CLINICAL PHARMACOLOGY APPROACH FOR DOSE SELECTION IN PRODUCT DEVELOPMENT UNDER THE ANIMAL RULE:

M & S APPLICATION IN ACUTE RADIATION SYNDROME

SANDEEP DUTTA, PHD

EXECUTIVE DIRECTOR, CLINICAL PHARMACOLOGY, M & S - AMGEN INC.

****MURAD MELHEM, JOHN HARROLD, PER OLSSON, LIVIAWATI WU, PHILIPPE JACQMIN, ISABELLE DELOR AND OTHER AMGEN CONTRIBUTORS**

BACKGROUND

- **Exposure to lethal amounts of penetrating radiation can deplete bone marrow stem cells, causing hematopoietic syndrome of acute radiation syndrome (HS-ARS) and impacting overall survival (OS)**
- **Granulocyte colony-stimulating factors, such as filgrastim and pegfilgrastim, reduce susceptibility to infection by increasing the number and function of neutrophils:**
  - **In NHPs, filgrastim treatment resulted in significantly better survival rates (79% vs 40%) following irradiation[1]**
- **Human clinical trials of acute radiation exposure are not feasible or ethical, so M & S were used to predict the impact of filgrastim treatment on human ANC recovery and survival following acute radiation exposure**

[1]Farese et al. *Radiat Res.* 2013;179:89-100.

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OBJECTIVES

- Quantitatively characterize granulopoiesis in NHPs and human subjects in response to
  - Radiation ± filgrastim (in NHPs)
  - Chemotherapy + filgrastim in humans
- Quantify the relationship between the absolute neutrophil count (ANC) time course and OS in NHPs after acute radiation ± filgrastim treatment
- Predict the ANC response and OS in human adult and pediatric subjects after acute radiation ± filgrastim treatment

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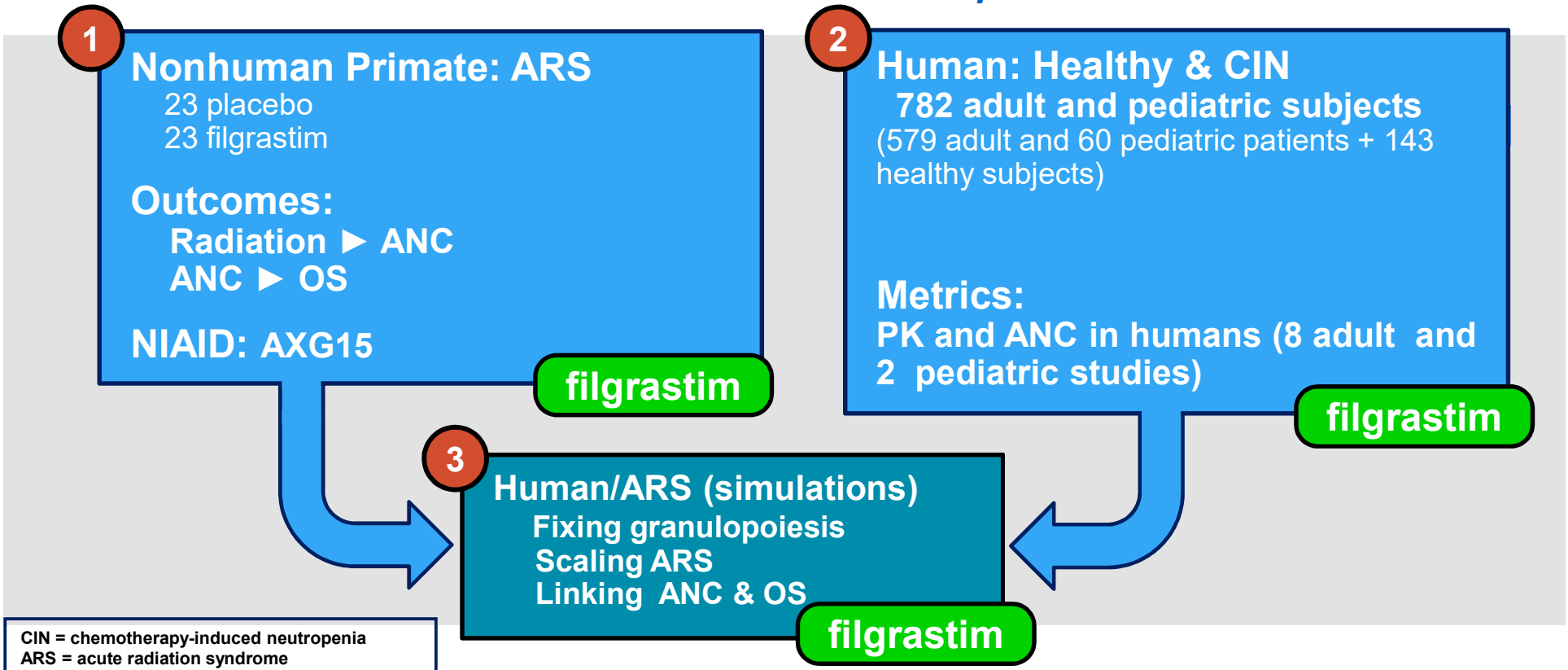
M&S CONNECT MISSING LINKS TO GENERATE EVIDENCE

