Gestire i pazienti nella real-life: come scegliere il farmaco giusto?

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FONDAZIONE ONCOLOGIA NIGUARDA ONLUS

Disclosures

Honoraria from Astellas Pharma, Bayer, BMS, Janssen Oncology, Novartis, Pfizer, Sanofi-Genzyme

Advisor roles for Janssen Oncology, Novartis, Sandoz, Sanofi-Genzyme

Gestire i pazienti nella real-life: *come scegliere il farmaco giusto?*

Principali aree di incertezza

- Eterogeneità della malattia e dei pazienti
- Assenza di fattori predittivi validati
- Confronto indiretto fra diverse opzioni
- Nessuna sequenza validata
- Trasferibilità dei risultati degli studi clinici (?)
- Scarsa conoscenza della biologia tumorale

Trasferibilità dei risultati degli studi nella pratica clinica

- Da una revisione della letteratura, la percentuale di screening failure negli studi di fase II/III è risultata essere del 26% (12-45%)[1]
- Il 32 % degli studi analizzati (13/19) non riportava le percentuali di screening failure[1]
- I criteri di esclusione più frequenti sono rappresentati da un'alterazione degli esami di laboratorio, comorbidità e dall'età avanzata[2]

1. Wong SE, et al. Clin Genitourin Cancer. 2017
2. Chao et al. Journal of Investigative Medicine. 2010

Current treatments for PCa: PS and elderly patients

Setting	Agent (trial)	PS ECOG 2 (%)	Age group (≥ 75 yrs, %)
CNPC	**Cabazitaxel** (CHAARTED)	1.5	NR
CNPC	**Abiraterone** (LATITUDE)	NR	21
CNPC	**Abiraterone vs Docetaxel** (STAMPEDE)	NR	NR
CRPC (Pre-CT)	**Abiraterone** (COU-302)	0	32.2
CRPC (Pre-CT)	**Enzalutamide** (PREVAIL)	0	36.3
CRPC (Pre-CT)	**Docetaxel** (TAX 327)	14% KPS ≤ 70%	NR
CRPC (Pre/post-CT)	**Radium-223** (ALSYMPCA)	13	28
CRPC (Post-CT)	**Abiraterone** (COU-301)	10	27.7
CRPC (Post-CT)	**Enzalutamide** (AFFIRM)	10	NR
CRPC (Post-CT)	**Cabazitaxel** (TROPIC)	8	NR

GLI ANDAMENTI TEMPORALI DELLA PATOLOGIA ONCOLOGICA IN ITALIA

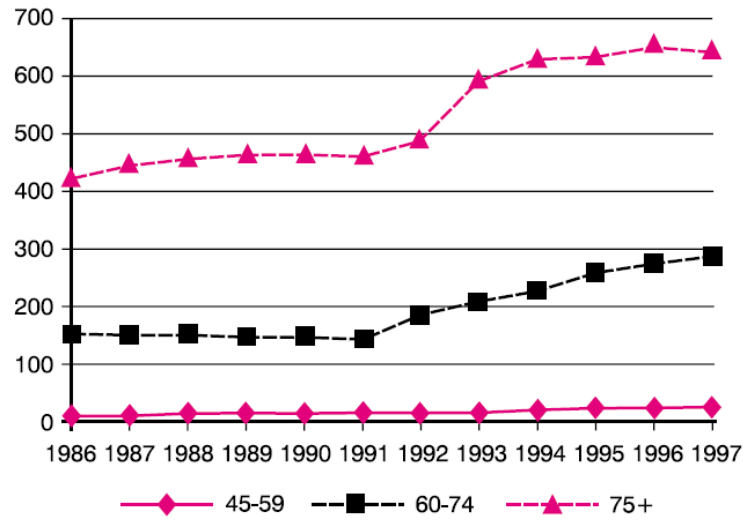


Figura 1. Tumore della prostata. Tassi di incidenza per classi d'età x 100.000.

Figure 1. Prostate cancer. Incidence rates by age-classes x 100,000.

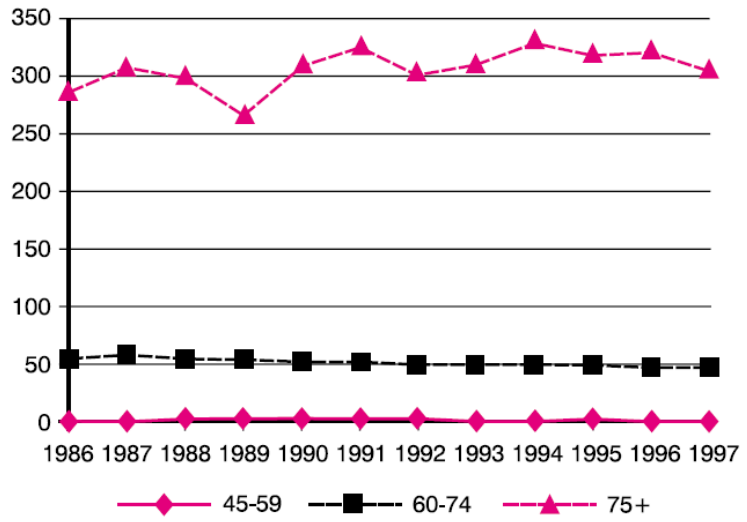


Figura 2. Tumore della prostata. Tassi di mortalità per classi d'età x 100.000.

Figure 2. Prostate cancer. Mortality rates by age-classes x 100,000.

Associazione Italiana Registri Tumori (*pool* AIRT), 2004

Età, comorbidità e politerapia

- Nel registro della Società Italiana di Medicina Interna (n = 4035), i pazienti di età **> 65 anni**, compresa fra **75-85 anni** o di età **> 85 anni** presentavano una prevalenza di patologie croniche del **38**, **50** e **64**%, rispettivamente[1]

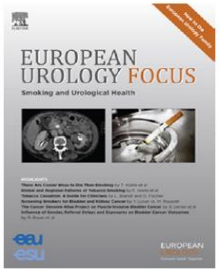
  Secondo uno studio del 2011 del Working Group Geriatrico AIFA, **una persona su due** di età > ai **65 anni** assume dai 5 ai 9 farmaci al giorno. Il gruppo di età tra i **75 e gli 84 anni** è stato esposto al più alto carico farmacologico, con il 55% dei soggetti trattati con 5-9 farmaci e il **14% con 10 o più farmaci**

1. Mannucci PM, et al. Intern Emerg Med (2014)

Data from EAP and «real-world» studies

HOW THEY LOOK LIKE

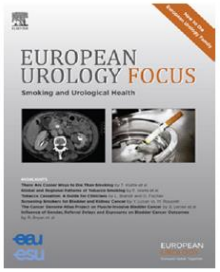
Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry

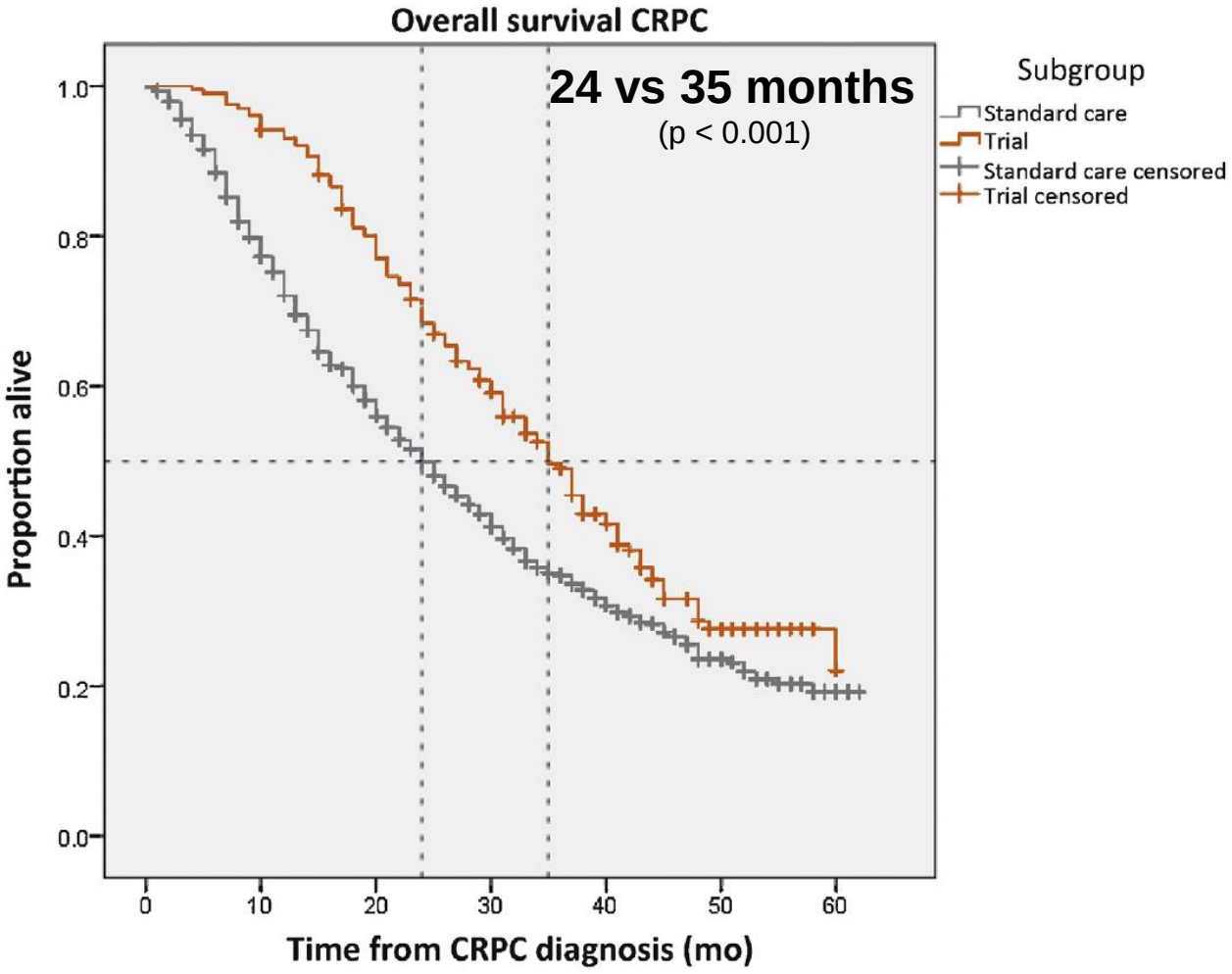


- A population-based, observational, retrospective registry (2010-2013)
- **1524** CRPC pts of which 203 had participated in trials at any time
- Patients in the trial group were significantly **younger and had less comorbidities**
- Docetaxel treatment was more frequently used in trial patients (85% vs 40%)

Westgeest HM, et al. Eur Urol Focus. 2016

Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry





Westgeest HM, et al. Eur Urol Focus. 2016

New Hormonal Agents

Safety of Enzalutamide in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel: Expanded Access in North America n=507

Joshua AM, et al. The prostate 2015

Abiraterone in chemo-naive patients with mCRPC: a systematic review of 'real-life' studies n=801

Marchioni M, et al. Ther Adv Urol 2018

Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial n=2134

Sternberg CN, et al. Lancet Oncol 2014

Safety and clinical outcomes of patients treated with abiraterone acetate after docetaxel: results of the Italian Named Patient Programme n=265

Caffo O, et al. BJU Int 2015

Summary:

EAP and real file studies confirm the findings of the pivotal trials.

Safety profile was consistent with that of RCTs

Radium-223

- **Radium-223 in an international early access program (EAP): Effects of concomitant medication on OS in mCRPC patients**
  Saad, et al. Lancet Oncol 2016

- **Radium-223 dichloride (Ra-223) in U.S. expanded access program (EAP)**
  Sartor O, et al. Oncologist 2018

- **A population-based study of the use of radium 223 in metastatic castration-resistant prostate cancer: Factors associated with treatment completion**
  Parimi S, et al. Can Urol Assoc J 2017

Summary:

In heavily pretreated pts, RA-223 was well tolerated with no new safety concerns

Chemotherapy

Toxicity	TROPIC [1]				European CUP/EAP	
	Mitoxantrone ($n = 371$)		Cabazitaxel ($n = 371$)		Cabazitaxel ($n = 746$)	
	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3
Haematological (%)						
Neutropenia	88	58	94	82	19.8	17.0
Anaemia	81	5	97	11	21.6	4.7
Leukopenia	92	42	96	68	10.6	7.4
Febrile neutropenia	–	1	–	8	5.5	5.4
Thrombocytopenia	43	2	47	4	4.7	1.1
Non-haematological (%)						
Diarrhoea	11	<1	47	6	34.6	2.8
Fatigue	27	3	37	5	25.2	4.2

Heidenreich, et al. Eur Urol 2013

Italian EAP of Cabazitaxel (n = 218)

- The most common **grade 3 or 4 hematological toxicities** were neutropenia (33.9%), leukopenia (15.6%), anemia (6.0%) and febrile neutropenia (5.0%), and the most common **grade 3 or 4 nonhematological toxicities** were asthenia (6.0%) and fatigue (3.7%)
- The median relative dose intensity was 98.3%

