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Title: Differential benefit of docetaxel-based chemotherapy in breast cancer patients according to baseline body mass index

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Body: Background:
According to the latest estimates, 63% of the women in the US are either overweight or obese. Lipophilic drugs, such as docetaxel (T), have a high affinity for adipose tissue and a resulting higher volume of distribution (Vd). We hypothesized that the local and distant efficacy of T-based chemotherapy would differ according to the patient's adiposity, as estimated by the body mass index (BMI).
Patients and methods:
We retrospectively analyzed data from all the patients from a prospective neo-adjuvant trial comparing fluorouracil, epirubicin and cyclophosphamide (FEC) to T-ET (EORTC10994, NCT00017095, n=1,856) and from an adjuvant trial comparing two non-T regimens to two T-containing regimens (BIG 2-98, NCT00174655, n=2,887). No capping for patients with a body surface area >2.0m^2 was recommended in the study protocols, except after the 1st amendment of BIG 2-98 when already 75% of the patients were accrued. Three subgroups of BMI were considered: BMI<25 (lean, L), 25≤BMI<30 (overweight, Ov) and BMI≥30 (obese, Ob). Pathological complete response (pCR) was defined, as in the initial study, as pT0/is. Distant metastasis free (DMFS) and overall survival (OS) were considered as endpoints.
Results:
In both trials, the distribution of the BMI categories and the associations of BMI with clinico-pathological parameters were similar in the T and non-T groups.
In the neo-adjuvant trial, there was no difference in pCR rate between the two treatment arms considering all patients (FEC: 24%, T-ET: 27%), however a significant decrease in pCR rate was observed with increasing BMI in the FEC arm (L: 26%, Ov: 23%, Ob:17%, p=0.049), but not in the T-ET arm (L: 27%, Ov: 26%, Ob:27%, p=0.802). These pCR rates were not explained by differences in relative dose intensity (RDI). Exploratory analyses revealed that obese patients with ER-positive cancer that achieved pCR in the T-ET arm presented with a worse DMFS and OS.
In the adjuvant trial, there was no difference in DMFS and OS according to BMI in the non-T group, while a decreased DMFS and OS was observed with increasing BMI category in the T-group, which could not be explained by RDI. Subgroup analyses within the BMI categories demonstrated that the differential efficacy of T was limited to the L patients (HRadj OS T vs non-T=0.76 (0.60-0.96), p=0.02).

Adjusted HR (95% confidence interval), p-value in BIG 2-98

		DMFS	OS
Non-T group	Ov vs L	1.19 (0.90-1.58), 0.21	0.96 (0.72-1.28), 0.80
	Ob vs L	1.09 (0.77-1.55), 0.62	1.09 (0.78-1.52), 0.61
T group	Ov vs L	1.22 (0.99-1.57), 0.06	1.24 (1.00-1.54), 0.05
	Ob vs L	1.52 (1.20-1.92), <0.001	1.68 (1.32-2.13), <0.001

Conclusion:
This analysis of two large trials highlights for the first time a differential response to T according to BMI at the local and distant level. We hypotheisze that due to its lipophilic nature, T is characterized by a high affinity for adipose-rich tissues such as the