MECHANISM-BASED MODELING USING INTERNAL/EXTERNAL DATA



CIN = chemotherapy-induced neutropenia
ARS = acute radiation syndrome
ANC = absolute neutrophil count
OS = overall survival
PK = pharmacokinetics

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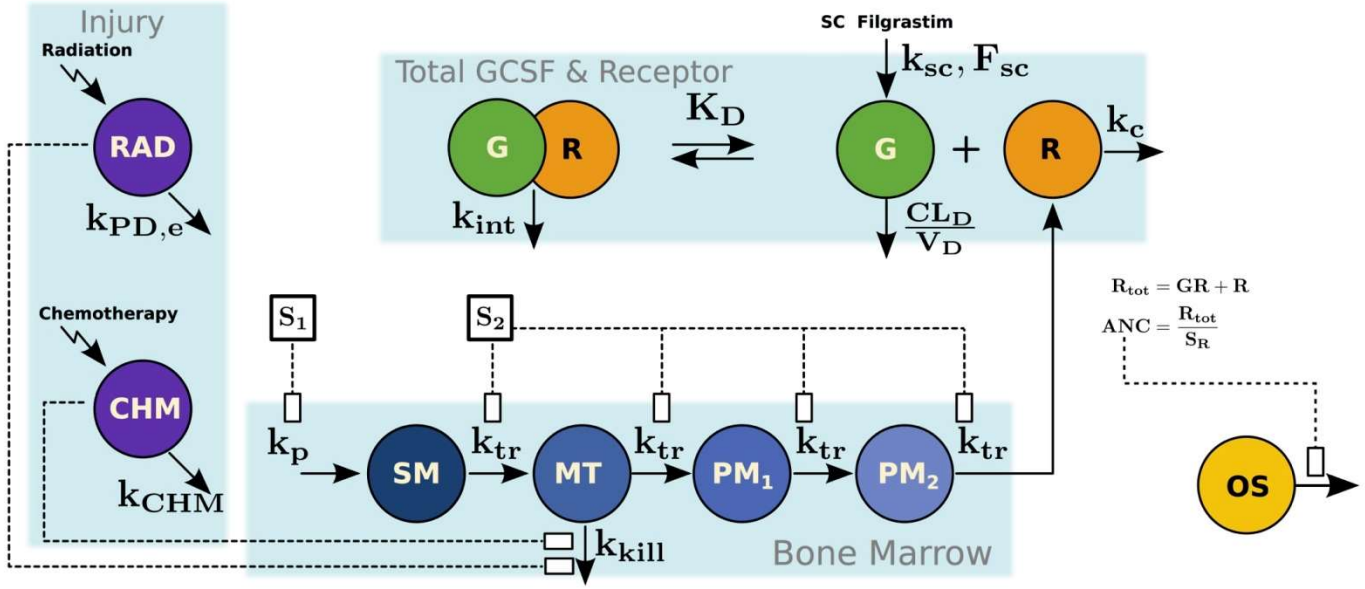
TRANSLATIONAL PK/PD MODEL



