Disclosure

- This slide deck has been provided as an educational resource
- Please note that denosumab is investigational and is not marketed anywhere in the world
- For additional information regarding this slide deck or to receive the most updated slides please contact:
  - Eduard Gasal, Amgen (Europe) GmbH
    eduard.gasal@amgen.com
    +41 41 369 04 37 (phone)

Denosumab in multiple myeloma

Prof Patrick Stiff

Cardinal Bernardin Cancer Center, Loyola University

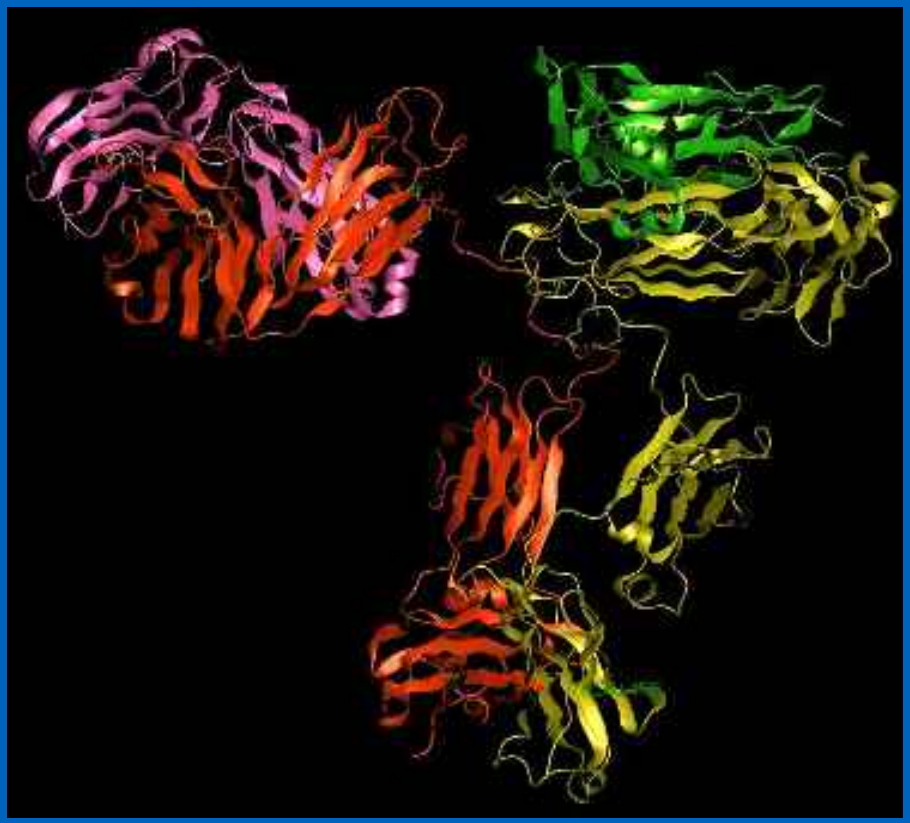
Illinois (USA)

Denosumab is investigational and is not marketed anywhere in the world

Denosumab

- Human mAb
- High affinity & specificity → RANK Ligand
- No neutralising antibodies detected in clinical trials
- Delivered s.c.

Model of denosumab



Bekker PJ et al. *J Bone Miner Res* 2004;19:1059-1066
Elliott R et al. *Osteoporos Int* 2007;18:S54:P149
McClung MR et al. *New Engl J Med* 2006;354:821-31

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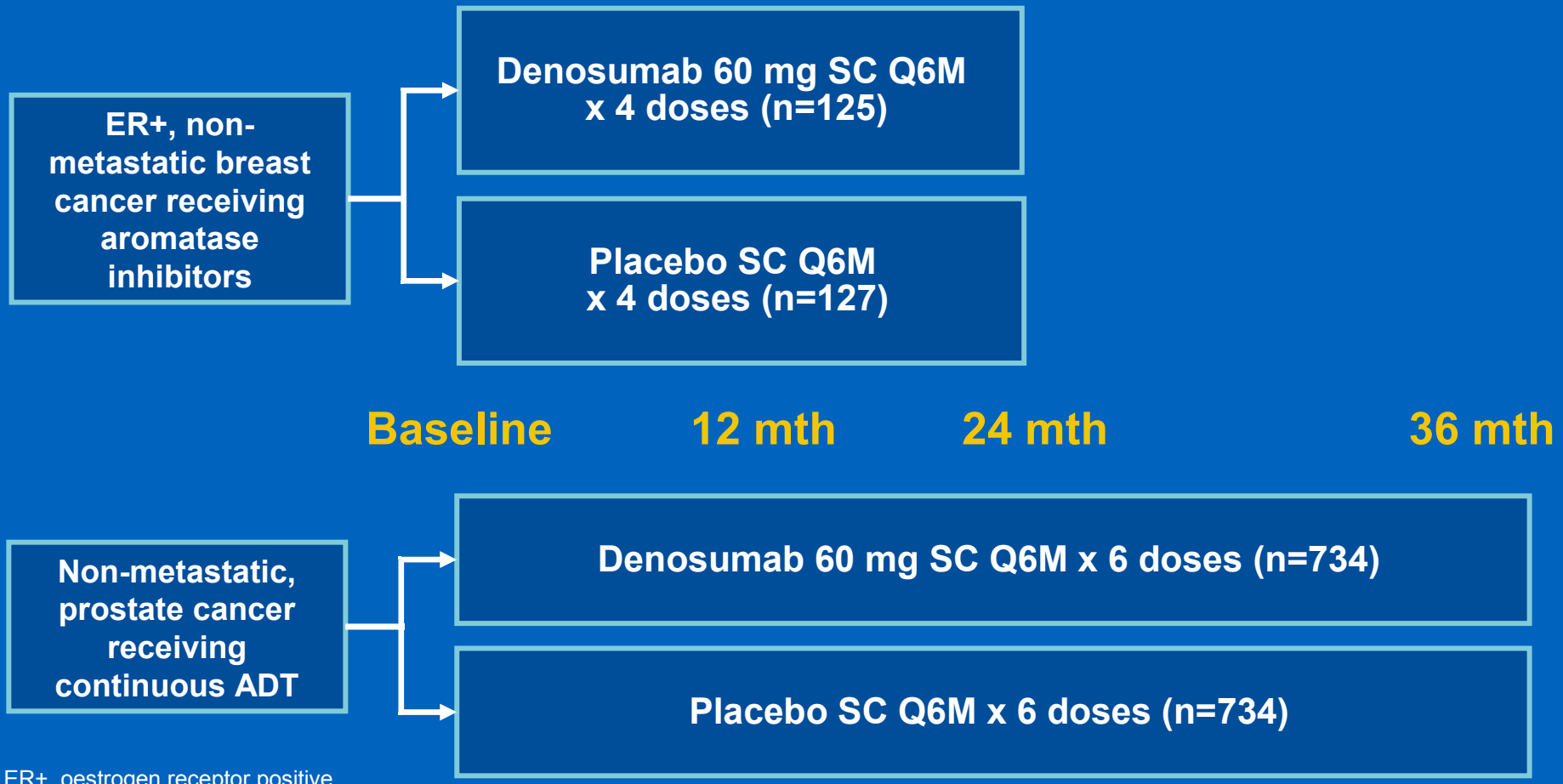
Denosumab in cancer treatment-induced bone loss (CTIBL)



