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EU authorisation of therapeutics for Acute Radiation Syndrome

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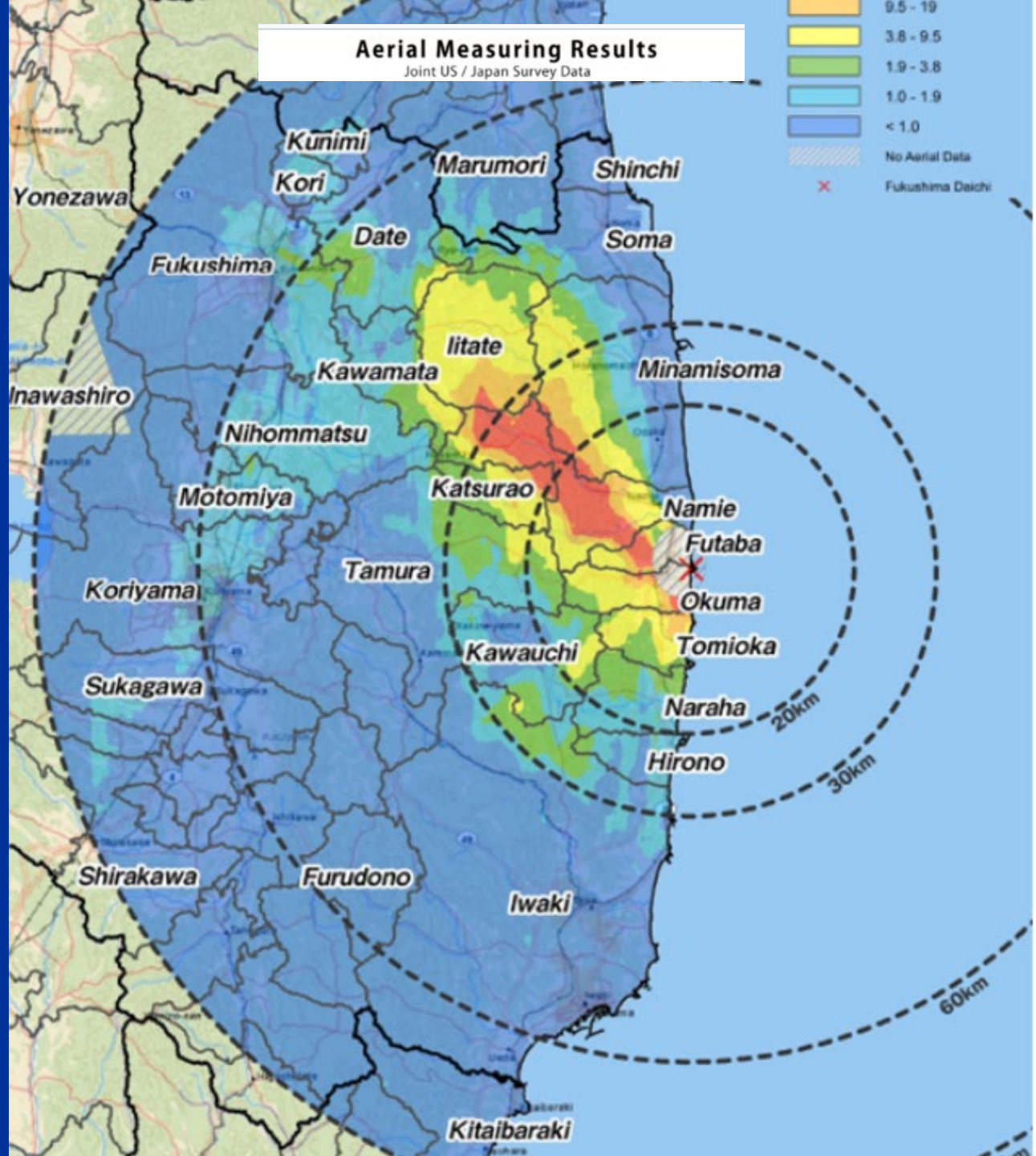

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Radiation exposure

As fears of a meltdown in Japan rise, so do the fears of radiation exposure.
What does radiation do to the human body?

