Everolimus added to adjuvant endocrine therapy in patients with high-risk hormone receptor-positive, human epidermal growth factor receptor 2-negative primary breast cancer

Everolimus added to adjuvant endocrine therapy in patients with high-risk hormone receptor-positive, human epidermal growth factor receptor 2-negative primary breast cancer: a randomized, double-blind, international phase III trial (UNIRAD; UCBG 211)

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Running head: Everolimus added to endocrine therapy in early breast cancer

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Disclaimers

ABSTRACT

Purpose: Everolimus, an oral inhibitor of the mammalian target of rapamycin, improves progression-free survival in combination with endocrine therapy (ET) in postmenopausal women with aromatase inhibitor-resistant metastatic breast cancer. However, the benefit of adding everolimus to ET in the adjuvant setting in early breast cancer is unknown.

Patients and methods: In this randomized double-blind phase III study, women with high-risk, hormone receptor-positive, human epidermal growth factor receptor 2-negative primary breast cancer were randomly assigned to everolimus or placebo for 2 years combined with standard ET. Stratification factors included ET agent, receipt of neoadjuvant versus adjuvant chemotherapy, progesterone receptor status, duration of ET prior to randomization, and lymph node involvement. The primary endpoint was disease-free survival (DFS). The trial is registered with ClinicalTrials.gov (NCT01805271).

Results: Between June 2013 and March 2020, 1,278 patients were randomly allocated to receive everolimus or placebo. At first interim analysis, the trial was stopped for futility and a full analysis undertaken once data snapshot complete. 147 patients have had a DFS event reported and at 3-years DFS did not differ between patients who received ET plus everolimus (88% [95% CI, 85-91]) or ET plus placebo (89% [95% CI, 86-91; hazard ratio = 0.95, 95% CI, 0.69-1.32, $P = 0.77$]). Grade ≥3 adverse events were reported in 22.9% of patients (29.9% with everolimus vs. 15.9% with placebo, $P < 0.001$). 53.4% everolimus-treated patients permanently discontinued experimental treatment early compared with placebo-treated 22.3%.

Conclusion: Among high-risk patients, everolimus added to adjuvant ET did not improve DFS. Tolerability was a concern, with more than half of patients stopping

everolimus before study completion. Everolimus cannot be recommended in the adjuvant setting.

Introduction

Endocrine therapy (ET) is the standard adjuvant treatment for patients with hormone receptor-positive, human epidermal growth factor receptor type 2 (HER2)-negative breast cancer. However, approximately 20% of patients experience disease recurrence in the first 10 years (1). Metastatic breast cancer is treatable but remains incurable, with a median overall survival (OS) for patients with hormone-receptor-positive, HER2-negative breast cancer of about 3 years and a 5-year survival rate of 35% (2). In the metastatic setting, combination therapies associating ET and targeted therapies have therefore emerged as new therapeutic strategies that enhance the efficacy of ET.

Dysregulation of the phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway has been shown to be largely involved in acquired resistance to ET (3). In combination with ET, everolimus, an oral mTOR inhibitor, improves progression-free survival (PFS) for advanced and metastatic hormone receptor-positive HER2-negative breast cancer previously treated by aromatase inhibitors (AIs) (4, 5). In the phase III BOLERO-2 trial that compared everolimus and exemestane to placebo and exemestane in 724 patients with hormone receptor-positive HER2-negative advanced breast cancer, a 4.6 -month prolongation in median PFS was observed (hazard ratio [HR] 0.45; 95% confidence interval [CI], 0.38 to 0.54; $P < 0.0001$). There was however no improvement in OS (4, 6). In the phase II TAMRAD study that compared everolimus and tamoxifen to tamoxifen alone in 111 patients with hormone receptor-positive HER2-negative AI-resistant metastatic breast cancer, the 6-month clinical benefit rate was 61% (95% CI, 47 to 74) with tamoxifen plus everolimus versus 42% (95% CI, 29 to 56) with tamoxifen alone, and time to progression increased from 4.5 months with tamoxifen

alone to 8.6 months with tamoxifen plus everolimus (5). However, the benefit of adding everolimus to ET in the adjuvant setting in early breast cancer is unknown.

In this double-blind, multicenter, international randomized trial, we aimed to compare the combination of adjuvant everolimus plus standard adjuvant ET to placebo plus ET in women with high-risk hormone receptor-positive HER2-negative early breast cancer (ClinicalTrials.gov NCT01805271).

Patients and methods

Patients

Eligible patients were women aged 18 years or older with estrogen receptor-positive human epidermal growth factor receptor type 2 (HER2)-negative early breast cancer at high risk of relapse, defined as ≥4 positive lymph nodes, ≥1 positive lymph node if surgery was performed after neoadjuvant chemotherapy or ET administered for ≥3 months; or 1-3 positive lymph nodes at primary surgery and an EPClin® score ≥3.3 (7). Patients had to have their primary tumor completely resected, with no clinically or radiologically detectable metastases at the time of inclusion. Inclusion criteria were initially limited to patients who had already received between 2.5 and 3.5 years of adjuvant ET, but were extended a year later to all patients who had received ET for at least 1 year and up to 4 years of ET, due to low inclusion rate. In 2017, the protocol was amended to authorize initiation of the study treatment at the same time as ET and up to 4 years from its beginning. Patients also had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate hematological, hepatic and renal functions. Exclusion criteria included previous cancer ≤5 years before study entry, except basal cell carcinoma of the skin or *in situ*

carcinoma of the cervix, significantly impaired lung function, known hypersensitivity to mTOR inhibitors, and any uncontrolled medical conditions.

The study was conducted in accordance with Good Clinical Practice principles, the Declaration of Helsinki, and all local regulations. All patients provided written informed consent. The study was approved by the French medicines agency (ANSM – Agence National de Sécurité du médicament des produits de santé), by an ethics committee (Comité de Protection des Personnes Sud-Est IV - Lyon) in September 2012 and by institutional review board of each participating center. A steering committee supervised the study, and an independent data monitoring committee (IDMC) met every years and was responsible for monitoring safety and efficacy in the trial participants.

