

“Eficiencia y Calidad de Vida en el manejo de recursos del Paciente Oncológico”

Impacto de la Enfermedad Metastásica ósea en la Calidad de Vida: Perspectiva desde la Oncología Médica



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Bone metastases can have serious and debilitating consequences – skeletal-related events (SREs)



Pathological fracture



Surgery to bone

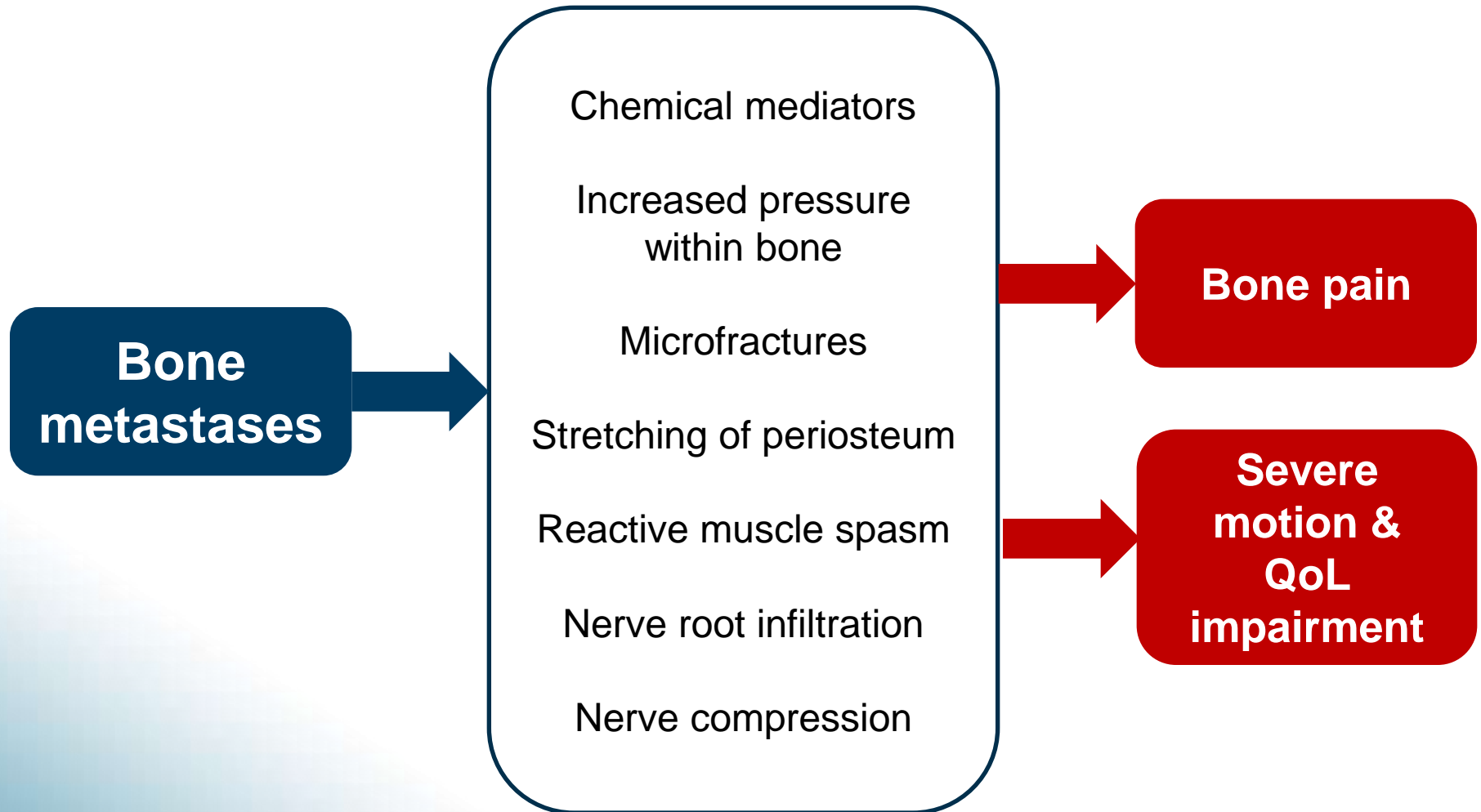


Spinal cord compression

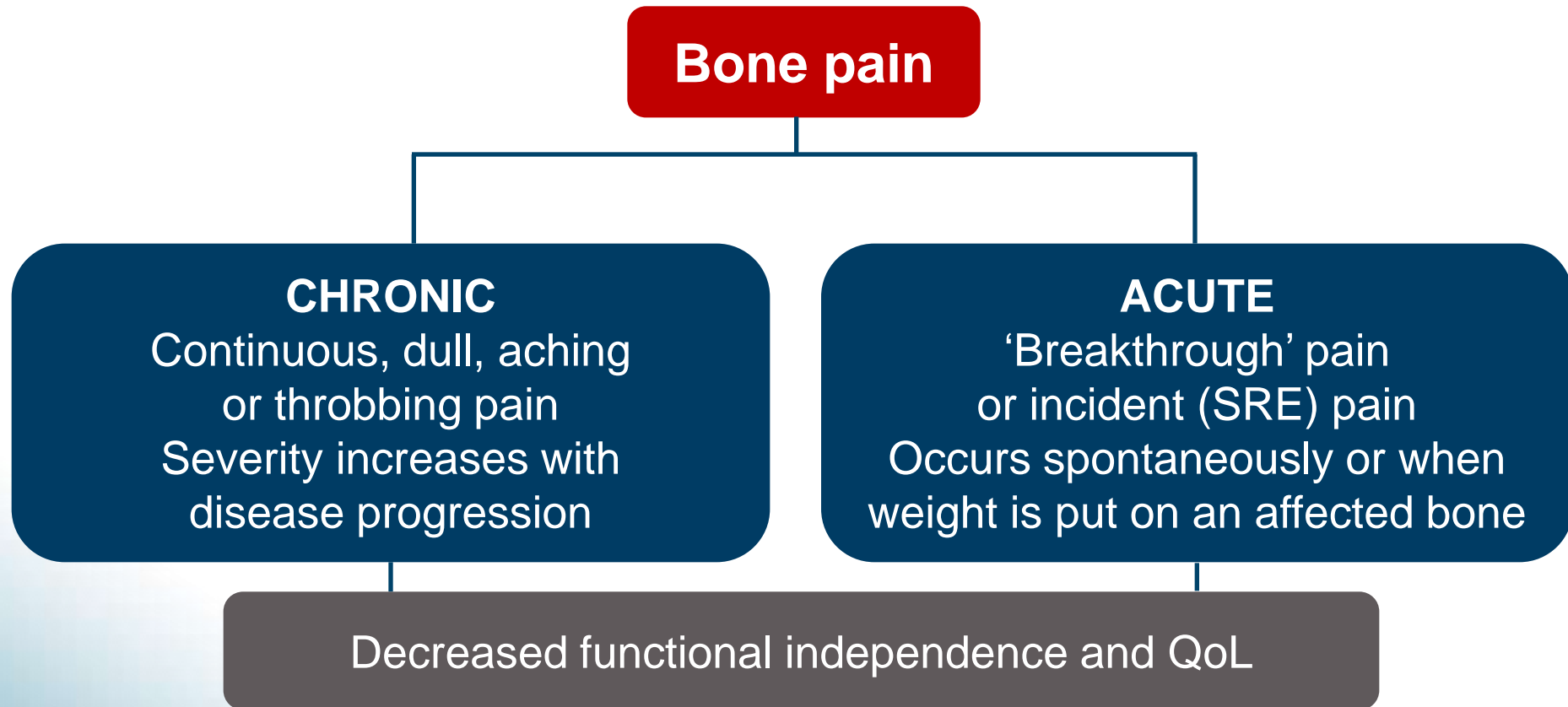


Radiation to bone

Bone metastases are the most common cause of pain in advanced cancer patients



Bone pain decreases patient functional independence and QoL



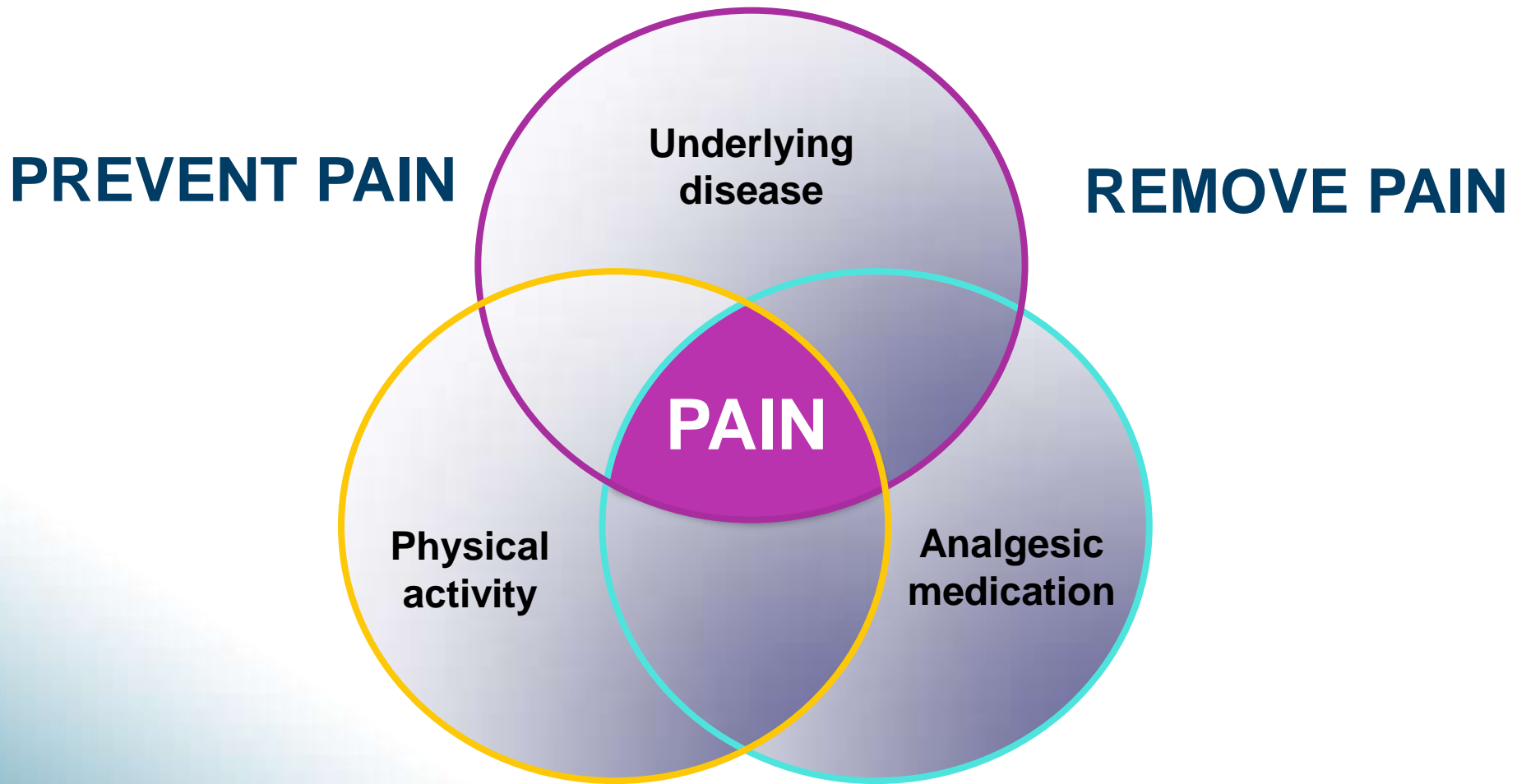
The majority of patients with bone metastases report having pain