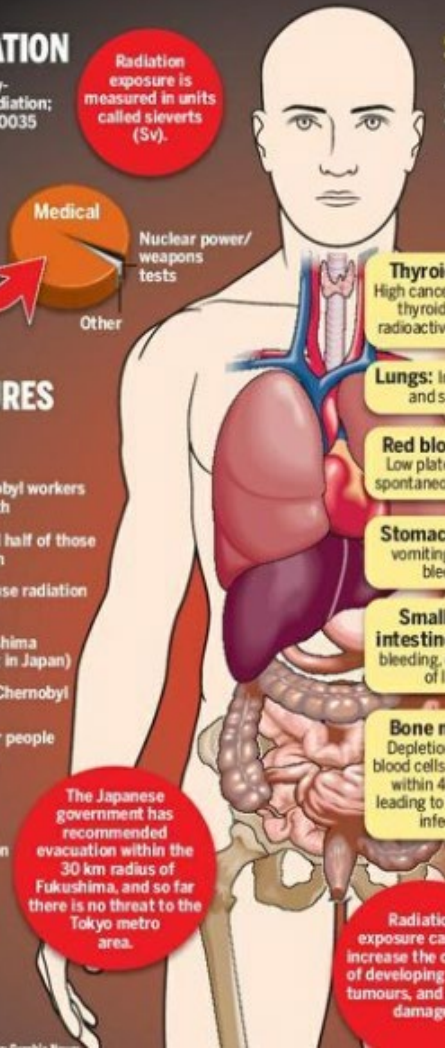
BACKGROUND RADIATION

Everybody is exposed to both naturally-occurring and artificial background radiation; levels typically range from 0.0015 – 0.0035 Sv/year:

Radiation exposure is measured in units called sieverts (Sv).

COMPARING EXPOSURES

10 Sv	Fatal within weeks
6	Typical levels in Chernobyl workers who died within a month
5	A single dose would kill half of those exposed within a month
1	A single dose could cause radiation sickness and nausea
0.4	Detected level at Fukushima (as of Tuesday morning in Japan)
0.35	Exposure of relocated Chernobyl residents
0.10	Recommended limit for people working with radiation every 5 years
0.01	Full-body CT scan
0.002	Typical natural radiation per year
0.0004	Mammogram x-ray
0.0001	Chest x-ray
0.00001	Dental x-ray



Thyroid gland: High cancer risk as the thyroid absorbs radioactive iodine-131

Lungs: Inflammation and scarring

Red blood cells: Low platelet count, spontaneous bleeding

Stomach: Nausea, vomiting, internal bleeding

Small/large intestine: Diarrhea, bleeding, destruction of lining

Bone marrow: Depletion of white blood cells (up to 50% within 48 hours), leading to high risk of infection

The Japanese government has recommended evacuation within the 30 km radius of Fukushima, and so far there is no threat to the Tokyo metro area.

Radiation exposure can also increase the chances of developing cancer, tumours, and genetic damage.

SYMPTOMS OF RADIATION EXPOSURE

Generally speaking, radiation sickness is brought on by a large dosage of radiation in a short period of time, but it has also occurred with long term exposure.

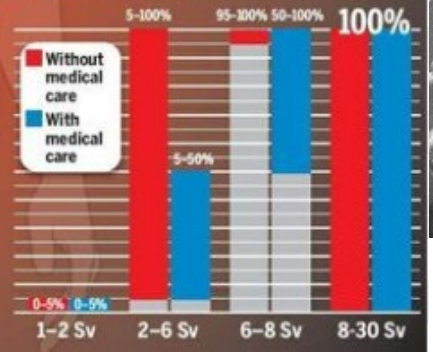
Early symptoms, exposure levels and time to symptom onset

