DANA-FARBER CANCER INSTITUTE

A Phase 3 Historically-Controlled Clinical Trial Investigating the Use of Defibrotide (DF) in the Treatment of Severe Veno-Occlusive Disease Following SCT

P G Richardson, MD[1], M Tomblyn, MD[2], N Kernan, MD[3], J Brochstein, MD[4], S Mineishi, MD[5], A Termuhlen, MD[6], S Arai, MD[7], S Grupp MD[8], E Guinan, MD[1], P Martin, MD[9], S Corbacioglu MD[10], E Holler MD[11], R D'Agostino, PhD[12], J Massaro PhD[12], A Hannah, MD[13], M Iacobelli, MD[13] and R Soiffer, MD[1].

[1]Dana-Farber Cancer Ctr, Mass General, Children's Hosp, Boston, MA; [2]Univ Minnesota Cancer Ctr, Minneapolis, MN; [3]Memorial Sloan-Kettering Cancer Ctr, New York, NY; [4]Hackensack Univ Med Ctr, Hackensack, NJ; [5]Univ Michigan, Ann Arbor MI; [6]Nationwide Children's Hospital; [7]Stanford Univ Med Ctr, Stanford, CA; [8]Children's Hosp of Philadelphia, Philadelphia PA; [9]Duke Univ Med Ctr, Durham, NC; [10]Univ Ulm, Ulm, Germany; [11]Klinikum der Univ Regensburg, Regensburg, Germany; [12]Boston Univ, Boston, MA and [13]Gentium,SpA, Villa Guardia, Como, Italy.

DF Treatment Trial

Background

- **Phase 2 clinical trials of DF in the treatment of severe VOD/MOF have demonstrated a complete response (CR) in 36-46% of patients (pts) with encouraging overall survival and tolerability (*Richardson Blood 2002; Richardson ASH 2006*).**
- **Given the life-threatening nature of VOD/MOF, a trial randomizing pts to placebo or best supportive care was considered but rejected by Investigators.**
- **A phase 3 trial, comparing DF in the treatment of VOD/MOF post-SCT to a contemporaneous historical control (HC) was therefore performed at 35 participating centers.**
- **DF was given at 6.25 mg/kg IV q6h; treatment duration was recommended for at least 21 days**

DF Treatment Trial

Methods:

Inclusion criteria:

- **Baltimore VOD criteria by D+21**
  - **total bilirubin ≥ 2.0 mg/dL with ≥ 2 of the following: hepatomegaly, ascites or 5% wt gain**
- **and either renal and/or pulmonary failure (MOF) by D+28.**
  - **Renal dysfunction: serum creatinine ≥ 3x baseline; OR creat clearance or GFR ≤40% admission value; OR dialysis dependence**
  - **Pulmonary dysfunction: O2 sat ≤ 90% on room air; OR requirement for oxygen supplementation; OR ventilator dependence**
    - **Dysfunction must be attributable to fluid overload or mechanical impingement from abdominal distention or hepatic enlargement and not to an infectious cause (e.g., documented pneumonia).**

DF Treatment Trial

Exclusion criteria:

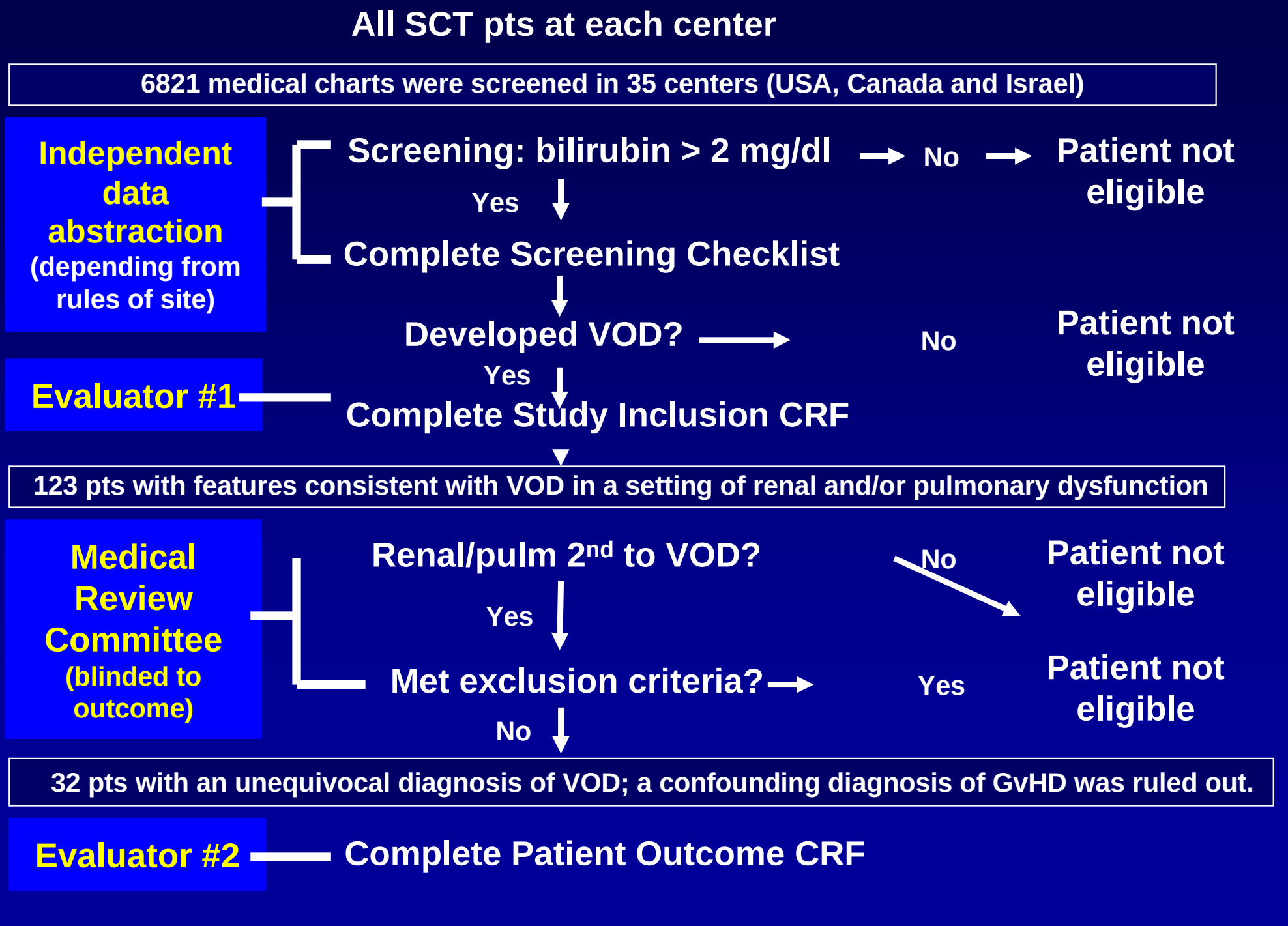
- **Severe GvHD involving liver or gut;**
  - **Documented diagnosis of GVHD, grade B-D according to the IBMTR Severity Index, involving the liver or gut, or documented diagnosis of GVHD, grade C or higher according to the IBMTR Severity Index, involving skin. (Pts with grade B GVHD involving only skin are eligible).**
- **Documentation of pre-existing (at the time of SCT) cirrhosis of the liver.**
- **An alternative diagnosis for ascites, wt gain and jaundice, such as fulminant viral hepatitis, at the time that severe VOD criteria are met.**
- **For pts with concurrent, confounding causes of liver dysfunction clinically evident or evident on ultrasound or other radiographic imaging or by medical assessment per institutional practice (such as evidence of biliary ductal dilatation, focal tissue defects or documented infectious hepatitis), biopsy (liver or other organ) and/or WHVPG measurements were to be obtained as necessary to rule out alternate diagnoses.**
- **Clinically significant bleeding.**
- **Need for >1 pressors to maintain BP.**

DF Treatment Trial

Methods: Historical Control (HC)

- The HC was created using a sequential review of medical charts starting 6 months prior to use of DF at each center (up to 1 Jan 1995).
- 35 centers sequentially reviewed up to 266 cases (in groups of 133 patients; not all centers reviewed 266).
- To determine HC eligibility, the Medical Review Committee (MRC, composed of 2 independent expert hematologists) assessed all pts who met VOD criteria with MOF.
- The MRC were provided data for each pt (a redacted medical chart or pt narrative, depending on the privacy laws for each center) only up to the date on which the pt met inclusion criteria.
- The MRC remained blinded to outcome data at all times.