Characteristic	Proportion of patients (%) [†] (N = 5723)
Pain status	
No pain	14.5
Mild pain	33.8
Moderate pain	20.3
Severe pain	25.0
Analgesic use	
No analgesic use	47.4
Opioid-based analgesic use	35.5

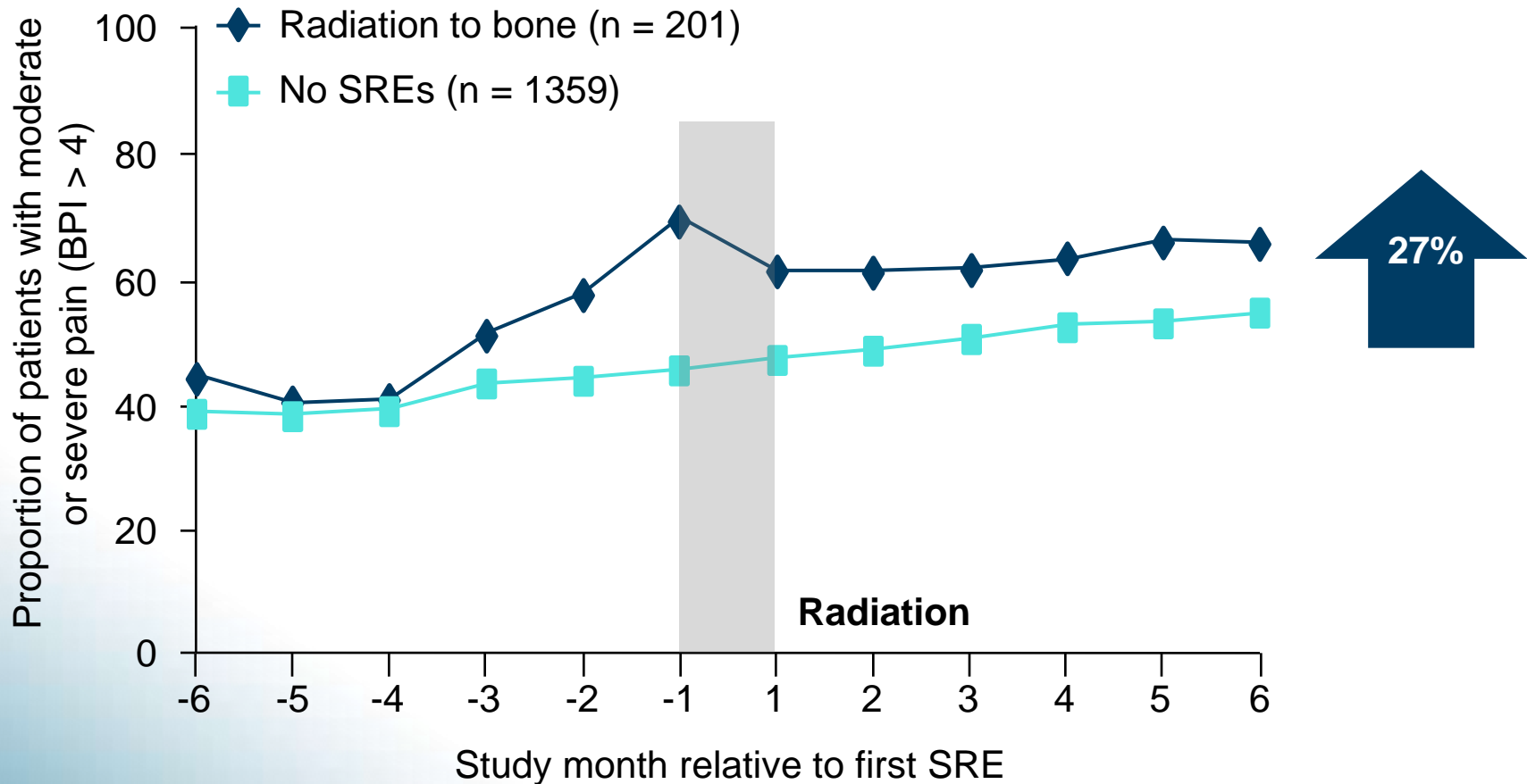
Typically bone pain is not adequately managed

[†]Data are pooled baseline data for patients in the three pivotal Phase III denosumab SRE prevention studies.

Bone pain is influenced by different factors



Moderate or severe pain is common in breast cancer patients with bone metastases, particularly among those who receive radiation to bone



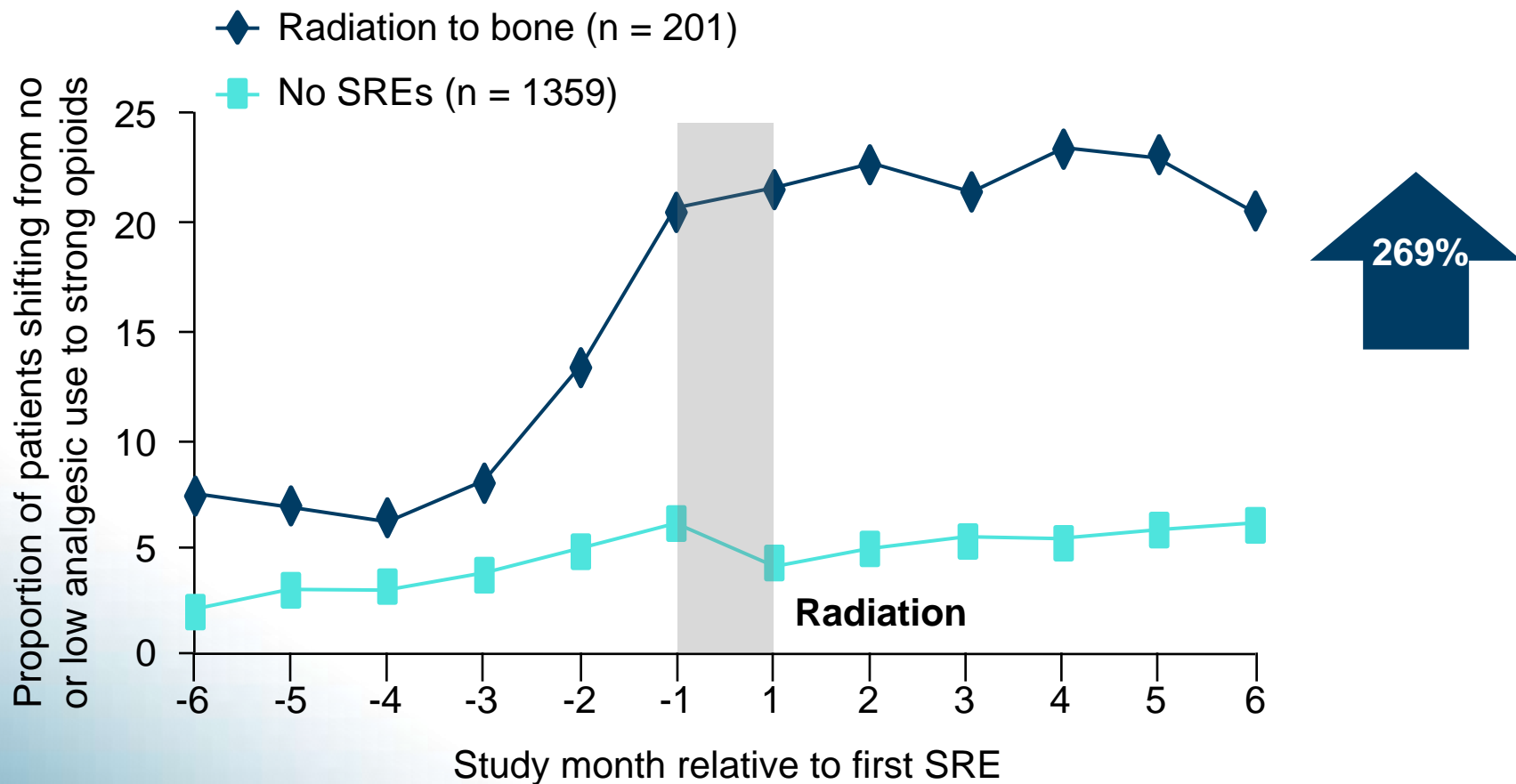
27%

Data are from the denosumab Phase III SRE prevention study in breast cancer patients.

BPI, Brief Pain Inventory; SRE, Skeletal-Related Events

Fallowfield L, et al. Poster presented at SABCS 2011 [Abstract P4-13-01].

Pain may not be fully attenuated by radiation to bone, even with increased analgesic use




Data are from the denosumab Phase III SRE prevention study in breast cancer patients.

