MADRID 2014 ESMO congress

Efficacy and safety in TANIA, a randomised phase III trial of continued or reintroduced bevacizumab after first-line bevacizumab for HER2-negative locally recurrent or metastatic breast cancer

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Disclosures

- G von Minckwitz: Research grants, honoraria for advisory boards and lectures (Roche)
- F Puglisi: Honoraria (Roche, Eisai, GlaxoSmithKline)
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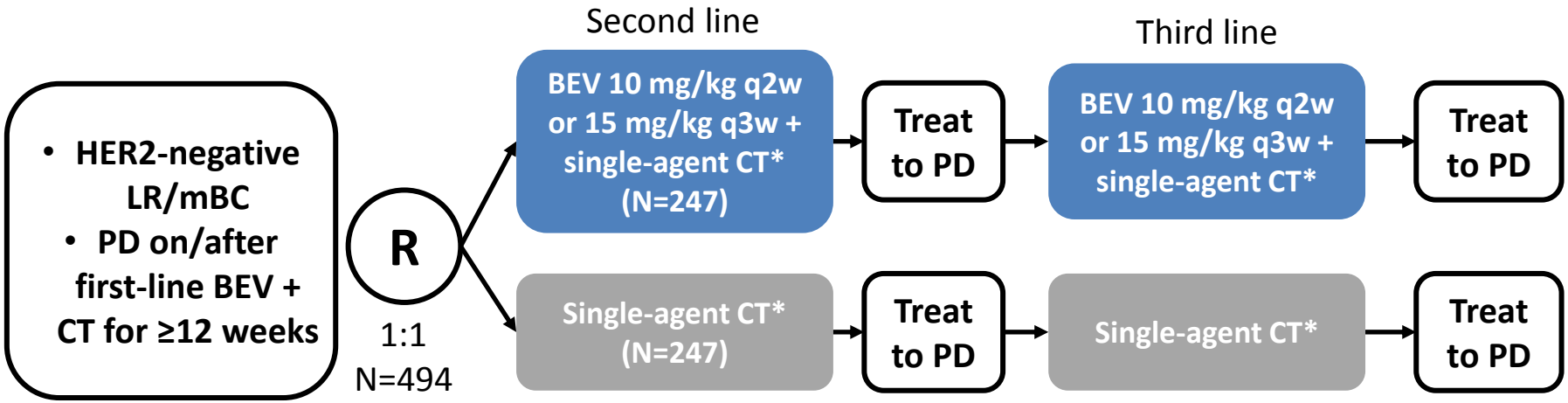
Rationale

- Randomised phase III trials in HER2-negative LR/mBC showed significantly improved PFS with addition of BEV to:
  - First-line chemotherapy (E2100, AVADO, RIBBON-1)[1–3]
  - Second-line chemotherapy in BEV-naïve patients (RIBBON-2)[4]
- Sustained VEGF blockade may be important for long-term disease control
  - Critical role of VEGF throughout the angiogenic pathway[5,6]
  - Continuous VEGF suppression needed to maximise BEV benefit in preclinical models[6]
  - In colorectal cancer, significantly improved PFS and OS with continued BEV versus chemotherapy alone in second line after first-line BEV,[7] supported by results of a second randomised phase III trial[8]
- TANIA trial designed to explore BEV beyond progression in LR/mBC

[1]Miller K, et al. NEJM 2009; [2]Miles D, et al. JCO 2010; [3]Robert N, et al. JCO 2011; [4]Brufsky AM, et al. JCO 2011; [5]Crawford Y & Ferrara N. Cell Tissue Res 2009; [6]Bagri A, et al. Clin Cancer Res 2010; [7]Bennouna J, et al. Lancet Oncol 2013; [8]Masi G, et al. Ann Oncol 2012

BEV = bevacizumab; LR/mBC = locally recurrent/metastatic breast cancer; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor

TANIA trial design



Stratification factors:

- **Hormone receptor status**
- **Time to first progression (<6 vs ≥6 months)**
- **Choice of chemotherapy (taxane vs non-taxane vs vinorelbine)**
- **LDH concentration (≤1.5 vs >1.5 × UNL)**

*CT options (investigator's choice, doublets not allowed): paclitaxel, nab-paclitaxel, docetaxel, capecitabine, gemcitabine, pegylated liposomal doxorubicin, non-pegylated liposomal doxorubicin, doxorubicin, epirubicin, vinorelbine, cyclophosphamide, ixabepilone (and in 3rd line only: eribulin)

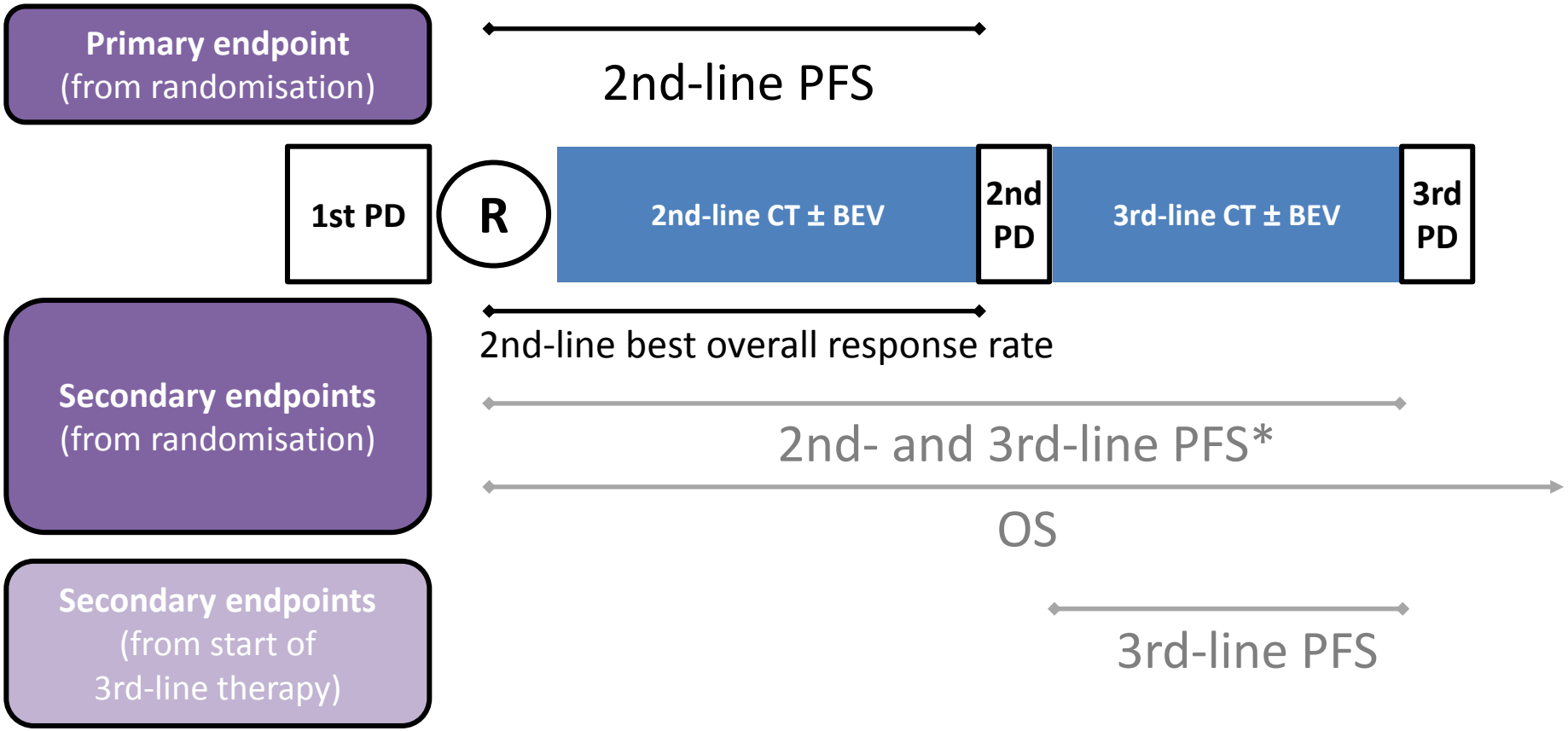
CT = chemotherapy; LDH = lactate dehydrogenase; nab = nanoparticle albumin-bound; PD = disease progression; R = randomisation; UNL = upper normal limit