Study design and treatment

Patients were randomly assigned in a 1:1 ratio to receive 2 years of placebo or 2 years of everolimus, added to ongoing ET. Patients were assigned to one of two treatment arms based on a dynamic randomization method by minimization according to Pocock and Simon algorithm. Randomization was stratified by ET agent (tamoxifen +/- luteinizing hormone-releasing hormone [LHRH] agonists vs. AI), previous adjuvant versus neoadjuvant chemotherapy or ET, progesterone receptor status (positive vs. negative), duration of ET (≤3 years vs. >3 years), and lymph node involvement (≥4 positive lymph nodes and ≥1 positive lymph node after neoadjuvant setting vs. 1-3 positive lymph nodes and high EPclin® score).

Everolimus was initially administered at 10 mg/day. Two years into the trial, toxicity appeared to be a significant problem, and the protocol was amended to allow the starting dose at 5 mg/day with the possibility to increase to 10 mg/day between

the first and the third month depending on toxicity so far observed. Patients were to be treated by everolimus/placebo for a maximum of two years. In case of grade 2 or 3 toxicity, treatment was stopped until toxicity was resolved and resumed at 5 mg/day (if started at 10 mg/day) or 5 mg/2 days (if started at 5 mg/day). In case of re-occurrence of grade 2 or 3 toxicity, treatment was interrupted and resumed at 5 mg/2 days for patients who were receiving 5 mg/day and permanently discontinued for those who were receiving 5 mg/2 days. At third occurrence, treatment was permanently discontinued. Patients were closely monitored for drug-related toxicity with the addition, from April 2013, of follow-up visits and phone calls, to allow earlier detection of adverse events. Detailed toxicities management were based on the Summary of Product Characteristics for Everolimus and systematically updated with each new version available.

The primary endpoint was disease-free survival (DFS), measured from the date of randomization. DFS events were defined as invasive local, regional, or metastatic relapse, contralateral breast cancer, or death from any cause. New second cancers of non-breast origin were not taken into account. Pre-planned subgroup analysis was performed on the stratification factors. Secondary endpoints included OS, event-free survival (EFS), distant metastasis-free survival (DMFS), second malignancies, and toxicity.

Statistical analysis

To detect a difference of 3% in the 2-year DFS (90% vs. 93%, HR=0.7)), 1,984 patients were to be randomized (992 in each treatment group) with 286 events required for the final analysis (85% power, two-sided test (log-rank test) and a significance level of 5%). Two interim analyses were planned after 95 (efficacy and

futility) and 191 events (efficacy). All efficacy data were summarized and analyzed in the intention-to-treat population, which included all the patients who had undergone randomization, regardless of the intervention received. Safety data were summarized in the safety analysis set (all patients who received at least one dose of everolimus or placebo).

The Kaplan–Meier method was used to estimate DFS and 3 years event rates. The HR and associated 95% CI were calculated with the use of a Cox proportional-hazards model. A pre-planned DFS analysis was performed in stratification subgroups for which HR and 95% CI were calculated by Cox model. Analyses of secondary efficacy endpoints used a method similar to that used in the DFS analysis.

Futility rules at the interim analysis were calculated based on the information fraction observed at this time (ratio between the number of events observed at the time of the interim analysis and the total number of events required for the final analysis). For the first interim analysis, futility was to be declared if the HR estimate was above 0.962.

Results

Patients and Treatment

A total of 1,278 patients were randomized between June 2013 and March 2020 in 72 centers in France, UK, and Belgium, to receive everolimus (n = 637) or placebo (n = 641) (Figure 1). Baseline characteristics were well balanced between the two treatment groups (Table 1). Median age was 54 years, interquartile range (IQR) = [48-63], 90% of patients had an ECOG performance score 0, and 66% were postmenopausal. At randomization, median ET treatment duration was 15 months, IQR = [4.9-29.9]. The most frequent ETs were tamoxifen (44%), letrozole (32%) and

anastrozole (19%). Only 7 patients (0.5%) received a LHRH agonist in combination with tamoxifen or an AI.

Thirty-four percent (n = 439) of patients initiated everolimus/placebo at 10mg and 64% (n = 812) started at 5 mg. Of the remaining 2%, 1 patient started at 2.5mg, 19 did not take the treatment and 7 had missing data. Median everolimus/placebo treatment duration was 16.1 months, IQR = [4.4-23.8], the treatment being shorter in those allocated everolimus (9.2 months IQR = [2.1-23.4]) than placebo (22.5 months IQR = [9.7-23.9]). Dose reduction occurred in 22.9% (n = 293) of patients (34.2% allocated everolimus vs. 11.7% allocated placebo, Fisher's exact test $P < 0.001$). Among the patients who started at 10 mg/day (n = 439), at least one dose reduction occurred in 46.8% (103/220) of patients allocated everolimus, compared with 11.0% (24/219) in the placebo group. Among those who started at 5 mg/day (n = 812), at least one dose reduction occurred in 28.4% (114/401) of patients allocated everolimus, compared with 12.4% (51/411) in the placebo group. Thirty-eight percent of patients permanently discontinued treatment early: 53.4% (n = 340) of those allocated everolimus, compared with 22.3% (n = 143) in the placebo group. The main reasons for discontinuation were adverse events (35.3% everolimus vs. 10.0% placebo), patient decision (15.2% vs. 7.2%) and disease progression (2.8 vs. 5.1%). Of interest, within the everolimus group, patients receiving tamoxifen as ET agent had a longer median everolimus treatment duration (12.8 months IQR= [2.7-23.6]) than those receiving AI (7.7 months, IQR = [1.9-22.6]) (log-rank $P = 0.007$). No similar difference was observed for the patients receiving placebo with either ET backbone (median duration on placebo 23.2 months, IQR = [10.7-23.9] vs. 21.1 months, IQR = [8.5-23.9] for patients receiving tamoxifen or AI, respectively).