ER+, oestrogen receptor positive
SC, subcutaneous
Q6M, once every 6 months
ADT, androgen deprivation therapy

Ellis GK et al. *J Clin Oncol* 2008;26:4875–4882
www.clinicaltrials.gov

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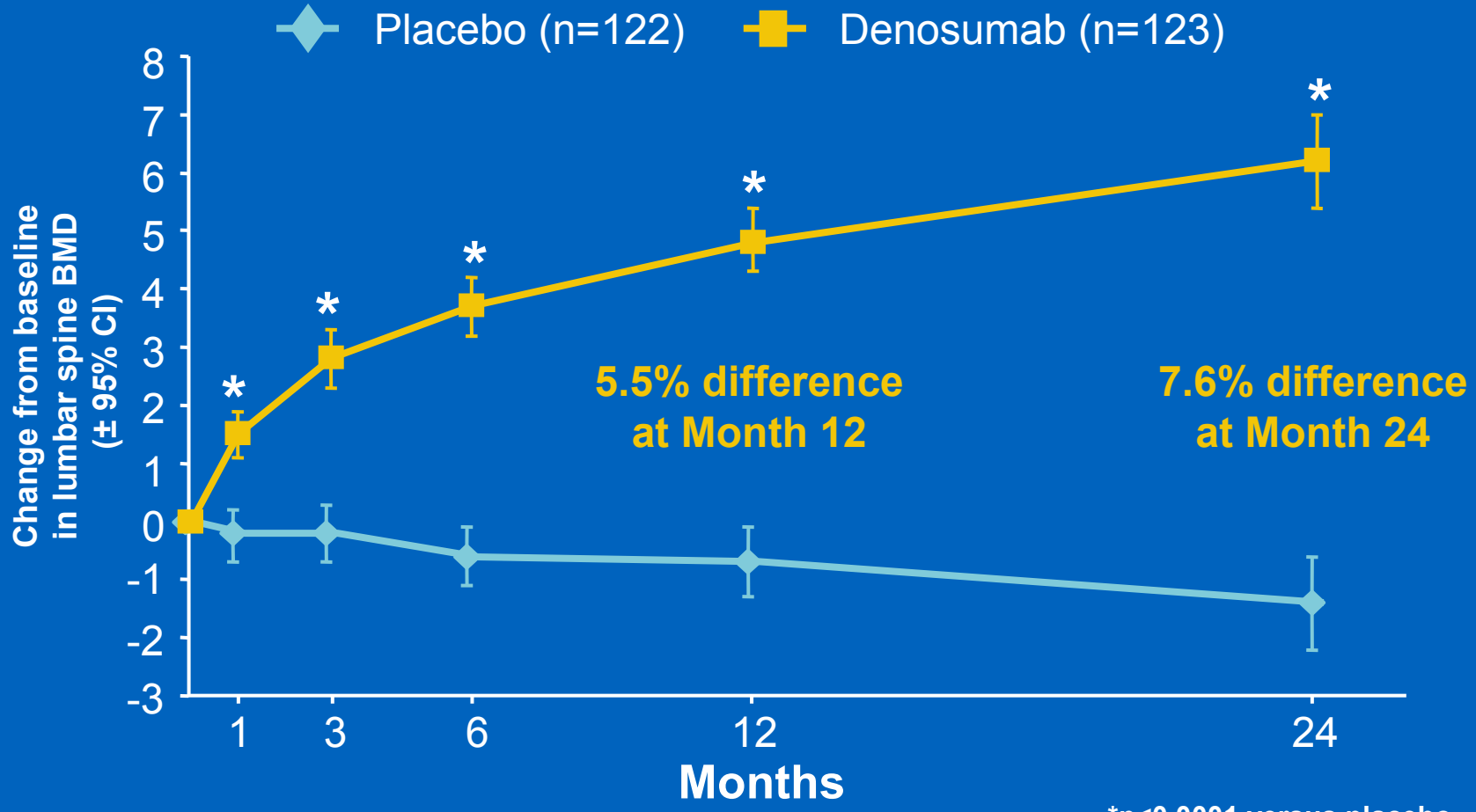
Cancer treatment-induced bone loss in breast cancer: denosumab significantly improved BMD



*p<0.0001 versus placebo

BMD, bone mineral density
CI, confidence interval

Ellis GK et al. *J Clin Oncol* 2008;26:4875-4882

Denosumab is investigational and is not marketed anywhere in the world

Cancer treatment-induced bone loss in prostate cancer: denosumab significantly improved BMD

- 1468 men with prostate cancer on androgen deprivation therapy (ADT), 3-year study
  - Significant increases in bone mineral density (BMD) at the lumbar spine (primary endpoint) and non-vertebral sites
  - Significant reduction by more than half of the incidence of new vertebral fractures (secondary endpoint) compared with those receiving placebo
  - Incidence and types of adverse events were generally similar between denosumab and placebo