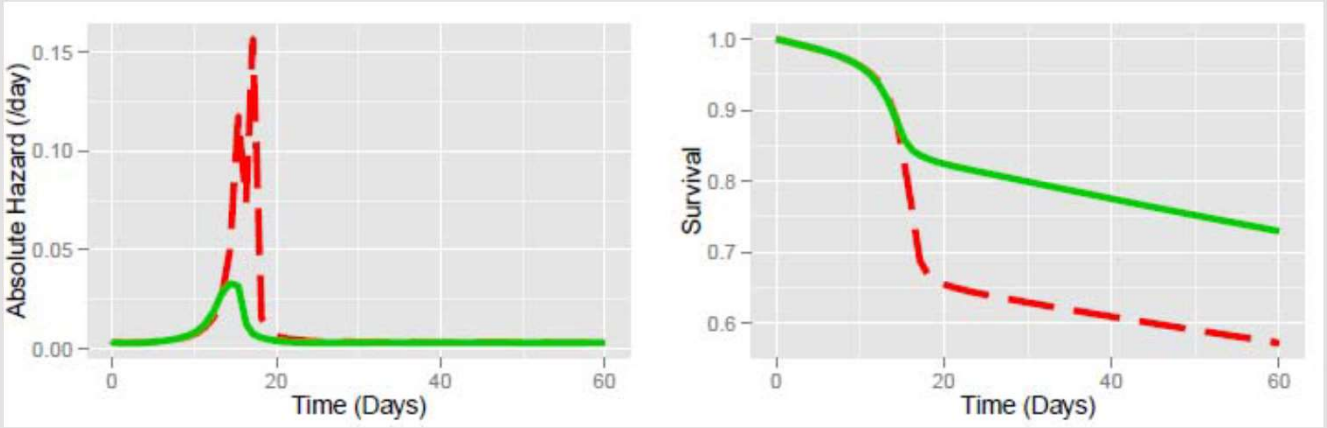
G = free G-CSF
R = free G-CSF receptor
GR = G-CSF/G-CSF receptor complex
R_{tot} = total G-CSF receptor concentration
K_D = G-CSF/G-CSF receptor dissociation constant
k_{int} = G-CSF/G-CSF receptor complex internalization rate
SC = subcutaneous
CL_D = G-CSF clearance
k_{kill} = rate of cell loss due to injury

V_D = G-CSF volume of distribution
k_{sc} = subcutaneous rate of absorption
F_{sc} = bioavailability
k_c = ANC elimination rate
SM = progenitor stem cells
MT = mitotic stem cells
PM_1 and PM_2 = precursor cells
k_p = rate of progenitor cell production
k_{tr} = maturation rate
S_1 and S_2 = stimulatory functions

RAD = radiation compartment
$k_{PD,e}$ = elimination rate of radiation effect
CHM = chemotherapy effect compartment
k_{CHM} = elimination rate of chemotherapeutic effect
ANC = absolute neutrophil count
S_R = ratio of G-CSF receptor to ANC values
OS = overall survival
□ = modulation of signals due to different interventions /injuries

OVERALL SURVIVAL MODEL IN NHP

- **An exponential survival model, *S(t)i* with a time-varying hazard, *λ(t)i***
- ***λ(t)i* was dependent on ANC delayed through an hypothetical effect compartment $ANC_{e(t)i}$**