Sample size calculations

- Primary endpoint: 2nd-line PFS
- Sample size calculated assuming:
  - 80% power
  - 5% significance level (two-sided)
  - Log-rank test
  - 2nd-line PFS 7.0 months (CT alone) → 9.3 months (CT + BEV)
    - HR 0.75
    - Assumed median in control arm takes into consideration permitted maintenance therapy and exclusion of patients with early PD
  - Recruitment period of 30 months
  - 5% dropout rate
- 2nd-line PFS events required in 384 of 488 patients
- We present the mature prespecified 2nd-line PFS analysis
  - Endpoints relating to 3rd-line therapy will be presented at the final analysis

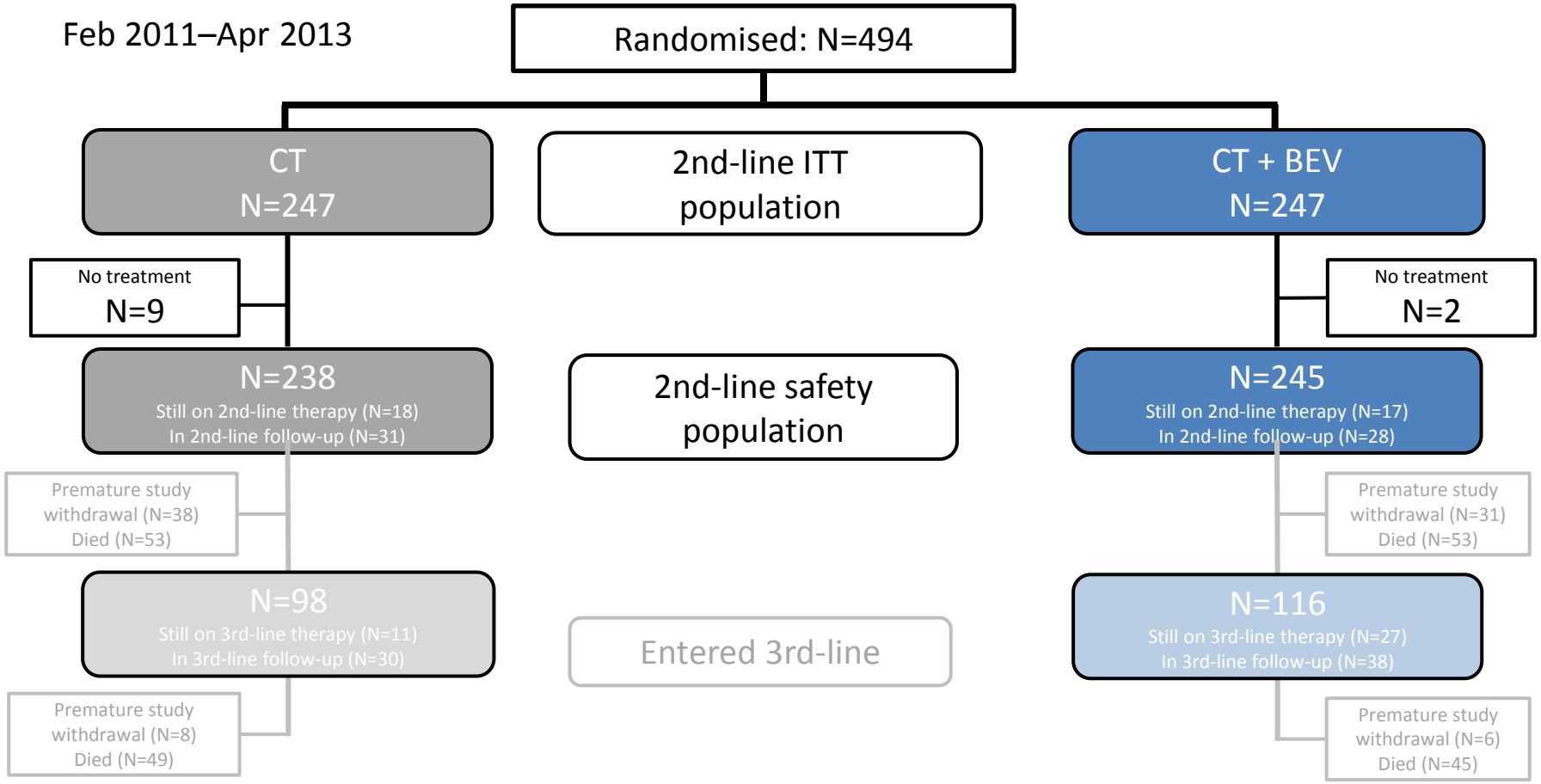
HR = hazard ratio

Summary of primary/secondary endpoints



*Following PFS2 concept from European Medicines Agency guideline
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137126.pdf

Patient flow



ITT = intent to treat

Baseline characteristics (ITT population)

Characteristic, n (%)	CT (N=247)	CT + BEV (N=247)
Median age, years (range)	54 (30–77)	56 (24–81)
Triple negative	57 (23.1)	49 (19.8)
LR/mBC at first diagnosis	49 (19.8)	37 (15.0)
Disease-free interval ≤12 months*	24 (9.7)	18 (7.3)
≥3 metastatic organ sites at baseline	88 (35.6)	80 (32.4)
First-line chemotherapy with bevacizumab		
Paclitaxel	180 (72.9)	182 (73.7)
Docetaxel	27 (10.9)	33 (13.4)
Capecitabine	46 (18.6)	39 (15.8)
Median first-line PFS, months	14.1	14.9
First-line PFS <6 months	32 (13.0)	25 (10.1)
LDH >1.5 × ULN	40 (16)	37 (15)

