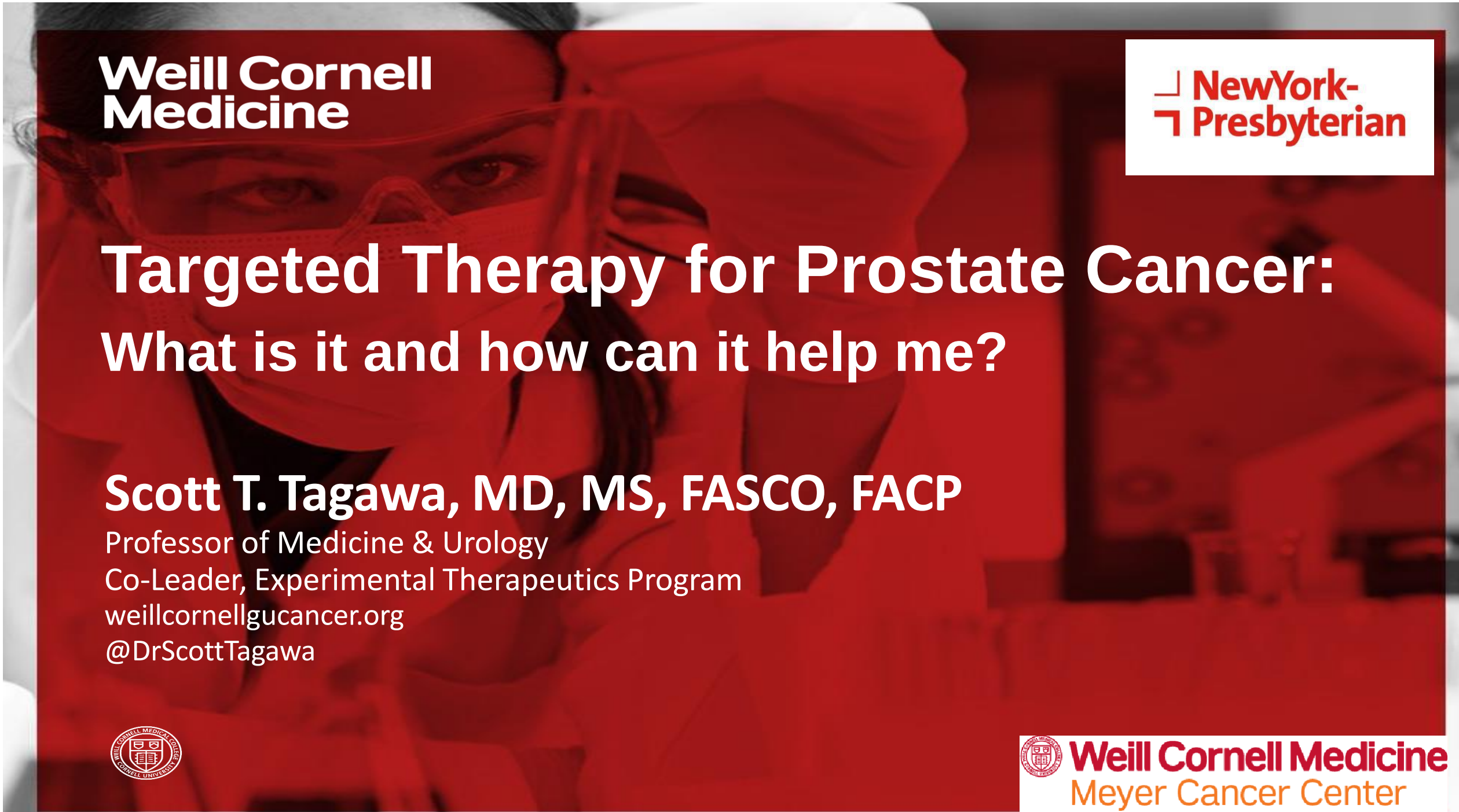

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NewYork-Presbyterian

Targeted Therapy for Prostate Cancer:
What is it and how can it help me?

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Weill Cornell Medicine
Meyer Cancer Center

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  - Sanofi, Medivation, Astellas, Janssen, Amgen, Progenics, Dendreon, Lilly, Genentech, Newlink, BMS, Inovio, AstraZeneca, Immunomedics, Aveo, Rexahn, Atlab, Boehringer Ingelheim, Millennium, Bayer, Merck, Abbvie, Karyopharm, Endocyte, Clovis, Seattle Genetics, Novartis, Gilead, POINT Biopharma, Ambrx, Clarity
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- Unpaid Consultant:
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- Patent:
  - Biomarkers for sacituzumab govitecan therapy (Immunomedics / Gilead / Weill Cornell)

May show off-label use and investigational agents

Targeted Therapy – various unofficial definitions

- Treatment that only affects bad parts, sparing good parts
- Treatment that hits the right target effectively
- Precision medicine
  - The right treatment for the right patient at the right time
- Treatment that seeks out certain targets

Prostate cancer targeted therapy implications (to be discussed)

- Molecular selection
  - Precision medicine
- Imaging
  - Paired with focal / local therapy
- Cell surface targeting

SIGNIFICANT ADVANCES IN SYSTEMIC THERAPY

- Hormonal Therapy
  - "ADT"= androgen deprivation therapy
    - LHRH agonists (e.g. leuprolide, goserelin), GnRH antagonist (e.g. degarelix, relugolix), surgical removal of testicles
  - First generation antiandrogens
    - Flutamide, bicalutamide, nilutamide
  - CYP17 inhibitors
    - Abiraterone
  - AR (signaling) inhibitors
    - Enzalutamide, apalutamide, darolutamide
- Chemotherapy
  - Taxanes (docetaxel), cabazitaxel)
  - Other (mitoxantrone), platinums)
- Immunotherapy
  - Sipuleucel-T, pembrolizumab
- Bone-targeted therapy
  - Radium-223
  - Zoledronic acid, denosumab
- Molecularly selected therapy
  - PARP inhibitors
    - Olaparib, rucaparib, talazoparib, niraparib
  - Lutetium Lu-177 vipivotide tetraxetan (^{177}Lu-PSMA-617)

(other ways of grouping)

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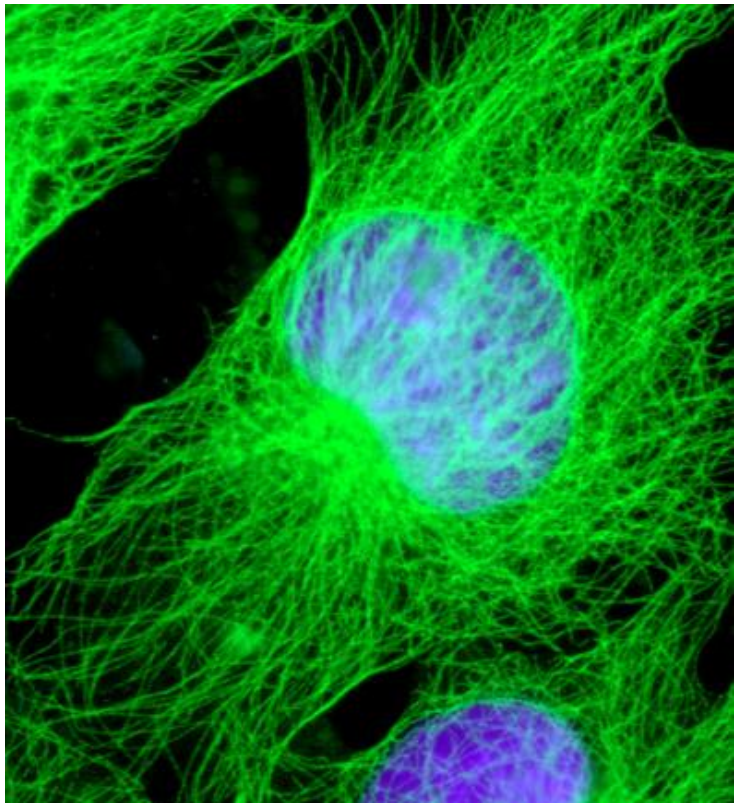
All of these are targeted agents
Nearly all have some data for "positive or negative selection"

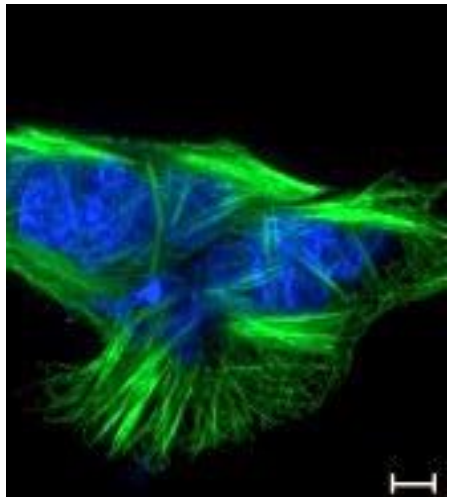
→ Major improvements in quantity and quality of life

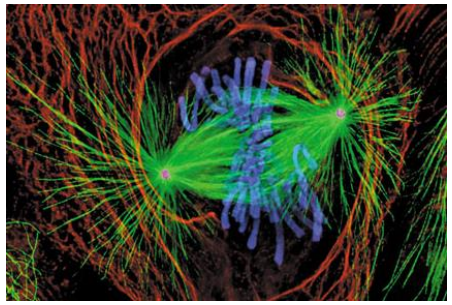
WHAT IS TARGETED THERAPY?