Efficacy

The number of DFS events to trigger the first interim analysis was reached in 2019 and the database was cleaned and locked on 3rd December 2019. At that time point, 122 DFS events were notified on 1,249 randomized patients. This analysis showed a HR of 1.08 (95% CI, 0.76 to 1.54); above the pre-defined threshold for concluding futility. The independent data monitoring committee met on the 19th of February 2020 and, based on the futility analysis results, coupled with other features of the trial, including accrual duration, treatment exposure and adverse events, recommended stopping inclusions and experimental treatment for futility, which was validated by the steering committee on the 2nd of March 2020. Message was sent to stop the inclusions and experimental treatment for the 238 patients still on study on 4th March 2020. A letter to patients was sent to sites on 16th March 2020. The database for the current analysis was locked on November 16, 2020. For the current analysis, median follow-up was 35.7 months, range 0.7 to 85 months (IQR = [19.9-47.4]). A total of 147 DFS events were recorded (143 recurrences and 4 deaths before relapse). No difference was observed in 3-year DFS between the two groups; 88% (95% CI, 85 to 91) in those allocated everolimus and 89% (95% CI, 86 to 91) in the placebo group (HR = 0.95; 95% CI, 0.69 to 1.32, log-rank *P* = 0.77)(Figure 2). A total of 49 death were reported, no difference was observed in 3-year OS (96%, 95% CI, 94 to 98 in those allocated everolimus vs. 96%; 95% CI, 94 to 97 in the placebo group; HR = 1.09, 95% CI, 0.62 to 1.92, *P* = 0.75) (Figure 3),similar results were observed with the other secondary efficacy endpoints (Supplementary Figure 1).

In a pre-planned subgroup analysis of DFS benefit, effects in each subgroup were consistent with the overall HR estimate. There was some suggestion of heterogeneity of estimates of effect between those treated on tamoxifen vs AI

backbone (*P* = 0.044)(Figure 4),. For the subgroup of patients receiving tamoxifen, 3-year DFS was 91%, 95% CI, 86 to 94 in the everolimus arm and 86%, 95% CI, 81 to 90 in the placebo arm (HR = 0.62; 95% CI: 0.37-1.06). For the subgroup of patients on AI, 3-year DFS was 87%, 95% CI, 82 to 90 in the everolimus arm vs. 91%; 95% CI, 87 to 93 in the placebo arm (HR = 1.25; 95% CI: 0.83-1.90) (Supplement figure 2). However, different biology of premenopausal vs postmenopausal patients could have been a confounding factor in this analysis.

Safety

Safety analysis was performed on patients who took at least one dose of study treatment (n = 1,259)(figure 1). Ninety-seven percent of patients had at least one adverse event (98.1% in those allocated everolimus vs. 96.5% in the placebo group). Grade ≥3 adverse events were reported among 22.9% (n = 288) of patients (29.9% in the everolimus-treated group vs. 15.9% in the placebo group, p<0.001)(Table 2). Serious adverse events were reported among 10.6% (n = 133) of patients (11.8% in the everolimus-treated group vs. 9.3% in the placebo group, *P* = 0.144). Among the patients who started at 10 mg/day, grade ≥3 adverse events were reported among 38.2% (n = 84) everolimus-treated patients, compared with 15.5% (n = 34) in the placebo group (Chi-2 test, *P* < 0.001). Among those who started at 5 mg/day, grade ≥3 adverse events occurred in 25.4% (n = 102) of everolimus-treated patients, compared with 16.1% (n = 66) in the placebo group (Chi-2 test, *P* < 0.001). In 243 patients (19.3%), grade ≥3 adverse events led to treatment withdrawal (29.6% in everolimus group vs. 9.1% in placebo group, *P* < 0.001). One treatment related death (0.2%) was attributed to everolimus (septic shock due to streptococcus septicemia in a patient who was treated at 10mg/day).

The most common grade 3 or 4 adverse events were oral mucositis (7.4% in the everolimus-treated group vs. 0.3% in the placebo group), hypertriglyceridemia (3.0% vs. 0.2%), hepatic alanine aminotransferase/aspartate aminotransferase/gamma-glutamyl transferase increase (2.2%vs. 1.7%), fatigue (1.9% vs. 1.3%) and hyperglycemia (1.4% vs. 0.2%) (Table 2).

Discussion

After a median of three years of follow-up of 1,278 patients with high-risk early breast cancer, no evidence was observed to suggest that everolimus given in combination with adjuvant ET improved DFS compared with ET alone. Insufficient drug exposure and inadequate biological activity in this specific situation could have contributed to this failure to detect benefit in early breast cancer when everolimus is clearly active in metastatic disease.

Despite our requirement for patient monitoring and investigators awareness, ~~with~~ 50% of patients stopped everolimus before study completion for toxicities or due to personal decisions, and one patient died from septicemia while receiving everolimus. Consistent with previous reports, the most common grade ≥3 adverse event was oral mucositis, observed in 7.4% of patients treated with everolimus-ET (4,5). BOLERO-II study reported a high discontinuation rate (29% due to adverse events with everolimus vs. 5% with placebo) (6). In the current study, an even higher percentage of patients in the everolimus-treated group stopped treatment early due to adverse events (35.3%). The limited options available to patients in the metastatic setting may explain the difference in patient acceptability faced with similar toxicities. More precise treatment guideline for common toxicities could have been necessary. In particular, after this study had started, dexamethasone mouthwash was shown to

reduce the risk of stomatitis (8). Above all, we did not managed to prevent a fatal event that was likely related to the experimental treatment. Everolimus has been linked to fatal events in the metastatic setting, with rates up to 0.7% in a meta-analysis (9). At the time of initiation of UNIRAD, few data were available for patient in the adjuvant setting and we expected this risk to be controllable for this selected and disease free population. In fact, in 2009, Baselga et al. did not report any toxic death for 138 patients treated with neo-adjuvant everolimus (10). In our study, 1 of 625 patients (0.16%) exposed to everolimus experienced a toxic fatal event, which is an incidence on part with what is reported for standard adjuvant chemotherapy (68 among 34882 patients, 0.19%, in the Cochran analysis of taxanes for adjuvant treatment of early breast cancer) (11). Nevertheless, the simple fact that everolimus may increase the risk of toxic death despite stringent patients selection and toxicity management awareness, does not allow to consider its use in the adjuvant setting unless it greatly improve disease control.