Not to scale, for illustration purposes only

Placebo subjects
G-CSF treated subjects

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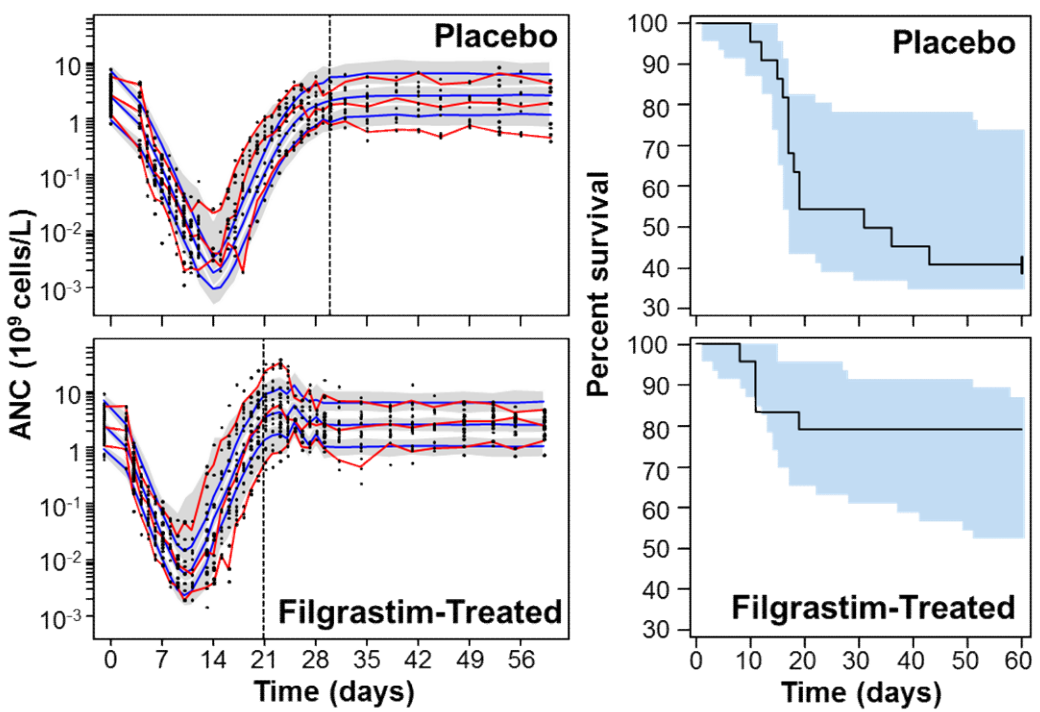
GRANULOPOIESIS MODEL:
ANC TIME COURSE AND SURVIVAL IN IRRADIATED NHP

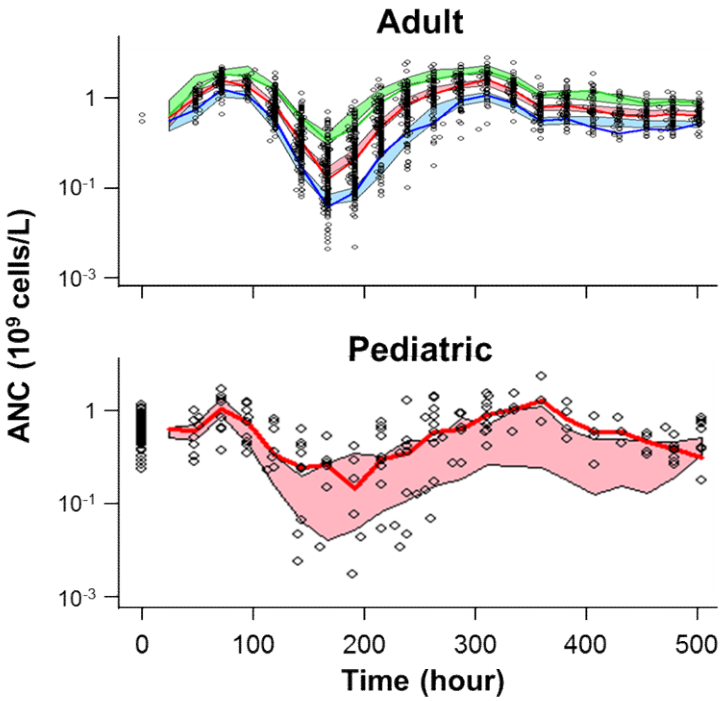


- Observed ANC data
- 5th, 50th, and 95th percentiles observed data
- 5th, 50th, and 95th percentiles predicted data
- 90% CI for model predictions
- Time of ANC recovery
- Observed survival data
- 95% prediction intervals