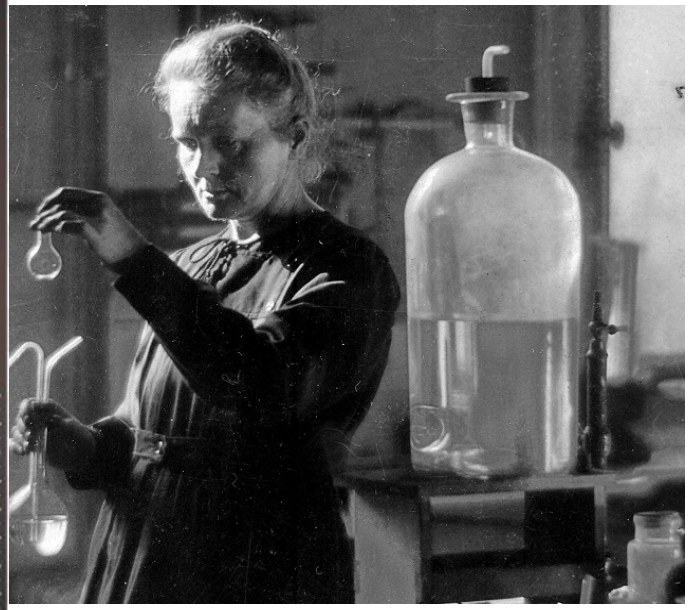
	1–2 Sv	2–6 Sv	6–8 Sv	8–10 Sv
Nausea, vomiting	6 hrs.	2 hrs.	1 hr.	10 min.
Diarrhea	–	8 hrs.	3 hrs.	1 hr.
Headache	–	24 hrs.	4 hrs.	2 hrs.
Fever	–	3 hrs.	1 hr.	1 hr.

Later symptoms

Dizziness, disorientation	–	–	1 wk.	Immediate
Weakness, fatigue	4 wks.	1–4 wks.	1 wk.	Immediate
Hair loss, bloody vomit and stools, infections, poor wound healing, low blood pressure	–	1–4 wks.	1 wk.	Immediate

CHANCES OF DEATH BASED ON EXPOSURE LEVEL





Source: http://www.concert-h2020.eu/en/Stakeholders/effects_health

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The EU authorization of sagramostim (Imreplys)

Recombinant human Granulocyte Monocyte –Colony Stimulating Factor (GM-CSF)

Stimulates progenitors of white cells and platelets enhances neutrophil/ monocyte/macrophage function

Indication: treatment of patients of all ages acutely exposed to myelosuppressive doses of radiation with haematopoietic sub-syndrome of acute radiation syndrome (H-ARS)

Only medicinal product for ARS approved in the EU. Approved under exceptional circumstances.

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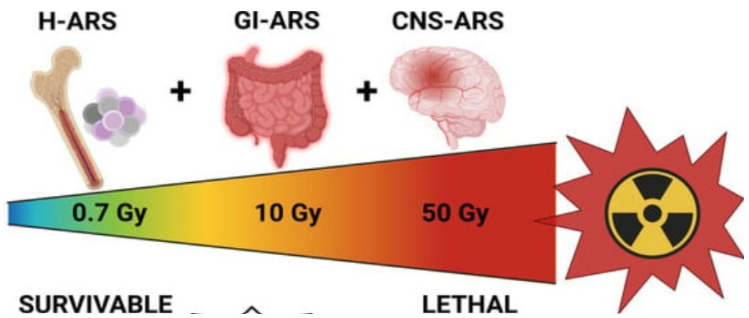
Acute radiation syndrome (ARS)

Acute illness caused by irradiation of the entire body (or most of the body) by high dose of penetrating radiation in a very short period of time (US CDC)

- Haematopoietic (H-ARS)
- Gastro-intestinal (GI-ARS)
- Cardiovascular/nervous system

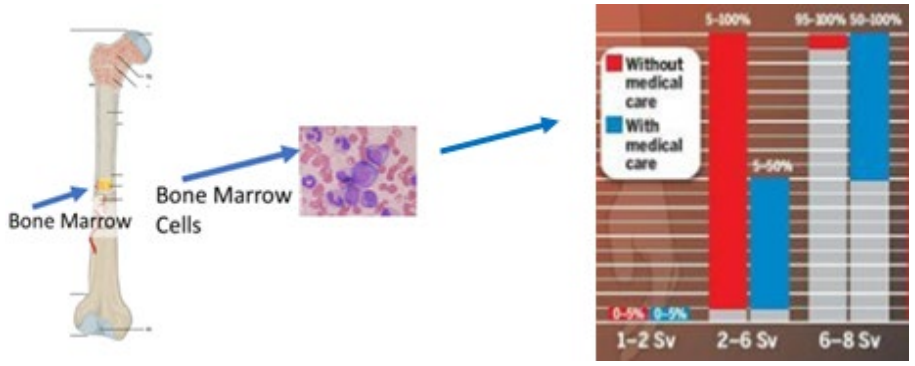


Cell Therapies for Acute Radiation Syndrome | MDPI

Haematopoietic sub-syndrome (H-ARS)

