Editorial Commentary

HER destiny too

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Some (most) famous people who have made huge contributions to science and society may not have anticipated their lasting fame; then again, if early on they visualized their success to the point of reckoned certainty, then they may, surely, have been bound for greatness. Central to this premise is the appreciable activity and perceived ascendancy of trastuzumab deruxtecan (T-DXd) in the treatment hierarchy of human epidermal growth factor receptor 2-positive (HER2$^+$) breast cancer. In the course of appraising the recently published paper by André *et al.* (1), this commentary attempts to address the meaning of destiny in the context of the DESTINY-Breast02 (hereafter referred to as DESTINY 02) clinical trial.

Destiny is a relatively simple term with multiple synonyms, all referring to a futuristic happening (usually of great import). Yet another conviction relates to providence in that the occurrence has been predetermined and beyond any form of control. From the mindset of the latter, trials involving human subjects should not be conducted with the outcomes being left to fate alone. With this in mind, the impressive results of DESTINY 02 favoring T-DXd raise the provocative question whether the striking differences in the key survival endpoints were destined to happen. At the crux of this supposition is the perceived dominion of this particular antibody-drug conjugate (ADC). As it happens, sequential deductions of outcomes from several HER2 clinical trials appear to substantiate the preclinical promise and preliminary activity observed in phase 1 clinical trials (2,3).

Even though cross-study analyses should be performed with caution, a number of telltale signs are provided to support of the proffered rhetorical question. First, the two treatment arms (in DESTINY 02), T-DXd and physician's choice of capecitabine (C) plus either trastuzumab or lapatinib. Another aspect of the design were the participants, nearly all of who had been treated previously with ado-trastuzumab emtansine (T-DM1). Looking back at two primary endpoints of the EMELIA study (4), median progression-free survival (mPFS) was 9.6 months in the T-DM1 arm and 6.4 months with C plus lapatinib [hazard ratio (HR), 0.65; 95% confidence interval (CI): 0.55–0.77; P<0.001] (*Table 1*); median overall survival (mOS) was also significantly longer with T-DM1 (30.9 *vs.* 25.1 months). Similar developments with respect to the same two endpoints (*Table 1*) were observed in the TH3RESA clinical trial comparing T-DM1 and physician's choice of treatment; improved mPFS (5,6). Prior data such as these concede the apparent inferiority of both regimens of physician's choice in DESTINY 02. In addition, since the closure of DESTINY 01 coincided with the opening of DESTINY 02, it is conceivable that some of the positive outcomes (with T-DXd) from the earlier trial were already beginning to materialize in a population of subjects whose prior therapies included trastuzumab and T-DM1; and in who, more than 50% previously received pertuzumab or other anti-HER2 therapies. Second, the configuration of T-DXd. Similar to T-DM1, tumor selectivity of T-DXd is conferred by binding of the antibody to an epitope located in the extracellular domain of HER2. Allowing that the antibody mechanisms of action will be identical (more on this later), elements related to the conjugation process manifest

