

#### RESPONSABILI SCIENTIFICI

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#### CREDITI ECM

Il corso ha ottenuto nr. 5,2 crediti ECM per  
Farmacista Ospedaliero; Medico Chirurgo,  
Specialità: Oncologia; Radioterapia; Urologia;  
Medicina Nucleare; Fisica Sanitaria.

#### PROVIDER ECM E SEGRETERIA ORGANIZZATIVA



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#### OBIETTIVO FORMATIVO

Linee guida, protocolli, procedure

CON LA SPONSORIZZAZIONE NON CONDIZIONANTE DI



## Indicazioni cliniche all'utilizzo della **Targeted Alpha Therapy** nel carcinoma prostatico

# 26 GIUGNO 2019

DALLE 15.30 ALLE 20.00

## MILANO

HOTEL GLAM  
Piazza Duca D'Aosta, 4/6

**HUMANITAS**  
UNIVERSITY

L'esperienza con radio 223 dell'Istituto  
Humanitas di Rozzano  
**M. Rodari, P.A. Zucali**

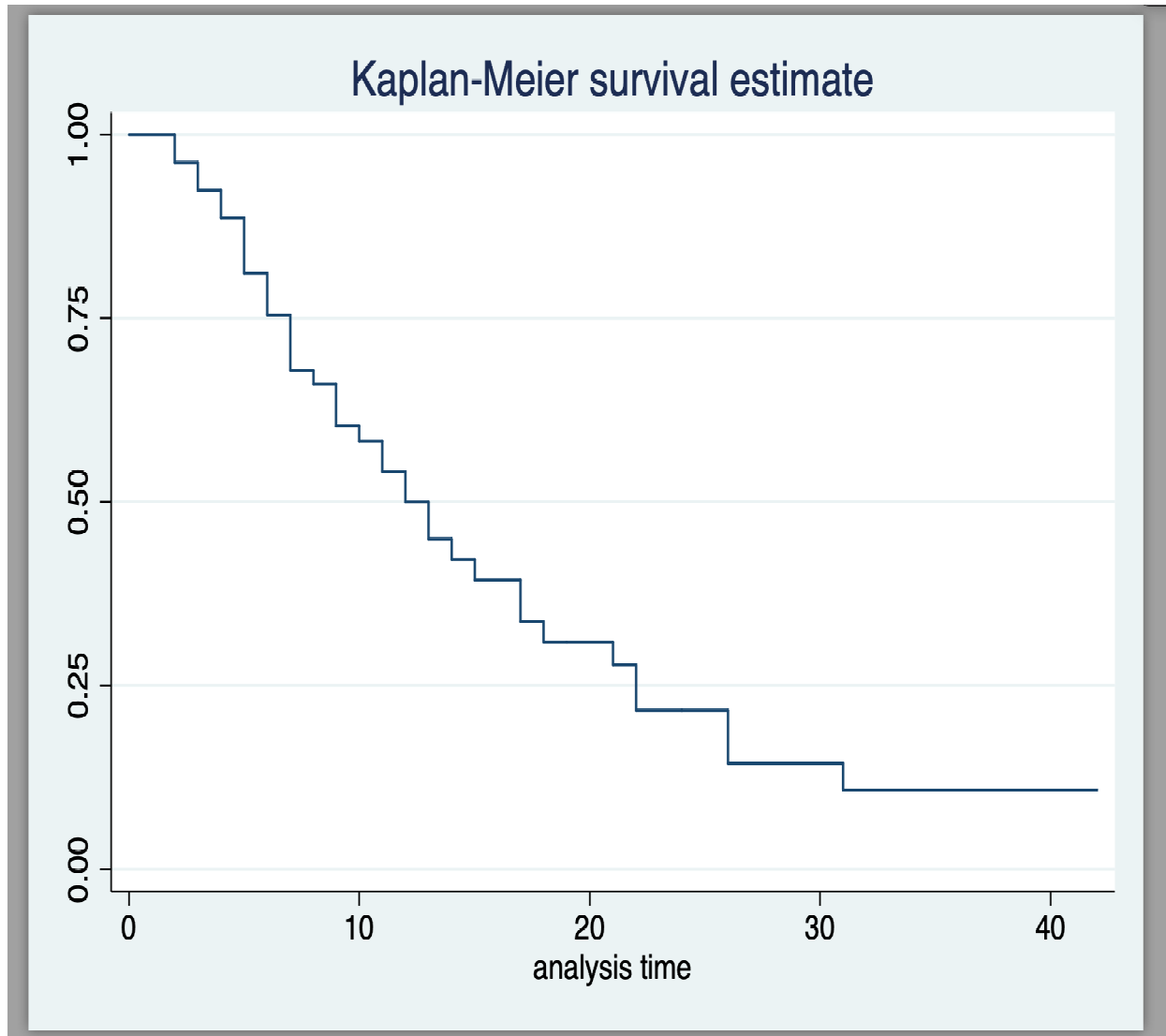
# Casistica Humanitas

Inizio terapia	Luglio 2015
Numero pazienti	60
Età media	73
Numero pazienti per analisi statistica	54 (10 pazienti ancora vivi)
Numero totale cicli di trattamento	258
Numero medio di cicli per paziente	4.4
Emoglobina media	11.4 g/dl
PSA medio	304.1 ng/ml

## Tempistica Esecuzione 223-Radio

1	BAT	11
2	BAT + CT	10
	BAT + Abiraterone	12
	BAT + Enzalutamide	4
3	BAT + Abiraterone + CT	5
	BAT + Abiraterone + Enzalutamide	5
	BAT + Abiraterone + Enzalutamide + CT	4
	BAT + Abiraterone + Enzalutamide + 2 CT	3

# Sopravvivenza



. mean sopravvivenza

Mean estimation                      Number of obs   =        53

	Mean	Std. Err.	[95% Conf. Interval]	
sopravvivenza	13.15094	1.314041	10.51413	15.78776

# The NEW ENGLAND JOURNAL of MEDICINE

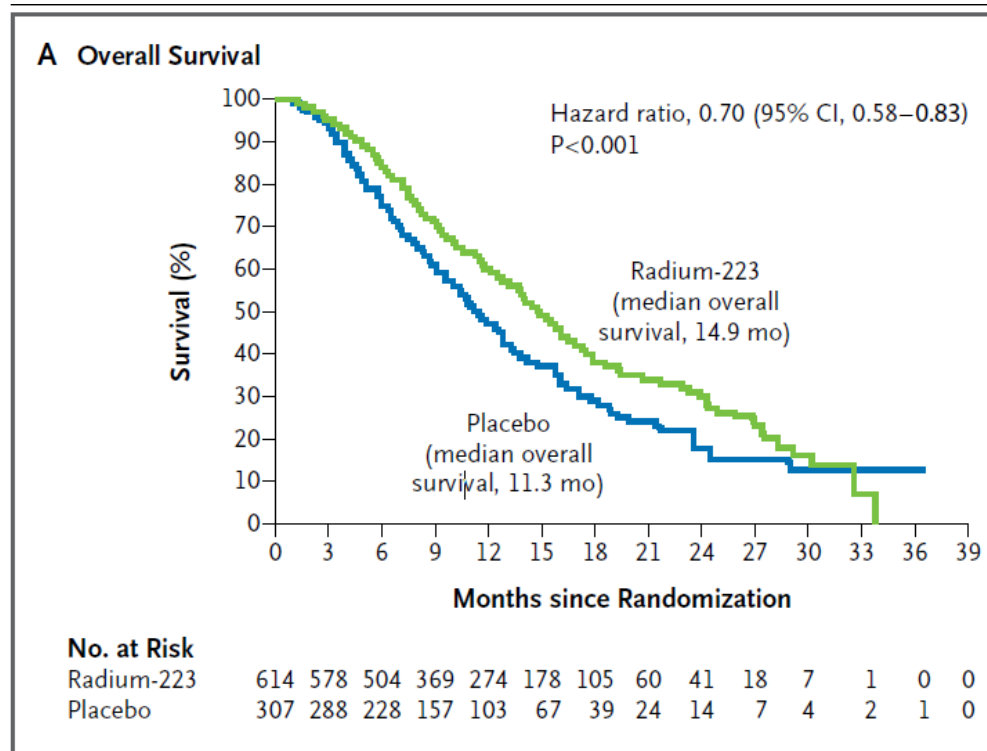
ESTABLISHED IN 1812

JULY 18, 2013

VOL. 369 NO. 3

## Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fossà, 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\*

