

IL RUOLO DEL CLINICO NELLA SCELTA TERAPEUTICA e NELLA GESTIONE DEL PAZIENTE IN TRATTAMENTO CON RADIO-223

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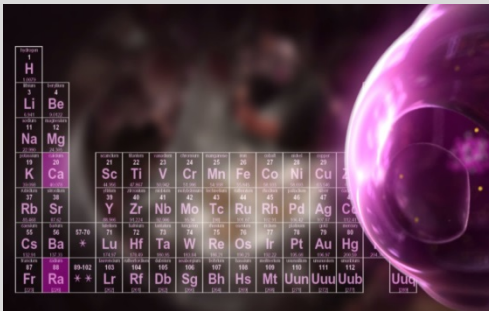
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Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.J. Helle, J.M. O'Sullivan, S.D. Fossa, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

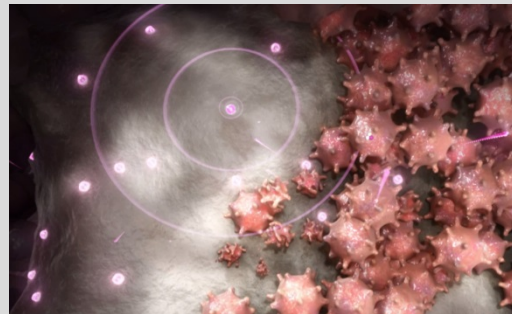
MECCANISMO D'AZIONE

Calcio mimetico



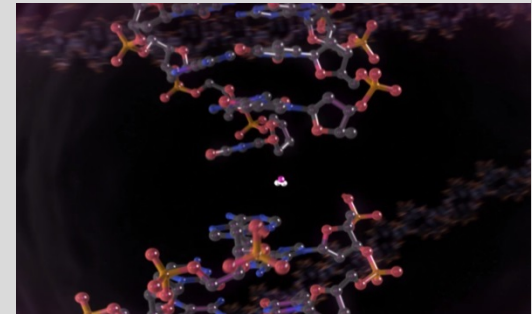
Il Radio è un **calciomimetico**, forma complessi con la componente minerale dell'osso, l'idrossiapatite, nelle aree di aumentato turnover quali le metastasi ossee.

Breve raggio



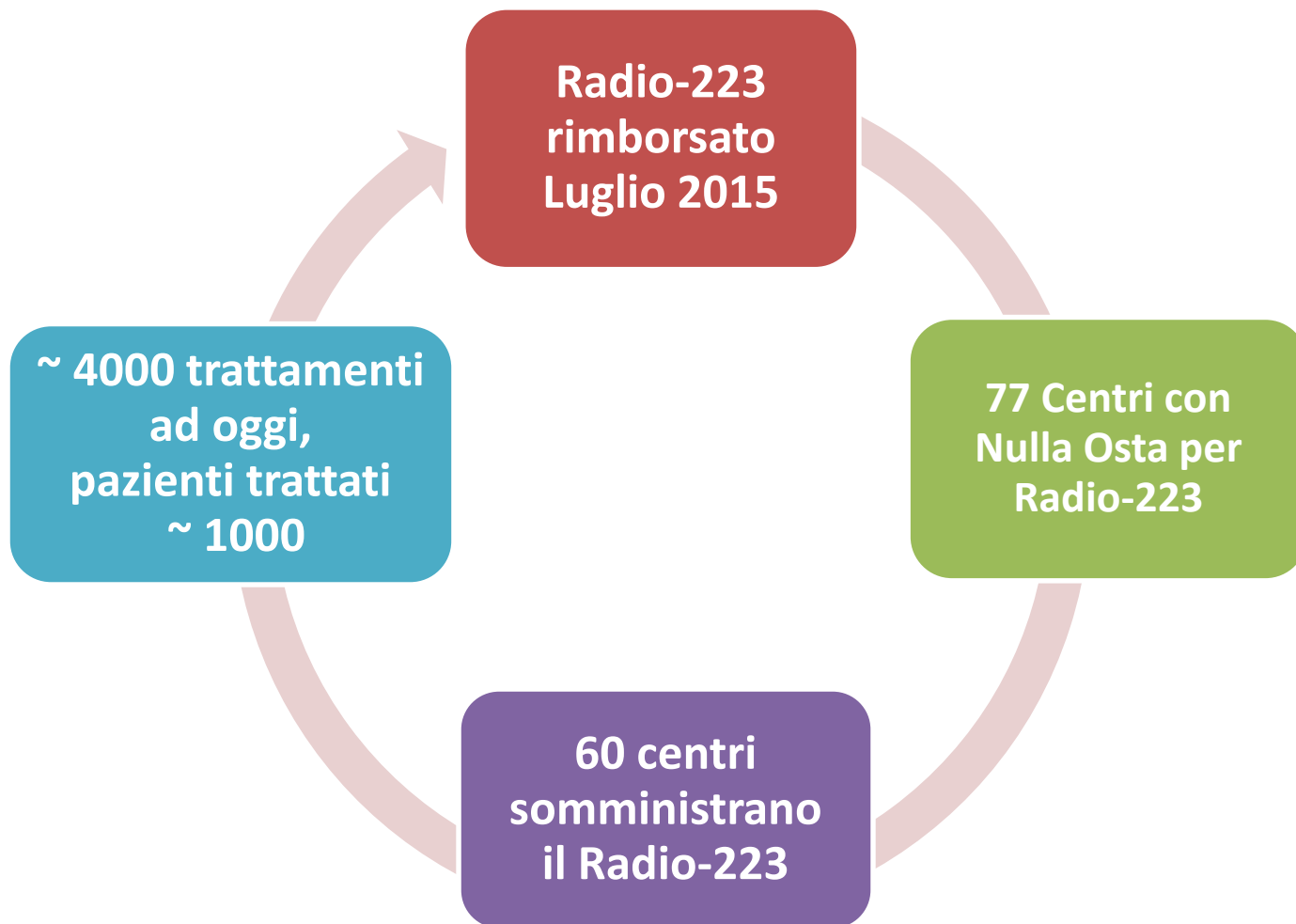
Il **breve raggio di penetrazione tissutale** delle particelle alfa emesse dal Radio (<10 diametri cellulari) **limita il danno ai tessuti sani circostanti.**

