INTERVIEW

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Tracks 1-12

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: You were heavily involved in the research development of capecitabine in both breast and colorectal cancer. How do you approach the dose and schedule of that agent today?

DR TWELVES: In a word, flexibly. I still use the 14-days-on, 7-days-off schedule, and for a fit, active patient I start with the full 2.5-g/m^2 dose, but I don't have a problem starting at the lower dose. Much debate has taken place about what that should be, and we published data a few years ago suggesting that more toxicity occurred with the full starting dose in the United States than elsewhere (Haller 2008).

Even if you start at the lower initial dose, many patients need modifications. I encourage using a low threshold for dose reducing, and I ask patients about

emerging toxicities. I prefer to dose reduce sooner rather than later, with the aim of maintaining treatment for as long as possible.

Tracks 6-10, 12

DR LOVE: You were also involved in the development of the antimicrotubule agent eribulin. Can you talk a bit about how that came about?

DR TWELVES: During the past 15 or 20 years, a focus has developed on marine organisms as a source of chemotherapy agents.

Eribulin, which was originally identified as an extract from a marine sponge, targets something that we consider a validated target — microtubules. We use vinca alkaloids and taxanes, so we know that targeting microtubules is a good approach, but eribulin was sufficiently novel to be of interest because it binds to microtubules in a different manner.

DR LOVE: Would you review the EMBRACE study?

DR TWELVES: EMBRACE was a large trial for patients with heavily pretreated disease (Cortes 2011; [3.1]). All patients had previously received an anthracycline, a taxane and up to 5 lines of prior chemotherapy. The patients on the treatment of physician's choice arm received a wide variety of therapies.

We first presented the overall survival data at ASCO 2010. At the time, no trial had been completed in which overall survival was achieved as the primary endpoint. The improvement in median survival was 2.5 months, and the increase in median survival represented a 23% improvement.

In the first analysis, only 55% of the events within the trial had occurred among the 750 patients on trial, so the data were relatively immature and the survival

3.1

EMBRACE Trial: Eribulin versus Treatment of Physician's Choice (TPC) for Patients with Previously Treated Locally Recurrent or Metastatic Breast Cancer

Endpoint (ITT population)	Eribulin	TPC	Hazard ratio	*p*-value
Median OS (n = 508, 254)	13.1 mo	10.6 mo	0.81	0.041
Median PFS* (n = 508, 254)	3.7 mo	2.2 mo	0.87	0.137
ORR* (CR + PR) (n = 468, 214)	12%	5%	—	0.002
CBR* (CR + PR + SD) (n = 468, 214)	23%	17%	—	—

* Independent review

ITT = intent to treat; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; CBR = clinical benefit rate; SD = stable disease ≥6 months

Cortes J et al. *Lancet* 2011;377(9769):914-23.

curves appeared to converge toward the lower portion. The *p*-value was 0.041, which some argued was barely significant. In the second analysis, however, the median improvement in survival increased from 2.5 to 2.7 months.

DR LOVE: How does the differential effect of age play into these results?

DR TWELVES: The benefits appear similar. When evaluating the age groups in terms of toxicity and efficacy, no obvious detriment or loss of efficacy is evident in older patients (Twelves 2011; [3.2]).

In terms of individual toxicities, the myelosuppression is real. If you take blood counts often enough, you see Grade III or IV neutropenia in up to half of the patients, but less than 5% of patients experience neutropenic sepsis. In our study, a little more than 8% of patients experienced Grade III or IV neuropathy (Twelves 2011; [3.3]).

We have a sister trial to the EMBRACE trial for patients with slightly less heavily pretreated disease (3.4). Those patients had not previously received capecitabine and were randomly assigned to the same experimental arm as in EMBRACE, which was compared to capecitabine. Hopefully we'll see the data in a year or so.

We're also studying eribulin and capecitabine in combination. We haven't presented data yet, but we haven't seen any unexpected toxicities. The combination is active, and we're looking to move into an expanded group of patients with mBC to obtain a better feel for clinical activity and toxicity.

DR LOVE: What about bringing eribulin into the adjuvant setting?

DR TWELVES: We don't have a head-to-head comparison of eribulin to another chemotherapy agent, but I believe we'll be more confident to move earlier in the disease once that has been conducted. Investigators are already piloting studies with other combinations, including combinations that ultimately might be used in the neoadjuvant or adjuvant settings. ■

3.2

Relationship between Age and Survival Outcomes with Eribulin in the Phase III EMBRACE Trial in Metastatic Breast Cancer

	ITT population			Response-evaluable population		
Age at recruitment	N	OS	PFS	N	ORR	CBR
<50	161	11.8 mo	3.5 mo	146	14.4	21.9
50-59	174	13.6 mo	3.7 mo	157	14.7	24.2
60-69	129	13.8 mo	3.8 mo	123	8.1	22.0
≥70	44	14.2 mo	4.2 mo	42	7.1	21.4

ITT = intent to treat; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; CBR = clinical benefit rate

Twelves C et al. *Proc ASCO* 2011;**Abstract 1060**.

3.3

EMBRACE Trial: Age-Based Assessment of Grade 3 and 4 Adverse Events with an Occurrence Rate of 5% or Higher

	Age <50 n = 160	Age 50-59 n = 171	Age 60-69 n = 128	Age ≥70 n = 44
Febrile neutropenia	5.0%	4.1%	3.9%	4.5%
Leukopenia	11.3%	15.2%	15.6%	13.6%
Neutropenia	36.9%	50.3%	46.9%	50.0%
Asthenia	2.5%	4.7%	6.3%	13.6%
Fatigue	3.1%	2.9%	3.9%	6.8%
Dyspnea	2.5%	2.3%	6.3%	9.1%

Twelves C et al. *Proc ASCO* 2011;**Abstract 1060**.

3.4

Phase III Trial of Eribulin versus Capecitabine for Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

Protocol ID: NCT00337103

Target Accrual: 1,100 (Closed)

Eligibility

Locally advanced or metastatic breast cancer

≤3 prior chemotherapies, including an anthracycline and a taxane

No prior treatment with capecitabine

ECOG ≤ 2

R

- Eribulin 1.4 mg/m², d1, 8 q21d
- Capecitabine 2.5 g/m², d1-14 q21d

www.clinicaltrials.gov. Accessed November 2011.

SELECT PUBLICATIONS

Capecitabine tablets [package insert]. South San Francisco, CA: Genentech USA Inc; 2011. Available at: **http://www.xeloda.com/hcp/dosing/modification/**.

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