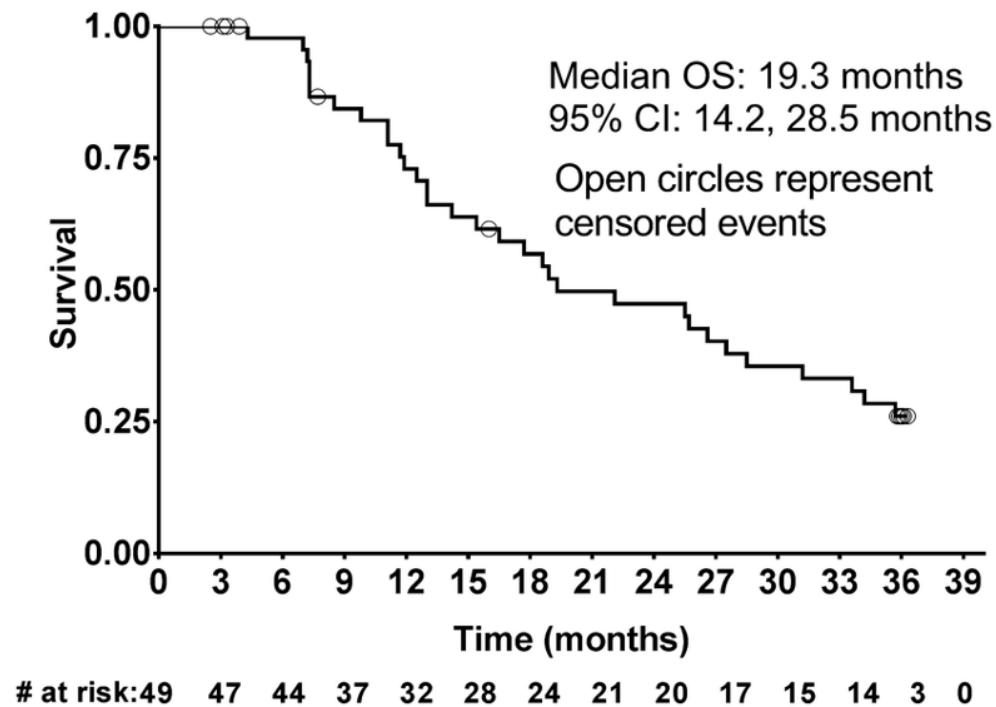




## Three-year follow-up of a phase II study of radium-223 dichloride in Japanese patients with symptomatic castration-resistant prostate cancer and bone metastases

Hirotsugu Uemura<sup>1</sup> · Hiroji Uemura<sup>2</sup> · Satoshi Nagamori<sup>3</sup> · Yoshiaki Wakumoto<sup>4</sup> · Go Kimura<sup>5</sup> · Hiroaki Kikukawa<sup>6</sup> · Akira Yokomizo<sup>7</sup> · Atsushi Mizokami<sup>8</sup> · Takeo Kosaka<sup>9</sup> · Naoya Masumori<sup>10</sup> · Yoshihide Kawasaki<sup>11</sup> · Junji Yonese<sup>12</sup> · Yasutomo Nasu<sup>13</sup> · Satoshi Fukasawa<sup>14</sup> · Takayuki Sugiyama<sup>15</sup> · Seigo Kinuya<sup>16</sup> · Makoto Hosono<sup>16</sup> · Iku Yamaguchi<sup>17</sup> · Takashi Akagawa<sup>18</sup> · Nobuaki Matsubara<sup>19</sup>

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# Caratteristiche pazienti - extent of disease no. (%)