Alta Energia Lineare



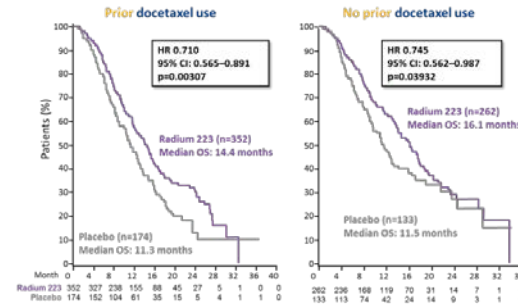
Il Radio emette **particelle alfa**, che causano principalmente rotture della doppia elica di DNA nelle cellule adiacenti, con un **effetto antitumorale sulle metastasi ossee.**

Radio-223 in Italia



PERCHE' USARE Ra223

- ❖ Efficacie pre e post-docetaxel (studio ALSYMPCA)
- ❖ Chemioterapia somministrata post-Ra223 è sicura dal punto di vista ematologico
- ❖ Se somministrato pre-chemioterapia si riduce il rischio trombocitopenia
- ❖ iEAP conferma associazione tra uso precoce e outcome (malattia meno estesa → completamento 6 cicli → miglior OS)



The Prostate 76:905-916 (2016)

Chemotherapy Following Radium-223 Dichloride Treatment in ALSYMPCA

Oliver Sartor,^{1,2*} Peter Hoskin,³ Robert E. Coleman,⁴ Sten Nilsson,⁵ Nicholas J. Vogelzang,⁶ Oana Petrenciuc,⁷ Karin Staudacher,⁸ Marcus Thuresson,⁹ and Christopher Parker¹⁰

Hematologic Safety of Radium-223 Dichloride: Baseline Prognostic Factors Associated With Myelosuppression in the ALSYMPCA Trial

Nicholas J. Vogelzang,¹ Robert E. Coleman,² Jeff M. Michalski,³ Sten Nilsson,⁴ Joe M. O'Sullivan,⁵ Christopher Parker,⁶ Anders Widmark,⁷ Marcus Thuresson,⁸ Lei Xu,⁹ Joseph Germino,¹⁰ Oliver Sartor¹¹

Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial

Fred Saad, Joan Carles, Silke Gillissen, Axel Heidenreich, Daniel Heinrich, Jeremy Gratt, Jérémy Lévy, Kurt Miller, Sten Nilsson, Oana Petrenciuc, Marcello Tucci, Manfred Wirth, Judith Federhofer, Joe M O'Sullivan, for the Radium-223 International Early Access Program Investigators*