Business Wire July 14, 2008

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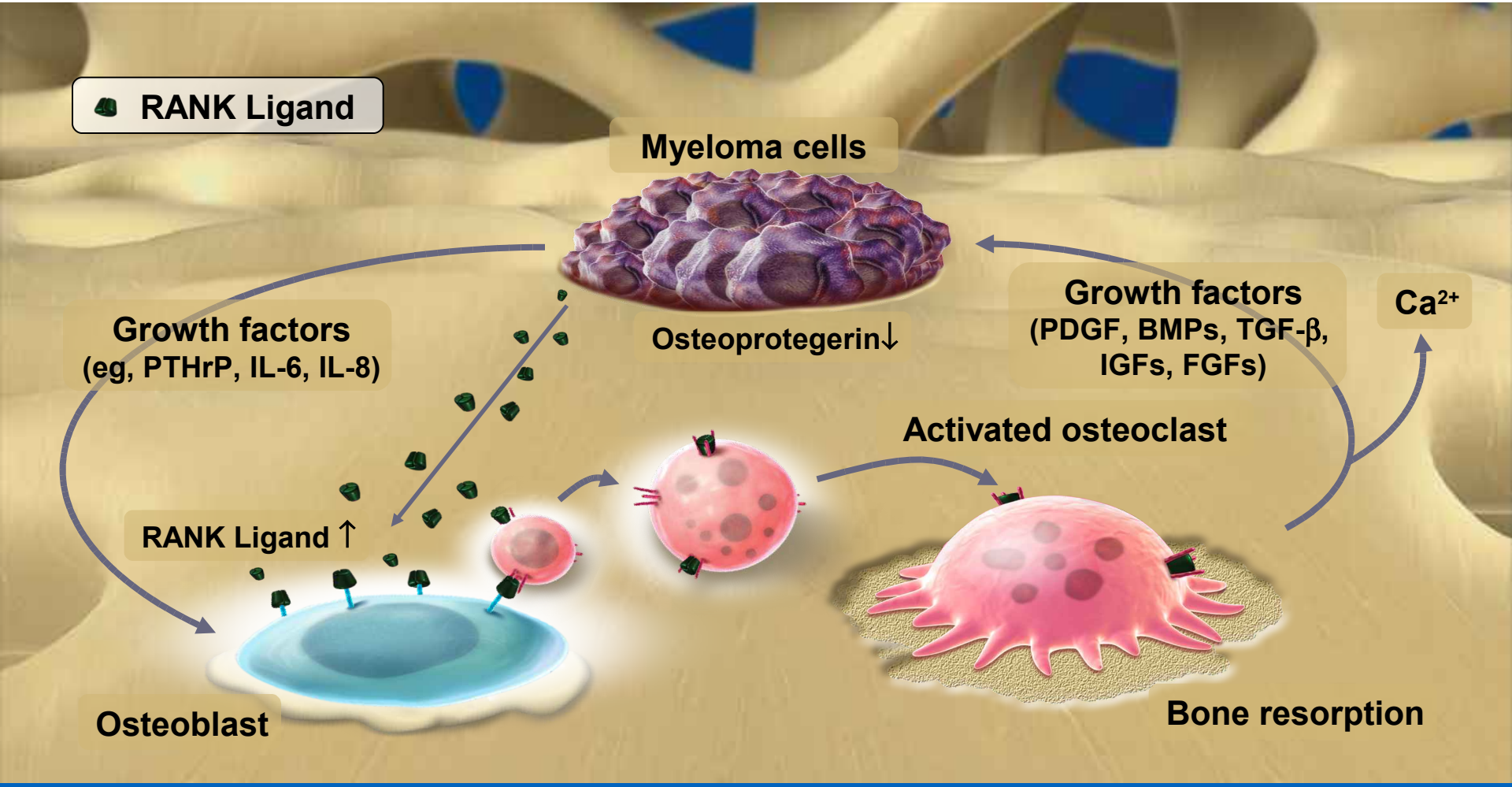
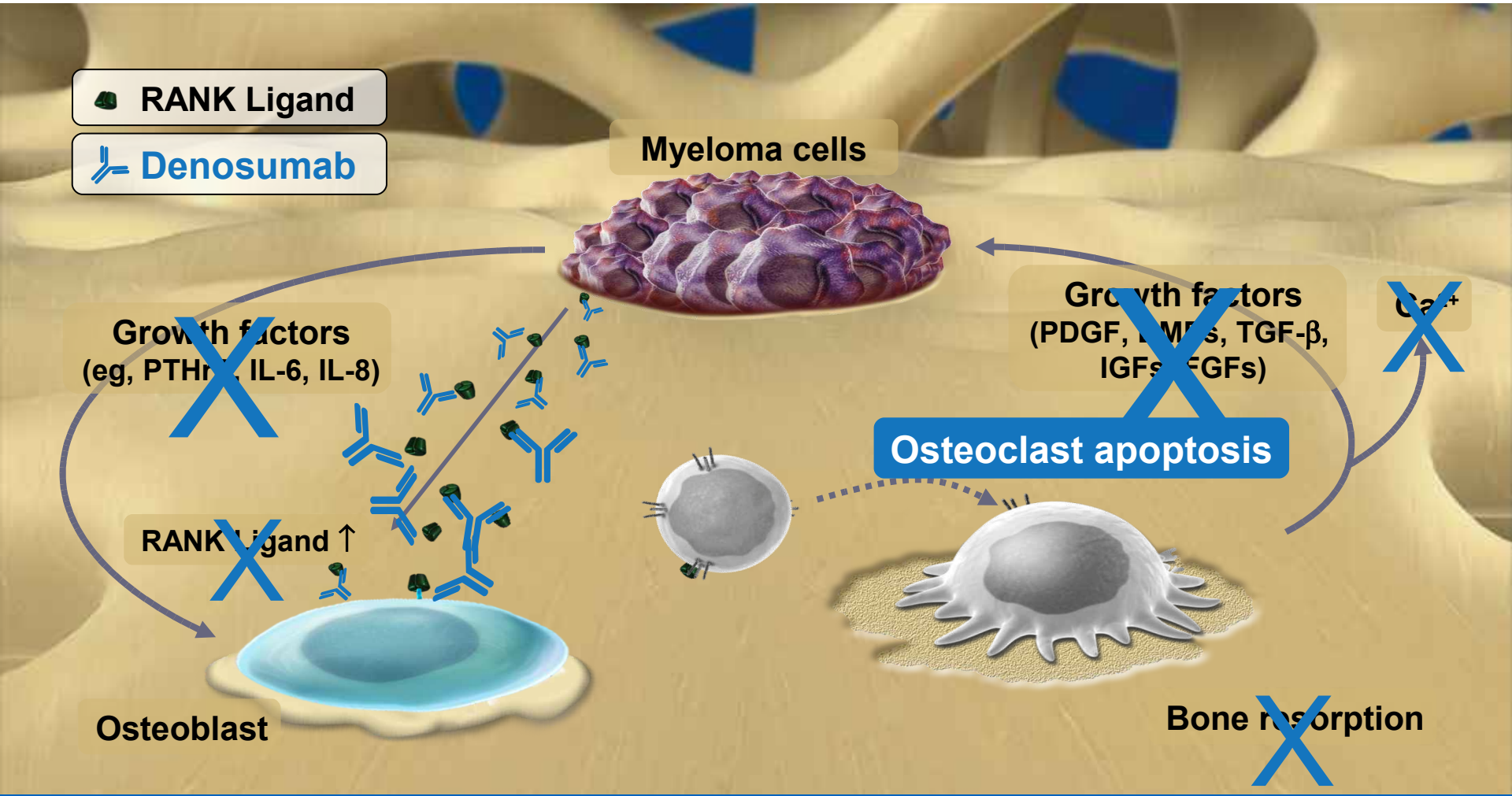
The ‘vicious cycle’ hypothesis of bone destruction in multiple myeloma