SRE, Skeletal-Related Events

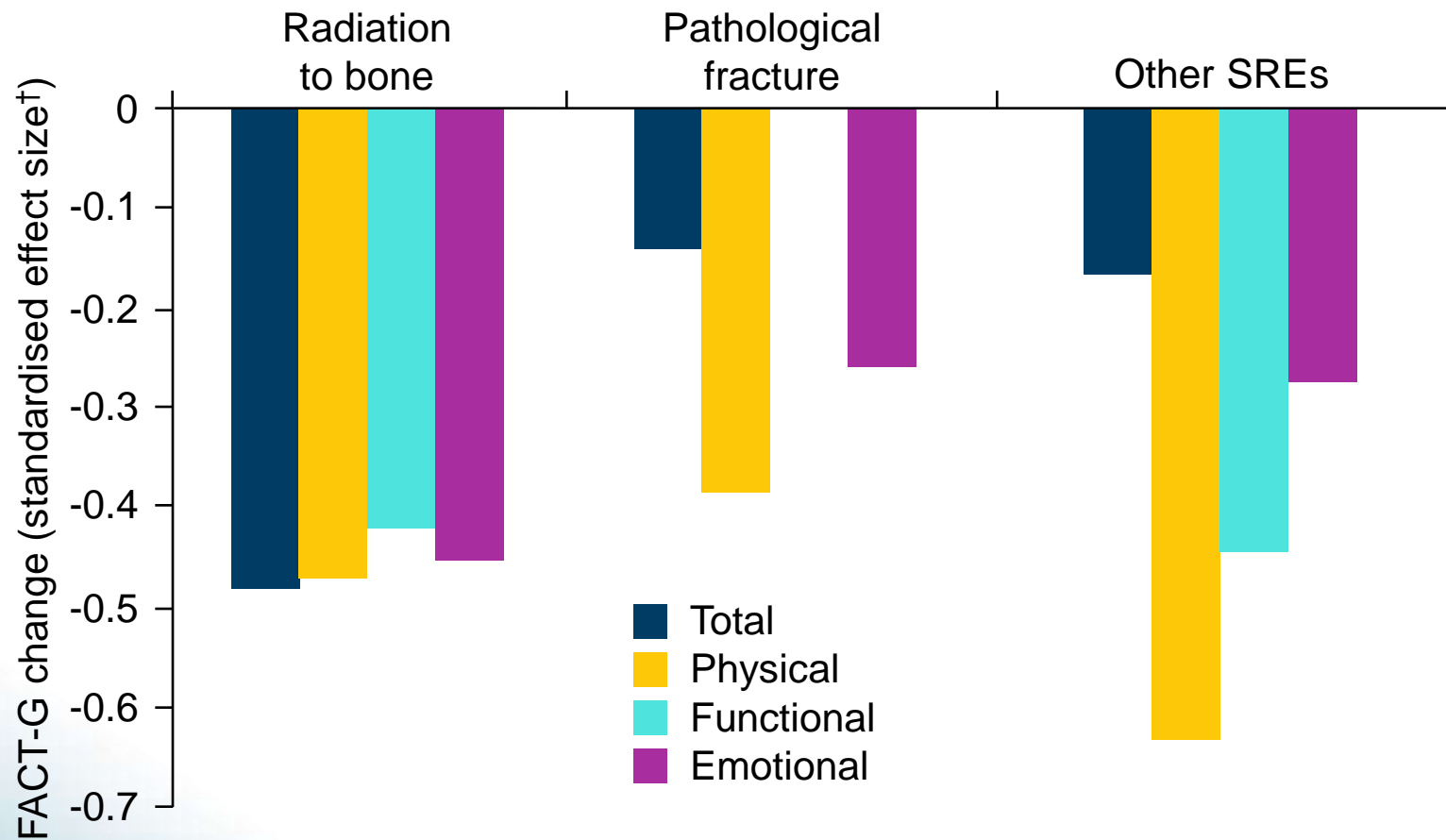
Fallowfield L, et al. Poster presented at SABCS 2011 [Abstract P4-13-01].

Radiation to bone and opioids have disadvantages as palliative therapies for advanced cancer

Radiation to bone ¹	Opioids ^{2,3}
Side effects	Side effects
Repeated hospital visits	Potential for addiction or non-adherence
Psychological impact <ul style="list-style-type: none"> •Sign that the disease is worsening •Recognition that the disease is severe enough to need radiation •Depression and anxiety 	Psychological impact <ul style="list-style-type: none"> •Sign that the disease is worsening •Association with 'end-of-life'
 Quality of Life	Optimal therapy requires a medical oncologist prescription & follow-up
Cost	Cost

1. Weinfurt KP, et al. Ann Oncol 2005;16:579–84;
 2. Induru RR, Lagman RL. Cleve Clin J Med 2011;78:449–64;
 3. Maltoni M. Ann Oncol 2008;19:5–7.

SREs are associated with reduced Quality of Life



†Computed by dividing the adjusted mean change by the baseline standard deviation from the entire trial sample. Data from 248 men with castration-resistant prostate cancer and bone metastases who experienced an SRE during a study of zoledronic acid vs placebo.

FACT-G, Functional Assessment of Cancer Therapy-General.

Weinfurt KP, et al. Ann Oncol 2005;16:579–84.

It is always worth while to prevent...

**Denosumab pivotal Phase III
SRE prevention studies**

Three denosumab pivotal Phase III SRE prevention studies were combined for an integrated analysis

The Integrated Analysis pooled individual patient data

Breast cancer
(N = 2046)

Prostate cancer
(N = 1901)

Other solid tumours*/
multiple myeloma
(N = 1776)

RANDOMISATION

Preplanned integrated analysis (N = 5723)

Denosumab 120 mg SC Q4W
+
Placebo IV Q4W
(n = 2862)

Supplemental
calcium and
vitamin D

Zoledronic acid 4 mg IV Q4W
+
Placebo SC Q4W
(n = 2861)

Denosumab is not indicated for use in patients with multiple myeloma (MM). Denosumab is investigational in that setting.

*Excluding breast or prostate.

Lipton A, Fizazi K, Stopeck A, et al. Eur J Cancer 2012;48:3082-3092.

IV, intravenous; Q4W, every 4 weeks; SC, subcutaneous.

The three denosumab pivotal Phase III SRE prevention studies included pain and HRQoL as exploratory endpoints

Primary

Time to first SRE
(non-inferiority)

Secondary

- Time to first SRE (superiority)¹
- Time to first and subsequent SRE (superiority, multiple-event analysis)¹
- Safety and tolerability¹

Exploratory

- Overall survival, disease progression, individual SREs and skeletal morbidity rate¹
- **Pain and HRQoL²**
- ONJ-related attributes¹

HRQoL, Health Related Quality of Life; SRE Skeletal-Related Events; ONJ, Osteonecrosis of the Jaw.

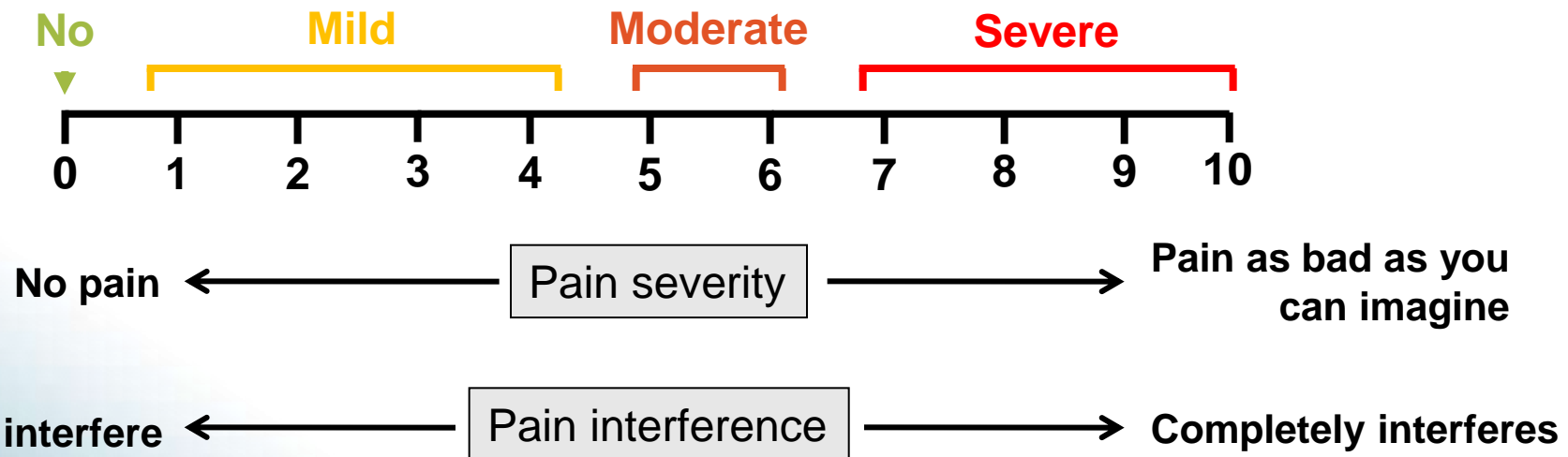
1. Lipton A, Fizazi K, Stopeck A, et al. Eur J Cancer 2012;48:3082-3092.

