Years of sorafenib investigation in advanced non-small cell lung cancer: is there a 'NExUS' linking an unsuccessful treatment and a potentially active one?

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Sorafenib, a multi-targeted receptor tyrosine-kinase inhibitor (TKI) with a supposedly predominant anti-angiogenic activity (inhibition of vascular endothelial growth factor receptor-2, -3 and platelet-derived growth factor ß), has been the subject of extensive clinical research in advanced non-small cell lung cancer (NSCLC). Unfortunately, randomized phase II and III trials, in which the drug was tested in combination with chemotherapy versus chemotherapy alone for either chemonaïve and pretreated non-squamous NSCLC patients, failed to show any survival improvement for the sorafenib experimental arms (1-3). Among these studies, the most recently published phase III 'NExUS' (NSCLC research Experience Utilizing Sorafenib) trial confirmed no survival prolongation with the addition of sorafenib to platinum-based chemotherapy, namely cisplatin/gemcitabine, as front-line therapy for patients with non-squamous advanced NSCLC (HR=0.98) (2). Undoubtedly, such a finding couples with that coming from the 'ESCAPE' (Evaluation of Sorafenib, CArboplatin and Paclitaxel Efficacy in NSCLC) trial in which sorafenib failed to improve survival when added to carboplatin/paclitaxel in a similar patient population (HR=1.15) (1). On the other hand, the 'ESCAPE' trial reported a detrimental effect on survival for the sorafenib arm in patients with squamous cell cancer (HR=1.85), which had a relevant impact on the ongoing 'NExUS' trial; in fact, the enrollment of patients with squamous cell histology was halted in the 'NExUS', thus leading to the exclusion from the primary efficacy population a total of 132 randomized patients (2). Unfortunately, two years and 772 patients later, the results of the 'NExUS' trial added little extra information, besides the notion that sorafenib does not improve survival in non-squamous cancer patients regardless of the platinum-based chemotherapy backbone with which it is combined (2).

Nevertheless, the 'NExUS' trial still showed a clinically modest but statistically significant prolongation in time to progression (HR=0.73) and progression-free survival (HR=0.83) for the sorafenib plus cisplatin/gemcitabine arm; of note, both curves clearly separated past six months since treatment initiation, namely at a time when non-progressive patients were continuing on maintenance sorafenib (2). Therefore, although the skepticals may argue that in the 'NExUS' trial only approximately half of patients scans underwent central radiologic review, it appeared as if sorafenib given as single-agent was associated with a certain degree of clinical activity; nevertheless, some activity was also shown in earlier phase II studies of sorafenib monotherapy as well as in the recently presented phase III 'MISSION' (Monotherapy administration of Sorafenib in patients with non-small cell lung cancer) trial, in which patients who had received at least two but no more than three previous lines of therapy were randomized to either sorafenib or placebo (4-6). However, given the invariably negative results demonstrated by the randomized phase III trials in terms of the primary survival endpoint, the question as to whether sorafenib investigation in NSCLC should be definitively abandoned because of lack of efficacy is very relevant (1,2,6). Certainly, in the absence of a validated predictive biomarker, we can conclude that we do not need more clinical studies of sorafenib in unselected patients. On the other hand, years of trials of anti-angiogenic agents in advanced NSCLC have returned so far no reliable biomarker of clinical activity, which does not necessarily mean that a therapy associated with a small benefit in a large patient population may not be highly beneficial for a selected group of individuals. Against this scenario, the most rational way to build future sorafenib trials would be that of learning from past results.

Firstly, ever since the early clinical development of the reversible epidermal growth factor receptor (EGFR)-TKIs

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Table 1. Clinical activity of sorafenib given either as single-agent or in combination with erlotinib in phase II studies of patients selected disease genotypes based on *KRAS* mutation status with or without a concomitant *BRAF* mutation.

Author [year]	Therapy	Prior lines of therapy	Disease genotype	No. of pts	OR n [%]	DC n [%]	PFS (months)	OS (months)
Smit [2011] (10)	Sorafenib	≥1	*KRAS* mut +	10	3 [30]	9 [90]	3.0	NR
Mellewa [2012] (11)	Sorafenib	≥1	*KRAS* mut +	57	5 [9]	30 [53]	2.3	5.3
Kelly [2011] (12)	Sorafenib	≥1	*KRAS* mut +	11	NR	60%	2.6	7.2
			KRAS WT	23	NR	71%	3.6	13.2
Kim [2011] (13)	Sorafenib	≥1	*KRAS* mut+and/or *BRAF* mut +	14	NR	11 [78.6]	NR	NR
Mok [2012] (14)	Sorafenib	≥1	*KRAS* mut +‡	34	2.9%	44.1%	2.6	6.4
			KRAS WT‡	132	8.3%	45.4%	2.7	11.0
Lind [2010] (15)	Sorafenib + erlotinib	None	*KRAS* mut +	5	0	3 [60]	3.8†	4.7
			KRAS WT	33	11[33.3]	25 [75.7]	5.6†	12.4
Spigel§ [2011] (16)	Sorafenib + erlotinib	1 or 2	*KRAS* mut +	7	NR	NR	2.2	5.3
			KRAS WT	25	NR	NR	3.3	9.2

