The improved long-term outcome of Denosumab-treated postmenopausal women with early luminal breast cancer is driven by patients with PR positive tumors

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Background

The biological effects of progesterone are mediated through the RANK/RANK-ligand system, which promotes tumor growth and malignant behavior in breast cancer models. In the large prospective, double-blind, placebo-controlled, phase 3 ABCSG 18 trial we have demonstrated that the addition of the RANK ligand denosumab dramatically reduces fractures compared to placebo, but also improves disease-free survival (DFS), and overall survival (OS) in aromatase inhibitor-treated postmenopausal patients with early luminal breast cancer.

	Placebo (N=1,012)	Denosumab (N=1,014)	Total (N=2,026)
Age at randomization (years)			
n	1,012	1,014	2,026
Median (Q1-Q3)	65.0 (58.0-70.0)	64.0 (58.0-70.0)	64.5 (58.0-70.0)
Min - Max	38.0-91.0	46.0-88.0	38.0-91.0
pT-stage			
T0/Tis/T1	748 (73.9%)	741 (73.1%)	1,489 (73.5%)
T2/T3/T4	261 (25.8%)	273 (26.9%)	534 (26.4%)
Missing	3 (0.3%)	0	3 (0.1%)
pN-stage			
pN0	740 (73.1%)	750 (74.0%)	1,490 (73.5%)
pN1	202 (20.0%)	203 (20.0%)	405 (20.0%)
pN>=2	65 (6.4%)	53 (5.2%)	118 (5.8%)
Missing	5 (0.5%)	8 (0.8%)	13 (0.6%)
Grade			
G1	236 (23.3%)	261 (25.7%)	497 (24.5%)
G2	613 (60.6%)	588 (58.0%)	1,201 (59.3%)
G3	156 (15.4%)	159 (15.7%)	315 (15.5%)
Gx	4 (0.4%)	4 (0.4%)	8 (0.4%)
Missing	3 (0.3%)	2 (0.2%)	5 (0.2%)
ER Allred status, local			
Positive	994 (98.2%)	996 (98.2%)	1,990 (98.2%)
Negative	6 (0.6%)	7 (0.7%)	13 (0.6%)
Missing	12 (1.2%)	11 (1.1%)	23 (1.1%)
PR Allred status, local			
Positive	909 (89.8%)	909 (89.6%)	1,818 (89.7%)
Negative	103 (10.2%)	105 (10.4%)	208 (10.3%)
Missing	0	0	0
HER2 status, local			
Negative	1,008 (99.6%)	1,011 (99.7%)	2,019 (99.7%)
Positive	0	0	0
Missing	4 (0.4%)	3 (0.3%)	7 (0.3%)
Ki-67, local (%)			
n	605	594	1199
Median (Q1-Q3)	10.0 (7.0 to 20.0)	10.0 (5.0 to 20.0)	10.0 (5.0 to 20.0)
Min - Max	0.0 to 90.0	0.0 to 90.0	0.0 to 90.0
Chemotherapy before randomization			
No	832 (82.2%)	838 (82.6%)	1,670 (82.4%)
Yes	180 (17.8%)	176 (17.4%)	356 (17.6%)

Table 1 Patient and tumor characteristics in the PR analysis population.

Results

Overall, luminal A-like tumors had a better DFS, DRFS, and OS than luminal B-like tumors, but PR expression *per se* was not prognostic in this large prospective clinical trial. Patients with PR positive tumors, however, who were treated with denosumab, enjoyed a considerably better long-term outcome than patients who had been randomized to the placebo arm (HR for DFS: 0.80; 95% CI 0.65-0.98; HR for DRFS: 0.68; 95% CI 0.51-0.90; HR for OS 0.63; 95% CI 0.46-0.88, Figure 1). In contrast, in patients with PR-negative tumors, no differences in long-term outcomes between the denosumab or placebo arm of the trial were observed (HR for DFS: 0.87; 95% CI 0.46-1.64; HR for DRFS: 1.19; 95% CI 0.53-2.66; HR for OS 0.99; 95% CI 0.37-2.65, Fig 2A-C). While the HR for DFS in denosumab vs placebo patients remained stable with increasing Allred scores, HRs for DRFS and OS improved with increasing Allred scores, thereby suggesting that the efficacy of denosumab depends on the degree of intra-tumoral PR expression (Table 2).

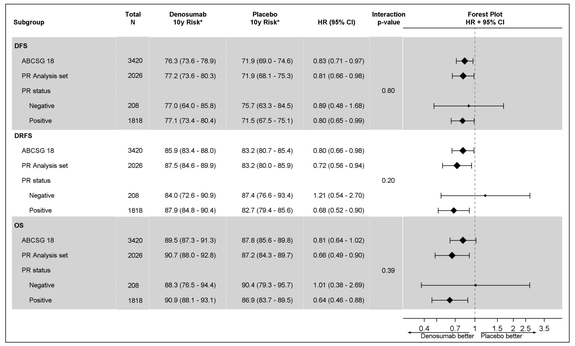


Figure 1 PR expression and long-term outcome in patients treated with or without denosumab.