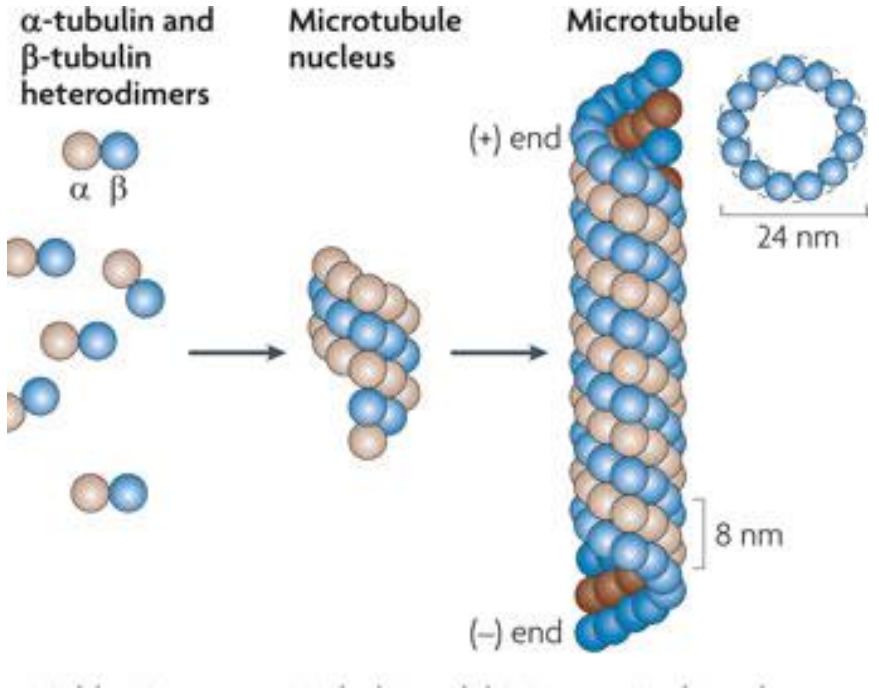
- Local therapy (treatment to one area) designed to spare other areas
  - Requires both sensitive imaging and focal treatment
- **Precision medicine**: the right treatment for the right patient at the right time
  - Often genomically selected approaches
- **Cell (surface) targeting**: usually systemic administration of an agent designed to attach to certain cells and bypass others

Taxanes: The Misunderstood Targeted Therapy





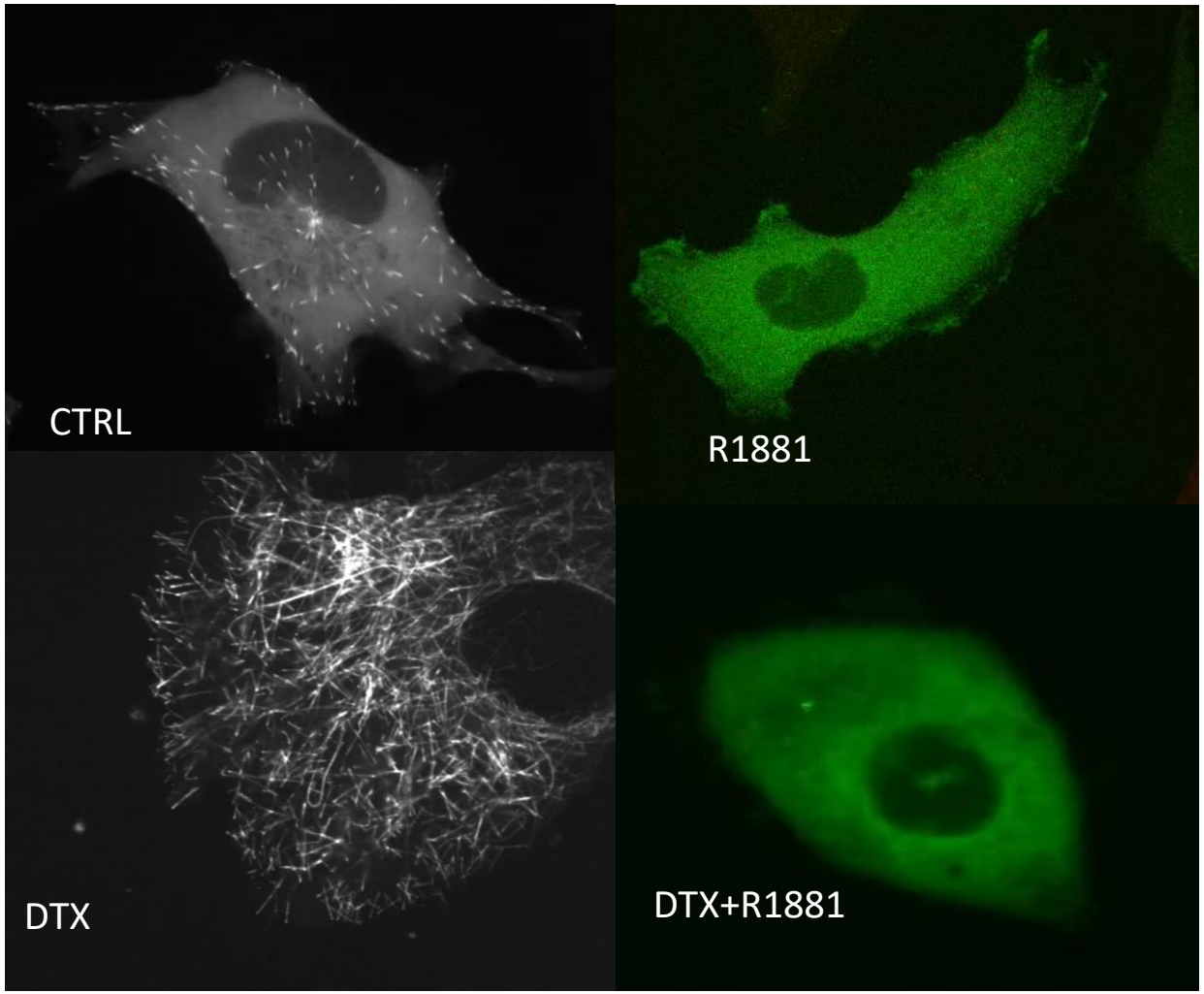


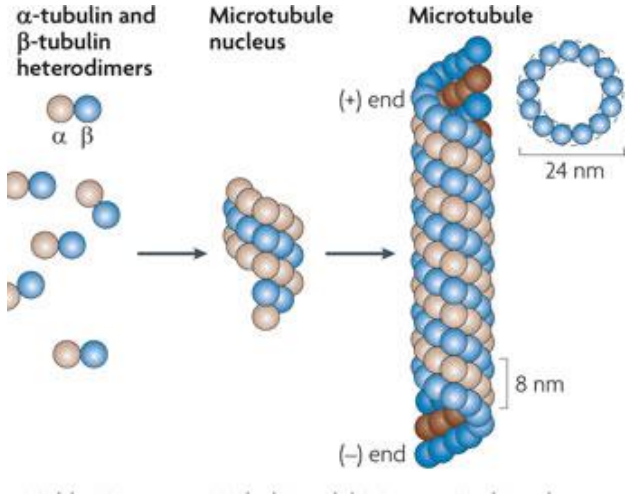


- MT-Targeting drugs show the broadest anti-tumor activity in comparison to all other classes of cancer chemotherapeutics.
- In breast cancer 7 of the 10 FDA-approved chemotherapy drugs are MTDs
- In prostate cancer the taxanes [docetaxel (Taxotere), cabazitaxel (Jevtana)] form the backbone of chemotherapy

Yet, MT inhibitors are still considered as "antimitotics" because the MT-regulated signaling and trafficking interphase pathways and their role in patient sensitivity/resistance remain poorly understood