Table 1 Comparative clinical endpoints of selected clinical trials

Trial details	EMELIA	TH3RESA	DESTINY 02	DESTINY 01	DESTINY 03
Phase	3	3	3	2	3
Number patients	991	602	608	184	524
Randomization	1:1	2:1	2:1	Single arm	1:1
Treatment arms	T-DM1 *vs.* L + C	T-DM1 *vs.* PC	T-DXd *vs.* C + T or C + L	T-DXd only	T-DXd *vs.* T-DM1
Prior lines of treatment (median)	1 (includes T and taxane)	4 (includes T, L, and taxane)	2–3 (includes T, T-DM1, taxane and P)	6 (includes T, T-DM1, taxane, and P)	1–2 (includes T, taxane, and P)
PFS (median)	9.6 *vs.* 6.4 mo; HR, 0.65; 95% CI: 0.55–0.77; P<0.001	6.2 mo (95% CI: 5.59–6.87) *vs.* 3.3 mo (95% CI: 2.89–4.14); HR, 0.528; 95% CI: 0.422–0.661; P<0.0001	17.8 mo (95% CI: 14.3–20.8) *vs.* 7.1 mo (95% CI: 5.5–8.4); HR, 0.37; 95% CI: 0.29–0.47; P<0.0001	16.4 mo (95% CI: 12.7–not reached)	28.8 mo (95% CI: 22.4–37.9) *vs.* 6.8 mo (95% CI: 5.6–8.2); HR, 0.33; 95% CI: 0.26–0.43; P<0.0001
OS (median)	30.9 *vs.* 25.1 mo; HR, 0.68; 95% CI: 0.55–0.85; P<0.001	22.7 mo (95% CI: 19.4–27.5) *vs.* 15.8 mo (95% CI: 13.5–18.7); HR, 0.68; 95% CI: 0.54–0.85; P=0.0007	39.2 mo (95% CI: 32.7–not estimable) *vs.* 26.5 mo (95% CI: 21.0–not estimable); HR, 0.66; 95% CI: 0.50–0.86; P=0.0021	NR	95% CI: 40.5–not estimable with 72 (28%) overall survival events *vs.* 95% CI: 34.0–not estimable with 97 (37%) overall survival events; HR, 0.64; 95% CI: 0.47–0.87; P=0.0037
Rate of any grade ≥3 AEs	41% *vs.* 57%	40% *vs.* 47%	41% *vs.* 31%	48.4%	52.1% *vs.* 48.3%
Major AEs	Thrombocytopenia, transaminitis *vs.* diarrhea, nausea, emesis, palmar-plantar erythrodysaesthesia	Thrombocytopenia, hemorrhage *vs.* neutropenia, febrile neutropenia	Neutropenia, anemia, nausea, ILD *vs.* diarrhea, palmar-plantar erythrodysaesthesia	Neutropenia, anemia, nausea, ILD	Neutropenia, anemia, nausea, ILD *vs.* Thrombocytopenia, transaminitis

T-DM1, trastuzumab emtansine; L, lapatinib; C, capecitabine; PC, physician's choice; T-DXd, trastuzumab deruxtecan; T, trastuzumab; P, pertuzumab; PFS, progression-free survival; mo, months; HR, hazard ratio; CI, confidence interval; OS, overall survival; NR, not reported; AE, adverse event; ILD, interstitial lung disease.

fundamental differences with apparent consequential effects. For instance, the tetrapeptide-based linker utilized in the antibody-DXd conjugate enhances plasma stability and undergoes cathepsin-mediated cleavage, liberating a cytotoxin with enhanced membrane permeability (7). The latter property is believed (though not uniformly accepted) to facilitate transcellular diffusion of DXd leading to a "bystander effect", a lethal digression encompassing cells in close proximity to $HER2^+$ tumor cells (8). Equally fascinating was the laboratory finding that the killing effect included tumor cells which did not express the oncogenic receptor. In contrast, conjugation in T-DM1 is achieved via a non-cleavable thioether [maleimidomethyl cyclohexane-1-carboxylate (MCC)] bond. Lysosome-bound uncoupling of the antibody results in release of lysine-MCC-$DM1^+$, a less permeable complex that has to be actively transported across lysosomal membranes in order to interact with tubulin (9). Furthermore, the less permeable linker-drug complex limits diffusion and (possible) induction of neighboring tumor cell kill (10). Third, the comparative activities of T-DXd and T-DM1. As a surrogate indicator of anti-tumor efficacy, mPFS was 9.6 months with T-DM1 (EMELIA) and 17.8 months (DESTINY 02); and 16.4 months (DESTINY 01) (11). Considering the generally accepted belief that prior lines of therapy affect clinical efficacy outcomes, (median) numerations for this variable were ≤1 and 2–3 in EMELIA and DESTINY 02, respectively; but perhaps even more notable was the mPFS in DESTINY 01 in subjects having a median of six prior cancer regimens. And aside from the purported bystander effect, a potentially valid explanation

