Metastatik Kastrasyona Duyarlı Prostat Kanserinde Yanıt Değerlendirme ve Takip

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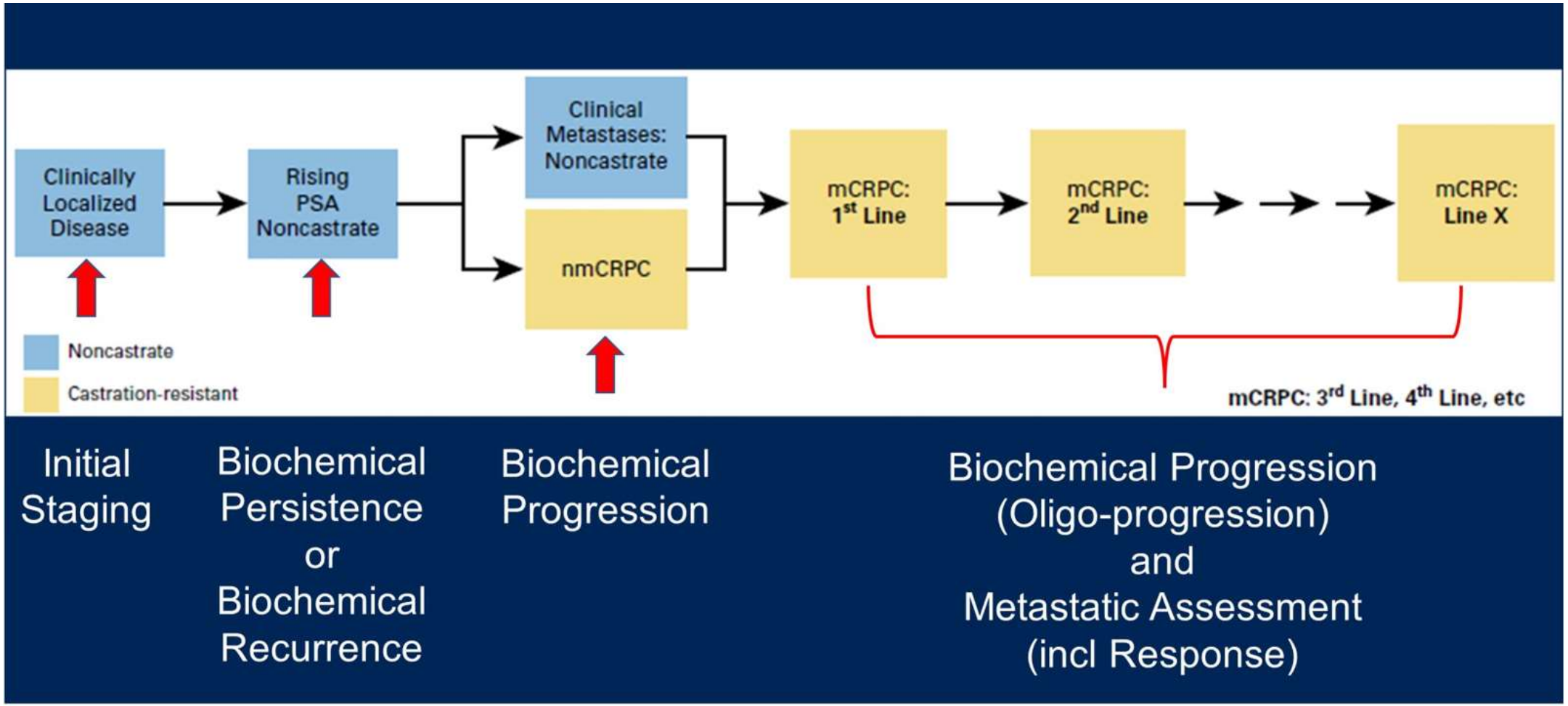
Tıbbi Onkoloji

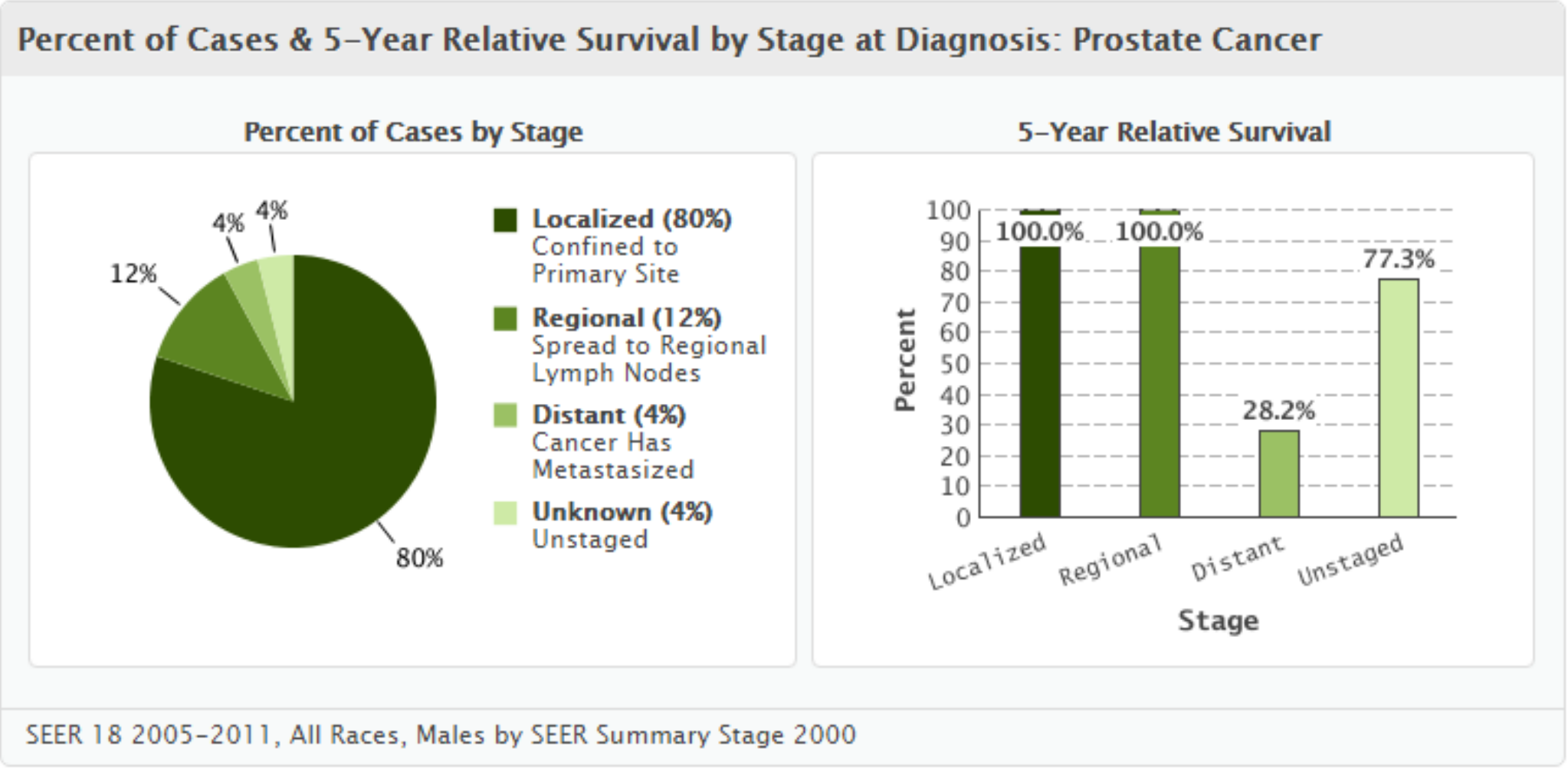
Ders Planı

- ❑Giriş
- ❑İdeal evreleme nasıl olmalı
- ❑Prostate Cancer Clinical Trials Working Group 3(PCWG3)kriterleri
- ❑RECIST 1.1 kriterleri
- ❑Flare döneminde yanıt değerlendirilmesi
- ❑PSA yanıtı PCWG2 kriterlerine göre değerlendirilmesi
- ❑Radyolojik progresyon, PSA progresyonu olmayan hasta grupları
- ❑PSA progresyonu olup, Radyolojik progresyon olmayan hastalar
- ❑PSMA PET-CT
- ❑Sonuç

Prostat Kanseri Klinik Seyir



Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavisi



İdeal Evreleme Nasıl Yapılmalı

	Intermediate Risk T2b and GS7 and/or PSA 10-20	High Risk (or greater) ≥T2c or GS 9-10 or PSA>20	Biochemical Relapse / Progression
NCCN (ver 1.2023)	PSMA PET (unfavorable)	PSMA PET	PSMA PET
ESMO PAN-ASIAN ESMO	CT/MRI + Bone Scan or PSMA PET	CT/MRI + Bone Scan or PSMA PET	PSMA PET
EUA	CT/MRI + Bone Scan	PSMA PET or whole body MRI	PSMA PET

Unfavorable = ≥2 intermediate risk factors (cT2b-cT2c, GG 1 or 2, PSA 10-20) or GG3 or ≥ 50% biopsy cores positive

PRESENTED BY: David M. Nanus, M.D., Professor of Medicine and Urology, Weill Cornell Medicine

İdeal Evreleme Nasıl Yapılmalı

ASCO* PC Imaging Guidelines (2020)

12

	Conventional Imaging	PSMA PET Scan
Newly Dxed hi-risk/very hi risk	Negative/Equivocal	Yes
	Positive	No
Rising PSA after prostatectomy - Planned salvage radiotherapy	Negative	Yes if candidate for salvage local Rx Yes
Rising PSA after radiotherapy	Negative	Yes if considering salvage local or regional therapy
Metastatic at Initial Diagnosis or After Initial Rx, Hormone Sensitive	Positive	Yes - if to clarify the burden of disease and shift the treatment intent from multimodality management of oligometastatic disease to systemic therapy
Nonmetastatic CRPC (M0)	Negative	Yes – if change in clinical care contemplated
Metastatic CRPC – PSA progression – CI progression	 Stable Progression	 Unclear utility No

*ASCO, ASTRO, AUA, ACR, SUO, SNMMI, Society of Abdominal Radiology

J Clin Oncol 2020 38;1963-1996

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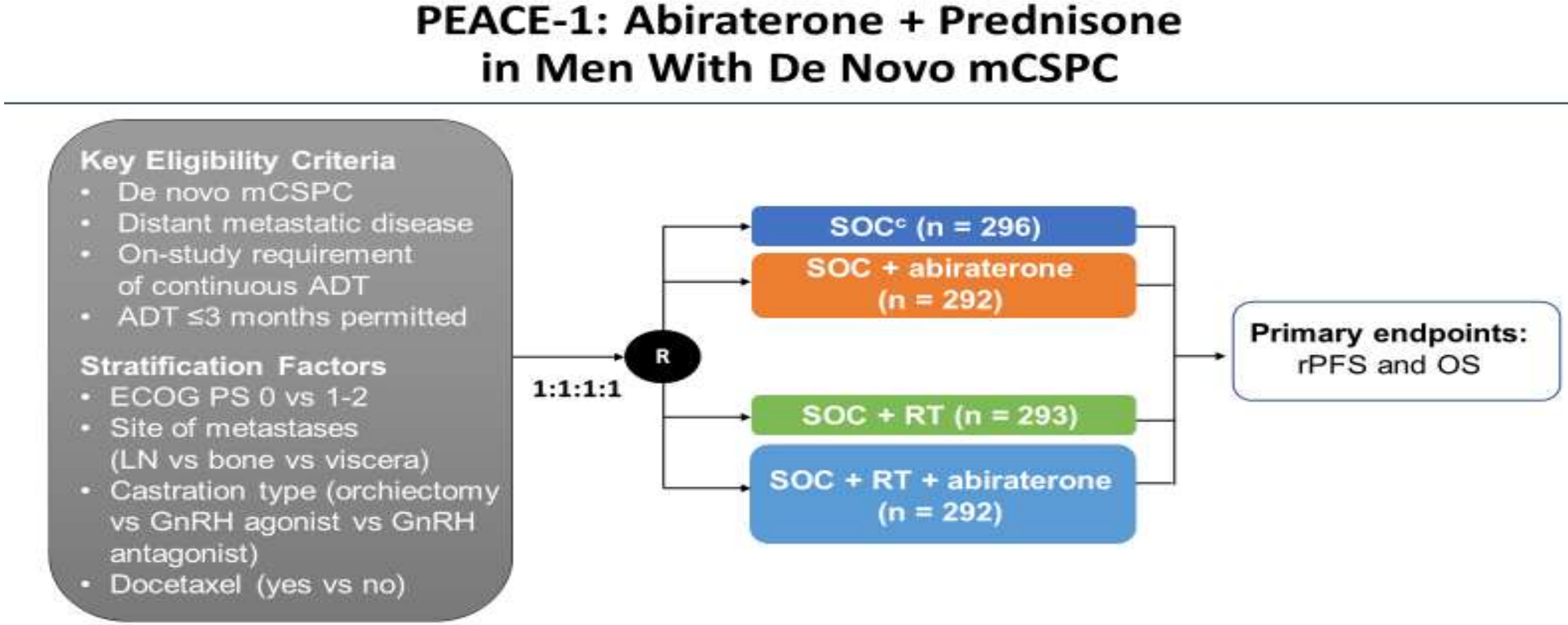
Metastatik Kastrasyona Duyarlı Prostat Kanserinde Tedaviye Yanıt Değerlendirmesi

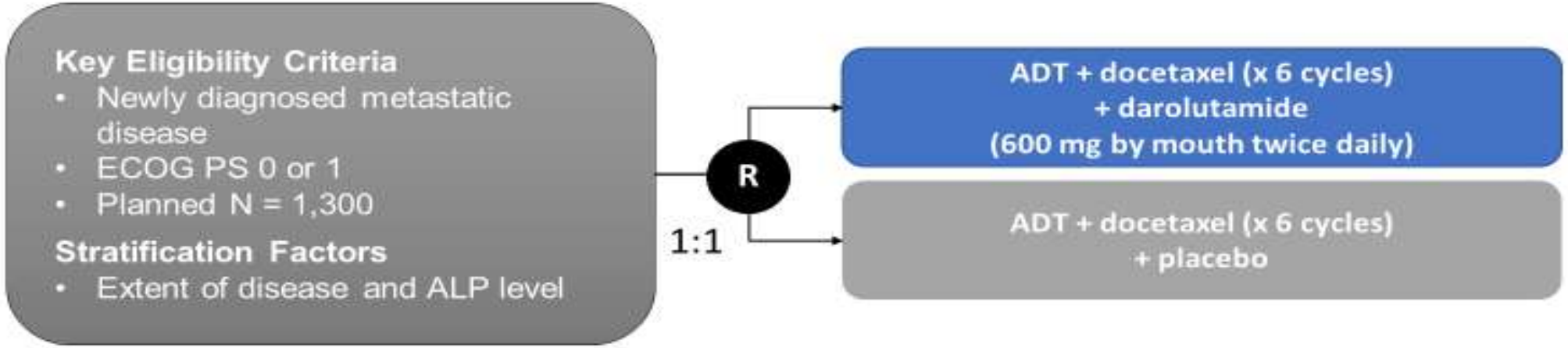


Fizazi K et al. *J Clin Oncol*. 2021;39(suppl 15):5000. Fizazi K. ESMO 2021. Abstract LBA5_PR.