- **Filgrastim (10 μg/kg daily) reduced the depth and duration of ANC suppression**
- **OS model for irradiated NHPs was driven by the depth and duration of ANC suppression**
- **ANC time course accounted for 76% (95% CI: 41%, 97%) of the filgrastim treatment effect on OS**

[1]Farese et al. *Radiat Res.* 2013;179:89-100.

GRANULOPOIESIS MODEL:
ANC TIME COURSE IN CIN HUMANS



◆ Observed data
– 10th percentile from observed data
– 50th percentile from observed data
– 90th percentile from observed data
Shaded areas indicate 95% CI simulated from the model, using 200 replicates

- **Prediction-corrected ANC time courses in response to chemotherapy-induced neutropenia and filgrastim are shown**
  - **Adults: 5 μg/kg daily (n = 103)**
  - **Pediatric:**
    - **5 μg/kg daily (n = 11)**
    - **10 μg/kg daily (n = 5)**
    - **15 μg/kg daily (n = 5)**

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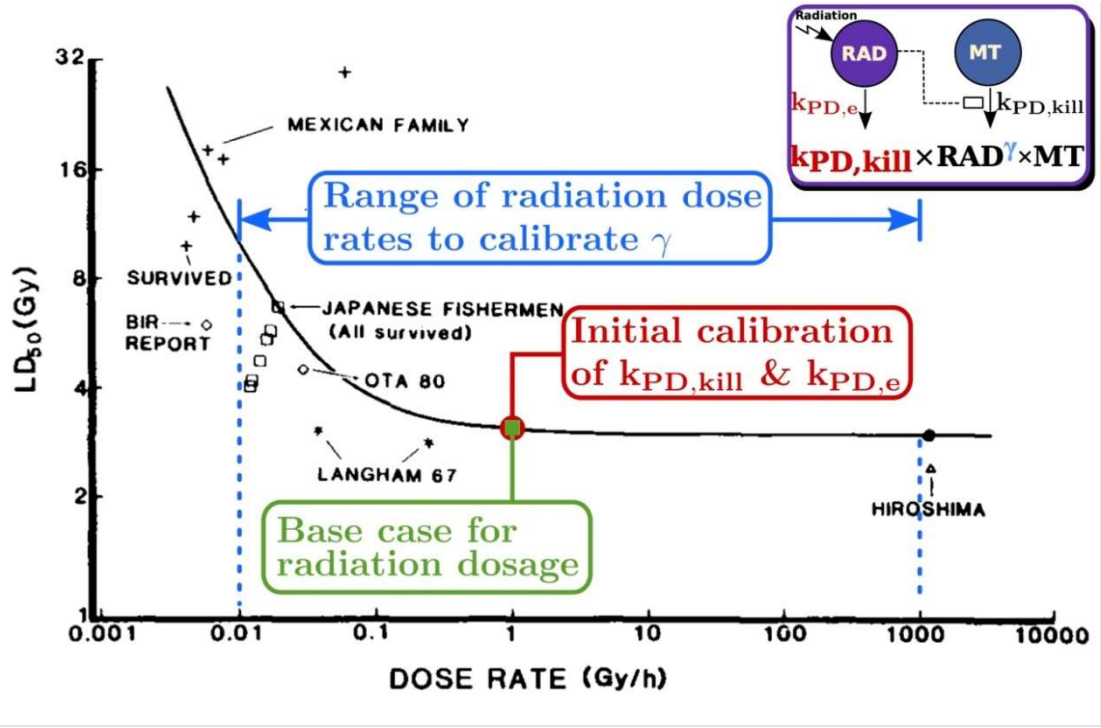
CALIBRATION OF SURVIVAL FOLLOWING RADIATION INJURY



- For the base case the values of relevant model parameters are adjusted to have a 50% mortality rate
- The sensitivity term is then estimated to predict a 50% mortality rate over a range of radiation dose rates

Adapted from Scott et al. *Br J Radiol*. 1990;63:862-70.

