Horizon Scanning in Oncology

Eribulin (Halaven®) as third- or late- line mono-therapy for advanced/metastatic breast cancer

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Eribulin (Halaven®) as third- or late- line mono-therapy for advanced/metastatic breast cancer

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1 Drug description

Generic/Brand name/ATC code:

Eribulin Mesylate (Eribulin), E7389/Halaven®/L01XX41

Developer/Company:

Eisai Europe Ltd.

Description:

Eribulin is a synthetic macrocyclic ketone analogue of halichondrin B, which is naturally found in marine sponges [1]. Eribulin stops the formation of mitotic microtubule spindles by binding to tubulin proteins [2]. Accordingly, eribulin blocks mitosis by disrupting the mitotic spindle system, leading to an incomplete mitosis cycle and consequently to cell death [1].

eribulin blocks mitosis by targeting the mitotic spindle system

In general, all cytotoxic drugs (like eribulin) act on heavily proliferating cells (i.e. performing many mitoses). Therefore, cytotoxic drugs foremost act on neoplasms' because tumour cells are usually proliferating heavily and are therefore targeted by the drug. On the other hand, common side effects are also induced in healthy tissue with strong proliferation (like bone marrow) by the same mechanism.

effect on tumour cells based on their proliferation speed

2 ml vials of Halaven®, containing 0.88 ml eribulin are available. The dosing is based on the patient's body surface area with a recommended dose of 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesylate) at day 1 and day 8 of a 21-day cycle [3].

single dose: 1.23 mg/m² eribulin

Eribulin is administered intravenously (i.v.) within 2-5 minutes. The administration should be performed with the necessary precautions regarding cytotoxic medical products [3].

i.v. application

2 Indication

Eribulin is indicated for locally advanced or metastatic breast cancer (BC) as a 3rd-line mono-therapy.

3rd-line drug for advanced BC

3 Current regulatory status

The EMA approved Halaven® "for the treatment of patients with **locally advanced or metastatic BC** who have progressed after at least two chemotherapeutic regimens for advanced disease" in March 2011. Prior therapy

indication in EMA approval citation

should have included an anthracycline and a taxane unless patients were not suitable for these treatments" [3].

indication in FDA approval citation

Eribulin was approved by the FDA in November 2010 for "the treatment of patients with **metastatic BC** who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting" [4].

approved in the US, Singapore, the EU and in Japan

Additionally, it is approved in Singapore [6] and in Japan [7] and market applications have been filed in Switzerland and Canada [6].

4 Burden of disease

incidence and age distribution in Austria
mortality and age distribution in Austria

In 2008, 4,570 women were newly diagnosed with BC and 1,500 died from BC in Austria [5]. Risk factors associated with the development of BC are age, positive family history, nulliparity, early menarche or genetic factors. The majority of women, that is about 80% , are diagnosed aged ≥ 50 years [6] and most breast cancer deaths appear in the 75-84 years-group (~28%). In the 65-74 years group, the 55-64 years-group and 85+years-group, the death rate is about 20% each. In younger women (45-54 years), death rates of 10% were recorded [6].

incidence and mortality 10-year trend in Austria

The age standardised (WHO World 2001) death rate (per 100,000 population) in women with invasive BC declined in the last ten years from 12.4 (1998) to 9.4 (2008) in Austria [6]. The age standardised incidence rate also dropped from 41.1 (1998) to 34.9 (2008) [6].

assumption: more than 5.000 women in Austria would need late line treatment

Cigler et al. [7] cite that about 20% of women with early stage BC develop metastases within 5 years; up to 10% present initially with metastatic disease. In Austria, about 5% of patients with initially diagnosed BC had disseminated disease [8]. Cure of metastatic BC and complete remissions after chemotherapy are rare, resulting in a median survival of about 18 to 24 months [7]. Only 5 -10% of women survive five or more years [6]. Assuming that 10% of women with breast cancer (the prevalence was 54,418 in 2007 in Austria [9]) are suffering from advanced/metastatic BC and need late line therapy would result in 5,542 women per year.

proportion of metastatic BC

TMN

The Tumour Node Metastasis (TNM) staging classification is used to determine the disease stage. Besides the staging of the primary tumour, the extent to which regional lymph nodes are involved and the absence or presence of distant metastases are taken into account, leading to four main stage groupings (stage I to IV) where metastatic BC is coded as stage IV, advanced BC as stage III [10]. Metastases are most common in the bones, liver or the lungs and cause, depending on the localisation, local symptoms. Most common are bone metastases leading to bone pain and pathologic fractures. Brain metastases can lead to imbalance, confusion, headache or local weakness or numbness [13].

prognostic factors

Prognostic factors for metastatic disease include the length of the relapse-free interval after the initial treatment, the number of metastases, locations involved (worse prognosis with hepatic, lymphangitic pulmonary metastases, bone marrow replacement, carcinomatous meningitis) and biological

markers (e.g., good prognosis is associated with hormone receptor (HR) positive state). Additionally, weight loss, poor performance status and age less than 35 years in woman with early stage BC have an unfavourable prognosis [11].

biological markers

Biological markers for prognosis as well as for therapeutic decisions include estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status.