Taxanes Inhibit the Dynamic MT-AR Signaling Axis





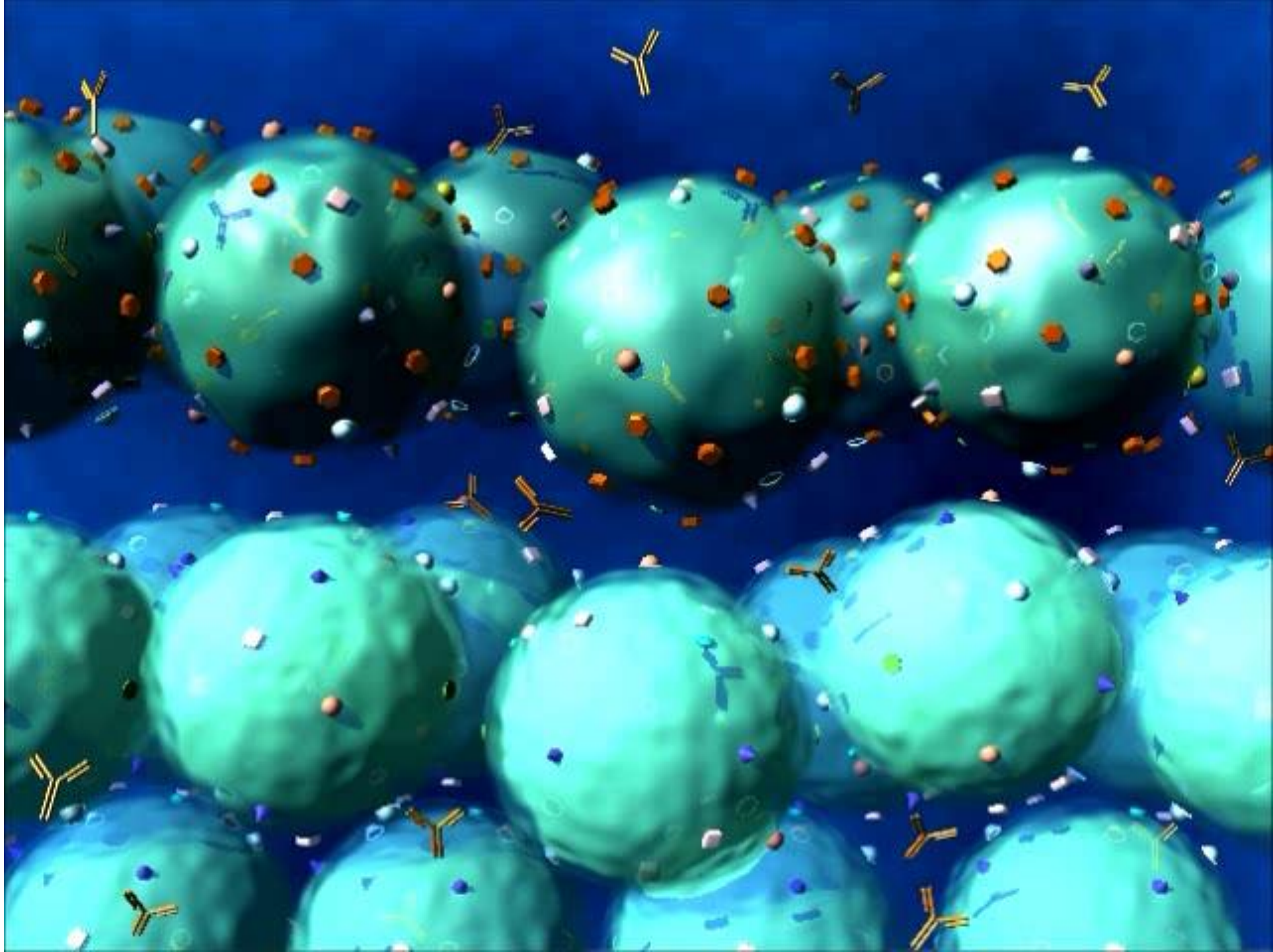
Darshan et al. Cancer Res. 2011
Thadani-Mulero et al. Cancer Res. 2012;
Thadani-Mulero, Portella et al. Cancer Res. 2014

Targeting

Engineer a targeting agent (i.e. key)

That will recognize a specific target (i.e. lock)

Upon binding to those selected target cells (usually cancer), the agent enters the cell (bringing whatever is attached to it)



What is PSMA?

Prostate-specific membrane antigen

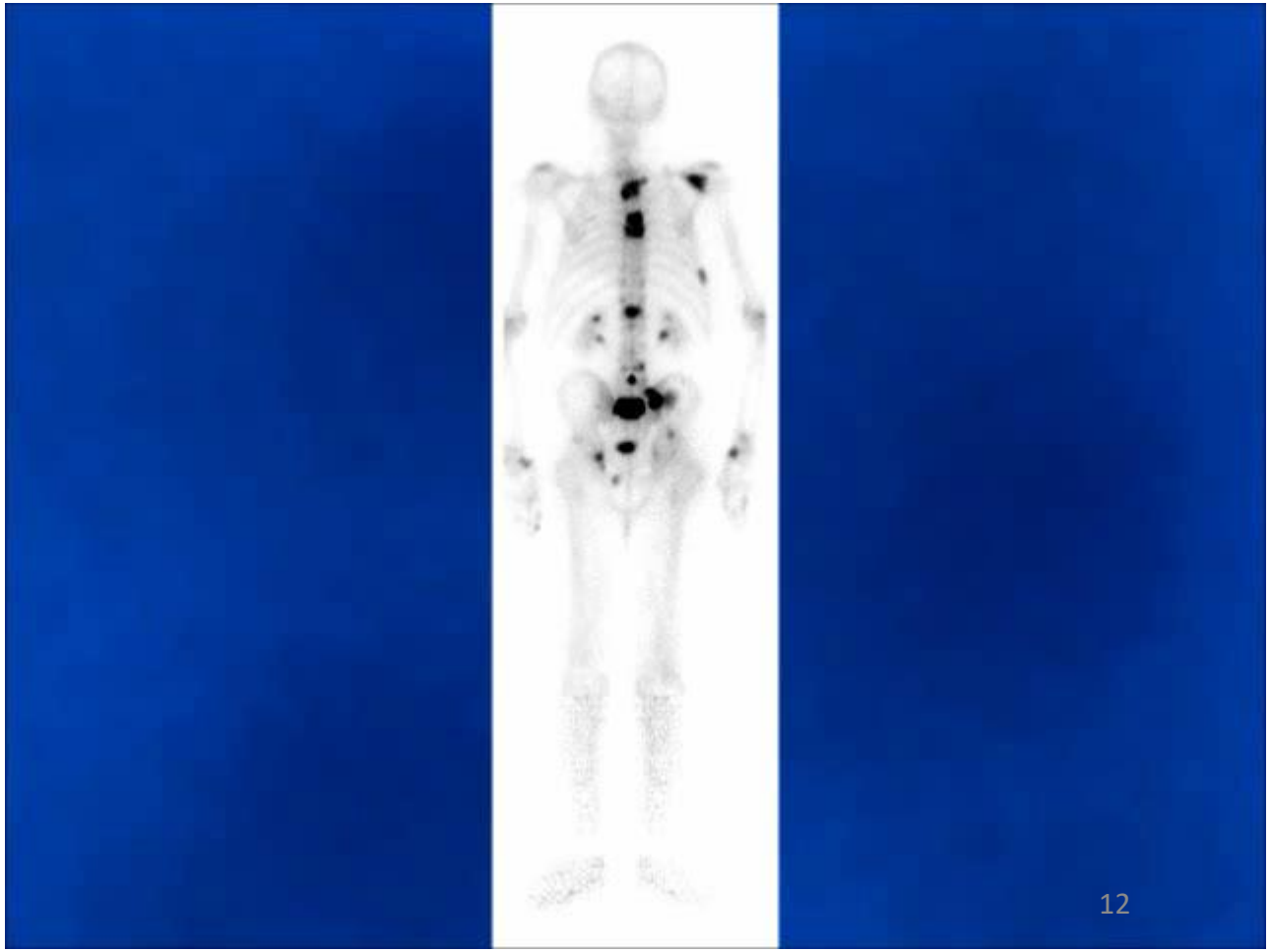
- **“PSMA is the single most well-established, prostate-restricted, cell membrane target known”**
  - Well-established = validated in cells and in humans in clinic
  - Prostate-restricted = distribution mostly* limited to prostate and prostate cancer
  - Cell membrane target = on the surface of cells
- PSMA remains a target of high interest in the current era
  - Especially important for higher grade (aggressive), metastatic (spread) tumors that grow despite hormonal therapy

*Luminal expression prox renal tubules, brush border small intestine, salivary and lacrimal glands
Also happens to be expressed on neovasculature of most solid tumors

Targeted Diagnostics (& Therapeutics)

- PSMA = a very specific lock present on tumor
- We have engineered specific “keys” that only target PSMA “locks”

and we can attach cancer killers or other molecules to keys that enter via locks



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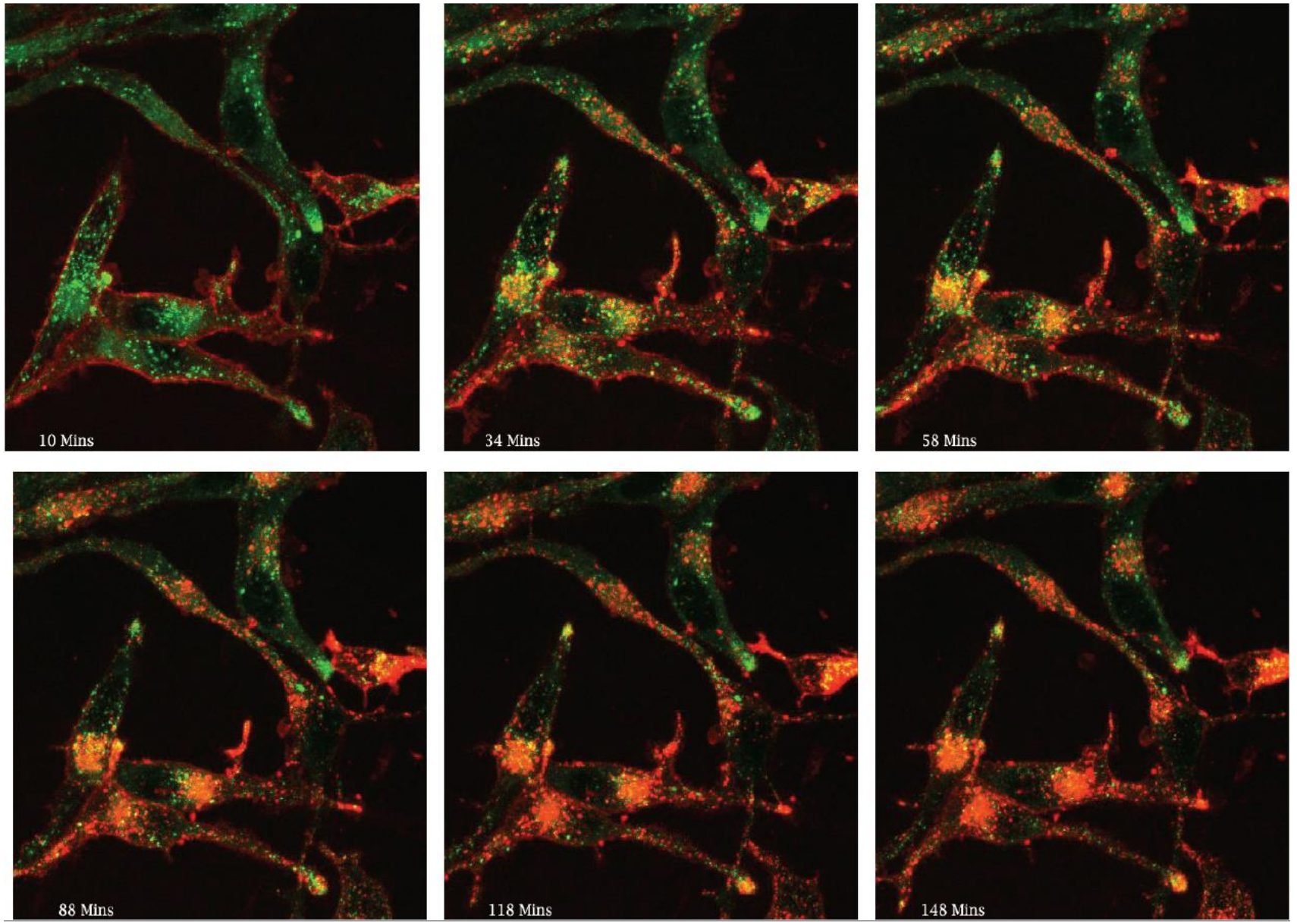