Le linee guida

Impiego in prima linea nei pazienti con malattia ossea sintomatica e senza malattia viscerale nota → ESMO 2015

clinical practice guidelines

Annals of Oncology 00: 1–9, 2015
doi:10.1093/annonc/mdv222

Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

C. Parker¹, S. Gillessen², A. Heidenreich³ & A. Horwich⁴, on behalf of the ESMO Guidelines Committee*

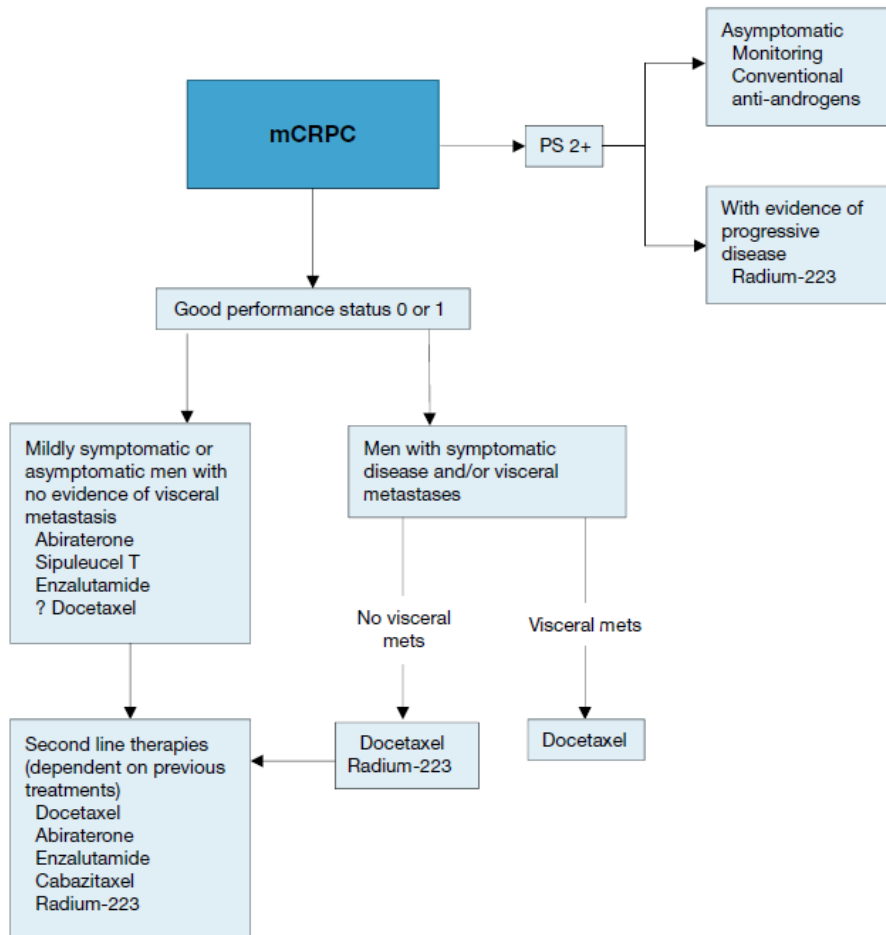
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Treatment of castrate-resistant prostate cancer (CRPC)

- Abiraterone or enzalutamide are recommended for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC [I, A].
- Radium-223 is recommended for men with bone-predominant, symptomatic metastatic CRPC without visceral metastases [I, A].
- Docetaxel is recommended for men with metastatic CRPC [I, A].
- Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC [II, B].
- In patients with metastatic CRPC in the post-docetaxel setting, abiraterone, enzalutamide, cabazitaxel and radium-223 (in those without visceral disease) are recommended options [I, A].

Le linee guida

Impiego in prima linea nei pazienti con malattia ossea sintomatica e senza malattia viscerale nota → EAU 2016



Le linee guida

Impiego in prima linea nei pazienti con malattia ossea sintomatica e senza malattia viscerale nota → NCCN 2016

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5					E = Efficacy of Regimen/Agent
4					S = Safety of Regimen/Agent
3					Q = Quality of Evidence
2					C = Consistency of Evidence
1					A = Affordability of Regimen/Agent
	E	S	Q	C	A

[NCCN Guidelines Index](#)
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SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER

[See Evidence Blocks on PROS-11A](#)

CRPC, studies positive² for metastases³

- Maintain castrate levels of serum testosterone (<50 ng/dL)
- Consider bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present
- Immunotherapy with sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0–1 (category 1) (See PROS-3)^{4,5}
- Palliative RT for painful bony metastases
- Best supportive care