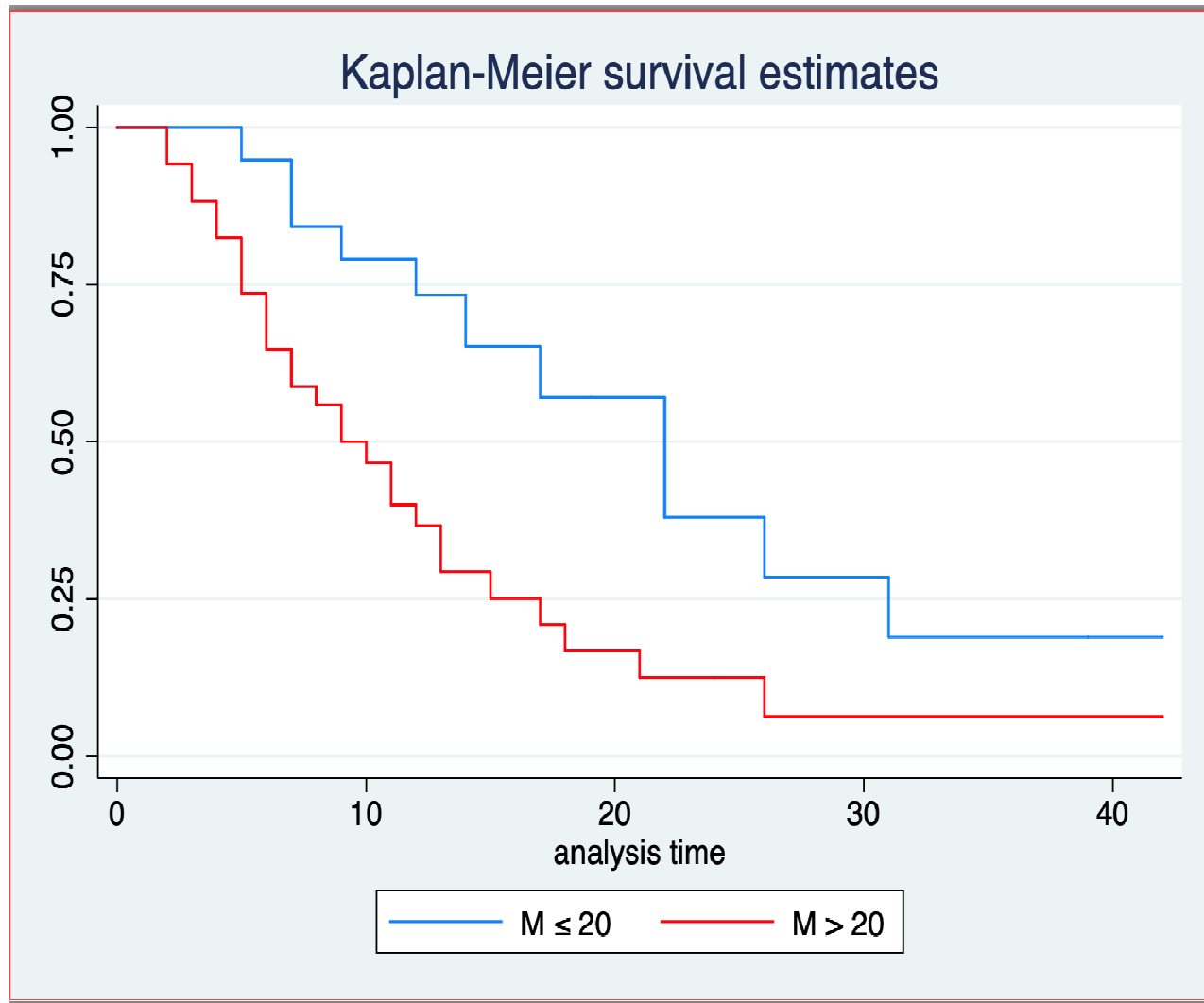
## ALSYMPCA study

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Radium-223 (N=614)	Placebo (N=307)
Extent of disease — no. (%)		
<6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
>20 metastases	195 (32)	91 (30)
Superscan¶	54 (9)	30 (10)
External-beam radiation therapy within 12 wk after screening — no. (%)		
Yes	99 (16)	48 (16)
No	515 (84)	259 (84)
Median biochemical values (range)		
Hemoglobin — g/dl	12.2 (8.5–15.7)	12.1 (8.5–16.4)
Albumin — g/liter	40 (24–53)	40 (23–50)
Total alkaline phosphatase — U/liter	211 (32–6431)	223 (29–4805)
Lactate dehydrogenase — U/liter	315 (76–2171)	336 (132–3856)
PSA — µg/liter	146 (3.8–6026)	173 (1.5–14500)

< 6 metastasi	4 (7)
6-20 metastasi	15 (28)
> 20 metastasi	33 (49)
Superscan	<b>9 (16)</b>
Emoglobina media	11.4 g/dl
Fosfatasi alcalina totale media	299 U/L
PSA medio	304.1 ng/ml

# Sopravvivenza secondo diffusione di malattia (> o < 20 M+)



```
. stsum, by(M_status)
```

```
failure_d: Exitus == 1
analysis time_t: sopravvivenza
```

M_status	time at risk	incidence rate	no. of subjects	Survival time		
				25%	50%	75%
0	330	.0333333	19	12	22	31
1	367	.0762943	34	5	9	17
total	697	.0559541	53	7	12	22

```
. sts test M_status, logrank
```

```
failure_d: Exitus == 1
analysis time_t: sopravvivenza
```

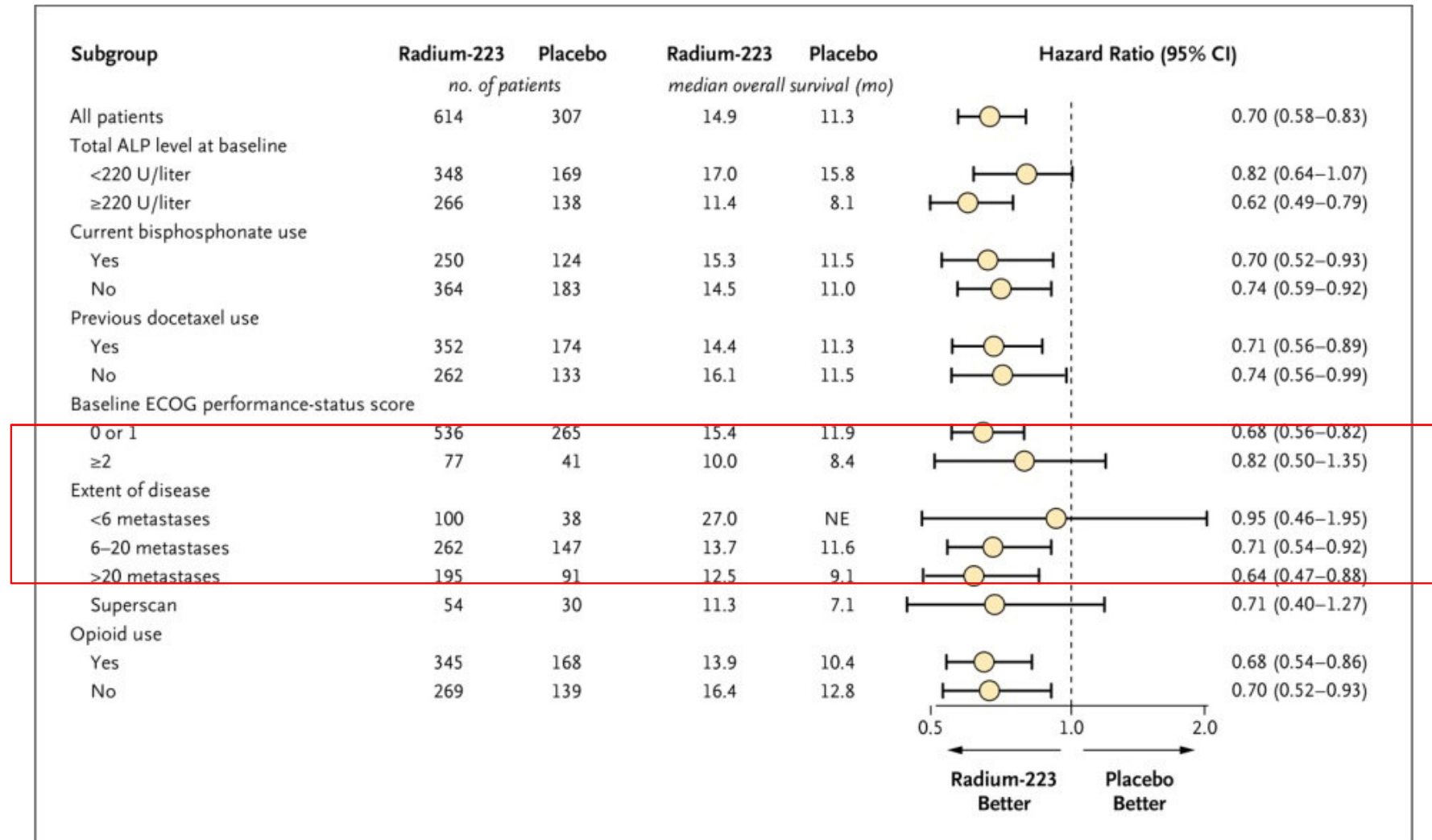
Log-rank test for equality of survivor functions

M_status	Events	
	observed	expected
0	11	19.12
1	28	19.88
Total	39	39.00

```
chi2(1) = 7.44
Pr>chi2 = 0.0064
```



# ALSYMPCA study



0 M ≤ 20

```
. by M_status, sort : summarize sopravvivenza
```

```
-> M_status = 0
```

Variable	Obs	Mean	Std. Dev.	Min	Max
sopravvive~a	19	17.36842	10.63125	5	42

```
-> M_status = 1
```