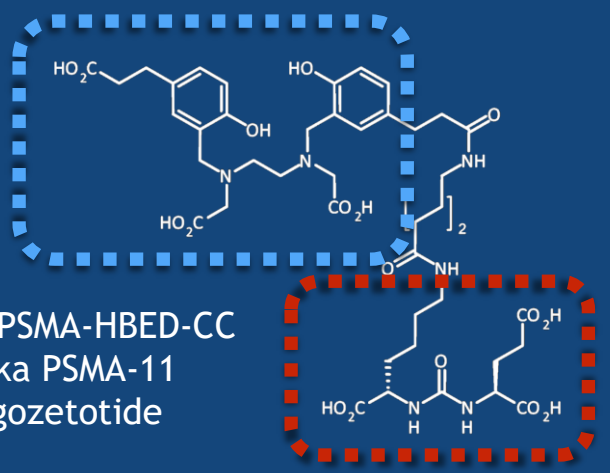
Snapshots from a 2.5 hour time-lapse confocal microscopy sequence of LNCaP incubated with directly red-labeled J591 (anti-PSMA) mAb and green-labeled lysosomes (lysotracker).
Rapid uptake of the J591 Ab into the lysosomal compartment (red+green = yellow) directly adjacent to the nucleus.

Current (modern) imaging tools:

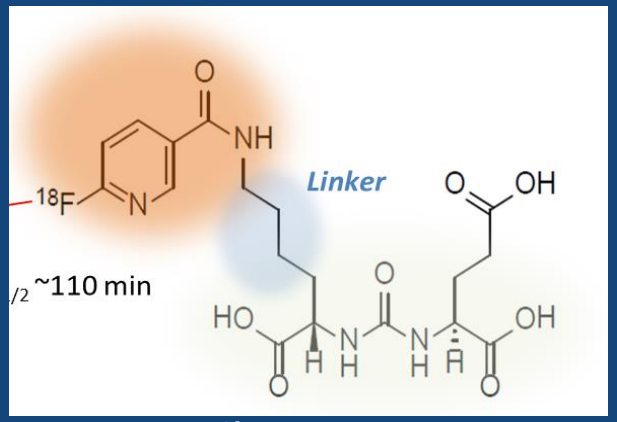
- Xray
- Ultrasound
- CT scans
- MRI
- Bone scan
  - ^{99m}Tc-MDP bone scintigraphy
- Other available/approved nuclear medicine techniques
  - ^{18}F-FDG-PET
  - ^{18}F-NaF bone PET
  - ^{11}C-choline PET
  - ^{18}F-fluciclovine (FACBC, Auxumin®) PET
  - ^{111}In-capromab penditide (Prostascint®) SPECT
  - ^{68}Ga-PSMA-11 (gozetotide, Illucix®, Locametz®) PET
  - ^{18}F-DCFPyL (piflufolastat, Pylarify®) PET
  - ^{18}F-rhPSMA-7.3 (flotufolastat, Posluma®) PET

(^{177}Lu-PSMA SPECT)

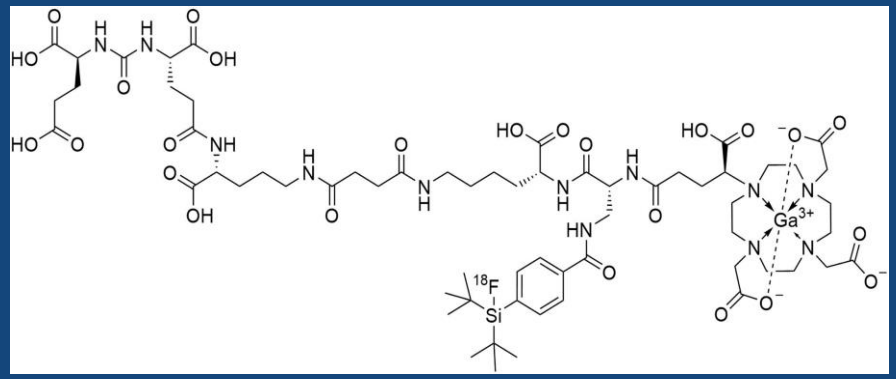
Multiple small molecule ligand inhibitors in clinic



