



Memorial Sloan Kettering
Cancer Center

The Drug Development Paradigm in Oncology:

Role of Imaging

Hedvig Hricak

MSKCC



Precision Medicine: Imaging in Clinical Trials and Drug Development*

Critical elements:

Patient Selection, Dose Finding & Treatment Response

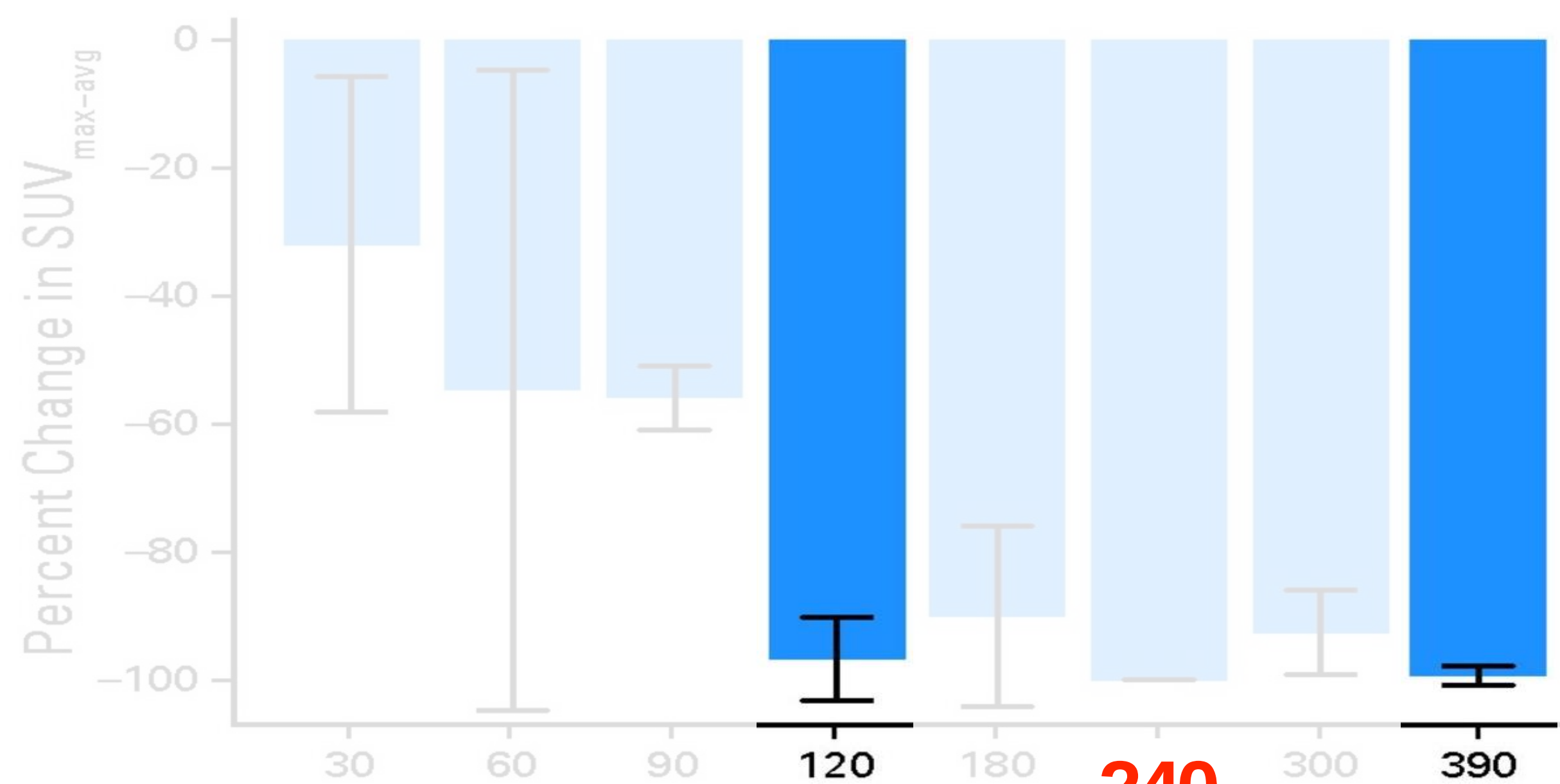
CHANGING PARADIGMS:

