Medical Countermeasures for the ARS: Evidence-Based Support and the FDA Animal Rule

Tom MacVittie
Dept of Radiation Oncology

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Medical Countermeasures for ARS/DEARE

Objectives today:

1. Establish criteria for defining efficacy of MCM
2. Underscore the value of supportive care as a MCM
3. Identify the only MCMs available today for possible U.S. FDA approval for IND and/or EUA

Radiation Environment

Bad News

Environment: Potential lethal exposure: uncontrolled, ill-defined, variable dose, shielding, combined injury

Good News

Forecast: nonuniform, heterogeneous exposure
----variable dose distribution----

Possible sparing of bone marrow and/or GI stem cells

Problem: Treatment protocol usually less than optimal

The Ugly

Combined injuries

MCM Development Against ARS/DEARE

What MCM are available today to treat lethally irradiated personnel given evidence-based support and adherence to the criteria of the FDA Animal rule

- What are the criteria for determining MCM efficacy?

MCM Development Against ARS/DEARE:

Supportive Evidence for MCM Efficacy

- published data in peer-reviewed literature:
  pre-clinical data base in mice, canine or NHP,
- Experimental endpoints: cell recovery, survival, radiation dose/range, admin schedule
- clinical data base: safety and efficacy,
- abstracts; presentations etc

FDA "Animal Rule" (AR)

"New Drug and Biological Drug Products: Evidence needed to demonstrate effectiveness of new drugs/biologics when human efficacy studies are not ethical or feasible"

Rule does not apply if approval can be based on other FDA efficacy standards (accelerated approval)

MCM Development Against ARS/DEARE:

Criteria for determining MCM efficacy?

- Well characterized animal model; two species
- Study endpoint: Clearly related to desired benefit in humans; morbidity/mortality
- PK/PD; linkage for dose/schedule to human
- Mechanism of action along time course of morbidity/mortality
- GLP-compliant pivotal study for efficacy
- Phase 1 safety trial
- MCM Efficacy at 24hr post exposure

Medical Countermeasures for ARS/DEARE

TODAY, there is only one treatment protocol available. It has two components:

1. Supportive Care

2. Hematopoietic growth factors, G-CSF, GM-CSF or peg G-CSF

Treatment Components

Supportive Care

- Fluids, blood products, nutrition, analgesics
  - administer based on clinical requirements/ signs, “trigger-to-treat” protocol
- Antibiotics
  - administered based on neutrophil count (afebrile) after lethal TBI

