Narsoplimab (OMS721) For the Treatment of Adult Hematopoietic Stem Cell Transplant-associated Thrombotic Microangiopathy

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Disclosures

Company name	Disclosure
Amgen	Advisory board, Research grant, Travel support
Novartis	Advisory board, Travel support
Pfizer	Advisory board
Celgene	Advisory board, Travel support
Italfarmaco	Advisory board, Research grant, Travel support
Gilead	Advisory board, Travel support
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Omeros	Advisory board

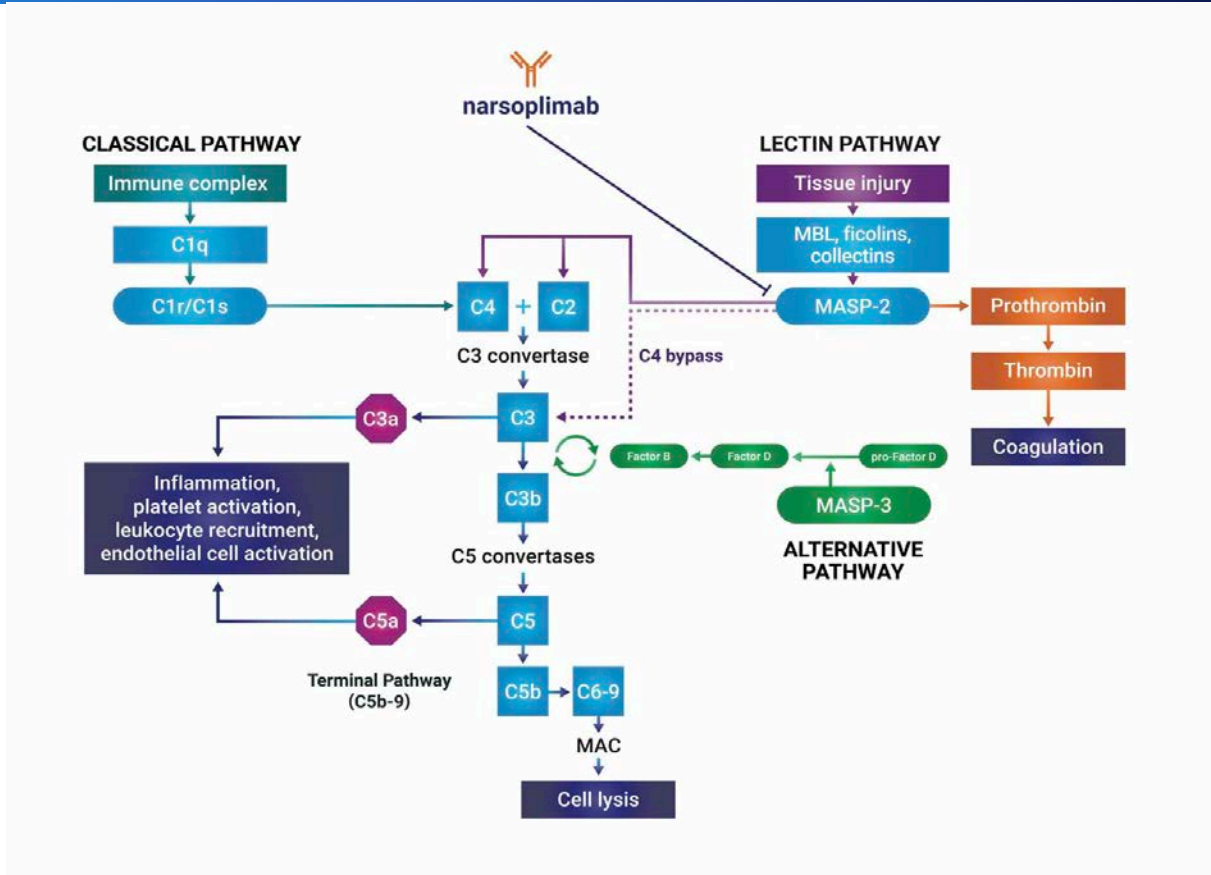
Hematopoietic Transplant-Associated Thrombotic Microangiopathy (HSCT-TMA): A Fatal Complication

- HSCT causes marked endothelial injury
  - Conditioning
  - Immunosuppressive drugs
  - Infection
- Endothelial injury causes “endothelial injury syndromes”
  - HSCT-TMA
  - GVHD
  - Diffuse alveolar hemorrhage
  - Veno-occlusive disease
  - Capillary leak syndrome
  - Idiopathic pneumonia syndrome
- Endothelial injury activates the lectin pathway of complement

Carreras E, Diaz-Ricart M. Bone Marrow Transplantation (2011) 46:1495-1502; Luft T, Benner A, et al., Lancet Haematol (2017) 4:e414-e423; Collard CD, Vakeva A, Morrissey MA, et al. Am J Pathol (2000) 156:1549-56.