Patients and Methods

Tumor histological grade, as well as immunohistochemically quantified Ki-67, estrogen receptor (ER), and progesterone receptor (PR) data were collected from 2,026 patients (Table 1: patient disposition). ER and PR were assessed according to the Allred score and considered positive if ≥3. Disease-free survival (DFS), distant recurrence-free (DRFS), and overall survival (OS) data were prospectively collected during a median follow-up (FU) of 8.1 years as part of the ABCSG 18 study. Cox Models were used to evaluate the association with outcome.

Conclusions

Our results indicate that the long-term outcome benefit for adjuvant denosumab in this large prospective randomized placebo-controlled trial is driven by patients with PR-positive tumors. The disruption of PR signaling, either via PR antagonization or by RANKL inhibition, could therefore be a promising therapeutic strategy in luminal breast cancer.

Variable	DFS HR (95% CI)	DRFS HR (95% CI)	OS HR (95% CI)
Prognostic role			
Allred score (0-8)	1.00 (0.96 - 1.04)	0.98 (0.93 - 1.03)	1.00 (0.94 - 1.06)
Allred classification (- vs +)	1.08 (0.78 - 1.50)	0.96 (0.63 - 1.47)	1.10 (0.65 - 1.84)
Predictive role			
Allred score	Interaction p=0.99	Interaction p=0.18	Interaction p=0.30
0	0.81 (0.48 to 1.35)	1.09 (0.57 to 2.10)	0.97 (0.44 to 2.14)
2	0.81 (0.55 to 1.17)	0.95 (0.59 to 1.53)	0.85 (0.48 to 1.51)
3	0.81 (0.59 to 1.10)	0.89 (0.60 to 1.31)	0.80 (0.50 to 1.29)
4	0.81 (0.63 to 1.04)	0.82 (0.60 to 1.14)	0.75 (0.51 to 1.11)
5	0.81 (0.65 to 1.00)	0.77 (0.58 to 1.02)	0.70 (0.51 to 0.98)
6	0.81 (0.66 to 0.98)	0.72 (0.55 to 0.93)	0.66 (0.48 to 0.90)
7	0.81 (0.65 to 1.00)	0.67 (0.50 to 0.89)	0.62 (0.44 to 0.87)
8	0.81 (0.63 to 1.04)	0.62 (0.44 to 0.88)	0.58 (0.39 to 0.87)
Allred classification	Interaction p=0.80	Interaction p=0.20	Interaction p=0.39
Negative	0.87 (0.46 to 1.64)	1.19 (0.53 to 2.66)	0.99 (0.37 to 2.65)
Positive	0.80 (0.65 to 0.98)	0.68 (0.51 to 0.90)	0.63 (0.46 to 0.88)

Table 2 PR expression by Allred score and long-term outcomes.

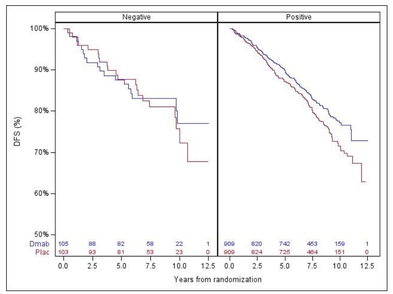


Figure 2A DFS in patients with PR-negative (left graph) and PR-positive (right graph) tumors with (blue line) or without (red line) denosumab treatment.

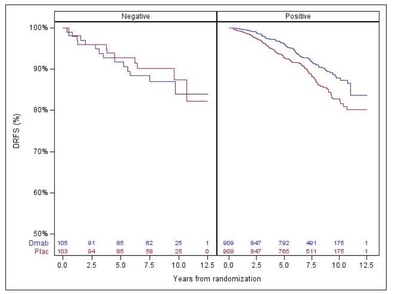


Figure 2B DRFS in patients with PR-negative (left graph) and PR-positive (right graph) tumors with (blue line) or without (red line) denosumab treatment.

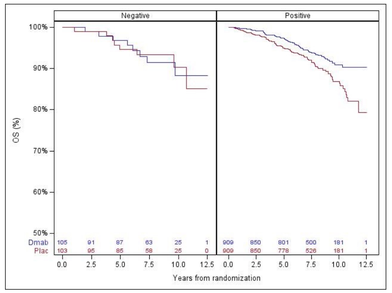


Figure 2C DRFS in patients with PR-negative (left graph) and PR-positive (right graph) tumors with (blue line) or without (red line) denosumab treatment.

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