Adapted from: Boyle WJ et al. *Nature* 2003;423:337−342; Roodman GD. *N Engl J Med* 2004;350:1655−1664; Roodman GD. *Leukemia* 2009;23:435–441

Denosumab may interrupt the vicious cycle of bone destruction in multiple myeloma



The above depiction is believed to be the mode of action of denosumab

Adapted from: Boyle WJ et al. *Nature* 2003;423:337−342; Roodman GD. *N Engl J Med* 2004;350:1655−1664

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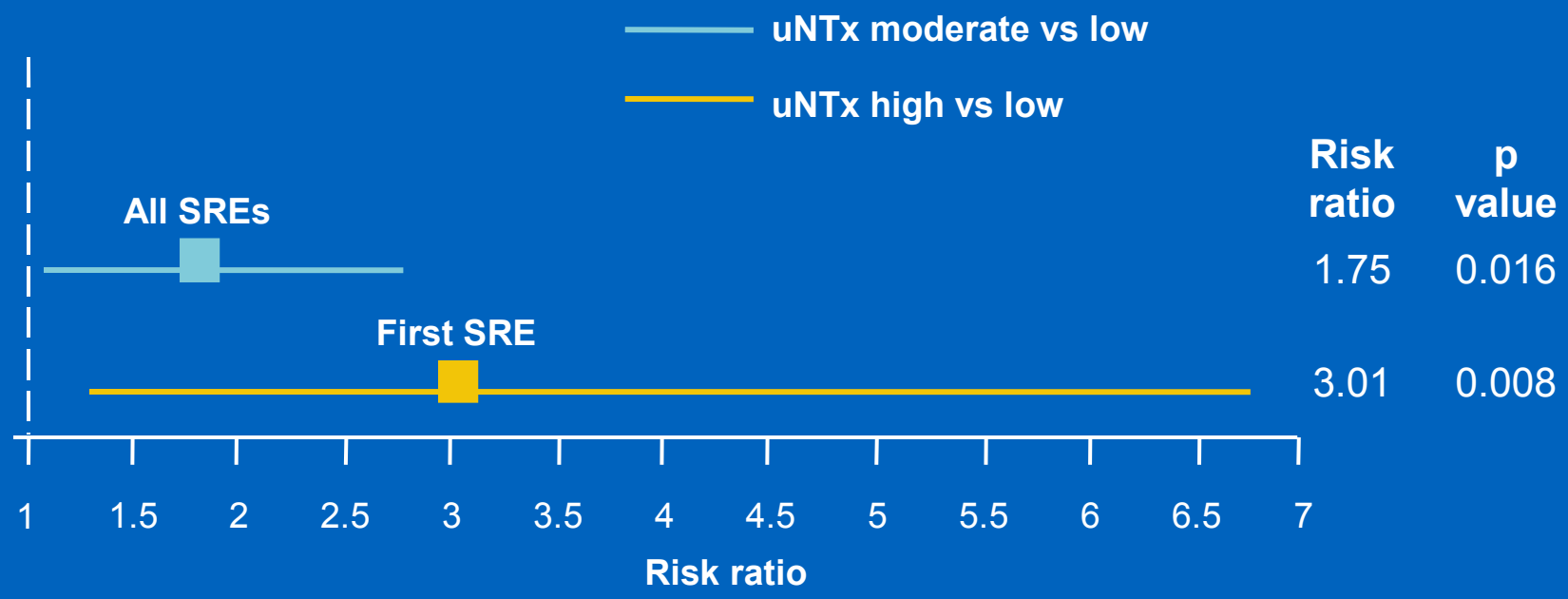
Markers of bone resorption predict skeletal-related events (SREs), cancer progression and survival

- Osteolysis results in release of bone products such as the amino- and carboxyterminal cross-linked telopeptides of type I collagen (uNTx and sCTx respectively)
- CTx and NTx can be measured from serum and urine (eg sCTx and uNTx) and used as surrogate markers of bone resorption (urinary values are corrected for creatinine)
- Elevated levels of sCTx and uNTx are predictive of skeletal-related events, cancer progression and death[1–5]

1. Coleman RE et al. *J Clin Oncol* 2005;23:4925–4935; 2. Brown JE et al. *J Nat Cancer Inst* 2005;97:59–69;
3. Brown JE et al. *Br J Cancer* 2003;89:2031–2037; 4. Costa L et al. *J Clin Oncol* 2002;20:850–856;
5. Terpos E. *Cancer Treat Rev* 2006;32 Suppl 1:15–19

