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CORRESPONDENCE

I Am No One. No One Is Perfect…Therefore I Am Perfect

TO THE EDITOR: Recently, Maruyama et al[1] and Kim et al[2] reported the definitive data of two trials comparing gefitinib with docetaxel in second-line treatment of metastatic non–small-cell lung cancer (NSCLC). In the former trial (V-16-32),[1] gefitinib did not reached noninferiority in comparison with docetaxel. Conversely, in the latter trial (INTEREST),[2] noninferiority was reached using a more powered clinical and statistical design. We appreciated the results of the V-16-32 trial and the strength of the clinical and statistical design of the INTEREST trial. However, we think some issues should be dealt with before these results can be translated into clinical practice.

At present, the INTEREST trial[2] is the only trial that shows the noninferiority of gefitinib in comparison with docetaxel in terms of 1-year survival rate. Such a result was not reached by Maruyama et al in the V-16-32 trial,[1] and it is unlikely that it can be hypothesized on the basis of the trial of Thatcher et al (ISEL trial),[3] which did not demonstrate any superiority of gefitinib in comparison with placebo. In our opinion, the assumption of every-3-weeks docetaxel as the gold standard of second-line treatments in NSCLC is fairly questionable. The TAX 317 trial demonstrated an improvement in overall survival with docetaxel 75 mg/m^2 when compared with best supportive care,[4] but only 55 patients were treated with this dose because of the relevant adverse effects observed with the original dose of docetaxel. After the TAX 317 trial, the clinical research has gone three different ways: first, to identify different schedules of docetaxel administration (weekly *v* every 3 weeks), using the design of the superiority trial; second, to compare novel molecules to every-3-weeks docetaxel, using the design of the noninferiority trial; and third, to use epidermal growth factor receptor inhibitors (gefitinib and erlotinib) as an alternative to chemotherapy.

In this context, the clinical development of gefitinib was quite controversial. It was registered for clinical use on the basis of two strongly questioned phase II trials (the IDEAL I and IDEAL II trials)[5-6]; afterwards, it dramatically fell down after the negative results of the ISEL trial,[3] and now it is trying to take a new lease on life mainly on the basis of the data of the INTEREST trial.[2] Apart from the interesting suggestions of the INTEREST trial, the key question that remains without any answer is who gets benefit from these data, as well as from those of all the other noninferiority trials designed and conducted in second-line treatment of NSCLC. Figure 1 reports the hazard ratios of all the randomized clinical trials published as full text that compared pemetrexed,[7] oral topotecan,[8] or gefitinib[1-2] with docetaxel using a noninferiority statistical design. All but the V-16-32 trial showed a noninferiority of the novel drug (pemetrexed, oral topotecan, and gefitinib) versus docetaxel 75 mg/m^2, which is known to have found its role uniquely on the outcome of the 55 patients of the TAX 317 trial.[4]

A few years ago, Garattini and Bertelè[9] warned clinicians against the risks of noninferiority trials, hypothesizing their unethical role in clinical research. Even though such a warning is maybe too extreme,

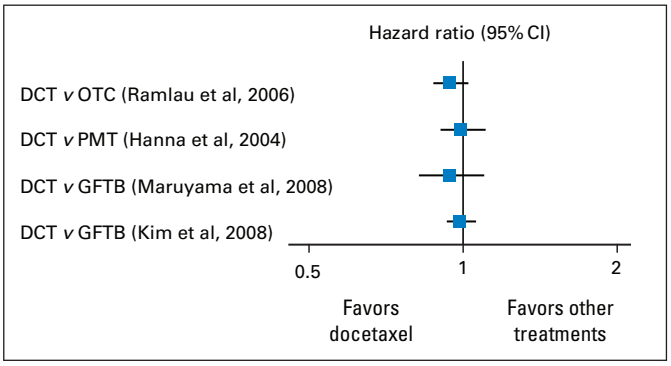

Fig 1. Hazard ratio of the four noninferiority trials comparing every-3-weeks docetaxel with other treatments. DCT, every-3-weeks docetaxel; OTC, oral topotecan; PMT, pemetrexed; GFTB, oral gefitinib.

we think that all the noninferiority trials,[1-2,7-8] and in particular the INTEREST trial,[2] should be read and interpreted with caution because of their controversial results. The noninferiority of gefitinib when compared with docetaxel is a quite interesting finding and encourages additional investigation about the actual role of this drug, but at present it is probably not enough to overcome the negative results of the ISEL and V-16-32 trials and to justify a generalized use of gefitinib in clinical practice. The ancient Greek philosophers named "*συλλογισμος*" (syllogism) the structure of argumentation supporting the rehabilitation of gefitinib (A is better than B, C is noninferior to A, therefore it follows that C is better than B). However, the actual format we can infer from the literature (gefitinib is noninferior to docetaxel [INTEREST trial],[2] but it is nonsuperior to placebo [ISEL trial],[3] which is inferior to docetaxel [TAX 317 trial][4]) could probably be better defined as a "*παραδοξος λογος*" (paradox). In our opinion, more evidence is needed to solve the problem of second-line treatment of NSCLC in clinical practice and to give one more chance to gefitinib.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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