Variable	Obs	Mean	Std. Dev.	Min	Max
sopravvive~a	34	10.79412	8.160435	2	42

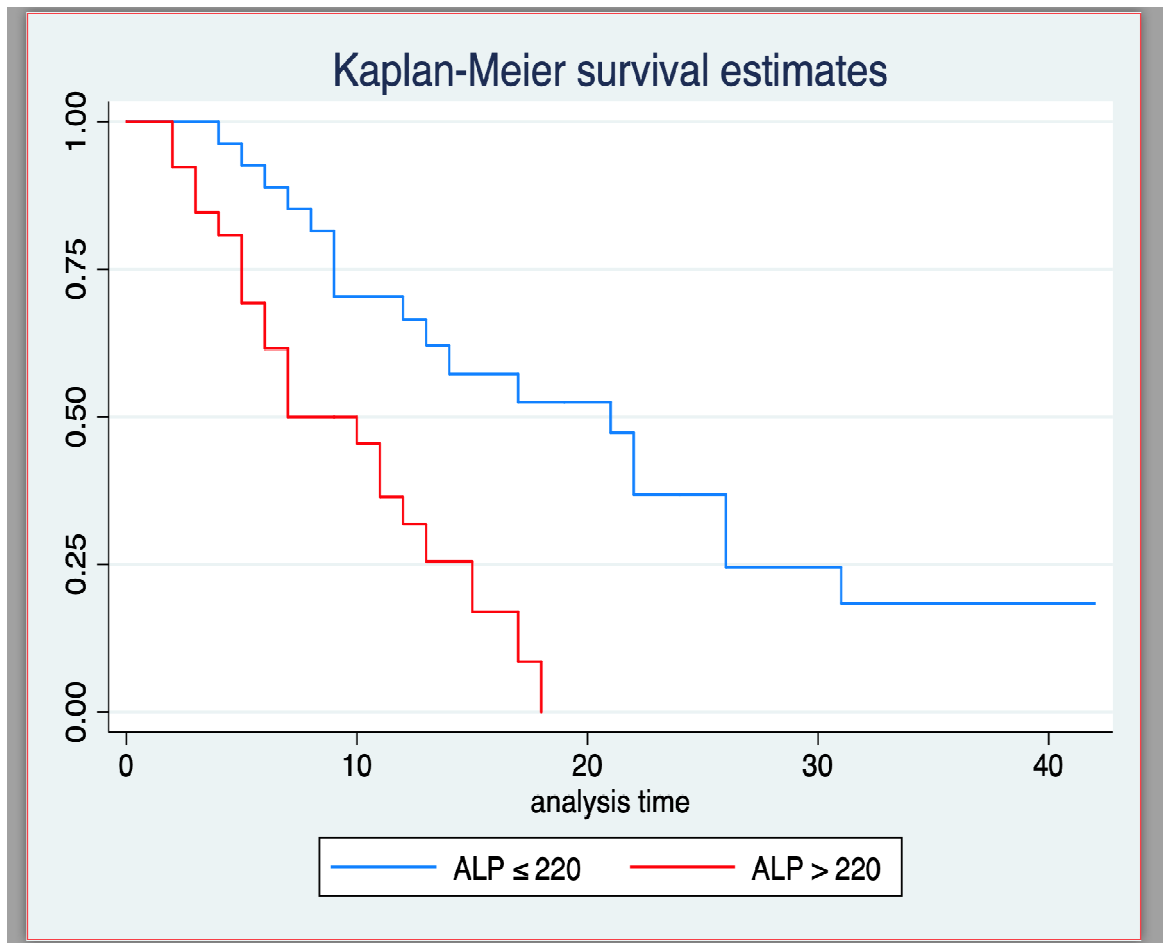
# Caratteristiche pazienti- total alkaline phosphatase ALP – no (%)

## ALSYMPCA study

Characteristic	Radium-223 (N = 614)	Placebo (N = 307)
Age		
Median (range) — yr	71 (49–90)	71 (44–94)
>75 yr — no. (%)	171 (28)	90 (29)
White race — no. (%)†	575 (94)	290 (94)
Total alkaline phosphatase — no. (%)		
<220 U/liter	348 (57)	169 (55)
≥220 U/liter	266 (43)	138 (45)
Current use of bisphosphonates — no. (%)		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)

Fosfatasi alcalina totale media	299 U/L
< 220	28 (51)
> 220	26 (49)

# Sopravvivenza ALP > o < 220



. stsum, by(ALP\_soglia)

failure\_d: Exitus == 1  
analysis time\_t: sopravvivenza

ALP_soglia	time at risk	incidence rate	no. of subjects	Survival time		
				25%	50%	75%
0	473	.038055	27	9	21	26
1	224	.09375	26	5	7	15
total	697	.0559541	53	7	12	22