Selection of HC



DF Treatment Trial

Methods:

- **Primary endpoint: CR by D+100**
  - **was defined as bilirubin < 2 mg/dL + resolution of MOF;**
- **Stratification variables:**
  - **allogeneic/autologous SCT**
  - **adult/pediatric**
  - **1 or 2+ SCTs**
  - **ventilator/dialysis dependence**
- **As this is a non-randomized study, the primary efficacy analysis compared CR by D+100, adjusted by quintiles of propensity score based on 4 stratification variables, at an overall two-sided 0.01 significance level *(Koch et al,1989).***
- **Secondary endpoint: mortality by D+100.**

DF Treatment Trial: Results

- For the HC, 6821 medical charts were screened, identifying 123 pts with features consistent with VOD in a setting of renal and/or pulmonary dysfunction that were reviewed for eligibility by the MRC.
- The MRC selected 32 cases as having an unequivocal diagnosis of VOD whose MOF was secondary to VOD, who met all protocol entry criteria; for all eligible pts, a confounding diagnosis of GvHD was ruled out.
- Following the interim analysis (comparing 61 DF pts to 32 HC pts), the DMC recommended an increase in HC sample size to 51 pts; given the large number of medical charts already reviewed, this was not considered feasible.
- In the DF-treated group, 102 pts were enrolled.
- The final analysis compared 102 DF pts to 32 HC pts

DF Treatment Trial: Results

- The 2 groups were balanced regarding stratification variables
- Baseline demographics (DF *vs* HC pts):
  - median age 21 *vs* 18 yrs
  - pediatric 43% and 44%
  - male 63% *vs* 53%
  - allogeneic SCT 88% *vs* 84%
  - prior SCT 13% *vs* 3%
- Ventilator/dialysis dependent 38% *vs* 38%
- Median time post-SCT to VOD diagnosis was 13 and 11 days
- Acute leukemia was the underlying diagnosis in 44% and 47%
- Median duration of DF therapy: 22 days (range 1-60 days)
- DF median daily dose: 19 mg/kg/day

DF Treatment Trial: Results

ITT Population was the primary population for all efficacy analyses:

All patients in the DF group; 32 pts selecteed by the MRC for the HC

	DF (n = 102)	Control (n = 32)	Confidence Intervals *	P value ***
CR (Day 100)	24% (24/102)	9% (3/32)	99%CI: -1 – 35% 95%CI: 3 – 30%	0.0148 (adjusted)** 0.0816 (unadjusted)
Mortality (Day 100)	62% (63/102)	75% (24/32)	95%CI: -32 – 3%	0.0508 (adjusted)** 0.0589 (unadjusted)

