Evidence Profile 5.2.5. Monoclonals vs. Bisphosphonates

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal (Denosumab)	Bisphosphonate	Relative (95% CI)	Absolute (95% CI)		
Pain relief (categorical) (follow up: 18 months)												
1 [1]	RCT	serious [A]	not serious	serious [B]	not serious	single study	156/975 (16%) [B]	171/951 (18%) [B]	**RR 0.89** [B] (0.67 to 1.10)	**20 fewer per 1,000** (from 15 more to 49 fewer)	Low	CRITICAL
Pain relief speed (follow up: 18 months)												
1 [1]	RCT	serious [A]	not serious	not serious	not serious	single study	747	745	**HR 1.02** (0.91, 1.15) [2.7 vs. 2.6 months]	**0.1 month**	Low	IMPORTANT
Pain reduction maintenance												
0									not estimable			CRITICAL
Skeletal-related events, any (follow up: range 25 weeks to 41 months)												
6 [2,3,4,5,6,7,8, C]	RCT	not serious	not serious	not serious	not serious	none	1284/4172 (31%)	1461/3959 (37%)	**RR 0.86** (0.81 to 0.91)	**39 fewer per 1000** (from 24 to 53 fewer)	High	IMPORTANT
Skeletal-related events, fracture (follow up: 18 months)												
2 [3, 5]	RCT	not serious	not serious	not serious	not serious	none	743/3888 (19%)	840/3881 (22%)	**RR 0.88** (0.78 to 0.96)	**26 fewer per 1000** (from 8 to 42 fewer)	High	IMPORTANT
Skeletal-related events, spinal cord compression (follow up: nd)												
1 [5]	RCT	not serious	not serious	not serious	not serious	single study	76/2862 (2.7%)	86/2861 (3.0%)	**RR 0.88** (0.65 to 1.20)	**4 fewer per 1000** (from 6 more to 10 fewer)	Moderate	IMPORTANT
Skeletal-related events, bone radiation (follow up: 18 months)												
2 [3, 5]	RCT	not serious	not serious	not serious	not serious	none	632/3888 (16%)	787/3881 (20%)	**RR 0.80** (0.73 to 0.88)	**37 fewer per 1000** (from 22 to 51 fewer)	High	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal (Denosumab)	Bisphosphonate	Relative (95% CI)	Absolute (95% CI)		
Skeletal-related events, bone surgery (follow up: nd)												
1 [5]	RCT	not serious	not serious	not serious	not serious	single study	64/2862 (2.2%)	72/2861 (2.5%)	**RR 0.87** (0.62 to 1.23)	**3 fewer per 1000** (from 6 more to 9 fewer)	Moderate	IMPORTANT
Skeletal-related events, hypercalcemia (follow up: 18 months)												
2 [3, 5]	RCT	not serious	not serious	not serious	not serious	none	64/3888 (1.6%)	111/3881 (2.9%)	**RR 0.58** (0.34 to 0.81)	**16 fewer per 1000** (from 7 to 22 fewer)	High	IMPORTANT
Quality of life (follow up: 18 months; assessed with: FACT-G; Scale: 0 to 100 [best] [D])												
1 [1]	RCT	serious [A]	not serious	serious [E]	not serious	single study	314/956 (33%) [F]	290/952 (30%) [F]	**RR 1.08** (0.95 to 1.23) [F]	**24 more per 1000** (from 17 fewer to 70 more)	Very Low	CRITICAL
Functional outcomes (follow up: 18 months; assessed with: ECOG; Scale: 0 to 100 [best] [D])												
2 [1,3]	RCT	serious [A]	not serious	serious [E]	not serious	none	1703	1697	**HR 0.89** (0.78 to 1.02) [16.0 vs. 14.9 mo] [G] **RR 1.07** (0.99 to 1.16) [H]	**1.1 month** **41 more per 1000** (from 4 fewer to 89 more)	Low	IMPORTANT
Adverse events: Osteonecrosis of the jaw (follow up: range 2.8 month to 41 months)												
3 [5 C]	RCT	not serious	not serious	not serious	not serious	none	52/2841 (1.8%)	37/2836 (1.3%)	**RR 1.40** (0.92, 2.13)	**5 more per 1000** (from 1 fewer to12 more)	High	IMPORTANT

Abbreviations: CI: *confidence interval;* ***ECOG:*** *Eastern Cooperative Oncology Group scale;* ***FACT-G****: Functional Assessment of Cancer Therapy–General****; HR:*** *hazard ratio;* ***N/A:*** *not applicable;* ***nd****: no data;* ***NS:*** *not statistically significant;* ***OR****: odds ratio;* ***RCT:*** *randomized controlled trial(s);* ***RR****: relative risk (log scale);* ***SRE:*** *skeletal-related event(s).*

Explanations

A. High percentage not analyzed.
B. Outcome is a decrease in pain by >=2/10 points, not pain relief.
C. Some data were compiled from Lipton 2012 (PMID 22975218), which combined Fizazi 2011 (PMID 21353695), Henry 2011 (PMID 21343556), and Stopeck 2010 (PMID 21060033).
D. Scales transformed to 0 to 100, as necessary.
E. FACT (total score) is a measure of quality of life that mix concepts of both quality of life and functional outcomes.
F. Improvement in FACT-G >=5/108 points.

G. Time to increase (worsening) in interference due to pain >=2/10 points, favors monoclonal.
H. ECOG performance status maintained, favors monoclonal.

Trials

1. Cleeland, C. S., Body, J. J., Stopeck, A., et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer; Feb 15 2013.
2. Stopeck, A. T., Lipton, A., Body, J. J., et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol; Dec 10 2010.
3. Martin, M., Bell, R., Bourgeois, H., et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res; Sep 01 2012.
4. Lipton, A., Steger, G. G., Figueroa, J., et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. Clin Cancer Res; Oct 15 2008.
5. Lipton, A., Fizazi, K., Stopeck, A. T., et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer; Nov 2012.
6. Henry, D. H., Costa, L., Goldwasser, F., et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol; Mar 20 2011.
7. Fizazi, K., Carducci, M., Smith, M., et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet; Mar 05 2011.
8. Fizazi, K., Lipton, A., Mariette, X., et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol; Apr 01 2009.
9. Body, J. J., Facon, T., Coleman, R. E., et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res; Feb 15 2006.