## Log-rank test for equality of survivor functions

ALP_soglia	Events observed	Events expected
0	18	27.10
1	21	11.90
Total	39	39.00

chi2(1) = 11.96  
Pr>chi2 = 0.0005

0 ALP ≤ 220

```
. by ALP_soglia, sort : summarize sopravvivenza
```

---

```
-> ALP_soglia = 0
```

Variable	Obs	Mean	Std. Dev.	Min	Max
sopravvive~a	27	17.51852	11.07794	4	42

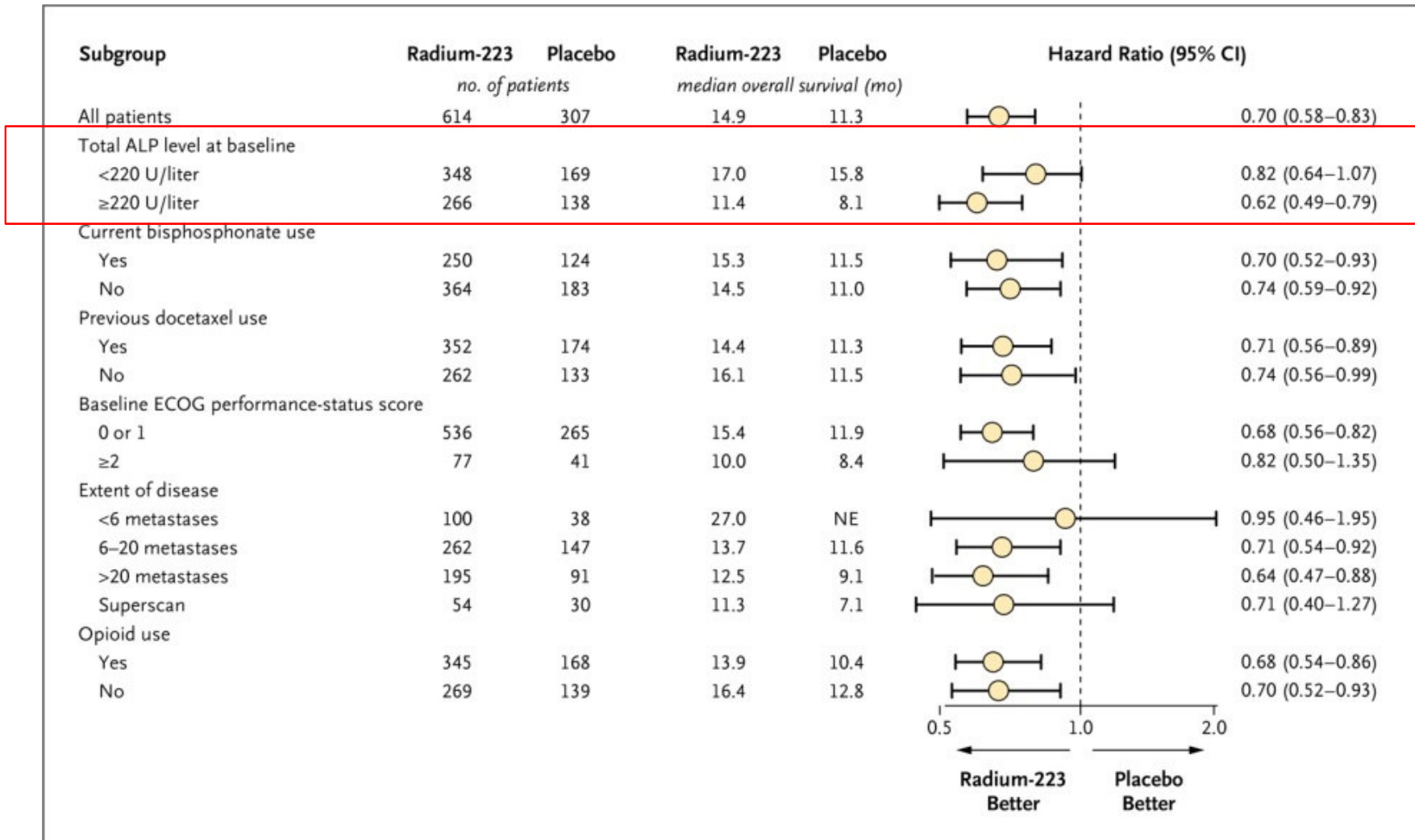
---

```
-> ALP_soglia = 1
```

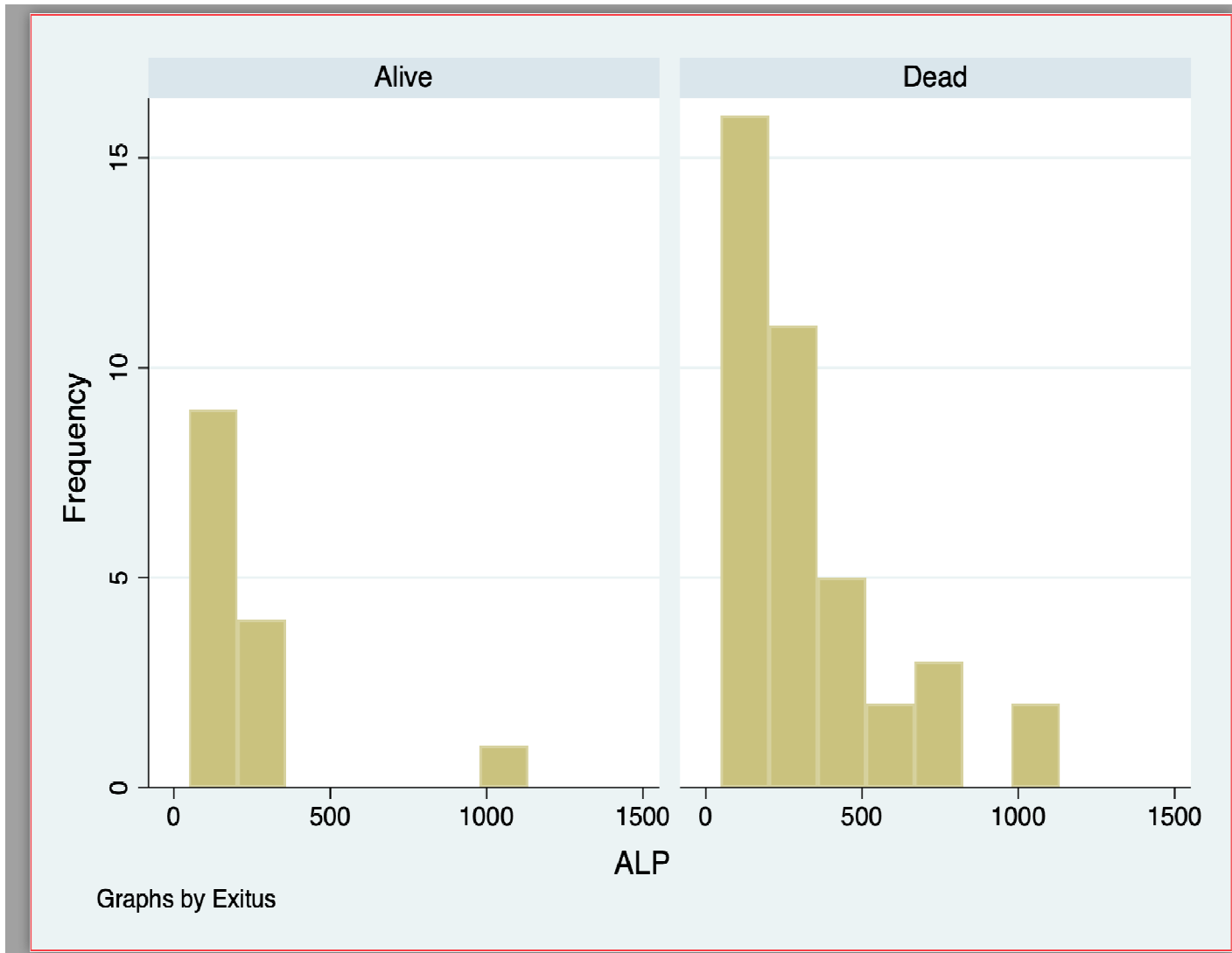
Variable	Obs	Mean	Std. Dev.	Min	Max
sopravvive~a	26	8.615385	4.552599	2	18

