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Longterm Follow-Up on Patients with EGFR-Mutated Lung Cancer Treated with an EGFR-TKI and Concurrent Chemotherapy and Literature Review: Is there a Tail on the Curve?

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Introduction

Nine major randomized clinical trials of 1st or 2nd generation Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs) *vs.* platinum-based chemotherapy in patients with newly diagnosed advanced EGFR-mutated lung cancer established EGFR-TKIs as the 1st-line standard of care. As detailed in Table 1 below, EGFR-TKIs demonstrated superiority over chemotherapy with respect to Overall Response Rates (ORR) of 56-85% *vs.* 15-47% and median Progression Free Survivals (PFS) of 8.0-13.7 months *vs.* 5.2-6.9 months, respectively. Despite the superiority of EGFR-TKIs over chemotherapy as initial therapy, treatment cross-over in both arms of the studies resulted in nearly equivalent overall survival strongly suggesting independent and non-cross resistant mechanisms of action between TKIs and chemotherapy [1-11]. Since additive to supra-additive effects can sometimes be achieved with the concurrent use of non-cross resistant treatments, we hypothesized that the concurrent use of EGFR-TKIs and chemotherapy may be superior to their sequential use.

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Patients and Methods

In 2008 we began to routinely offer patients with EGFR mutated lung cancer the addition of carboplatin-based chemotherapy within the first 4 weeks of treatment with erlotinib 100-150 mg per day if there was radiological evidence of any disease regression (concurrent approach), rather than treating with chemotherapy at the time of disease progression after an initial TKI response (sequential approach). This followed a 3 year pilot study in which the feasibility, safety and timing of concurrent chemotherapy was explored in over 20 patients treated with either gefitinib or erlotinib [12]. Over a 6 year interval, 44 patients agreed to this approach (Table 2) and received either carboplatin + pemetrexed (27 patients) +/- bevacizumab (9 patients), carboplatin + gemcitabine (4 patients), or carboplatin + paclitaxel + bevacizumab) (4 patients) within 4 weeks of the start of erlotinib after radiological documentation of disease regression. Erlotinib maintenance treatment was continued until disease progression in all patients. Adenocarcinoma was the most common histological tumor type observed (86.5%; n = 38), whereas 4 patients (9%) had poorly differentiated carcinoma and 2 patients (4.5%) had other histologies (1 mixed adeno-squamous cell carcinoma and 1 large-cell carcinoma). The majority of tumors included in the analysis harbored common EGFR mutations, with 20 patients (45%) and 18 patients (41%) reported to have exon 19 deletion or L858R mutation, respectively. Other EGFR mutation types seen were: G719X mutation in exon 18 (n=1) and mutation in exon 19 of unspecified type (n=1). In 4 patients, the specific EGFR mutation type was not specified.

Results

Interim results have been previously reported in abstract form [13] but long-term follow-up is now available. Thirty-four of the 44 patients (77%) achieved a partial response by RECIST criteria and an additional 5 patients achieved 10-29% tumor regression on CT scan within 22-29 days following the start of erlotinib and began treatment immediately with concurrent chemotherapy. Five patients had between <10% decrease and up to 15% increase in tumor size. Treatment with

Table 1: Randomized clinical trials of EGFR-TKI versus chemotherapy as first line treatment in patients with EGFR-mutated lung cancer.

Study	EGFR-TKI *vs.* Chemo	No. Pts per Arm	ORR	MedianPFS (mos)	OS (mos)
IPASS [1]	Gefitinib	132*	71%	9.5	21.6
	PacCarbo	129*	47%	6.3	21.9
WJTOG	Gefitinib	86	62%	9.2	36
34052	DocCis	86	32%	6.3	39
First-	Gefitinib	26*	85%	8	27
SIGNAL [3]	GemCis	16*	38%	6.3	26
NEJ002 [4]	Gefitinib	114	74%	10.8	27.7
	PacCarbo	114	31%	5.4	26.6
EURTAC [5]	Erlotinib Cis/Cb +	86	58%	9.7	22.9
		87	15%	5.2	19.6
	G/Doc				
OPTIMAL [6]	Erlotinib	82	83%	13.7	22.8
	GemCarbo	72	36%	4.6	27.2
LUX-lung 3 [7,9]	Afatinib	230	56%	11.1	28.2
	PemCis	115	23%	6.9	28.2
LUX-lung 6 [8,9]	Afatinib	242	67%	11	23.1
	GemCis	122	23%	5.6	23.5
CONVINCE [10]	Icotinib	148	-	11.2	30.5
	Pem/Cis	137		7.9	32.1