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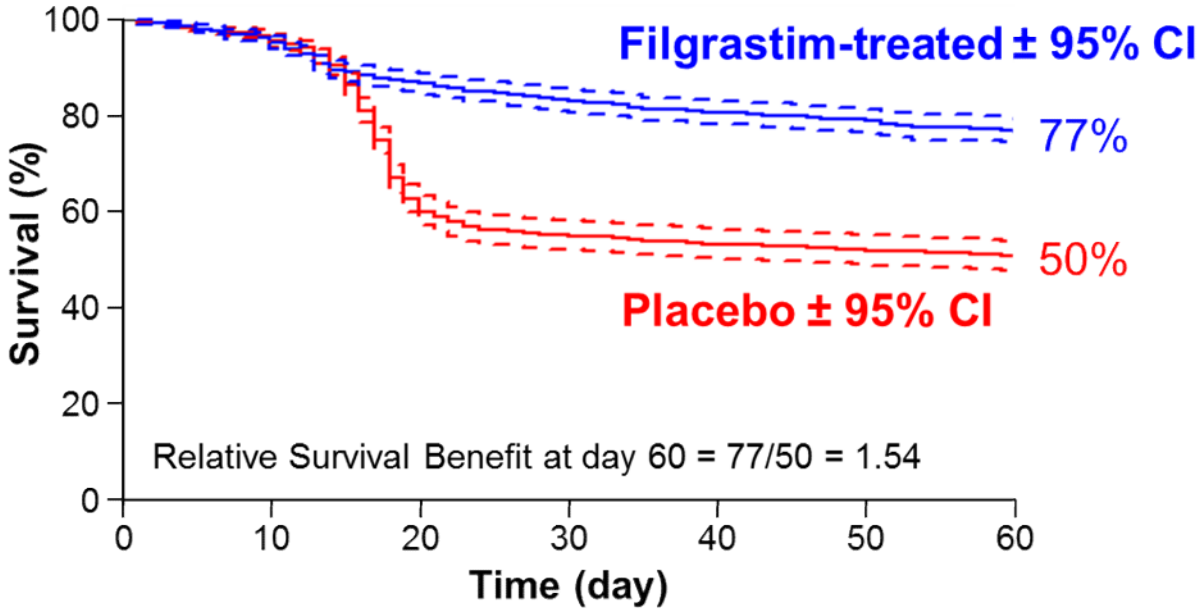
FILGRASTIM TREATMENT IS PREDICTED TO INCREASE HUMAN OS



- Humans were at highest risk for neutropenia from day 10–21 after acute radiation exposure
- Filgrastim treatment increased the proportion of patients alive on day 60 by ~50% compared to placebo

Base Case: Adults exposed to 3 Gy of irradiation at 1 Gy/hr (LD_{50}) and administered 5 μg/kg filgrastim daily for 4 weeks starting 1 day after radiation exposure

