INTERVIEW

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Tracks 1-15

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Track 2 Effect of personalized therapy based on ERCC1 and RRM1 on overall survival in advanced NSCLC

Track 3 Studies evaluating chemotherapy based on ERCC1 and RRM1 expression status

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Tracks 1-2

DR LOVE: Would you discuss your research related to the molecular markers ERCC1 and RRM1, presented at the World Lung Congress 2009?

DR SIMON: At the Moffitt Cancer Center, we completed four Phase II studies, and one of these — the MADeIT trial — involved the use of molecular analysis to individualize therapy based on DNA repair proteins as molecular markers — ERCC1 and RRM1 — in patients with Stage IV NSCLC and good performance status.

ERCC1 is used to predict platinum sensitivity or resistance, and RRM1 predicts for gemcitabine sensitivity or resistance. Based on the levels of these markers, patients were assigned to four different regimens (4.1): carboplatin/gemcitabine, carboplatin/docetaxel, gemcitabine/docetaxel or docetaxel/vinorelbine (Simon 2007).

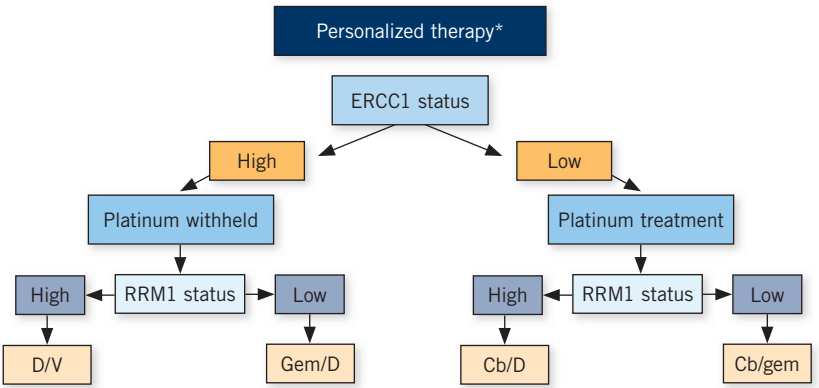
After the results of the other Phase II studies were published, we updated the data on PFS and overall survival. We divided the entire data set from all four studies into a personalized therapy group — patients from the MADeIT study — and a standard therapy group — the other three studies. According to data from up to 48 months of follow-up, patients who received personalized therapy had a better overall survival, 12.3 months, compared to patients in the standard therapy group, with 8.1 months (4.1; [Simon 2009]).

We hypothesized that the administration of platinum-based chemotherapy to patients with low ERCC1 will kill most or all of the cells with low ERCC1. However, the remaining cells are forced to adapt to platinum exposure by upregulating ERCC1 to survive. Similarly, we believe that patients with low RRM1 who are exposed to gemcitabine upregulate RRM1 to survive the

4.1

Personalized Therapy (MADeIT Study) versus Standard Therapy in Advanced NSCLC

Efficacy	Personalized therapy* (N = 58)	Standard therapy† (N = 128)
Median OS	12.3 mo (10.1 to 17.1)	8.1 mo (6.1 to 11.4)
Median PFS	7.0 mo (4.8 to 9.0)	4.5 mo (3.2 to 5.3)



OS = overall survival; PFS = progression-free survival; D/V = docetaxel/vinorelbine; Gem/D = gemcitabine/docetaxel; Cb/D = carboplatin/docetaxel; Cb/gem = carboplatin/gemcitabine

Standardized treatment† = carboplatin/gemcitabine → docetaxel OR carboplatin/paclitaxel/atrasentan OR docetaxel/gefitinib

* Data from the Phase II study 13208 (MADeIT; Simon 2007); † Data from the Phase II studies 12621 (Chiappori 2005), 13303 (Chiappori 2008) and 12905 (Simon 2008)

Simon G et al. *Proc IASLC* 2009;**Abstract D7.6**.

onslaught of gemcitabine-based chemotherapy. Patients with high ERCC1 and high RRM1, although they may not respond to a platinum agent or gemcitabine, have more indolent disease.

