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EDITORIAL

Tucatinib approval by EMA expands options for HER2-positive locally advanced or metastatic breast cancer

AT THE GATES OF APPROVAL

On 10 December 2020, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for Tukysa (tucatinib) in combination with trastuzumab and capecitabine for the treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic breast cancer (BC) who have received at least two prior anti-HER2 treatment regimens.[1]

The EMA's recommendation is mainly based on the HER2CLIMB phase II trial, which randomized BC patients to receive trastuzumab and capecitabine with either tucatinib or placebo. Tucatinib demonstrated efficacy compared with placebo in terms of both progression-free survival (PFS) and overall survival (OS).[2] A key unique feature of the HER2CLIMB trial was that, out of the ∼600 patients enrolled, 291 patients had brain metastases (BMs) at baseline. Furthermore, of these 291 patients, 60% had new or active BMs at study entry, defined as either new lesions or untreated lesions at baseline, or previously treated but progressing existing lesions. Of note, such patients have been traditionally excluded from enrollment in clinical trials. This is the first randomized trial in which an OS benefit for patients with BC and BMs was observed, which is an unmet medical need, especially in HER2-positive metastatic BC, where the occurrence of BMs is frequent, with at least half of patients developing BMs over the course of their disease. Until now, we had no drugs approved for the systemic treatment of BMs.

In light of these clinical results, EMA's announcement about tucatinib expands options for HER2-positive advanced BC (ABC).

TALES OF A FUTURE PAST

Approximately 15%-20% of BCs overexpress HER2.[3] To date, the standard of care in first-line treatment of patients with HER2-positive ABC is trastuzumab plus pertuzumab and a taxane. In second-line treatment, trastuzumab emtansine (T-DM1) is the treatment of choice. For patients with HER2-positive BC progressing during or within 12 months after adjuvant trastuzumab, T-DM1 is considered the standard first-line treatment.

Although systemic treatment options have improved over the past two decades, most patients with HER2-positive metastatic BC eventually die of their disease.[4] In addition, as newly discovered regimens prolong survival, the incidence of BMs, for which active treatment options are limited, increases.[5,6] Treatment of BMs includes locoregional approaches, such as neurosurgical resection and stereotactic or whole-brain radiation therapy.[7] However, systemic drugs, including HER2-targeted agents and chemotherapy, exert a limited intracranial antitumor activity. Such an issue is even more complicated due to the under-representation of patients with BMs in randomized, clinical trials, which usually exclude such patients, thus lacking solid data.[8-10]

Tucatinib is an oral tyrosine kinase inhibitor (TKI) highly selective for the kinase domain of HER2, with minimal inhibition of epidermal growth factor receptor.[11] During its preclinical characterization and in the early-phase clinical settings, tucatinib has demonstrated efficient brain penetration.[12,13] In a phase 1b dose escalation trial started in 2008, the combination of tucatinib with trastuzumab and capecitabine displayed promising antitumor activity in patients with HER2-positive metastatic BC, including those with BMs (Table 1).[11]

The approval was based on the results of the phase II HER2CLIMB trial, which randomized HER2-positive BC patients to receive trastuzumab and capecitabine with either tucatinib or placebo.[2] Tucatinib demonstrated efficacy compared with placebo in PFS [7.8 months versus 5.6 months; hazard ratio (HR): 0.54, 95% confidence interval (CI): 0.42-0.71, $P < 0.001$] and OS (21.9 months versus 17.4 months; HR: 0.66, 95% CI: 0.50-0.87, $P = 0.0048$).[2] Prior treatment with capecitabine or lapatinib were exclusion criteria, although patients who had received lapatinib >12 months before enrollment were eligible.[2]

Among the 511 patients with measurable disease at baseline, an objective response was confirmed in 40.6% (95% CI: 35.3-46.0) of patients in the tucatinib-combination group and 22.8% (95% CI: 16.7-29.8) of patients in the placebo-combination group ($P < 0.001$).[2] Notably, patients with untreated BMs were allowed to enter the study, unless immediate management was needed, in which case they could be enrolled after local intervention.[2] Overall, patients with BMs represented 48% ($N = 198$, tucatinib arm) and 46% ($N = 93$, control arm) of the study population, with median duration of PFS of 7.6 months (95% CI: 6.2-9.5) and 5.4 months (95% CI: 4.1-5.7) for the experimental and control arm, respectively. An exploratory subgroup analysis