2. Cleeland CS, et al. Ann Oncol 2010;21(Suppl 8):viii379 [Abstract 1248P].

Pain assessment

Pain was evaluated at baseline, Day 8 and monthly

- Pain was evaluated with the Brief Pain Inventory-Short Form (BPI-SF)
- The BPI-SF consists of 11 questions that assess:
 - Pain severity at its ‘worst’, ‘least’, ‘average’ and ‘now’
 - Pain interference with daily functions
- Patients rate pain severity and interference using an 11-point numerical rating scale



Prevention of pain progression

Selected pain endpoints in denosumab SRE prevention trials

Prevention of pain progression

- Time to pain worsening in patients with no or mild pain (0–4) at baseline[†]
 - Moderate or severe pain (worst pain score > 4 points)
 - Patients with pain worsening (≥ 2 -point increase)

Analgesic use

- Time to increase in analgesic use
 - Patients progressing from no or low analgesic use (AQA ≤ 2) to strong opioid use (AQA ≥ 3)[‡]

Pain interference

- Proportion of patients with increased or decreased pain interference^{*}

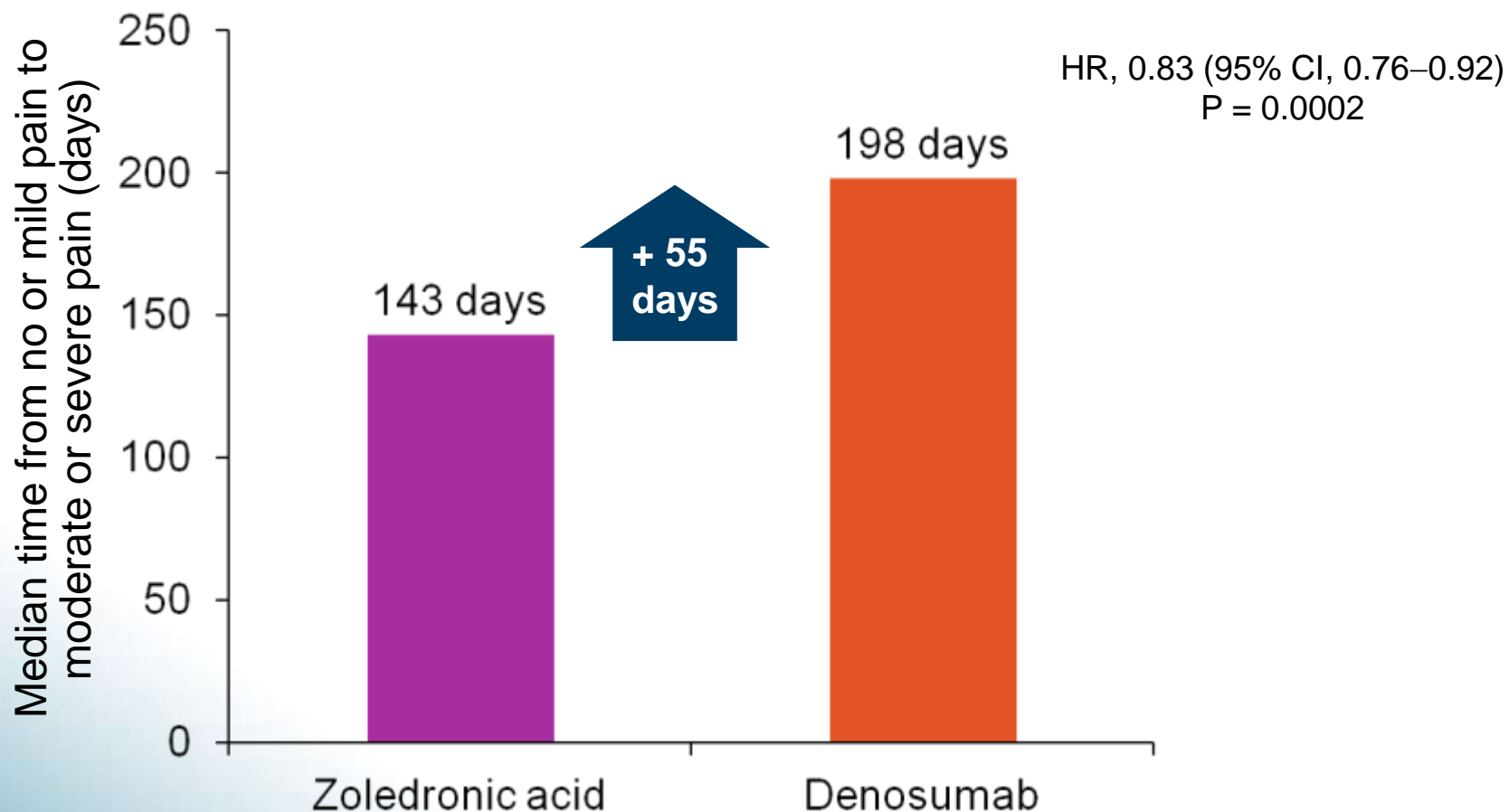
[†]On the 11-point BPI-SF;

[‡]On the 8-category Analgesic Quantification Algorithm (AQA);

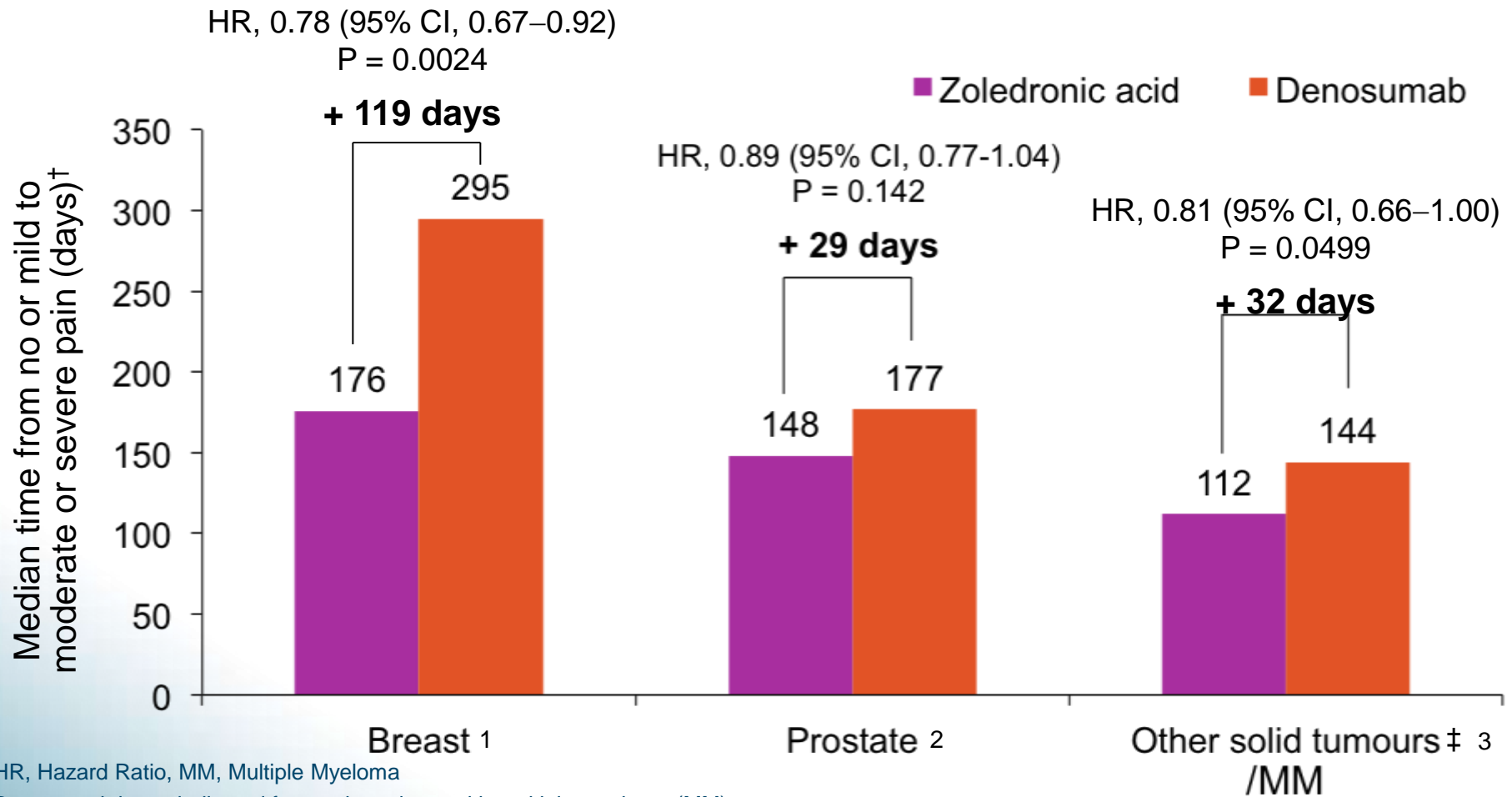
^{*}7 pain interference domains on the BPI-SF.

Denosumab delayed pain progression by almost 2 months vs zoledronic acid

Patients progressing to moderate or severe pain (> 4 points)
among patients with no or mild pain (0–4) at baseline



Denosumab consistently delayed pain progression vs zoledronic acid across tumour types