^{68}Ga-PSMA-HBED-CC
aka PSMA-11
gozetotide



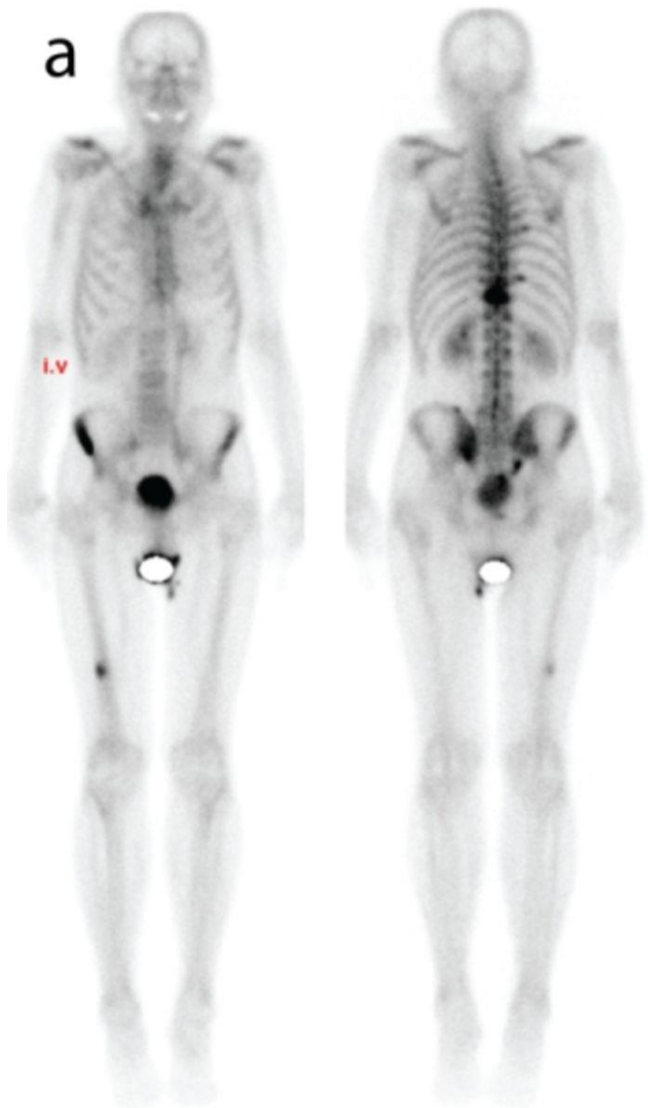
^{18}F-DCFPyL
aka PYL
piflufolastat

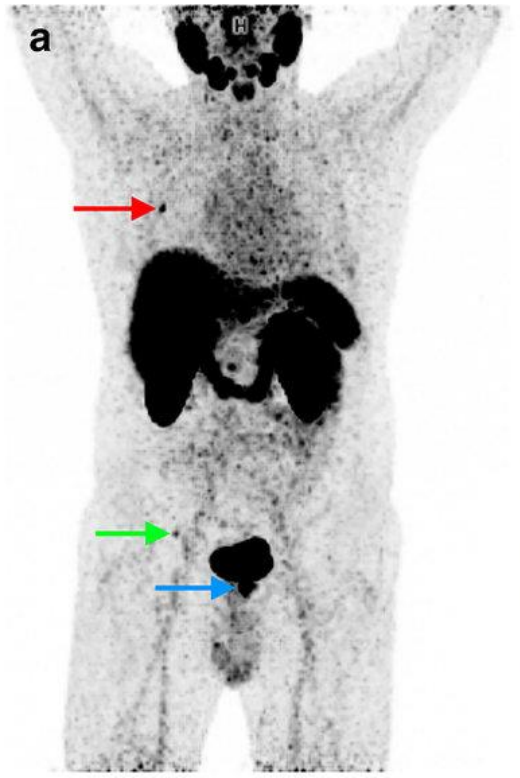


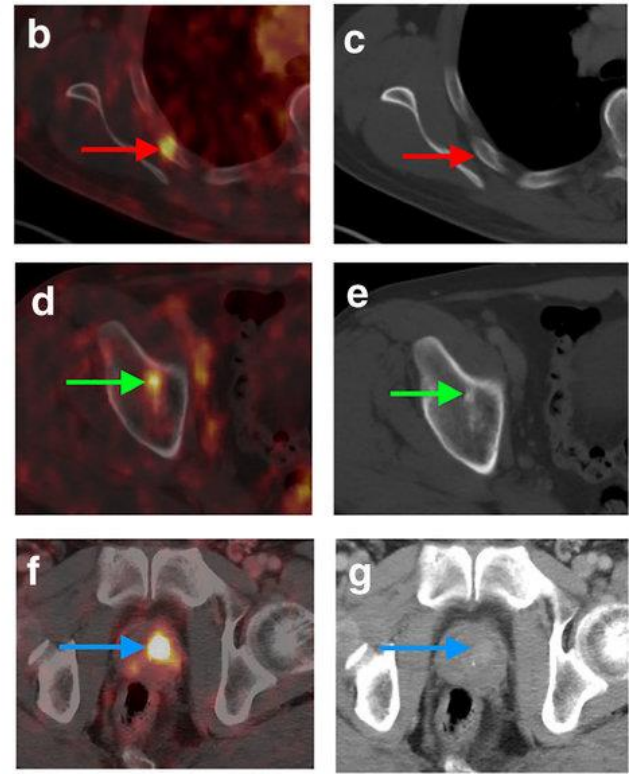
^{18}F-rhPSMA-7.3
flotufolastat

- **Generally with similar urea PSMA ligand binding domain**
- **Linker for radionuclide**
- **"Minor" differences in radioisotope**
  - Different imaging properties; practicalities = cost, availability
- **Some with different biodistribution**
  - Urinary excretion for most

Examples: PSMA PET vs “standard” imaging







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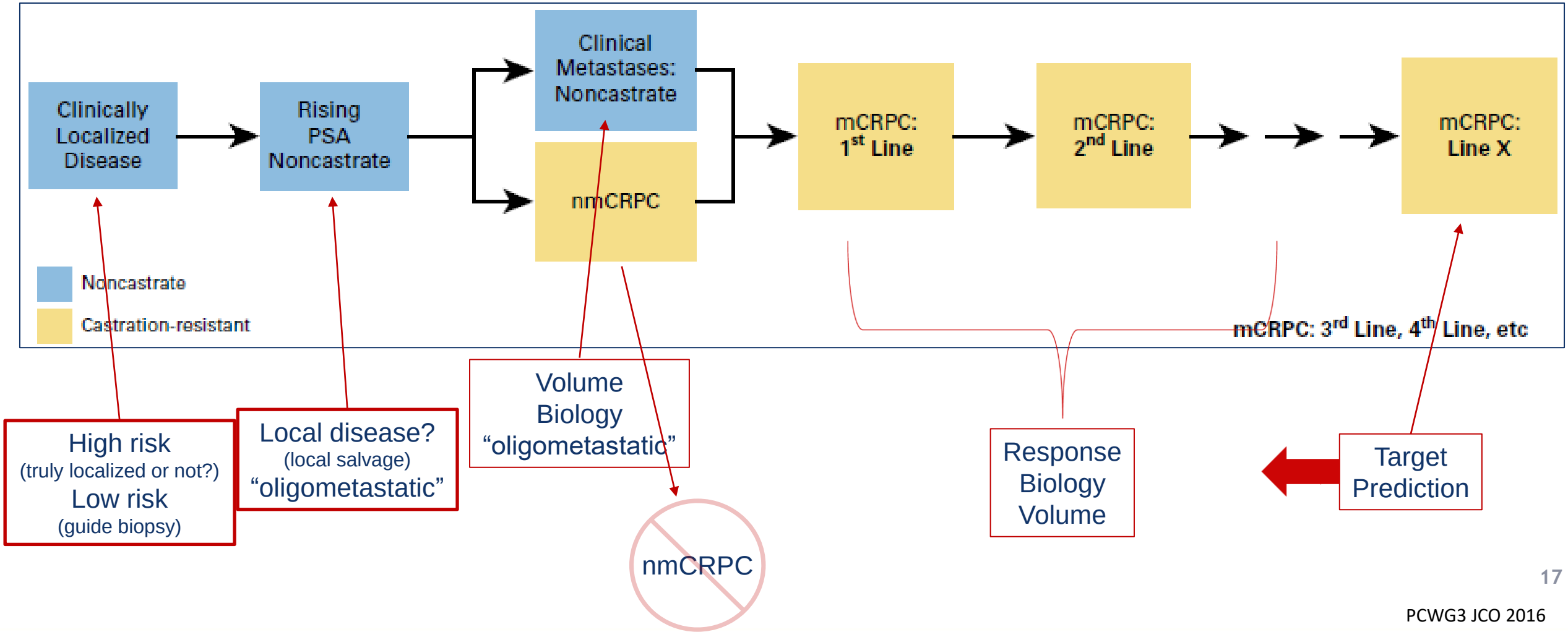
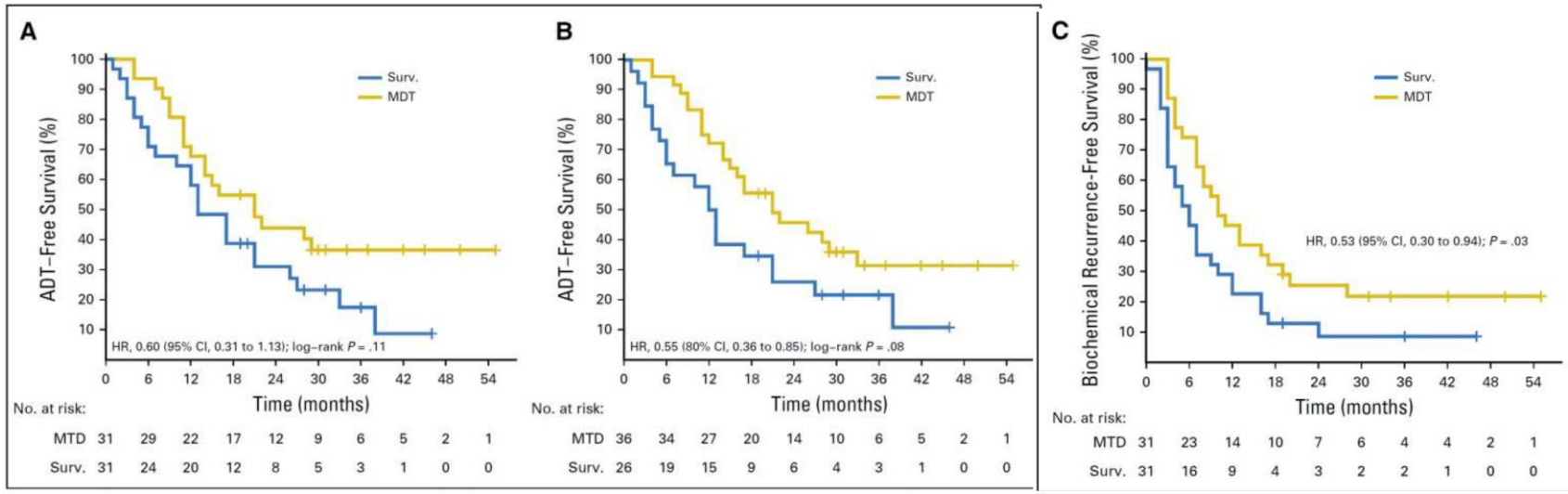
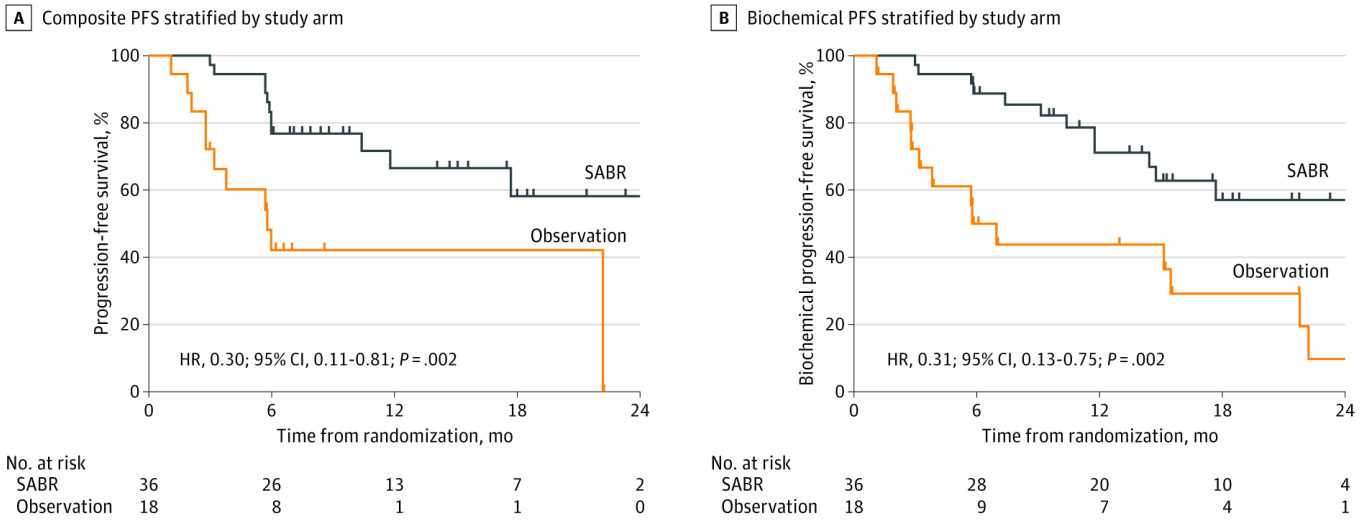
PSMA PET to address imaging deficiencies for men with prostate cancer