Therefore, we hypothesized that when we expose patients to personalized therapy, based on ERCC1 and RRM1, we are forcing the upregulation of these markers, consequently causing more indolent disease behavior.

Track 8

DR LOVE: What are your thoughts on the newer so-called irreversible EGFR TKIs, such as BIBW 2992?

DR SIMON: BIBW 2992 is an irreversible inhibitor of HER1/HER2. When a compound is irreversibly bound to a receptor, that receptor is blocked. Therefore, to survive, cells dependent on EGFR signaling make additional receptors. Consequently, we administer irreversible TKIs using a continuous dosing schedule to keep blocking the newly formed receptors. Generally speaking, these irreversible agents bind tightly.

In a Phase II study of BIBW 2992, the disease control rate was 95 percent in a cohort of patients with EGFR mutation-positive disease (Shih 2009; [4.2]). At this time, a randomized Phase III trial is comparing BIBW 2992 to cisplatin/pemetrexed as first-line treatment for patients with EGFR mutation-positive disease (4.3). It is also being evaluated in the third-line setting in a cohort of patients who have failed on erlotinib. These patients are being randomly assigned to BIBW 2992 or placebo (4.3).

In cell lines, resistance to erlotinib or gefitinib can be attributed to the T790 mutation. T790 adds a bulky methionine group in the ATP-binding pocket. Because the group is bulky, it sterically hinders the attachment of the TKI to the ATP-binding pocket (Kobayashi 2005; [4.4]). Some of the irreversible inhibitors are still able to bind despite the presence of the steric hindrance, which could be an advantage for agents like BIBW 2992. ■

4.2 **LUX-Lung 2 Trial: Best Response According to RECIST and Type of EGFR Mutation in Patients Receiving Second-Line BIBW 2992 (N = 67)**

	Mutation type			
	Del 19	L858R	Other	Total
Partial response (PR) + complete response (CR)	75%	66%	36%	**64%**
Stable disease (SD)	25%	28%	55%	31%
Disease control rate (PR + CR + SD)	100%	94%	91%	**95%**
Progressive disease	0%	6%	9%	4%

Median progression-free survival (second line): 10.2 months

Shih J et al. *Proc ASCO* 2009;**Abstract 8013**.

4.3

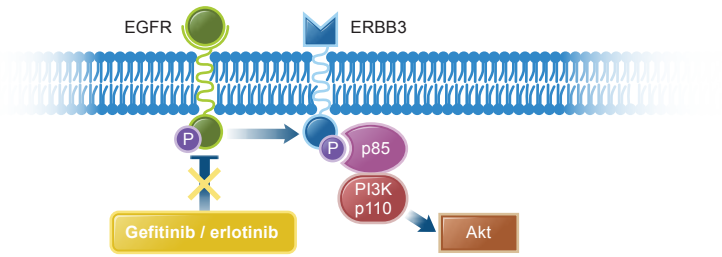
Phase III Studies of the Irreversible EGFR/HER2 TKI BIBW 2992 in Advanced NSCLC

Protocol	Phase	N	Treatment	Eligibility
LUX-Lung 1	III	560	BSC + BIBW 2992 BSC + placebo	• Stage IIIB (with pleural effusion)-IV • 1 to 2 prior lines of chemotherapy • PD ≥ 12 weeks of erlotinib or gefitinib
LUX-Lung 3	III	330	BIBW 2992 Cisplatin/pemetrexed	• Stage IIIB (with pleural effusion)-IV • EGFR mutation-positive • No prior chemotherapy or EGFR-targeted therapy

www.clinicaltrials.gov. Accessed December 2009.

4.4

Steric Hindrance Associated with T790M Mutation Results in Acquired Resistance to Gefitinib or Erlotinib



T790M adds a bulky methionine group in the ATP-binding pocket, which sterically hinders the attachment of EGFR TKIs. Gefitinib and erlotinib are unable to inhibit EGFR phosphorylation in the presence of EGFR T790M. EGFR signaling persists in the presence of gefitinib or erlotinib, leading to persistent erbB3 and Akt phosphorylation. The irreversible EGFR TKIs, such as BIBW 2992, are still able to bind despite the presence of steric hindrance and may be able to prevent EGFR phosphorylation and overcome resistance.

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