---

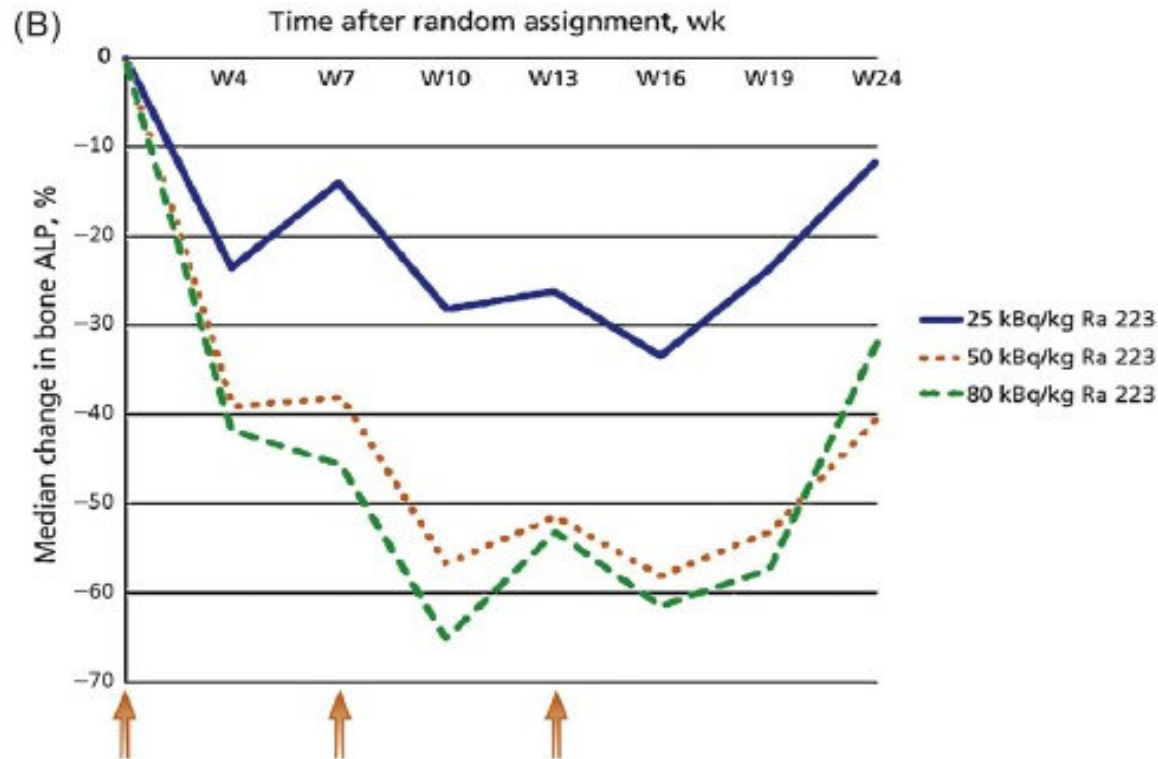
# ALSYMPCA study



# Fosfatasi Alcalina/sopravvivenza



# ALP: UN POSSIBILE PREDITTORE DI RISPOSTA

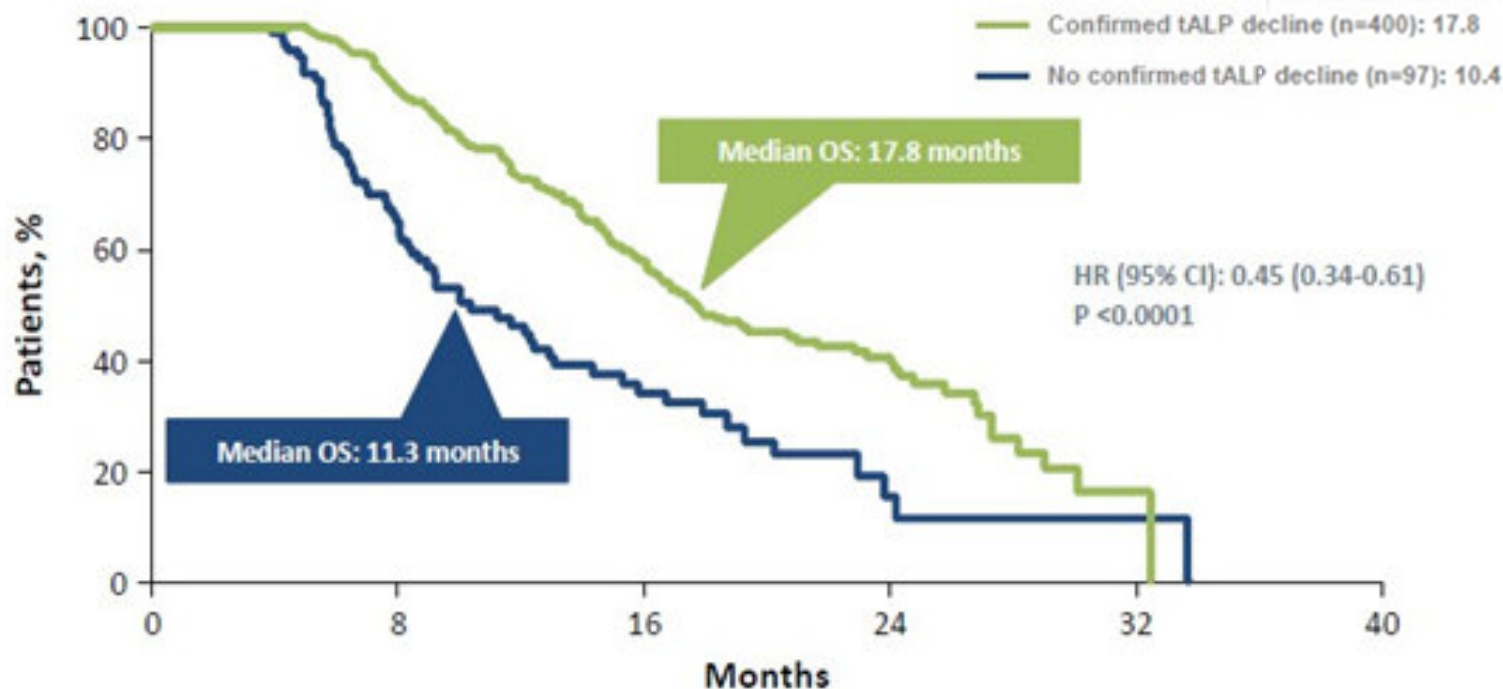
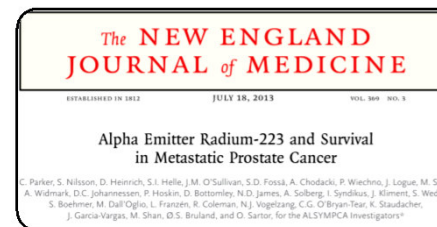


Lo studio ha evidenziato che i livelli di ALP ossea diminuiscono del 50% rispetto al basale nel 16%, 67% e 66% dei pazienti trattati rispettivamente con dosaggi di Radio-223 pari a un'attività di 25, 50 e 80 kBq/kg ( $p < 0,0001$ ),

- Si è osservata diminuzione della ALP ossea rispetto al basale durante il trattamento nei pazienti responder a Radium 223
- PSA aumenta anche nei responder



# RISPOSTA DELLA ALP



\*Confirmed tALP decline was defined as any decrease from baseline at week 12, confirmed ≥3 weeks later.

I pazienti che presentano una diminuzione di ALP alla 12esima settimana beneficiano di una OS significativamente prolungata rispetto ai pazienti in cui la riduzione dei livelli di questo biomarker non è confermata

# Sopravvivenza Docetaxel si/no

## ALSYMPCA study

**Table 1. Baseline Characteristics of the Patients.\***

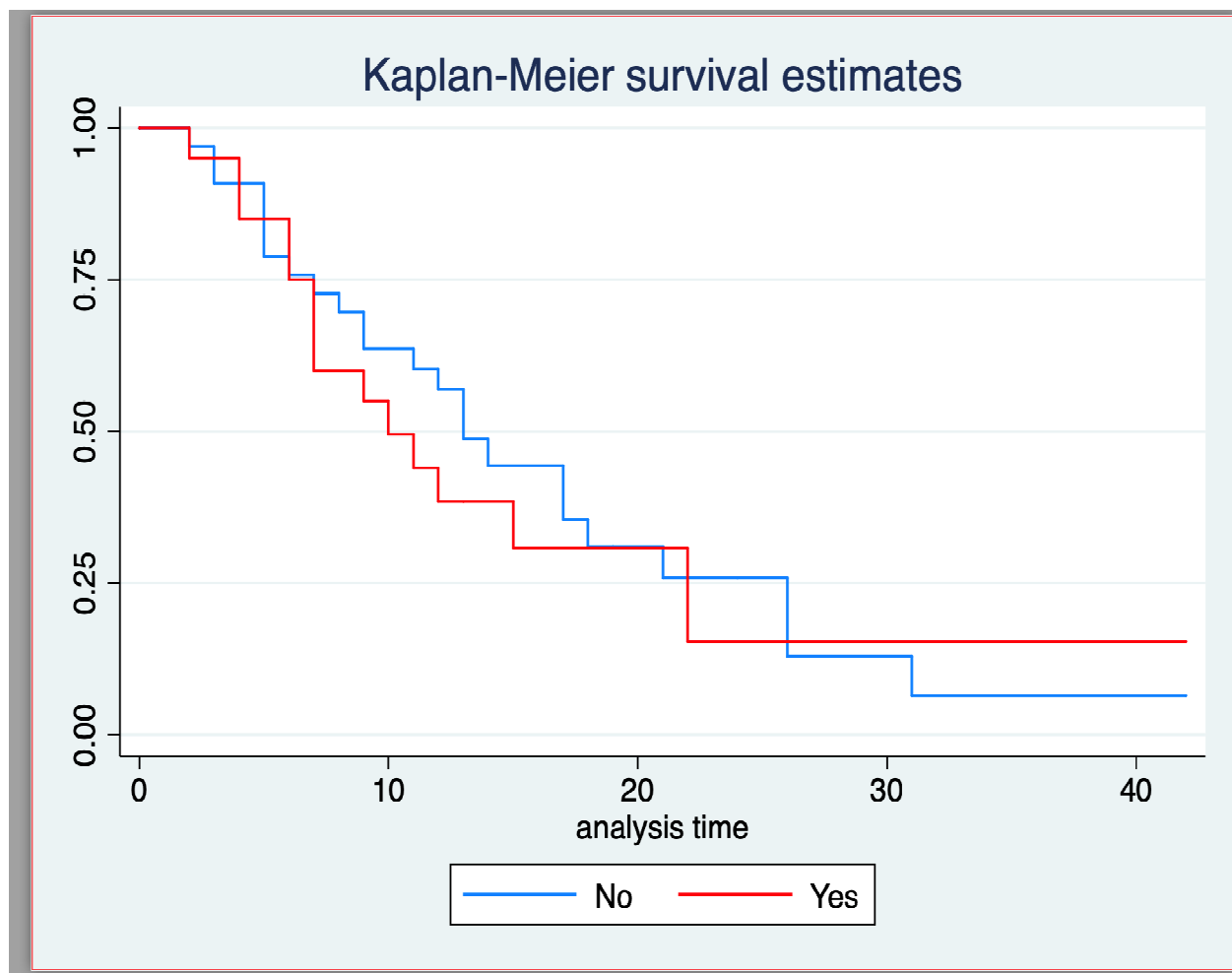
Characteristic	Radium-223 (N = 614)	Placebo (N = 307)
<b>Age</b>		
Median (range) — yr	71 (49–90)	71 (44–94)
>75 yr — no. (%)	171 (28)	90 (29)
White race — no. (%)†	575 (94)	290 (94)
<b>Total alkaline phosphatase — no. (%)</b>		
<220 U/liter	348 (57)	169 (55)
≥220 U/liter	266 (43)	138 (45)
<b>Current use of bisphosphonates — no. (%)</b>		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)
<b>Any previous use of docetaxel — no. (%)</b>		
Yes	352 (57)	174 (57)
No	262 (43)	133 (43)