5 Current treatment

eribulin indicated in advanced BC

The indication for eribulin, as defined by the EMA, is metastatic BC or locally advanced BC that has progressed after at least two chemotherapeutic regimens given for advanced disease.

palliative treatment goal

In cases when the disease has progressed to advanced disease, the aim of the therapy is palliative. Treatment goals are then to prolong life, to improve quality of life (QoL) and to palliate symptoms.

systemic therapy in metastatic BC

While the primary strategy for metastatic BC is the administration of systemic therapy, options for locally advanced BC are, additional, surgery and radiation. Systemic therapy might thus be delivered as adjuvant, neo-adjuvant therapy as monotherapy or in combinations. Details of the treatment of advanced BC have been described in a recent Horizon Scanning Document on lapatinib [12].

Treatment of metastatic BC

individually tailored approach

The treatment of metastatic BC should be tailored individually according to the tumour biology, locations, receptor status and patient dependent factors (tumour symptom burden, "accumulated" toxicity, resistance to former therapies, patient preferences). It can be divided into "early-" line therapies (first-line, second-line) and late-line (third-line or later-line) therapies.

First- and second- (early-) line therapeutic options in metastatic BC

- Chemotherapy

anthracycline or taxane alternatives

In advanced disease anthracycline or taxane are accepted as the most effective drugs in metastatic BC. Chemotherapy with anthracycline or taxane should therefore be administered as first-line and second-line therapeutics except in patients that could benefit from endocrine (HR positive) or combined therapy (see below). For deciding if an anthracycline or a taxane should be given initially, prior exposure to these drugs and particular side effect patterns need to be considered.

alternatives to anthracycline or taxane

Other agents such as capecitabine, gemcitabine, vinorelbine or etoposide which are also independent of the receptor status can be considered as alternatives for early-line therapy in patients with a contraindication to anthracyclines or taxanes [13].

- Endocrine therapy

in HR positive patients

In patients with HR positive metastatic BC and a less aggressive phenotype of cancer, the treatment of advanced disease should start with endocrine therapy, followed by a second-line endocrine strategy. In contrast, patients with positive HR status and an aggressive phenotype, should nevertheless

receive chemotherapy followed by a second-line maintenance endocrine therapy. If the phenotype has changed to a more aggressive form after initial hormone therapy, second-line chemotherapy is indicated subsequently [11].

- Combination therapy

combinations with HER2-directed drugs

In human epidermal growth factor receptor 2 (HER2) positive patients, HER2-directed therapies can be used either in combination with chemotherapy or endocrine therapy [13].

combined chemotherapy

A combined chemotherapy regimen is also an option in the first-line setting. This combination (with a stronger tumour effect but also higher toxicity compared with sequential administration) can be offered to patients that need immediate relief of severe tumour-related symptoms [14].

- Other treatment strategies

local treatment of metastases

While systemic therapy is usually the main therapeutic strand, additional local approaches may be indicated. E.g. surgery and/or radiation may be applied in patients with limited systemic metastases.

Late-line therapy in metastatic BC

attuned to previous treatment

Little guidance exists for the optimal late-line strategy. Receptor status, previous exposure to cancer drugs and patient aspects ("cumulated toxicity") may determine the strategy. Substantial evidence gaps exist – for example – how third- or later-line therapies compare with best supportive care [11]. Options of third-line or later line therapy include vinca alkaloids, gemcitabine, capecitapine, ixabepilone (commentary: that is not an alternative treatment in all European countries, only in France) and paclitaxel [15].

additive palliation therapy

Beside systemic therapy regimes, palliation can be achieved by radiation of metastases, osteoclast inhibition for bone metastases and pain medication.

Treatment of recurrent local-regional BC

Local recurrences should be considered for further local treatment. As there is a risk that metastases might develop, systemic therapy should also be applied. The evidence for patients in this situation is limited [16].