Bracarda S, et al. Future Oncol 2014

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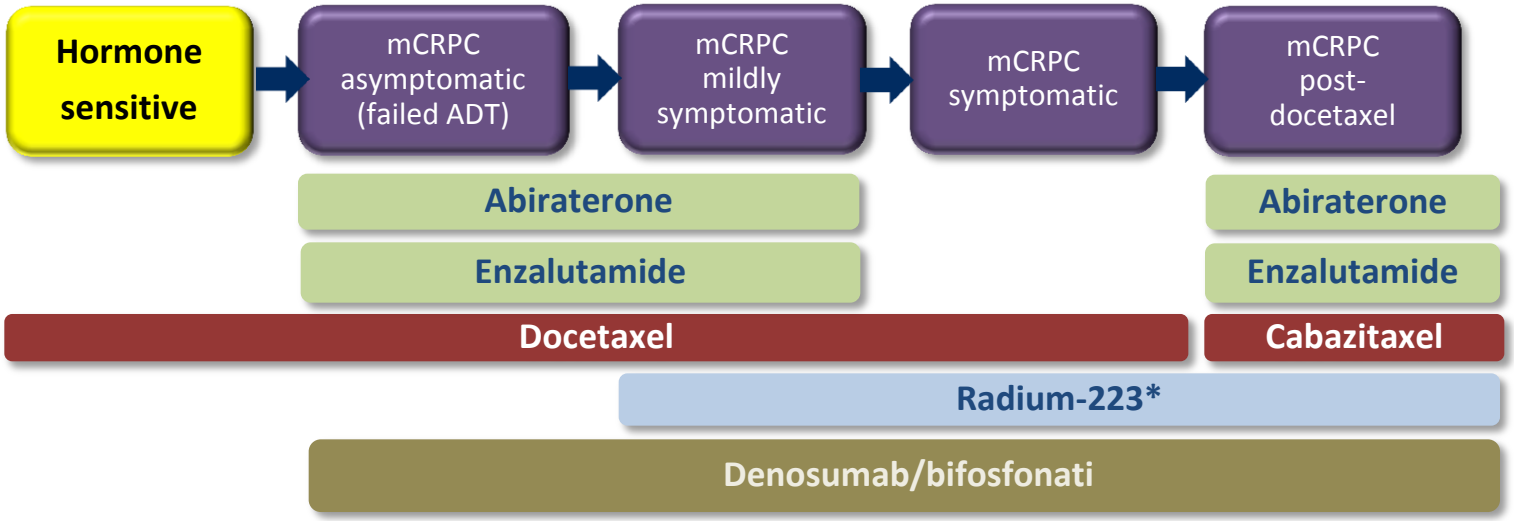
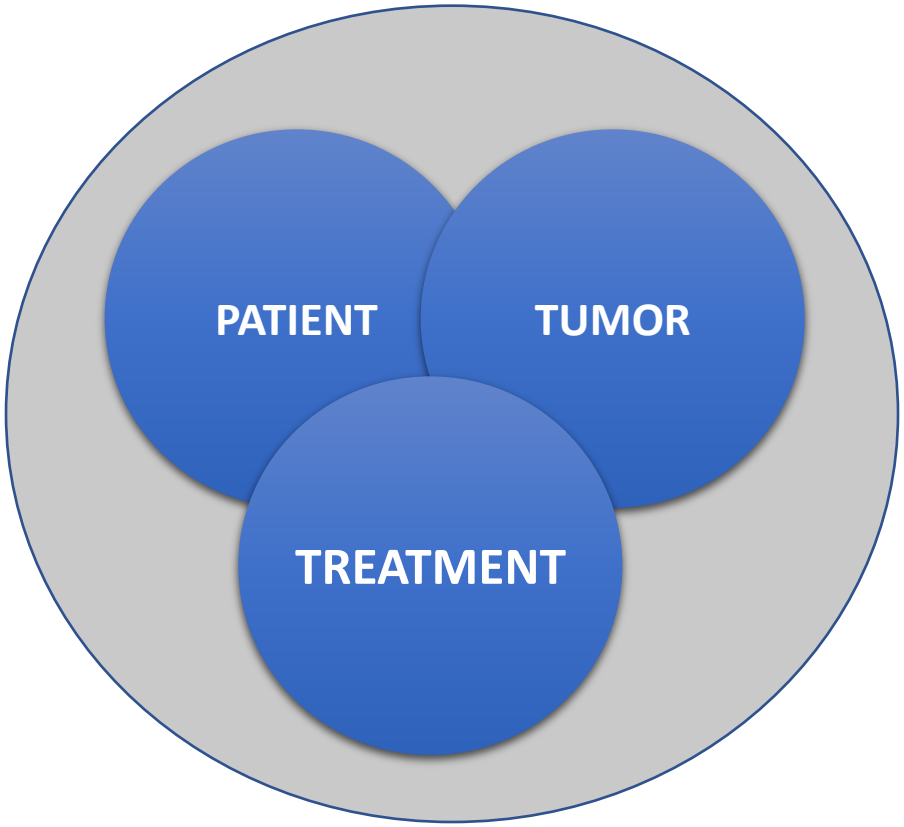


*Symptomatic Bone Mets

Therapy Selection in Real-life



Age

Performance status

Comorbidities/ polipharmacy

QoL

Patient preference (?)

Symptoms

Burden

Clinical course

PSA

Biology

Experience Efficacy/Toxicity Cost Evidence Guidelines

Duration Cross-resistance/MoA QoL

Therapy Selection in Real-life

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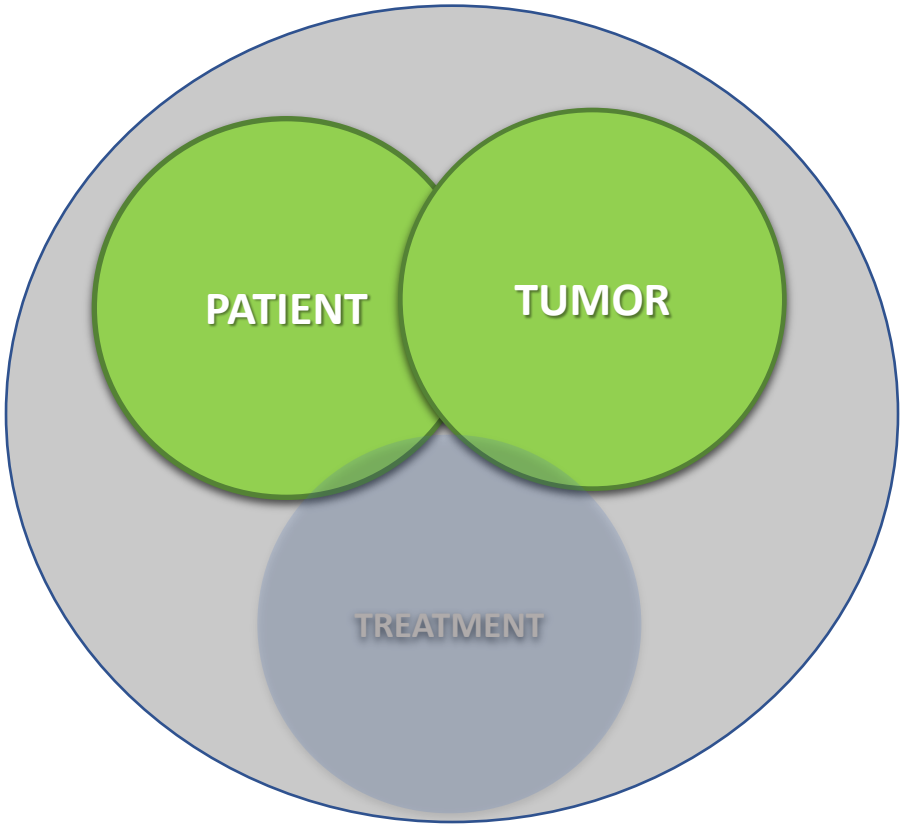


Symptoms

Burden

Clinical course

PSA

Biology?