Metastatik Kastrasyona Duyarlı Prostat Kanserinde Tedaviye Yanıt Değerlendirmesi

ARASENS: Phase 3 Trial

International trial conducted at >300 sites in 23 countries



- **Primary endpoint:** OS
- **Key Secondary endpoints:** time to mCRPC, time to initiation of subsequent anticancer therapy, time to SSE-free survival, time to first SSE, time to pain progression

https://clinicaltrials.gov/ct2/show/NCT02799602. Smith MR et al. ASCO GU 2022. Abstract 13. Smith MR et al. *N Engl J Med*. 2022;386:1132-1142.

Radiographic progression-free survival(rPFS)

- Randomizasyon tarihinden, radyolojik progresyon ya da herhangi bir sebepten ölüme kadar geçen süre

- Yumuşak doku yanıt ve progresyonu, RECIST 1.1 kriterlerine göre, Kemik progresyon ve yanıtını, Prostate Cancer Clinical Trials Working Group 3(PCWG3)kriterlerine göre değerlendirilir

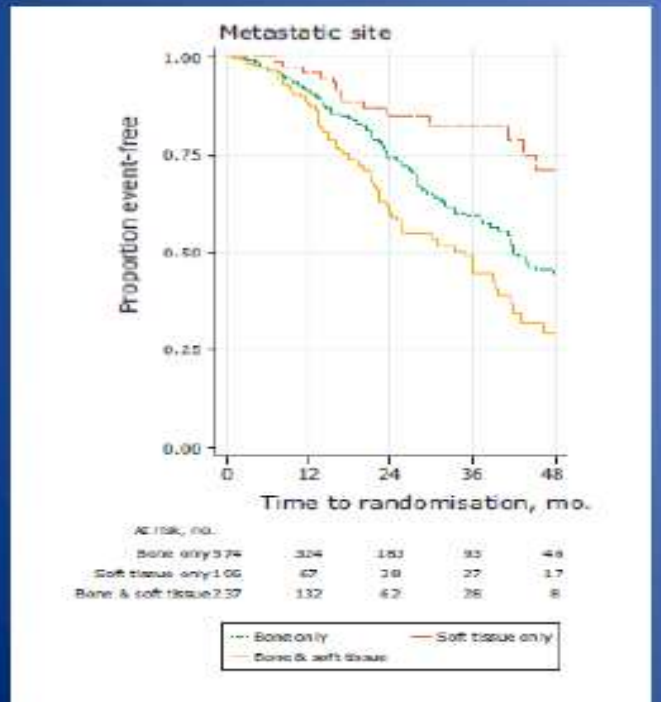
- PSA yanıtı PCWG2 kriterlerine göre değerlendirilir

Metastatik Kastrasyona Duyarlı Prostat Kanserinde Tedaviye Yanıt Değerlendirmesi

Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

Nicholas David James[a,], Melissa R. Spears[b], Noel W. Clarke[c], David P. Dearnaley[d,e], Johann S. De Bono[d,e], Joanna Gale[f], John Hetherington[g], Peter J. Hoskin[h], Robert J. Jones[i], Robert Laing[j], Jason F. Lester[k], Duncan McLaren[l], Christopher C. Parker[d,e], Mahesh K.B. Parmar[b], Alastair W.S. Ritchie[b], J. Martin Russell[m], Räto T. Strebel[n], George N. Thalmann[o], Malcolm D. Mason[k], Matthew R. Sydes[b]*

EUROPEAN UROLOGY 67 (2015) 1028–1038



STAMPEDE ÇALIŞMASI; 917 KONTROL KOLUNDE(ADT alan) BULUNAN M1 HASTALARIN SONUÇLARI

Hastaların %62 yalnız kemik ve %26 kemik+yumuşka doku met.(lenf nodu metastazı)

2 Yıllık sağkalım; yumuşak doku met.%85

Kemik met.%75

Yumuşak doku+kemik met.%60

2yılık FFS; yumuşak dokuda %54, kemik met %28 , yumuşak doku+kemik met.%18

Radiographic progression-free survival(rPFS)

Overall Response Assessment

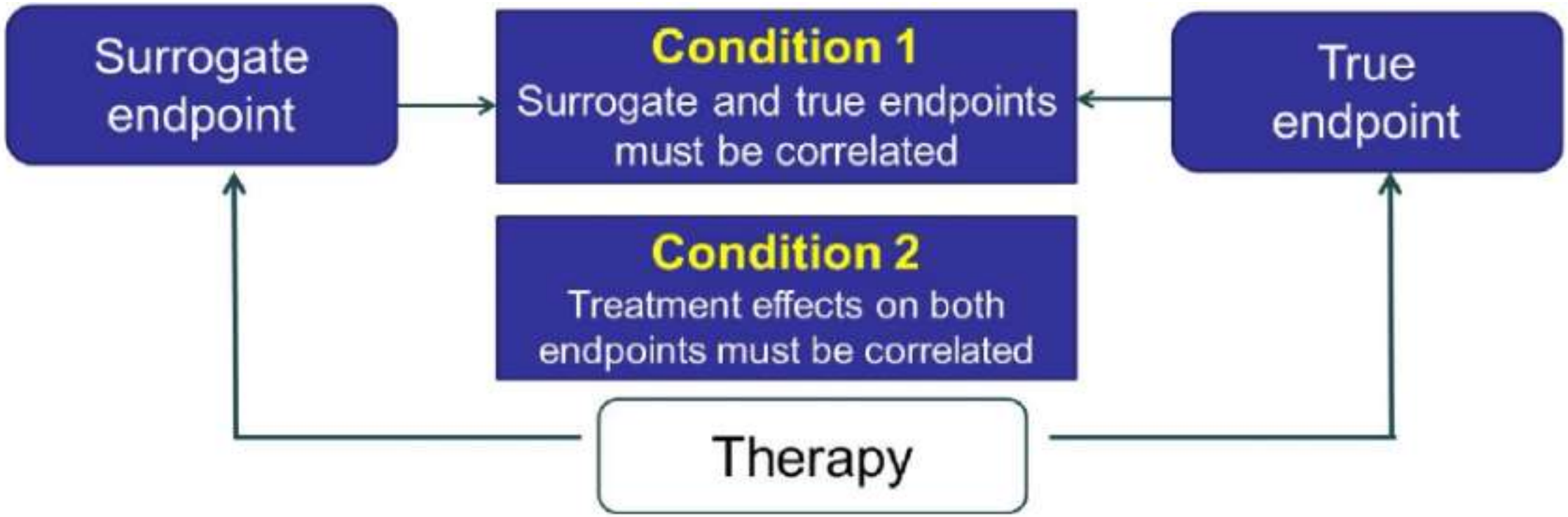
Soft tissue lesions (rules of RECIST 1.1)

+

Bone lesions (rules of PCWG)

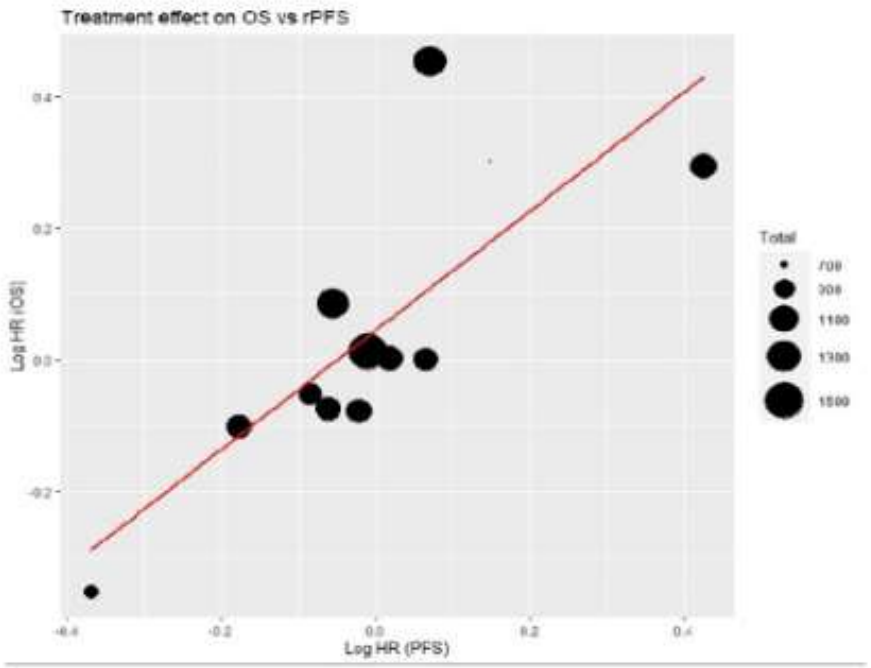
PCWG-Modified RECIST 1.1

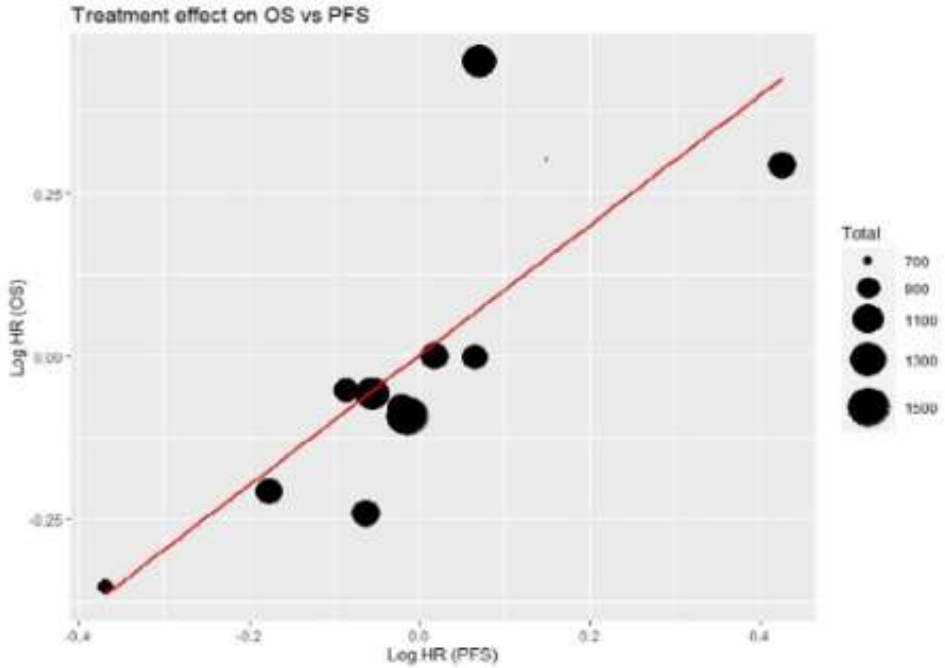
rPFS metastatik prostat kanserinde OS için surrogate belirteçmi



Halabi at al, 2021 ASCO Annual Meeting

rPFS metastatik prostat kanserinde OS için surrogate belirteç mi





At the trial level, the correlation between rPFS and OS was R^2 = 0.50 (95 % CI = 0.39-0.70) while it was 0.53 (95 % CI = 0.38-0.67) for PFS and OS.

Halabi at al, 2021 ASCO Annual Meeting

Metastatik Kastrasyona Duyarlı Prostat Kanserinde Genel Değerlendirme

Table 4. Suggested Frequency of Assessment for Commonly Used Measures in Metastatic Prostate Cancer Clinical Trials

Measure*	PCWG2 Frequency (2008)	PCWG3 Frequency (2015)†
Clinical		
Symptoms/ performance status	Every cycle	Retained
Blood-based markers		
PSA	By cycle (every 3 or 4 weeks)	Retained
ALK, LDH	By cycle (every 3 or 4 weeks)	Retained
Serum chemistry, CBC	Not addressed	By cycle (every 3 to 4 weeks)
Circulating tumor cells	Not addressed	By cycle (every 3 to 4 weeks) if available
Imaging		
Bone scans	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
CT/MRI	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
Patient-reported outcomes	Not addressed	By cycle (every 3 to 4 weeks)
Analgesic consumption (opioids/no opioids)	Not addressed	By cycle (every 3 to 4 weeks)

Abbreviations: ALK, alkaline phosphatase; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

*All measures should be assessed at baseline to determine changes over time.

†There may be exceptions to these suggestions: in nonmetastatic castration-resistant prostate cancer trials, for example, imaging assessment intervals of 16 weeks are advised. Likewise, in long-term responders (> 2 to 3 years of clinical benefit and no signs of clinical or biomarker progression), reduced frequency of imaging is reasonable, such as every 16 to 24 weeks (4 to 6 months).

PCWG3, JCO 2016

Metastatik Kastrasyona Duyarlı Prostat Kanserinde Genel Değerlendirme

7.2.6 ***Guidelines for follow-up during hormonal treatment***

Recommendations	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every 3–6 months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
As a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong

EUA guidelines, 2023

RECIST1.1 kriterlerine göre kemik dışı lezyonların değerlendirilmesi

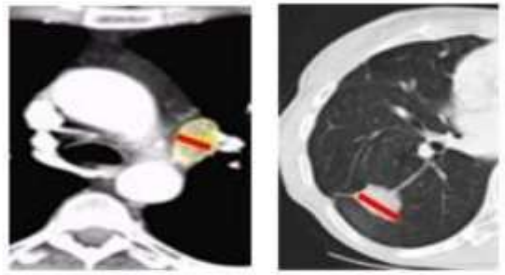
Baseline – Soft Tissue Target Lesions

Identify ALL malignant soft tissue lesions

Decide which are "measurable"
- Non-nodes ≥ 10 mm longest diameter
- Lymph nodes ≥ 15 mm short axis
- Reproducible

From these, select "target"
- Up to 10 total, 5 per organ
  - RECIST 1.1 says 5 max (2/organ)
  - Merck trials: up to 5 more
- Lymph nodes are collectively an "organ"
- Representative of total disease burden

Lymph nodes: short axis



Non-nodal: longest diameter

RECIST1.1 kriterlerine göre kemik dışı lezyonların değerlendirilmesi

Baseline – Document Soft Tissue Non-Target Lesions

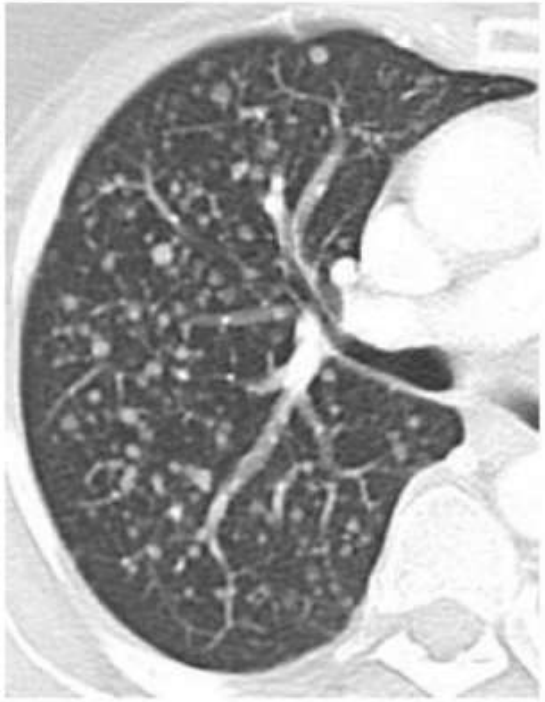
Non-target (NT): all other clearly malignant lesions

All non-measurable lesions in soft tissue

- Extranodal lesions <10 mm, nodes 10-14 mm
- No reproducible measurements
  - Unclear margins
  - Infiltrative, or spreading along surfaces
  - Locations that move (lung bases, bowel wall)
- Malignant fluid collections (effusions, ascites)

Measurable lesions beyond those chosen as target

Brain lesions



RECIST1.1 kriterlerine göre kemik dışı lezyonların değerlendirilmesi

Calculation of Soft Tissue Response

1. Measure soft tissue targets
2. Visually assess soft tissue non-targets
3. Search for new soft tissue lesions
4. Combine into soft tissue response

Target Soft Tissue Lesions

Response	Definition
CR	All resolved
PR	Sum ≥ 30% ↓ from baseline
SD	Not enough change for PR or PD
PD	Sum ≥ 20% ↑ from nadir • And ≥ 5mm absolute increase
NE	One or more lesions not evaluable

Non-Target Soft Tissue Lesions

Response	Definition
CR	All resolved
Non-CR / Non-PD	Still present
PD	Unequivocal progression
NE	One or more lesions not evaluable

%current Slide% of %totalSlides%

New Soft Tissue Lesions

	Definition
Yes	Definitely present
No	Not present, or uncertain

PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi

- Etkili olmayan bir tedaviye maruziyeti en az indirmek ve aynı zamanda gereksiz işlemden kaçınmak için ideal kemik sintigrafisi süresi

- Flare döneminde 8-9 haftada bir

- Altı ay sonrası 12 hafta bir

PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi

What is Flare?