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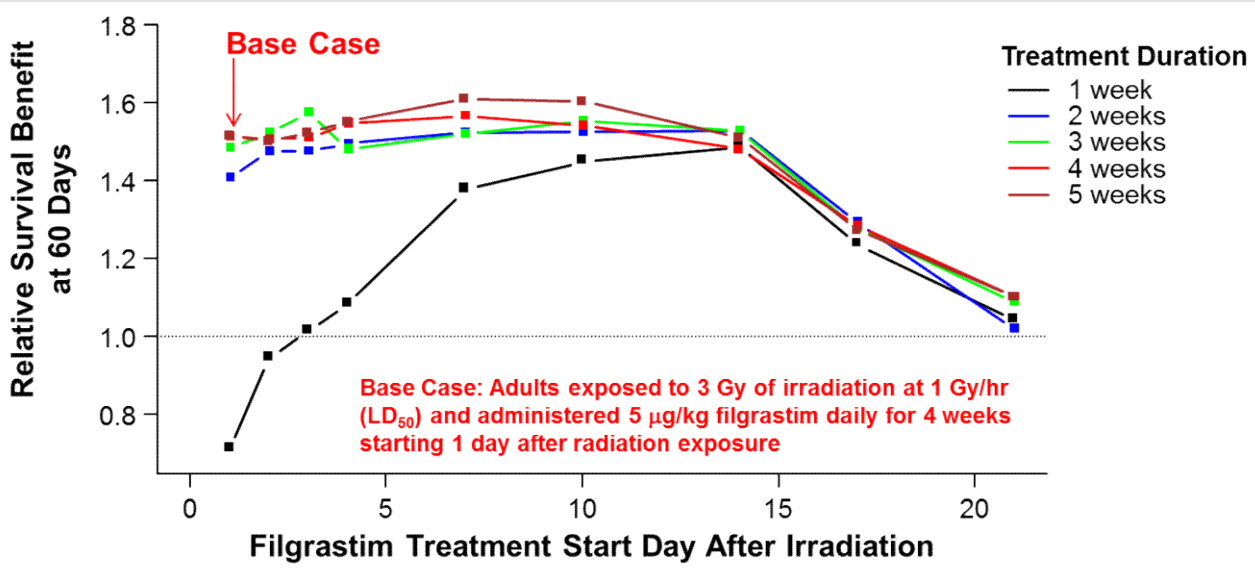
HUMAN OS BENEFIT WILL DEPEND ON THE ONSET AND DURATION OF FILGRASTIM TREATMENT



- Optimal OS benefit is provided by longer durations of filgrastim (≥ 2 weeks) initiated within 14 days of radiation exposure
- No additional OS benefit is seen with treatment durations longer than 3 weeks, when initiated between day 4–14 after radiation exposure

Source: Adapted from Harrold J, Jacqmin P, Olsson P, Delor I, Morrow PK, Yang BB, Chow A, Perex-Ruixo JJ. 56th ASH Annual Meeting and Exposition presentation. December 6-9, 2014.

