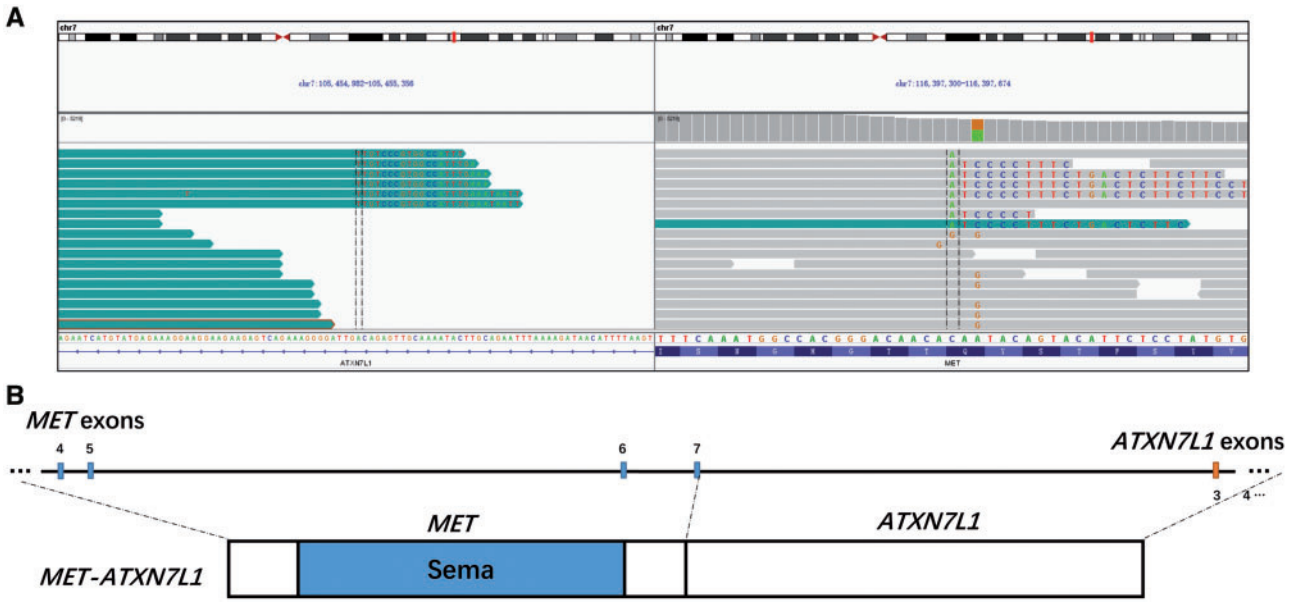

Figure 1. *MET–ATXN7L1* fusion is clinically actionable. The integrative genomics viewer snapshot of *MET–ATXN7L1* (A); schematic representation of the *MET–ATXN7L1* fusion protein domain structure (B).

MET gene fusion is relatively rare and may be a promising molecular target for individualized diagnosis and treatment of lung adenocarcinoma. We summarized case reports involving MET fusions in NSCLC (Supplementary Table S1, available at *Annals of Oncology* online). Continued efforts to explore driver gene alterations are warranted.

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Disclosure

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Vitamin K1 cream significantly reduces incidence and severity of cetuximab-related acneiform skin rash in women: a post hoc analysis of the EVITA trial

Patients treated with drugs targeting the epidermal growth factor receptor (EGFR) frequently develop acneiform skin toxicities. These skin reactions can impair treatment adherence and clinical outcome [1]. Prophylactic treatment with doxycycline reduces the severity of skin toxicities [2].

Recently, the prophylactic effects of vitamin K1 cream (Reconval K1) in addition to doxycycline were explored in a double-blind, randomized phase II trial (EVITA) in patients receiving cetuximab-based treatment of metastatic colorectal