Narsoplimab

- Narsoplimab (OMS721) is an investigational fully human IgG4 MoAb
- It binds to mannan-binding lectin-associated serine protease-2 (MASP-2)
- MASP-2 is the effector enzyme of the lectin pathway of complement
- Narsoplimab leaves the classical pathway function fully intact



Narsoplimab

- Narsoplimab has received orphan drug designations from both FDA and EMA
- Narsoplimab has been granted breakthrough therapy designation by FDA for HSCT-TMA and for IgA nephropathy
- Narsoplimab is also in Phase 3 clinical trials for other lectin pathway-associated diseases, including IgA nephropathy

HSCT-TMA Pivotal Trial: Design

- Single-arm, open-label design
- Initiated as a Phase 2 trial; following receipt of breakthrough therapy designation and discussion with FDA, converted to a pivotal trial
- Protocol specified that patients receive narsoplimab once weekly for ≥ 4 weeks

HSCT-TMA Pivotal Trial: Key Inclusion and Exclusion Criteria

Inclusion

- Are age ≥ 18 at screening (Visit 1)
- Persistent HSCT-TMA defined as having all of the following at least 2 weeks following modification or discontinuation of calcineurin inhibitors:
  - Platelet count < 150,000/μL
  - Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > ULN, or haptoglobin < LLN)
  - Renal dysfunction (doubling of serum creatinine compared with pre-transplant level).

Exclusion

- Had eculizumab therapy within 3 months prior to screening
- Positive direct Coombs test
- Active systemic bacterial or fungal infection requiring antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care is allowed)

HSCT-TMA Pivotal Trial: Objectives

Primary

- Response-based efficacy endpoint requiring:
  - Improvement in TMA laboratory markers of platelet count and lactate dehydrogenase (LDH)

    AND
  - Improvement in clinical status
- Safety and tolerability

Secondary

- Survival
- Change from baseline in laboratory markers

HSCT-TMA Pivotal Trial: Laboratory Endpoints

Improvement in Laboratory Markers

LDH < 1.5 UL

+

Platelet count

- Baseline ≤ 20,000/μL
  - Triple baseline and absolute count > 30,000 and freedom from platelet transfusion
- Baseline > 20,000
  - Increase by at least 50% and absolute count > 75,000 and freedom from platelet transfusion

HSCT-TMA Pivotal Trial: Clinical Endpoints

Organ	Criteria for Improvement in Clinical Outcome
Blood	Transfusion freedom
Renal	Reduction of creatinine > 40% or Normalization of creatinine and reduction of creatinine > 20% or Discontinuation of renal replacement therapy
Pulmonary	Extubation and discontinuation of ventilator support or Discontinuation of non-invasive mechanical ventilation (continuous positive pressure ventilation)
Gastrointestinal (Tissue diagnosis)	Improvement assessed using the gastrointestinal measures in the Mount Sinai Acute GVHD International Consortium
Neurological	Limited to stroke, PRES, seizures, weakness