Experience Efficacy/Toxicity Cost Evidence Guidelines

Duration Cross-resistance MoA

Eterogeneità dei pazienti

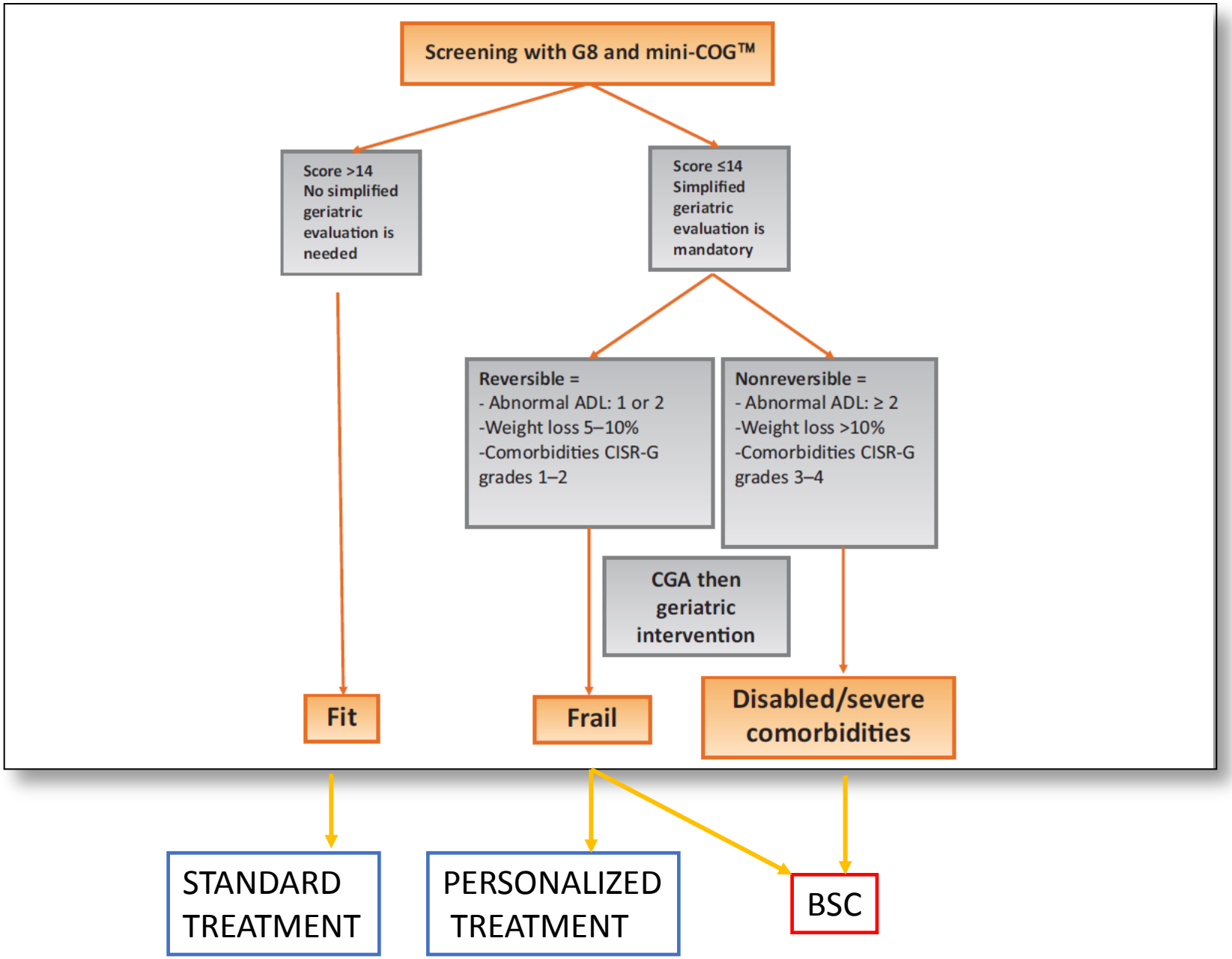
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology

Recommendations:

- In pts **≥65 yrs** receiving chemotherapy, **geriatric assessment (GA) should be used** to identify vulnerabilities that are not routinely captured in oncology assessments
- The Expert Panel recommends that clinicians apply the results of GA to develop an integrated and **individualized plan** for pts that informs **treatment selection** by helping to estimate risks for adverse outcomes and to identify nononcologic problems that may be amenable to intervention

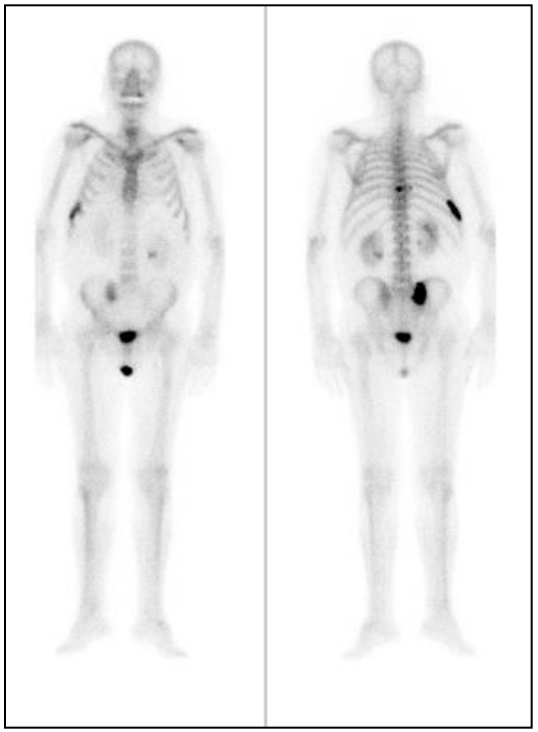
Mohile, SG, et al. J Clin Oncol 2018



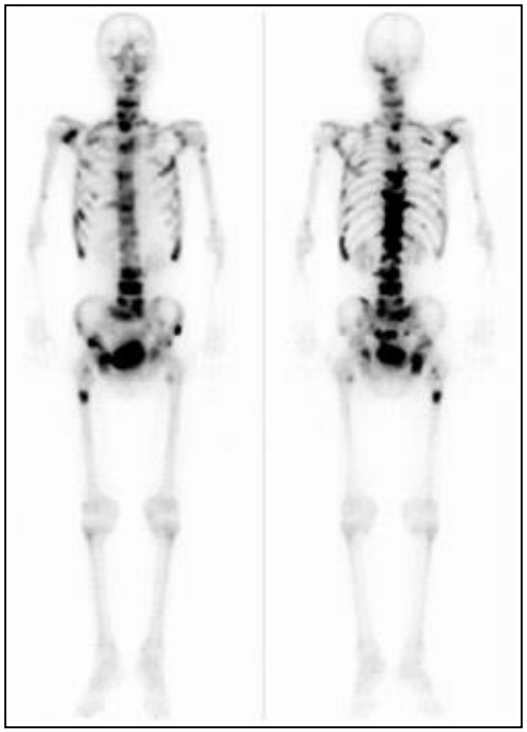
Modified from Droz JP, et al EUROPEAN UROLOGY (2017)