HR, Hazard Ratio, MM, Multiple Myeloma

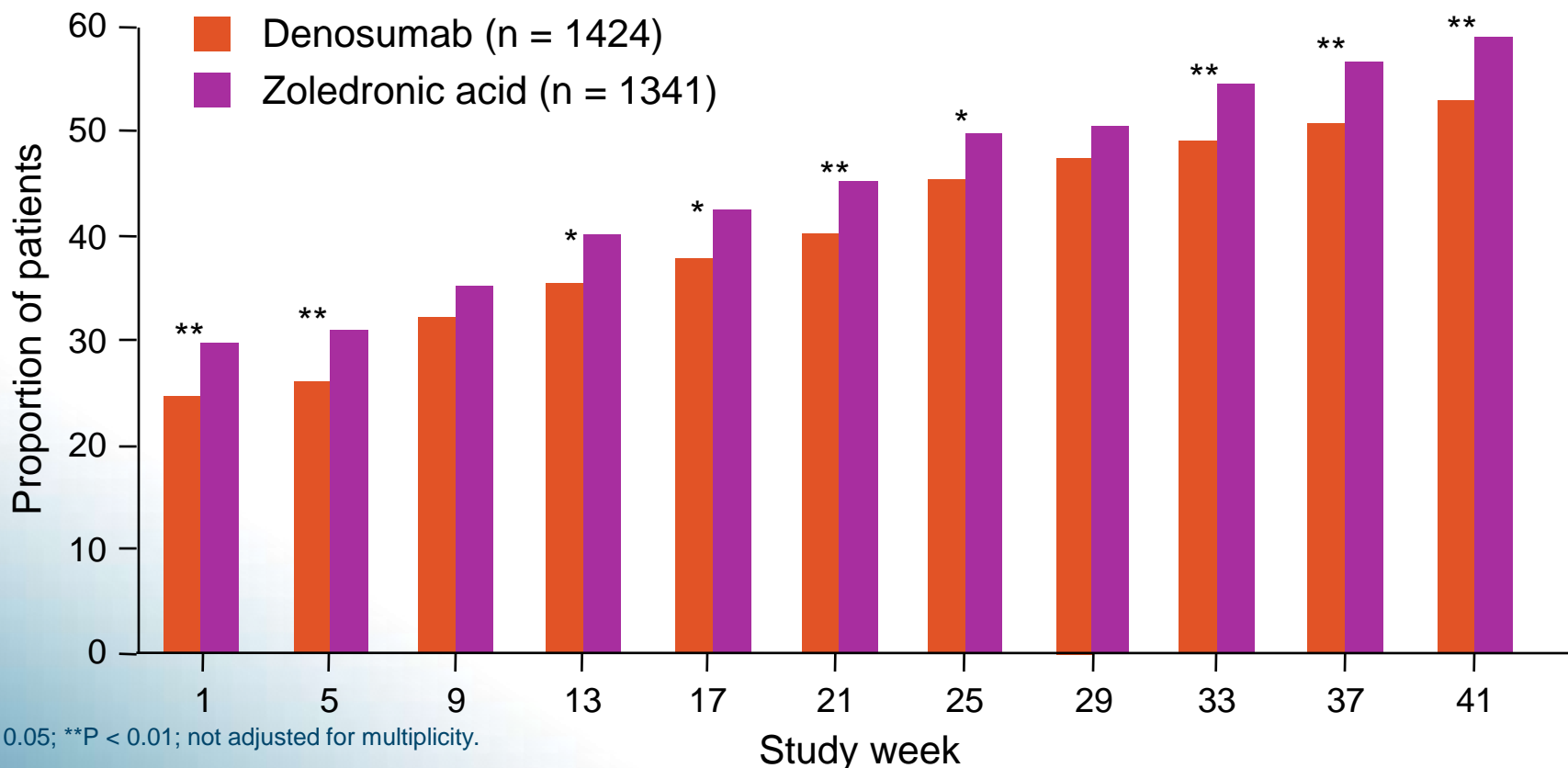
Denosumab is not indicated for use in patients with multiple myeloma (MM).
Denosumab is investigational in that setting.

1. Stopeck A, et al. J Clin Oncol 2010;28(Suppl 15): [Abstract 1024];
2. Brown JE, et al. Eur Urol Suppl 2011;10:336 [Abstract 1091];
3. Fallowfield L, et al. Oral presentation at EMCC 2011 [Abstract 7004].

[†]Patients with pain worsening (≥ 2 -point increase) among patients with no or mild pain (0–4) at baseline. [‡]Excluding breast and prostate. MM, multiple myeloma.

A lower proportion of patients on denosumab reported pain worsening (≥ 2 -point increase) vs zoledronic acid

Patients with pain worsening (≥ 2 -point increase) among patients with no or mild pain (0–4) at baseline



*P < 0.05; **P < 0.01; not adjusted for multiplicity.

Analgesic use

Selected pain endpoints in denosumab SRE prevention trials

Prevention of pain progression

- Time to pain worsening
 - Moderate or severe pain (worst pain score > 4 points) in patients with no or mild pain (0–4) at baseline[†]
 - Patients with pain worsening (≥ 2 -point increase) among patients with no or mild pain (0–4) at baseline[†]

Analgesic use

- Time to increase in analgesic use
 - Patients progressing from no or low analgesic use (AQA ≤ 2) to strong opioid use (AQA ≥ 3)[‡]

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- Proportion of patients with increased or decreased pain interference^{*}

[†]On the 11-point BPI-SF;

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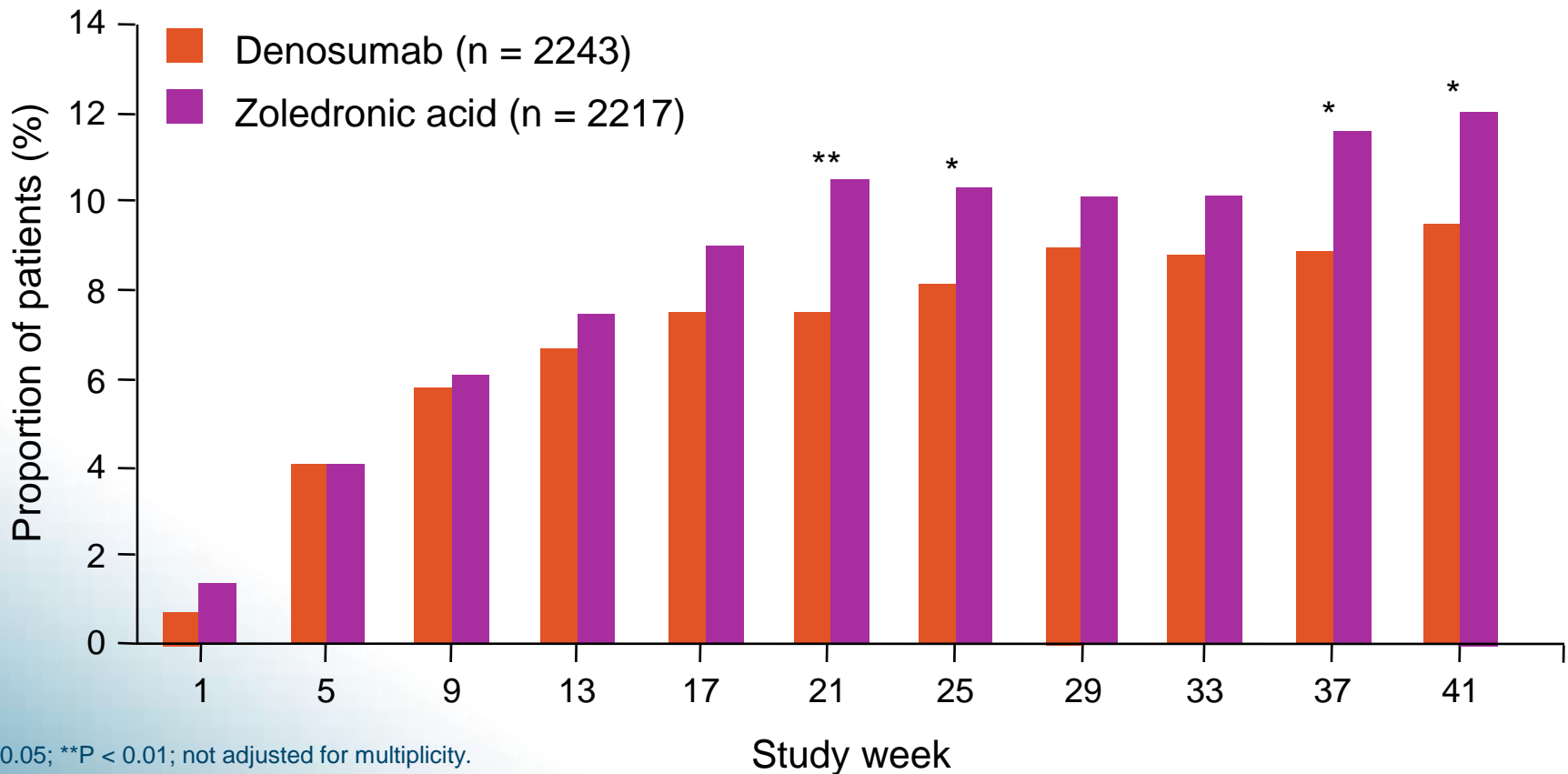
Analgesic quantification algorithm (AQA) used to score analgesic medication needs

AQA score	Description
0	No analgesic
1	Non-opioid analgesics
2	Weak opioids (meperidine, codeine, tramadol)
3	Strong opioids \leq 75 mg OME per day
4	Strong opioids > 75–150 mg OME per day
5	Strong opioids > 150–300 mg OME per day
6	Strong opioids > 300–600 mg OME per day
7	Strong opioids > 600 mg OME per day

An AQA score \geq 3 points represents strong opioid use

A lower proportion of patients on denosumab progressed from no or low analgesic use to strong opioid use vs zoledronic acid

Patients progressing from no or low analgesic use (AQA ≤ 2) to strong opioid use (AQA ≥ 3)