6 Evidence

54 records
1 phase III trial
2 phase II trials

A systematic literature search in medical databases (Medline, Embase, CRD) in addition to a hand search resulted after removal of duplicates in 54 records overall. Of those, 3 records were included: 2 phase II trials [15, 17] and 1 phase III trial [18].

Table 1 Summary of efficacy

Study title: Eribulin monotherapy versus treatment of physician's choice in patients with metastatic BC (EMBRACE)			
Study identifier	ClinicalTrial.gov: NCT00388726; E7389-G000-305; EudraCT Number: 2006-001949-34		
Design	Randomised (2:1 ratio), two-arm open-label multi centre study; N = 762 [18] allocation randomly to 2 treatment groups (508 eribulin, 254 TPC); stratification on geographical region, previous capecitabine treatment and HER2 status		
	Duration	Enrolment: Nov, 2006 - Nov 2008 Median follow-up: The Duration was estimated to be 26.5 month with 630 patients enrolled (to reach the target number of 411 events (deaths)) [19] First Cut-off: 12 May 2009 [20] Data Cut-off: 3 March 2010 [20] ITT Analysis	
Hypothesis	Superiority of OS		
Treatment groups	Intervention		1.4 mg/m² eribulin mesylate (=1.23 mg/m² eribulin) iv. during 2 -5 min on day 1 and day 8 of a 21-day cycle
	Control		Treatment of physician's choice (TPC), defined as any single-agent chemotherapy or hormonal or biological treatment approved for the treatment of cancer and to be administered according to local practice; radiotherapy; or symptomatic treatment alone); Among patients who actually received TPC (n=247): 25% vinorelbine, 19% gemcitabine, 18% capecitabine, 15% taxanes, 10% anthracyclines, 10% other chemotherapies, 4% hormonal therapy
Endpoints and definitions [18]	**Overall survival** (primary endpoint)	OS	Date of randomisation to death or to last date known alive (censored)
	Progression-free survival (secondary endpoint)	PFS	From randomisation to the earliest date of disease progression or death (from any cause), or censored (as for overall survival) [18]
	Tumour response (other reported outcome)	CR, PR, SD, PD	Complete response, partial response, stable disease, progressive disease Tumour response was assessed with Response Evaluation Criteria in Solid Tumours (RECIST)[21]) every 8 weeks (within 1 week), or sooner if disease progression was suspected ("Complete or partial responses needed confirmation 4 weeks or more later.").
	Clinical benefit rate (other reported outcome)	CBR	Duration of complete or partial response or stable disease of at least 6 months' duration
	Objective response rate (Secondary endpoint)	ORR	Complete response or partial response
	Median duration of response (other reported outcome)	DoR	Time from the first documented response until disease progression, death from any cause, or date of censoring

Results and analysis			
Analysis description	Primary analysis: Overall survival including the intention-to-treat (ITT) population, with a two-sided stratified log-rank test at a nominal significance level of 0·049 (adjusted for interim analysis) Cox regression model to calculate the hazard ratio (HR)		
Analysis population	Characteristics	762 women with locally recurrent or metastatic BC mean age: Ø 55 ECOG performance status 0, 1, 2: 42%, 49%, 8%; HER2 positive: 16%; ER and/or PgR positive: 64%; ER and PgR negative: 25%; median number of previous chemotherapy regimes : 4; refractory to taxane, capecitabine, anthracycline: 81%, 68%, 58%; previous surgery, radiotherapy: 86%, 81%; previous hormone therapy 1x, 2x, 3x, >3x: 41%, 23%, 11%, 9%	
	Inclusion	age ≥ 18 ; confirmed BC; between two and five previous chemotherapy regimens, including an anthracycline and a taxane, and two or more regimens for locally recurrent or metastatic BC; progression within 6 months or less of latest chemotherapy; adequate bone marrow, liver, and renal function; ECOG performance status of 0–2; and life expectancy of 3 months or more	
	Exclusion	previous participation in an eribulin trial; use of any investigational drug within 4 weeks of the study; treatment with chemotherapy, radiation, trastuzumab, or hormone therapy within 3 weeks of the study; known brain metastases unless treated and stable; and pre-existing neuropathy of grade higher than 2	
Results (Only results of the 'independent review' [18] are presented)	Treatment group	Eribulin	TPC
	Number of subjects	508	254
	OS (months) median 95% CI	 13.1 11.8 - 14.3	 10.6 9.3 – 12.5
	Deaths Absolute number (%)	 274 (54%)	 148 (58%)
	1-year survival rate (%)	53.9	43.7
	Quality of life (QoL)	NR	NR
	PFS (months) median 95% CI	 3.7 3.3 – 3.9	 2.2 2.1 – 3.4
	Tumour response (absolute number of patients (%)) CR PR SD PD not evaluable	 3 (1%) 54 (12%) 208 (44%) 190 (41%) 12 (3%)	 0 (0%) 10 (5%) 96 (45%) 105 (49%) 3 (1%)
	CBR 95% CI	106 (23%) 18.9 – 26.7	36 (17%) 12.1 – 22.5
	ORR 95% CI	57/468 (12%) 9.4 – 15.5 %	10/214 (5%) 2.3 – 8.4
	DoR (months) median 95% CI	4.2 3.8 – 5.0	6.7 6.7 – 7.0