Eterogeneità della malattia

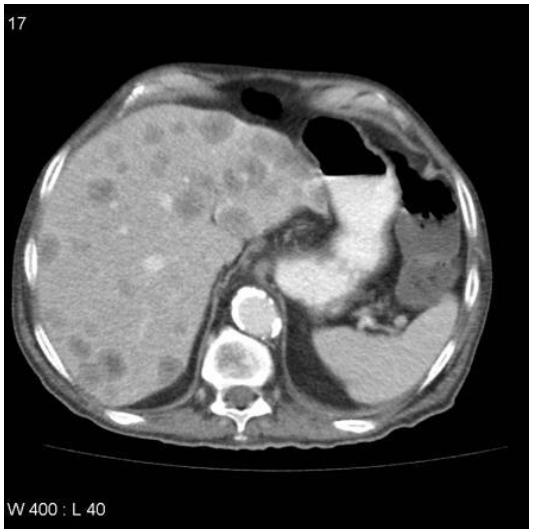
Case 1



Case2



Case 3



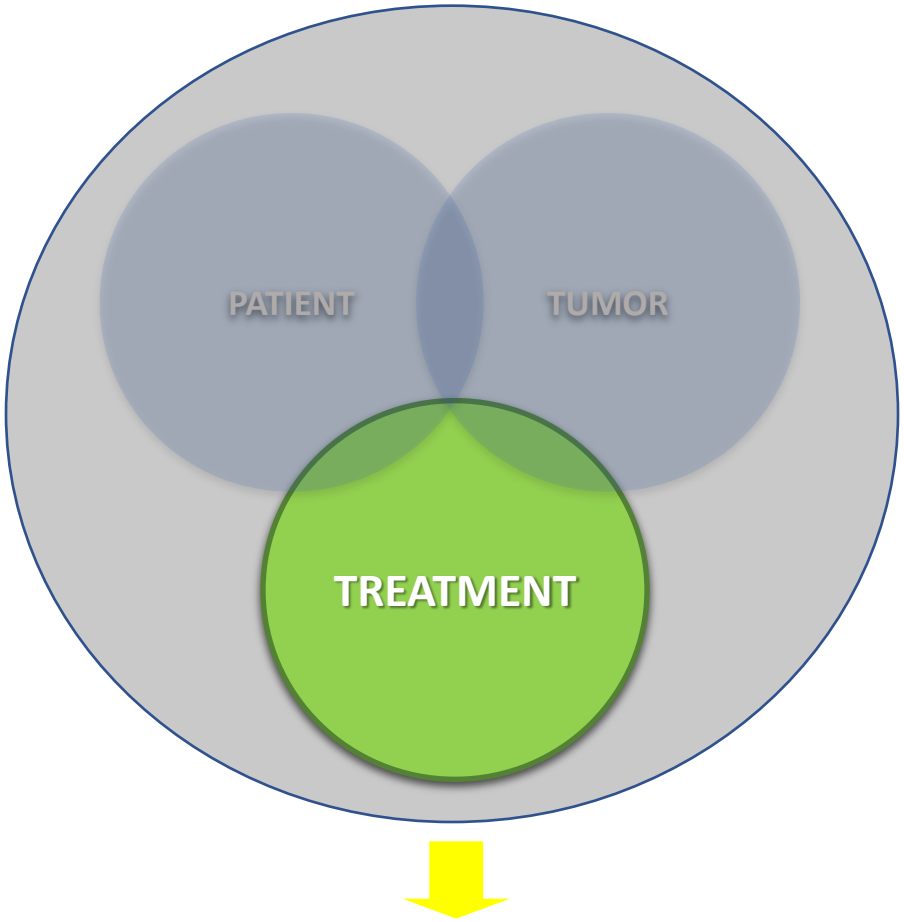
Therapy Selection in Real-life

Age

Performance status

Comorbidities

Patient preference (?)



Symptoms

Burden

Clinical course

PSA

Biology?

Experience **Efficacy/Toxicity** **Cost** **Evidence** **Guidelines**
Duration **Cross-resistance/MoA** **QoL**

Drug	Abiraterone	Enzalutmide	Docetaxel	Cabazitaxel	Radium-223
Absorption	Oral	Oral	Intravenous	Intravenous	Intravenous
Methabolism	Hepatic: CYP3A4 and SULTA21	Hepatic: CYP3A4 and CYP2C8	Hepatic: CYP3A4	Hepatic: CYP3A4/5 and CYP2C8	No hepatobiliary or renal excretion
Elimination	88% faeces 5% urine	14% faeces 71% urine	75% faeces 6% urine	76% faeces 4% urine	Faeces (mainly) 5% urine

ENZIMI	ABIRATERONE	ENZALUTAMIDE	CABAZITAXEL
CYP2D6	YES	-	
CYP2C8	-	YES	
CYP3A	YES	YES	YES
CY2B6	-	-	
CYP2C9	-	YES	
CYP2C19	-	YES	

Riassunto delle caratteristiche dei prodotti

Profilo di tollerabilità

Agente	Eventi avversi più comuni
Abiraterone	Cardiaci/ipertensione Epatici Fatigue Ipokaliemia/iperglicemia Edema
Enzalutamide	Fatigue SNC Cadute Ipertensione
Cabazitaxel	Neutropenia/anemia Fatigue Neuropatia Nausea/vomito/diarrhea iperglicemia
Docetaxel	Neutropenia/anemia Fatigue Neuropatia Nausea/vomito/diarrhea iperglicemia
Radium-223	Anemia Piastrinopenia Neutropenia Fatigue

Progressione ad ABI/ENZA:
Cross-Resistenza tra ARTA

Author	Year published	N patients	Duration of 2nd treatment	↓ PSA ≥ 50%	Median PFS
No prior ENZA					
De Bono et al.[1] (COU-AA-302)	2011	797	8 mos	29%	5.8 mos
ENZA→ABI					
Loriot et al.[2]	2013	38	3 mos	8%	2.7 mos
Noonan et al.[3]	2013	30	13 wks	3%	3.6 mos