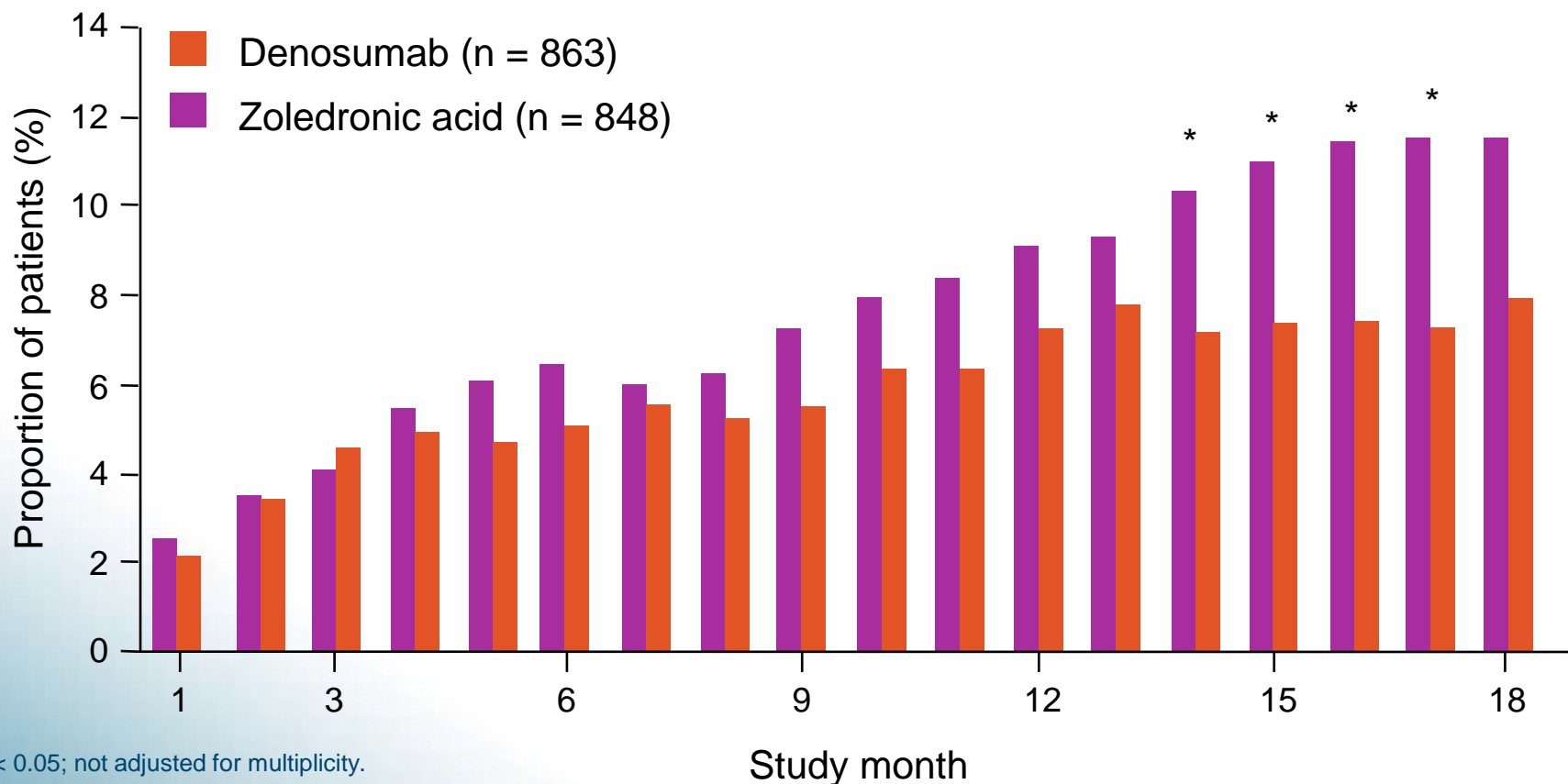
*P < 0.05; **P < 0.01; not adjusted for multiplicity.

AQA, Analgesic Quantification Algorithm

Cleeland CS, et al. Ann Oncol 2010;21:8s [Abstract 1248P].

A lower proportion of patients on denosumab progressed from no or low analgesic use to strong opioid use vs zoledronic acid

Patients progressing from no or low analgesic use (AQA ≤ 2) to strong opioid use (AQA ≥ 3)



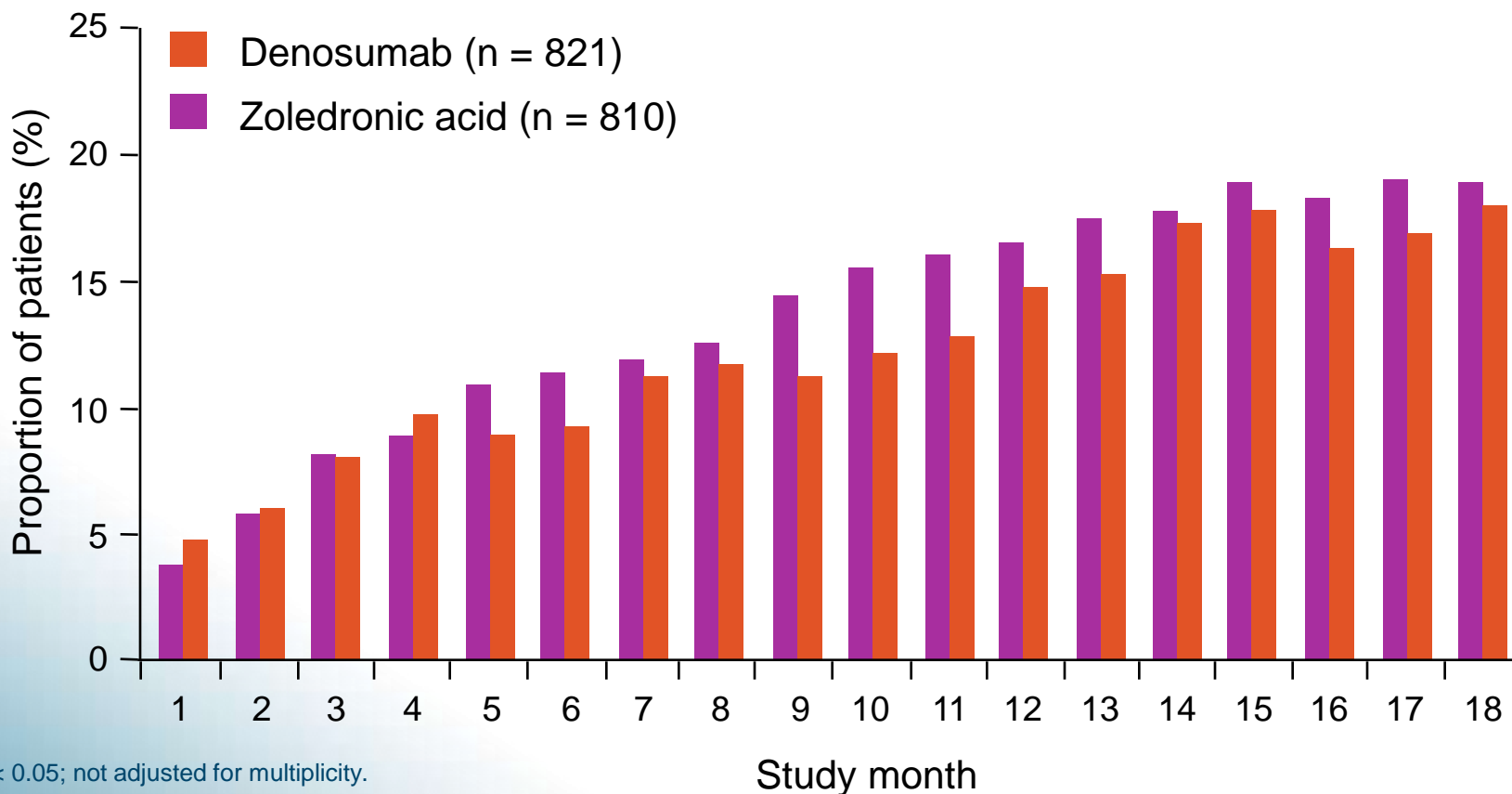
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AQA, Analgesic Quantification Algorithm

Cleeland CS, et al. Poster presented at SABCS 2010 [Abstract P1-13-01].

A lower proportion of patients on denosumab progressed from no or low analgesic use to strong opioids vs zoledronic acid

Patients progressing from no or low analgesic use (AQA ≤ 2) to strong opioid use (AQA ≥ 3)



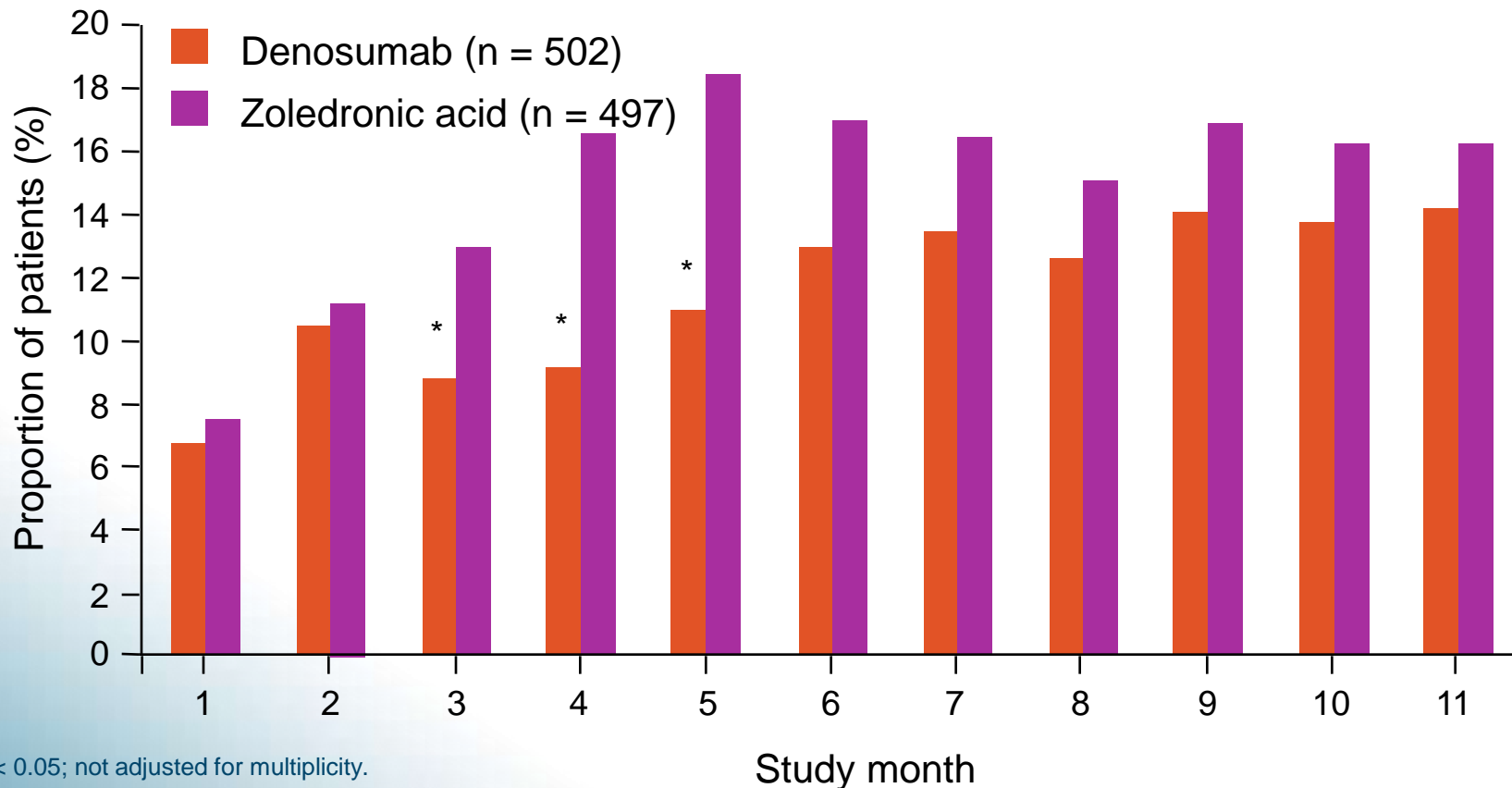
*P < 0.05; not adjusted for multiplicity.