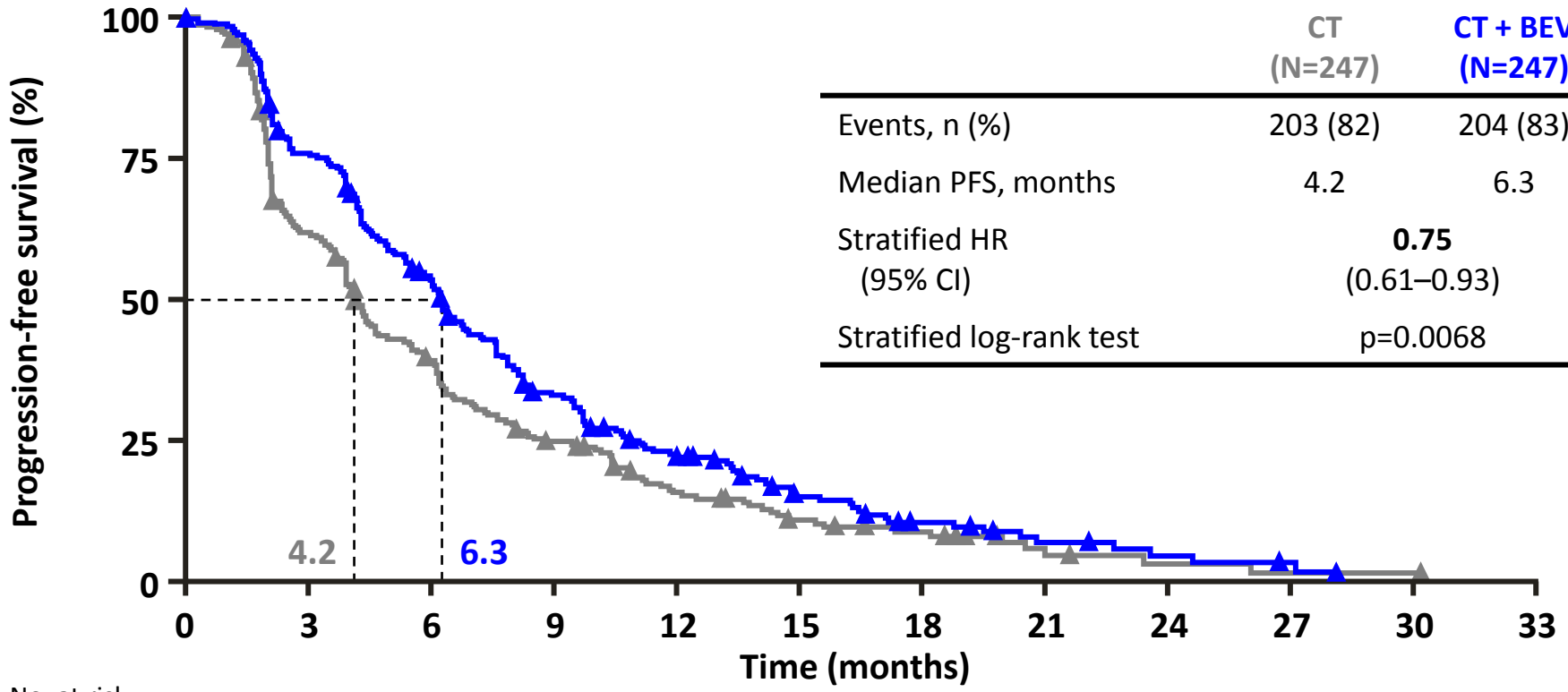
*Patients with both early BC and LR/mBC, defined from diagnosis of early BC to diagnosis of LR/mBC.

Investigator-selected second-line chemotherapy

Second-line CT, n (%)	CT (N=238)	CT + BEV (N=245)
Taxane*	**25 (10.5)**	**24 (9.8)**
Paclitaxel	11 (4.6)	16 (6.5)
Nab-paclitaxel	8 (3.4)	4 (1.6)
Docetaxel	6 (2.5)	4 (1.6)
Anthracycline	**34 (14.3)**	**36 (14.7)**
Non-pegylated liposomal doxorubicin	20 (8.4)	17 (6.9)
Pegylated lipsomal doxorubicin	8 (3.4)	7 (2.9)
Doxorubicin	2 (0.8)	7 (2.9)
Epirubicin	4 (1.7)	5 (2.0)
Other	**179 (75.2)**	**184 (75.1)**
Capecitabine	142 (59.7)	148 (60.4)
Vinorelbine*	26 (10.9)	29 (11.8)
Gemcitabine	10 (4.2)	5 (2.0)
Cyclophosphamide	1 (0.4)	2 (0.8)

*Stratification factors: taxane, vinorelbine, the rest (non-taxane)

Primary endpoint: Second-line PFS



	CT (N=247)	CT + BEV (N=247)
Events, n (%)	203 (82)	204 (83)
Median PFS, months	4.2	6.3
Stratified HR (95% CI)	**0.75** (0.61–0.93)	
Stratified log-rank test	p=0.0068	