erlotinib was continued in these patients but all 5 developed disease progression within 2 months and were crossed over to standard chemotherapy. With a median follow-up of 95 months (range, 51-124 months), the median Progression Free Survival (PFS) was 22 months (95% CI, 2.6 to 124+ months). The median Overall Survival (OS) on an intent-to-treat basis (all 44 patients) was 40 months (95% CI, 29.4-54 months) (Figure 1). The median OS is 46 months in the 39 patients who received erlotinib and concurrent chemotherapy and 11 months in the 5 patients who failed to achieve significant tumor reduction with erlotinib and who crossed over early to sequential chemotherapy alone. At this time 38 of the 44 patients (86%) have died. Fourteen (32%) survived 5 years or longer with 4 (9%) alive and disease free at 5.1, 7.8, 8.3 and 8.7 years, 2 alive with metastases at 5.2 and 6.1 years, 5 (11%) died with brain and leptomeningeal metastases only (no systemic disease) at 5.4, 5.5, 6, 7.4 and 10.1 years, 2 died with systemic disease progression at 5.1 and 8.2 years, and 1 died disease-free at 9.8 years with pulmonary fibrosis.

Discussion and Literature Review

Although this is an uncontrolled study, the duration of response and survival suggests that concurrent EGFR-TKI and chemotherapy may provide for improved outcome compared to sequential treatment in some patients with EGFR-mutated lung cancer. The 32% survival at 5 years or more is particularly impressive and it is notable that that the 10 year survival projects to 14% (95% CI = 3%-24%) suggesting a possible "tail on the curve."

Five (11%) of our patients died after 5 years of follow-up with brain and leptomeningeal metastases only and no evidence of systemic disease. We believe this observation reflects the poor pharmacologic penetrance of erlotinib and chemotherapy into the CNS. We cannot, of course, exclude biological factors for these late CNS relapses. This

Table 2: Baseline patients and disease characteristics (n=44).

Variable	Classification	Result, n (%)	
Age, years	Median	68	
	Range	40-88	
Gender	Female	23	-52
	Male	21(48)	
Race	Caucasian	34	-77
	Asian	8 (18)	
	African American	2	-5
Smoking history	Current Smokers	2	-5
	Former Smokers	17	-39
	Never-smokers	24	-54
	NA*	1	-2
Disease stage	IVa	9 (21)	
	IVb	25	-57
	Recurrent disease	10	-23
Disease sites	Lung/pleura	38	-88
	LN (regional and distant)	34	-79
	Bone	17	-39
	Liver	5 (12)	
	Adrenal	4	-9
	Other	3	-7
Brain metastasis	Present	11	-25
	None	33	-75
ECOG PS	0	9 (20)	
	1	28	-64
	2	4	-9
	3	1	-2
	NA*	2	-5
Weight loss >5%	Yes	9 (20)	
	No	34	-78
	NA*	1	-2
Tumor histological type	Adenocarcinoma	37 (84))	
	Large-cell carcinoma	1	-2
	Squamous-cell carcinoma	1	-2
	Other type	5 (12)	
EGFR mutation type	Exon 19 del	20	-45
	L858R	18	-41
	Other type	2	-5
	Unspecified	4	-9

*NA, data not available.

Abbreviations: LN: Lymph Nodes; ECOG PS: Eastern Cooperative Oncology Group performance status

observation, however, increases the hope that 3rd generation EGFR-TKIs, such as osimertinib, that possess superior CNS penetrance and efficacy may further improve long-term survival [13,14] if and when combination studies are pursued.

Several randomized clinical trials further support the hypothesis that EGFR-TKIs and concurrent chemotherapy is superior to the standard sequential approach (Table 3). In FASTACT 2 [12], 451

Table 3: Consistent and clinically meaningful improvement in overall survival with an EGFR-TKI and concurrent chemotherapy.

Study	Treatment	No. of Pts.	ORR	Median PFS	Median OS
Dudnik et al.	E + Chemo	44	87%*	22 mos	37.4 mos
FASTACT-2 [15]	GCE	49	-	16.8 mos	31.4 mos
	GC	48		6.9 mos	20.6 mos
CALGB 30406 [16]	ECP	33		17.2 mos	38.1 mos
	E	33		14.1 mos	31.3 mos
NEJ005 [17]	CPG	41	87.80%	18.3 mos	41.9 mos
	CP	39	84.60%	15.3 mos	30.7 mos
	GPC	40	82.50%	17.5 mos	32.6 mos
Han et al. [18]	PC	40	32.50%	5.7 mos	24.3 mos
	G	41	65.90%	11.9 mos	25.8 mos