- › **Patient Selection:** Imaging as an in vivo companion diagnostics
- › **Dose finding:** Change from Maximum Tolerated Dose (MTD) to Biologically Relevant Dose (BRD)
- › **Treatment Response**

*Imaging approaches to optimize molecular therapies: R. Weissleder, M. C. Schwaiger, S. S. Gambhir, H. Hricak ; Science Translational Medicine 2016

Imaging in Drug Development: Dose Finding

Phase I Study of ARN-509 (androgen receptor antagonist): Role of ^{18}F -FDHT in Defining the Biologically Relevant Dose*



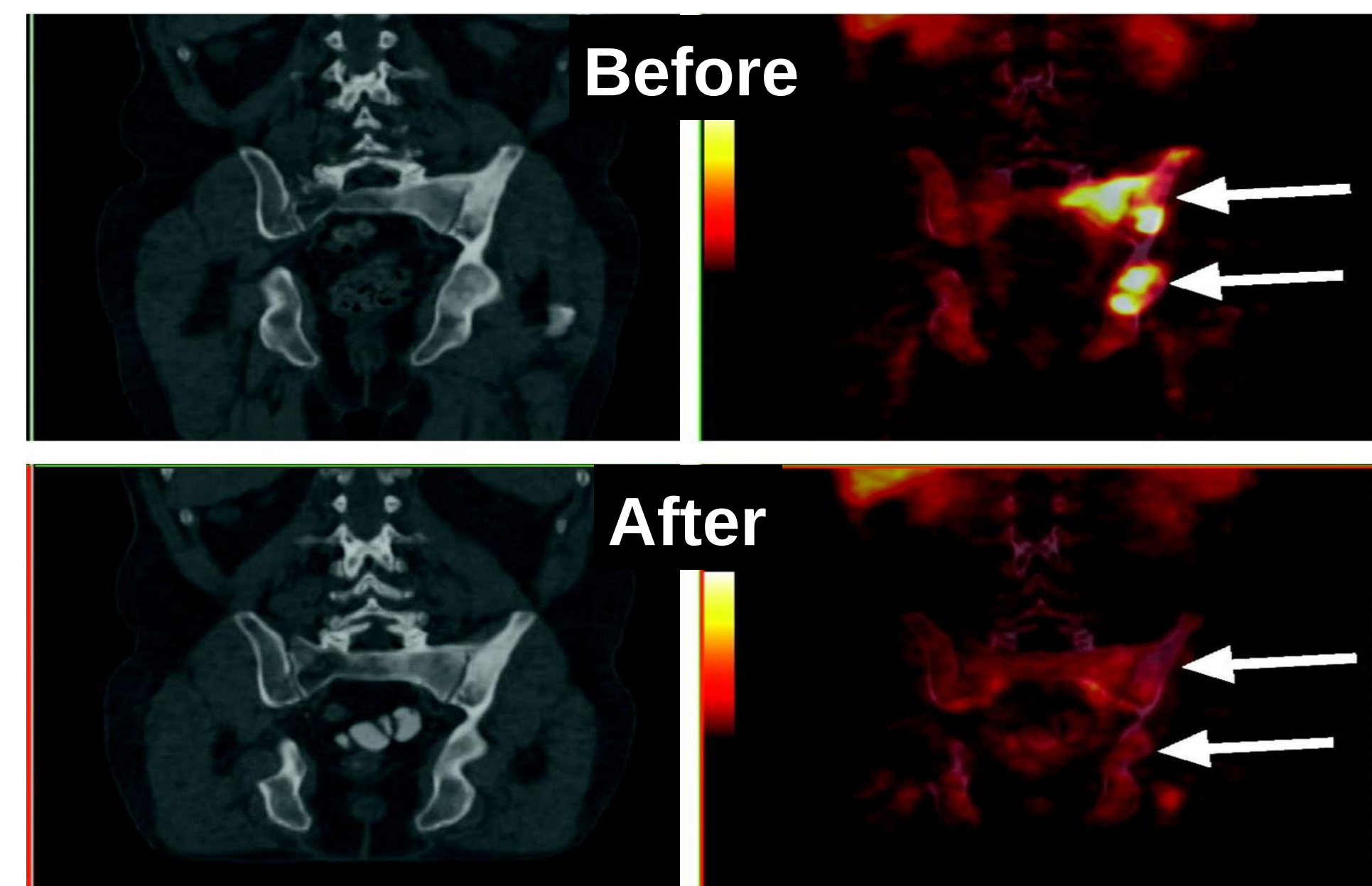
BRD

MTD

No. of Patients

2 2 2 2 2 1 4 1
Biologically Relevant Dose

11 3 25 6
Maximum Tolerated Dose



^{18}F -FDHT PET/CT

Imaging in Drug Development: Dose Finding

Phase I Study of GDC-0810 (ER antagonist): Role of ^{18}F -FES in Defining the Biologically Relevant Dose*

Patient-Centered Value-Driven Population Health

^{18}F -FES PET/CT used as a biomarker of ER suppression during Phase I dose escalation trial showed ER downregulation with >90% decrease in SUV for **BRD= 600mg/day – dose chosen for Phase II trial**

MSKCC Molecular Imaging Probe and Radiotherapeutic Agent IND's

(N = 41 (30 open; 11 completed))

Imaging Agent	Imaging Target		Cancer Site
Small Molecules (Imaging)			
[¹¹ C]-choline	tumor metabolism		Recurrent prostate cancer

Imaging in Drug Development:
Technical Feasibility to develop In Vivo
Molecular Diagnostics (new tracers) is no
longer a limiting factor

[⁸⁹ Zr]-DFO-5B1	CA19.9		Pancreas
[⁸⁹ Zr]-Df-IAB22M2C	cytotoxic human T cells		Melanoma
Antibodies and Fragments (Therapy)			
[¹³¹ I]-8H9	8H9 antigen		Multiple tumors e.g. Leptomeninges (pediatrics)
[¹³¹ I]-3F8	disialoganglioside GD2		Neuroblastoma (pediatrics)
Nanoparticles (Imaging)			
[¹²⁴ I]-Cdot nanoparticles	Avβ3		Melanoma
Hyperpolarized Agents (Imaging)			
[¹³ C]-pyruvate	Cancer metabolism		Prostate and other solid tumors

IND Enabling Stage:[⁸⁹Zr]-DFO-transferrin; [⁸⁹Zr]-DFO-MLYE44789A; [⁸⁹Zr]-DFO-pertuzumab; [¹¹C]-acetate, [¹¹C]-thymidine, [¹¹C]-glucose, [¹¹C]-martinostat

Completed Studies (n = 11): [¹⁸F]-FIAU (gene expression), [¹⁸F]-ML10 (apoptosis), [⁶⁴Cu]-ATSM (hypoxia), [¹²⁴I]-IAZGP (hypoxia), [⁶⁸Ga]-Her2 F(ab') (HER2), [¹⁸F]-FACBC (amino acid metabolism), [¹²⁴I]-A33, [¹²⁴I]-G250 (CA9 antigen), [¹¹¹In]-DOTA-cG250 (CA9 antigen), [⁹⁰Y]-DOTA-cG250 (CA9 antigen), [²²⁵Ac]-lintuzumab (anti-CD33)

Imaging in Drug Development: Challenges

1. Validation and FDA approval for In-vivo companion diagnostics
2. Infrastructure – How many sites can participate in a trial using Molecular Imaging (new tracers beyond FDG PET/CT) in patient selection and BRD dose finding
3. People – oncology expertise in diagnostic radiology and nuclear medicine