Relative risk of SREs depends on level of uNTx in MM

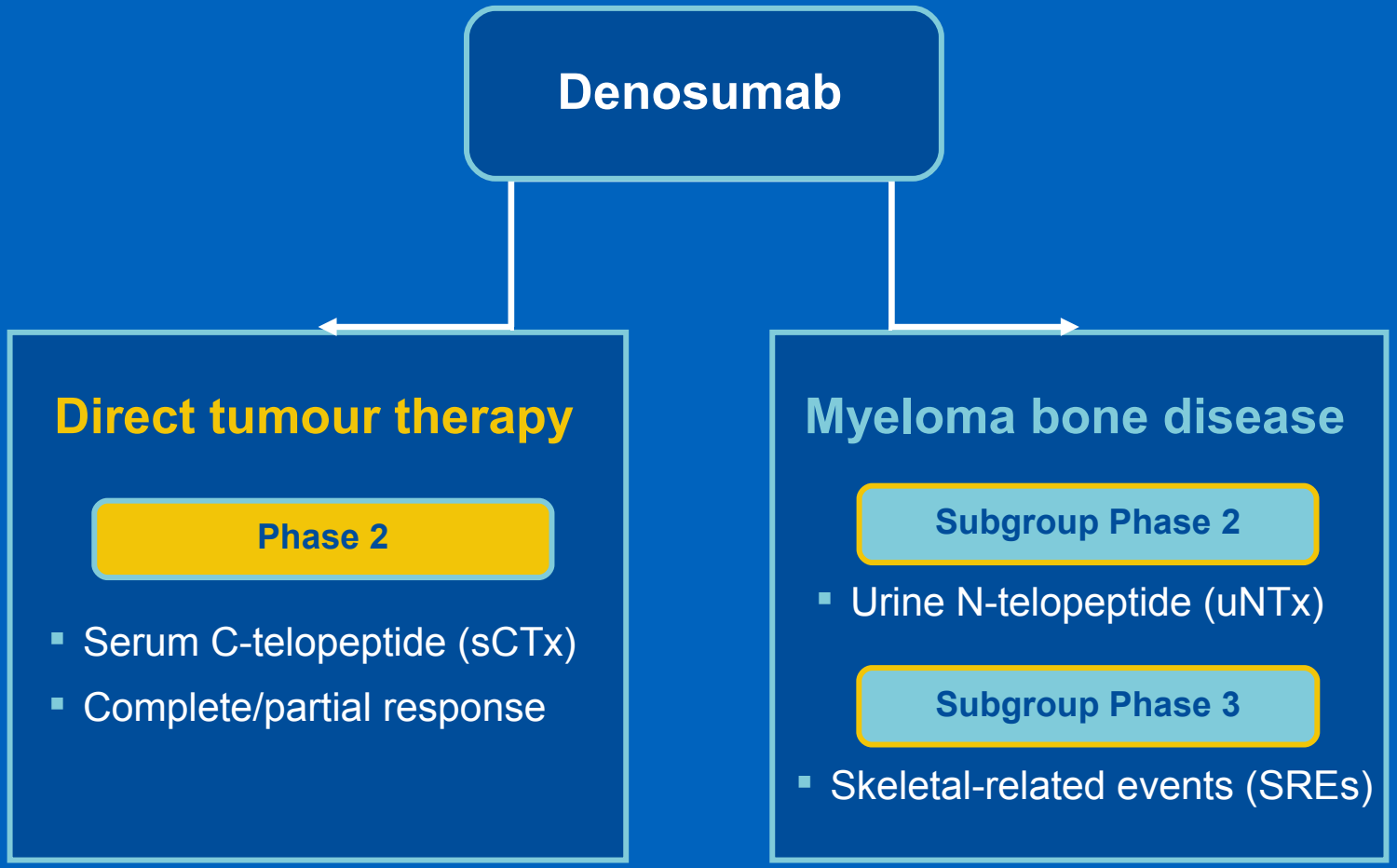


uNTx:

- Breakdown product of bone collagen
- Bone resorption marker
- Correlates with extent of lytic disease, SREs and survival

Lipton A et al. *Clin Lymphoma Myeloma* 2007;7:346−353; Coleman RE, et al. *J Clin Oncol* 2005;23:4925−4935

Denosumab clinical trials: multiple myeloma



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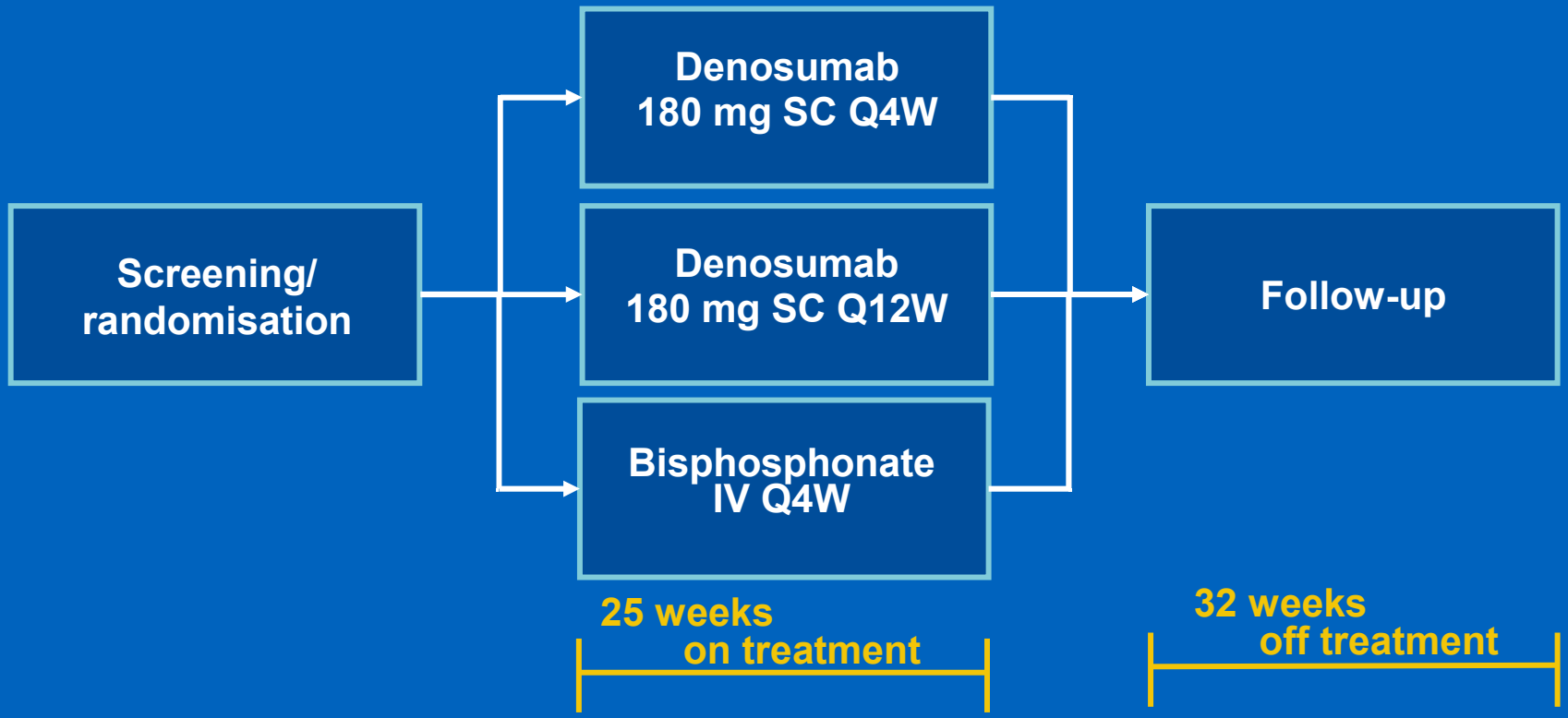
Phase 2, randomised, open-label, multicentre study: in patients with carcinomas or MM previously treated with bisphosphonates