Bone healing around dying tumor

Early “new” lesions: existed at baseline but were not seen

“Flare window” = 12 weeks after therapy

Flare Fenomeni

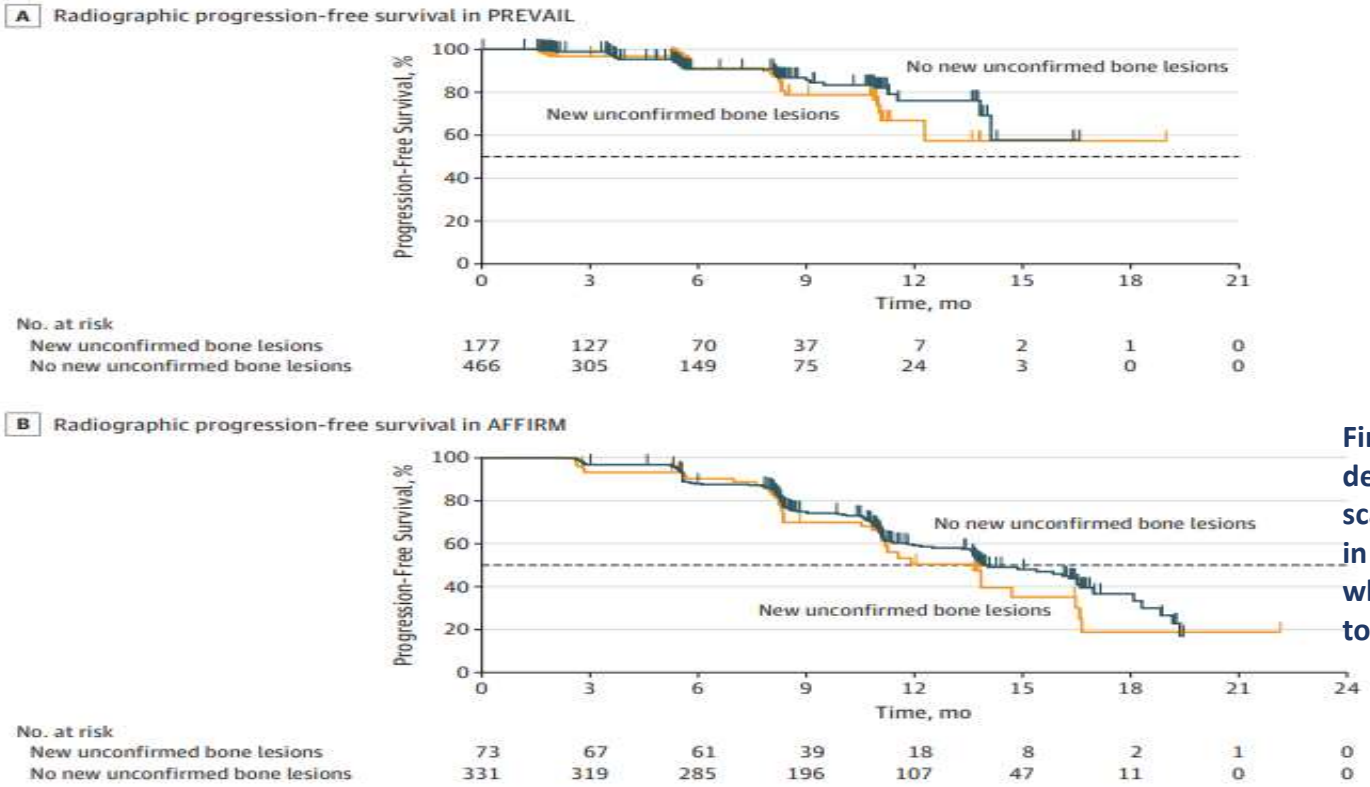
Study	Treatment	Study design	Type of imaging	No. of patients	Worsened bone scan at 3rd month	Bone flare	Pain flare	PSA flare
Pollen[23]	ADT ± CHT	Prospective	BS	33	9% (3/33)	6% (2/33)	n/a	n/a
Johns[22]	Leuprolide	Prospective	BS	26		19% (5/26)	n/a	n/a
Cook[21]	Leuprolide	Prospective	BS	22	0/22	41% (9/22)	n/a	n/a
Ryan[5]	Abiraterone	Prospective	BS/ CT/MRI	23	52% (12/23)	48% (11/23)	24%	n/a
Messiou[25]	CYP17 inhibitor	Retrospective	CT	39	21% (8/39)	8% (3/39)	n/a	n/a
De Giorgi[36]	Abiraterone	Retrospective	FCH PET/CT	43	29% (12/42)	10% (4/42)	n/a	n/a
Morris[37]	Abiraterone	Retrospective	BS/ CT/MRI	1088	15% (166/1088) at week 8	2.5% (27/1088) at week 12	n/a	n/a
Modi[46]	Radium-223	Retrospective	BS	29	n/a	21% (6/29)	52%	10%
Keizman[47]	Radium-223 ± abiraterone or enzalutamide	Retrospective	BS or CT	113	26% (29/113)	20% (23/113)	27%	n/a
Aggarwal[29]	Enzalutamide	Prospective	PSMA PET	8#	n/a	6/8 (75%)	n/a	n/a
Isensee[52]	Radium-223	Retrospective	BS	19	21% (4/19)	15.8% (3/19)	n/a	n/a
Kadomoto[53]	Abiraterone or enzalutamide	Retrospective	BS	31	45% (14/31)	26% (8/31)	n/a	n/a
De Laroche[54]	Abiraterone	Prospective	SPECT-CT	19	26% (5/19)	21% (4/19)	n/a	n/a
Armstrong[42]	Enzalutamide	*Post hoc* retrospective	BS	872* 800**	20%* (177/872) 9%** (73/800)	27.5%* at week 9 and 13 18.1%** at weeks 17 and 25	n/a	n/a

*Chemotherapy-naive patients enrolled in the PREVAIL trial.
**Chemotherapy-treated patients enrolled in the AFFIRM trial.
#Four castration-sensitive prostate cancer + four castration-resistant prostate cancer patients.
ADT, androgen deprivation therapy; BS, bone scan; CHT, chemotherapy; CT, computed tomography; FCH PET/CT; 18F-fluorocholine positron emission tomography/computed tomography; MRI, magnetic resonance imaging; n/a, not available; SPECT, single photon emission computed tomography.

Conteduca V, Ther Adv Med Oncol 2021

Flare Fenomeni-Sağkalım İlişkisi

Figure 2. Radiographic Progression-Free Survival (rPFS) in PREVAIL and AFFIRM Among Men Treated With Enzalutamide Who Had a Decrease in Prostate-Specific Antigen Level or an Objective Soft-Tissue Response, With or Without New Unconfirmed Lesions Detected on Follow-up Bone Scans Over Time



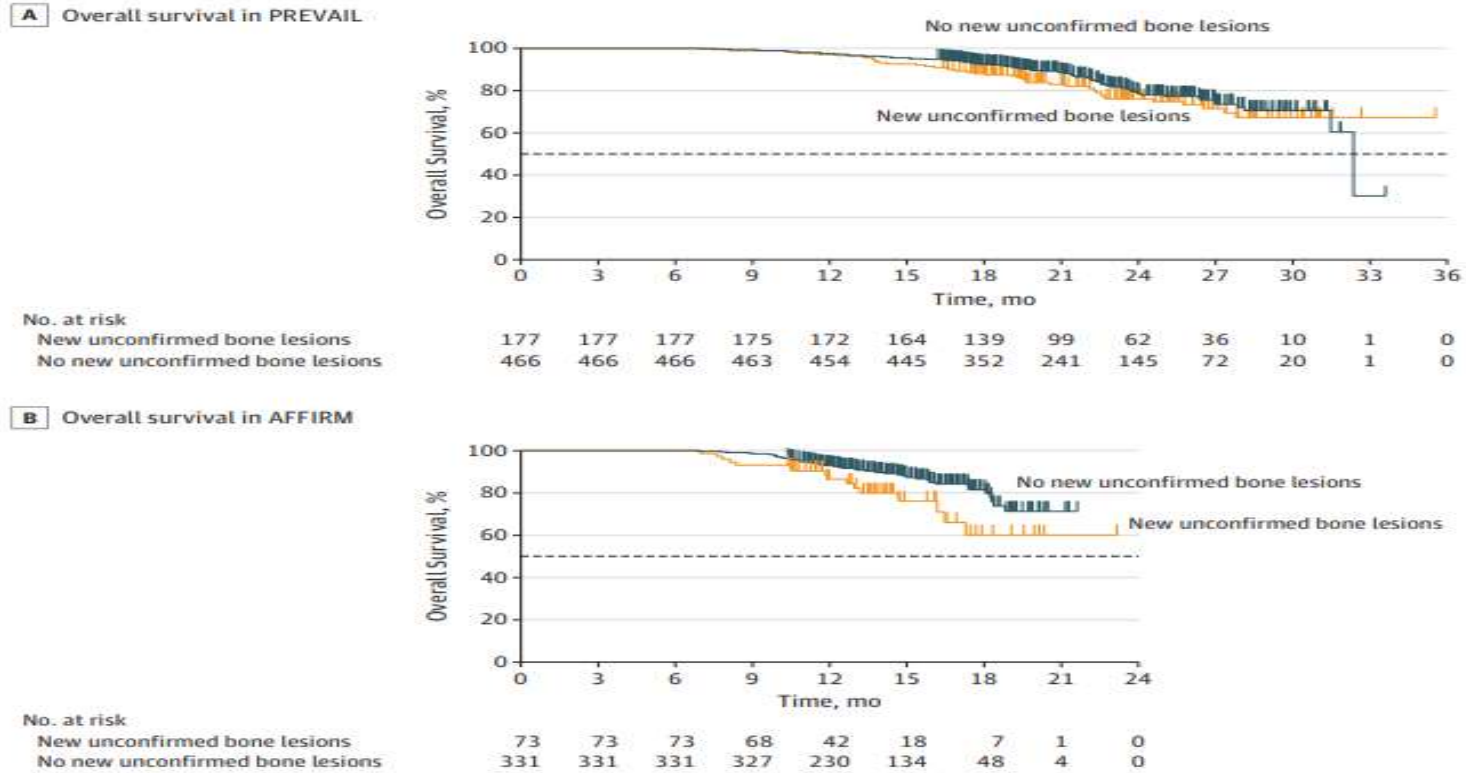
A, Median rPFS in PREVAIL among men with new unconfirmed bone lesions (n = 177), not reached (NR [95% CI, 12.3 months to NR]); and median rPFS in PREVAIL among men with no new unconfirmed bone lesions (n = 466), NR (95% CI, 14.1 months to NR); hazard ratio, 1.37 (95% CI, 0.81-2.30); *P* = .23. B, Median rPFS in AFFIRM among men with new unconfirmed bone lesions (n = 73), 13.6 months (95% CI, 11.1-16.5 months); and median rPFS in AFFIRM among men with no new unconfirmed bone lesions (n = 331), 13.9 months (95% CI, 13.6-16.5 months); hazard ratio, 1.21 (95% CI, 0.83-1.75); *P* = .32. Horizontal dashed lines indicate the median.

First, new unconfirmed lesions were detected on the first posttreatment bone scan in 2 large phase 3 trials was observed in 18.1% to 27.5% of men with mCRPC whose disease was otherwise responding to enzalutamide

Andrew J. Armstrong, JAMA Oncology 2019

Flare Fenomeni

Figure 3. Overall Survival (OS) in PREVAIL and AFFIRM Among Men Treated With Enzalutamide Who Had a Decrease in Prostate-Specific Antigen Level or an Objective Soft-Tissue Response, With or Without New Unconfirmed Lesions Detected on Follow-up Bone Scans Over Time



A, Median OS in PREVAIL among men with new unconfirmed bone lesions (n = 177), not reached (NR [95% CI, NR to NR]); and median OS in PREVAIL among men with no new unconfirmed bone lesions (n = 466), 32.4 months (95% CI, 31.5 months to NR); hazard ratio, 1.25 (95% CI, 0.85-1.83). B, Median OS in AFFIRM among men with new unconfirmed bone lesions (n = 73), NR (95% CI, 16.5 months to NR); and median OS in AFFIRM among men with no new unconfirmed bone lesions (n = 331), NR; hazard ratio, 1.94 (95% CI, 1.10-3.44). Horizontal dashed lines indicate the median.