Bone marrow failure → profound neutropenia, thrombocytopenia, anaemia → infections, bleeding, multi-organ failure

- Survival hinges on bone marrow recovery
- Growth factors to stimulate production and function of white blood cells (neutrophil/monocyte/macrophages)
- Platelet and red cells recovery also crucial



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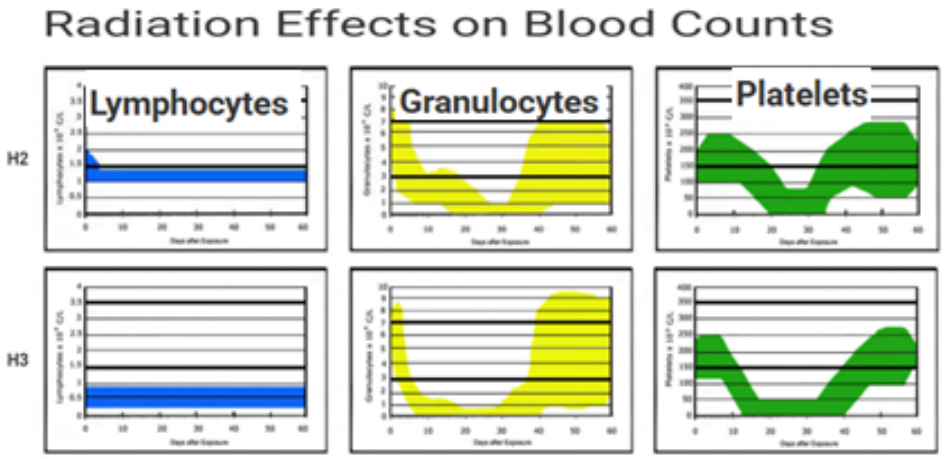
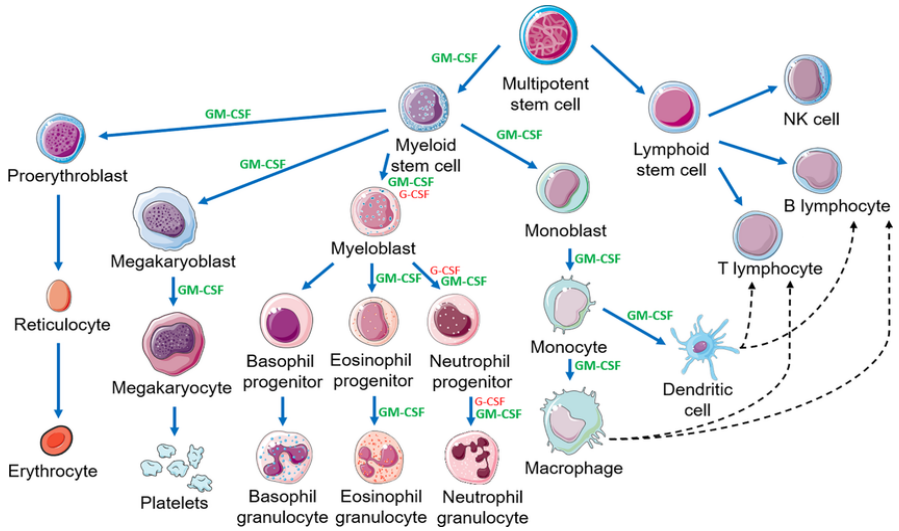
Clinical relevance of the mechanism of action



Radiation Effects on Blood Counts (2) - Illustration - Radiation Emergency Medical Management



Product / active substance / class	H-ARS indication (simplified
Neupogen® – Filgrastim (G-CSF)	Treatment of patients with H-ARS after a radiological or nuclear incident
Neulasta® – Pegfilgrastim (pegylated G-CSF)	Treatment of patients with H-ARS after a radiological or nuclear incident
Leukine® – Sargramostim (GM-CSF)	Treatment of adult and paediatric patients with H-ARS after myelosuppressive radiation exposure.
Nplate® – Romiplostim (TPO receptor agonist)	Treatment of adult and paediatric patients with H-ARS to improve survival by enhancing platelet recovery.