- Stratification by tumour type and screening urine N-telopeptide levels
- Patients had the option of entering a ongoing 2-year extension study

Q4W, once every 4 weeks; Q12W, once every 12 weeks

Fizazi K et al. *J Clin Oncol* 2009;27:1564−1571

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Inclusion/exclusion criteria

- Key inclusion criteria
  - Histologically confirmed carcinomas (except lung) or MM
  - Radiographic evidence of ≥1 bone lesion
  - Performance status ≤2
  - uNTx >50 nmol/L/mM corrected for creatinine at screening despite IV BP treatment for ≥8 weeks before enrollment
- Key exclusion criteria
  - >2 prior SREs
  - Radiation to the bone ≤2 weeks before randomisation
  - Radioisotopes directed to bone ≤8 weeks before randomisation
  - Unresolved toxicities >grade 2 from prior anticancer therapy
  - Brain metastases

Fizazi K et al. *J Clin Oncol* 2009;27:1564−1571

Phase 2 endpoints

- Primary
  - Proportion of patients with uNTx <50 nmol/L/mM corrected for creatinine at Week 13
- Secondary
  - Proportion of patients with uNTx <50 during the course of the study
  - Time to reduction of uNTx <50
  - Duration of uNTx <50
  - Percent change in sCTx from baseline to Week 25
  - Percent change in uNTx from baseline to Week 25
  - Incidence of hypercalcaemia
  - Time to first on-study skeletal-related events
  - Proportion of patients experiencing skeletal-related events
  - Incidence of adverse events

Fizazi K et al. *J Clin Oncol* 2009;27:1564−1571

Baseline characteristics: tumour type

Tumour type	IV BPs (n=37) n (%)	All SC denosumab (n=74) n (%)
Breast	16 (43)	30 (40)
Prostate	17 (46)	33 (45)
Multiple myeloma	3 (8)	6 (8)
Other solid tumour	1 (3)	5 (7)

Fizazi K et al. *J Clin Oncol* 2009;27:1564–1571

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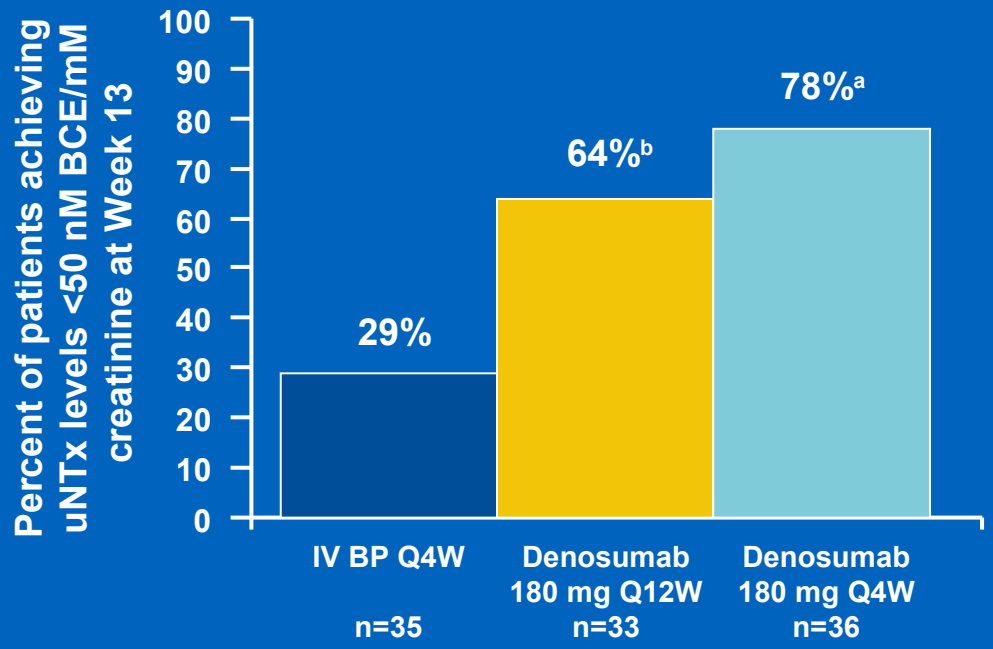
Phase 2 results: urine N-telopeptide (uNTx) levels at Week 13