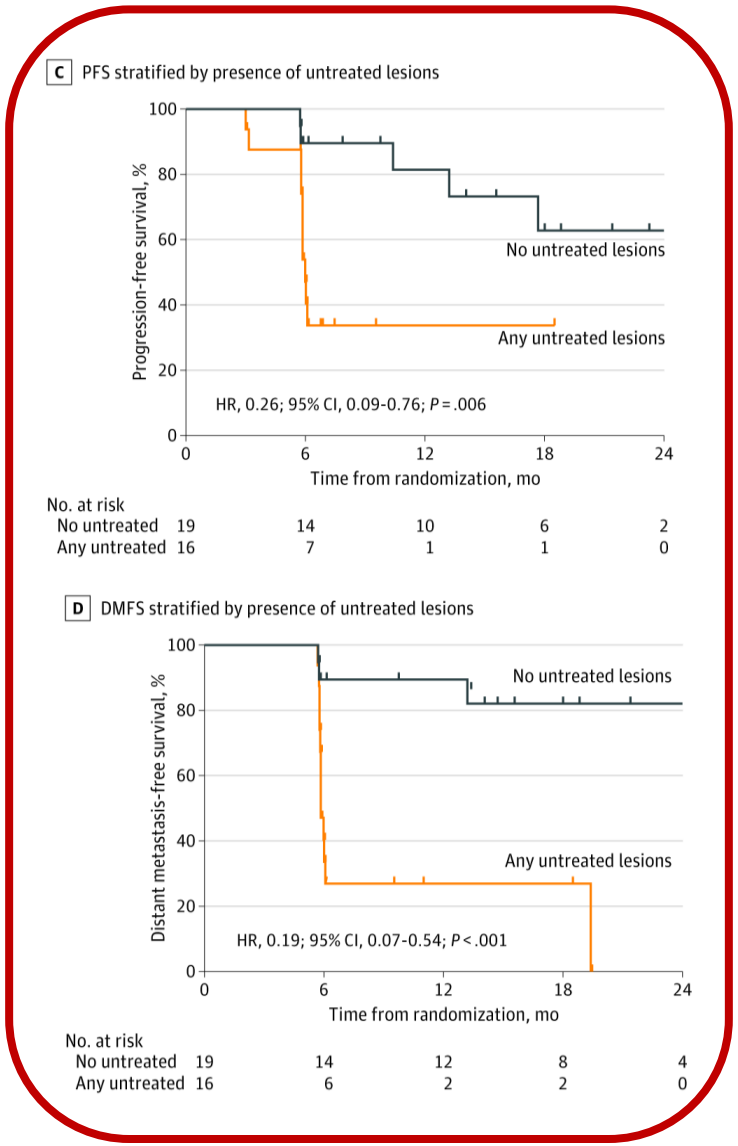


PCWG3 JCO 2016

Metastasis-directed therapy to “oligometastatic” sites

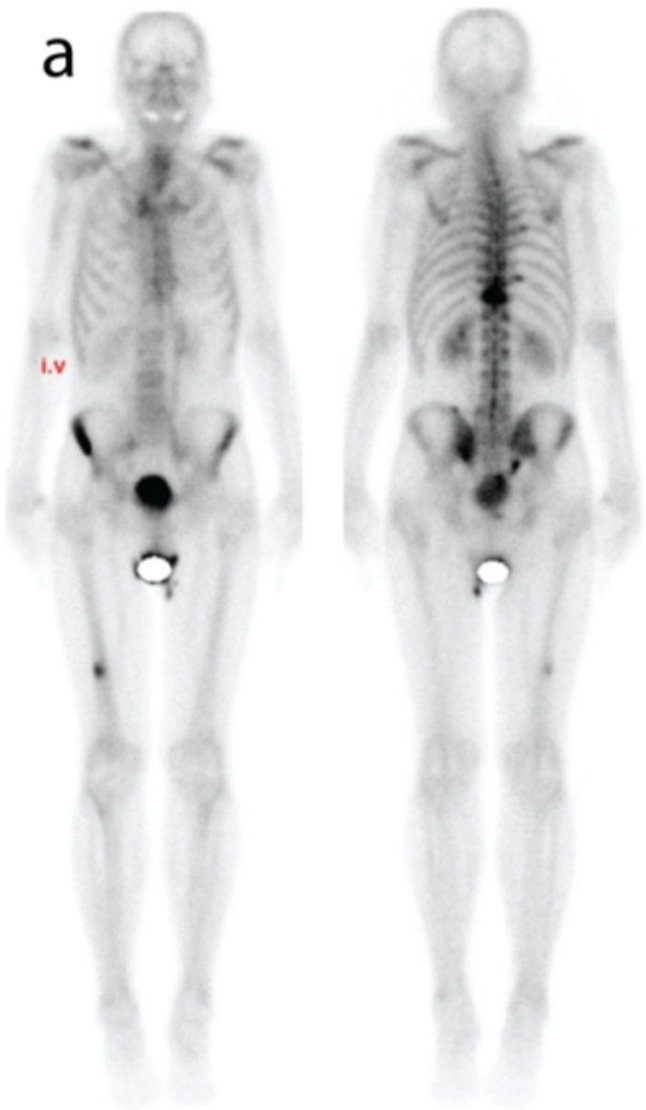


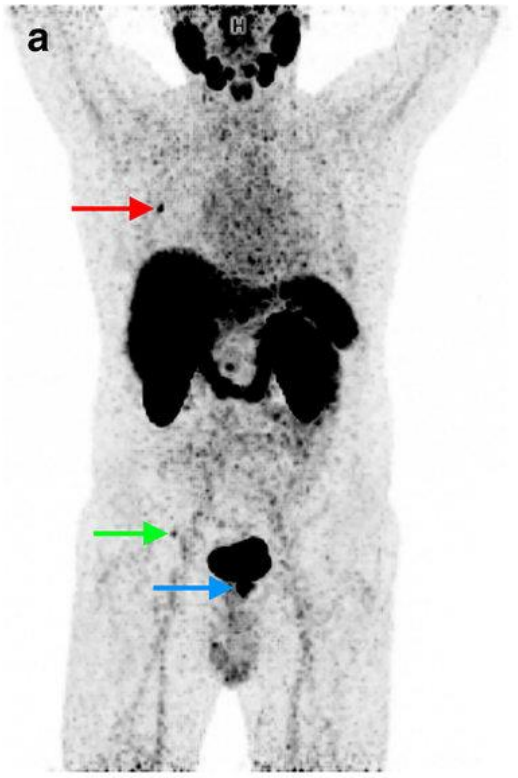


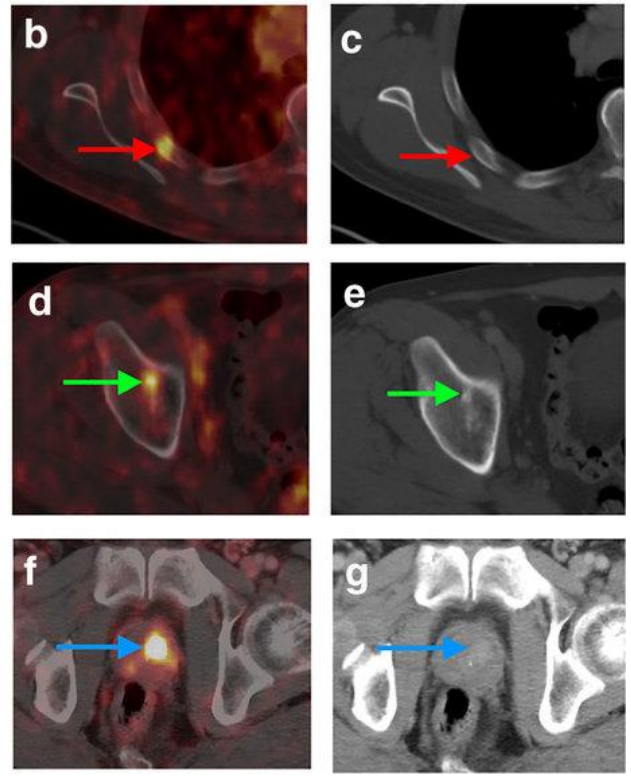


With PSMA PET

PSMA PET vs “standard” imaging revisited







For tumor-directed therapy, want to utilize a sensitive imaging modality to decide where to treat (and where to avoid)
Examples:
Surgery, radiation, ablation [cryotherapy, radiofrequency ablation, irreversible electroporation (IRE), ultrasound (HIFU)], embolization