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Evidence package supporting the Efficacy of sagramostim

Non-clinical

- Non-human primate (NHP) H-ARS models with standardised supportive care
- Sargramostim subcutaneous after irradiation; predefined dosing regimens; follow-up to 60 days

Clinical

- Human safety and PK data oncology, HSCT and other settings
- Limited experience in radiation accident victims.

Context Human challenge studies not ethical; field trials not feasible

Is the totality of evidence predictive of clinical benefit in patients with H-ARS?

- Conclusions on benefit/risk
- Post- marketing obligations

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Main non-clinical studies

TSK0144	1017-3493 (Delayed study)	FY14-045
Primary endpoint: Mortality at Day 60 **Secondary endpoints:** recovery of blood cell lines, rate of bacterial infections, remission of clinical signs of H-ARS		
Sargramostim s.c. starting **48h after Total Body Irradiation (TBI) at $LD_{50/60}$** until ANC ≥ 1000/µL post-nadir for 3 consecutive days or ANC ≥ 10,000/µL	Sargramostim s.c. starting at **different time points (48-120h) after TBI at $LD_{70/80}$** until ANC ≥ 1000/µL post-nadir for 3 consecutive days or ANC ≥ 10,000/µL for 3 consecutive days	Sargramostim s.c. started 24h or 48h after TBI at $LD_{50/60}$ through Day 18 or until ANC >1000 µL
108 NHPs (M+F)	308 NHPs (M+F)	105 NHPs (M)
4 arms: 1) sagramostim (S); 2) 6.55 Gy vehicle (V); 3) 7.13 Gy S ; 4) 7.13 Gy vehicle (V)	4 arms; 1) S 48h, 72h, 96h, 120h; 2) V 48h; 3) S + Azithromycin; 4)	2 arms: sagramostim (S) and vehicle (V)
Supportive care: analgesics, parenteral fluids, anti-emetics, nutritional support, antibiotics	Supportive care: analgesics, parenteral fluids, anti-emetics, nutritional support, antibiotics	Supportive care: analgesics, parenteral fluids, anti-emetics, nutritional support, antibiotics

Study TSK0143 (NHP, non GLP) supportive evidence

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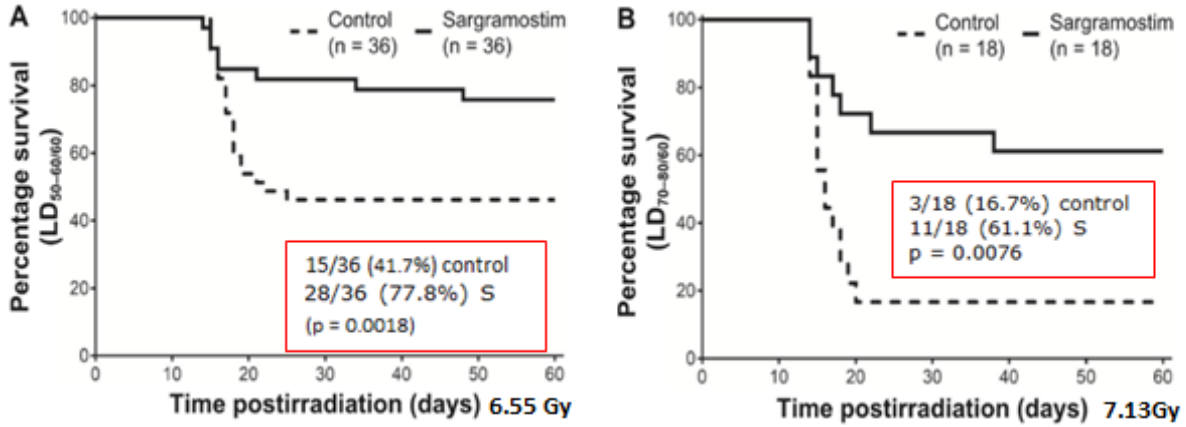
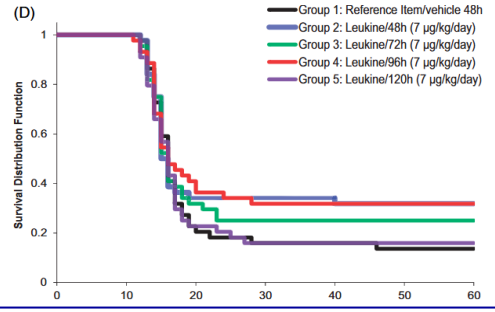
Results: Survival and Haematological recovery