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Table 1. Key clinical trials of tucatinib for breast cancer patients

ID	Drug(s)	Indication	Phase	Status
HER2CLIMB-02 NCT03975647	Tucatinib, T-DM1	HER2-positive metastatic BC	III	Recruiting
I-SPY 2 NCT01042379	Tucatinib, chemotherapy	BC	II	Recruiting
NCT03501979	Tucatinib, capecitabine, trastuzumab	Leptomeningeal metastases in HER2-positive metastatic BC	II	Recruiting
HER2CLIMB-04 NCT04539938	Tucatinib with T-DXd	HER2-positive metastatic BC	II	Recruiting
HER2CLIMB NCT02614794	Tucatinib, placebo, capecitabine, trastuzumab	HER2-positive metastatic BC	II	Active, not recruiting
TRIPLET NCT02025192	Tucatinib, capecitabine, trastuzumab	HER2-positive metastatic BC	Ib	Completed
NCT01983501	Tucatinib, T-DM1	HER2-positive metastatic BC	Ib	Completed
NCT00650572	Tucatinib	HER2-positive solid malignancies	I	Completed

BC, breast cancer; HER2, human epidermal growth factor receptor 2; ID, identifier; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

specifically focused on patients harboring BMs ($N = 291$) disclosed that the addition of tucatinib improved intracranial PFS (9.9 months versus 4.2 months, $P < 0.0001$; HR: 0.48, 95% CI: 0.34-0.69, $P < 0.00001$) and OS (18.1 months versus 12 months, $P = 0.005$; OS HR, 0.58; 95% CI: 0.40-0.85; $P = 0.005$).[14] Finally, among the 75 patients with active BMs and measurable intracranial disease at baseline, intracranial objective response rate was improved (47.3% versus 20%, $P = 0.03$).[14] Such results are consistent with the efficient brain penetration of tucatinib (Table 2).[11,12]

Table 2. Features and properties of tucatinib

Chemical name	N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-N4-[3-methyl-4-([1,2,4] triazolo[1,5-a]pyridin-7-yloxy)phenyl] quinazoline-4,6-diamine
Alternative names	ONT-380, ARRY-380, irbinitinib, 937263-43-9, Tukysa (tradename)
Class	Small molecule, TKI
MoA	Highly selective for the kinase domain of HER2, minimal inhibition of EGFR. Prevention of signal transduction pathways, resulting in growth inhibition and cell death.
Route	Oral administration
PD	HER2 IC_{50} 6.9 nmol/l
PK	Vd ≈ 1670 l, plasma protein binding 97%, CL 148 l/h, half-life ≈ 8.5 h CNS penetration[a]: high passive permeability (P_{app}, 12.6 × 10^{-6} cm/s). Normal brain: $C_{ss,ave} = 5.37$ ng/ml (TER, 1.6), ($K_{p,uu}$) 0.47. Brain tumors: $C_{ss,ave}$ 15.6 ng/ml (TER, 4.7), $K_{p,uu} = 1.37$ (↑ drug penetration).
AEs	Common: diarrhea, palmar-plantar erythrodysesthesia syndrome, anemia, decreased phosphate, nausea. Sporadic: hepatotoxicity (↑ALT, ↑AST, ↑ALP, ↑bilirubin), vomiting, stomatitis, decreased appetite, rash, renal impairment (increased creatinine, decreased magnesium, potassium, or sodium). Infrequent: arthralgia, weight decreases, peripheral neuropathy, epistaxis.

AEs, adverse events; ALP, alkaline phosphatase[2,13]; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CL, clearance; CNS, central nervous system; $C_{ss,ave}$, steady-state average concentration; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IC_{50}, half maximal inhibitory concentration; $K_{p,uu}$, unbound brain-to-unbound plasma concentration ratio; MoA, mechanism of action; N, nitrogen; P_{app}, passive permeability; PD, pharmacodynamics; PK, pharmacokinetics; TER, target engagement ratio; TKI, tyrosine kinase inhibitor; Vd, volume of distribution; ↑, increased.

