Editorial Commentary

Light on the horizon for HER2 overexpressing non-small cell lung cancer?

Kira-Lee Koster[1]^, Martin Früh[1,2]

[1]Department of Medical Oncology and Haematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [2]Faculty of Medicine, University of Bern, Bern, Switzerland

Correspondence to: Martin Früh, MD. Department of Medical Oncology and Haematology, Cantonal Hospital St. Gallen, Rorschacher Strasse 95, 9007 St. Gallen, Switzerland. Email: martin.frueh@kssg.ch.

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Human epidermal growth factor receptor 2 (HER2) alterations are established drug targets in multiple malignancies including breast cancer, gastric cancer and non-small cell lung cancer (NSCLC). HER2 is part of the HER/ERBB receptor tyrosine kinase family with four subunits consisting of an extracellular, transmembrane and intracellular tyrosine kinase domain. Unlike the better known human epidermal growth factor receptor 1 (HER1) [i.e., epidermal growth factor receptor (EGFR)], HER2 is lacking a ligand and dimerization with other subunits is usually required for permanent activation leading to downstream activation of PI3K-AKT and MEK-ERK signaling pathways. The three principal mechanisms of oncogenic activation of HER2 include *HER2* gene mutations (1–4%), *HER2* amplifications (2–5%) and HER2 protein overexpression (2–30%), although considerable overlap and frequent presence of co-alterations exist which adds to the complexity when interpreting trial results (1).

The armamentarium of active drugs targeting HER2 comprise monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and antibody drug conjugates (ADCs). In lung cancer, HER2 directed therapies had been excessively investigated in the past with limited success. The focus lied mostly in the drug class of non-selective pan HER TKIs such as dacomitinib, neratinib and afatinib, which also had significant activity against the EGFR wild type receptor, thus contributing to relevant side effects involving the skin and mucosal membranes (2-5). In addition, response rates were around 20% and therefore rather modest. Of note, newer and more selective HER2 TKIs such as zongertinib and BAY 2927088 with less activity against EGFR are looking very promising with both agents being more active and less toxic in early clinical trials (6,7). Like in breast cancer, the older ADC ado-trastuzumab emtansine was explored in *HER2* mutant NSCLC as well. Although response rates were around 50%, median progression-free survival (PFS) reported in these trials was only 5 months or less (8,9). In addition, HER2 directed monoclonal antibodies in combination with different chemotherapies have shown to be tolerable but did not improve outcomes in comparison to chemotherapy alone although larger trials have not been performed (10-12).

More effective ADCs such as trastuzumab deruxtecan (T-Dxd) have recently emerged as new treatment options not only for HER2 positive breast cancer, gastro-oesophageal and gastric cancer but also in *HER2* mutated lung cancer. T-Dxd consists of a monoclonal HER2 antibody, a cleavable linker and an exatecan-derivative topoisomerase I inhibitor. Activation within the cancer cells occurs by peptides releasing the payload. The improved

^ ORCID: 0000-0002-6549-8124.

efficacy of T-Dxd in comparison to older ADCs is believed to result from a higher activity of the topoisomerase I inhibitor versus the microtubulus inhibitor emtansine and the higher drug-to-antibody ratio of T-Dxd. In addition, T-Dxd has been shown to have a highly membrane-permeable payload. The bystander effect of T-Dxd is contributing to the improved efficacy and may also maintain efficiency in cases of tumour heterogeneity (13-17).

Given the higher incidence of HER2 overexpression compared to *HER2* mutation in NSCLC, more patients could potentially benefit from a targeted approach. After exploration of ADCs in NSCLC patients with HER2 overexpression have been discouraged due to sobering results of trastuzumab emtansine it is now experiencing a reappraisal with the trial by Smit *et al.* with T-Dxd in this 2-cohort study of two different doses of T-Dxd [6.4 mg/kg (49 patients enrolled) and 5.4 mg/kg (41 patients enrolled)] (18,19). Importantly, only patients with HER2 immunohistochemistry (IHC) overexpression (IHC 2+ or 3+) were included and patients with *HER2* mutations, which were studied separately in another cohort of the DESTINY-Lung01 trial, were excluded (14). They reported an overall response rate (ORR) by independent review in a third of the patients including two complete responses. PFS and overall survival were in the order of 6 and 12 months, respectively, and no new toxicities were reported, again confirming the more favourable toxicity profile of the lower and approved dose of 5.4 mg/kg, particularly with regards to lung toxicity (19).

These results clearly demonstrate activity of T-Dxd in this pretreated NSCLC patient population with HER2 overexpression. HER2 overexpression has not typically been a biomarker for which patients have routinely been tested to date. Although intriguing, there are limitations to this trial: first, caution should be exercised when interpreting a non-comparative cohort study with a novel and potentially toxic agent. These trials typically select for better prognostic patients who fulfil stringent inclusion criteria such as a performance status of 0–1 despite multiple previous lines of treatments, minimal time allowed from last treatment including radiation of 4 weeks and time-consuming central tissue testing. All these criteria select for fit patients with a less indolent disease not requiring immediate treatment and may not be representative for the regular patient in clinical practice. Second, although most patients had been pretreated with chemotherapy and immunotherapy, only a quarter of the patients previously received docetaxel which is an approved and active second line option widely considered standard of care with or without an additional anti-angiogenic agent. Whether T-Dxd outperforms docetaxel and an anti-angiogenic agent would have to be addressed in a randomized controlled trial. Third, given the mechanism of action of T-Dxd, it would theoretically be expected, that higher HER2 protein on the surface of the cancer cells would result in more drug being internalized resulting in higher efficacy. However, primary progression was observed in 22% of the patients in the cohort with 6.4 mg/kg as opposed to the cohort with patients with *HER2* mutations reported earlier, where only 3% had primary progression, indicating the limitations of HER2 overexpression as a predictive biomarker in this setting. Overall, in the larger trials of patients with *HER2* mutated NSCLC results were more favourable: responses were observed in half of the patients and the PFS was around 8 months in the study by Li *et al.* and up to nearly 15 months in the study by Goto *et al.*, respectively. T-Dxd in patients with *HER2* mutations was therefore the first ADC in NSCLC that received approval by the Food and Drug Administration (14,20).

