benefit is necessary for helping delivery of expansive interventions to our patients [10]. The proposed NNT-guided model for negotiations of costs for new anticancer drugs may represent an intriguing alternative to current methods. It may also have the advantage of a dynamic adaptive pricing method for the same drug employed in first-, second-, or third-line settings, and according to its different clinical impacts with NNT calculations.

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disclosure

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Genome sequencing for nonsmall-cell lung cancer identifies a basis for nintedanib sensitivity†

RET fusion genes were recently identified as a new type of ‘druggable’ driver gene in 1%–2% of lung adenocarcinomas [1], and several clinical trials are already under way to address the therapeutic effects of RET tyrosine kinase inhibitors, such as vandetanib and cabozantinib, in individuals with RET fusion-positive nonsmall-cell lung cancer (NSCLC) [2]. No selective RET inhibitors are currently available in clinical practice, however.

We now describe the case of a 60-year-old never-smoking woman with lung adenocarcinoma of stage IV (T4N2M1 according to the UICC 6th edition of TNM lung cancer staging). An amplification-refractory mutation system test revealed that the tumor was wild type for EGFR, and rearrangement of ALK was not detected by fluorescence in situ hybridization (FISH) with break-apart probes. After the failure of first-line platinum-based chemotherapy with carboplatin–paclitaxel plus an investigational antiangiogenic agent, the patient was enrolled in June 2010 in a dose-escalation phase I study of nintedanib combined with docetaxel for Japanese patients with advanced NSCLC (conducted by Boehringer Ingelheim Pharma GmbH & Co. KG; NCT00876460) [3]. She received nintedanib (BIBF 1120) orally at 150 mg twice daily plus docetaxel at 75 mg/m2 every 3 weeks. Although she showed a radiographic response to the drug combination,

—

 ayrıntısız tablo 1. NNT analizi sonuçları CORRECT ve CONCUR denemeleri

<table>
<thead>
<tr>
<th>Trial</th>
<th>Months</th>
<th>Regorafenib</th>
<th>Placebo</th>
<th>NNT</th>
<th>CI−</th>
<th>CI+</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORRECT</td>
<td>3</td>
<td>80.3</td>
<td>72.7</td>
<td>18.1</td>
<td>11.3</td>
<td>71.2</td>
<td>760</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>52.5</td>
<td>43.5</td>
<td>10.9</td>
<td>6.6</td>
<td>44.9</td>
<td>262</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>38.2</td>
<td>30.8</td>
<td>10.4</td>
<td>6.1</td>
<td>44.3</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>24.3</td>
<td>24.0</td>
<td>10.7</td>
<td>6.2</td>
<td>44.6</td>
<td>53</td>
</tr>
<tr>
<td>CONCUR</td>
<td>3</td>
<td>92.4</td>
<td>76.4</td>
<td>10.2</td>
<td>7.5</td>
<td>20.5</td>
<td>104</td>
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<td>52.3</td>
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<td>5.0</td>
<td>3.1</td>
<td>12.2</td>
<td>123</td>
</tr>
</tbody>
</table>

NNT, number needed to treat; CI−, lower limit of the 95% confidence interval; CI+, upper limit of the 95% confidence interval.

†The results of this study were presented in part at the 1st ESMO Asia Congress, Singapore, 18–21 December 2015.
A prospective clinical trial is thus warranted to test nintedanib plus docetaxel versus docetaxel alone in patients with advanced NSCLC of any histology showed that the drug combination was associated with a significant and clinically meaningful improvement in overall survival in predefined patients with an adenocarcinoma tumor histology [7]. Tumor samples have not been collected, however, to identify the mechanisms underpinning the response to nintedanib in combination with docetaxel in such patients.

In the present study, we carried out multiplex testing to identify mutations potentially predictive of such a response in a patient who manifested long-term efficacy of nintedanib treatment. Our analysis identified a CCDC6-RET fusion but no other activating mutations. It is possible that docetaxel rather than nintedanib conferred the clinical benefit observed in the present case and that this benefit persisted after docetaxel discontinuation. Nintedanib has also not been tested in mice bearing tumor xenografts that express RET fusion proteins, although it does inhibit the tyrosine kinase activity of RET in addition to that of angiokinases in vitro [6]. Our findings nevertheless suggest that CCDC6-RET fusions identified by multiplex testing are potential targets for nintedanib therapy. A prospective clinical trial is thus warranted to test nintedanib in patients with lung adenocarcinoma positive for RET rearrangement.
Many men with castrate-sensitive metastatic prostate cancer should not receive chemotherapy’ by Tannock et al.

We would like to thank Drs Tannock and Sternberg for their comments [1] on the 2015 ESMO Clinical Practice Guidelines on Cancer of the Prostate [2]. We agree that the three randomised trials of early docetaxel in men with hormone-naive prostate cancer are important and practice changing. Meta-analysis of those trials shows that early docetaxel for metastatic disease has a substantial overall survival advantage (hazard ratio 0.77, 95% confidence interval 0.68–0.87, \( P < 0.0001 \)), with 4-year overall survival improved from 40% to 49% [3]. This 9% absolute benefit compares favourably with any other intervention for advanced prostate cancer and represents a major advance in the treatment of men with metastatic disease. In the light of this survival benefit, we believe that men with metastatic prostate cancer should be offered early docetaxel unless there is a good reason to the contrary.

In light of the toxicity, and even occasional mortality, associated with docetaxel, Tannock and Sternberg question whether early docetaxel is indicated for men with ‘low-volume’ disease, and those who present with metastases after previous radical local treatment. Men in these subgroups were eligible for all three trials but they represented a minority of the patients included, and they have a more favourable prognosis and so contributed a small proportion of events to the survival analysis.

This question raises the generic issue of how to apply overall trial results to small subgroups. The standard approach is to assume that the main result applies to the whole population unless good evidence exists to the contrary [4]. The purpose of subgroup analysis is not to test whether the treatment effect is significant in each individual subgroup, but rather to test for significant heterogeneity of effect between subgroups [5, 6]. With regard both to volume of disease and to use of prior radical treatment, no significant heterogeneity of effect has been reported in any of the three trials. It is certainly possible that there are subgroups that do not benefit from early docetaxel, but the three trials have not provided evidence to support this hypothesis.

We regard all three trials as consistent with the same effect size across all subgroups examined. Indeed, it is possible that men with low volume disease and those with prior radical treatment might benefit more, and not less, from early docetaxel. After all, they have a better prognosis, and so the same relative survival benefit would translate into a larger absolute benefit.

In our view, current evidence supports a recommendation for early docetaxel in men with metastatic hormone-naive prostate cancer who are fit enough for chemotherapy. However, ‘medicine asks you to make perfect decisions with imperfect information’ [7], and all guidelines are imperfect. We accept that there is an important role for clinical judgement, as well as guidelines, when making treatment decisions in the clinic.

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