It is possible that everolimus may not be sufficiently effective to reverse early resistance to AI in the adjuvant setting. In fact, most patients included in randomized studies that showed its efficacy in the metastatic setting had secondary endocrine resistance (5, 6). UNIRAD was stopped early for futility at the first interim analysis, and, as a consequence, we cannot rule out a better efficacy of everolimus for preventing late recurrences. Furthermore, while randomization was initially limited to patients who had already received between 2.5 and 3.5 years of adjuvant ET, it was subsequently broadened, due to poor recruitment, to 0-4 years of ET, meaning that patients were coming into the trial at varied time-points since completion of their primary therapy. This further added a degree of heterogeneity in terms of tumor biology and hormone resistance mechanism. Yet, in the pre-planned subgroup

analysis, there was no interaction between the time on ET before inclusion (more or less than 3 years) and everolimus efficacy

The DFS analysis showed that 11% of patients of this high-risk population who received standard adjuvant chemotherapy and ET had already relapsed at 3-year follow-up, and the projected 5-year DFS is no more than 80%. This indicates the importance of identifying new agents added to ET in such patients. Following demonstrated efficacy and safety in the metastatic setting (12-14), studies have been conducted in hormone receptor-positive HER2-negative high-risk early breast cancer combining CDK4/6 inhibitors and ET in the adjuvant setting. The PALLAS trial that compared palbociblib plus ET to ET alone in patients with hormone receptor-positive stage II-III HER2-negative early breast cancer was stopped early for futility (15). As with UNIRAD, the benefits observed in the metastatic setting were not seen in the adjuvant setting with palbociclib. Of interest, there is a high similarity between the populations included in PALLAS and UNIRAD (3-year DFS of 88.5% for the placebo arm of PALLAS, vs. 89% for UNIRAD) and with respect to experimental treatment discontinuation for toxicities/patient decision (42% for PALLAS vs. 48% for UNIRAD) (15). On the other hand, in the MonarchE trial that randomized 5,637 patients to receive abemaciclib plus ET, or ET alone, the risk of developing an invasive DFS event was reduced by 29% in the abemaciclib arm (16). Of note, the MonarchE study population had an even poorer prognosis than the one included in our study. Indeed, the 2-year DFS in the placebo group was 88.7%, equivalent to the 3-year DFS of the UNIRAD population (89%). Furthermore, only 17% of patients in the abemaciclib plus ET group discontinued treatment due to adverse events, as most who required dose reduction or interruption due to adverse events remained on treatment. .

In summary, this first phase III clinical trial of adjuvant everolimus in combination to standard hormone therapy for patients with estrogen receptor-positive, HER2-negative early breast cancer failed to show improvement in DFS and was stopped after the initial interim analysis for futility. Added toxicity was significant and early treatment discontinuation may be in part responsible for the lack of observed benefit. Follow-up will continue to evaluate long-term outcomes. At the present time, everolimus cannot be recommended in the adjuvant setting.

Tables and Figures

Table 1: Baseline patient characteristics

Table 2: Adverse events experienced by ≥10% of patients

Figure 1: CONSORT flow diagram

Figure 2: Disease-free survival

Figure 3: Overall survival

Figure 4: Forest plot of hazard ratios for disease-free survival according to stratification factors

Supplementary Figures (online only)

Supplementary Figure 1:

a) Event free survival

b) Distant metastasis-free survival

Supplementary Figure 2: Subgroup analysis on Hormone therapy backbone

a) DFS on everolimus and placebo in the tamoxifen subgroup

b) DFS on everolimus and placebo in the AI subgroup

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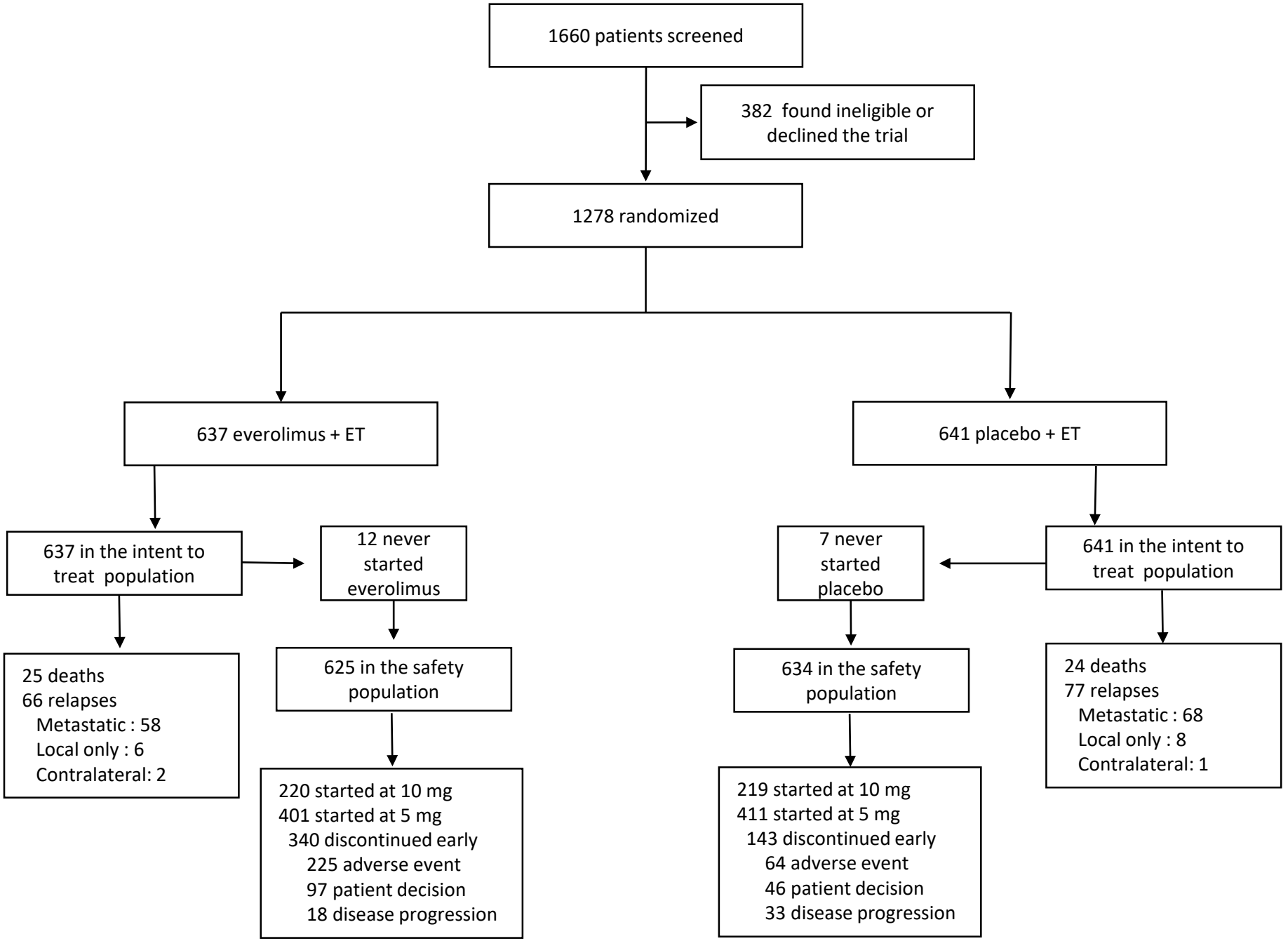
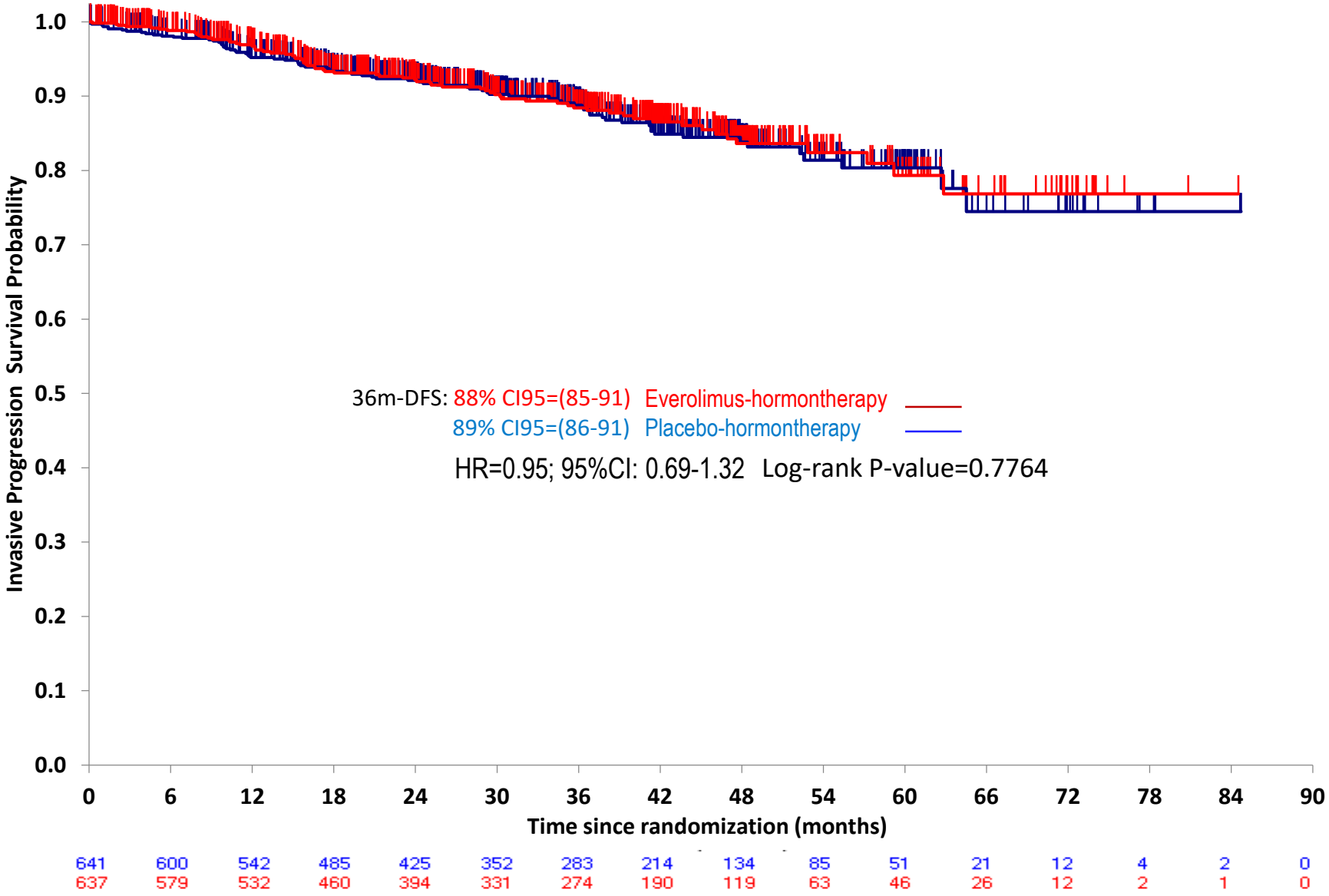
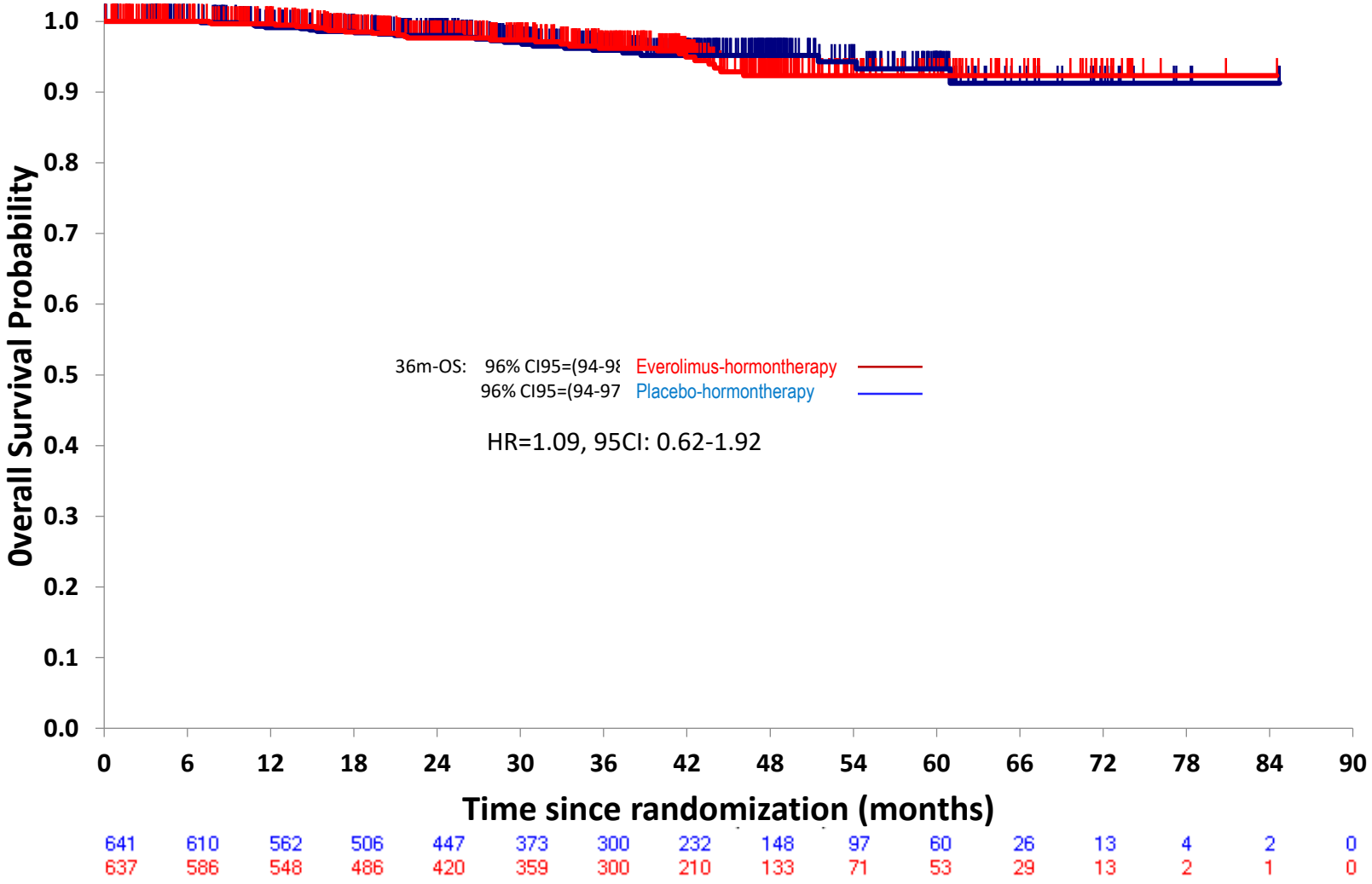
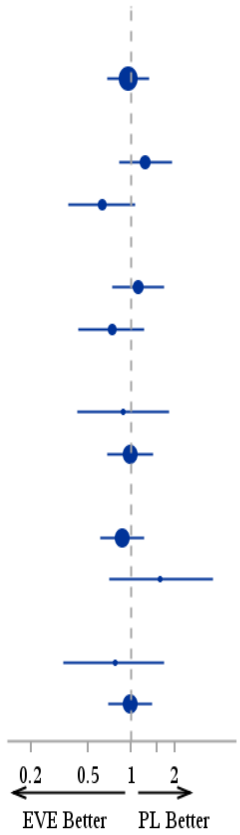