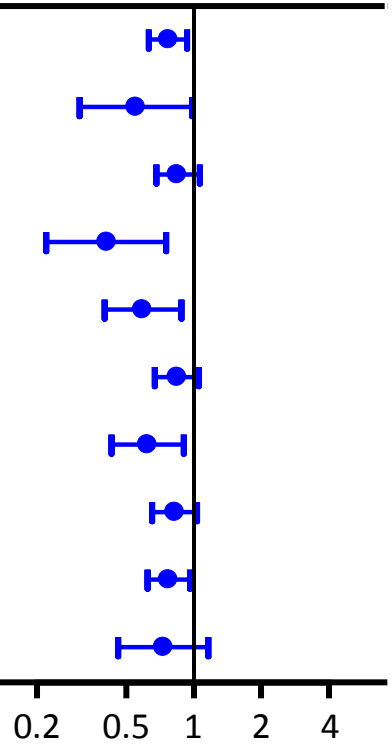
No. at risk

CT	247	141	88	51	28	17	12	4	2	1	1	0
CT + BEV	247	178	122	89	43	25	14	7	4	2	0	0

Median duration of follow-up: 15.9 months (CT) vs 16.1 months (CT + BEV)

Subgroup analyses of second-line PFS by stratification factor

Subgroup	No. of events/patients (%)		Median PFS, months		Unstratified HR (95% CI)
	CT	CT + BEV	CT	CT + BEV	Favours CT + BEV / Favours CT
All	203/247 (82)	204/247 (83)	4.2	6.3	
Taxane	25/32 (78)	26/32 (81)	**3.2**	**6.9**	
Non-taxane*	156/191 (82)	151/188 (80)	**4.4**	**6.0**	
Vinorelbine	22/24 (92)	27/27 (100)	**2.4**	**6.5**	
Triple negative	56/60 (93)	45/56 (80)	**2.1**	**4.9**	
ER and/or PgR positive	147/187 (79)	159/191 (83)	**4.7**	**6.7**	
First-line PFS <6 months	61/69 (88)	54/68 (79)	**3.9**	**5.1**	
First-line PFS ≥6 months	142/178 (80)	150/179 (84)	**4.6**	**6.4**	
LDH ≤1.5 × ULN	167/207 (81)	168/210 (80)	**4.4**	**6.3**	
LDH >1.5 × ULN	36/40 (90)	36/37 (97)	**2.1**	**5.8**	



