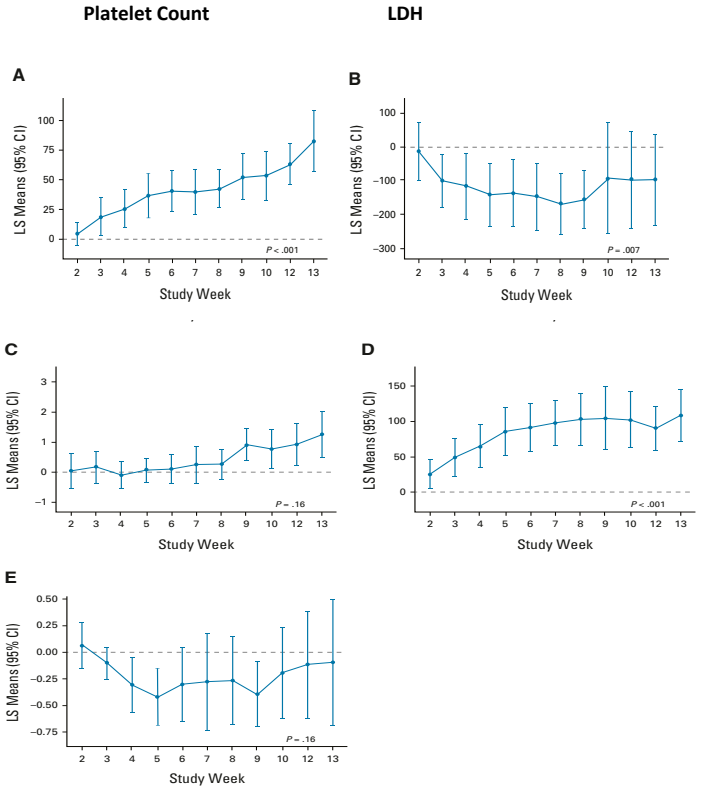
- Single-arm, open-label, phase 2 study of 28 poor-risk patients with persistent HSCT-TMA
- Dosing regimen: 4 mg/kg IV narsoplimab once weekly for ≥ 4 weeks

Primary endpoints:

- Efficacy (response-based):
  - Improvement in TMA laboratory markers of platelet count and LDH
  - Improvement in clinical status
  - Safety and tolerability

Secondary endpoints:

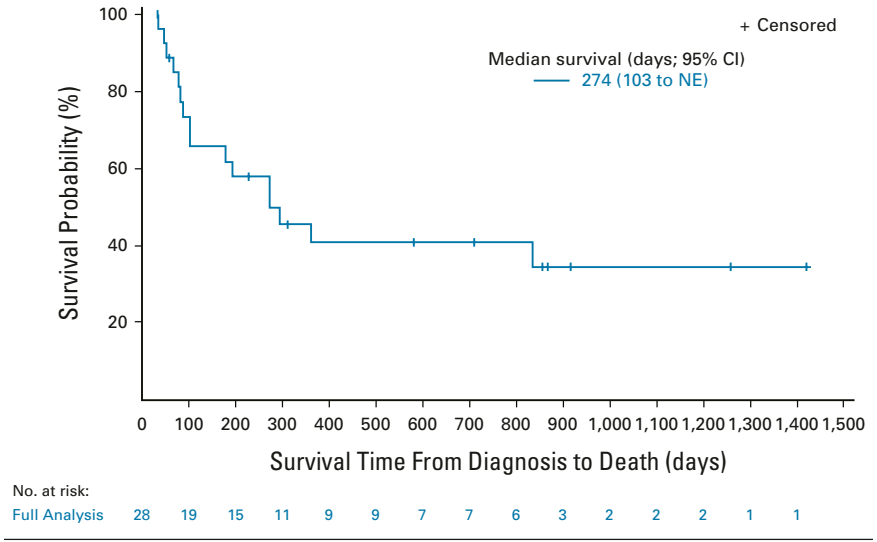
- Survival (100-day and overall)
- Change from baseline in laboratory markers



Khaled SK, et al. ….and Rambaldi A.: J Clin Oncol. 2022;40:2447-2457.