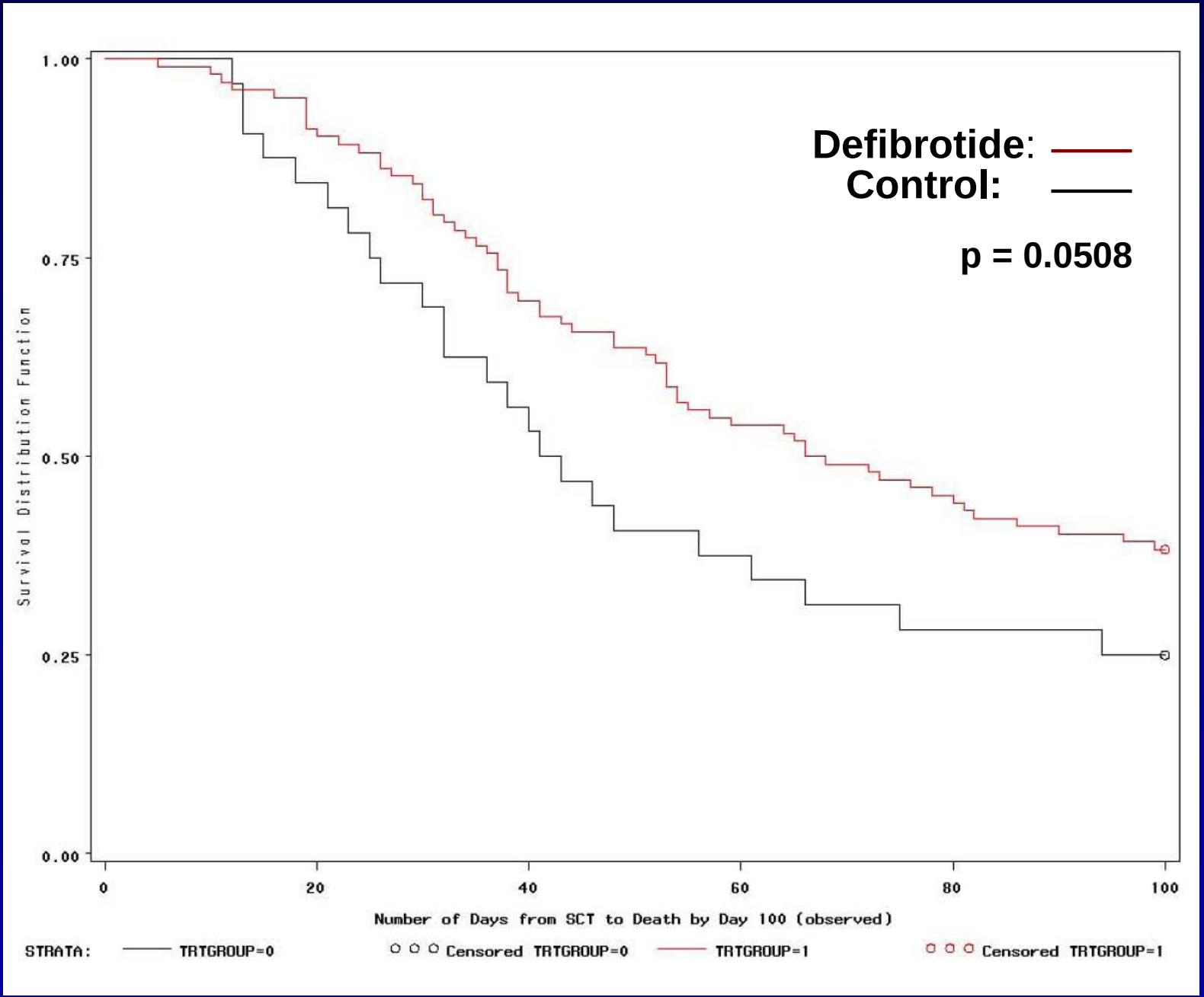
* on difference in CR rate

** adjusted by quintiles of propensity score based on 4 stratification variables;
Stratification variables: 1) allogeneic/autologous SCT, 2) adult/pediatric, 3) 1 or 2+ SCTs, 4) ventilator/dialysis dependence.

*** p value for CR from Chi Square Test; p value for Mortality from stratified Logrank Test.

Strong correlation of Complete Response to Survival in both DF and HC groups (p<0.0001, p=0.0016).

DF Treatment Trial: Mortality by Day+100



DF Treatment Trial: Results

ITT Population: Subgroup Analysis

CR at Day +100	DF	Control	P value (unadjusted)
Pediatrics (<= 16 yrs)	36% (16/44)	7% (1/14)	0.0364
Adults (> 16 yrs)	14% (8/58)	11% (2/18)	0.7687
Allogeneic	17% (15/90)	11% (3/27)	0.4828
Autologous	75% (9/12)	0% (0/5)	0.0048
Ventilator Dependence – Yes	8% (4/52)	10% (2/21)	0.7965
Ventilator Dependence – No	40% (20/50)	9% (1/11)	0.0508
Dialysis Dependence – Yes	12% (6/49)	10% (1/10)	0.8414
Dialysis Dependence -- No	34% (18/53)	9% (2/22)	0.0266

DF Treatment Trial: Results

PP (Per Protocol) population (all pts who had 21 days DF):
Primary and secondary endpoints analysis

