

Rechallenge with Zongertinib after Trastuzumab Deruxtecan in *HER2*-mutant lung cancer: a case report

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Abstract

A **65-year-old man** with advanced lung adenocarcinoma underwent comprehensive genomic profile testing using a blood sample after completion of standard therapy, which identified a ***HER2* mutation**. The *HER2*-tyrosine kinase inhibitor (TKI); zongertinib achieved partial response; however, the tumor grew, prompting a repeat biopsy 22 months later. Repeat biopsy demonstrated *HER2* protein expression and *HER2* amplification, and treatment was switched to antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd), resulting in tumor shrinkage. After 17 months of treatment, a biopsy of the enlarged tumor revealed that *HER2* protein expression decreased and *HER2* amplification had disappeared, whereas the *HER2* mutation remained. On this basis, zongertinib was re-administered, and the treatment was successful.

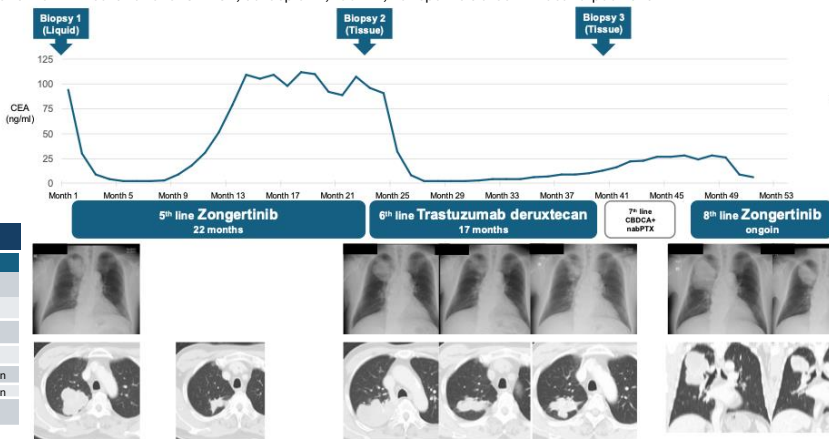
Summary of gene testing results

Biopsy	Gene Test Assay	Sample	Gene	DNA Sequence Variants		Copy Number Variations	
				Amino Acid Change	VAF (%)	Copy Number	Class
1	FoundationOne Liquid CDx	Blood	<i>HER2</i>	A775_G776insVMA	0.62		
			<i>TP53</i>	splice site 782+1G>A	0.21		
2	Oncomine Precision Assay	Primary lesion	<i>HER2</i>	A775_G776insVMA	92	20.19	Amplification
			<i>FGFR3</i>			4.94	Amplification
3	Oncomine Precision Assay	Primary lesion	<i>HER2</i>	A775_G776insVMA	59		

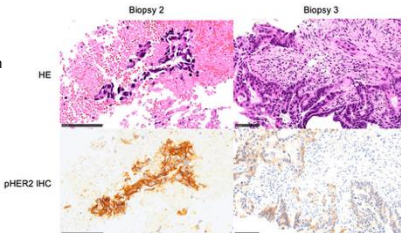
RESULTS

Clinical course after 5th line therapy

Following the diagnosis, the patient underwent four different chemotherapy regimens, including cancer immunotherapy, over a period of 22 months. After receiving zongertinib therapy as the fifth line of treatment, the patient achieved a partial response. After a total of 22 months of treatment with zongertinib, Trastuzumab deruxtecan was administered; the treatment response was favorable, and administration was continued for 17 months. Following treatment with cytotoxic anticancer agents, zongertinib therapy was re-administered as the eighth line, resulting in marked tumor shrinkage within one month. Abbreviations: CBDCA, carboplatin; nabPTX, nanoparticle albumin-bound paclitaxel.



Pathological findings



As shown in Figure 1, Biopsy 2 and Biopsy 3 are samples obtained after resistance to 5th line zongertinib therapy and that obtained after resistance to 6th line trastuzumab deruxtecan therapy, respectively. Biopsy 2 shows high *HER2* expression consistent with the cancer cells, whereas Biopsy 3 shows reduced expression. Abbreviations: HE, hematoxylin eosin staining; IHC, immunohistochemical staining. Bars:100 mm.

DISCUSSIONS & CONCLUSION

- Immunohistochemistry (IHC) confirmed high *HER2* protein expression and *HER2* amplification (Fig.2 and Table 1). This suggests that antibody of the ADC successfully recognized and bound to the target. This finding is consistent with those reported by McMahon *et al.* [1].
- It has been reported that treating breast cancer cell lines with *HER2*-TKIs such as tucatinib or lapatinib, increases *HER2* expression by reducing receptor ubiquitination [2]. They conducted combination experiments with the ADC formulation trastuzumab-emtansine (T-DM1) and found that increasing the number of inactivated *HER2* molecules on the cell surface via TKIs enhanced T-DM1 internalization.
- In our case, a biopsy of the primary tumor was performed even after the development of T-DXd resistance, and IHC revealed decreased *HER2* protein expression (Fig.2). Additionally, genomic sequencing was performed using the Oncomine Precision Assay, which revealed the presence of a *HER2* exon 20 insertion mutation, whereas no *HER2* amplification was detected (Table 1).
- We previously reported that one mechanism of resistance to *HER2*-directed ADCs involves payload resistance mediated by upregulation of ABC transporters [3]; however, additional mechanisms, including *HER2* domain IV mutations, truncation or deletion of the *HER2* extracellular domain, and loss of *HER2* have also been reported [4].
- This case report highlights the value of serial biopsy-based molecular reassessment and supports the potential role of TKI, ADC circulate treatment in biomarker-evolving *HER2*-mutant disease.