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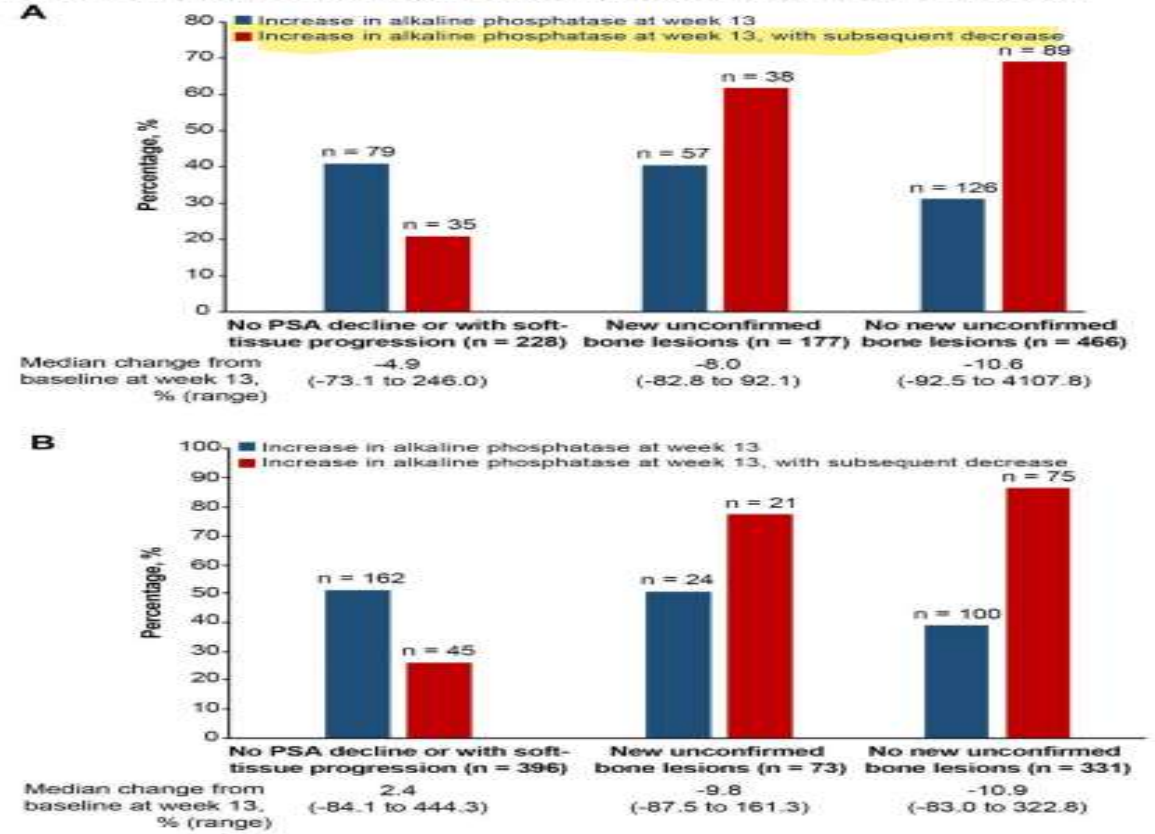
Fenomeni-Sağkalım İlişkisi

eFigure 4. Change in Alkaline Phosphatase at Week 13 in PREVAIL (A) and AFFIRM (B) in Men Treated With Enzalutamide With No PSA Decline or With Soft-Tissue Radiographic Progression, or Who Had a Decline in PSA or Objective Soft-Tissue Response, With or Without New Unconfirmed Bone Scan Lesions



Abbreviation: PSA, prostate-specific antigen.

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PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi

PCCTC Bone Scan Assessment Tool

8 Week Scan Date: (_____/_____/_____)

Patient Identifier:

Protocol Number: | Protocol Start Date:

Is tracer uptake related to metastatic disease?

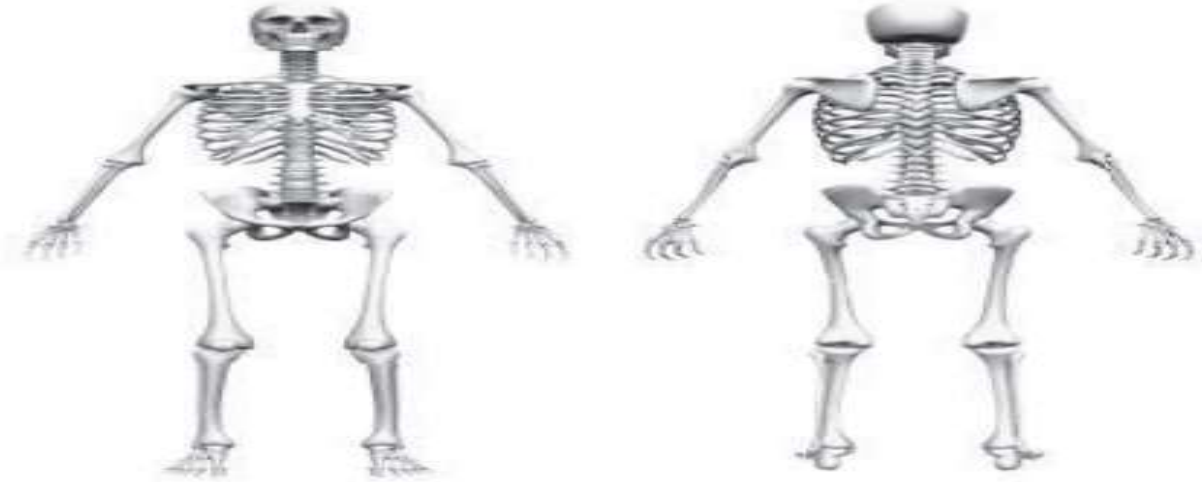
◯ Yes ◯ No

NOTE: If "NO", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check Region(s) of NEW Disease:

- ❑ Skull
- ❑ Thorax
- ❑ Spine
- ❑ Pelvis
- ❑ Extremities



If yes, indicate total number of NEW lesions compared to Baseline Scan (Date:___/___/___)

(select one)

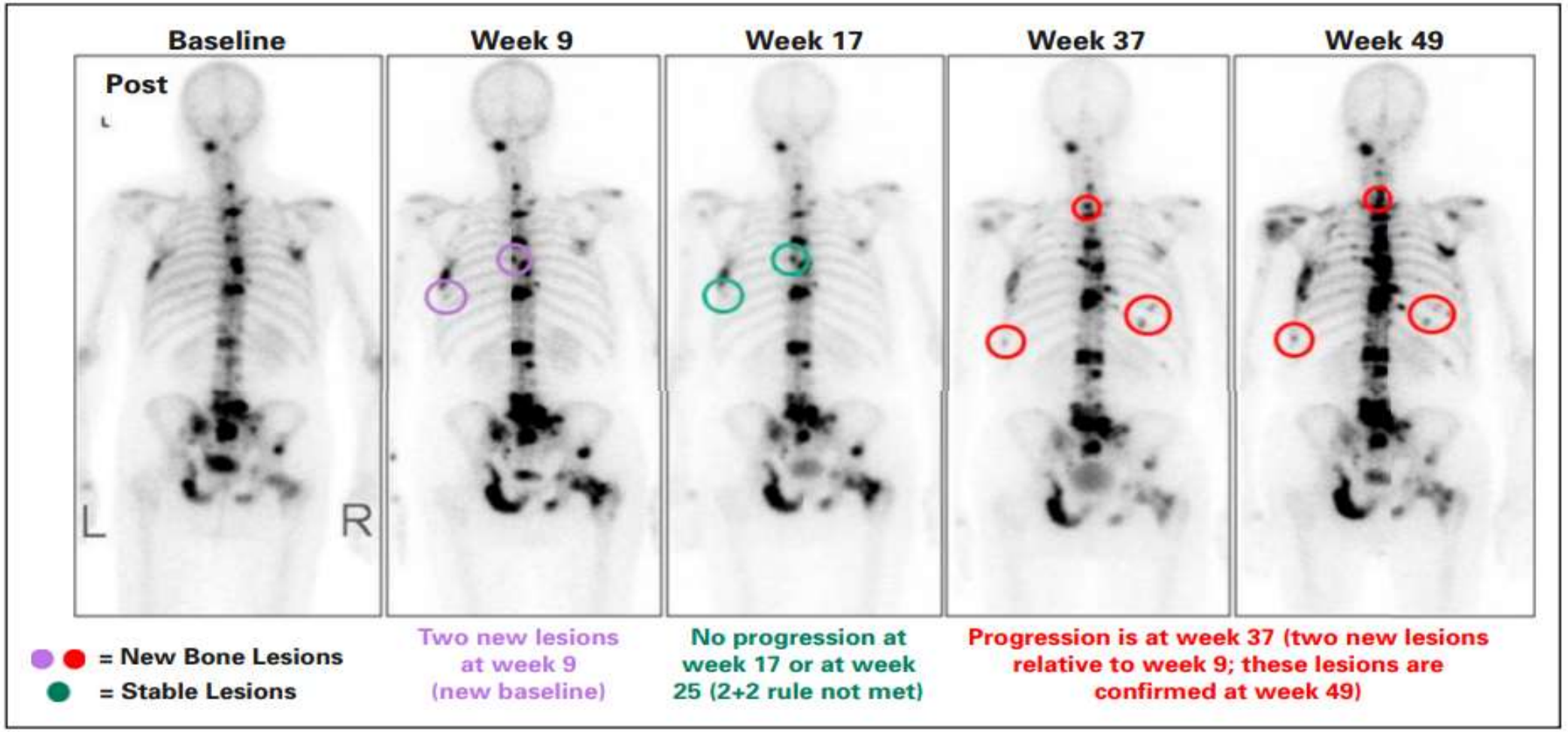
◯0 ◯1 ◯2 ◯3 ◯4 ◯5 ◯>5

*Presence of new lesions at this time does not confirm progression *

Clinical Impression (circle one)

◯ Improved ◯ Stable ◯ Progression

PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi



PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi

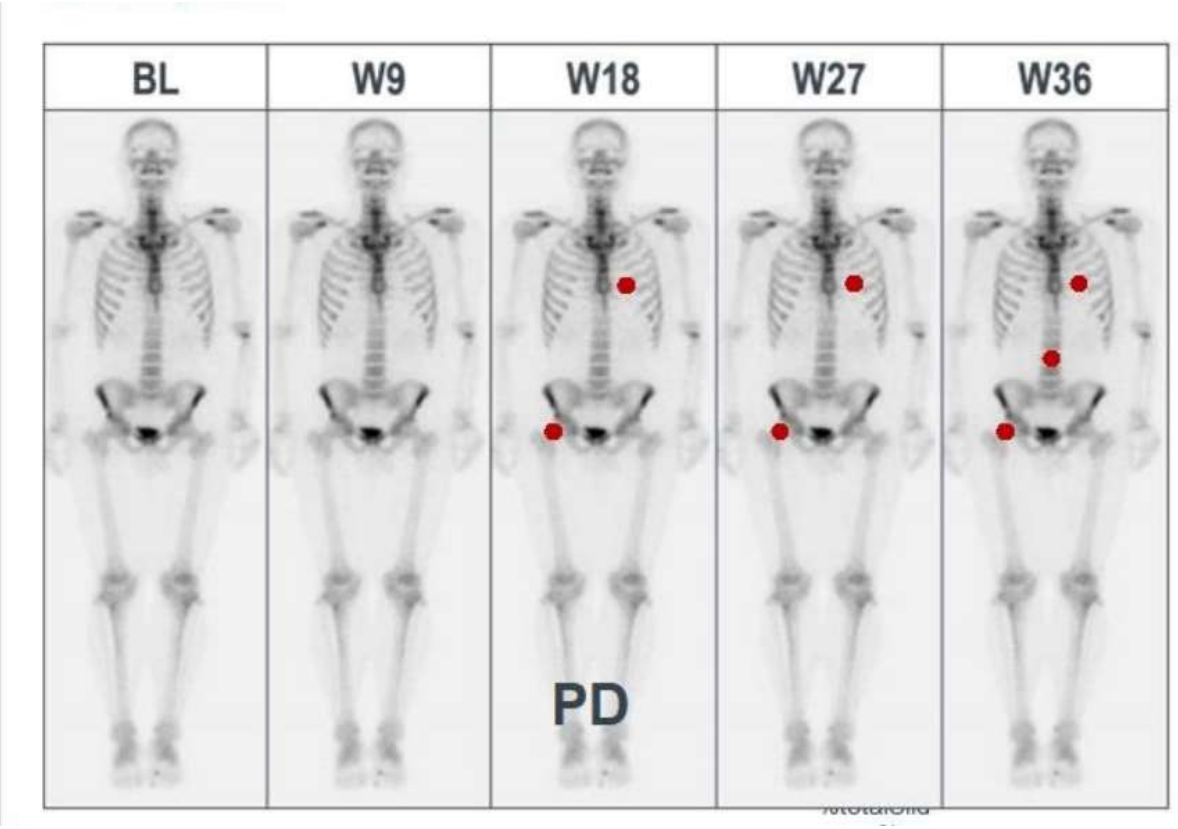
Bone PD

- PD
  - ≥2 new bone lesions
  - Not flare
  - Persistent

- Flare window: "2+2"
  - ✓ ≥2 new bone lesions in flare window +
  - ✓ ≥2 new bone lesions on next scan outside flare window
  - ❖ New lesions in flare window NOT confirmed as PD ignored on later scans

- Outside flare window
  - ≥2 new bone lesions, persistent on a second scan at least 6 weeks later
  - Need not appear on same visit

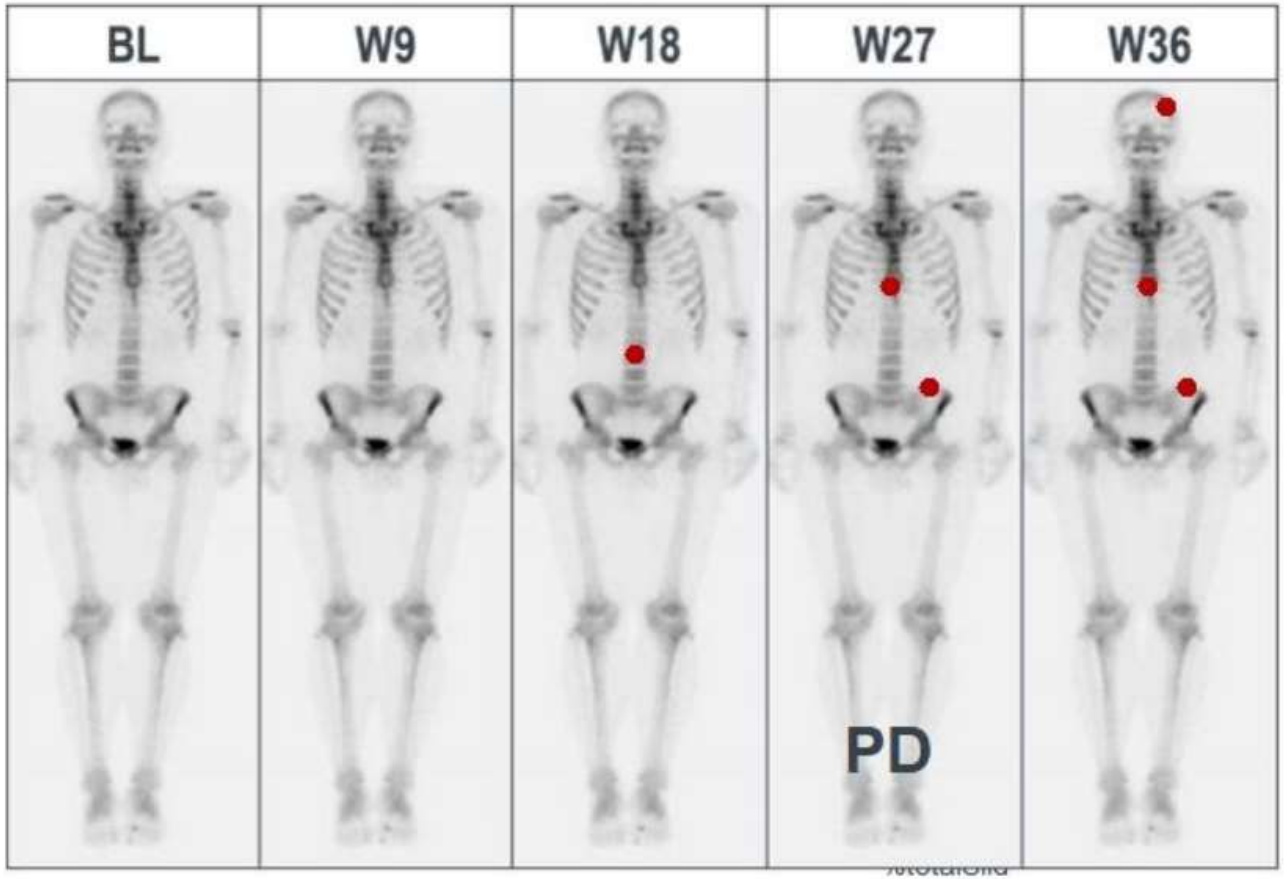
PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi



Explanation:

- 2 new lesions outside flare window (Wk 18). At Wk 18 this would be PDu.
- Wk 27, new lesions persist, so PD confirmed.
- PD timepoint changed to Wk 18.

