conclusions from a 596-patient clinical study, i.e. the side effect profiles are similar. Pumo et al. [1] noted a difference in serious adverse event rates between s.c. and i.v. trastuzumab in this phase III HannaH trial (NCT00950300) [3]. A later analysis with additional follow-up reported that these differences were small and often based on rare events, with no observable pattern [4]. There were no such differences in healthcare professional-reported serious adverse event rates in PrefHer, although there were differences in the overall adverse event rates between s.c. and i.v., which were driven by more grade 1 events in the s.c. period [2]. As PrefHer was a trial which focused on patients’ experiences, patients were also directly asked about side effects. Patients reported that s.c. was the least painful route and caused less bother from bruising or irritation than i.v. [2]. Indeed, the second main reason why patients preferred s.c. trastuzumab was that it caused less pain/discomfort and fewer side effects compared with the i.v. formulation [2]. There is clearly a discrepancy between healthcare professional-reported adverse events and how the patients feel, which should be addressed in future studies.

PrefHer’s interviews were very thorough; even before patients were randomized, they were asked for their hypothetical preference during a pretreatment interview. Of the 54% of patients who expressed a priori preference for i.v. trastuzumab or no preference after giving informed consent, 84% stated a final preference for s.c. trastuzumab [2]. Following the crossover period, proportions of patients overwhelmingly preferring s.c. trastuzumab were also similar in those who did or did not receive i.v. trastuzumab before randomization [2], adding to the robustness of the findings.

In conclusion, the totality of the evidence from HannaH and PrefHer confirms that s.c. trastuzumab has a similar efficacy [3, 4] and safety profile [2–5] to the i.v. formulation, and that the majority of patients prefer s.c. over i.v. administration [2, 5].

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Concomitant ALK translocation and other non-EGFR gene in NSCLC: knowledge in the making

We read with great interest the two papers published recently on Annals of Oncology, regarding concomitant ALK translocation with EGFR and KRAS mutations [1, 2]. Although, the use of high-sensitive methodologies (as mutant-enriched next-generation sequencing) increased the rate of lung cancer with concomitant EGFR and ALK rearrangement, these data confirming that lung cancer with ALK rearrangement show high genetic heterogeneity. Only a few years ago, we consider ALK and EGFR mutually exclusive but today we not only detect concomitant ALK and EGFR mutations [3], but are able to treat these patients prolong their survival with different target agents targeting different target [4]. At the present time, based only sporadic case report explored the role of different target agents in NSCLC when concomitant mutations are present, it is difficult to understand how is the best sequence of treatment.

In our clinical experience, we found a different concomitant mutation with ALK rearranged. On September 2012, a thoracic lobectomy was carried out on a 46-year-old woman, no smoker, with a definitive histopathological examination of NSCLC with adenocarcinoma features, with lymph node involvement in one-third of resected lymph node; stage pT2a pN1: stage IIB (based on 7th edition of TNM classification).

A primary assessment on pathological tissue resulted negative for EGFR mutations and weakly positive (4% of cells) for ALK
gene rearranged. Considering the clinical and pathological anamnestic data of the patient, we carried out a deeply new evaluation of the tumor sample. We evaluated the mutational status of EGFR and K-RAS by bidirectional Sanger sequencing, ALK by FISH and immunohistochemistry (IHC), ROS-1-gene and RET (10q11.21) rearrangement by FISH, and expression (IHC) and amplification of HER-2 proteins. Both of EGFR was confirmed as wild type. Re-analysis for EGFR and KRAS confirmed for both the wild-type status. ROS-1-gene and RET (10q11.21) resulted negative. ALK gene rearrangement was detected by FISH (break Apart Rearrangement Probe, Abbott Molecular, Les Plaines, IL) in ∼15% of the tumor cells (Figure 1A); IHC showed a diffuse and strong positivity for ALK (clone D5F3) (Figure 1B). Forty percent of the tumor cell membranes were completely and intensely stained with anti HER-2 (Herceptest, Dako, Glostrup, DK) (Figure 1C). Furthermore, we found HER-2/Neu amplification evaluated by DDISH (Ventana, Tucson, AZ) (Figure 1D). Bidirectional Sanger sequencing was negative for HER-2 mutations. On May 2014, patients developed a progression disease with bilateral adrenal lesions and started first-line treatment with cisplatin (70 mg/mq) and pemetrexed (500 mg/mq) 1q21, for four cycles. Patients continued treatment with maintenance pemetrexed at the present time on-going.

In this report, we showed for the first time, that over EGFR mutations, Her-2 gene [5] amplification could be occur in patients with ALK translocation, confirming the heterogeneity of non-small-cell lung cancer with adenocarcinoma histology. The findings improve our knowledge about intratumor heterogeneity of non-small-cell lung cancer, in particular when ‘druggable’ or sensitive mutations are detected. These aspects could be used to explore the role of dual-inhibition with target agents, which at the present time are missed, excluding sporadic report.

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