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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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 vanetanib 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,

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†The results of this study were presented in part at the 1st ESMO Asia Congress, Singapore, 18–21 December 2015.

Table 1. Results of the number-needed-to-treat analysis in the CORRECT and the CONCUR trials

<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></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></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>123</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>66.6</td>
<td>52.3</td>
<td>5.6</td>
<td>4.0</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>46.7</td>
<td>22.7</td>
<td>4.6</td>
<td>3.1</td>
<td>10.8</td>
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<td>14.8</td>
<td>5.0</td>
<td>3.1</td>
<td>12.2</td>
<td>53</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.
docetaxel was discontinued after 22 cycles as a result of her development of lower extremity edema and fatigue, and nintedanib monotherapy was continued thereafter. A total of 48 treatment cycles (26 cycles of nintedanib alone) was administered over 33 months before documentation of disease progression in March 2013 (Figure 1A). The most severe adverse events during treatment with docetaxel and nintedanib were neutropenia of grade 4, elevation of alanine aminotransferase of grade 3, rash of grade 2, and edema of grade 2, whereas those during nintedanib monotherapy were anemia of grade 2 and rash of grade 1. She did not achieve a tumor response to subsequent treatment with erlotinib plus an investigational drug.

To identify mutations that might have rendered this patient highly susceptible to nintedanib therapy, we applied next-generation sequencing panels that cover both mutational hotspots in 409 cancer-related genes [4] as well as 72 major variants of ALK, RET, ROSI, and NTRK1 fusion transcripts [5], with DNA and RNA extracted from lung tumor tissue obtained by transbronchial biopsy as the respective analytes (a detailed description of the analyses is provided in supplementary Materials and Methods, available at Annals of oncology online). The multiplex genetic testing identified a CCDC6-RET fusion gene in tissue specimens obtained for lung cancer diagnosis (Figure 1B), with no other actionable mutations being detected (supplementary Table S1, available at Annals of Oncology online). We verified this chromosomal inversion using FISH, which revealed a split in the signals for probes that flank the RET translocation site in tumors positive for the CCDC6-RET fusion (Figure 1C).

The proof of principle for the efficacy of vascular endothelial growth factor (VEGF) inhibition in NSCLC has been demonstrated in clinical trials of bevacizumab. Nintedanib was developed as an angiogenesis inhibitor that targets multiple kinases including receptors for VEGF (VEGFR1 to 3), platelet-derived growth factor (PDGFRA and β), and fibroblast growth factor (FGFR1 to 3), and preclinical studies showed that it was able to achieve sustained blockade of VEGFR2 in vitro as well as to delay or arrest tumor growth in xenograft models of human solid malignancies [6]. Furthermore, a phase III trial of 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.

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**Figure 1.** (A) Chest computed tomography scans of the patient showing disease burden before treatment, after a response to nintedanib, and at the time of development of nintedanib resistance. (B) Junction reads for CCDC6-RET fusion transcripts as determined by next-generation sequencing (NGS). Nucleotides are indicated by different colors. (C) Break-apart FISH analysis of tumor tissue of the patient with a 5'-RET probe (green) and a 3' RET probe (red). The RET rearrangement is indicated by the presence of a single isolated red signal (arrowhead). The wild-type RET locus is revealed by unsplit red and green signals (white, arrow). Nuclei are stained with 4′,6-diamidino-2-phenylindole.
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Reply to the letter to the editor
‘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-naïve 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 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-naïve 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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