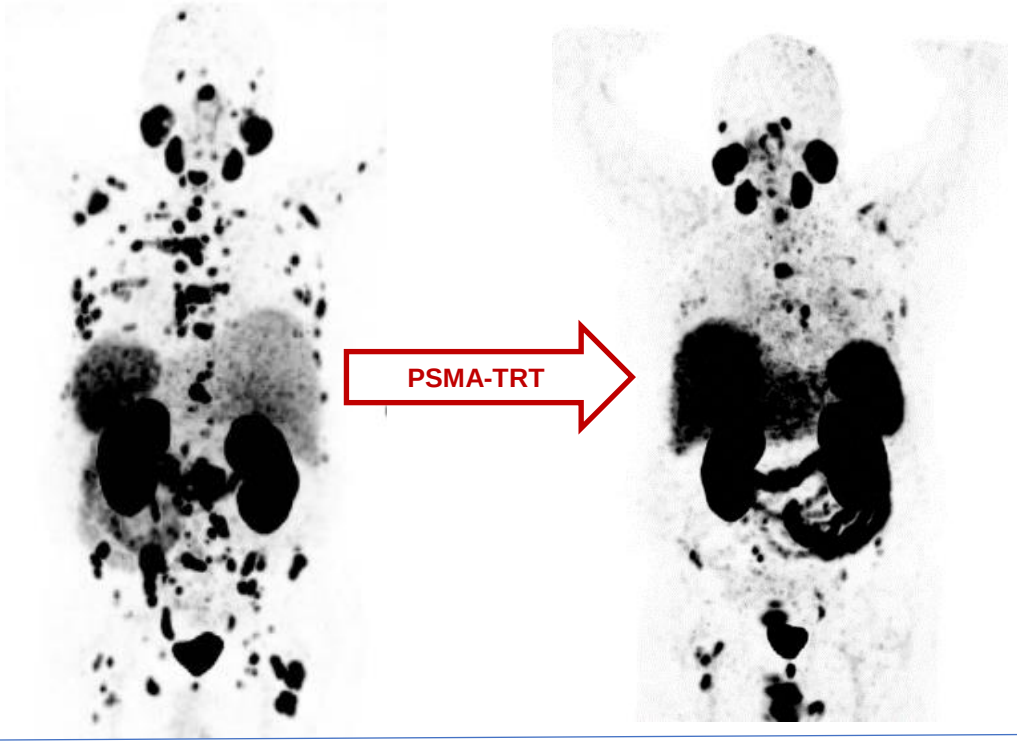
What is PSMA-TRT?

Prostate-specific membrane antigen-targeted radionuclide therapy

[RLT = radioligand therapy]
[RIT = radioimmunotherapy]
[RPT = radiopharmaceutical therapy]

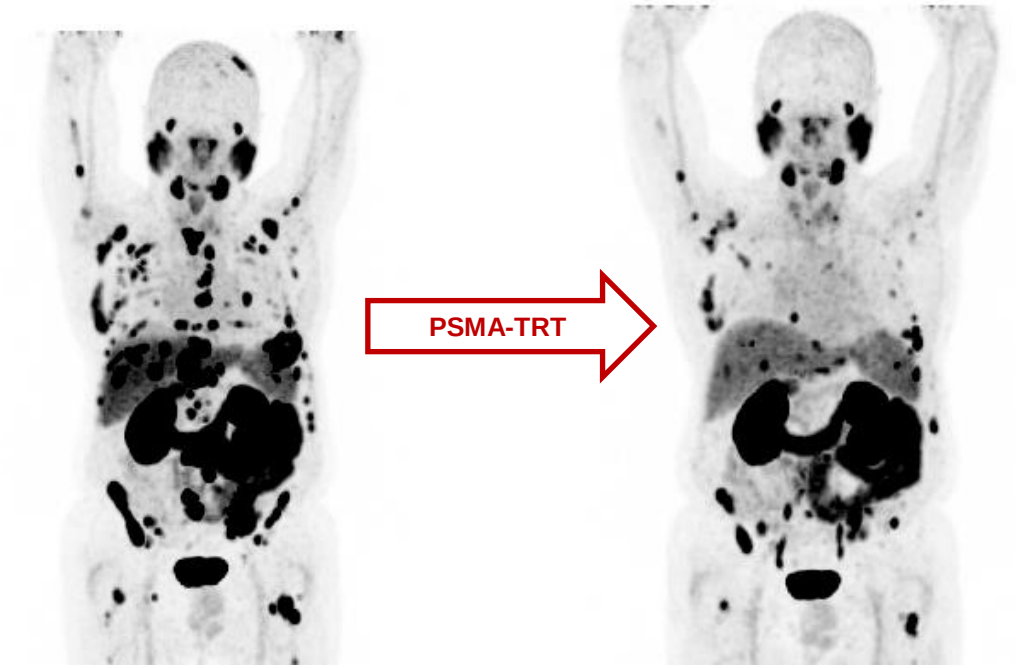
- Administration of systemic radiation (IV) which ends up in PSMA+ cells
- **PSMA-targeting vehicles (keys)**
  - Different properties mostly related to size
    - Small molecules, antibodies
  - Affects kinetics (how long in blood) and biodistribution (where it lands)
- **Radionuclide = radioactive particle (kills cells)**
  - Usually β- or α-emitters (also auger for therapy; gamma/PET imaging)
    - Some more potent, some affect larger areas
  - Efficacy and toxicity partially related to properties

62 yo with prior docetaxel, cabazitaxel, sipuleucel-T, abiraterone, enzalutamide, radium-223, cabazi / carbo



87.8% PSA decline
40.1% CTC decline

70 yo with prior docetaxel, carboplatin, lenalidomide, abiraterone, enzalutamide, ^{177}Lu-PSMA



88.1% PSA decline
100% CTC decline

Side Effects
(“Treatment emergent adverse events”)

Patients, n (%)	All grades		Grade 3–5	
				OC alone = 205)
Fatigue				(2.4)
Bone marrow su				(6.8)
Leukopenia				(0.5)
Lymphopenia				(0.5)
Anemia				(4.9)
Thrombocyto				(1.0)
Dry mouth				(0.0)
Nausea and v				(0.5)
Renal effects				6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

If this is “targeted therapy”, why are there side effects?

With ^{177}Lu-PSMA-617 there was more:

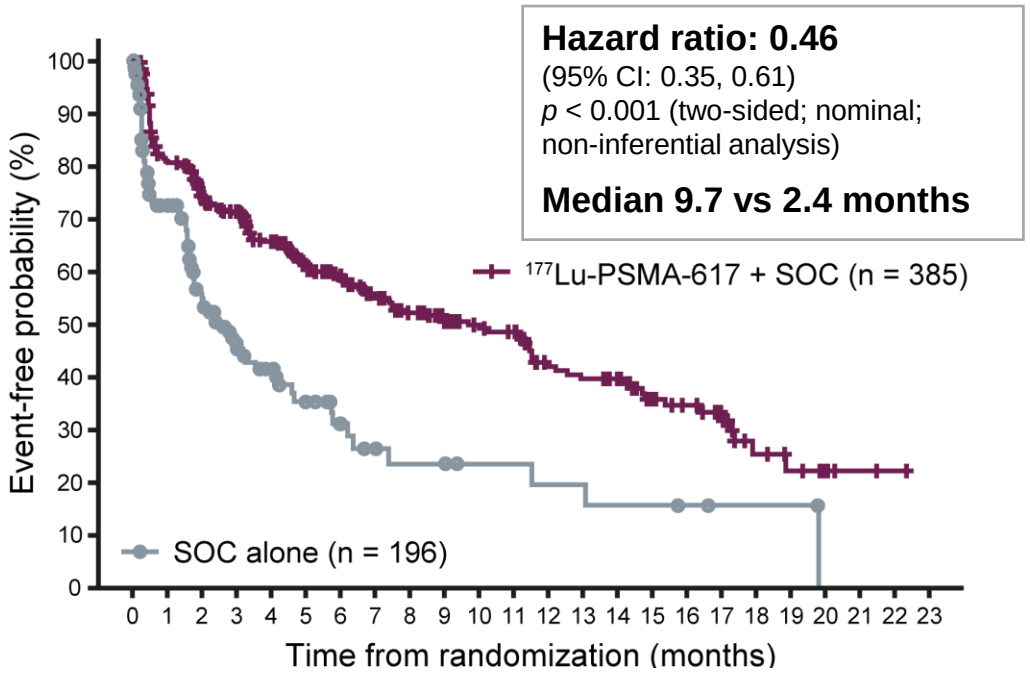
1) Fatigue
2) Decrease in blood counts
(low white blood cells might increase risk of infection,
low red blood cells may lead to fatigue or shortness of breath,
low platelets may lead to bleeding)
3) Dry mouth
4) Nausea and vomiting