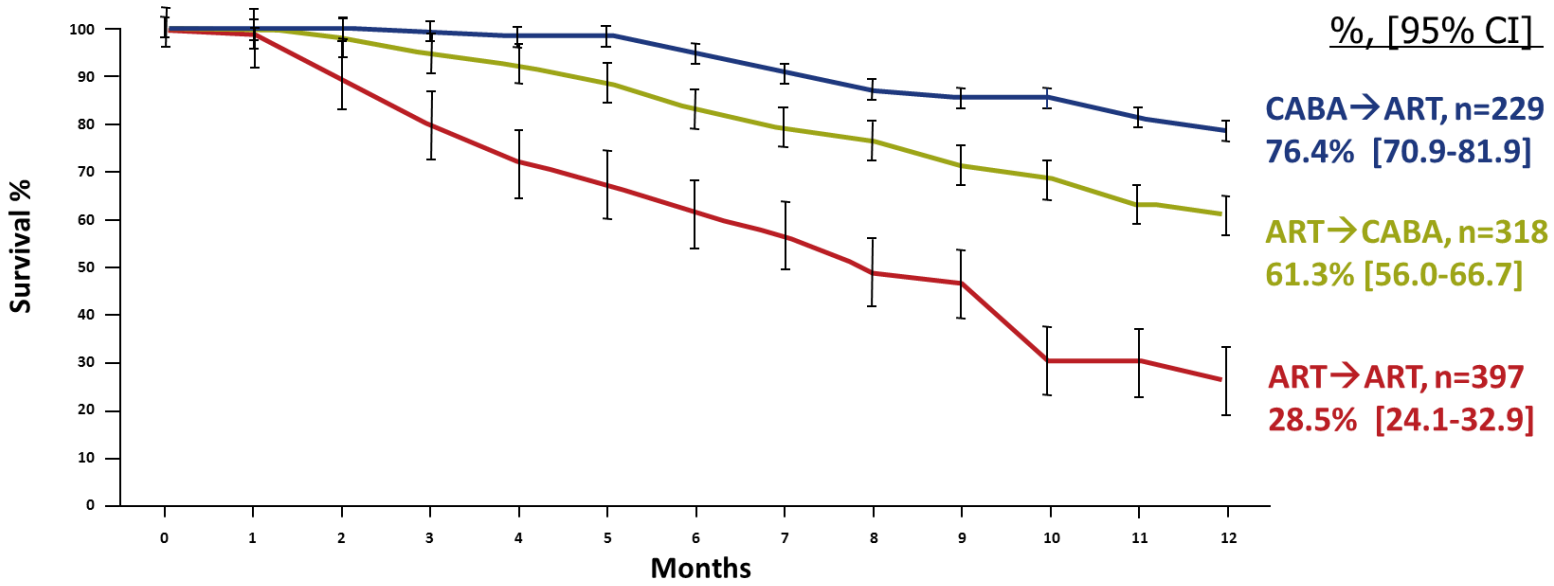
[1] prospective randomized trial of ABI/P vs P in mCRPC (post-DOC);
[2-3] trials are retrospective studies in mCRPC pts (post-DOC).

- **NICE (UK) does not permit use of sequential ART if there is progression on first ART[3]**
- Preferred treatment option if patient fit → chemotherapy

1. De Bono J et al. N Engl J Med. 2011;364:1995-2005; 2. Loriot Y et al. Ann Oncol. 2013;24:1807-12; 3. Noonan KL et al. Ann Oncol. 2013;24:1802-7.

Systematic Review of 13 Published Retrospective Studies in mCRPC (N=1,016)

12-month cumulative OS rate by sequence (post-DOC)



Poor outcome when novel AR-targeted agents are prescribed in sequence

ART: novel AR-targeted agent (abiraterone acetate or enzalutamide)

Maines F et al. Crit Rev Hematol Oncol 2015;96:498-506

Population-based Analysis of Treatment Toxicity Among Men With Castration-resistant Prostate Cancer: A Phase IV Study

- Retrospective cohort study of **2439** men aged **≥65 years** treated for mCRPC with **abiraterone, enzalutamide, docetaxel, or cabazitaxel** from 2003 to 2015

- Treatment with **chemotherapeutic** agents was associated with an **increased risk of hospitalizations** and **emergency room visits** to manage these complications (mainly due to infection/neutropenia)

Wallis CJD, et al. Urology. 2018

Advanced Prostate Cancer Consensus Conference APCCC 2017

Table 4 – Definition "unfit" for docetaxel

What are meaningful definitions "not being suitable for docetaxel", apart from allergy to the substance ("docetaxel ineligible")?	Yes (%)	Only in combination with other factors (%)	No (%)	Abstain (%)
Severe hepatic impairment (eg, ALT/AST > 5 × ULN and/or bilirubin > 3 × ULN)	96	2	2	0
Neuropathy grade ≥2	82	18	0	0
Platelets $<50 \times 10^9$/l and/or neutrophils $<1.0 \times 10^9$/l	81	15	4	0
Frailty assessed by geriatric or other health status evaluation	69	29	2	0
Performance status ≥2 for reasons other than cancer	62	32	4	2
Moderate hepatic impairment (eg, ALT/AST > 3–5 × ULN and/or bilirubin > 1.5–3 × ULN)	52	48	0	0

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

Gillessen S, et al EUROPEAN UROLOGY 7 3 (2 01 8)

2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial

Findings 177 patients were randomly assigned to the 2-weekly docetaxel group and 184 to the 3-weekly group. 170 patients in the 2-weekly group and 176 in the 3-weekly group were included in the analysis. The 2-weekly administration was associated with significantly longer TTTF than was 3-weekly administration (5·6 months, 95% CI 5·0–6·2 *vs* 4·9 months, 4·5–5·4; hazard ratio 1·3, 95% CI 1·1–1·6, p=0·014). Grade 3–4 adverse events occurred more frequently in the 3-weekly than in the 2-weekly administration group, including neutropenia (93 [53%] *vs* 61 [36%]), leucopenia (51 [29%] *vs* 22 [13%]), and febrile neutropenia (25 [14%] *vs* six [4%]). Neutropenic infections were reported more frequently in patients who received docetaxel every 3 weeks (43 [24%] *vs* 11 [6%], p=0·002).

Interpretation Administration of docetaxel every 2 weeks seems to be well tolerated in patients with castration-resistant advanced prostate cancer and could be a useful option when 3-weekly single-dose administration is unlikely to be tolerated.

	2-weekly docetaxel (n=170)	3-weekly docetaxel (n=176)	Hazard ratio (95% CI)	p value
Median (95% CI) TTTF (months)	5·6 (5·0–6·2)	4·9 (4·5–5·4)	1·3 (1·1–1·6)	0·014
Median (95% CI) TTP or death (months)	15·8 (13·6–18·1)	14·6 (13·2–16·0)	1·3 (1·0–1·6)	0·047
Median (95% CI) overall survival (months)	19·5 (15·9–23·1)	17·0 (15·0–19·1)	1·4 (1·1–1·8)	0·021
PSA response	84 (49%)	74 (42%)	..	0·486
Best response to treatment				0·952
Complete or partial response	39 (23%)	38 (22%)	..	..
Stable disease	78 (46%)	80 (46%)	..	..
Disease progression	14 (8%)	19 (11%)	..	..
Not available	39 (23%)	39 (22%)	..	..

Medians and 95% CIs are estimated values from Kaplan-Meier analyses. TTTF=time to treatment failure. TTP=time to progression. PSA=prostate-specific antigen.