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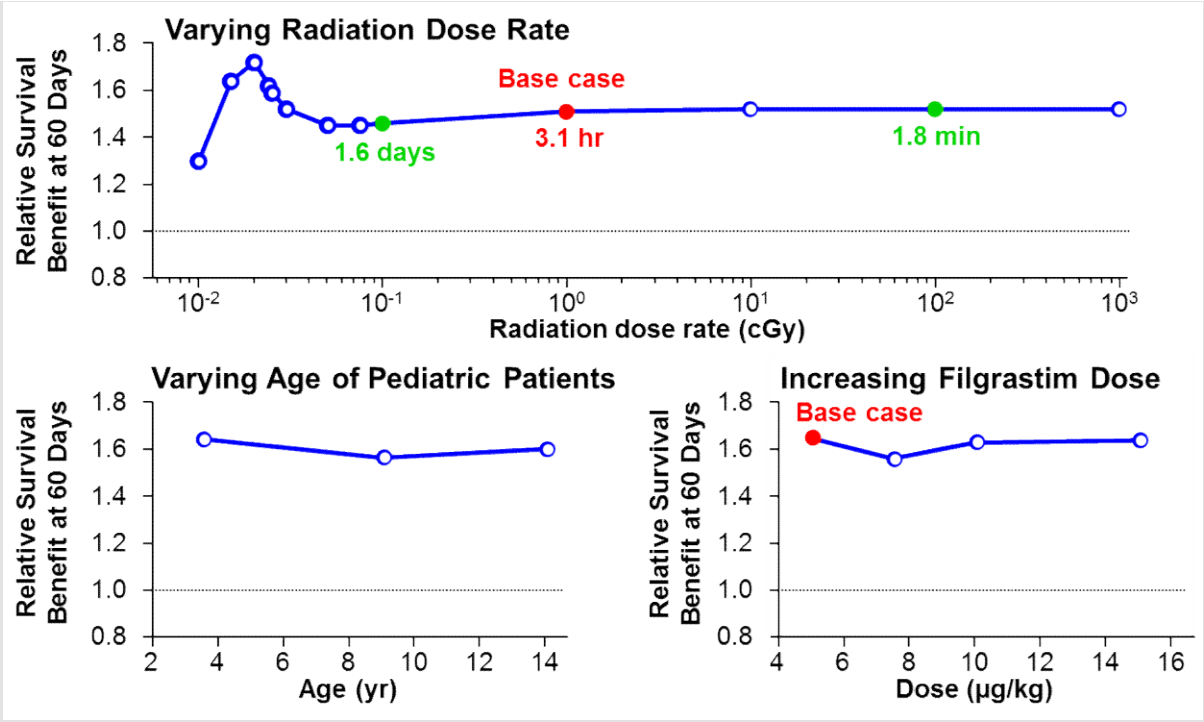
VARYING RADIATION DOSE RATE, AGE, AND FILGRASTIM DOSE HAVE LITTLE IMPACT ON SURVIVAL



MODEL-BASED FILGRASTIM DOSAGE RECOMMENDATIONS IN PATIENTS WITH HS-ARS

- **10 µg/kg as a single daily subcutaneous injection.**
- **Administer as soon as possible after suspected or confirmed exposure to radiation doses > 2 Gy.**
- **Continue administration until the ANC > 1,000/mm^3 for 3 consecutive CBCs or > 10,000/mm^3 after a radiation-induced nadir.**

Indication for filgrastim and peg-filgrastim: increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

Source: Amgen's US Package Insert for NEUPOGEN® (filgrastim).

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MODEL-BASED FILGRASTIM DO

----------INDICATIONS AND USAGE----------

NEUPOGEN is a leukocyte growth factor indicated to

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1.5)
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) (1.6)

----------DOSAGE AND ADMINISTRATION----------

- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.1)
- Patients with cancer undergoing bone marrow transplantation
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy
  - 10 mcg/kg/day subcutaneous injection (2.3)
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis (2.3)
- Patients with congenital neutropenia
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily (2.4)
- Patients with cyclic or idiopathic neutropenia
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily (2.4)
- Patients acutely exposed to myelosuppressive doses of radiation
  - 10 mcg/kg/day subcutaneous injection (2.5)

Acute Radiation Syndrome).

Source: Amgen's US Package Insert for NEUPOGEN® (filgrastim).

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ACKNOWLEDGMENTS

The presenter greatly appreciates the numerous internal colleagues and external collaborators on this complex project. Their modeling and simulation expertise and diligence are the key to accomplish the work in record time.

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BACKUPS

MODEL-BASED DOSAGE RECOMMENDATIONS OF G-CSF IN PATIENTS WITH H-ARS

- **Filgrastim:**
  - 10 mcg/kg as a single daily subcutaneous injection.
  - Administer as soon as possible after suspected or confirmed exposure to radiation doses > 2 Gy.
  - Continue administration until the ANC > 1,000/mm^3 for 3 consecutive CBCs or > 10,000/mm^3 after a radiation-induced nadir.
- **Pegfilgrastim:**
  - Two doses, 6 mg each, administered subcutaneously one week apart.
  - Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels > 2 Gy. Administer the second dose one week after the first dose.

Indication: Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

Source: Amgen's US Package Insert for NEUPOGEN® (filgrastim) and NEULASTA ® (pegfilgrastim).

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