Docetaxel

SI 20 (37)

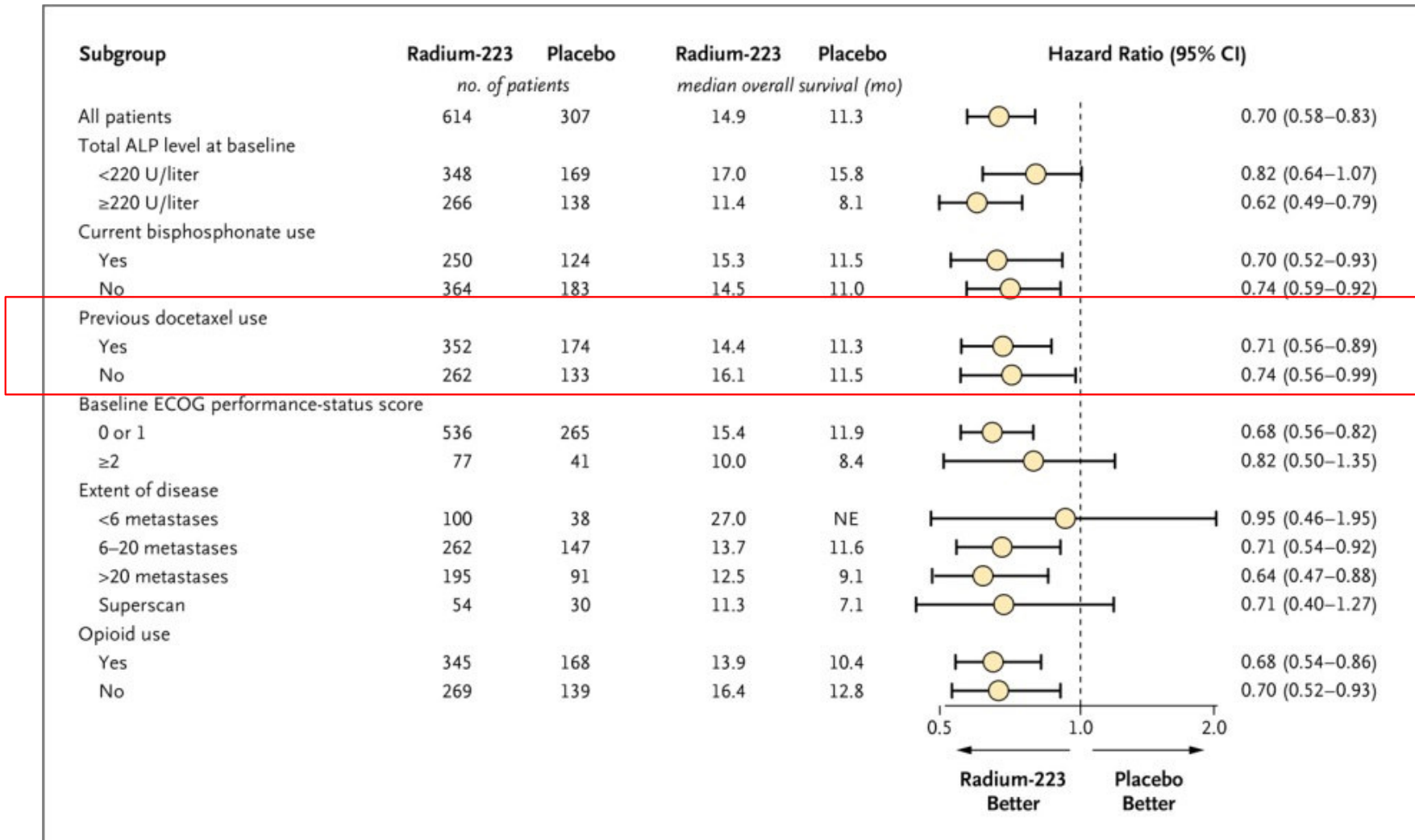
NO 34 (63)