Table 2: **Summary of primary and secondary outcomes**

Kellokumpu-Lehtinen PL, et al. Lancet Oncol 2013

Cabazitaxel: possibile personalizzazione del trattamento

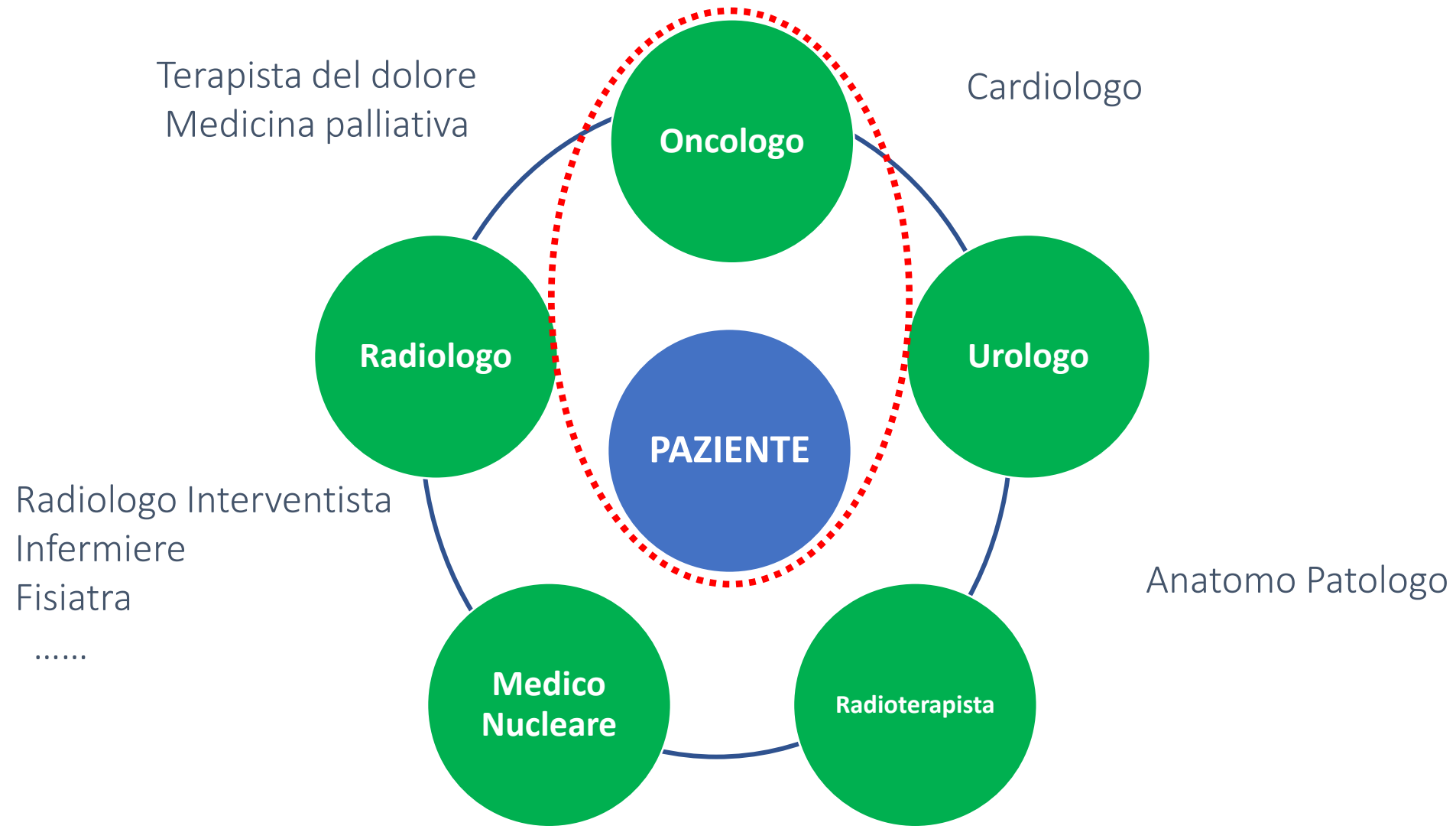
Trial	Phase 3	EAP	Phase 3	Phase 3	Phase 2	Phase 2
	TROPIC [7] 25 mg/m^2	EU-EAP [32] 25 mg/m^2	FIRSTANA [10] 20 mg/m^2	PROSELICA [11] 20 mg/m^2	BIWEEKLY [33] 16 mg/m^2	WEEKLY* 10 mg/m^2 (Unfit patients)
ECOG 2	7%	10.5%	4.4%	9.7%	27.9%	50%
Median age (years)	68	67.7	68	68	70	73.9
Median PSA	143.9 ng/ml	NA	76 ng/ml	451.4 ng/ml	77.7 ng/mL	186 ng/mL
G-CSF use	NA	68%	NA	NA	100%	1.4%
MAIN TOXICITY (% overall/% of severity G3/G4 events)						
Neutropenia	94%/82%	17%	65.2%/37.8%	66.6%/41.8%	NA/11.6%	14.2%/5.8%
Leucopenia	96%/68%	7.4%	NA	NA	NA	29.9%/2.8%
Febrile Neutropenia	8%	5.4%	2.4%	2.1%	4.7%	0%
Thrombocytopaenia	47%/4%	1.1%	35.3%/1.6%	35%/2.6%	NA/9.3%	20%/10%
Diarrhoea	47%/6%	2.8%	32.5%/3.5%	NA/0.4%	NA/7%	35.7%/1.4%