- *Survival benefit with sargramostim administered within 48 hours after irradiation compared with supportive care alone*
- *Survival improvement up to 96 h post-irradiation*
- *Survival differences accompanied by faster recovery of neutrophils (time to recovery to ANC ≥ 500/µL and ANC ≥ 1000/mL) and platelets, and fewer infection-related deaths*
- *Maximum duration of treatment 24 days; average 15 days*





Study 1	TBI Dose	Sargramostim (N=36)	Vehicle control (N=36)	Statistical significance (log-rank test)
Time to recovery (days), median days (95% CI)				
ANC ≥ 500/µL	6.55 Gy	17 (16, 18)	19 (18, 20)	p<0.0001
ANC ≥ 1 000/µL		18 (17, 18)	20 (19, 20)	p<0.0001
Platelet count ≥ 20 000/µL		16 (NE, NE)	18 (18, NE)	p=0.0008

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Supportive clinical data

- **Tier 2**
- randomized, placebo-controlled clinical trials in patients with indications in which bone marrow gets compromised (e.g. autologous /allogeneic bone marrow transplant, acute myeloid leukaemia)
- **Tier 3:** clinical studies and narratives (anecdotical cases of accidental exposure to radiation)
- Survival benefits in TBI NHPs tightly linked to neutropenia and platelet recovery — effects also seen when sargramostim is used in human oncology and transplant settings.

Table 22: Clinical Studies in Special Populations

	Age 0-17 (Paediatric subjects number /total number)	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Studies	***448 / 899***	***35 / 899***	***0 / 899***	***0 / 899***
Study 301	9 / 44	0 / 44	0 / 44	0 / 44
Study 302	3 / 62	0 / 62	0 / 62	0 / 62
Study 305	0 / 117	33 / 117	0 / 117	0 / 117
Study 9002	23 / 109	1 / 109	0 / 109	0 / 109
Study 501	53 / 207	1 / 207	0 / 207	0 / 207
Study 001.0005 (Part B1)	60 / 60	0 / 60	0 / 60	0 / 60
Study 001.0005 (Part B2)	264 / 264	0 / 264	0 / 264	0 / 264
001.0006	36 / 36	0 / 36	0 / 36	0 / 36
Non-Controlled Studies	***98 / 285***	***43 / 285***	***7 / 285***	***0 / 285***
Study 308001	22 / 22	0 / 22	0 / 22	0 / 22
Study 202	9 / 13	0 / 13	0 / 13	0 / 13
Study 502	26 / 26	0 / 26	0 / 26	0 / 26
Study 701	2 / 58	15 / 58	4 / 58	0 / 58
Study 702	0 / 10	3 / 10	0 / 10	0 / 10
Study 703	14 / 27	0 / 27	0 / 27	0 / 27
Study 704	0 / 12	6 / 12	1 / 12	0 / 12
Study 705	0 / 12	2 / 12	0 / 12	0 / 12
Study 706	4 / 29	0 / 29	0 / 29	0 / 29
Study 707	0 / 10	1 / 10	1 / 10	0 / 10
Study 708	0 / 16	4 / 16	0 / 16	0 / 16
Study 709	0 / 23	10 / 23	1 / 23	0 / 23
Study 710	0 / 6	2 / 6	0 / 6	0 / 6
Study 9208	21 / 21	0 / 21	0 / 21	0 / 21