1660 patients screened
382 found ineligible or declined the trial
1278 randomized
637 everolimus + ET
641 placebo + ET
637 in the intent to treat population
12 never started everolimus
7 never started placebo
641 in the intent to treat population
25 deaths
66 relapses
Metastatic : 58
Local only : 6
Contralateral: 2
625 in the safety population
634 in the safety population
24 deaths
77 relapses
Metastatic : 68
Local only : 8
Contralateral: 1
220 started at 10 mg
401 started at 5 mg
340 discontinued early
225 adverse event
97 patient decision
18 disease progression
219 started at 10 mg
411 started at 5 mg
143 discontinued early
64 adverse event
46 patient decision
33 disease progression

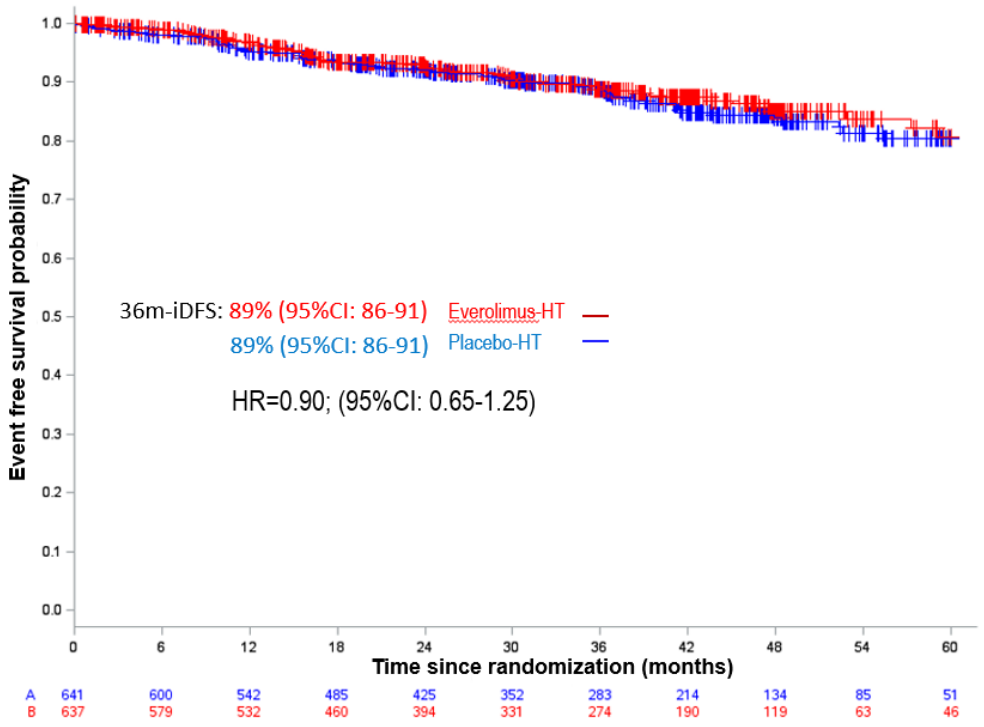

Invasive Progression Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
36m-DFS: 88% CI95=(85-91) Everolimus-hormontherapy
89% CI95=(86-91) Placebo-hormontherapy
HR=0.95; 95%CI: 0.69-1.32 Log-rank P-value=0.7764
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Time since randomization (months)
641 600 542 485 425 352 283 214 134 85 51 21 12 4 2 0
637 579 532 460 394 331 274 190 119 63 46 26 12 2 1 0


Overall Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
36m-OS: 96% CI95=(94-98 Everolimus-hormontherapy
96% CI95=(94-97 Placebo-hormontherapy
HR=1.09, 95CI: 0.62-1.92
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Time since randomization (months)
641 610 562 506 447 373 300 232 148 97 60 26 13 4 2 0
637 586 548 486 420 359 300 210 133 71 53 29 13 2 1 0

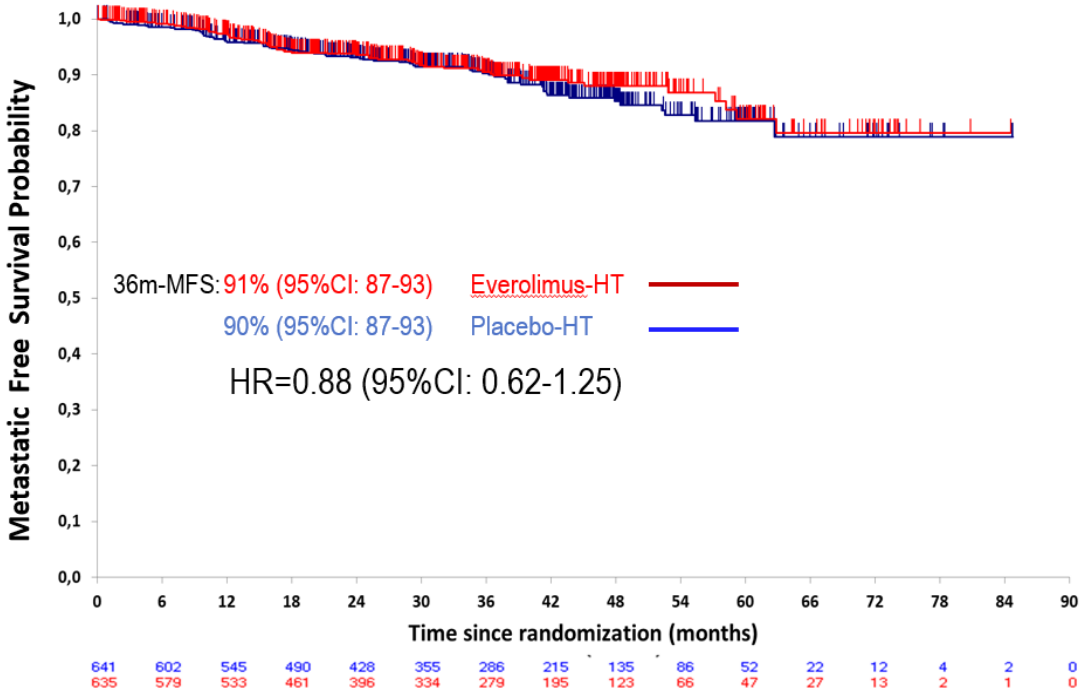
Subgroup	PL	EVE	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All	77/641 (12%)	70/637 (11%)	0.94 [0.68- 1.31]
Tamoxifen vs. Aromatase inhibitor			.....
Aromatase inhibitor	41/388 (10.6%)	48/385 (12.5%)	1.25 [0.82- 1.90]
Tamoxifen	36/253 (14.2%)	22/252 (8.7%)	0.63 [0.36- 1.05]
Previous adjuvant vs. neoadjuvant CT/HT			.....
Adjuvant CT/HT	44/474 (9.3%)	45/474 (9.5%)	1.11 [0.73- 1.68]
Neoadjuvant CT/HT	33/167 (19.8%)	25/163 (15.3%)	0.73 [0.43- 1.22]
PR: positive vs. negative			.....
PR : Negative	16/92 (17.4%)	13/89 (14.6%)	0.88 [0.42- 1.83]
PR : Positive	61/549 (11.1%)	57/548 (10.4%)	0.98 [0.68- 1.40]
Duration of hormone therapy before inclusion			.....
<=3 years	67/540 (12.4%)	57/543 (10.5%)	0.86 [0.60- 1.23]
>3 years	10/101 (9.9%)	13/94 (13.8%)	1.58 [0.69- 3.69]
>=4N+ or >=1N+ after neoadjuvant setting vs 1-3N+ and EPClin score high			.....
1-3N+ and EPClin score high	15/208 (7.2%)	10/204 (4.9%)	0.77 [0.33- 1.69]
>=4N+ or >=1N+ after neoadjuvant setting	62/433 (14.3%)	60/433 (13.9%)	0.98 [0.69- 1.40]