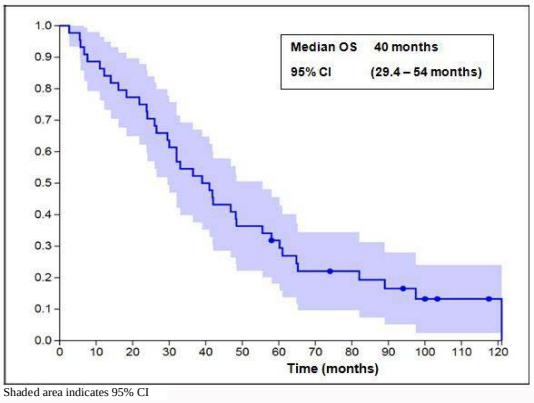

Figure 1: Kaplan-Meier survival curve for all 44 patients.

patients were randomly assigned 1:1 to receive chemotherapy consisting of gemcitabine on days 1 and 8 plus cis- or carboplatin on day 1 every 4 weeks plus "intercalated" erlotinib on days 15-28 of each cycle (GCE) *vs.* chemotherapy plus placebo (GC). EGFR mutation status was analyzed in 241 (53%) patients and demonstrated EGFR wild type in 136 patients and EGFR-activating mutations in 97. Treatment benefit occurred almost exclusively in the EGFR-mutant subgroup with a median PFS of 16.8 months in 49 patients receiving GCE and 6.9 months in 48 patients receiving GC. Although 41 of the 48 patients (85.4%) in the GC arm crossed-over to sequential treatment with an EGFR-TKI at the time of disease progression, their median overall survival was significantly inferior to the GCE group (20.6 months *vs.* 31.4 months, respectively, Hazard ratio = 0.48, range 0.27-0.84, p = 0.0092). There were no statistically significant differences in PFS or OS in patients with EGFR wild type lung cancer randomized to receive GCE *vs.* GC.

CALGB 30406 was a randomized phase II trial of erlotinib alone or combined with carboplatin and in 174 patients with a never smoking or light former smoking history (E *vs.* ECP) [13]. EGFR mutation analyses were successful in 164 patients (91%) and demonstrated EGFR sensitizing mutations in 33 patients in each arm of the study. Planned subset analyses in this EGFR-mutated subgroup demonstrated an improvement in PFS from 14.1 months to 17.2 months and in OS from 31.3 months to 38.1 months in the E *vs.* ECP group, respectively, although these differences did not reach statistical significance.

NEJ005 was a randomized phase II trial of carboplatin + pemetrexed every 3 weeks + concurrent gefitinib 250 mg/day (CP+G) *vs.* carboplatin + pemetrexed alone (CP) in 80 patients with EGFR-mutated lung cancer [14]. Patients in the CP arm alternated to gefitinib at the time of disease progression (sequential approach). Response rates were similar in both groups (87.8% and 84.6%, respectively) but the CP+G arm achieved an increase in PFS (18.3 *vs.* 15.3 months, hazard ratio = 0.71 (0.42-1.20), p = 0.20) and an increase in median survival (41.9 *vs.* 30.7 months). Because of the relatively small size of this randomized phase II trial, none of the differences in outcome reached statistical significance. Notably, the results in the concurrent arm are very close to the results in our uncontrolled single arm study detailed above.

Finally, Han et al. Recently reported the results of a prospective, three-arm randomized phase II clinical trial of gefitinib + pemetrexed/carboplatin (GPC) *vs.* pemetrexed/carboplatin (PC) *vs.* gefitinib alone (G) in 121 patients with advanced or metastastic EGFR-mutated lung cancer. The Overall Response Rates (ORRs) were 82.5%, 32.5% and 65.9%, respectively and the median PFSs were 17.5 months, 5.7 months, and 11.9 months, respectively in the GPC, PC and G arms. A high proportion of patients with disease progression received 2nd line therapy including 65% in the GCP arm (primarily other chemotherapy), 95%, in the CP arm (87.5% EGFR-TKI and 7.5% other chemotherapy), and 75.6% in the G arm (68.3% other chemotherapy and 7.3% other EGFR-targeted therapy). Despite the relatively high rate of successful cross-over treatment in this study, Overall Survival (OS) was significantly longer in the GCP arm compared to the CP arm (HR = 0.46, p = 0.016) and in the GCP arm compared to the G arm (HR = 0.36, p = 0.001). The median OS were 32.6 months, 24.3 months, and 25.8 months respectively in the three arms.

All 5 studies in Table 3 demonstrate a consistent and clinically meaningful improvement in overall survival with an EGFR-TKI and concurrent chemotherapy compared to standard sequential treatment with either an EGFR-TKI followed by chemotherapy or vice versa. Long-term follow-up from our small uncontrolled phase 2 study is the first to suggest that survival beyond 5 years and, indeed, beyond 10 years is achievable in patients with stage IV EGFR-mutated lung cancer. These data are hypothesis-generating and sufficiently provocative that prospective randomized trials should be performed. Given that 11% of our patients died after 5 years from brain or leptomeningeal-only metastases and that 3rd generation EGFR-TKIs, such as osimertinib, effectively cross the blood brain barrier, the argument in favor of this approach even more compelling.

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