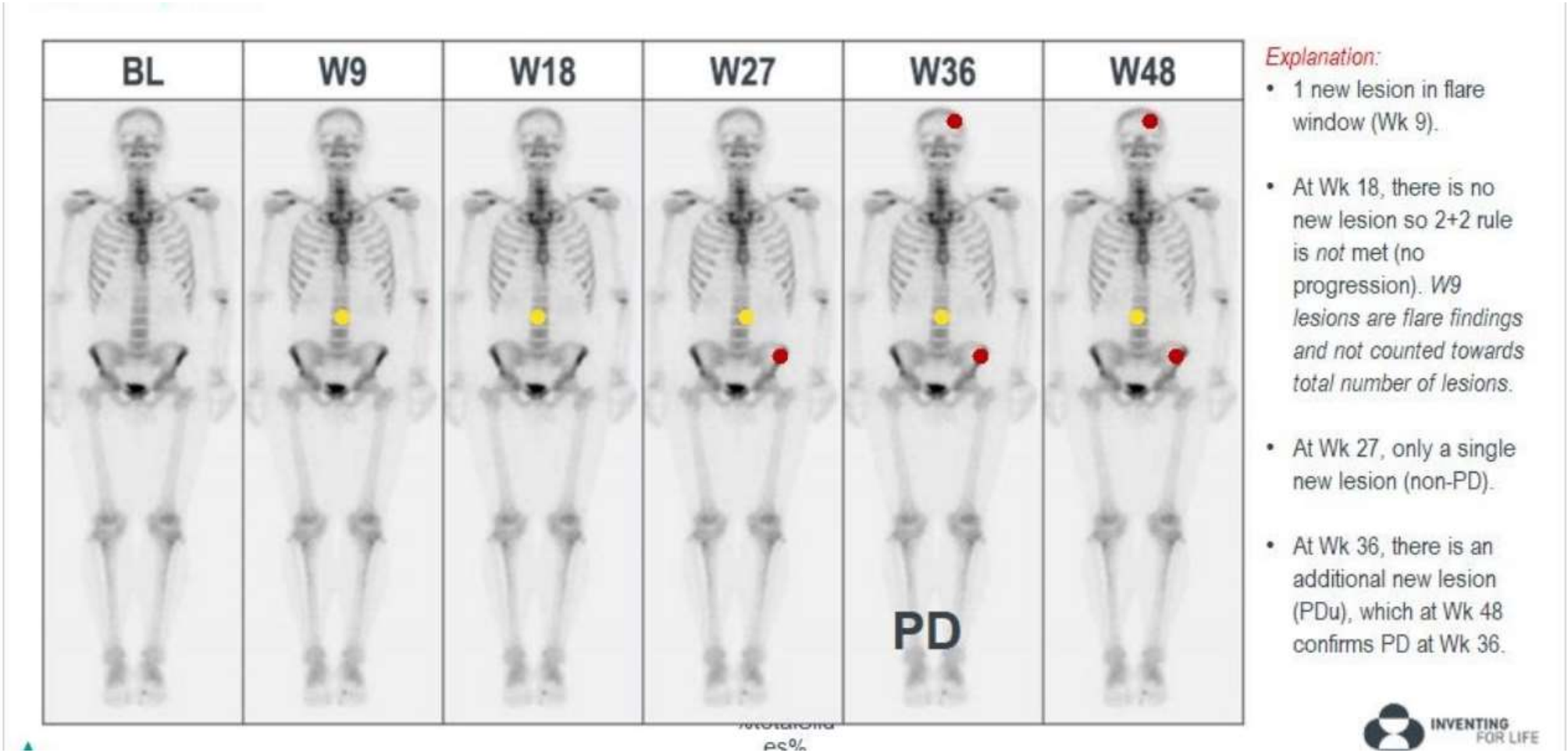
PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi



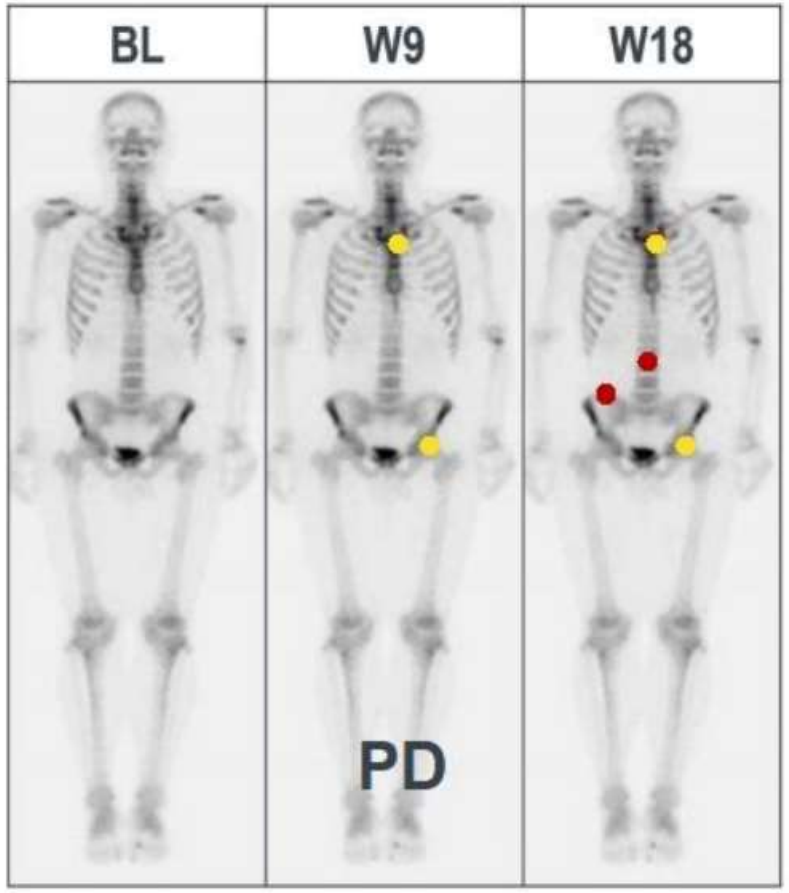
Explanation:

- 1 new lesion outside flare window does not meet requirement for PDu.
- At Wk 27, 2 new lesions (PDu), which persist at Wk 36.
- PD is confirmed. Timepoint of PD changed to Wk 27.

PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi



PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi

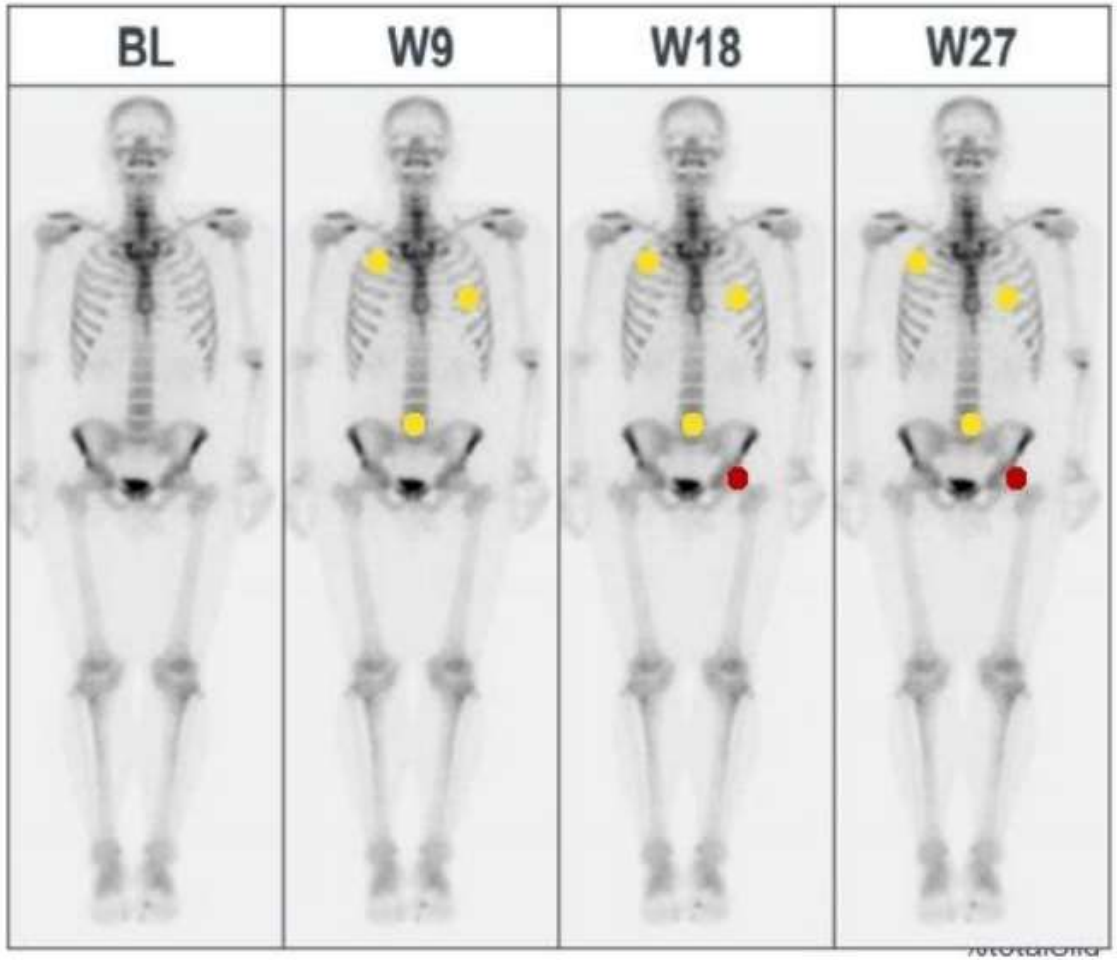


Explanation:

- Two new lesions in flare window at Wk 9 (PDu).
- At Wk 18, new lesions persist, and 2 additional new lesions.
- The **2+2 rule** is met and Wk 9 assessment changed to PD.

%current
Slide% of
%totalSlid

PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi

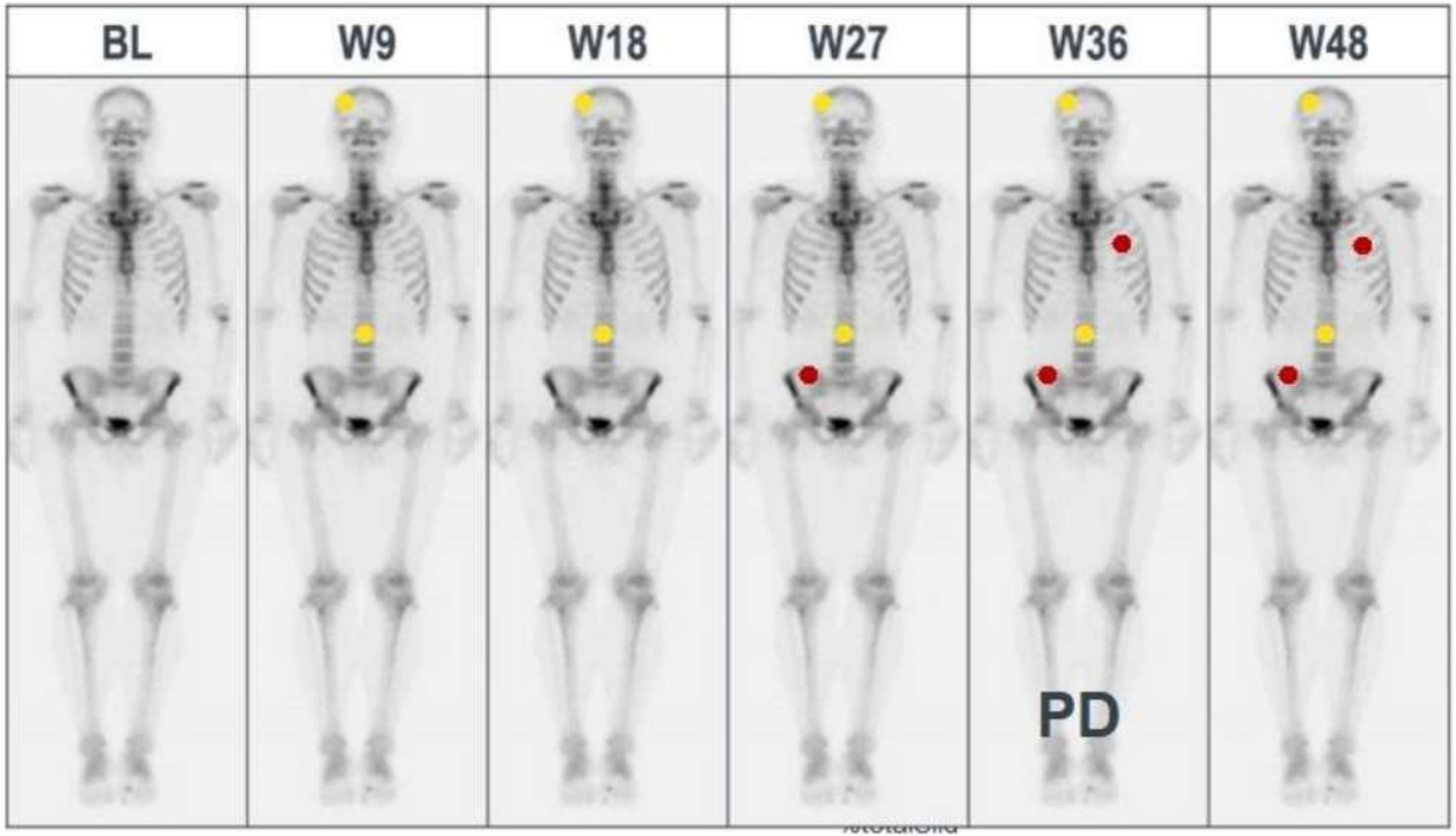


Non-PD

Explanation:

- ≥2 new lesions in flare window (Wk 9; PDu).
- At Wk 18, 1 new lesion; 2+2 rule is *not* met (no progression). *W9 lesions are thus flare, and not counted towards total number of lesions.*
- At Wk 27, only the single new lesion at Wk 18 is seen, so there is no PD.

