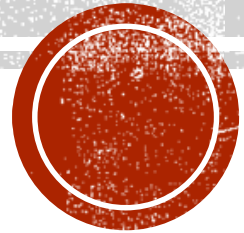
CLINICAL TRIALS IN MDS

Dr S Green
Consultant Haematologist
Hull University Teaching Hospitals



OVERVIEW

- Why?
- Types
- Considerations
- Updates
- Current trials

WHY?

- Discovering new treatments
- Optimising ‘old’ treatments
- New ways to diagnose

TYPES

- Biobanking/Registry
- Supportive care
- Non-intensive treatment
- Intensive treatment

THINGS TO CONSIDER

- Eligibility
  - patient criteria – IPSS, IPSS-R
  - upfront treatment vs treatment failures
  - fitness for intensive treatment
- Location (trial sites)

LUSPATERCEPT

blood®

1 The Medalist Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Anemia in Patients with Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) with Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

Pierre Fenaux, MD PhD[1], Uwe Platzbecker, MD[2], Ghulam J. Mufti[3], Guillermo Garcia-Manero, MD[4], Rena Buckstein, MD FRCPC[5], Valeria Santini[6], María Díez-Campelo[7], Carlo Finelli, MD[8], Mario Cazzola[9], Osman Ilhan, MD[10], Mikkael A. Sekeres, MD MS[11], José F. Falantes[12], Beatriz Arrizabalaga, MD PhD[13], Flavia Salvi[14], Valentina Giai[14], Paresh Vyas, MRCP FRCP FRCPath[15], David Bowen, MD[16], Dominik Selleslag, MD[17], Amy E. DeZern, MD[18], Joseph G. Jurcic, MD[19], Ulrich Germing, MD[20], Katharina S. Götze, MD[21], Bruno Quesnel[22], Odile Beyne-Rauzy[23], Thomas Cluzeau, MD PhD[24], Maria Teresa Voso[25], Dominiek Mazure[26], Edo Vellenga[27], Peter L Greenberg, MD[28], Eva Hellstrom Lindberg, MD PhD[29], Amer M. Zeidan, MBBS MHS[30], Abderrahmane Laadem, MD[31], Aziz Benzohra[32], Jennie Zhang[31], Anita Rampersad[31], Peter G. Linde[33], Matthew L. Sherman[33], Rami S. Komrokji, MD[34], **Alan F. List, MD**[34]

Blood 2018 132:1; doi: https://doi.org/10.1182/blood-2018-99-110805

Endpoints	Luspatercept	Placebo	P-Value
RBC-TI ≥8 weeks (weeks 1-24)	37.9% (58/153)	13.2% (10/76)	< 0.0001
RBC-TI ≥12 weeks (weeks 1-24)	28.1% (43/153)	7.9% (6/76)	0.0002
RBC-TI ≥12 weeks (weeks 1-48)	33.3% (51/153)	11.8% (9/76)	0.0003
HI-E ≥ 8 weeks (IWG 2006, weeks 1-24)	52.9% (81/153)	11.8% (9/76)	< 0.0001

- Treatment with luspatercept resulted in a significantly reduced transfusion burden compared with placebo
- *Regulatory submissions planned in the United States and Europe in the first half of 2019*

REDDS

A Feasibility Randomized Trial of Red Cell Transfusion Thresholds in Myelodysplasia

Simon Stanworth, Sally Killick, Zoe McQuilten, Marina Karakantza, Heather Smethurst, Laura Pankhurst, Renate L Hodge, Valerie Hopkins, Helen Thomas, Alison J Deary, Rena Buckstein, Jeannie Callum, Yulia Lin, and David Bowen

Blood 2018 132:527; doi: https://doi.org/10.1182/blood-2018-99-112949

MONOCLE

Results of a Phase 2 Trial of the Monocyte-Targeted Histone Deacetylase Inhibitor Tefinostat (CHR-2845) in Chronic Myelomonocytic Leukemia (CMML) — the UK Monocle Study

Steven Knapper, Michael Dennis, Mark W Drummond, Robert K. Hills, Richard James Dillon, Christopher Pocock, Dominic J. Culligan, Paresh Vyas, Daniel Wiseman, Joanna Zabkiewicz, Marie Hodges, Catherine Cargo, Jan Taylor, Laura Upton, Melissa Wright, and David Bowen