Corrected for creatinine



[a]p<0.001 vs IV BP
[b]p≤0.005 vs IV BP

Fizazi K et al. *J Clin Oncol* 2009;27:1564−1571

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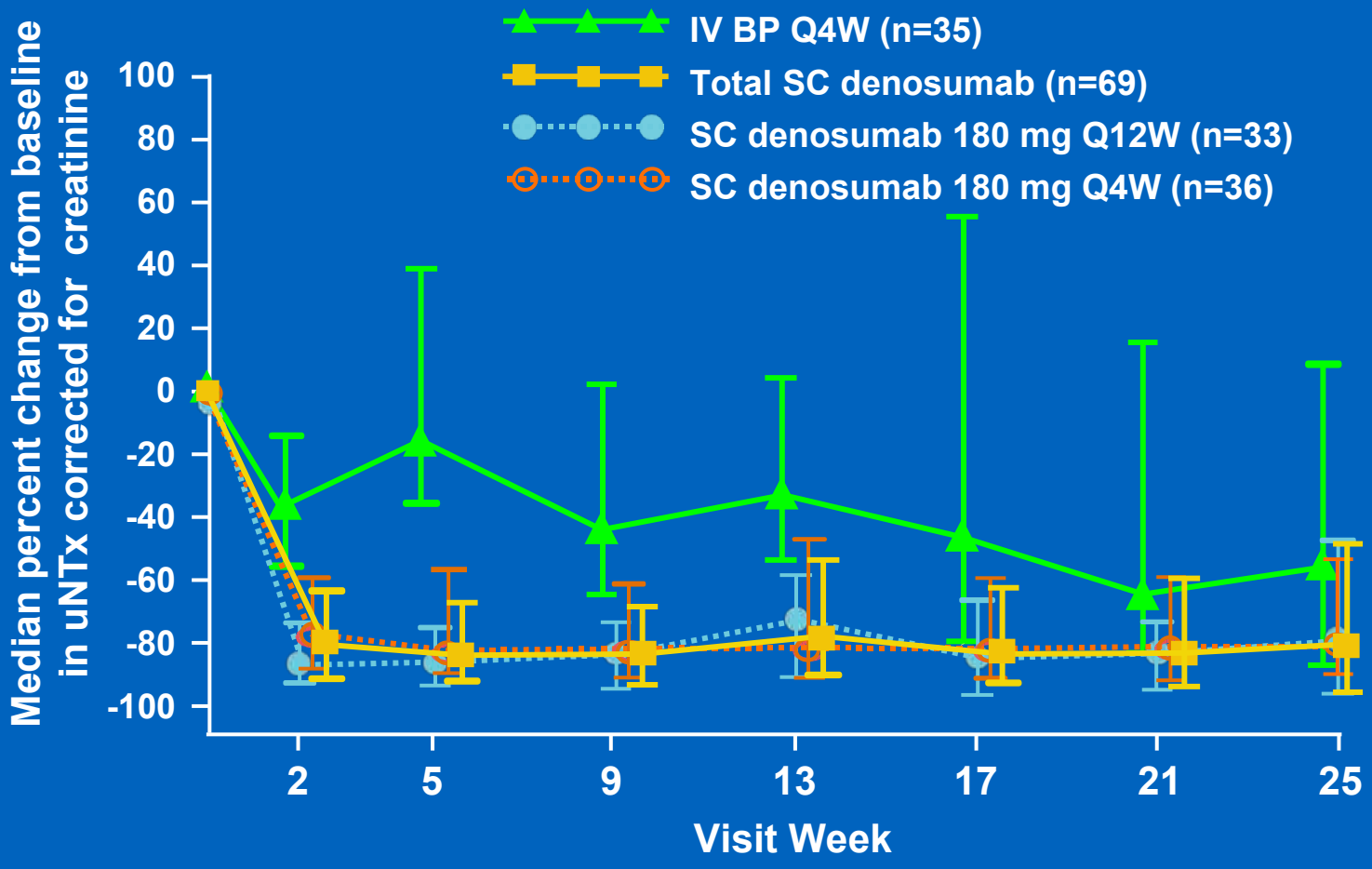
Median percent change in urine N-telopeptide (uNTx) from baseline



Fizazi K et al. *J Clin Oncol* 2009;27:1564–1571

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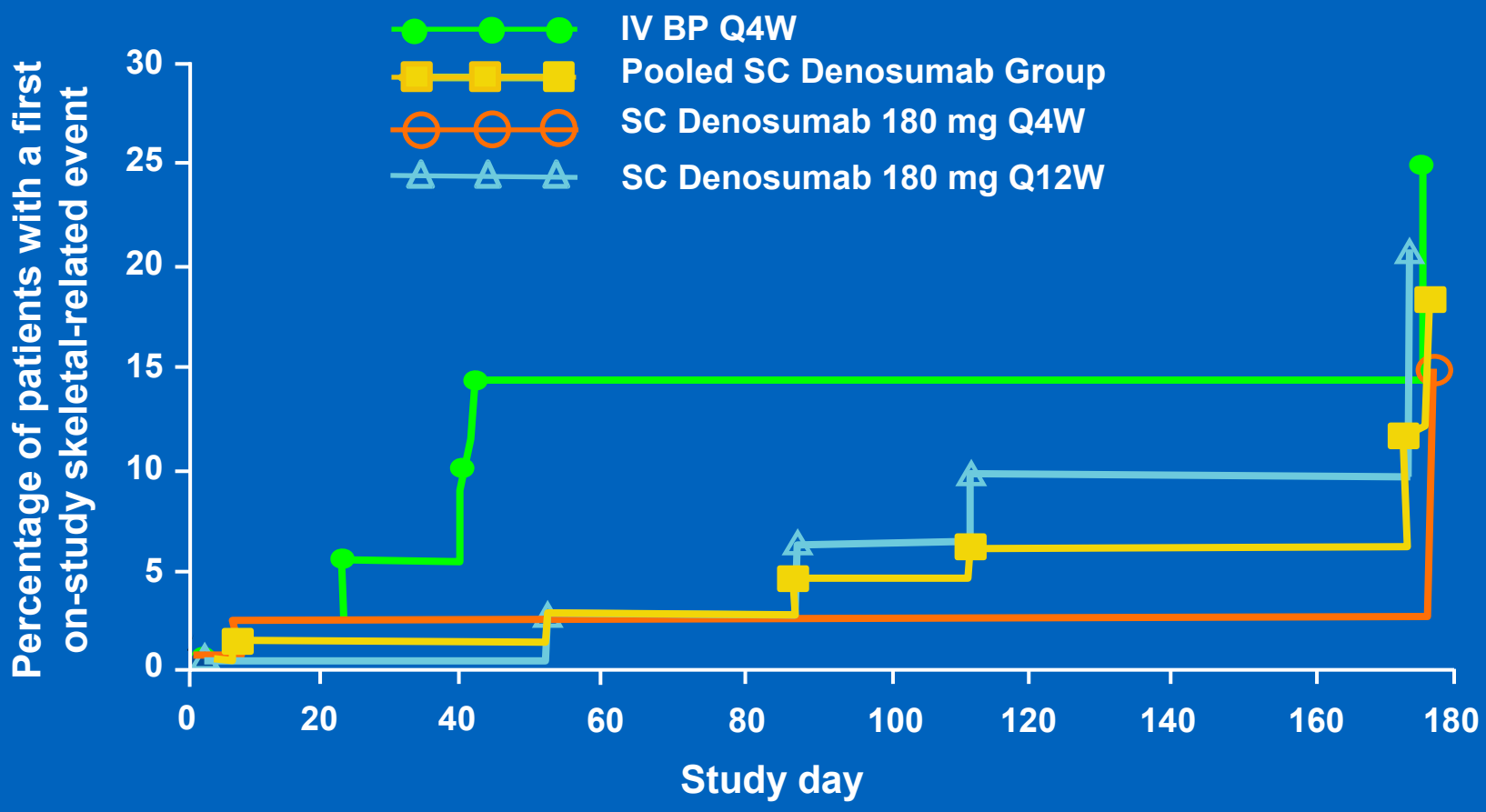
Effects of denosumab on other bone markers