for the shorter mPFS in EMELIA relates to inclusion of patients who progressed on prior taxane therapy suggesting alterations in tubulin dynamics manifested as partial cross-resistance to the maytansinoid derivative (DM1). The substantially shorter mPFS (6.8 months with T-DM1 *vs.* 28.8 months with T-DXd) in DESTINY 03 adds further credence to this supposition (12,13). Fourth, trastuzumab's contribution to the overall antitumor effect. Even though developed to inhibit formation of HER2 homodimers thereby hindering activation of downstream signaling pathways, the bulk of the antibody's therapeutic activity occurs via Fc-dependent recruitment of innate cellular and protein components (14,15). The importance of immune mechanisms such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) should, therefore, not be underestimated. Accordingly, and even if speculative, the extent of exposure to trastuzumab could be meaningful. Based on the dosages of the ADCs (5.4 mg/kg, T-DXd *vs.* 3.6 mg/kg, T-DM1) used in the clinical trials, the uncertainty relates to whether the 50% higher dose of the former translates to more favorable immunomodulatory effects of the antibody.

Although initially considered a third-line option in the metastatic disease setting, the results of DESTINY 02 (and 03) support recommendations for use after progression on trastuzumab/pertuzumab plus a taxane. While the notable activity observed in all of the DESTINY-Breast clinical trials merits its place in therapy, two subject matters emerge. One, pertains to the perceived superiority of the microtubule as a breast cancer target. It is widely accepted that the taxanes are one of the two most active classes of drugs in this disease. Moreover, four other classes of agents, including the maytansine derivative, that disrupt microtubule activity have also been approved. Conversely, early reports involving targeted inhibition of topoisomerase I for patients with taxane-refractory breast cancer did little to argue otherwise (16,17). However, the emergence of T-DXd revives the initial resolve of topoisomerase I as a viable therapeutic mark. Still, and again heeding the caution of inter-study comparisons, the mPFS of 17.8 months (and 28.8 months) in DESTINY 02 (and 03), respectively, rivals (and even exceeds) the 18.7 months achieved with front-line pertuzumab/trastuzumab/docetaxel (CLEOPATRA) (18). And though not inevitable, contemplating human trials to further define front-line therapy may soon be a matter of course. In view of this, a clinical trial comparing T-DXd plus pertuzumab against trastuzumab, taxane, and pertuzumab as initial therapy in the metastatic disease setting would address this clinically relevant question (NCI Clinical Trials.gov identifier: NCT04784715). At the same time, the study may not be able to determine target superiority conclusively. Nonetheless, and because of DESTINY, the efficacy endpoints should favor the T-DXd-based regimen, an end result that cannot be attributed to topoisomerase I inhibition alone without considering the contributions of tumor-specific drug delivery and collateral tumor cell kill. Regardless whether the outcomes are comparable, the results could still be beneficial from a safety perspective. On the whole, while drug-related adverse events (any grade) occurred in nearly all (98%) subjects treated with T-DXd, the incidence of grade ≥3 neutropenia (8% *vs.* 2%), nausea/emesis (4–7% *vs.* 1–3%), and anemia (8% *vs.* 3%) were higher with T-DXd compared to physician's choice of treatment (in DESTINY 02). Arguably, the major concern associated with T-DXd relates to pulmonary toxic events. Forty-two [*vs.* 1 in the physician's choice (PC) arm] subjects developed interstitial lung disease/pneumonitis; two of which were fatal. Of note, the latter figure was lower despite having approximately 70% more subjects than DESTINY 01, an outcome which could be attributed to closer monitoring and earlier intervention of any suspected lung disease. Lastly, while the frequency of drug discontinuations was higher with T-DXd, drug-related dose reductions and treatment interruptions occurred more often among those in the PC arm. If the T-DXd-containing regimen is found to be advantageous, then the second matter relates to whether microtubule catastrophe following progression on initial targeted inhibition of topoisomerase I will be as bold in the reverse order. Intuitively, it should as the mechanisms of action are distinct. Even so, one common mechanism of resistance to topoisomerase inhibitors is upregulation of *MDR1* (the multi-drug resistance) gene resulting in overexpression of the drug efflux pump protein, P-glycoprotein. And cross-resistance to both topoisomerase and microtubule inhibitors has been observed (19,20).