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Pain interference

Selected pain endpoints in denosumab SRE prevention trials

Prevention of pain progression

- Time to pain worsening
 - Moderate or severe pain (worst pain score > 4 points) in patients with no or mild pain (0–4) at baseline[†]
 - Patients with pain worsening (≥ 2-point increase) among patients with no or mild pain (0–4) at baseline[†]

Analgesic use

- Time to increase in analgesic use
 - Patients progressing from no or low analgesic use (AQA ≤ 2) to strong opioid use (AQA ≥ 3)[‡]

Pain interference

- Proportion of patients with increased or decreased pain interference*

BPI-SF pain interference assesses impact on activity, affect and sleep

BPI interference domains:

Pain interference with activity:

- General activity
- Walking ability
- Normal work

Pain interference with affect:

- Mood
- Relations with others
- Enjoyment of life

Pain interference aggregate:

- Activity + affect + sleep
(7 items in total)

8. Circle the one number that best describes how, during the last week, pain has interfered with your:

8.1 General Activity

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

8.2 Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

8.3 Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

8.4 Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

8.5 Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

8.6 Sleep

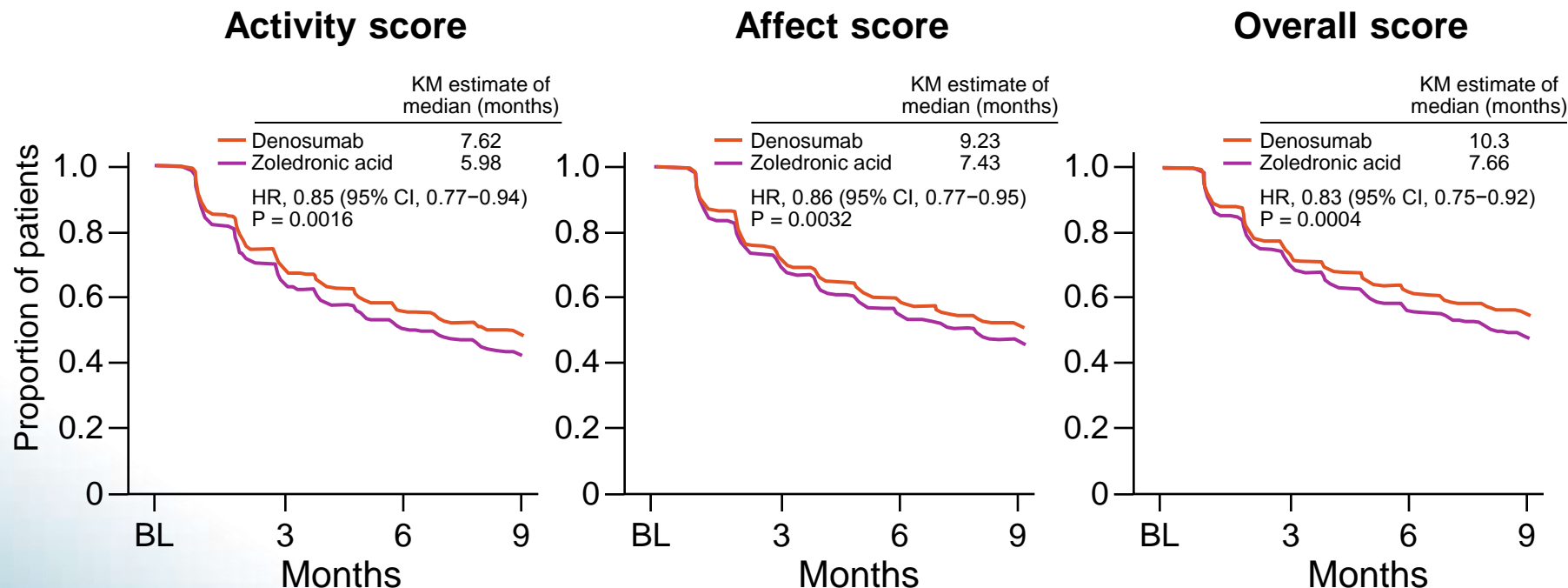
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

8.7 Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

Denosumab reduced the risk of increased pain interference vs zoledronic acid on all three scales

Proportion of patients free of increased pain interferences (≥ 2 -point increase) among patients with no or mild pain at baseline



Health-related quality of life

Functional Assessment of Cancer Therapy- General (FACT-G) used to assess HRQoL

QoL improvement

≥ 5-point increase is considered a clinically meaningful improvement in HRQoL

QoL deterioration

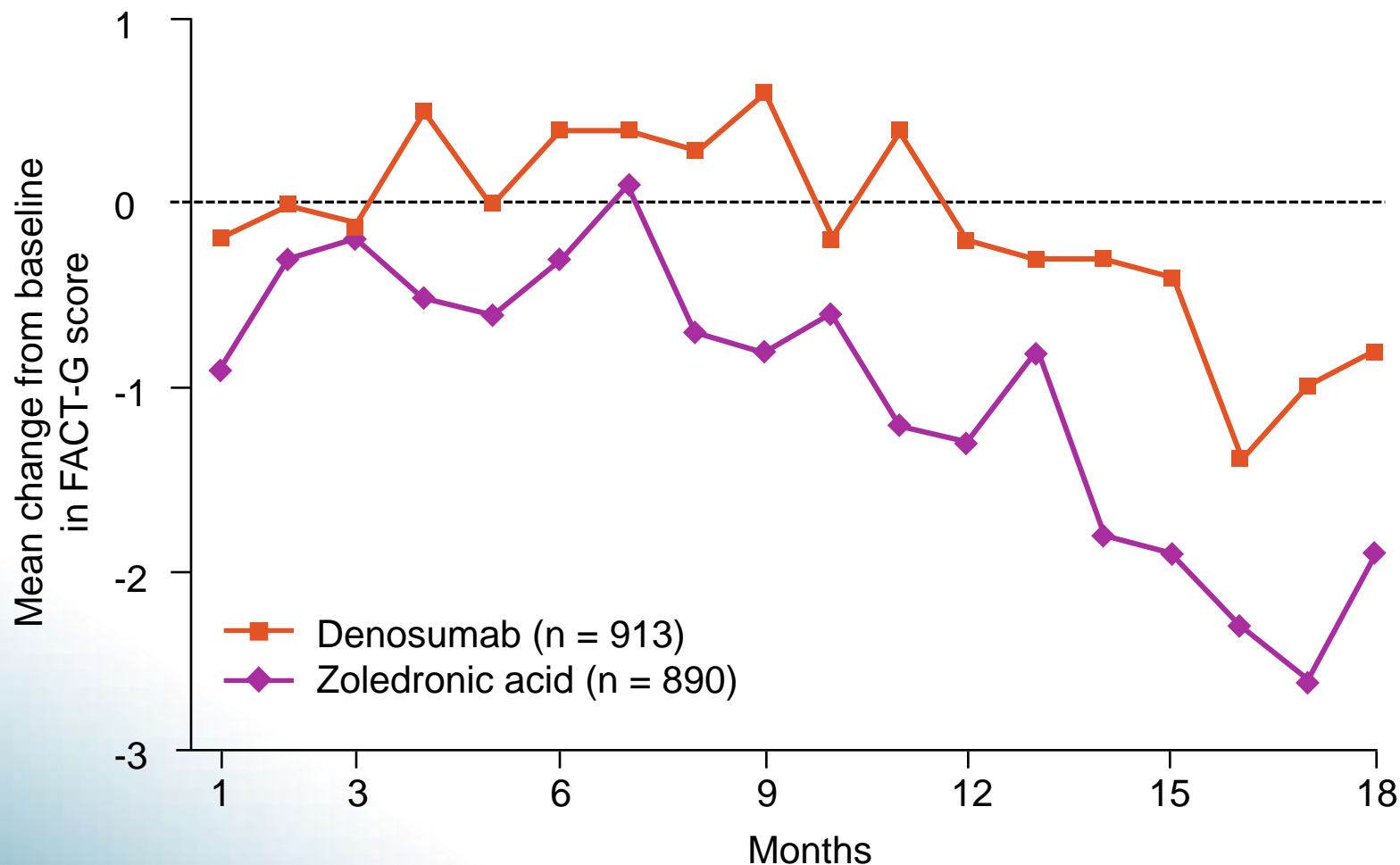
≥ 5-point reduction is considered a clinically meaningful worsening in HRQoL