A Phase 2 Trial with Narsoplimab for high-risk HSCT-TMA

Response, n (%)	FAS (N = 28)
Responders [95% CI]	**17/28 (61) [41, 79]**
Improvement in TMA markers, overall	**17/28 (61)**
Platelet count improvement	14/23 (61)
Baseline ≤ 20×10^9	3/6 (50)
Baseline > 20×10^9	11/17 (65)
LDH improvement to < 1.5 × ULN	21/28 (75)
Improvement in organ function, overall	**20/27 (74)**
Kidney function	18/27 (67)
Pulmonary function	NA
Neurologic function	3/6 (50)
GI function	1/1 (100)
Achievement of transfusion independence, overall	**12/25 (48)**
From platelet transfusions	8/18 (44)
From RBC transfusions	11/22 (50)



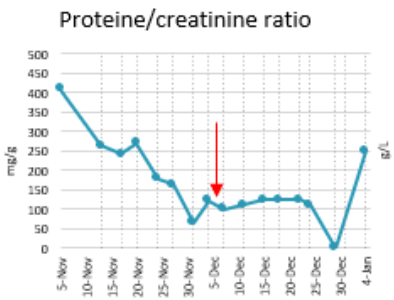
FAS, full analysis set;

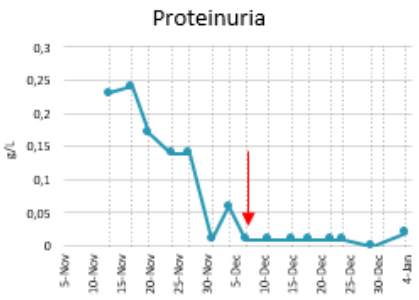
MAGIC, Mount Sinai Acute GVHD International Consortium; NA, not applicable.

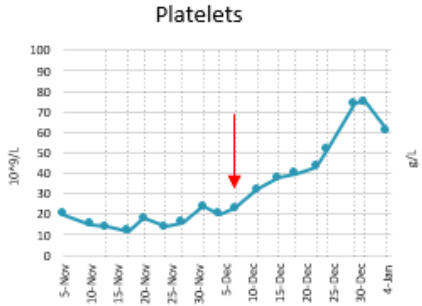
Khaled SK, et al. ….and Rambaldi A.: J Clin Oncol. 2022;40:2447-2457.

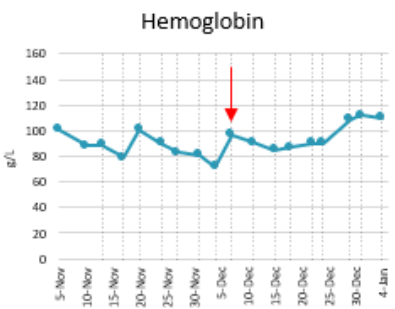
Case study: a 67-year-old patient with GvHD and TA-TMA

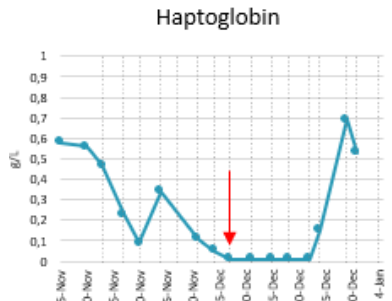
Narsoplimab treatment schedule: 4 mg/kg twice a week, a total of 16 doses (8 weeks)

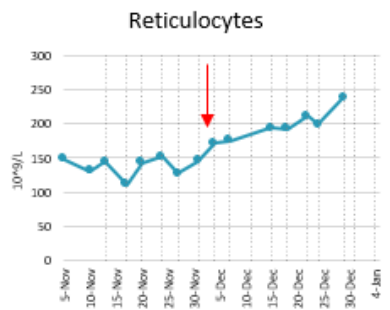


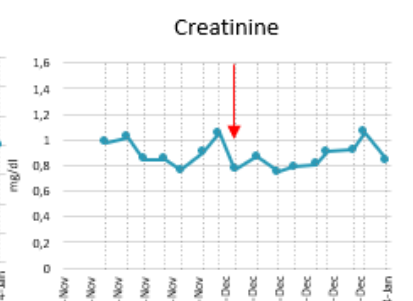












Case study: a 67-year-old patient with high risk MDS

- **08/08/2023 (last follow up, day +1082)**

Disease status:

- CR confirmed (immunophenotype, karyotype) on day +30, +60, +91, +182, +382, +727