ER ... estrogen receptor; PgR ... progesterone receptor; HR ... hormone receptor HER2 ... human epidermal growth factor receptor 2; ECOG ... Eastern Cooperative Oncology Group; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease; ORR: objective response rate; CBR: clinical benefit rate; DoR: duration of response.

Effect estimate per comparison	Comparison groups		Intervention vs. Control
	OS	HR	0.81
		95% CI	0.66 – 0.99
		P value	0.041
	PFS	HR	0.87
		95% CI	0.71 – 1.05
		P value	0.137
	ORR	Point estimate	NR
		Variability	NR
		P value	0.002
	DoR	P value	0.159

NR ... not reported

Table 2 Most frequent adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0)

	EMBRACE - NCT00388726		
Grade	**Outcome (%)**	**Eribulin** (n= 503)	**TPC** (n=247)
Non-hematologic AEs*			
All Grades	Asthenia/fatigue	54	40
	Peripheral neuropathy	35	16
	Nausea	35	28
	Dyspnoea	16	13
	Bone pain	12	9
	Mucosal inflammation	9	10
	Palmar-plantar erythrodysaesthesia	1	14
Grade 3 or 4	Asthenia/fatigue	9	10
	Peripheral neuropathy	8	2
	Nausea	1	2
	Dyspnoea	4	3
	Bone pain	2	2
	Mucosal inflammation	1	2
	Palmar-plantar erythrodysaesthesia	< 1	4
Grade 4	Asthenia/fatigue	1	0
	Other AEs	< 1	< 1
hematologic AEs			
All grades	Neutropenia	52	30
	Leucopenia	23	11
	Anaemia	19	23
Grade 3 or 4	Neutropenia	45	21
	Leucopenia	14	6
	Anaemia	2	4
Grade 4	Neutropenia	24	7
	Leucopenia	2	1
	Other AEs	< 1	< 1
Grade 5	Treatment-related deaths, absolute number (%)	5 (1%)	2 (1%)

** AEs with a frequency of 1% or less in either arms within the Grade III or Grade IV category are not displayed here but reported in trial publication([18]): By name the not listed AEs are: alopecia, constipation, arthralgia/myalgia, weight loss, pyrexia, anorexia, headache, diarrhoea, vomiting, back pain, cough, pain in extremity*

study population and inclusion criteria

treatment group: eribulin
control group: various chemotherapeutics

In the EMBRACE trial [18], 762 heavily pre-treated (including a taxane and an anthracyclin) women with locally recurrent or metastatic BC received either eribulin or TPC. Patients had received at least 2 chemotherapies and had signs of progressive disease within the last 6 months. Eribulin was assigned to 508 patients overall. 254 women were allocated to the control arm to receive TPC, which comprised various approved regimens for the third-line therapy of BC. Agents included were vinorelbine (an anti-tubulin alcaloid), gemcitabine (nucleotide analogue), capecitabine (orally-administered pro-drug of 5-flourouracil), taxanes (an anti-tubulin), anthracyclines (cytostatic antibiotic) and other cytotoxic drugs or hormone therapy. To be included, patients had to have an Eastern Cooperative Oncology Group performance status of 0–2 and a life expectancy of more than 3 months.

survival benefit

At the end of the data cut-off, 274 patients (54%) had died in the eribulin group and 148 in the TPC group (58%), **median OS** was 13.1 in the eribulin group and 10.6 in the TPC group. The calculated HR was 0.81 (95% CI: 0.66 – 0.99; p=0.0041), indicating a significant improvement in **overall survival (OS)** for the eribulin group.