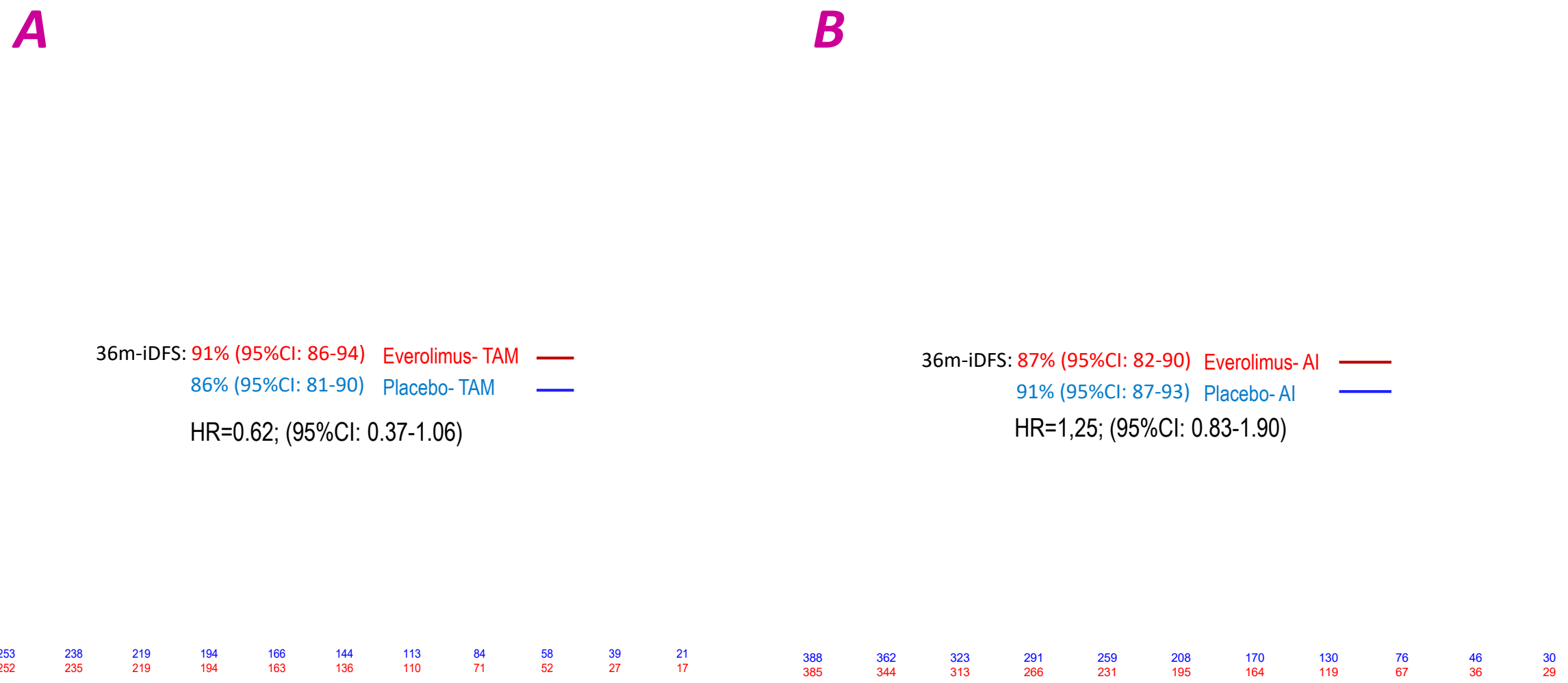


A


Event free survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
36m-iDFS: 89% (95%CI: 86-91) Everolimus-HT
89% (95%CI: 86-91) Placebo-HT
HR=0.90; (95%CI: 0.65-1.25)
0 6 12 18 24 30 36 42 48 54 60
Time since randomization (months)
A 641 600 542 485 425 352 283 214 134 85 51
B 637 579 532 460 394 331 274 190 119 63 46

B


Metastatic Free Survival Probability
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
36m-MFS: 91% (95%CI: 87-93) Everolimus-HT
90% (95%CI: 87-93) Placebo-HT
HR=0.88 (95%CI: 0.62-1.25)
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Time since randomization (months)
641 602 545 490 428 355 286 215 135 86 52 22 12 4 2 0
635 579 533 461 396 334 279 195 123 66 47 27 13 2 1 0


A
36m-iDFS: 91% (95%CI: 86-94) Everolimus- TAM
86% (95%CI: 81-90) Placebo- TAM
HR=0.62; (95%CI: 0.37-1.06)
253 238 219 194 166 144 113 84 58 39 21
252 235 219 194 163 136 110 71 52 27 17
B
36m-iDFS: 87% (95%CI: 82-90) Everolimus- AI
91% (95%CI: 87-93) Placebo- AI
HR=1,25; (95%CI: 0.83-1.90)
388 362 323 291 259 208 170 130 76 46 30
385 344 313 266 231 195 164 119 67 36 29