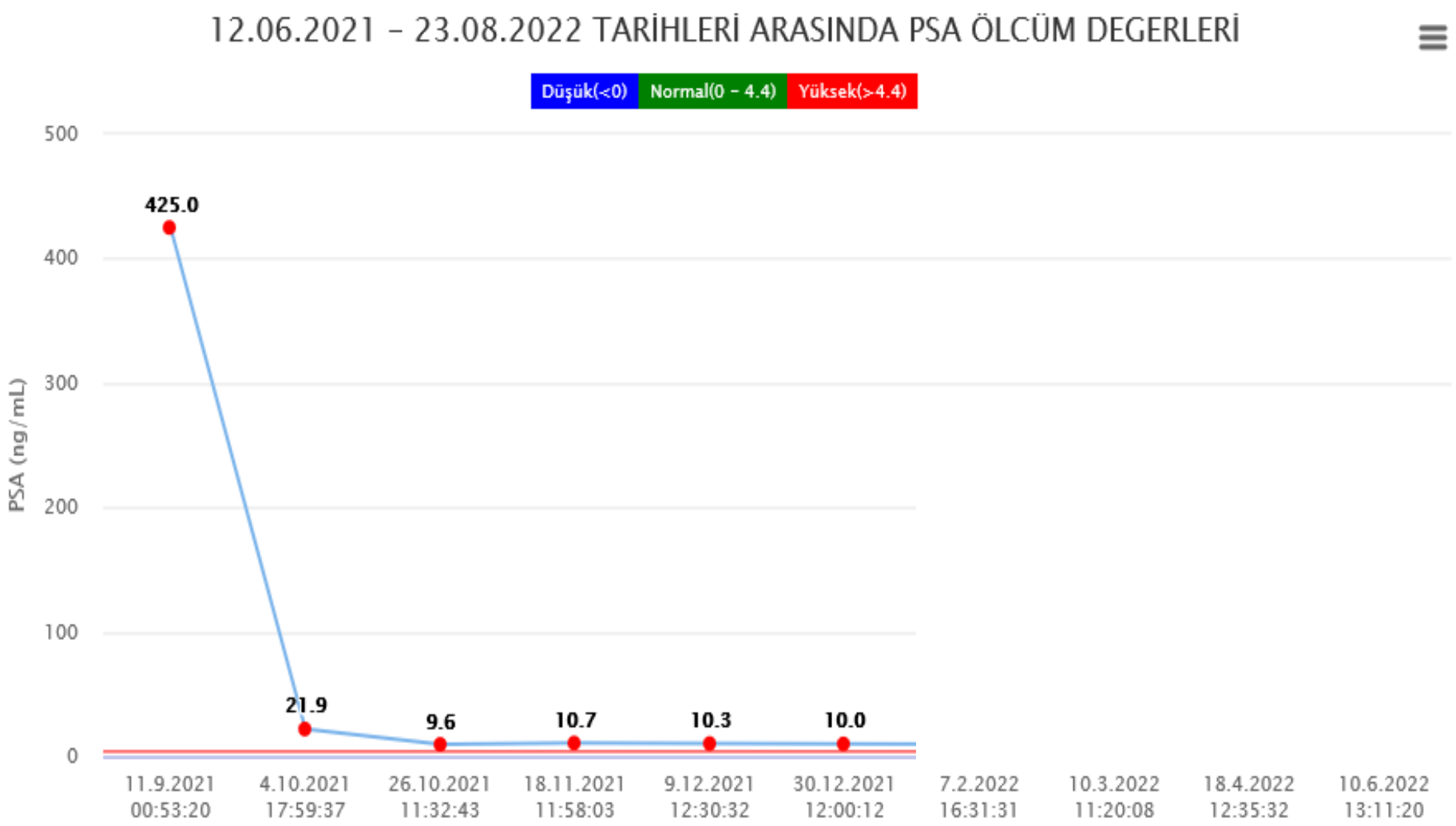
PCWG3 kriterlerine göre
Kemik metastazlarının değerlendirilmesi



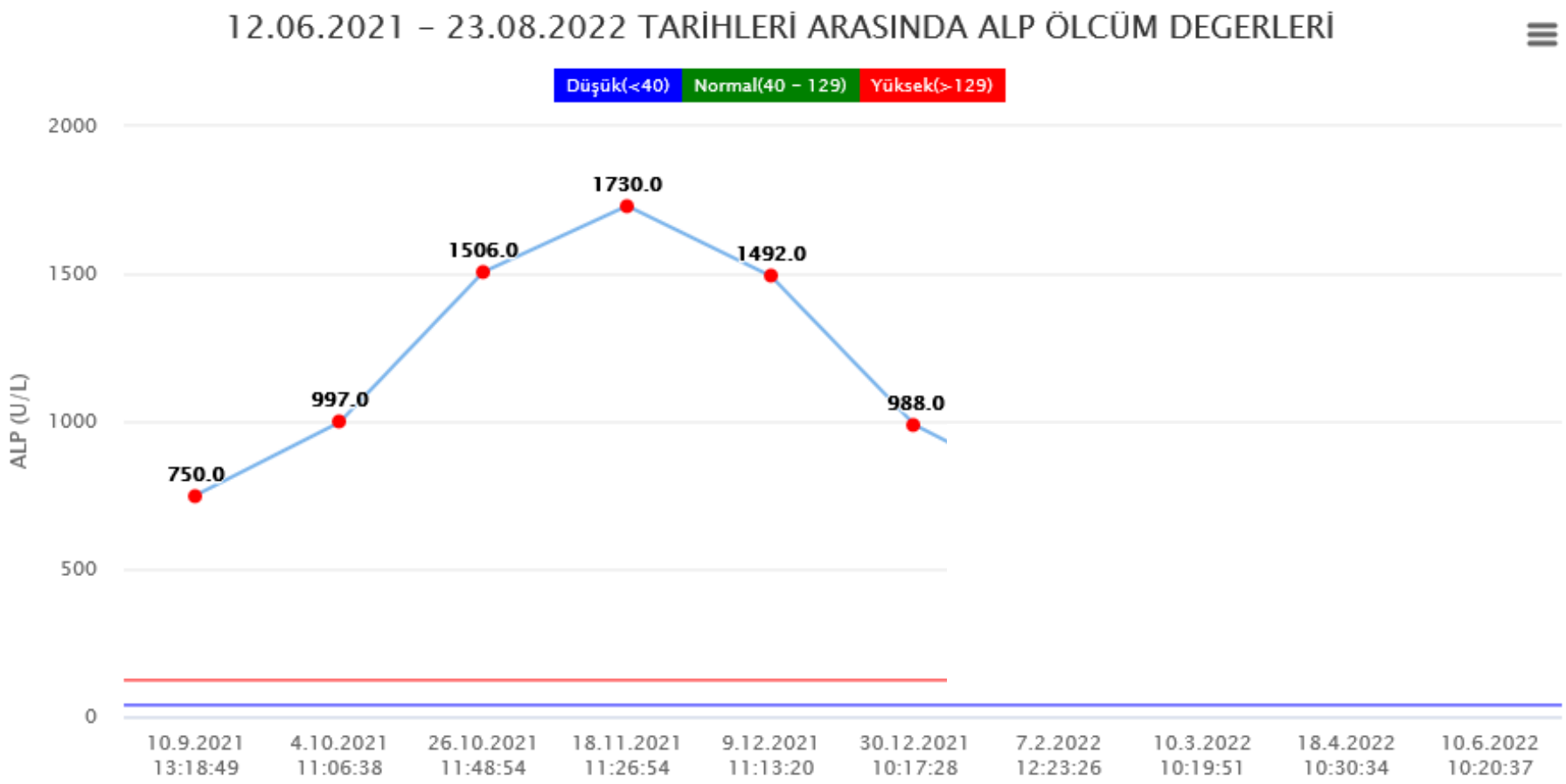
Explanation:

- ≥2 new lesions in flare window (Wk 9; PDu).
- At Wk 18, there is no new lesion so 2+2 rule is *not* met (no progression). *W9 lesions are flare findings and not counted towards total number of lesions.*
- At Wk 27, only a single new lesion at Wk 18 is seen, so there is no PD.
- At Wk 36, there is an additional new lesion (PDu), which at Wk 48 confirms PD at Wk 36.

Tedavi sonrası PSA yanıtı



Tedavi Sonrası ALP Düzeyi



PCWG2 kriterlerine göre PSA yanıtının değerlendirilmesi

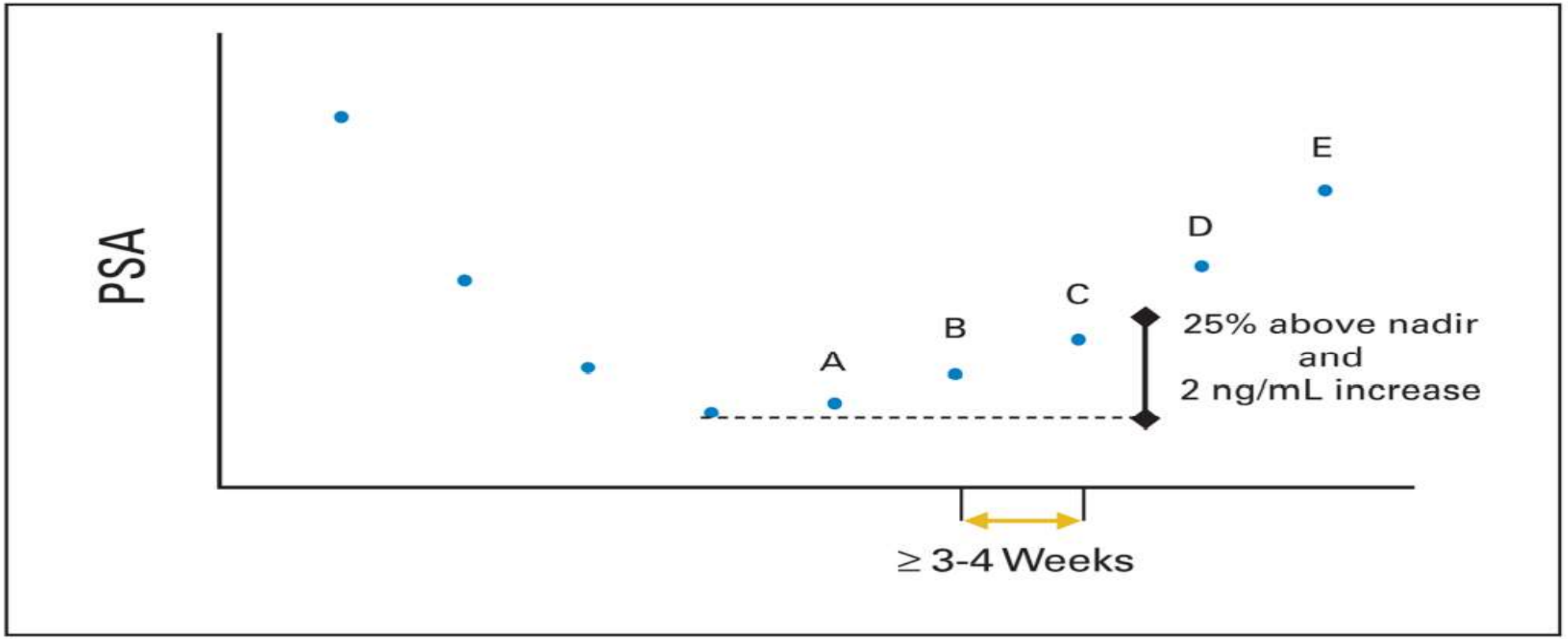


Fig. 4.
Prostate-specific antigen (PSA) progression. An increase of 25% and absolute increase of 2 ng/mL or more above the nadir. Values A, B, and C show rising PSA values that do not meet the criteria. Value D is the first PSA value that is greater than 25% and more than 2 ng/mL above the nadir, confirmed with a further rise in PSA shown by value E. For reporting purposes, PSA progression would be recorded on the date value D was obtained.

PCWG2 kriterlerine göre PSA yanıtının değerlendirilmesi

Variable	PCWG1 (1999)[1]	PCWG2 (2007)
PSA	Monitor PSA ≥ 1/month	Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression Ignore early rises (prior to 12 weeks) in determining PSA response
	PSA response: Defined a PSA partial response as a > 50% decline from baseline (measured twice 3 to 4 weeks apart)	**For control/relieve/eliminate end points:** Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot[32]*
	Progression: After decline from baseline: progression = 50% increase from nadir and an increase of at least 5 ng/mL, or back to baseline, whichever was lowest	**Progression:** **Decline from baseline**: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend)†
		The requirement of an increase of 5 ng/mL is decreased to 2 ng/mL, and the requirement for a 50% increase is reduced to 25%
	Record duration of PSA decline	Recording the duration of PSA decline of little value
		No decline from baseline: PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks

PSA progresyonu OS için surrogate belirteçmi

PFS as Significant Predictor of Overall Survival in Men With CRPC

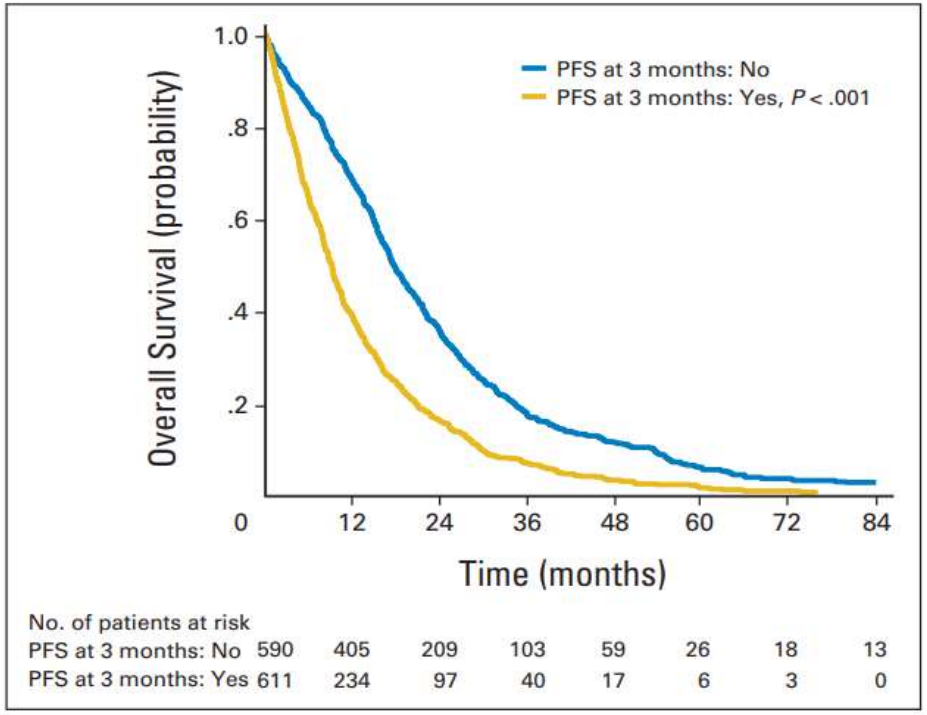


Fig 1. Kaplan-Meier survival curves by progression-free survival (PFS) at 3 months.