exploratory subset analysis

An exploratory subset analysis according to stratification factors showed a significantly longer OS in region 1 (n=488) for eribulin than for TPC (median 13.1 months [95% CI: 11.8 – 14.9] and 10.1 months [95% CI 8.4 – 10.9], respectively) (HR: 0.72; 95% CI 0.57 – 0.92 p=0.009). Region 1 included 488 patients from North America, Western Europe and Australia, while region 2 included 193 patients from Eastern Europe, Russia and Turkey and region 3 81 patients from Latin America and South Africa. In these last two regions, OS was similar for eribulin and TPC; however sample sizes were substantially smaller than that of region 1, and recruitment started much later. Results are thus less mature [18].

beneficial ORR

The secondary end point, **progression-free survival** (**PFS**), on the other hand, did not show favourable results for the eribulin group (I 3.7 months versus C 2.2 months). In contrast, the **objective response rate** (**ORR**; sum of complete and partial response) was 12% in the eribulin arm and 5% in the TPC arm (p=0.002).

more AEs in the eribulin group

more neutropenia and leucopenia

Haematological, as well as non-haematological side effects of all grades were overall more often observed in the eribulin group than in the control group. Concerning **grade 4 adverse events (AEs)**, neutropenia was the most common AE and occurred in 24% in the eribulin group and in 7% in the control group; leucopenia in 2% in the eribulin group and in 1% in the TPC group. Other grade 4 AEs were uncommon and occurred at maximum in 1%. 5 deaths related to treatment (i.e. 1%) occurred in the eribulin group due to febrile neutropenia, lung infection, and bronchopneumonia and dyspnoea. 2 patients (i.e. also 1%) died in the TPC group (febrile neutropenia, aspergillosis).

Grade III or IV haematological AEs neutropenia and leucopenia were more frequent in the eribulin group compared to TPC: 45% vs. 21% (neutropenia) and 14% vs. 6% (leucopenia). While most of the **grade III or grade IV non-haematological AE**s were almost equally frequent in both arms (see Table 2), peripheral neuropathy was more frequent in the eribulin arm (8% vs. 2%), conversely, palmar-plantar erythrodysaesthesia was seen more often in the TPC arm. **Non-haematological AEs of all grades** differed between the two groups. Accordingly, asthenia/fatigue, peripheral neuropathy, nausea, dyspnoea was clearly dominant in the eribulin group. Conversely, only palmar-plantar erythrodysaesthesia was more common in the TPC group.

neutropenia and leucopenia much more frequent in treatment with eribulin

eribulin with more peripheral neuropathy

more all grade AE with eribulin

According to the investigators, the outstanding result of the study is the improvement in OS of heavily pre-treated BC patients. This result was the base for positive approvals in the USA, Europe and other countries.

6.1 Efficacy and safety - further studies

Cortes et al. [17] published the results of "Study 211" (a single arm, open label phase II, multicenter study). The study population consisted of 291 women with locally advanced or metastatic BC which had been treated previously with an anthracycline, a taxane and capacitabine. Patients received 1.4 mg/m^2 eribulin at day 1 and 8 of a 21-day cycle. 269 patients were evaluable and met the key enrolment criteria [20]. The ORR, the primary endpoint, was 9.3% (95% CI: 6.1% to 13.4%). **Median PFS** was 2.6 months (0.03 to 13.1 months), **median OS** was 10.4 months (range: 0.6 – 19.9) and **OS rate after 6 months** was 72.3%.
The most common treatment-related **AEs** of any grade were asthenia/fatigue (65%), alopecia (60%), neutropenia (60%), nausea (44%) peripheral neuropathy (33%), and anaemia (28%). While neutropenia was manageable by dose delays/reductions or by the application of haematopoietic stimulants, peripheral neutropenia (no standard treatment available) was common, but less frequent (6.9 % grade III and 0% grade IV), when indirectly compared to studies about similar drugs 6 deaths occurred in this study, of which one was due to unknown reason and possibly treatment related [20]. **QoL** parameters indicated neither a decline nor an improvement among patients with tumour response. Patients who responded, showed a decline of **pain** visual analogue scale **(VAS) scores**. The authors concluded that eribulin has antitumor activity in heavily pre-treated patients and that the safety profile is manageable and acceptable.

phase II:

"Study 211"