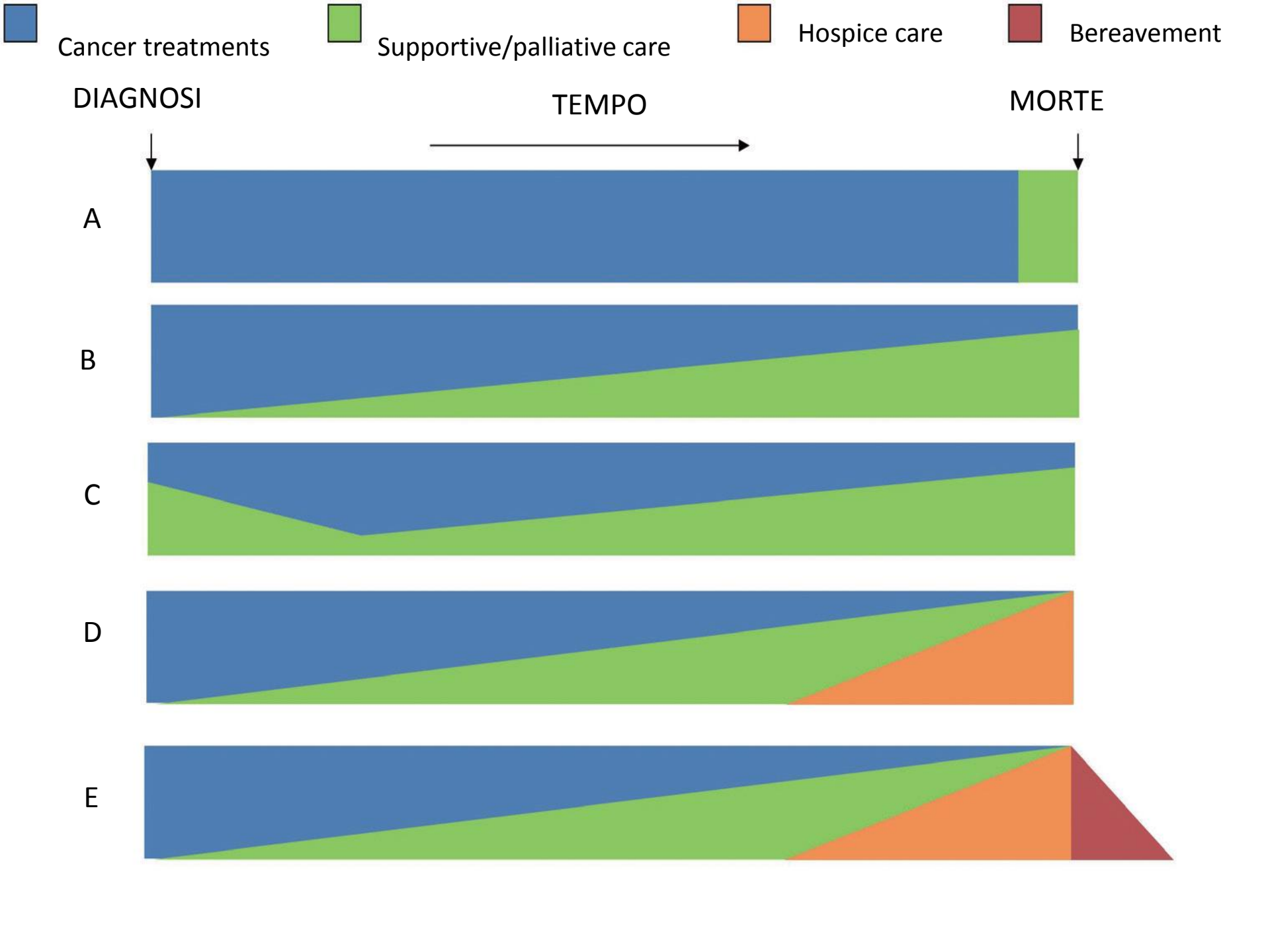
Una personalizzazione del trattamento con cabazitaxel migliora la tollerabilità e non sembra compromettere il beneficio terapeutico

Modified from Climent MA, et al Eur J Cancer (2017)

*Unfit patients: ECOG-PS 2, previously dose reduction of DTX due to febrile neutropenia, previous radiotherapy (>25% of bone marrow reserve)

Gestione multidisciplinare




Cancer treatments
Supportive/palliative care
Hospice care
Bereavement
DIAGNOSI
TEMPO
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A
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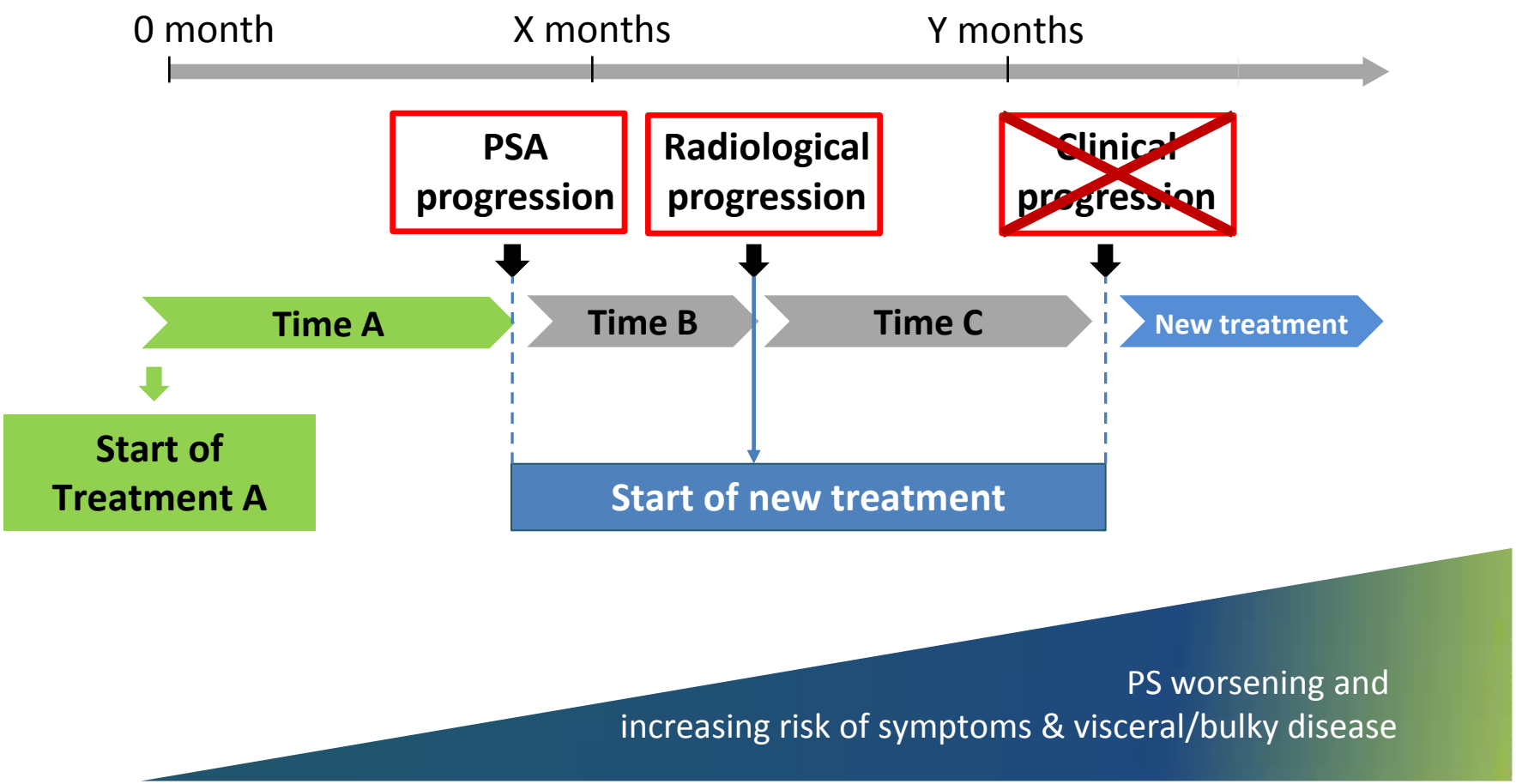
Treatment optimization



Conclusioni

• Negli ultimi anni nuovi agenti hanno modificato la storia naturale del carcinoma della prostata, migliorando la sopravvivenza complessiva e la qualità di vita

• Il profilo di tollerabilità varia in relazione al meccanismo d'azione ed è generalmente ben gestibile anche al di fuori dei trials clinici

• Gli eventi avversi attesi, la modalità di somministrazione e le comorbidità dei pazienti rappresentano ulteriori elementi da considerare per il decision making nella pratica clinica

• La personalizzazione del trattamento, una gestione attenta e multidisciplinare del paziente e degli effetti collaterali possono permettere di massimizzare i risultati terapeutici

Grazie per l’attenzione

Ospedale Niguarda
Cancer Center

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