IDSA, NCCN, clinical trials, Chernobyl

Radiation Exposure: Treatment Components

Supportive Care is the single best protocol today

1. Preclinical data base in canines and NHPs show an increase in survival after lethal doses of TBI.

2. Increases MST of decedents.

3. May be the only therapy used at the optimal schedule.
   - antibiotics: d5+
   - Transfusion: d20+

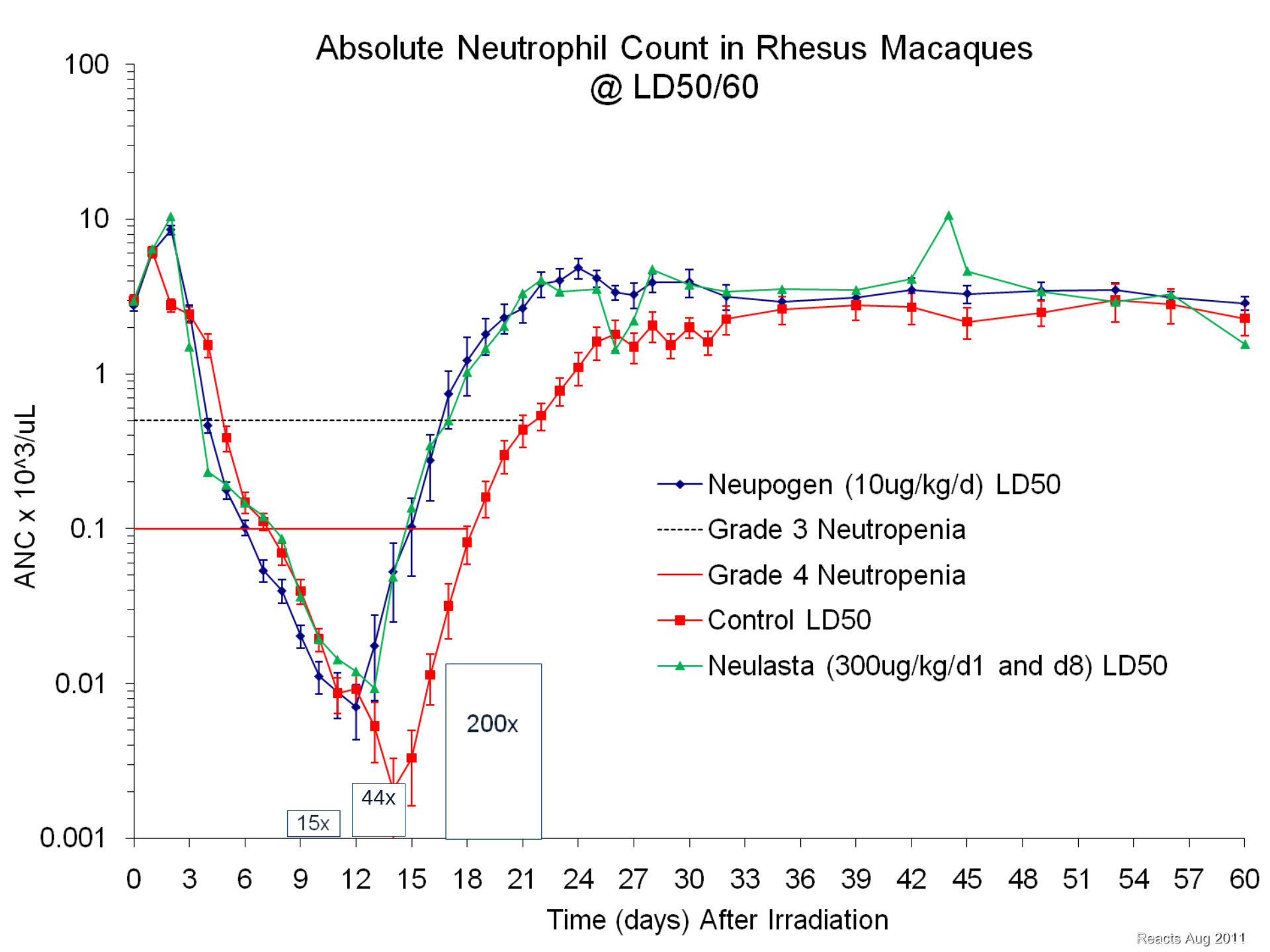
Current MCM Treatment for H-ARS

Hematopoietic-ARS

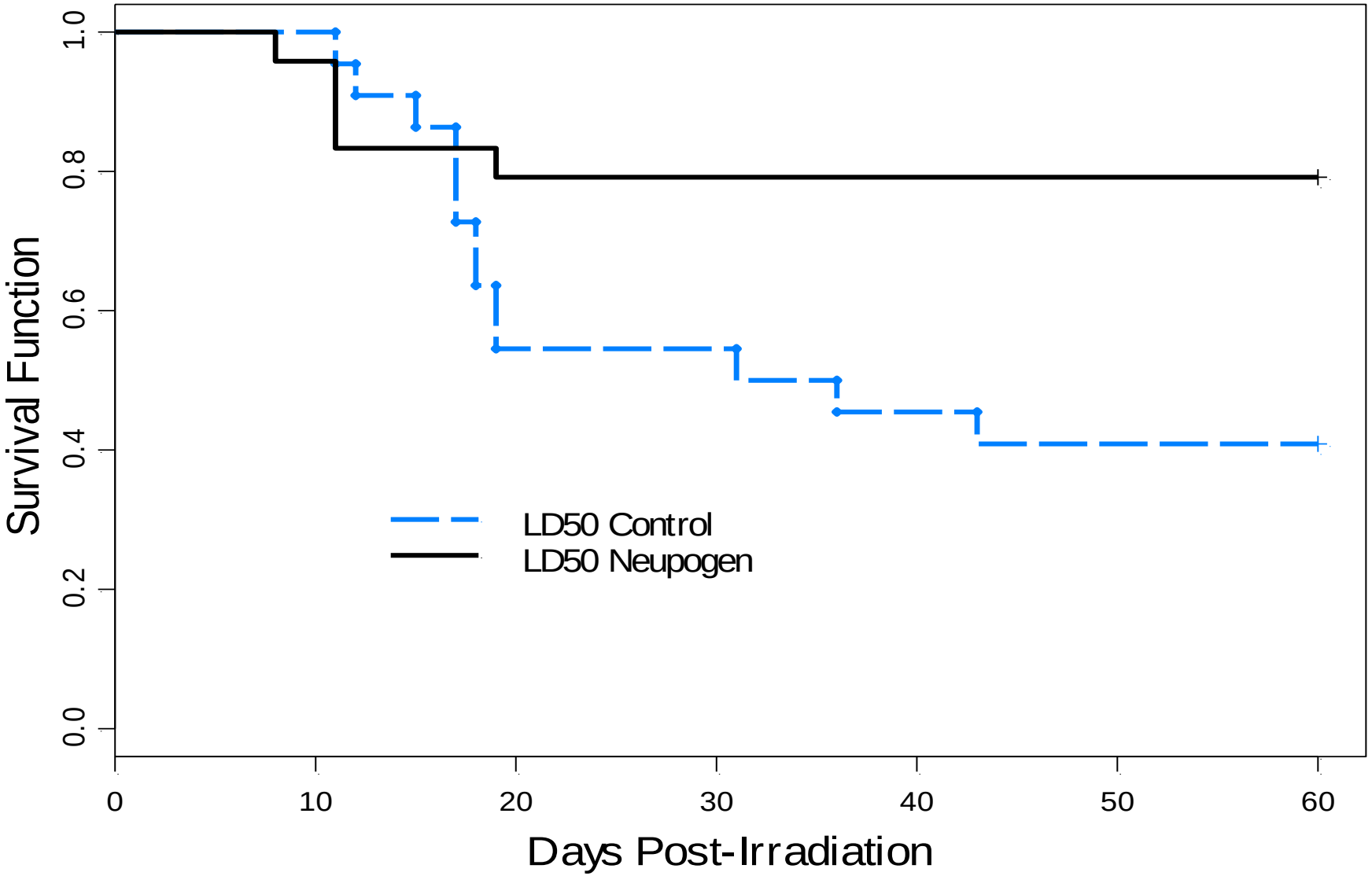
MCM

- Supportive care ++++
- Drug
  - G-CSF ++++
  - GM-CSF ++
  - Peg G-CSF ++

- Substantial and consistent data base in mice, canine, NHP; G-CSF > GM-CSF > peg G-CSF


Absolute Neutrophil Count in Rhesus Macaques
@ LD50/60
100
10
1
0.1
0.01
0.001
ANC x 10^3/uL
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
Time (days) After Irradiation
Neupogen (10ug/kg/d) LD50
Grade 3 Neutropenia
Grade 4 Neutropenia
Control LD50
Neulasta (300ug/kg/d1 and d8) LD50
15x
44x
200x
Reacts Aug 2011

Kaplan-Meier Survival Curves



Neupogen 21% lethality (n=24); Control 59% lethality (n=22)

MCM Treatment Against the ARS/DEARE: Summary

H-ARS:

Supportive care

- G-CSF; peg G-CSF
- GM-CSF

Lung Injury:

- Supportive care

GI-ARS:

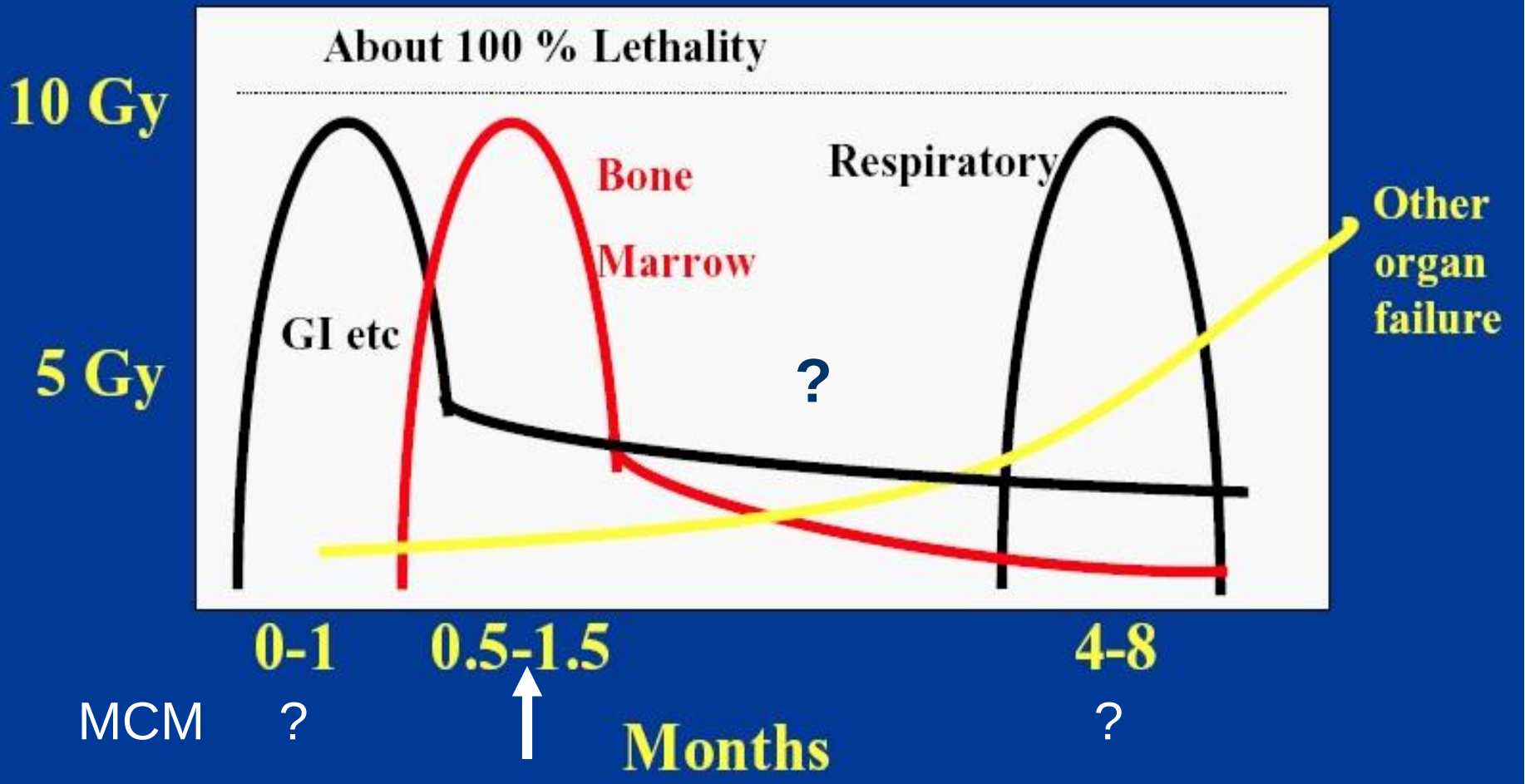
- Supportive care

Multiple Organ Injury

- Supportive care

Acute causes of death at various times following whole body exposure

Fred Mettler, IOM Mtg June 08



MCM Development Against ARS/DEARE: CSFs and their key +/- data base

- G-CSF: Inc survival at LD60, GLP+ study, statistically designed random, blinded trial, Ph1 +, FDA-approved, large data base
- GM-CSF: No mid-lethal trial as above. Modest data in NHP, Ph 1+, FDA-approved
- Peg G-CSF: No mid-lethal trial as above. Modest data in NHP and mice, Ph1+, FDA-approved

Radiation Emergency Medical Management: HHS and **European Consensus

*Cytokines (H-ARS) administered ASAP
- Determine the extent of residual hemopoiesis,

*cytokines: G-, GM-, peg G-CSF; **KGF ??

*Tpo, Tpo R agonists, Epo, SCF not recommended

www.remm.nlm.gov; Health Physics 98(6):825-832; 2010

MCM Development Against ARS/DEARE: Gaps in Knowledge

- MCM efficacy in "reality MOI" models,
- Define MOI models for MCM efficacy
- Animal models of pediatric/elderly,
- Poly-pharmacy: MCM interaction; MCM effects on other concurrent sequelae,
- Mechanism of action (MoA) along time course of morbidity/mortality
- MCM administration schedule/MoA

FDA Regulatory Mechanisms for Emergency Use of MCM

EUA: Applicability

- Unapproved products
- Approved products for unapproved uses

Potential MCM against ARS/DEARE

Hemopoietic

- Maxygen G-34
- IL-12
- Angiotensin (1-7)
- ExRad
- RxBio
- Cell-based Rx MPc CLT008

Pro- anti-oxidants, -inflammatory, -apoptosis

- Nrf-2 activators
- AEOL10150
- RxBio

Thrombopoietic

- Angiotensin (1-7)