In "Study 201" (phase II, open label, single arm, multicenter study) [15] 103 heavily pre-treated (a median of 4 previous treatments) women were assigned to eribulin at day 1, 8 and 15 (28-day cycle). Due to frequent neutropenia at day 15, a protocol amendment was made, and a second group of patients received eribulin only at day 1 and 8 of a 21-day cycle. Of 87 patients, **ORR** per-protocol was 11.5%. The median **PFS** was 2.6 months and the median **OS** was 9.0 months. The most common grade III and IV **toxicities** were neutropenia (64%), leucopenia (18%), fatigue (5%), peripheral neuropathy (5%), and febrile neutropenia (4%). Two deaths occurred due to neutropenic sepsis and thrombocytopenia and were considered as probably related to treatment [20].

phase II

"Study 201"

7 Estimated costs

one dose of eribulin: € 400

In Austria, the manufacturer price for one 2ml-vial injectable solution of Halaven® containing 0.88 mg (= 0.44mg/ml) is € 400.- [22]. Assuming a mean body surface area (BSA) of 1.7m², a dose of 2.1 mg eribulin (1.2g/1 m²) should be administered. Therefore, 3 vials are required, resulting in costs of € 1,200.-. Two injections (day 1 and day 8) are needed within one 21-day cycle summing up to € 2,400.- for one cycle. In the eribulin-arm of the EMBRACE trial, 503 women of the treatment arm received at least 5 cycles, adding up to total costs of about € 12,000.- for a treatment per person.

2400 € for one cycle

Moreover, assuming the average BSA, every administration of eribulin would leave a rest of 0.54 mg, corresponding to costs of € 245.-. Therefore, of the total treatment costs, € 2,450.- would be wasted, unless hospitals prepare cancer drugs centralised.

8 Ongoing research

Two phase III trials with eribulin are planned to be completed in 2011 (www.clinicaltrials.gov):

Metastatic Breast Cancer

QoL data

- NCT00337103: E7389 (eribulin) Versus Capecitabine in Patients With Locally Advanced or Metastatic Breast Cancer Previously Treated With Anthracyclines and Taxanes. The primary completion date is September 2011.

This study will be of importance, since the authors of the EMBRACE trial announced [8] that study NCT00337103 will also publish QoL data.

Soft Tissue Sarcoma

- NCT01327885: Phase III Study to Compare the Efficacy and Safety of Eribulin With Dacarbazine in Subjects With Soft Tissue Sarcoma. Primary completion date is August 2011.

other indications in research

details on neurotoxicity indication as "early" line therapeutic

The list of Phase II trials on eribulin that are recorded on www.clinicaltrials.gov shows one study NCT00879086 "Eribulin Mesylate and Ixabepilone" that focuses on neuropathy. The risk of neuropathy is a major consideration in eribulin including treatment decision in advanced cancer. Therefore, the results of this study are of importance in weighing benefit and harm of eribulin.

breast cancer subtypes other tumours

early-line settings

Other planned and ongoing studies on eribulin indicate that eribulin is also tested for a variety of other cancers such as solid tumours, non-small cell lung cancer or prostate cancers. It is also studied for specific subgroups of breast cancer (e.g. NCT01269346: HER2 Positive Breast Cancer; NCT01268150: HER2 Negative Breast Cancer) and for

the early-line setting (NCT01328249: Early Stage Breast Cancer; NCT01269346: First-line Therapy; NCT01268150: First-Line Therapy), indicating that the therapeutic use of eribulin could extend in future.

9 Commentary

safety

Patients with metastatic BC have an unmet clinical need for improved therapy in this stage of disease, because there is a lack of effective therapy in this setting. Eribulin was recently approved by the EMA and the FDA [3][4], mainly based on the results of the EMBRACE trial [18]. The most noteworthy result of the EMBRACE study is that, for the first time, improvements in OS were found in the late-line setting of metastatic BC.

approval from EMA and FDA

unmet needs in patients with advanced metastatic disease

Based on the results from the EMBRACE trial the EMA's Committee of Medical Products for Human Use subsumed that the low tolerability of eribulin is outweighed by the positive effect on survival, resulting in an overall positive benefit risk balance [20]. However, some issues regarding the EMBRACE trial should be pointed out.

positive balance of benefits and harms according to EMA review

critical issues for discussion:

patient relevance of survival benefit?

Firstly, the therapeutic aim for patients with metastatic BC is, besides prolongation of OS, the improvement of QoL. But, data for this outcome are still missing, thus hampering a judgement on the balance of benefits and harms. Moreover, without knowing if QoL is improved, or at least maintained by administering eribulin, the gain of 2.5 months in OS is put into perspective. Thus, the question is whether this result represents a clinically relevant finding, foremost as a recent survey amongst clinicians and patients highlighted the fact that expectations in minimum improvements in OS for new therapies differ between these two groups [23]. The majority of physicians (i.e. 48%) considered an incremental improvement in OS of 4–6 months as meaningful, whereas 46% of patients expected a gain of more than 12 months. Even though these gains were expected for first-line therapies of metastatic breast cancer, patient preferences have to be taken into account, especially within the late-line setting.

small effect?