Study Results

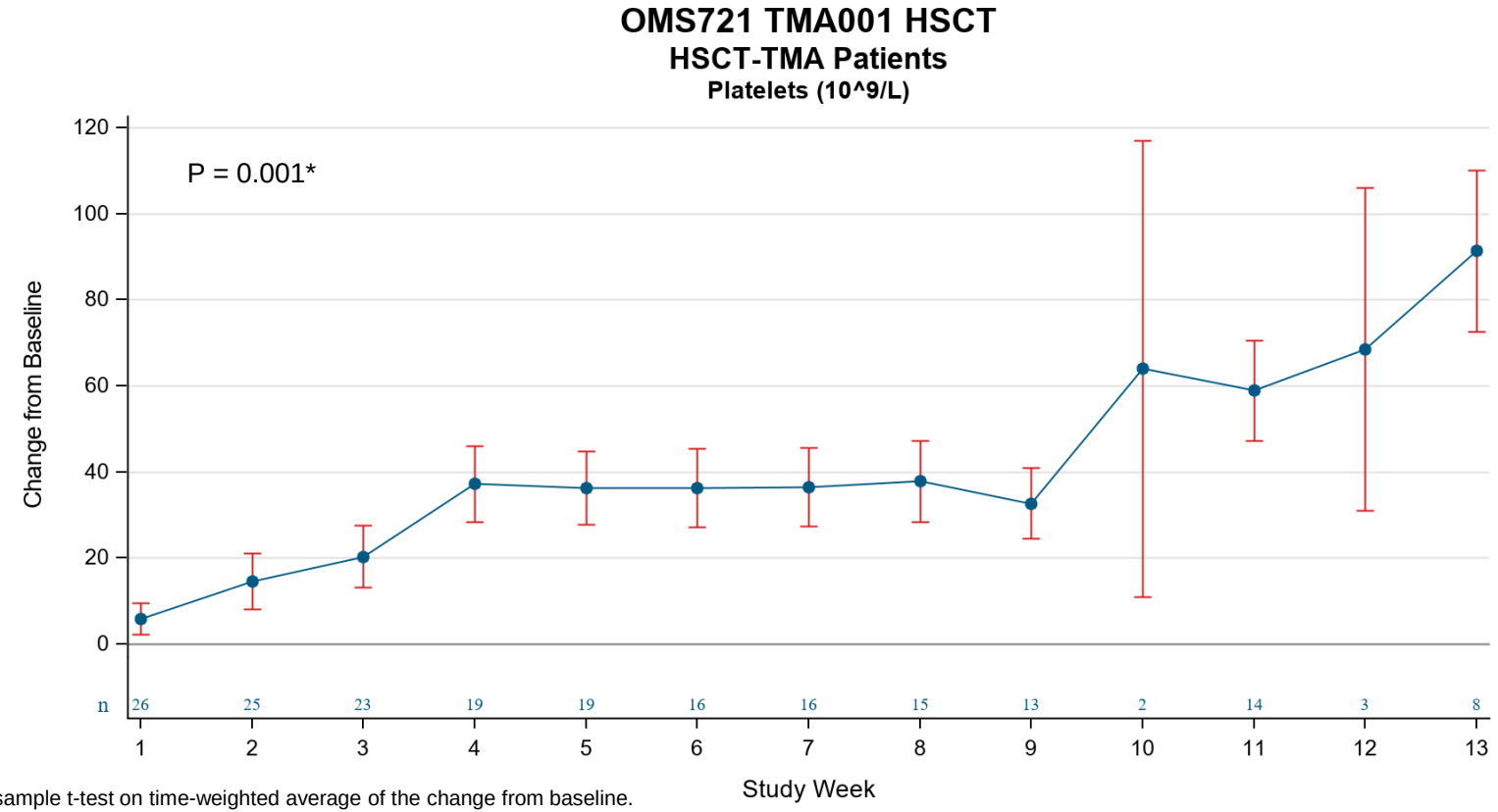
Study Population

Demographics	N = 28
Mean age (years)	48
Male gender, n (%)	20 (71)
Malignant underlying disease, n (%)	96
Risk factors:	
Presence of GVHD, n (%)	18 (64)
Significant infection, n (%)	21 (75)
Non-infectious pulmonary complications (IPS or DAH), n (%)	4 (14)
Neurological signs, n (%)	14 (50)

The study population was high-risk – 93% had multiple risk factors for poor outcomes