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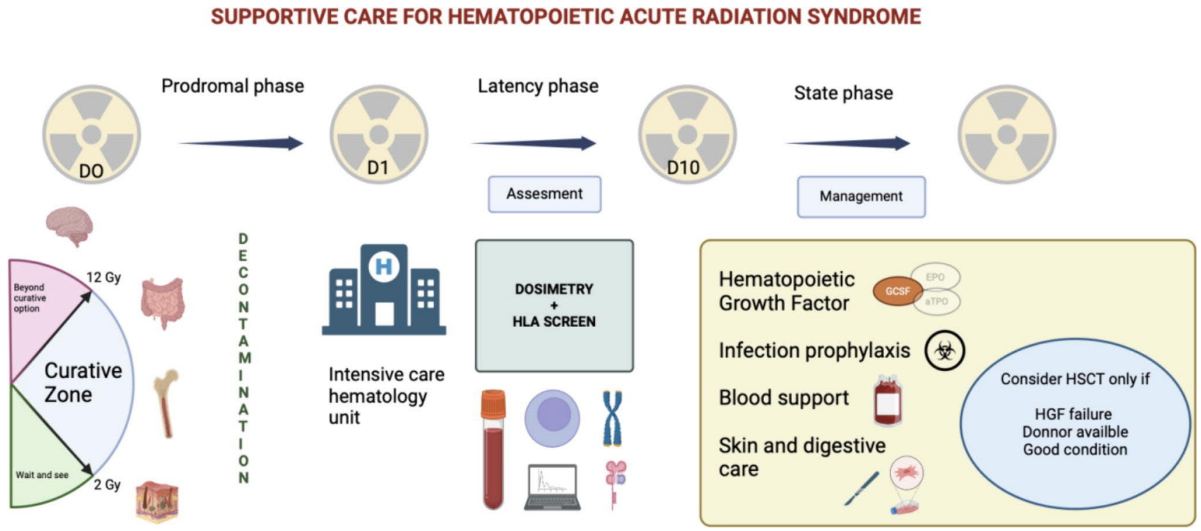
Critical aspects of study design in H-ARS

- Timing of administration compared to challenge (proposed indication)
- Use minimum radiation dose linked to interpretable endpoints
  - Dose levels ($LD_{50\text{-}60/60;}$ $LD_{80/60;}$ $LD_{x/60?}$)
  - Dose measure
- Reflecting potential clinical use
  - Administration route
  - Time to treat (‘delayed’ treatment)
  - Use in combination?
  - Background treatment
- Control arm(s)
- Endpoints
  - Survival at D60
  - Haematology endpoints
  - Other



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From models to humans-key translational aspects in H-ARS

	NHP H-ARS models	Human ARS
Pathophysiology match	✓✓✓	✓✓✓
Exposure pattern	✓✓	✓✓
Comorbidities & age	✓	✓✓✓
Supportive care realism	✓✓✓	✓✓
Dose–response	✓✓✓	✓✓

From Farese AM et al., Health Phys 2012'; MacVittie TJ et al.; Waselenko JK et al. 2004; diCarlo et al.; Singh VK et al.; López M et al, Radiat Prot Dosimetry 2011.

- Species: rhesus macaques, similar haematopoietic and immune systems to humans
- Drug effects on bone marrow/haematology well understood and clinically relevant
- Pathophysiology and clinical picture after irradiation recapitulates human H-ARS
- Standardised supportive care: fluids, anti-emetics, antibiotics; no intensive, individualised care, to mimic mass-casualty management

- Radiation exposure
  - NHPs studies 6-7 Gy
  - Human H-ARS historical threshold > 2 Gy
- Special populations (children, elderly, comorbidities)
- Females?
- Real-life supportive care?
- Human dose-response knowledge from limited clinical data in conditions with bone-marrow impairment