Another issue regarding the effect on survival is that the upper limit of the confidence interval is close to 1.0– which indicate that the observed difference is small (HR = 0.81 ; 95% CI: 0.66 – 0.99). Thus, eventual protocol violations might have an impact on the conclusion. On the other hand, it should be mentioned, that an updated analysis showed at least slightly improved results (HR = 0.81; 95% CI: 0.68 – 0.97) [20].

target population includes subpopulations with probable differing prognosis

Moreover, the study population comprised women with all kind of breast cancers, regardless of their receptor status, a fact which does not reflect current practice. Therefore, it is impossible to identify subgroups which might benefit the most or might have a higher vulnerability to AEs of eribulin therapy. Similarly, no descriptions of AEs in relation to survival or to the state of tumour control are provided in the publication. Hence, it remains unclear, if patients with a more or less beneficial effect from the therapy were more or less affected by AEs.

toxicity in patients with beneficial outcomes?

no QoL and no pain relieve measures

adequacy of therapies in the control group?

One additional point of concern is the adequacy of the therapy in the control group. Firstly, it can be questioned why no single control group participant received best supportive care only. Secondly, many patients with positive HER2 receptors who were not previously treated with trastuzumab had been included in the trial and, additionally, no therapy with trastuzumab (that is indicated for HER2 positive patients) was applied in the control group. Indeed, it would be important to know the clinical response if these patients were treated with trastuzumab and subsequently to eribulin. Thirdly, no in-

formation on algorithms or guidelines that grounded the TPC decisions are presented.

no blinding

Furthermore, in the EMBRACE trial the participants and the investigators were not blinded to treatment allocation. In general, blinding is clearly recommended in controlled trials to increase the methodological robustness.

different indications by FDA and EMA

Another issue is that different definitions of breast cancer indications for eribulin were defined by the FDA and the EMA. According to the EMA, eribulin is indicated in progressive cases of "locally advanced and metastatic disease". While the EMA defines "locally advanced and metastatic disease" as "breast cancer that has spread beyond the original tumour" [3], it is a matter of interpretation, for which particular indications, beyond metastatic disease, eribulin is indicated. In comparison, the FDA did not adopt the indication "...locally advanced or metastatic breast cancer..." that was proposed by the applicant. Instead, the indication was limited to metastatic BC, because only two cases of locally recurrent breast cancer, and no cases other than metastatic cancer were included in the study population of the EMBRACE trial [24].

rising usage of eribulin expected

The costs of eribulin are comparable to other available treatment options. However, it is likely that eribulin will soon be used for earlier lines of therapies for BC. Also, trials are under way assessing eribulin for other tumours, such as lung cancer or bladder cancer. Therefore, the costs of eribulin might eventually add-up.

recommended: more evidence on QoL and on additional comparisons

Future research should complement the existing evidence on eribulin. On the one hand, information regarding QoL and pain relieve is needed, and, on the other hand, studies should address direct comparisons of eribulin with alternative approaches. Thus, studies that compare eribulin with placebo and best supportive care and with other late line therapeutics would be of value. Thereby, specific study populations regarding prognostic factors (e.g. receptor status) should be defined.

Resume

survival benefit

The EMBRACE trial [18] demonstrated a significant improvement in OS for eribulin, but also high toxicity. The trial has some methodological weaknesses which might undermine the robustness of the results. In addition, against the clinical benefit obtained with eribulin, it should be clarified if this important advantage is sufficient and adequate to offset the adverse events that were often serious and more frequent. Finally, to date, the lack of data on the QoL makes even more difficult the evaluation of the true clinic advantage following treatment with eribulin. In 2011, a head-to-head phase III trial (eribulin versus capecitabine; NCT00337103) and two phase II studies (NCT00879086, NCT00965523) are expected to be completed. This new evidence will be of great importance to assess the overall balance of benefits and harms of eribulin compared with other treatment alternatives.

questions on the balance of benefit and harm remain

major additional evidence expected within2011

References

[1] Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, et al. In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer research. 2001 Feb 1;61(3):1013-21.

[2] Smith JA, Wilson L, Azarenko O, Zhu X, Lewis BM, Littlefield BA, et al. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. Biochemistry. 2010 Feb 16;49(6):1331-7.