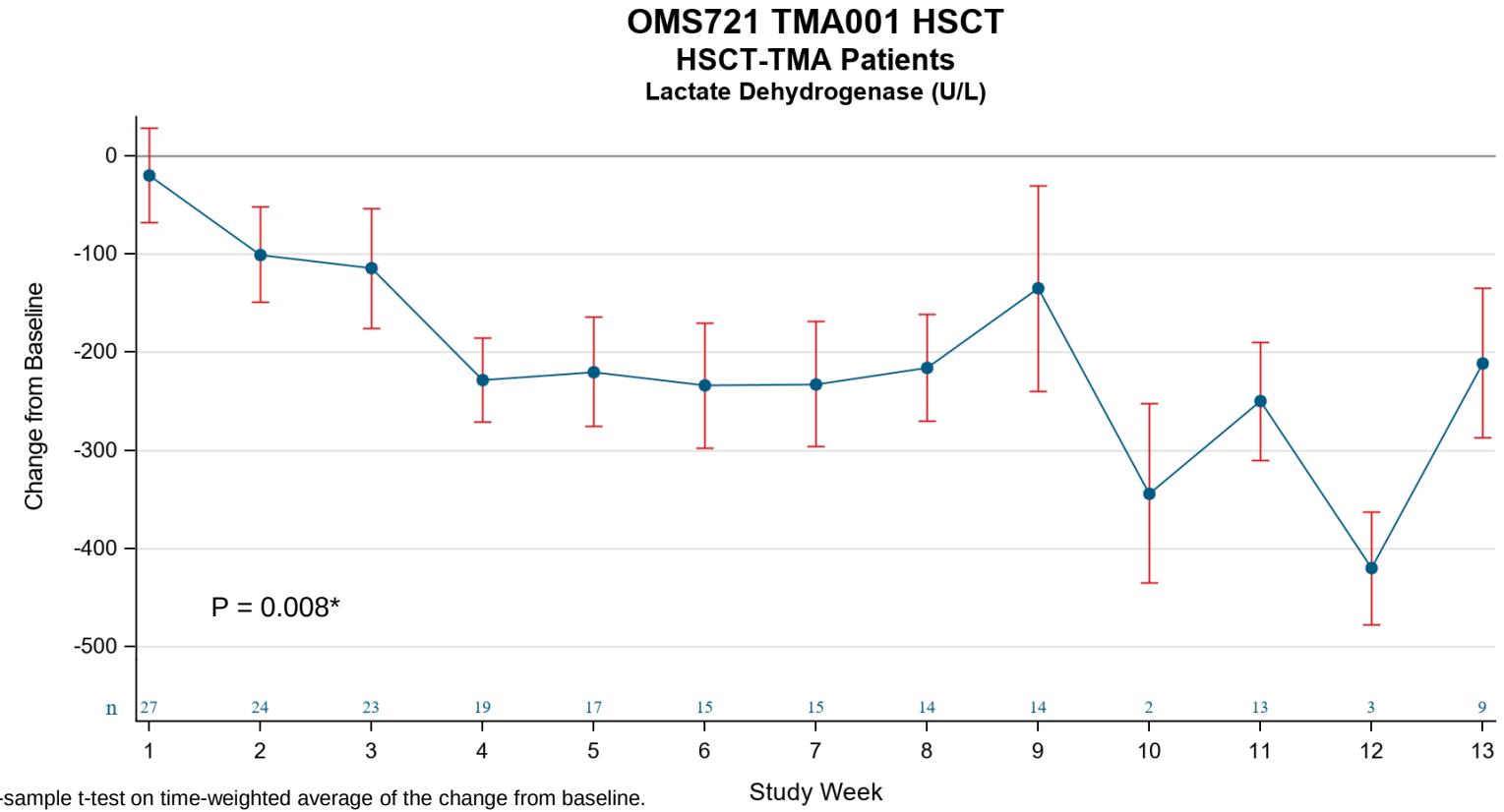
GVHD, graft versus host disease; IPS, idiopathic pulmonary syndrome; DAH, diffuse alveolar hemorrhage.

