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/vinorelbine; 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 9 months [3]. Our patient, combining systemic and local therapies, lived 92 months from the diagnosis of 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 breast cancer. 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.

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**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 3-year risk of locoregional 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 <3-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...
underlying regression model. For other independent investigators wishing to evaluate (i.e. validate) on other data, it is absolutely vital that the underlying model, namely all regression coefficients (which the authors have done), plus the baseline survival at 5 years (which the authors have not done) are clearly reported. In the absence of the full model, independent validation of the model is not possible.

The Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Initiative (www.tripod-statement.org) recently published the TRIPOD reporting guideline for clinical prediction models. The TRIPOD guideline is similar to other well-known reporting guidelines (e.g. CONSORT, STROBE, and PRISMA) designed to help authors, peer-reviews, and journal editors in ensuring that the essential items describing the development or validation of a clinical prediction model are clearly reported [3]. Accompanying the reporting guideline is an extensive Explanation & Elaboration article describing the rationale for the checklist item, but also highlighting many methodological considerations when developing or validation a clinical prediction model [4].

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Concomitant EGFR and KRAS mutations in ALK-rearranged lung cancer

We read with interest the paper by Won et al. [1] recently describing a significant rate of patients with non-small-cell lung cancer (NSCLC) harboring dual genetic alterations of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). In particular, the use of high-sensitivity methodologies (as mutant-enriched next-generation sequencing) in detecting EGFR mutations lead to increase the rate of lung cancer with concomitant EGFR mutation and ALK rearrangement from 4.4% to 15.4%.

The discovery of this subset of NSCLC characterized by dual EGFR and ALK alterations does represent an important therapeutic issue since these patients may take a great advantage in terms of therapeutic options, survival and quality of life.

We recently focused our attention on this finding describing a patient with exon 21 L858R EGFR mutation and ALK rearrangement in the same tumor cells and reviewing similar cases reported in the literature [2]. Surprisingly, at least 42 patients have been previously described, but the occurrence of this phenomenon is still probably underscored. In a retrospective analysis (personal unpublished observations) of our last 18 ALK-rearranged cases, 3 patients (16.6%) had a concomitant EGFR (exon 19 A746-E750del) or Kirsten rat sarcoma viral oncogene homolog (KRAS) (G12C and G12D) mutations. In another study by Cabillic et al. [3], the authors identified 8 (5.8%) EGFR-mutated cases (4 with L858R, 3 harboring 19 del and 1 case with L858R + T790M) and 14 (10%) KRAS-mutated cases among 139 immunohistochemistry and/or fluorescent in situ hybridization ALK-positive NSCLC. Interestingly, the unique dual ALK-positive and KRAS-mutated adenocarcinoma treated with crizotinib experienced early disease relapse.

The work by Yang et al. [4] and data from our recent review [2] seem to indicate a major clinical benefit in initially treating dual EGFR- and ALK-positive patients with an EGFR tyrosine kinase inhibitor (TKI), whereas patients treated in the study by Won et al. [1] had a better response with crizotinib. As correctly suggested by the authors [1], the fact that 7 of 8 patients treated with crizotinib had a low EGFR mutation burden identified by high-sensitivity molecular techniques could reasonably explain the better response on crizotinib than that observed with an EGFR TKI.

Another interesting finding emerging from these data is that the co-existence of EGFR and/or KRAS mutations in patients with ALK-rearranged lung cancer may act as a primary resistance mechanism, possibly justifying the lack of response observed in 20%–30% of ALK-positive patients treated with crizotinib in clinical trials [5].

Needless to say that the demonstration of these concomitant gene alterations may have a crucial role in the comprehension of the mechanisms of resistance when treating patients with specific inhibitors, but also in switching and modulating molecular therapies against ALK and EGFR depending on the prevalence of the activated molecular pathway and even in supporting the use of combined targeted therapies blocking both cancerogenic mechanisms.

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