Blood 2018 132:1818; doi: https://doi.org/10.1182/blood-2018-99-110356

REGISTRY / BIOBANKING

- MDSBio
- Kaleidoscope – Lenalidomide
  - Transfusion dependent patients with IPSS low or int-1 MDS and isolated del (5q)
  - followed up on the registry for 3 years or until death/consent withdrawal

INVESTIGATIONAL MEDICINAL PRODUCTS

- Standard treatment – Azacitidine, low dose cytarabine
- Azacitidine has shown a survival advantage when compared with conventional therapies and has also shown activity in IPSS lower-risk patients. However, about 40% of patients do not respond and most patients show a loss of response within 2 years.
  - median OS of 19 months (based on trial data of selected patients) and 13–16 months (based on real-life analyses) for most patients with HR-MDS

- Novel agents
  - addition to standard treatment
  - monotherapy
  - Targeting genetic mutations

Blood Cancer Journal **volume 8**, Article number: 55 (2018)

FT-2102

- IDH1 mutation
- A phase 1/2 study of FT-2102 as a single agent and in combination with Azacitidine or low dose cytarabine.
- Safety and effectiveness of FT-2102
- Patients with AML or MDS which is relapsed or refractory to standard therapy and/or for which standard therapy is contraindicated or which has not adequately responded to standard therapy.

MEDI4736

- Durvalumab, Tremelimumab (monoclonal antibodies)
- programmed cell death ligand 1 (PD-L1)
- Phase 1 study to determine the safety and tolerability of MEDI4736 as Monotherapy or in Combination with Tremelimumab With or Without Azacitidine

INSPIRE (RIGOSERTIB)

- Phase 1/2 study (22 patients) suggests that rigosertib has an acceptable side-effect profile and may benefit some patients with myelodysplastic syndromes (MDS). Researchers found that rigosertib stabilized bone marrow blasts, and improved peripheral blood counts in 53% of patients.
- Median survival was 15.7 and 2.0 months for responders and non-responders, respectively.
- Various proteins interact with RAS contributing to its cancer causing activity. Rigosertib inhibits these interactions
- Phase 3 study investigate the survival of MDS patients receiving intravenous Rigosertib after failure of treatment with a Hypomethylating agent (HMA), Azacitidine or Decitabine

LeukRes. 2018 Jan;64:10-16. doi: 10.1016/j.leukres.2017.11.006. Epub 2017 Nov 11

RFUSIN2AML2

- Immune gene therapy
- This is a phase I study intended to identify the safety and tolerability of an "AML Cell Vaccine" given to eligible MDS and AML patients who have achieved a best response of complete remission or partial remission following their first or second course of standard induction chemotherapy.
- Patients for whom the optimal therapy in CR1 would be to undergo allogeneic bone marrow transplantation, but for whom this procedure is either not recommended (e.g. due to comorbidities) or not available (e.g. lack of a suitable donor).
- Exclusion: favourable prognostic profile; previously undergone or will be able to undergo allogeneic transplantation; previous or current treatment with any form of investigational immunotherapy
- King's College Hospital NHS Trust, London

BRIGHT (GLASDEGIB)

- Glasdegib disrupts cancer stem cell survival. This has the potential to reduce the development of drug resistance and prevent relapse.
- Phase 1 study aimed at determining the safety and effectiveness of Glasdegib in combination with Azacitidine
- Previously untreated higher-risk MDS, AML or CMML
- Assessing complete remission rates and adverse events.

PANTHER (PEVONEDISTAT)

- Prevents the activity of a specific enzyme (Nedd8 activating enzyme) and thus may result in the inhibition of tumour cell growth and survival.
- This is a phase 3 study to determine if combining Pevonedistat with Azacitidine improves survival when compared with single agent Azacitidine
- Higher risk MDS, CMML, low blast count AML

MDS Current Trials UK

We aim to list an easily understandable description of any MDS clinical trials currently opened to recruitment in the UK.

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Research FOR Patients

MDS Clinical Trials

30 JAN 2019

PANTHER: Clinical Trial Open to Recruitment

1. **SUB-TYPE OF MDS:** Higher risk MDS, CMML, low blast count AML
2. **SEVERITY OF MDS:** Intermediate, high risk or very high risk MDS as defined by the World Health Organization (WHO) criteria or Revised International Prognostic Scoring System (IPSS-R)
3. **NAME OF DRUG:** Azacitidine, Pevonedistat

Read full story

30 JAN 2019

BRIGHT: Clinical Trial Open to Recruitment

QUESTIONS