No →

- Abiraterone^{1,6b} with prednisone (category 1)
- Docetaxel^{1,6c} with prednisone (category 1)
- Enzalutamide¹ (category 1)
- Radium-223 for symptomatic bone metastases (category 1)^{6d}
- Clinical trial
- Secondary hormone therapy
 - ▶ Antiandrogen
 - ▶ Antiandrogen withdrawal
 - ▶ Ketoconazole ± hydrocortisone
 - ▶ Corticosteroid
 - ▶ DES or other estrogen²

Yes →

- Docetaxel^{1,6c} with prednisone (category 1)
- Enzalutamide¹ (category 1)
- Abiraterone^{1,6b} with prednisone
- Alternative chemotherapy (mitoxantrone with prednisone)^{6,7}
- Clinical trial
- Secondary hormone therapy
 - ▶ Antiandrogen
 - ▶ Antiandrogen withdrawal
 - ▶ Ketoconazole ± hydrocortisone
 - ▶ Corticosteroid
 - ▶ DES or other estrogen²

Progression after:

- Abiraterone
- Enzalutamide
- Docetaxel
- See [Subsequent Therapy for M1 CRPC: No Visceral Metastases \(PROS-12\)](#)
- See [Subsequent Therapy for M1 CRPC: Visceral Metastases \(PROS-13\)](#)

Progression after all other therapies

¹See Principles of Imaging (PROS-8).

²See Principles of Androgen Deprivation Therapy (PROS-F).

³See Principles of Immunotherapy and Chemotherapy (PROS-G).

⁴DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/day and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.

⁵Sipuleucel-T has not been studied in patients with visceral metastases.

⁶For patients who are not candidates for docetaxel-based regimens.

^{6a}Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

^{6b}Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).

SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER^{ee}

Prior therapy enzalutamide/abiraterone

No visceral metastases

Prior therapy docetaxel

- Docetaxel with prednisone (category 1)^x
 - Abiraterone¹ with prednisone
 - Enzalutamide
 - Radium-223 for symptomatic bone metastases (category 1)
 - Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
 - Clinical trial
 - Other secondary hormone therapy
 - ▶ Antiandrogen
 - ▶ Antiandrogen withdrawal
 - ▶ Ketoconazole
 - ▶ Ketoconazole + hydrocortisone
 - ▶ Corticosteroid
 - ▶ DES or other estrogen²
 - Best supportive care
-
- Enzalutamide (category 1)
 - Abiraterone¹ with prednisone (category 1)
 - Radium-223 for symptomatic bone metastases (category 1)
 - Cabazitaxel with prednisone (category 1)^x
 - Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
 - Clinical trial
 - Docetaxel rechallenge^x
 - Alternative chemotherapy (mitoxantrone with prednisone)^x
 - Other secondary hormone therapy
 - ▶ Antiandrogen
 - ▶ Antiandrogen withdrawal
 - ▶ Ketoconazole
 - ▶ Ketoconazole + hydrocortisone
 - ▶ Corticosteroid
 - ▶ DES or other estrogen²
 - Best supportive care

²DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/day and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.

^{ee}Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

^xSee Principles of Androgen Deprivation Therapy (PROS-F).

^xSee Principles of Immunotherapy and Chemotherapy (PROS-G).

Le linee guida

Impiego in prima linea nei pazienti con malattia ossea sintomatica e senza malattia viscerale nota → AIOM 2016

