Incidence and management of mTOR inhibitor-associated pneumonitis in patients with metastatic renal cell carcinoma

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The administration of mammalian target of rapamycin (mTOR) inhibitors can give rise to a potentially life-threatening adverse event, often referred to as ‘non-infectious pneumonitis’ (NIP), which is characterized by non-infectious, non-malignant, and non-specific inflammatory infiltrates. Patients usually present with cough and/or dyspnoea. We provide a brief description of the mechanism of action of mTOR inhibitors and their overall safety in patients with metastatic renal cell carcinoma (mRCC) and review the literature on mTOR inhibitor-associated NIP in patients with solid tumours. The review was used to derive questions on the diagnosis, management, and monitoring of mRCC patients with NIP, and to develop a decision tree for use in routine clinical practise. A key recommendation was the subdivision of grade 2 NIP into grades 2a and 2b, where grade 2a is closer to grade 1 and grade 2b to grade 3. This subdivision is important because it takes into account the nature and severity of clinical symptoms potentially related to NIP, either the onset of new symptoms or the worsening of existing symptoms, and thus determines the type and frequency of follow-up. It also helps to identify a subgroup of patients in whom treatment, if effective, may be continued without dose adjustment.

Key words: everolimus, mammalian target of rapamycin inhibitor, pulmonary toxicity, renal cell carcinoma, solid tumour, temsiroliusm

introduction

The treatment of solid tumours has benefited over recent years from the development of therapies targeting factors involved in angiogenesis and maintenance of tumour growth. The first such treatments for metastatic renal cell carcinoma (mRCC) were either inhibitors of the tyrosine kinase activity (TKIs) of several growth factor receptors present on the surface of endothelial cells [e.g. vascular endothelial growth factor receptor (VEGFR)] or monoclonal antibodies directed against circulating VEGF [1–4]. Lately, however, inhibitors of another molecular target, namely, the mammalian target of rapamycin (mTOR), have been developed. mTOR is a serine/threonine kinase which was discovered empirically during studies on rapamycin (sirolimus). Rapamycin, a macrocyclic lactone produced by the fungus Streptomyces hygroscopicus, has immunosuppressive, antimicrobial, and antitumour properties. Unlike TKIs that have several targets and are thus promiscuous, mTOR inhibitors have only one known target, namely mTOR, which exerts a central control function. Signalling elements lying both upstream and downstream of mTOR are dysregulated in many human cancers. Approved mTOR inhibitors for the treatment of mRCC are temsiroliusm and everolimus [5, 6].

Pulmonary toxicity is known to be associated with over 450 drugs including several classes of anticancer agent [7–10], and mTOR inhibitors are no exception [11]. This article will focus on a potentially serious class-related adverse effect (AE) of mTOR inhibitors, known as ‘non-infectious pneumonitis’ (NIP), which is characterized by non-infectious, non-malignant inflammatory infiltrates. At onset of the complication, patients with mTOR inhibitor-associated pneumonitis usually present with cough and/or dyspnoea and/or hypoxemia, and sometimes with systemic symptoms such as fever and fatigue. At times, no clinical impact is manifest and only changes on high-resolution computed tomography (HRCT)-scans are observed. We shall briefly describe the mechanism of action and overall safety of mTOR inhibitors, review the literature on mTOR inhibitor-associated NIP in patients with solid tumours, and use this review to derive a decision tree on NIP management and surveillance in mRCC patients.
**mechanism of action and efficacy of mTOR inhibitors in mRCC**

The mTOR pathway [phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR] is a critical signalling pathway associated with tumour growth and survival, and angiogenesis [12–14]. It is sensitive to input from multiple signals (e.g. growth factors, hormones, nutrients, and stress) and responds to growth factor signalling by specifically enhancing the translation of messenger RNAs encoding key proteins involved in cell metabolism, growth, and division, and in responses to stress (e.g. hypoxia or DNA damage). Aberrant activation of mTOR is thought to occur in ~50% of human malignancies [15]. A possible mechanism is increased activation of Akt arising from the loss of tumour suppressor gene PTEN (phosphatase and tensin homologue on chromosome 10) function. Such loss is observed in many cancers including mRCC.

mTOR exists in the form of two molecular complexes, mTORC1 and mTORC2, but only the former would be susceptible to inhibition by rapamycin analogues. The two best characterised pathways lying downstream of mTOR are mediated by ribosomal protein S6 kinase (S6K1), on the one hand, and by eukaryotic initiation factor binding protein (4E-BP1), on the other. Activation of either PI3K and/or Akt and/or loss of PTEN suppressor function results in activation of S6K1 and 4E-BP1 by mTOR kinase. mTOR inhibitors bind with high affinity to a cytoplasmic protein FKBP-12 to form a complex that interacts with mTOR kinase. This blocks downstream signalling events, affecting the synthesis of cell cycle regulators such as cyclin D and decreasing hypoxia-inducible transcription factor (HIF) expression. It is mainly through the synthesis of HIFs that mTOR controls the production of proteins involved in angiogenesis (e.g. VEGF) and in other responses that increase supplies of nutrients and energy for growing cells.

In short, inhibition of mTOR activation may affect nutrient uptake by tumour cells and cell metabolism, impact negatively on cell growth and division, reduce the response of neovascular cells to growth factors, and possibly induce apoptosis [16].