Though unrelated to the direct evaluation of T-DXd, one other aspect of the study that requires reflection concerns the unbalanced allocation format. In DESTINY 02, twice as many patients were randomized to the new intervention relative to the comparator arm. This assignment schema may be appropriate when the treatments being tested are costly. Likewise, unequal allocation is defensible especially when acquisition of additional safety information could be of consequence. In this scenario, the larger number of

subjects in the arm of interest confers a gain in statistical power for assessing particular adverse effects. In addition, though more assumption than science, is the assertion that asymmetrical designation expedites recruitment or minimizes withdrawal and could (albeit not absolutely) benefit a greater percentage of the enrolled subjects. While the use of disproportionate assignment can be justified in some instances, a number of arguments can be made to the contrary. Foremost, if the treatment arms were of clinical parity, then there would be no reason to believe that the new intervention would be better than the comparator regimen. Again, this may not have been the case as initially posed. Furthermore, pre-established lack of treatment equipoise would inevitably result in dissimilar clinical benefit. Next, ethical concerns may be present. For example, while the claim regarding accelerated enrollment and reduced egress may in fact be true, willingness to participate because the odds are greater (i.e., probability) of receiving what is perceived by the investigators as being better must be balanced against the equally important implication that one-third of the subjects will knowingly be designated to the inferior treatment arm. Is it also possible that some clinicians were reluctant to have their patients participate because of the chance of randomization to the latter arm? Endmost, uneven allocation requires a larger sample size to achieve comparable statistical power. Specifically, 12% more subjects will be required with a 2:1 randomization compared to assignment on a 1:1 basis (21).

Notwithstanding the foregoing comments, T-DXd is highly active, and a significant addition and therapeutic option for HER2 (high and low)-expressing breast cancers. Even if the spirit in which this commentary initially embraced the concept of divine will, a more tangible, secular aspect of DESTINY 02 which ultimately inspired the outcomes of this study appears to be related to the ADC itself. While subtle, a few innovative features could account for its perceived superiority. Although sharing the same basic framework as T-DM1, the second-generation ADC features a cytotoxic munition parcel that is 10 times more potent than the active form of the topoisomerase I inhibitor irinotecan (8). Considering the magnitude of potency, it is intriguing to speculate that the activity of the exatecan derivative may parallel anthracycline-mediated inhibition of topoisomerase II as both enzymes have essential roles in DNA replication. And ever mindful of the safety profile, the potential for intolerable systemic toxicity appears to be attenuated by the selective, lysosomal-confined, cleavage of the plasma-stable linker. Different also, the drug-antibody ratio (DAR) of approximately 8 is more than double the DAR of T-DM1 enabling delivery of more DXd (per binding event) to tumor cells (7).

More than a decade ago, an editorial appeared in the New England Journal of Medicine related to the promise of ADCs in breast cancer (22). In that paper, T-DM1 was lauded for the improvement in mPFS and mOS, differences of 3.2 and 5.8 months, respectively, as second-line therapy over the comparator regimen. In DESTINY 02, the mPFS was nearly double (and mOS was >8 months longer than) those figures with T-DXd (in the third-/fourth-line settings). If the results were meaningful then (i.e., 2012), certainly the outcomes from the current paper must be even more noteworthy, and confirmatory of DESTINY 01. Lastly, regardless of the meaning of destiny alluded to in this opinion piece, ultimately it is the patients who, potentially, are poised to benefit. And that is their destiny too.

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