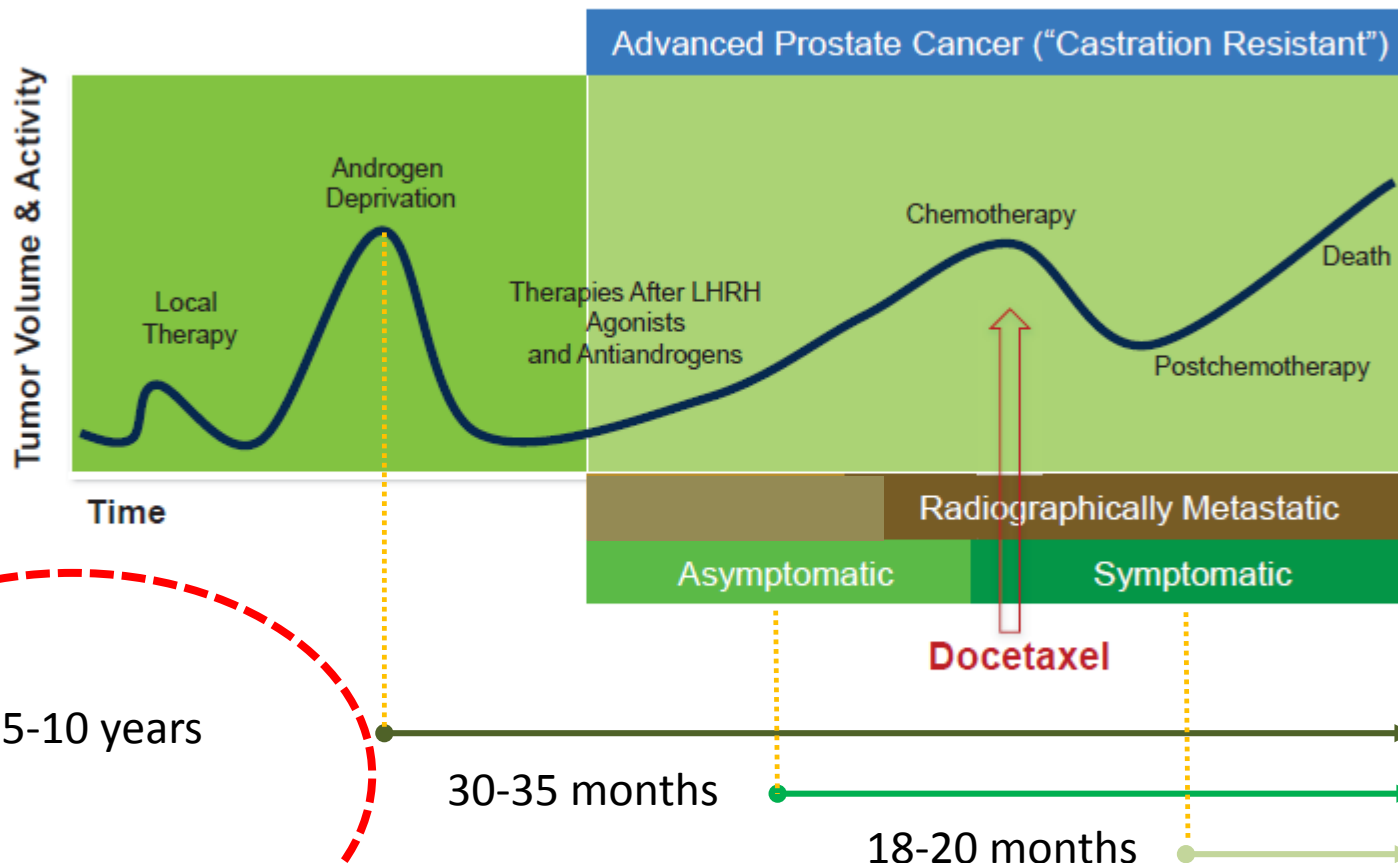
5.5.2.6. Targeted alpha therapy (Terapia radiometabolica)

QUESITO CLINICO N°22

Nei pazienti con metastasi ossee sintomatiche il trattamento con Radium-223 è suscettibile di impiego in alternativa alla chemioterapia o all'abiraterone acetato o all'enzalutamide?

Terapia antiandrogeniche	<u>Targeted Alpha Therapy</u>	Chemioterapia	Terapia di supporto
ADT Abiraterone Enzalutamide	Radium-223 dichloride	Docetaxel Cabazitaxel	Strontium-89 Samarium-153 Rhenium-186 Acido Zoledronico Denosumab Steroidi

Il tumore della prostata



¹Tannock et al. *N Engl J Med* 2004; 351(15): 1502-1512; ²Berthold et al. *Clin Can Res* 2008;14(9): 2763-2767

Domanda:

**Perché il clinico
(oncologo/radioterapista/urologo) ha
un ruolo centrale nella gestione del
paziente e nella definizione del
trattamento?**

Il ruolo del clinico

Conosce la patologia fin dall'esordio

Conosce i farmaci



Si rapporta agli altri specialisti



Gestisce le tossicità



Cosa abbiamo....

- ✓ **DOCETAXEL/CABAZITAXEL:** se buon PS, malattia viscerale, malattia sintomatica
- ✓ **ENZALUTAMIDE, ABIRATERONE:** se assenza di sintomi o sintomi minimi, buona risposta a precedente ADT
- ✓ **RADIUM-223:** nei pazienti con malattia ossea, sintomatici, senza metastasi viscerali note



Le domande a cui cercheremo di rispondere

- ✓ **Paziente candidabile: come lo definisco? Qual è il corretto algoritmo terapeutico?**
- ✓ **Esperienza: da condividere e ampliare**
 - importanza del TMD
 - hub&spoke
- ✓ **Il meccanismo d'azione e il ruolo della malattia ossea**
- ✓ **La terapia medico-nucleare e i possibili eventi avversi**
- ✓ **Gestione del trattamento e del paziente**