[a] Information about CNS penetration is based on a whole-body physiologically-based pharmacokinetic (PBPK) model integrated with a four-compartment permeability-limited brain model developed and verified for predicting tucatinib concentration-time profiles in the plasma, cerebrospinal fluid, brain, and brain tumors.

The most common adverse events in the tucatinib arm were diarrhea (any grade: 80% versus 53% in the control arm; grade ≥ 3 diarrhea: 12.9% versus 8.6% in the control arm), palmar-plantar erythrodysesthesia syndrome, fatigue, nausea, and vomiting (Table 2).[2] Patients in the tucatinib arm experienced a higher rate of transaminitis, even though typically low-grade, transient, and reversible.[2]

So, the recent recommendation of the CHMP for marketing authorization in the European Union (EU) is only the most recent achievement in the history of a compound that in 2016 was granted Fast Track designation in the USA, in 2017 gained Orphan Drug designation for BMs, and in 2019 Breakthrough Therapy Designation by the Food and Drug Administration (FDA).

Tucatinib is already marketed in the USA, where on 17 April 2020, the FDA issued approval to this drug in combination with trastuzumab and capecitabine for adult patients with advanced unresectable or metastatic HER2-positive BC, including those with BMs, who have received one or more prior anti-HER2-based regimens in the metastatic setting.[15]

In the European World Health Organization (WHO) region, tucatinib has been approved only in Switzerland, where on 12 May 2020 the Swiss Agency for Therapeutic Products (Swissmedic) granted approval to the drug with the same indications provided by the FDA.[16] The approvals stand for the first time under the aegis of Project Orbis, an initiative of the FDA Oncology Center of Excellence that provides a framework for concurrent submission and review of oncology products among international partners.[15,16] Among them, the Australian Therapeutic Goods Administration granted approval on 12 August 2020, after Canada and Singapore. In the EU, the Marketing Authorization Application for tucatinib was validated by EMA in January 2020. On 10 December 2020, the CHMP adopted a positive opinion, recommending the granting of the marketing authorization.[1]

BACK TO THE FUTURE

The successful story of the *HER2* gene, identified in 1982-1984, evolved with the identification of HER2-positive BC and the quest for targeted agents.[16-18] Years later, tucatinib