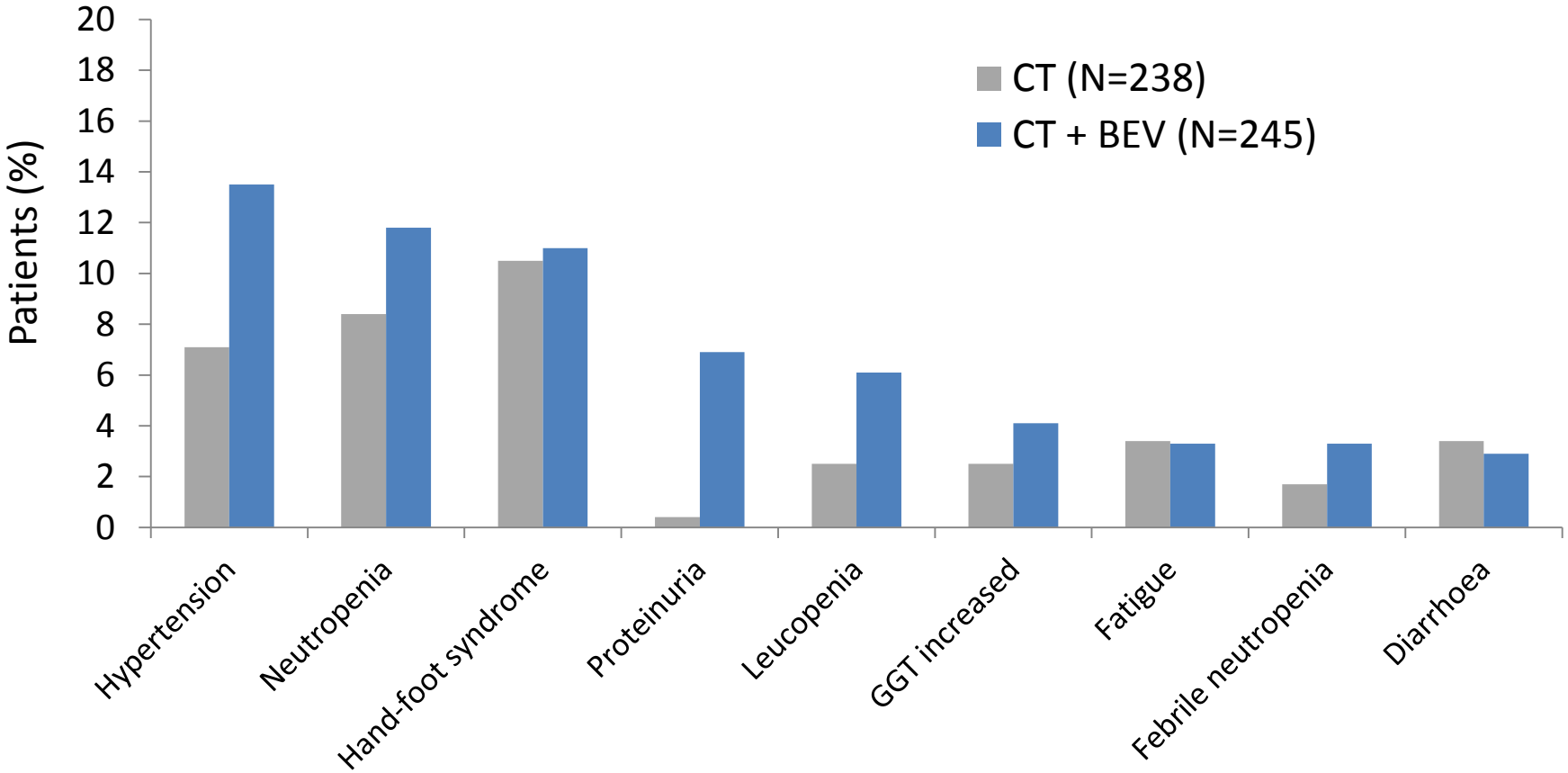
*Excluding vinorelbine

Secondary endpoints: Best response* (second-line treatment from randomisation)

Endpoint	CT (N=185)	CT + BEV (N=182)
Overall response rate, % (95% CI)	16.8 (11.7–22.9)	20.9 (15.2–27.5)
Difference (95% CI)	4.1 (–4.2 to 12.4) p=0.3457	
Stable disease, %	33.5 (26.8–40.8)	48.9 (41.4–56.4)
Disease progression, %	41.1 (33.9–48.5)	24.2 (18.1–31.1)
Duration of response	(N=31)	(N=38)
Median, months (95% CI)	10.6 (4.4–16.7)	8.3 (6.1–10.3)

*Response Evaluation Criteria in Solid Tumors version 1.0

Most common grade ≥3 AEs (≥3%, second-line safety population)



GGT = gamma glutamyltransferase

Median duration of CT: 3.9 months (CT) vs 4.4 months (CT + BEV); median duration of BEV: 4.5 months (CT + BEV)

Conclusions

- TANIA showed that in BEV-pretreated LR/mBC, further BEV improves second-line PFS (stratified HR 0.75, p=0.0068; median 4.2 → 6.3 months)
  - Continuous VEGF suppression appears to be important, consistent with findings in metastatic colorectal cancer
  - Median PFS in control arm shorter than expected but consistent with subgroup data from contemporary trials evaluating second-line capecitabine[1,2]
- Similar effect of second-line BEV irrespective of prior BEV
  - HR of 0.75 in TANIA (BEV-pretreated) and 0.78 in RIBBON-2 (BEV-naïve)
- No new BEV safety signals observed
- Biomarker and further subgroup analyses will be reported at SABCS 2014
- Final OS and third-line endpoint results anticipated in mid 2015

[1]Brufsky AM, et al. JCO 2011; [2]Baselga J, et al. JCO 2012

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