	DF (n = 61)	Control (n = 32)	Confidence Intervals *	P value ***
CR (Day 100)	29.5% (18/61)	9% (3/32)	99%CI: 0 – 43% 95%CI: 5– 38%	0.0091 (adjusted)** 0.0274 (unadjusted)
Mortality (Day 100)	51% (31/61)	75% (24/32)	95%CI: -46 – -8%	< 0.0001 (adjusted)** 0.0004 (unadjusted)

* on difference in CR rate

** adjusted by quintiles of propensity score based on 4 stratification variables;
Stratification variables: 1) allogeneic/autologous SCT, 2) adult/pediatric, 3) 1 or 2+ SCTs, 4) ventilator/dialysis dependence.

*** p value for CR from Chi Square Test; p value for Mortality from stratified Logrank Test.

DF Treatment Trial : Safety

- Eligible pt population had a diagnosis of VOD with either severe pulmonary and/or renal dysfunction; DF and HC pts enrolled ~10-11 d following SCT.
- Most common AEs in both the TG and HC were consistent with those associated with SCT, VOD/MOF or underlying disease.
- Most common drug-related AEs of Grade 3/4/5 severity: hemorrhage (pulmonary hemorrhage, gastrointestinal hemorrhage), coagulopathy/TTP or hypotension
- 65% (n=66 DF pts) and 69% (n=22 HC pts) experienced a hemorrhagic AE:
  - TG patients noted more hemorrhage for catheter/procedural related hemorrhage (15% and 3%);
  - DF pts noted fewer GI hemorrhage (19% and 47%)
  - Similar incidence for respiratory hemorrhage (epistaxis 13% and 16%; pulmonary hemorrhage 12% and 9%; pulmonary alveolar hemorrhage 6% and 6%); CNS hemorrhage (8% and 3%) and renal hemorrhage (13% and 16%)
- 18 DF pts withdrew from the study due to a possibly drug-related AE (hemorrhage, coagulopathy, and hypotension)

Conclusions:

- **Use of DF results in an increased rate of CR compared to a Historical Control (24% versus 9%; p = 0.0148) and a strong trend towards decreased mortality (62% versus 75%; p = 0.0508)**
  - **Pediatric pts showed the greatest improvement in CR (36% vs 7%; p = 0.036)**
  - **Use of DF was associated with improved outcome in less sick pts**
    - **For pts without ventilator dependence: CR equaled 40% vs 9%; p=0.051**
    - **For pts without dialysis dependence CR equaled 34% vs 9 %; p=0.027**
- **D+100 CR strongly correlated with D+100 survival in both DF and HC groups**

Conclusions (cont.)

- Although used in a critically ill population, DF was generally well tolerated
  - Hemorrhage (the most common drug-related AE) was similar between the two arms (DF and HC)
  - 18% of pts treated with DF withdrew due to a possibly drug-related AE
- DF-associated toxicities consistent with those reported in prior studies
- Use of DF in the treatment of SCT pts with severe hepatic VOD in association with renal and/or pulmonary failure can be recommended

Future Directions:

- Earlier intervention (i.e. prior to the development of advanced MOF)
- Combination studies (e.g. DF with N-acetyl cysteine, ATIII)
- Prophylaxis (Allo-SCT, high risk Auto-SCT)
- Role in specific high risk groups (e.g. Sirolimus – exposed pts)

Acknowledgements:

Clinical teams:

Dose-Finding Study: DFCI, Boston-Children's, MGH, Beth Israel, City of Hope, Duke, Fred Hutchinson/Seattle Children, Memorial Sloan Kettering, Johns Hopkins

Additional USA Centers: UMinnesota, WashingtonU, MDACC, Hackensack, CHOP, Emory, UMichigan, UChicago, UPennsylvania, Chicago Children's Memorial, Ohio State, US Oncology, Loyola, UNebraska, Mayo, Stanford, Oregon, Indianapolis BMT, Nationwide Children's

Canadian Centers: Montréal, Toronto General, Sick Children's, British Columbia

Israeli Centers: Rambam, Hadassah

Nursing and House Staff Teams

Gentium:

M Iacobelli MD

A.L. Hannah, MD

Robin Hume, MS

DSMB and MRC

FDA Orphan Products Program

The Patients and their Families