Platelet Count Change from Baseline Over Time in All Patients



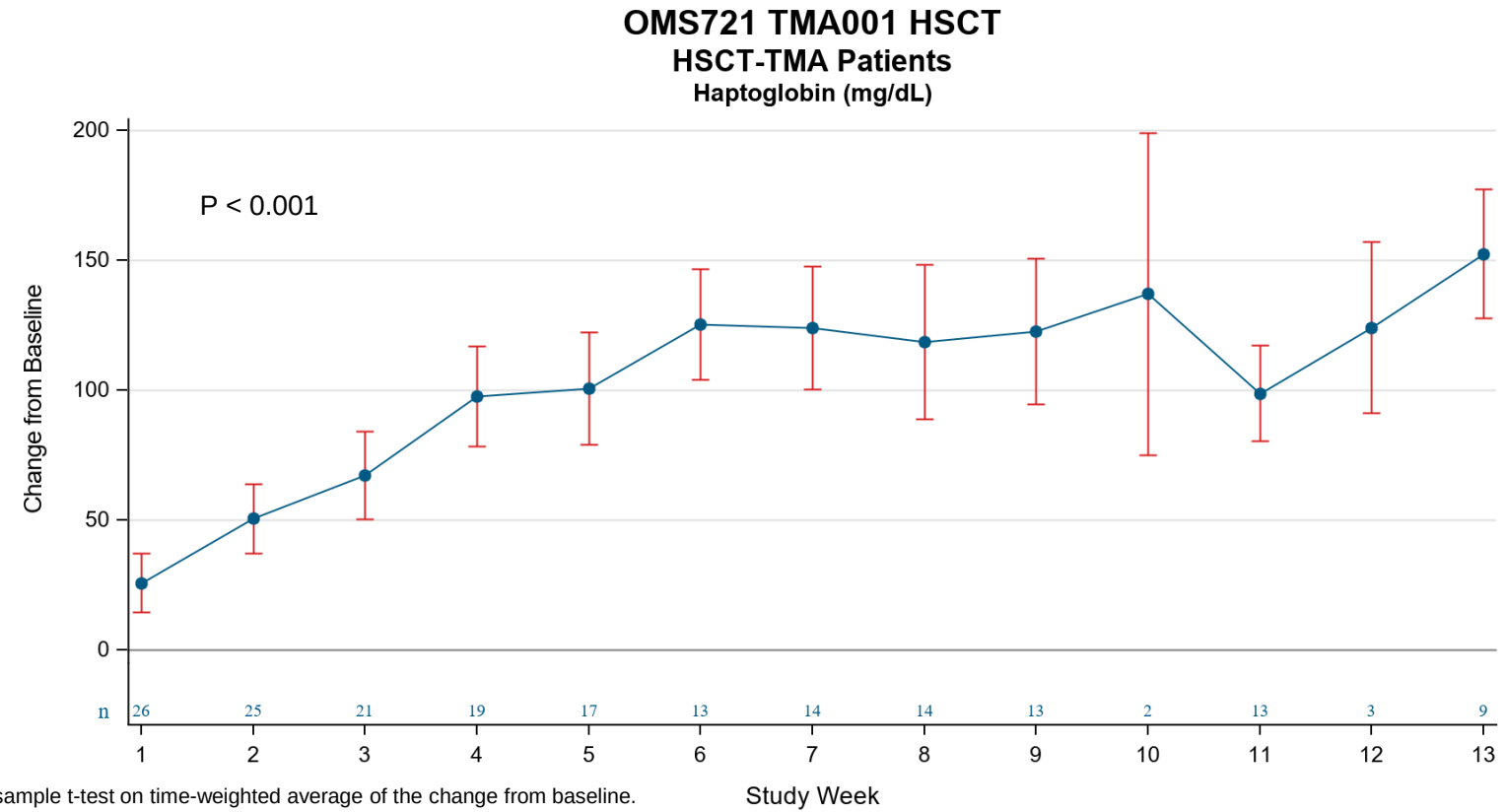
* One-sample t-test on time-weighted average of the change from baseline.

LDH Change from Baseline Over Time in All Patients



* One-sample t-test on time-weighted average of the change from baseline.

Haptoglobin Change from Baseline Over Time in All Patients



* One-sample t-test on time-weighted average of the change from baseline.

Response

Population	Complete Response Rate (%)
All treated patients (N=28) (95% CI)	54% (15/28) (34% to 72%)
Patients treated per protocol (≥ 4 weeks of dosing) (n=23) (95% CI)	65% (15/23) (43% to 84%)

100-Day Survival Following HSCT-TMA Diagnosis

Population	100-Day Survival
All treated patients (N=28)	68% (19/28)
Patients treated per protocol (≥ 4 weeks of dosing) (n=23)	83% (19/23)
Treatment responders (n=15)	93% (14/15)

Safety and Tolerability: Most Common Adverse Events in >10% of Patients

- Narsoplimab was well tolerated in this very sick population with multiple comorbidities
- The most commonly reported adverse events were nausea, vomiting, diarrhea, hypokalemia, neutropenia and fever
- The observed adverse events are comparable to those typically seen in the post-transplant population
- 21% of patients died during the trial due to causes common in HSCT

Preferred Term, n (%)	(N = 28)
Any Event	26 (92.9)
Vomiting	9 (32.1)
Diarrhoea	8 (28.6)
Hypokalaemia	7 (25)
Nausea	7 (25)
Neutropenia	7 (25)
Pyrexia	7 (25)
Cytomegalovirus Infection	5 (17.9)
Anaemia	4 (14.3)
Back Pain	4 (14.3)
Fatigue	4 (14.3)
Graft Versus Host Disease	3 (10.7)
Haemorrhoids	3 (10.7)
Headache	3 (10.7)
Hypertension	3 (10.7)
Hypoalbuminaemia	3 (10.7)
Lower Respiratory Tract Infection	3 (10.7)
Oedema Peripheral	3 (10.7)
Pruritus	3 (10.7)

Conclusion

- Most narsoplimab-treated patients achieved a complete response with a significant improvement in laboratory markers and in clinical status
- 100-day survival was similarly impressive across all groups (responders, per-protocol, and intent-to-treat)
- No safety signal was observed
- Submission of a rolling Biologics Licensing Application to FDA for HSCT-TMA has been initiated; completion targeted next quarter
- European Marketing Authorization Application in preparation for same indication

Thank You

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