[3] EMEA. Annex 1 SUMMARY OF PRODUCT CHARACTERISTICS. 2011 [cited 2011-04-27]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002084/WC500105112.pdf

[4] FDA. APPLICATION NUMBER: 201532 APPROVAL LETTER. 2010 [cited 2011-04-27]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201532Orig1s000Approv.pdf

[5] STATISTIK AUSTRIA. Brust (C50) - Krebsinzidenz (Neuerkrankungen pro Jahr), Österreich ab 1983. 2010 [cited 2011-05-20]; Available from: http://www.statistik.at/web_de/static/brust_c50_-_krebsinzidenz_neuerkrankungen_pro_jahr_oesterreich_ab_1983_021696.pdf

[6] Zielonke N. KREBSINZIDENZ UND KREBSMORTALITÄT IN ÖSTERREICH. 2010 [cited 2011-05-20]; Available from: http://www.statistik.at/dynamic/wcmsprod/idcplg?IdcService=GET_NATIVE_FILE&dID=76167&dDocName=045664

[7] Cigler T, Vahdat LT. Eribulin mesylate for the treatment of breast cancer. Expert Opin Pharmacother. 2010 Jun;11(9):1587-93.

[8] STATISTIK AUSTRIA. Brust (C50) - Krebsinzidenz nach Stadium, Jahresdurchschnitt (2006/2008). 2010 [cited 2011-05-20]; Available from: http://www.statistik.at/web_de/static/brust_c50_-_krebsinzidenz_nach_stadium_jahresdurchschnitt_20062008_021700.pdf

[9] STATISTIK AUSTRIA. Cancer prevalence as of 31.12.2007 by localization and sex. 2011 [cited 2011-05-30]; Available from: http://www.statistik.at/web_en/static/results_overview_cancer_prevalence_055177.pdf

[10] UpToDate. Breast cancer. 2010 [cited 2010-03-31]; Available from: http://www.uptodate.com/online/content/topic.do?topicKey=breastcn/9760&selectedTitle=6~150&source=search_result#H1

[11] Hayes D. Systemic treatment for metastatic breast cancer: General principles. 2011 [cited 2011-05-16]; Available from: http://www.uptodate.com/contents/systemic-treatment-for-metastatic-breast-cancer-general-principles?view=print

[12] Nachtnebel A. Lapatinib ditosylate (Tyverb®/Tykerb®) as first-line therapy for the treatment of advanced/metastatic breast cancer. 2010 [cited 2011-05-15]; Available from: http://www.eprints.hta.lbg.ac.at/882/1/DSD_HSO_Nr.09.pdf

[13] Hayes D. Systemic treatment for metastatic breast cancer: Single agent chemotherapy. 2011 [cited 2011-05-12]; Available from: http://www.uptodate.com/contents/systemic-treatment-for-metastatic-breast-cancer-single-agent-chemotherapy?view=print

[14] Gluck S. Chemotherapy regimens in metastatic breast cancer. Clinical Advances in Hematology and Oncology. 2011;9(1):47-8.

[15] Vahdat LT, Pruitt B, Fabian CJ, Rivera RR, Smith DA, Tan-Chiu E, et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2009 Jun 20;27(18):2954-61.

[16] National Cancer Institute. Stage IIIB, Inoperable IIIC, IV, Recurrent, and Metastatic Breast Cancer. 2011 [cited 2011-05-15]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page7

[17] Cortes J, Vahdat L, Blum JL, Twelves C, Campone M, Roche H, et al. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. J Clin Oncol. 2010 Sep 1;28(25):3922-8.

[18] Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011 Mar 12;377(9769):914-23.

[19] FDA. APPLICATION NUMBER: 201532 STATISTICAL REVIEW(S). 2011 [cited 2011-04-27]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201532Orig1s000StatR.pdf

[20] EMEA. Assessment Report for Halaven Eribulin. 2011 [cited 2011-04-27]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002084/WC500105115.pdf

[21] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. Journal of the National Cancer Institute. 2000 Feb 2;92(3):205-16.

[22] Personal communication with Eisai GesmbH; 2011-05-12

[23] Sheik-Yousouf A, Gandhi S, Dukhovn S, Verma S. A comparison of physician and patient perceptions of clinically important endpoints in the treatment of Metastatic Breast Cancer (MBC). European Journal of Cancer Supplements. 2010;8(3):77.

[24] FDA. APPLICATION NUMBER: 201532 MEDICAL REVIEW(S). 2010 [cited 2011-04-27]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201532Orig1s000MedR.pdf