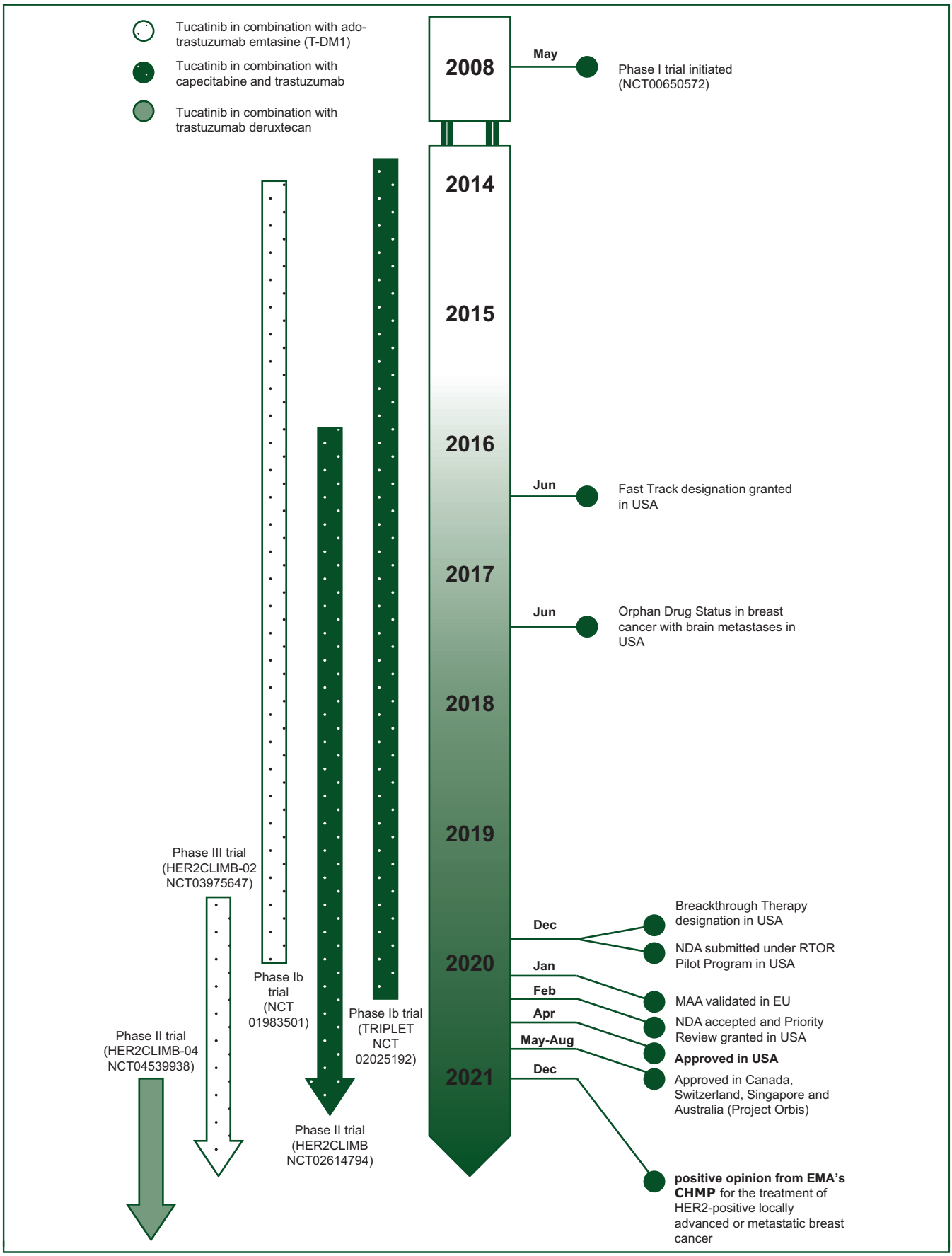

Figure 1. History of tucatinib development.
CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; HER2, human epidermal growth factor receptor 2; MAA, Marketing Authorization Application; NDA, New Drug Application; RTOR, Real-Time Oncology Review.

was developed by Array BioPharma and licensed to Cascadian Therapeutics (subsequently part of Seattle Genetics).[17] Ultimately, the forthcoming EMA's registration of tucatinib for HER2-positive ABC represents another achievement in a scientific saga lasting for more than three decades (Figure 1).

This further step will represent for many European patients the availability of a new valuable therapeutic option. Indeed, the third-line treatment of HER2-positive ABC has traditionally been considered a field of uncertainty, since decisions were taken upon studies enrolling a patient population different from the one treated to date.[18] Although the lack of comparative studies did not allow for recommendations about any specific sequencing, the development of novel anti-HER2 agents rapidly affected the field and shaped recent guidelines.[19] In this regard, the recently FDA-approved tucatinib-based combination represents a further valid choice, with the added value of its intracranial and extracranial efficacy in patients with BMs.[2] With the evolving therapeutic options in the landscape of HER2-positive ABC, improving patient selection is more and more crucial. In the near future, we will be called to optimally manage and sequence all the available drugs, considering also that some patients will have received T-DM1 in the adjuvant setting, in case of residual invasive disease after completion of neoadjuvant therapy, and the new drugs that are enriching the therapeutic armamentarium, such as the earlier discussed tucatinib as well as trastuzumab-deruxtecan.[20,21]

In an ideal world, rapid access to all newly available anticancer drugs should be guaranteed to all patients. However, this is far from the reality, as access to new cancer medicines differs significantly across different countries.[22] The two key aspects for those involved in reimbursement decisions are the level of evidence required to decide and pricing, which can be challenging for some innovative oncology compounds such as tucatinib.[22] Since ESMO has declared achieving equal access to cancer care as one of its major goals, we hope that cooperation and dialogue between stakeholders will ensure that high-quality cost-effective medical oncology care will include compounds such as the newcomer tucatinib.

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