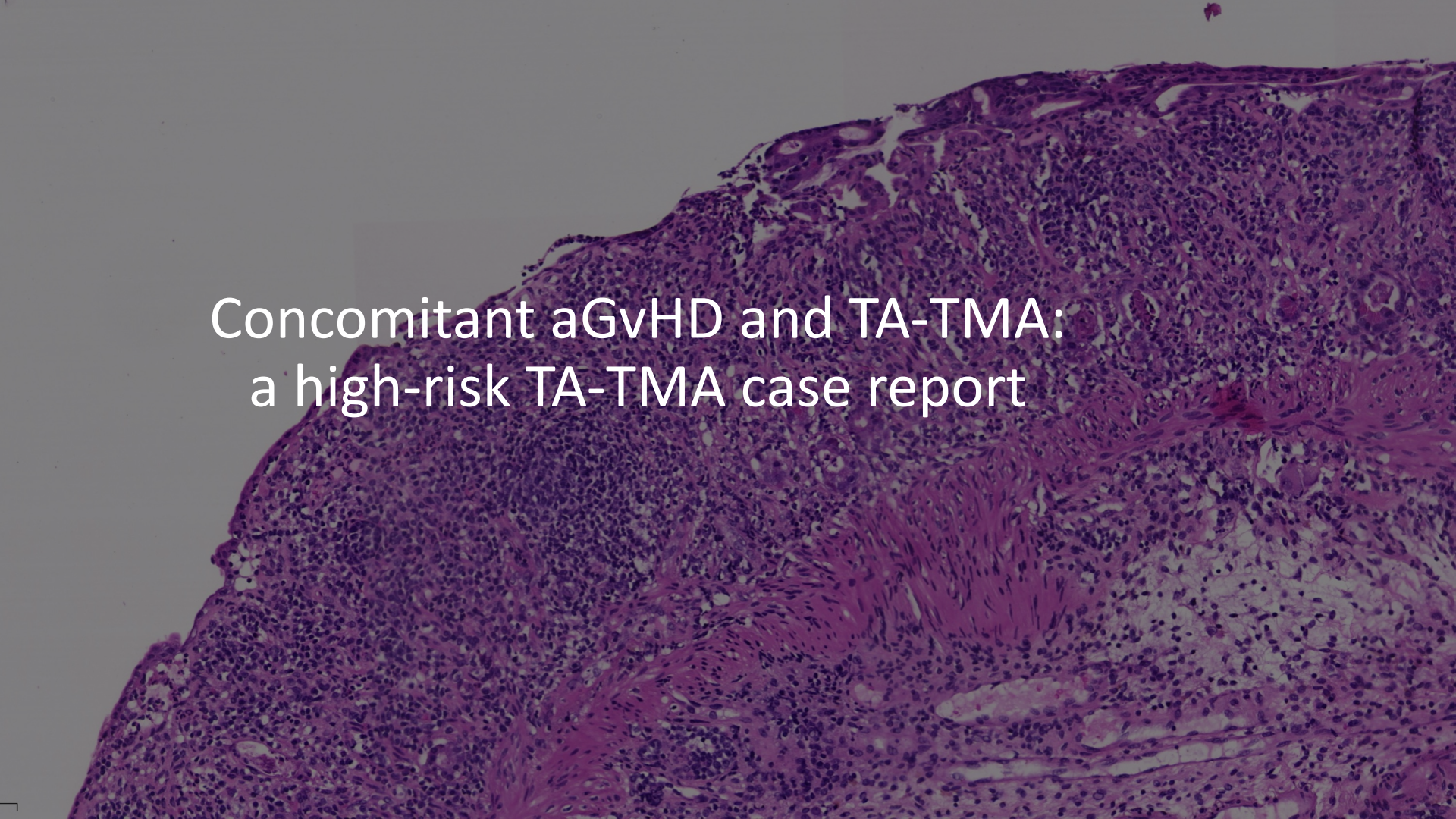
Chimerism:

- Full donor on day +30, +60, +182, +382, +727

Blood count:

- Hb: 13,5 g/dL
- PLT: 81x10^9/L
- WBC: 4.5x10^9/L
- **Kidney function:**
- Creatinine: 0.91 mg/dL
- **GvHD**: No
- **TA-TMA**: No clinical or laboratory evidence

Concomitant aGvHD and TA-TMA: a high-risk TA-TMA case report



Conclusions

- HSCT-TMA is a rare, but frequently lethal transplant complication
- There are currently **no approved treatments** for HSCT-TMA.
- A concomitant diagnosis of **GvHD** and **TA-TMA** is frequent and represents a **therapeutic challenge.** Patients with acute GvHD and concomitant or sequential TA-TMA should **not withdraw CNIs.**
- **Complement inhibition** is increasingly recognized as a rationale, patho-physiologically driven, potentially effective treatment strategy.
- In a poor risk population with HSCTA-TMA, **Narsoplimab** proved to be effective and safe with a low rate of infectious complications.


Thank you