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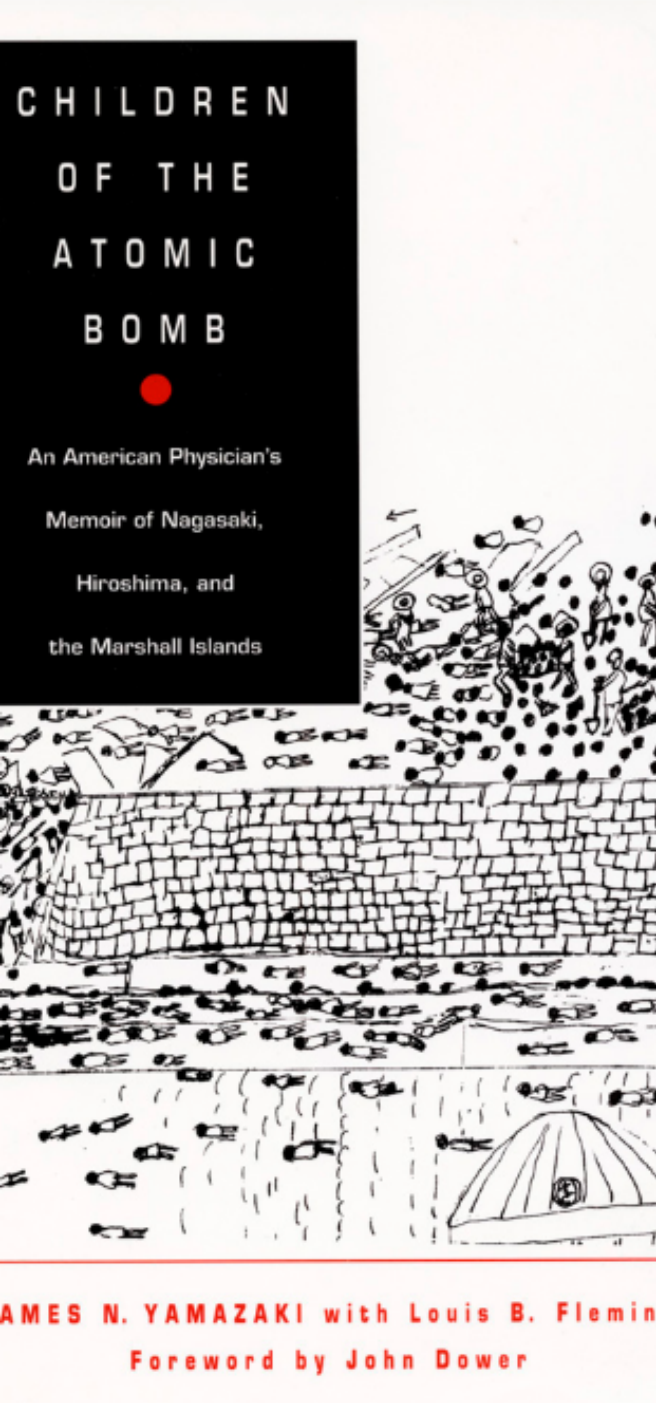

Special populations: paediatric development

- Children more radiosensitive than adults lower LD 50/60 expected
- Juvenile studies usually not requested in medical countermeasures developments based on non-clinical efficacy
- Same H-ARS pathophysiology as adults
- No difference in mechanism of action of sagramostin between adults and children
- Paediatric dose extrapolated with modelling (adult NHPs; phase 1 data)
- For sagramostim, some paediatric data available from clinical studies in autologous BMT, allogeneic BMT, BMT failure or engraftment delay, prophylaxis for nosocomial infections in pre-term newborns

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral
EMEA-003568-PIP01-23

Area	Description
Quality-related studies	Not applicable
Non-clinical studies	**Study 1 (TSK0143)** Pilot efficacy study of sargramostim in irradiated rhesus monkeys. **Study 2 (TSK0144, TSK0144-amend1)** Randomized, blinded, placebo-controlled efficacy study of sargramostim in irradiated rhesus monkeys. **Study 3 (FY14-045, FY14-045-amend1)** Nonclinical study evaluating the survival benefit from sargramostim relative to control groups in an established haematopoietic subsyndrome of acute radiation syndrome (H-ARS) model in male rhesus monkeys. **Study 4 (1017-3493)** Sargramostim - blinded time to dosing efficacy study in irradiated rhesus monkeys that have received minimal supportive care.
Clinical studies	**Study 5 (PTX-01-009 H-ARS)** Retrospective, observational study to assess the clinical benefit and safety of sargramostim in children from birth to less than 18 years of age exposed to myelosuppressive doses of radiation following a radiological and/or nuclear incident in a European Union member state or country from the European Economic Area.
Modelling and simulation analyses	**Study 6 (POH0547)** Population Pharmacokinetic (PopPK) analysis of sargramostim in healthy adults and application to exposure simulation for adult and paediatric populations.

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Conclusions

- Data from studies in NHPs were considered adequate for supporting sagramostim in H-ARS due to its similarity to humans in haematopoietic stem cell biology, bone marrow distribution, and radiation effects
- sagramostim showed similar biological activity in NHPs and humans, allowing for relevant dose extrapolation
- Supportive clinical efficacy data from other indications and cases of accidental high-dose radiation exposure
- Overall well controlled model, with understandable pathophysiology
- Product with, medical plausibility, and non-clinical results measuring hard endpoints (survival) and clinically relevant (all secondary endpoints)
- (relative) role of clinical data

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