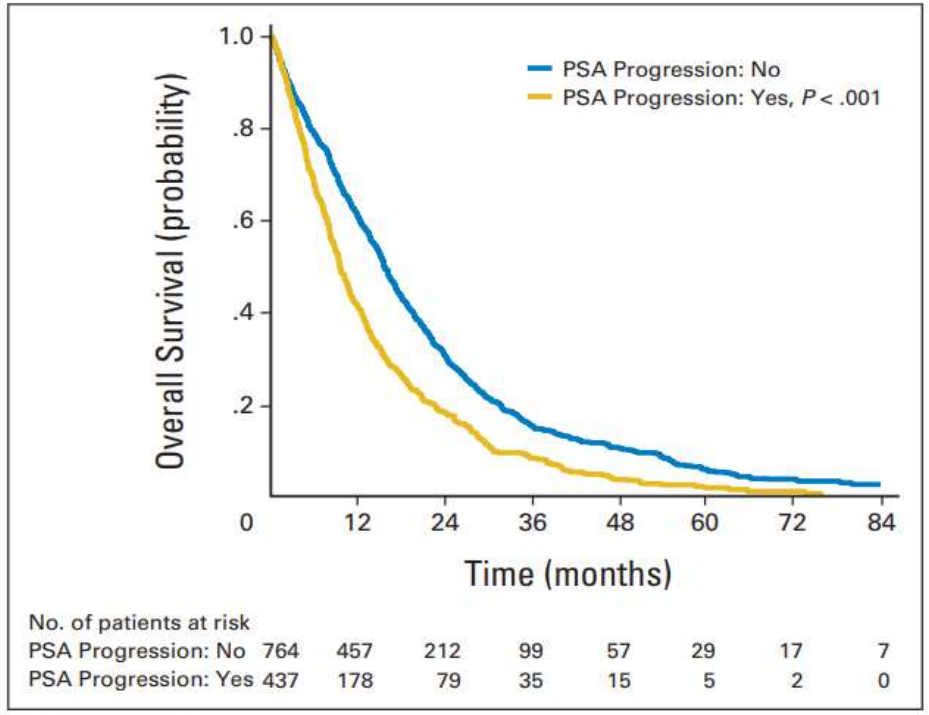


Fig 2. Kaplan-Meier survival curves by biochemical progression using Prostate-Specific Antigen Working Group 1999 Criteria (PSAWG1) at 3 months. PSA, prostate-specific antigen.

Halabi et al, J Clin Oncol 2009

Tedavi sonrası ideal PSA değeri ne olmalı

Overall Survival after Androgen Deprivation in New Metastatic Prostate Cancer

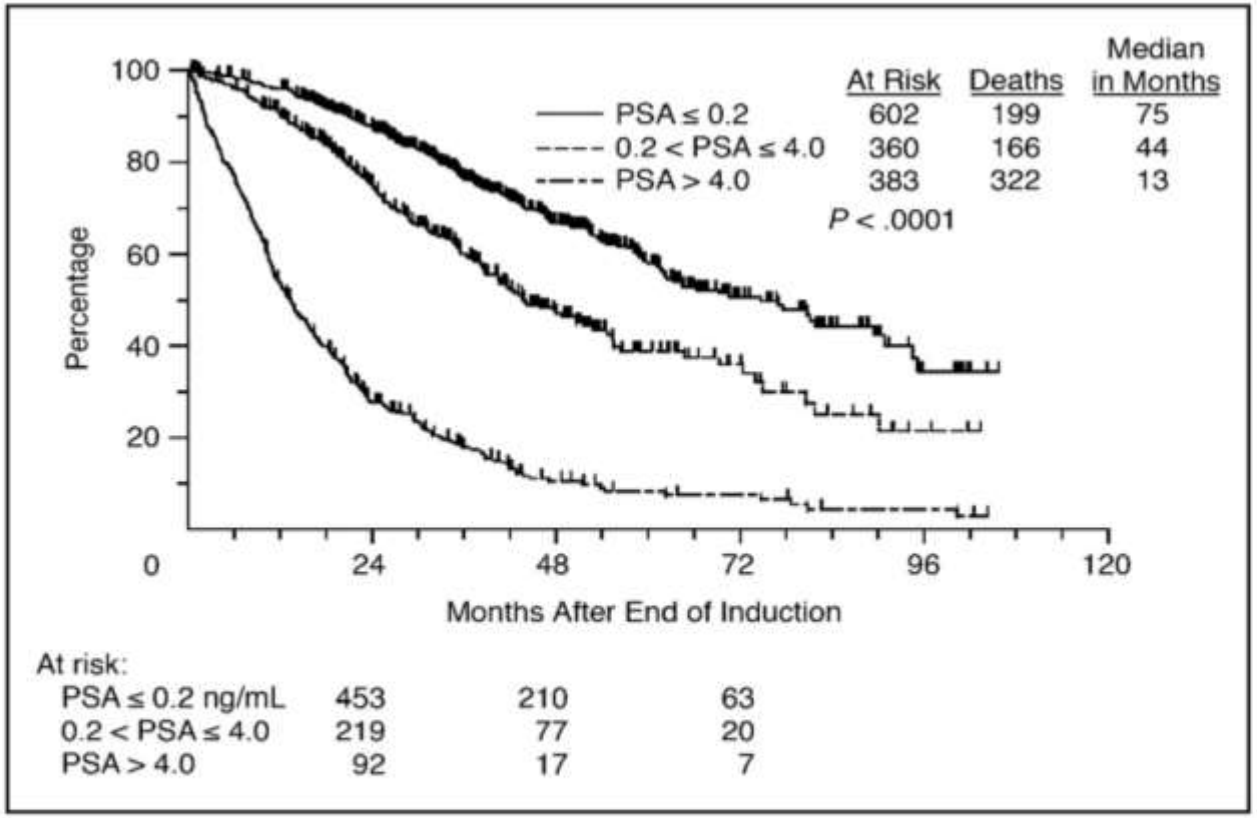


Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction
Maha Hussain: Journal of Clinical Oncology 2006; 24 3984-3990.

Courtesy of Simon Chowdhury, MD, PhD

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

POSTER 5072

RADIOGRAPHIC PROGRESSION IN THE ABSENCE OF PROSTATE-SPECIFIC ANTIGEN (PSA) PROGRESSION IN PATIENTS WITH METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC): *POST HOC* ANALYSIS OF ARCHES

ANDREW J. ARMSTRONG, MD, MSC,[1] NICOLAS MOTTET, MD, PHD,[2] TARO IGUCHI, MD, PHD,[3] RUSSELL Z. SZMULEWITZ, MD,[4] JEFFREY HOLZBEIERLEIN, MD,[5] ARNAULD VILLERS, MD, PHD,[6] ANTONIO ALCARAZ, MD, PHD,[7] BORIS ALEKSEEV, MD,[8] NEAL D. SHORE, MD,[9] FRANCISCO GOMEZ-VEIGA, MD, PHD,[10,*] BRAD ROSBROOK, MS,[11] FABIAN ZOHREN, MD, PHD,[11] HO-JIN LEE, PHD,[12] GABRIEL P. HAAS, MD,[12] ARNULF STENZL, MD,[13] ARUN A. AZAD, MBBS, PHD[14,†]

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*FRANCISCO GOMEZ-VEIGA WAS AFFILIATED WITH HOSPITAL UNIVERSITARIO DE SALAMANCA, GITUR-IBSAL DURING THE CONDUCT OF THE STUDY.
†ARUN A. AZAD WAS AFFILIATED WITH MONASH HEALTH DURING THE CONDUCT OF THE STUDY.

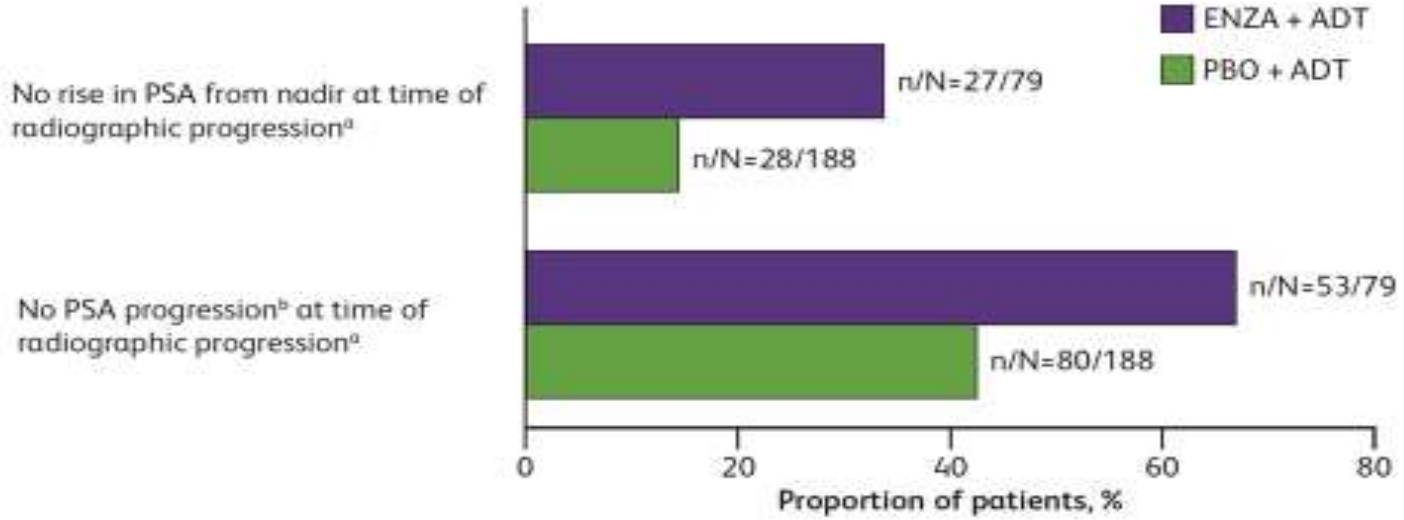
Presented at the 2022 American Society of Clinical Oncology Annual Meeting | June 3–7, 2022

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

Results

- At time of radiographic progression, most patients (67.1%) treated with enzalutamide plus ADT did not have PCWG2-defined PSA progression, while 34.2% did not have any rise in PSA from nadir (**Figure 1**)
- In comparison, 42.6% of those treated with placebo plus ADT did not have PCWG2-defined PSA progression, and 14.9% did not have any rise in PSA from nadir at time of radiographic progression
- Of the total study population, 9.2% (53/574) of patients treated with enzalutamide plus ADT and 13.9% (80/576) of patients treated with placebo plus ADT had radiographic progression without PCWG2-defined PSA progression

Figure 1. Co-occurrence of radiographic progression and increasing PSA



[a]Radiographic progression was assessed by independent central review or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurred first; [b]PSA progression was defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, confirmed by a second consecutive value at least 3 weeks later.

ADT=androgen deprivation therapy; ENZA=enzalutamide; PBO=placebo; PCWG2=Prostate Cancer Clinical Trials Working Group 2; PSA=prostate-specific antigen.

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

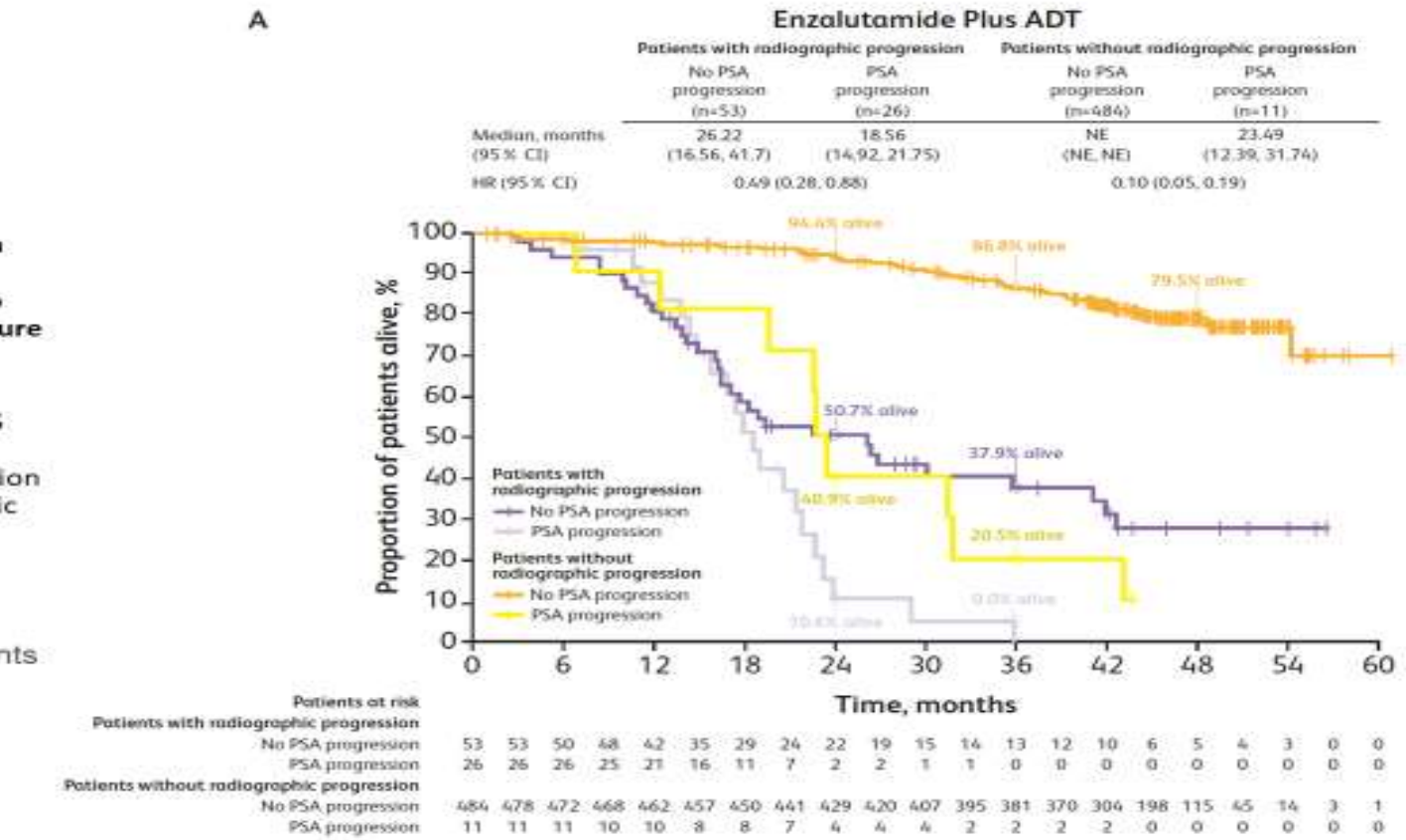
Results

Efficacy

- Patients who had radiographic progression had poorer survival outcomes in both treatment arms compared with those who did not have radiographic progression (**Figure 2**)
  - Of the patients treated with enzalutamide plus ADT, the median OS was shorter among patients with PSA progression and radiographic progression compared with those with radiographic progression only (**Figure 2A**)

Figure 2. Kaplan-Meier curves of OS by radiographic and PSA progression in patients treated with A) enzalutamide plus ADT

A



ADT=androgen deprivation therapy; CI=confidence interval; HR=hazard ratio; NE=not estimable; OS=overall survival; PSA=prostate specific antigen.