TIME TO WORSENING IN HEALTH-RELATED QUALITY OF LIFE AND PAIN

***Ad hoc* analyses**

FACT-P total score
Time to worsening favoured the ^{177}Lu-PSMA-617 arm

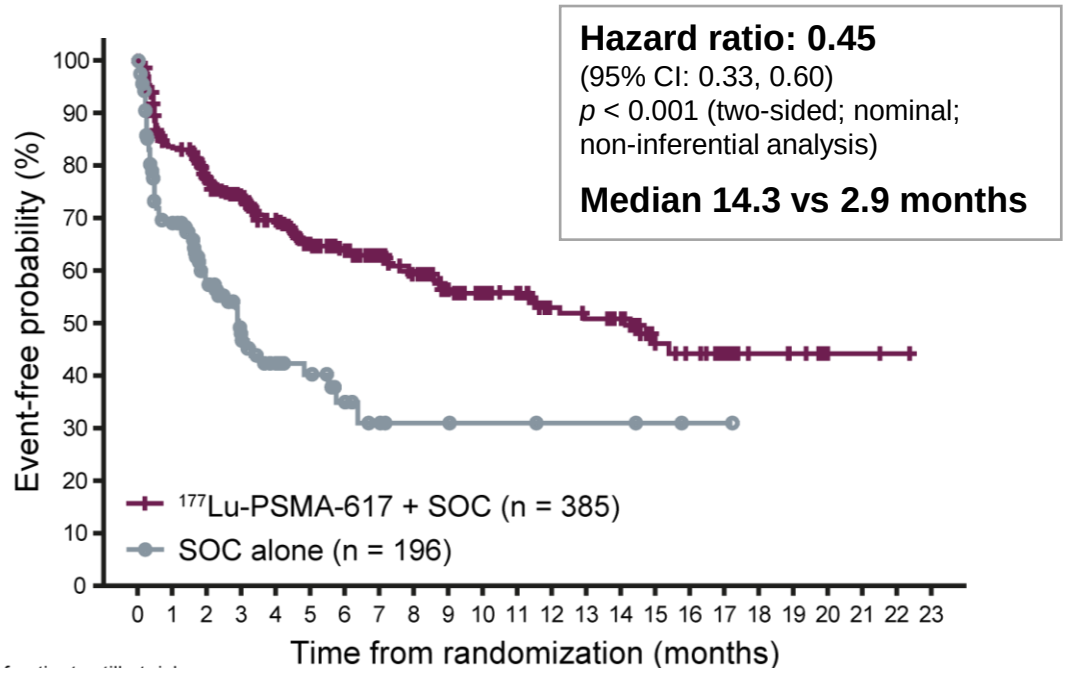
rPFS analysis set (n = 581)



Time to the first occurrence of ≥ 10-point decrease in FACT-P total from baseline

BPI-SF pain intensity
Time to worsening favoured the ^{177}Lu-PSMA-617 arm

rPFS analysis set (n = 581)

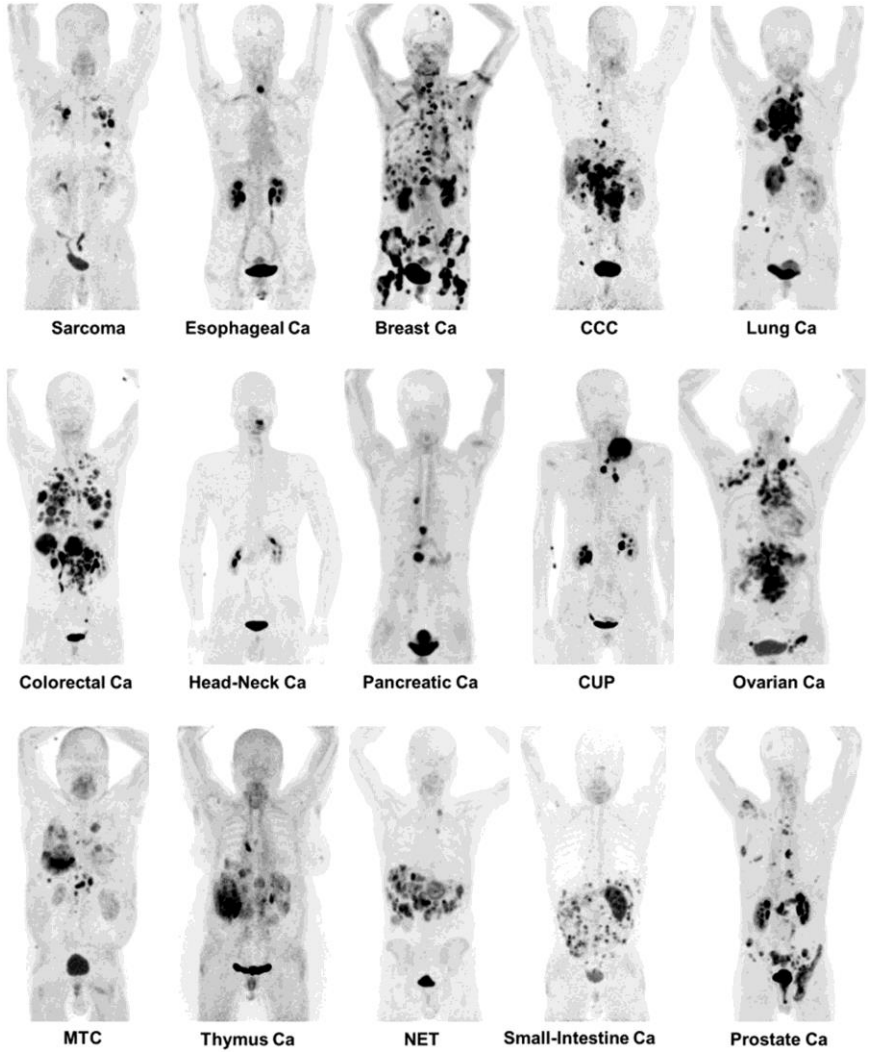


Time to the first occurrence of ≥ 30% or ≥ 2-point increase in BPI-SF pain intensity from baseline

BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy – Prostate; PSMA, prostate-specific membrane antigen; SOC, protocol-permitted standard of care

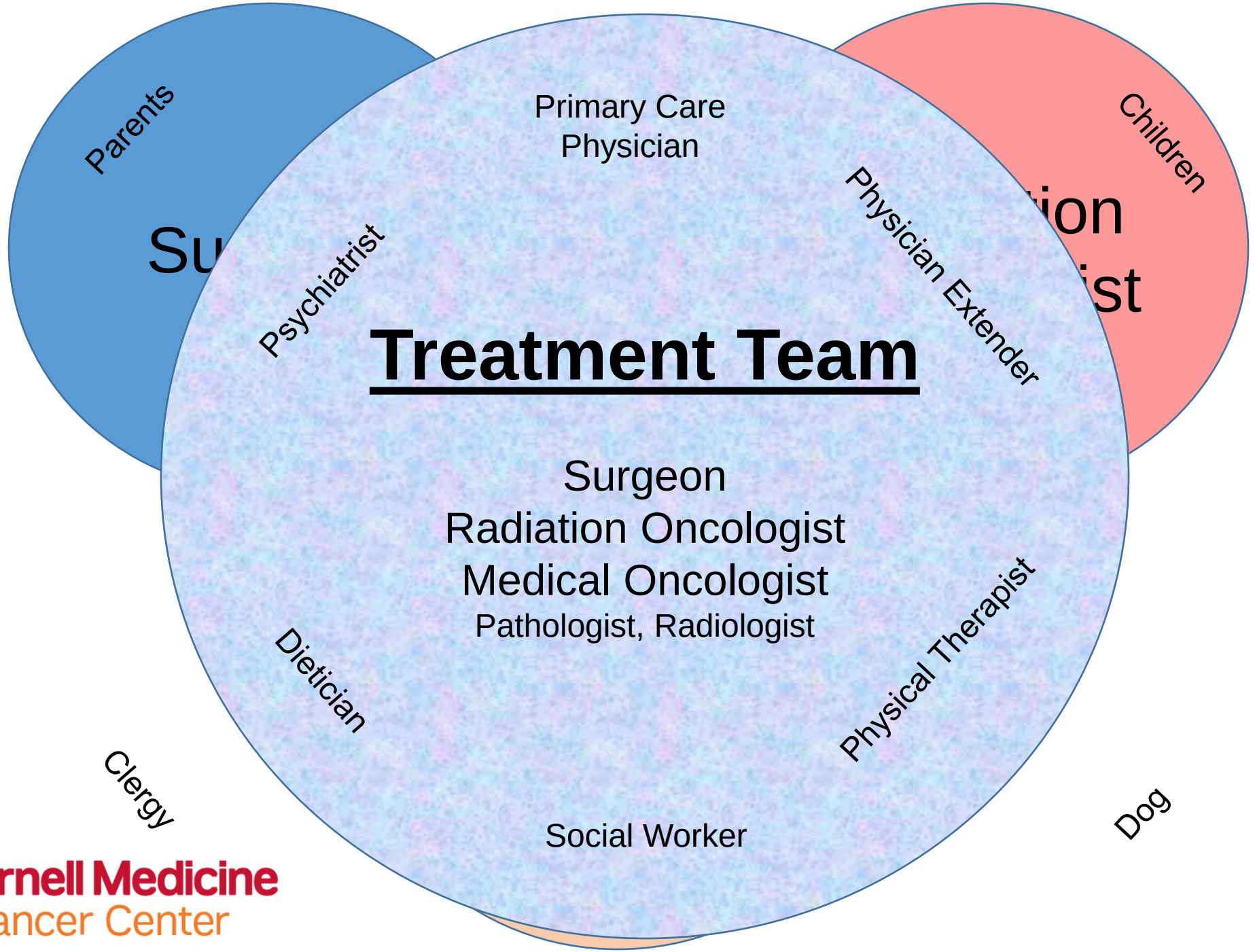
Targets in development

- FAP
  - Multiple tracers in human studies
- DLL3
- hK2
- PARP1
- PD-L1
- CTLA4
- DHT
- FLT
- CD46
- TROP2
- B7H3
- STEAP1
- CEACAM5
- CA-IX



Kratochwil et al JNM 2019

My bias…



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Brian Gonzalez (Moffitt)

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PATIENTS AND THEIR FAMILIES