Functional Assessment of Cancer Therapy -- FACT-G

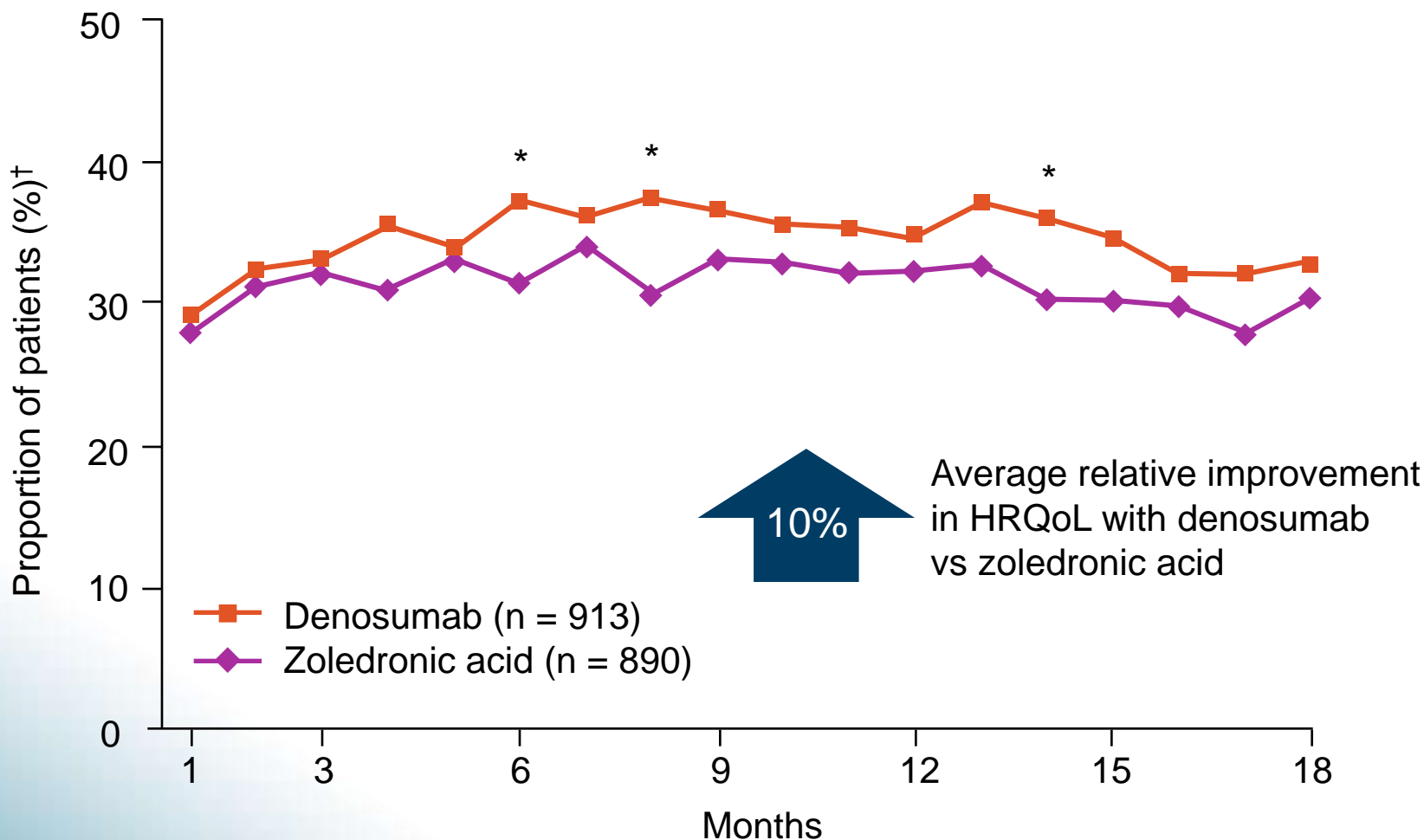
Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
<u>PHYSICAL WELL-BEING</u>						
001	I have a lack of energy.....	0	1	2	3	4
002	I have nausea.....	0	1	2	3	4
003	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
004	I have pain.....	0	1	2	3	4
005	I am bothered by side effects of treatment.....	0	1	2	3	4
006	I feel ill.....	0	1	2	3	4
007	I am forced to spend time in bed.....	0	1	2	3	4
<u>SOCIAL/FAMILY WELL-BEING</u>						
008	I feel close to my friends.....	0	1	2	3	4
009	I get emotional support from my family.....	0	1	2	3	4
010	I get support from my friends.....	0	1	2	3	4
011	My family has accepted my illness.....	0	1	2	3	4
012	I am satisfied with family communication about my illness.....	0	1	2	3	4
013	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box <input type="checkbox"/> and go to the next section.</i>						
014	I am satisfied with my sex life.....	0	1	2	3	4
<u>EMOTIONAL WELL-BEING</u>						
015	I feel sad.....	0	1	2	3	4
016	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
017	I am losing hope in the fight against my illness.....	0	1	2	3	4
018	I feel nervous.....	0	1	2	3	4
019	I worry about dying.....	0	1	2	3	4
020	I worry that my condition will get worse.....	0	1	2	3	4
<u>FUNCTIONAL WELL-BEING</u>						
021	I am able to work (include work at home).....	0	1	2	3	4
022	My work (include work at home) is fulfilling.....	0	1	2	3	4
023	I am able to enjoy life.....	0	1	2	3	4
024	I have accepted my illness.....	0	1	2	3	4
025	I am sleeping well.....	0	1	2	3	4
026	I am enjoying the things I usually do for fun.....	0	1	2	3	4
027	I am content with the quality of my life right now.....	0	1	2	3	4

In breast cancer, denosumab was associated with higher HRQoL than zoledronic acid



A higher proportion of patients on denosumab had a clinically meaningful improvement (≥ 5 -point increase) in HRQoL vs zoledronic acid



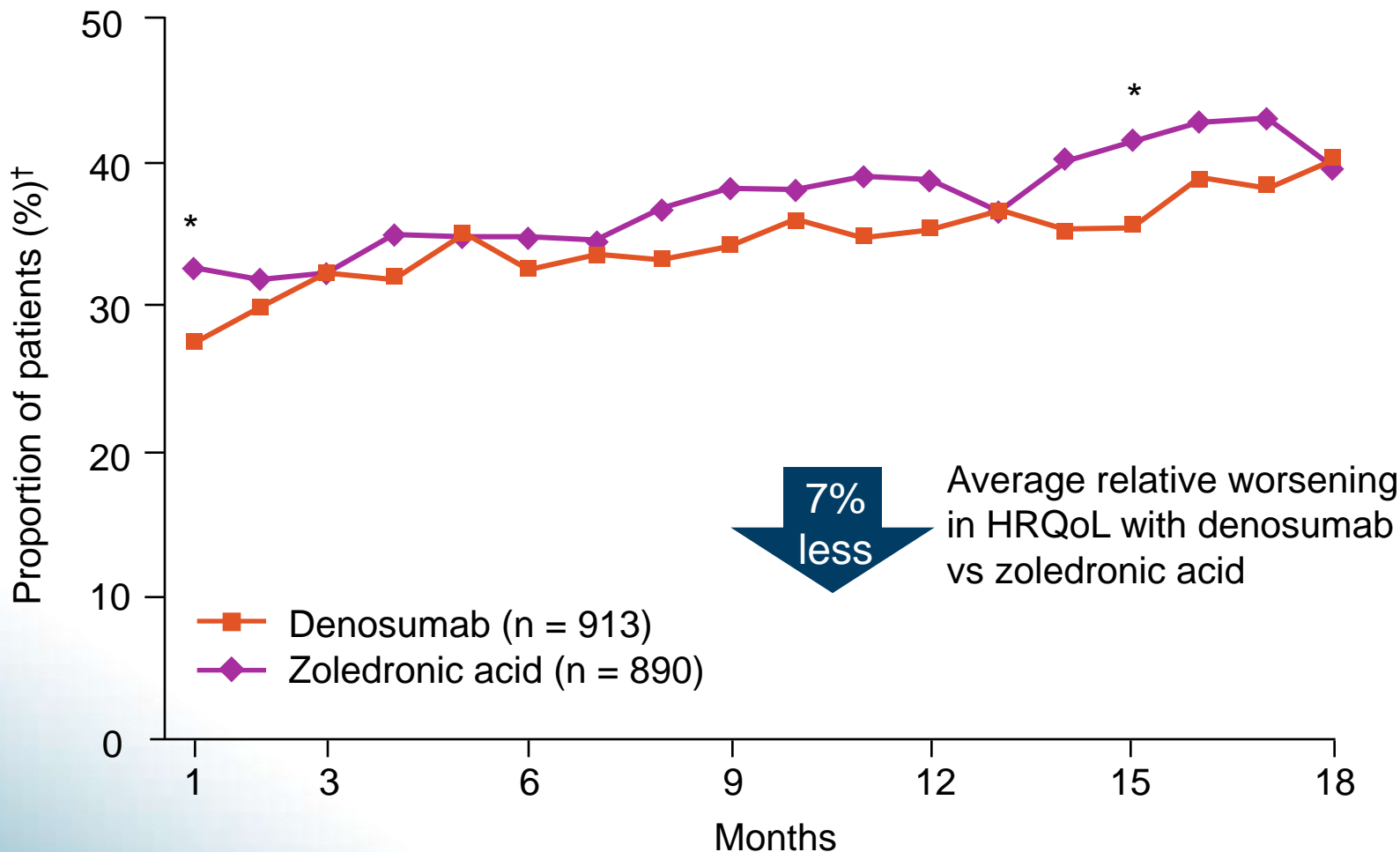
*P < 0.05.

†Proportion with clinically meaningful improvement (≥ 5 -point increase) in HRQoL on FACT-G score.

HRQoL, Health Related Quality of Life; FACT-G, Functional Assessment of Cancer Therapy-General

Fallowfield L, et al. Poster presented at ASCO BCS 2011 [Abstract 272].

A lower proportion of patients on denosumab had a clinically meaningful worsening (≥ 5 -point decrease) in HRQoL vs zoledronic acid



*P < 0.05.

†Proportion with clinically meaningful improvement (≥ 5 -point decrease) in HRQoL on FACT-G score.

HRQoL, Health Related Quality of Life; FACT-G, Functional Assessment of Cancer Therapy-General

Fallowfield L, et al. Poster presented at ASCO BCS 2011 [Abstract 272].

Conclusions

- SREs are associated with pain and negatively affect all aspects of patient quality of life¹
- Bone-targeted therapy has a role in pain management
- Denosumab compared with zoledronic acid is associated with:
 - Delayed progression to moderate or severe pain in patients with no or mild pain^{2–5}
 - Delayed progression from no or low analgesic use to strong opioid use⁵
 - Reduced risk of increased pain interference⁶
 - More patients reporting QoL improvement and fewer patients reporting QoL deterioration⁷

SRE, Skeletal-Related Event; QoL, Quality of Life

1. Weinfurt KP, et al. *Ann Oncol* 2005;16:579–84; 2. Stopeck A, et al. *J Clin Oncol* 2010;28(Suppl 15) [Abstract 1024];
3. Brown JE, et al. *Eur Urol Suppl* 2011;10:336 [Abstract 1091]; 4. Fallowfield L, et al. Oral presentation at EMCC 2011 [Abstract 7004];
5. Cleeland CS, et al. *Ann Oncol* 2010;21(Suppl 8):Viii379 [Abstract 1248P]; 6. Von Moos E, et al. In press;
7. Fallowfield L, et al. Poster presented at ASCO BCS 2010 [Abstract 272].

¡ Muchas gracias !