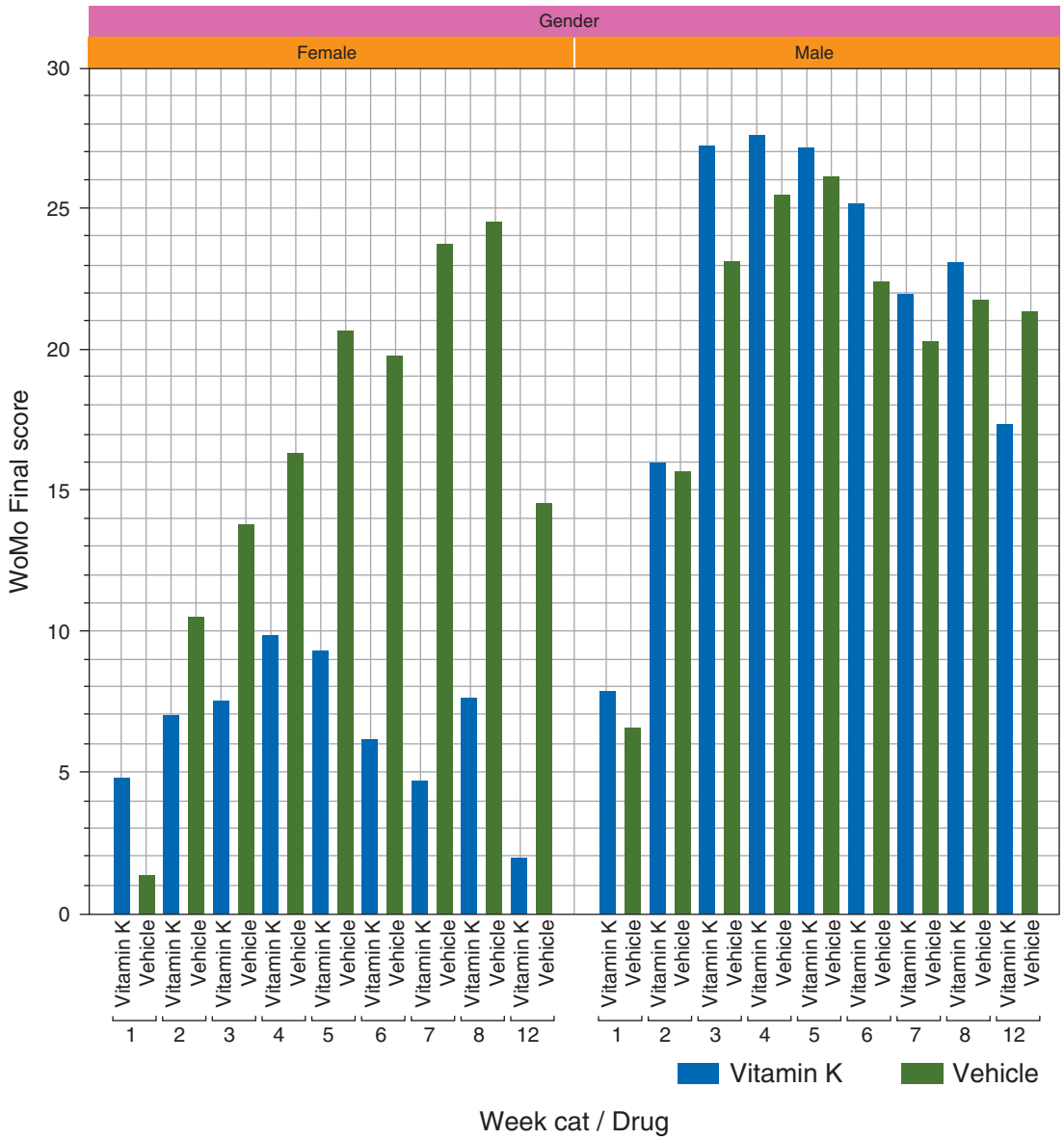

Figure 1. Mean values for the WoMo Final score according to gender (women: left part; men: right part), allocated to treatment arm (vitamin K: blue bars; vehicle: green bars), and treatment week.

cancer [3]. Vitamin K1 cream or vehicle was applied twice daily for 8 weeks, followed by a 4-week observation period. Since NCI CTC skin toxicity criteria mostly reflect the percentage of the affected body surface, in the EVITA trial the more thorough tripartite WoMo skin rash grading score [4] was used as main secondary end point. EVITA demonstrated a trend towards less severe skin rash in vitamin K1-treated patients in terms of the WoMo score [3].

In the present post hoc analysis of the EVITA trial, including a total of 122 patients ($n = 37$ females, $n = 85$ males), the effects of vitamin K1 were further explored according to gender and treatment arm. The main findings of the gender specific analysis of the WoMo Final score are lower mean values in women treated with vitamin K1 compared with those treated with vehicle cream starting from week 1 and increasing over time (Figure 1). For woman, these differences become statistically significant starting from week 5 on ($P < 0.05$). Until week 8, there was still a high percentage of data available (78%, 29/37 female patients). The consistency of the efficacy of vitamin K1 cream in improving the values of the WoMo Final score is remarkable, especially because for men an effect of vitamin K1 cream was not seen at any time point. The observed effect was also confirmed by modeling these data using mixed effect longitudinal multiple linear regression analysis.

The analysis of the WoMo Final score revealed a comparably high number of women developing no rash at all when treated with both, doxycycline and vitamin K1 cream. Few women were graded with a severe WoMo Final score during the course of treatment (~5% in the vitamin K1 arm). Contrarily, very few men presented without signs of skin rash from week 2 on, and the

percentage of men with severe skin rash over time averaged in the range of 15% despite vitamin K1 treatment. The finding that the positive effects of vitamin K1 cream on skin lesions are restricted to female patients could be caused by several reasons. We found no gender-specific adherence differences to study treatment or imbalances between arms in terms of dose intensity and treatment duration with cetuximab.

Gender-specific expression patterns or hormonal modulation of EGFR might play a role for the better effect of vitamin K1 on female skin. Expression of EGFR in the facial skin is likely to be higher in men because of the terminal character of the facial hair and the higher density of sebaceous glands [5]. It is therefore conceivable that the dose of vitamin K1 (0.1%) and/or the frequency (b.i.d.) of cream administration was insufficient to observe an effect in men.

The size of the observed effect and the benefit for women appears to be large enough to justify the recommendation of vitamin K1 cream (Reconval K1) as a prophylactic treatment in addition to doxycycline in women initiating anti-EGFR treatment. However, since derived on a post-hoc analysis, our findings need to be further verified by an independent study.

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Comment on 'Validation of the diagnosis of mesothelioma and BAP1 protein expression in a cohort of asbestos textile workers from Northern Italy'

In a recent paper, Boffetta et al. [1] reported on the results of their pathological revision of mesothelioma diagnoses among 127 decedents from a cohort of Italian asbestos-textile workers. Incidentally, they estimated that 'sensitivity of the classification of the Registry (certain confirmed mesothelioma versus other) was 83% and the specificity 34%'. Such estimates question registration quality at the Registry of Malignant Mesotheliomas (RMM) of Piedmont, a collaborating centre of the Italian National Mesothelioma Registry, but cannot be checked based on