The results now reported for HER2 overexpressing NSCLC in the study by Smit *et al.* are in line with other HER2 overexpressing tumours. The DESTINY-PanTumor02 phase 2 trial showed a PFS of around 7 months and an ORR of nearly 40% by independent central review across all included tumour types (21). This study recently resulted in the approval of T-Dxd for adult patients with HER2 positive (IHC 3+) solid tumours after having received prior treatment without further treatment options by the Food and Drug Administration. In our opinion, supported by the results of Smit *et al.*, testing of patients with NSCLC in the absence of standard treatment options or available clinical trials can be considered if access to T-Dxd is ensured. In the study by Smit *et al.*, 20% of patients in the 6.4 mg/kg cohort and 41% of patients in the 5.4 mg/kg cohort were tested HER2 IHC 3+ whereas the remainder of patients were HER2 IHC 2+ (19). The results suggest that there is also activity in patients with HER2 IHC 2+ NSCLC. More studies are required to determine a potential differential effect of T-Dxd in IHC 2+ versus 3+ patients with NSCLC as the current patient numbers do not allow a final conclusion. The current approval by the Food and Drug Administration is based on studies including all cancer entities, however, further studies are required to investigate whether patients suffering from NSCLC with HER2 IHC 2+ overexpression may have the same benefit (21). Due to the emerging interest in testing for HER2 alterations in NSCLC, a consensus guideline has been released by

the European Society of Medical Oncology, suggesting a standardization of HER2 testing worldwide (22).

Recently, a retrospective analysis by Odintsov *et al.* tested more than 5,000 patients with NSCLC for *HER2* amplification using next generation sequencing. *HER2* amplification has been identified in 0.9% of tested lung adenocarcinomas (33/3,799 patients), with a high overlap of HER2 overexpression. Of note, their definition of high amplification differed from other trials (≥6 copy numbers) (23). This could be another area where T-Dxd could be further explored as previously reported results suggesting no relevant correlation in NSCLC between HER2 overexpression and *HER2* amplification detected by fluorescence in situ hybridization (FISH) (24,25).

It is noteworthy that in the current trial by Smit *et al.* several patients responded after previous treatment with EGFR TKIs (19). In this clinical situation, both *HER2* amplification as well as HER2 overexpression are known to contribute to treatment resistance. More data in this patient population accompanied by biomarker analyses would be of interest as despite the large number of other ADCs such as datopotamab and patritumab deruxtecan and bispecific antibodies directed against MET and EGFR, the exploration of further active agents in the setting of EGFR TKI resistance remains an important area of medical need.

Given the overall favourable toxicity profile of the lower dose of 5.4 mg/kg T-Dxd monotherapy reported in the discussed study, T-Dxd might be a possible treatment option in elderly or frail patients, who may not tolerate or decline the platinum-based chemotherapy. Of note, no neutropenia of grade 3 or higher has been reported in the lower dose 5.4 mg/kg cohort (24% of patients in the 6.4 mg/kg cohort). Further studies investigating this vulnerable patient population in combination with immunotherapy would be desirable in this regard.

Although lung toxicity has been reported to occur rarely under the close observation in the trial discussed (5% in the lower dose cohort including 2% with grade 5), it remains to be seen whether these low rates will translate into a real world setting. Patients with advanced or metastatic NSCLC, who have received previous treatment lines including immunotherapy and may have been exposed to radiotherapy or have undetected underlying interstitial lung disease may be at a higher risk for lung toxicity with T-Dxd. This should be further assessed in future studies including real world data collection.

Indicative of the ongoing search for the optimal clinical setting and ideal biomarker, multiple trials with HER2 directed ADCs in NSCLC either as monotherapy or in combination are currently ongoing. These include the phase III DESTINY-Lung04 in *HER2* mutated NSCLC patients in first line versus standard of care (NCT05048797), the DESTINY-Lung03 phase Ib as first line treatment HER2 overexpressing NSCLC in combination with immunotherapy and with or without chemotherapy (NCT04686305), a phase I/II trial with SHR-A1811 in patients with HER2 overexpression, amplification or mutation (NCT04818333), the HUDSON phase II umbrella trial after progression on immunotherapy and chemotherapy (NCT03334617) and a phase II trial in patients with *HER2* mutation, amplification or overexpression with disitamab vedotin plus the anti programmed cell death protein 1 (PD-1) inhibitor tislelizumab and chemotherapy or the EGFR TKI furmonertinib (NCT05847764).

Where do the study results of Smit *et al.* leave us for the moment: T-Dxd offers a novel option in patients with HER2 overexpressing NSCLC without standard treatment options and may also be a valuable potential treatment option in earlier treatment lines in the future. However, many questions remain, which need to be explored in further clinical trials. These include the exploration of standardized, disease specific tests, the efficacy in HER2 IHC 2+ NSCLC, the activity and safety in vulnerable subpopulations and optimal treatment sequence.

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