# Sopravvivenza Docetaxel si/no

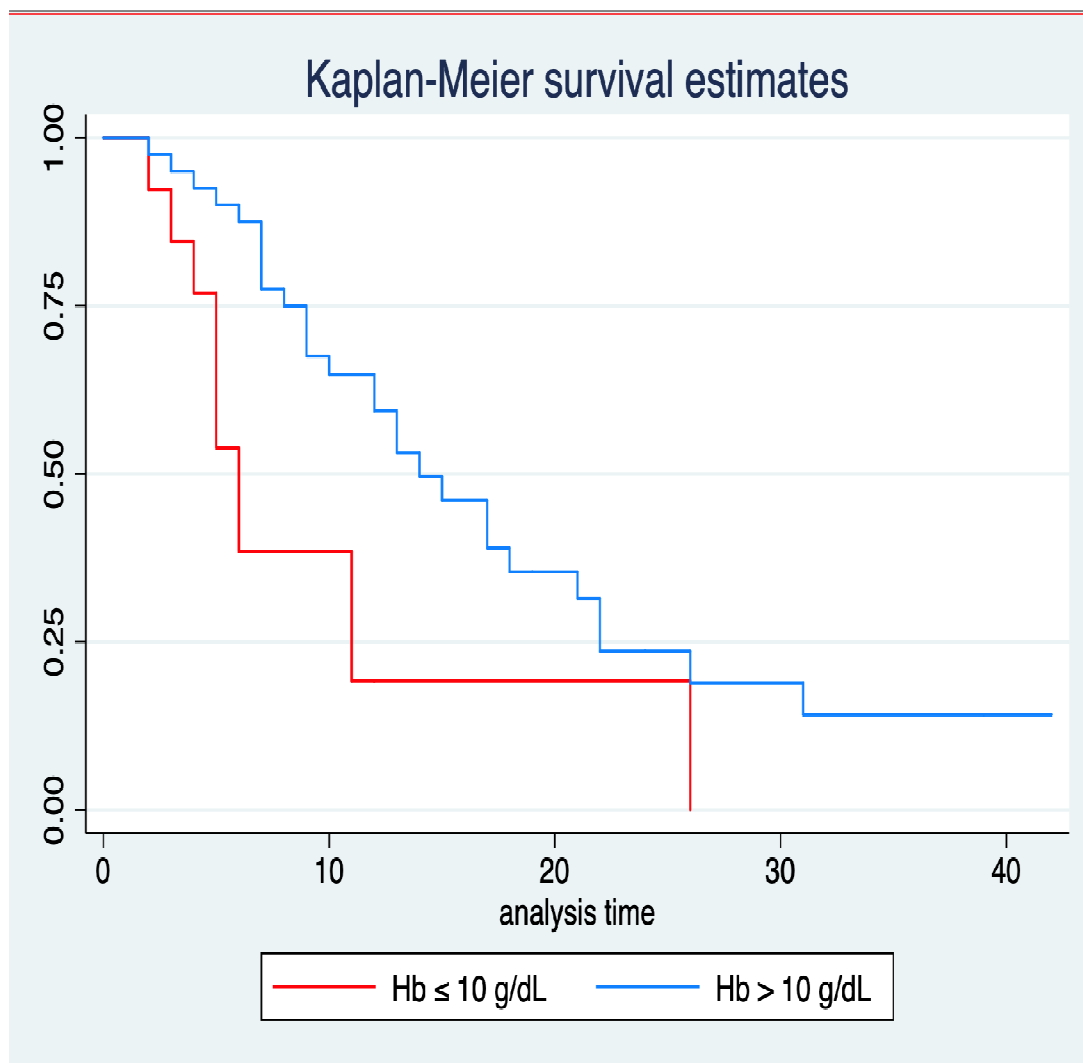


Sopravvivenza Docetaxel si 12.9  
Sopravvivenza Docetaxel no 13.2

# ALSYMPCA study



# Sopravvivenza per Emoglobina > o < 10 g/dl



```
. sts test HBcat, logrank
```

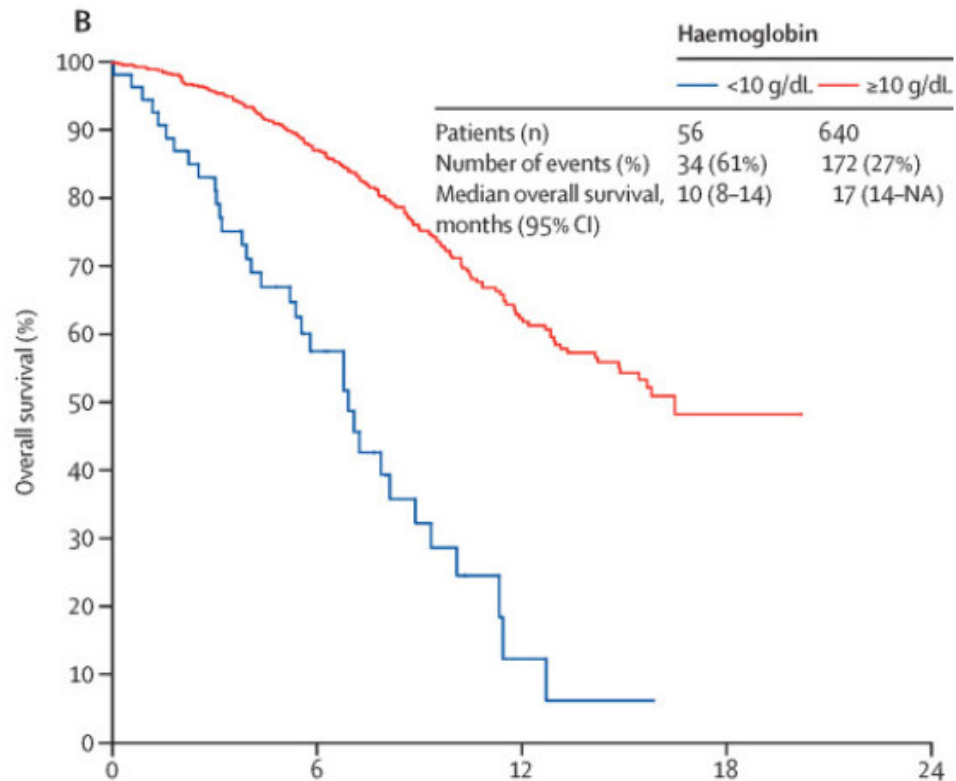
```
failure_d: Exitus == 1  
analysis time_t: sopravvivenza
```

Log-rank test for equality of survivor functions

HBcat	Events observed	Events expected
0	11	5.51
1	28	33.49
Total	39	39.00

```
chi2(1) = 6.98  
Pr>chi2 = 0.0083
```

# IEAP: ANALISI DI SOPRAVVIVENZA PER LIVELLI BASALI DI EMOGLOBINA



I livelli di Hb al basale sono risultati discriminanti ai fini dell'esito della terapia (OS / qualità di vita).

**Comprendere la causa dell'anemia e intervenire opportunamente per compensarla aumenta le probabilità del paziente di riuscire a completare il trattamento con Radio-223 e trarne il massimo beneficio di sopravvivenza.**

# Terapia concomitante con difosfonati no. (%)

## ALSYMPCA study

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Radium-223 (N=614)	Placebo (N=307)
Current use of bisphosphonates — no. (%)		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)

Difosfonati	
SI	16 (30)
NO	38 (70)

Subgroup	Radium-223 <i>no. of patients</i>	Placebo	Radium-223 <i>median overall survival (mo)</i>	Placebo	Hazard Ratio (95% CI)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)

Sopravvivenza difosfonati si 16.2  
Sopravvivenza difosfonati no 10.9

# Terapia concomitante con difosfonati

## Meeting Abstracts

Home

Search Abstracts

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Meeting Home

### Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333/PEACE III trial comparing enzalutamide and Ra223 versus enzalutamide alone: An interim safety analysis.

Sub-category:  
Advanced Disease

Category:  
Genitourinary (Prostate) Cancer

Meeting:  
2019 ASCO Annual Meeting

Attend this session at the  
2019 ASCO Annual Meeting!

Session: Genitourinary (Prostate) Cancer

Type: Oral Abstract Session

Time: Friday May 31, 2:45 PM to 5:45 PM

Location: Arie Crown Theater

**Background:** Skeletal fractures, pathological or not, are a frequent and underestimated side-effect of systemic treatment of metastatic castration resistant prostate cancer (mCRPC). The ERA223 trial (NCT02043678) was recently unblinded following the report of a significant increase in the fracture rates when abiraterone is combined with Ra223. Hence, FDA and EMA advised against this combination. The question whether mandated use of bone protecting agents (BPA), zoledronic acid or denosumab, would have mitigated the fracture risk and whether this risk also exists in the enzalutamide/Ra223 combination is presently unknown. **Methods:** The phase III EORTC-1333-GUCG/PEACEIII (NCT02194842) trial compares enzalutamide vs. a combination of Ra223 and enzalutamide in asymptomatic or mildly symptomatic mCRPC patients ([https://www.eortc.org/research\\_field/clinical-detail/1333/](https://www.eortc.org/research_field/clinical-detail/1333/)). After the unblinding of ERA223, the trial was amended (v4.0, April 19, 2018) to mandate that all patients must start a BPA. We report the fracture rate in the safety population of 146 treated patients as of 28/01/2019. **Results:** Overall, 54.2% of the patients in the enza/Ra223 arm and 51.4% of the enza arm did not receive BPA; 18.0% in the enza/Ra223 arm and 27.0% in the enza arm did not use BPA at randomization, but started during protocol treatment according to the v4.0 amendment. 27.8% and 21.6% respectively, received BPA as of randomization. In total, 45.8% of enza/Ra223 patients and 48.6% of enza only patients receive bone protection on treatment. The fracture rate is reported in the table. **Conclusions:** There is a 13% risk of fracture with enzalutamide in asymptomatic mCRPC, in line with previous reports. This risk is significantly increased to 33% when Ra223 is added to enzalutamide. Strikingly, the risk is almost abolished by mandatory continuous administration of BPA starting at least 6 weeks before the first injection of Ra223, thus emphasizing the importance of treating mCRPC patients with BPA. Clinical trial information: [NCT02194842](https://www.eortc.org/research_field/clinical-detail/1333/)

	Enza/Ra223 With BPA n=33	Enza With BPA n=36	Enza/RA223 Without BPA n=39	Enza Without BPA n=38*	Total n=146
<b>Bone fracture</b>					
<b>N</b>	1	0	13	5	19
<b>%</b>	3%	-	33%	13%	13%
<b>95% CI</b>	0-16%	-	19-50%	4-28%	8-20%