DC, disease control; No., number; NR, not reported; OR, overall response; OS, overall survival; PFS, progression-free survival; pts, patients; WT, wild type; ‡Either in the plasma or in tissue; P-value of comparison vs. placebo for PFS and OS in KRAS mutant and WT of 0.279 and 0.079, respectively. Biomarker treatment interaction analysis: P-value =0.743; †Time-to-progression; §Randomized study.

gefitinib and erlotinib for advanced NSCLC, we learned that the concomitant administration of TKIs with chemotherapy is probably not an optimal strategy (7). In fact, similarly to EGFR-TKIs, sorafenib inhibits tumor growth by inducing G1 cell cycle arrest, thus potentially interfering with the cycle-dependent toxicity of chemotherapy when this is administered concomitantly (8). Therefore, pharmacodynamic separation achieved by intermittent delivery of sorafenib intercalated with chemotherapy as well as its sequential administration following front-line induction chemotherapy seem to be two reasonable therapeutic strategies that certainly need to be tested in future clinical trials.

Secondly, due to its BRAF inhibitory effect, it has been postulated that sorafenib treatment might be particularly beneficial for patients with a hyperactivation of the Ras/Raf/MEK/ERK prosurvival/anti-apoptotic signaling pathway, which might be the case of tumors harboring a *KRAS* and/or *BRAF* mutation (approximately 1/4 of all NSCLCs) (9). Consistently, studies attempting at relating the activity of sorafenib to *KRAS* mutation have documented an encouraging degree of clinical activity in the so biologically selected group of patients (Table 1). In fact, with the exception of the MISSION trial, in which the small number of tumor tissues collected for *KRAS* analysis (only 10% of the total) might have influenced significantly the reliability of the data on biomarker analysis, sorafenib has been shown to provide a disease control rate in 53% to 90% of advanced NSCLC patients with aberrant *KRAS* activation (Table 1). Importantly. these results are significantly superior to those obtained with approved second- or third-line therapies (i.e., erlotinib or docetaxel) in an analogous *KRAS*-mutant population of patients (17,18). On the other hand, *EGFR* mutation positive NSCLCs should be excluded from further sorafenib testing, since *EGFR*-mutant disease is best targeted by *EGFR*-inhibitors. In fact, due to its EGFR 'oncogene addiction', EGFR-mutant NSCLC is highly dependent on EGFR signaling even at later stages of the disease and despite progression on treatment with EGFR-TKIs (19,20). In addition, a recent study evaluating first-line erlotinib plus sorafenib suggested no benefit from the combination in the *EGFR*-mutant population compared with what it could have been expected with erlotinib alone (Table 2), thus confirming in the clinic the lack of synergistic activity of the dual blockade of EGFR and angiogenesis in *EGFR*-mutants (15,16,21).

Finally, since in most cases a single drug cannot achieve the optimal inhibitory concentrations for all the targets, combination strategies seem to be the best way to proceed in order to maximize antitumor activity and prevent escape mechanisms. As for sorafenib, preclinical studies, strongly support its use in association with drugs aimed at targeting the Ras/Raf/MEK/ERK pathway, and clinical trials should soon be initiated in order to test this hypothesis (22-24).

In conclusion, similarly to what has been observed with other multi-targeted receptor TKIs, the achievement of positive clinical data with sorafenib in NSCLC has been hampered by the fact that no biomarker of sensitivity has been identified. However, just by learning from the past, besides implementing correlative studies either in plasma and in tumor tissue, future sorafenib studies should be limited to non-oncogene addicted NSCLC, possibly testing sorafenib either intercalated or

Table 2. Clinical activity of sorafenib given either as single-agent or in combination with erlotinib in phase II studies of patients with selected disease genotypes based *EGFR* mutation with or without EGFR gene amplification.

Author [year]	Therapy	Prior lines of therapy	Disease genotype	No. of pts	OR n [%]	DC n [%]	PFS (months)	OS (months)
Kelly [2011] (12)	Sorafenib	≥1	EGFR mut +	5	NR	40%	NR	NR
			EGFR WT	18	NR	69%	NR	NR
Kim [2011] (13)	Sorafenib	≥1	EGFR mut+and/or EGFR FISH +	23	NR	9 [39%]	NR	NR
Mok [2012] (14)	Sorafenib	≥1	EGFR mut +‡	44	6.8%	40.9%	2.7	13.9
			EGFR WT‡	122	7.4%	46.7%	2.7	8.3
Lind [2010] (15)	Sorafenib + erlotinib	None	EGFR mut +	7	5 [71.4]	7 [100]	6.9†	Not reached
			EGFR WT	31	6 [19.3]	22 [71]	5.0†	6.3
Spigel§ [2011] (16)	Sorafenib + erlotinib	1 or 2	EGFR mut +	2	NR	NR	Not reached	Not reached
			EGFR WT	43	6 [13.9]	20 [46.5]	3.38	8.11

DC, disease control; No., number; NR, not reported; OR, overall response; OS, overall survival; PFS, progression-free survival; pts, patients; WT, wild type; ‡Either in the plasma or in tissue; P-value of comparison vs. placebo for PFS and OS in EGFR mutant and WT <0.001 in both cases. Biomarker treatment interaction analysis: P-value =0.015; †Time-to-progression; §Randomized study.

sequentially to chemotherapy. Also, biological combination strategies with sorafenib and other *KRAS*-targeting agents should be pursued given the solid preclinical rationale showing that a more complete blockade of the Ras/Raf/MEK/ERK pathway may result into increased anti-tumor activity and prevention of resistance mechanisms.

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