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

Eur Urol Oncol. 2020 December ; 3(6): 717–724. doi:10.1016/j.euo.2020.07.001.

Patterns of Cancer Progression of Metastatic Hormone-sensitive Prostate Cancer in the ECOG3805 CHAARTED Trial

Alan H. Bryce[a,*], Yu Hui Chen[b], Glenn Liu[c], Michael A. Carducci[d], David M. Jarrard[e], Jorge A. Garcia[f], Maha Hussain[g], Mario Alfredo Eisenberger[h], Elizabeth R. Plimack[i], Nicholas J. Vogelzang[j], Robert S. DiPaola[k], Lauren Harshman[l], Christopher J. Sweeney[l]

[a]Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ, USA

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

Disease progression pattern by treatment arm and disease volume

Disease progression pattern	High volume		Low volume	
	ADT + D	ADT alone	ADT + D	ADT alone
Concurrent PSA PD and clinical PD [a], *n* (%)	18 (9.5)	28 (13.2)	8 (11.9)	3 (3.4)
PSA PD first and then clinical PD [b], *n* (%)	81 (42.6)	96 (45.1)	23 (34.3)	38 (42.7)
PSA PD only [c], *n* (%)	48 (25.3)	37 (17.4)	15 (22.4)	24 (27.0)
Clinical PD only [d], *n* (%)	43 (22.6)	52 (24.4)	21 (31.3)	24 (27.0)
Total	190	213	67	89

ADT = androgen deprivation therapy; D = docetaxel; PD = progressive disease; PSA = prostate-specific antigen.

[a] PSA PD and clinical PD were observed within a month (including 32 patients with onset of PSA PD observed within 1 mo of clinical PD but subsequent PSA to confirm that progression was not available).

[b] PSA PD was observed at least 1 mo prior to clinical progression (including 21 patients with onset of PSA PD observed at least 1 mo prior to clinical progression but subsequent PSA to confirm that progression was not available).

[c] Patients experienced PSA PD, but clinical PD has not been observed yet.

[d]

Bryce A at al, Eur Urol Oncol. 2020

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

	Clinical PD first		Current PSA and clinical PD PSA PD then clinical PD PSA PD only	
	N = 140 %	%	*N* = 419 %	%
N	76		226	
Number of events	76		165	
Median (mo)	8.5		17.8	
95% CI	(5.7, 11.3)		(14.2, 20.1)	

ADT = androgen deprivation therapy; CI = confidence interval; PD = progressive disease; PSA = prostate-specific antigen; QOL = quality of life.

[a] Only patients with first disease progression observed at least 6 mo after randomization were included in the analysis.

[b] Only patients with first disease progression observed at least 12 mo after randomization were included in the analysis.

[c] As QOL assessment was administered at baseline, and at 3, 6, 9, and 12 mo, only patients with baseline QOL assessment available and follow-up QOL assessment administered within 4 mo prior to first disease progression were included in this analysis. There are 70 and 212 patients meeting the criterion in the "clinical PD first" and "other" categories, respectively.

[d] QOL change is defined as change in the FACT-P total score from baseline to the follow-up visit prior to disease progression. For example, a patient with disease progression at 8 mo has QOL change calculated as follows: FACT-P total score at 6 mo – FACT-P total score at baseline.

[e] $p = 0.14$ by Wilcoxon rank-sum test.

[f] Time to clinical progression is defined as the time from randomization to clinical progression. Patients without clinical progression were censored at the date of last disease assessment.

Bryce A at al, Eur Urol Oncol. 2020

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

OPEN

Prostate Cancer and Prostatic Diseases (2017) 20, 221–227
www.nature.com/pcan

ORIGINAL ARTICLE

Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: *post hoc* analysis of PREVAIL

AH Bryce[1], JJ Alumkal[2], A Armstrong[3], CS Higano[4], P Iversen[5], CN Sternberg[6], D Rathkopf[7], Y Loriot[8], J de Bono[9], B Tombal[10], S Abhyankar[11,15], P Lin[12], A Krivoshik[13], D Phung[14] and TM Beer[2]

BACKGROUND: Advanced prostate cancer is a phenotypically diverse disease that evolves through multiple clinical courses. PSA level is the most widely used parameter for disease monitoring, but it has well-recognized limitations. Unlike in clinical trials, in practice, clinicians may rely on PSA monitoring alone to determine disease status on therapy. This approach has not been adequately tested.
METHODS: Chemotherapy-naive asymptomatic or mildly symptomatic men ($n = 872$) with metastatic castration-resistant prostate cancer (mCRPC) who were treated with the androgen receptor inhibitor enzalutamide in the PREVAIL study were analyzed *post hoc* for rising versus nonrising PSA (empirically defined as > 1.05 vs $\leqslant 1.05$ times the PSA level from 3 months earlier) at the time of radiographic progression. Clinical characteristics and disease outcomes were compared between the rising and nonrising PSA groups.
RESULTS: Of 265 PREVAIL patients with radiographic progression and evaluable PSA levels on the enzalutamide arm, nearly one-quarter had a nonrising PSA. Median progression-free survival in this cohort was 8.3 months versus 11.1 months in the rising PSA cohort (hazard ratio 1.68; 95% confidence interval 1.26–2.23); overall survival was similar between the two groups, although less than half of patients in either group were still at risk at 24 months. Baseline clinical characteristics of the two groups were similar.
CONCLUSIONS: Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients treated with enzalutamide. As restaging in advanced prostate cancer patients is often guided by increases in PSA levels, our results demonstrate that disease progression on enzalutamide can occur without rising PSA levels. Therefore, a disease monitoring strategy that includes imaging not entirely reliant on serial serum PSA measurement may more accurately identify disease progression.

PSA progresyonu olmayan hastalarda radyolojik değerlendirme aralığı

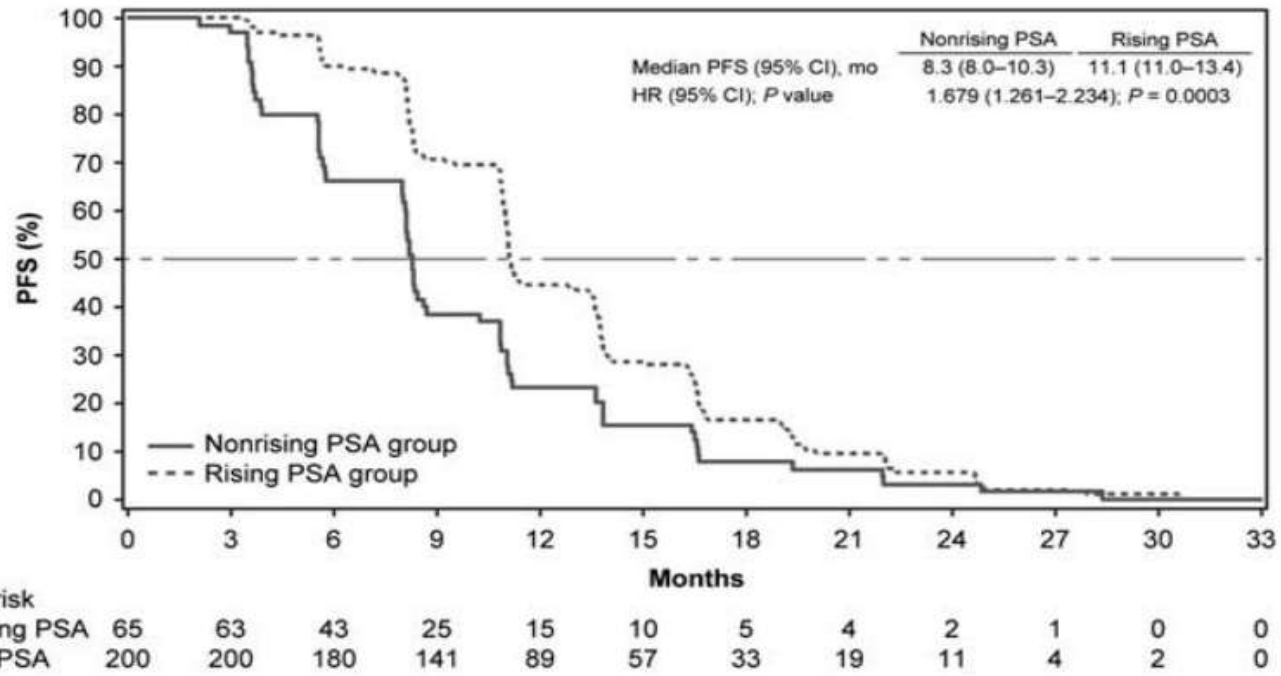


Figure 1. Kaplan–Meier estimates of progression-free survival. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Metastatik Kastrasyona Duyarlı Prostat Kanserinde Tedaviye Yanıt Değerlendirmesi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer

NCCN Guidelines Index
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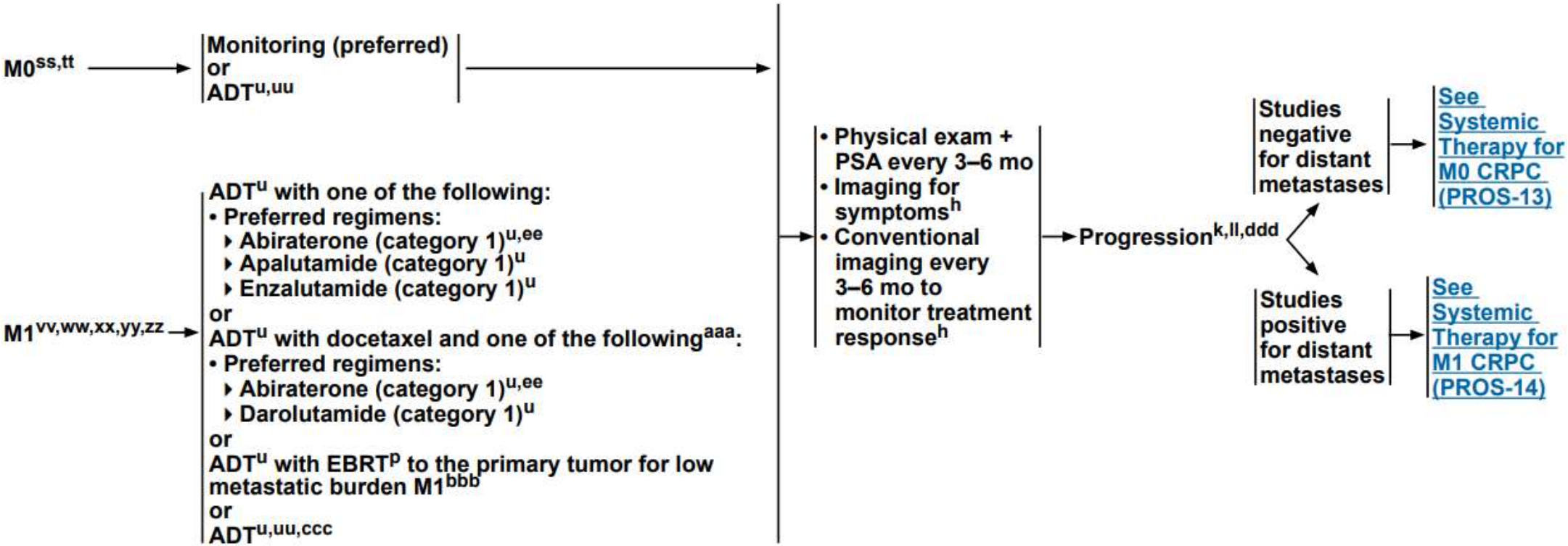
Discussion

SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER[rr]



PSMA PET-CT

Comparison of RECIST 1.1, PCWG3, and PPP Tumor Response Criteria

Pattern of Response	RECIST 1.1 (1)	PCWG3 (10)	PPP Criteria (37)
Progressive disease	Appearance of new lesions, ≥20% increase in the sum of length diameters of target lesions, or unequivocal increase of non-target lesions	Development of new lesions or growth of preex-isting lesions	Appearance of two new PSMA-positive lesions, one new PSMA-positive lesion plus clinical or laboratory data consistent with progression,* or ≥30% increase in size or uptake plus clinical or laboratory data consistent with progression*
Bone lesions	Nonmeasurable	Nonmeasurable	Target (if PSMA positive)
Standard imaging modality	CT or MRI	CT or MRI; bone scanning	PSMA PET
Target	Nodes >15 mm, tumors >10 mm	Similar to those listed in the RE-CIST 1.1 column	Any PSMA-positive lesion
Nontarget	Nodes 10–15 mm, tumors <10 mm, bone lesions, simple cystic lesions, malignant brain tumors, nonmeasurable lesions (leptomeningeal disease, asci-tes, effusions, and lymphan-gitic spread)	Similar to those listed in the RE-CIST 1.1 column	Not applicable
Maximum number of lesions	Up to two lesions per organ, up to five lesions per examination	Up to five lesions per organ	Not applicable
Imaging intervals	6–8 weeks	8–12 weeks	6–9 weeks

Note.—PPP = PSMA PET Progression. Numbers in parentheses are references.
*Confirmation required by biopsy results or other imaging modality findings.

Barbosa F, RadioGraphics 2020

PSMA PET-CT

PPP Criteria

Progression criterion	Explanation
2 or more new PSMA-positive lesions	Appearance of 2 or more new PSMA-positive distant lesions
1 new PSMA-positive lesion	Appearance of 1 new PSMA-positive lesion plus consistent clinical or laboratory data and recommended confirmation by biopsy or correlative imaging within 3 mo of PSMA PET
No new lesions but size increase	Increase by ≥30% in size or uptake plus consistent clinical or laboratory data and confirmation by biopsy or correlative imaging within 3 mo of PSMA PET

Sonuç

- Evre IV Kastrasyona duyarlı prostat kanserinde yanıt RECIST 1.1 ve PCWG3 kriterlerine göre yapılır
- Değerlendirme BT/MR ve TVS kullanılır
- Flare dönemi(12 hafta≤) TVS'de 2 ≥lezyon ve 6-8 hafta sonra +2≥ konfirme edilmesi durumunda progresyon kabul edilir(2+2 kuralı)
- Flare döneminde, PSA ve ALP artışı progresyon olarak kabul edilmez ≥12 hafta sonrası değerler yanıt için kullanılır
- Flare dönemi dışında 2 ≥lezyon ve 6-8 hafta sonra bu lezyonlar konfirme edilmişse progresyon olarak kabul edilir
- PSA yanıtı olan, semptom olmayan hastalarda 3-6 ay aralığında radyolojik değerlendirme önerilir
- PSA progresyonu(PCWG2 kriterleri) tedavi değiştirmek için yeterli olmamakla beraber, genel olarak radyolojik progresyonun öncüsü ve kötü gidişle ilişkilidir.
- Ağrı ve diğer semptomların varlığı tedaviye yanıt ve prognoz öngörmede yardımcı olabilir.
- PSMA-PET için daha çok çalışmaya ihtiyaç vardır ve tedavi yaklaşımını değiştirmeyecekse rutin önerilmez