- Denosumab also suppressed:
  - Serum C-telopeptide
  - Aminoterminal propeptide type-1 procollagen
  - Tartrate-resistant acid phosphatase
  - Bone-specific alkaline phosphatase
  - Osteocalcin
- Escape from suppression of serum C-telopeptide and urine N-telopeptide was noted in more patients receiving continuing IV BP therapy and SC denosumab 180 mg Q12W than those receiving SC denosumab Q4W

Fizazi K et al. *J Clin Oncol* 2009;27:1564−1571

Patients experiencing first on-study skeletal-related event



Fizazi K et al. *J Clin Oncol* 2009;27:1564–1571

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Safety: most common adverse events in >10% of denosumab patients

	IV BP Q4W (n=35) n (%)	All SC denosumab (n=73) n (%)
Bone pain	12 (34)	21 (29)
Nausea	7 (20)	17 (23)
Anaemia	8 (23)	17 (23)
Constipation	6 (17)	16 (22)
Asthaenia	7 (20)	15 (21)
Peripheral oedema	1 (3)	11 (15)
Diarrhoea	4 (11)	10 (14)
Paraesthesia	3 (9)	10 (14)
Thrombocytopenia	2 (6)	9 (12)
Fatigue	4 (11)	8 (11)
Back pain	5 (14)	8 (11)

Fizazi K et al. *J Clin Oncol* 2009;27:1564−1571

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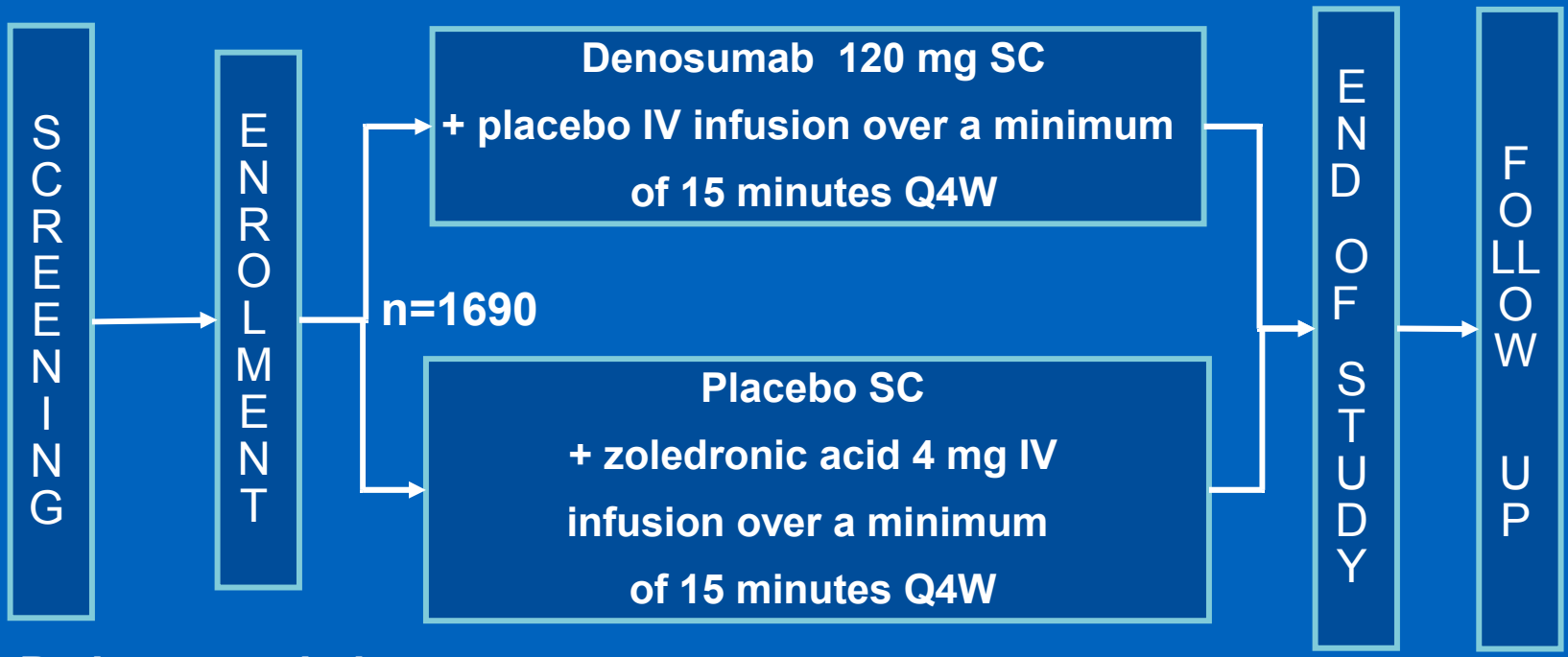
Phase 3 study of denosumab in solid tumours and MM

Primary endpoint: time to first on-study skeletal-related event
Secondary endpoint: multiple events analysis



Patient population:

- Evidence of at least 1 bone metastasis
- No prior treatment with IV bisphosphonates
- 6 months survival expected

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