omitting ‘radiation to bone’ as a component of an SSE. We defined the triad of pathological fracture, spinal cord compression and need for surgery to bone as ‘morbid skeletal events’ (MSEs).

With this analysis (Table 1), we demonstrate that while ZA demonstrated a significant delay in MSE compared with placebo ($P = 0.004$), there was no significant benefit of denosumab over ZA for both first and subsequent MSE ($P = 0.07$ and 0.35, respectively). Further, risk–benefit analysis (number needed to treat/number needed to harm) [5], suggests that, for example, to prevent one pathologic fracture or spinal cord compression using denosumab, 6–12 additional patients would experience a grade 3/4 toxicity or hypocalcaemia when compared with using ZA while 1–2 additional patients would experience ONJ.

Taken together, we suggest that the routine use of antiresorptive agents in men with metastatic castrate refractory prostate cancer, as quantified by SREs and SSEs, is inappropriate if men are responding to anticancer therapy. MSE analysis may be more relevant but we concur with Tombal that more work needs to be done to optimize the choice, timing and length of administration of agents and present our analysis to stimulate further discussion.

R. Leibowitz-Amit1, L. Khoja2, I. F. Tannock2 & A. M. Joshua2*

1Oncology Institute & Cancer Research Center, Sheba Medical Center, Tel-Hashomer, Israel;
2Princess Margaret Cancer Centre, Toronto, Canada
(*E-mail: anthony.joshua@uhn.ca)

disclosure
The authors have declared no conflicts of interest.

references

doi: 10.1093/annonc/mdv039
Published online 28 January 2015

Letter to the editor concerning ‘Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA’

It was with great interest that we read the manuscript by Krop et al. [1] published in Annals of Oncology evaluating the efficacy and safety of trastuzumab–emtansine (T-DM1) versus capecitabine–lapatinib (XL) in patients with treated, asymptomatic CNS metastases at baseline and, similar to the EMILIA ITT population [2], T-DM1 was associated with significantly improved OS compared with XL in this subgroup.

Recently, the incidence of brain metastases in HER2-positive breast cancer increased, likely because of the availability of...
effective systemic therapies [3]. There are currently no systemic therapies approved; capecitabine plus lapatinib is an option [4, 5]. With regard to trastuzumab, its activity in the CNS has always been considered very poor, because of difficulty of penetration and insufficient activation of antibody-dependent cellular cytotoxicity (ADCC) in the brain.

We report the case of a 63-year-old woman with HER2-positive brain metastases who experienced long-term remission during treatment with T-DM1. The patient was offered T-DM1 as sixth line of treatment in the setting of a disease progressing at multiple sites in the bone and the brain. Prior treatments included several lines of chemotherapy combined with anti-HER2 agents: docetaxel/trastuzumab; cisplatin/trastuzumab; lapatinib/capecitabine; trastuzumab/venorelbine; cisplatin/gemcitabine. The diagnosis of brain metastases (two bilateral cerebellar lesions with maximum size of 6 mm), was performed in December 2006, for which she received stereotactic radiotherapy followed by a partial brain irradiation 8 months later, because of the appearance of two new centimetric lesions in the frontal region. After that, owing to the administration of several lines of treatments, the brain lesions were substantially controlled until February 2013, when it was documented brain progression disease (a new left frontal lesion of 18 mm and a new cerebellar lesion of 22 mm) while bone lesions were stable. The patient had no neurological symptoms with KPS 100%. Therefore, in March 2013, the patient was treated systemically with T-DM1 (3.6 mg/kg/3 weeks). The treatment was well tolerated and a progressive significant decrease in size of the brain lesions was observed (the frontal metastases reduced from 18 to 3 mm and the cerebellar lesion from 22 to 4 mm). No new brain lesions were evident and neither neurological symptoms nor a deterioration of her general health status was observed for 15 months of T-DM1 therapy, until meningeal carcinomatosis occurred.

According to Krop’s experience, our case shows that T-DM1 could play a significant role in the treatment of brain metastases even in patients with heavily pretreated HER2-positive metastatic breast cancer. These patients currently have limited treatment options and poor prognosis, with median survival from diagnosis of CNS metastases of 13 months [3]. Our patient, combining systemic and local therapies, lived 92 months from the diagnosis of CNS disease. Possible explanations for the effectiveness of the treatment could be the impaired blood–brain barrier enabling the penetration of T-DM1 into the CNS compartment, the ability of emtansine to activate the ADCC in the brain and the improved control of systemic extracranial disease.

This case suggests that T-DM1 is worthy of further investigation in patients with HER2-positive brain metastases.

J. Foglietta1, G. Metro1, L. Crinò1 & S. Gori2

1Department of Medical Oncology, S. Maria Della Misericordia Hospital, Perugia;
2Department of Medical Oncology, Sacro Cuore Don Giuseppe Calabria, Negrar, Italy

(*E-mail: jennifer.foglietta@libero.it)

**Disclosure**
The authors have declared no conflicts of interest.

#### references

doi: 10.1093/annonc/mdv040
Published online 28 January 2015

**How can I validate a nomogram? Show me the model**

We read with great interest the recent paper by van Gijn et al. [1] describing the development of three nomograms to predict the 5-year risk of local recurrence, distant metastases, and death in rectal cancer patients treated with optional short-term radiotherapy. However, some aspects surrounding the methodology, and more importantly reporting, raise a number of issues that potentially limit the usefulness of the nomograms.

Focusing first on methodology, it is rather disappointing and unclear, why patients with <5-year follow-up were excluded from the analysis; for local recurrence, this meant over 1000 patients were excluded from the analysis. The authors reported using Cox regression; therefore, these patients should have included in the analysis and censored at their last known follow-up, and it therefore seems a waste to throw away such potentially important and informative data. Moving on to evaluating model performance, while the Hosmer–Lemeshow statistic is widely used, it has long been discredited as a useful measure of calibration (i.e. how close the predictions agree with what was observed). The statistic gives no indication on the magnitude or direction of any miscalibration, and calibration plots are generally recommended as being a much more informative assessment of calibration [2].

Moving on to reporting, it is disappointing that the description of the statistical methods is somewhat lacking. The description of how the models were developed, including how the predictors were selected to be included in the models, is somewhat sparse. The final, and arguably, the most important reporting issue relates to the presentation of the model, the authors presumably though it is not stated produced nomograms to aid in the uptake of the model; as a calculation of a patient’s individual probability of recurrence, metastases or death can be done with the need of a calculator. While there is nothing wrong with presenting a nomogram, it should be noted that a nomogram is not a model, but merely a graphical presentation of the