Supplementary data (available at *Annals of Oncology* online) lists available mTOR inhibitors with their approved indications. The archetypal mTOR inhibitor, rapamycin (sirolimus), is used in transplant immunosuppression and, although it has shown anticancer activity in experimental models, does not have any approved clinical indications as an anticancer agent. Temsirolimus is used as a first-line therapy in mRCC patients with a poor prognosis [5, 17]. Everolimus is used as second-line therapy after TKI or monoclonal antibody (anti-VEGF) failure in all risk groups [6]. Table 1 summarises efficacy data from pivotal phase III randomised controlled trials on these drugs in mRCC patients. Temsirolimus has also been approved in the treatment of relapsed or refractory mantle cell lymphoma and everolimus in the treatment of tuberous sclerosis associated subependymal giant cell astrocytoma [19–21]. Everolimus, used either as a single agent or in combination, has led to meaningful increases in median progression-free survival (PFS) in recent placebo-controlled phase III trials in patients with neuroendocrine (carcinoid and pancreatic) tumours who have failed cytotoxic chemotherapy [22, 23]. Both products are under investigation in the phase II and III settings for a wide variety of other malignancies ([24], see also clinicaltrials.gov). A fourth mTOR inhibitor, ridaforolimus (formerly deforolimus, AP23573, MK-8669; Ariad Pharmaceuticals Inc., Cambridge, MA) has recently met the primary end point of improved PFS compared with placebo in a phase III trial conducted in patients with metastatic soft-tissue or bone sarcomas who previously had a favourable response to chemotherapy.

**safety of mTOR inhibitors in patients with mRCC**

mTOR inhibitors are generally well tolerated, with a toxicity pattern somewhat different from that of TKIs. The toxicity of temsirolimus and everolimus in mRCC patients has been reviewed in several papers [25–32]. The main drug-related AEs reported during phase III trials are listed in Table 2 by type and by decreasing incidence recorded for everolimus. As these

**Table 1. Phase III trials of temsirolimus and everolimus in patients with metastatic renal cell carcinoma**

<table>
<thead>
<tr>
<th>Line</th>
<th>Eligibility</th>
<th>Patients</th>
<th>Overall response rate (%) (95% CI)</th>
<th>Median PFS (months) (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolimus</td>
<td>First line</td>
<td>209</td>
<td>8.6 (4.8–12.4)</td>
<td>5.5 (3.9–7.0)</td>
<td>0.66 (0.53–0.81)*</td>
<td>10.9 (8.6–12.7)</td>
</tr>
<tr>
<td>IFN-α</td>
<td>Intermediate and poor risk</td>
<td>207</td>
<td>4.8 (1.9–7.8)</td>
<td>3.1 (2.2–3.8)</td>
<td>3.8 (3.6–5.2)</td>
<td>7.3 (6.1,8.8)</td>
</tr>
<tr>
<td>Hudes et al., 2007 [5]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + BSC</td>
<td>Second line</td>
<td>277</td>
<td>1.8</td>
<td>4.9 (4.0–5.5)</td>
<td>0.33 (0.25–0.43); P &lt; 0.001</td>
<td>14.8</td>
</tr>
<tr>
<td>Motzer et al., 2010 [6]</td>
<td></td>
<td>139</td>
<td>0</td>
<td>5.5 (4.6,5.8)</td>
<td>0.32 (0.25–0.41); P &lt; 0.001</td>
<td>14.4</td>
</tr>
<tr>
<td>Everolimus</td>
<td>All risk groups, VEGFR TKI failure</td>
<td>267</td>
<td>1.3</td>
<td>3.1 (2.2–3.8)</td>
<td>3.8 (3.6–5.2)</td>
<td>7.3 (6.1,8.8)</td>
</tr>
<tr>
<td>(10 mg/day orally) + BSC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*From FDA summary [18].

BSC, Best supportive care; CI, confidence interval; NA, not available; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
data do not arise from head-to-head studies, a direct comparison between the drugs should be avoided. The most common AEs for both drugs were stomatitis, asthenia, fatigue, cough, rash, and diarrhoea. Grade 3 and 4 AEs were relatively rare and often tended to be metabolic in nature. Everolimus has shown no apparent signs of cumulative toxicity even though it is administered as second-line treatment after TKI or anti-VEGF monoclonal antibody failure. Virtually, all the above-listed AEs can be managed effectively in most patients with medical treatment or supportive interventions.

One potential serious AE of mTOR inhibitors is NIP. NIP is characterised by non-specific, non-malignant inflammatory infiltrates and negative bacterial tests for blood and bronchoalveolar lavage (BAL). In pivotal studies, NIP (all grades) occurred in 9.9% of patients on everolimus (second-line) [33] and ~2% of patients on temsirolimus (first-line) [26]. This latter incidence is now considered to be an underestimation [29].

**Pathology** has revealed non-specific interstitial pneumonitis, bronchiolitis obliterans organising pneumonia, alveolar haemorrhage, desquamative interstitial pneumonia, and vasculitis. However, the pathogenesis of mTOR-induced NIP has not yet been elucidated. Suggested mechanisms are a cell-mediated autoimmune response after exposure of cryptic antigens or T-cell-mediated delayed-type hypersensitivity [34, 35]. It has also been speculated that mTOR inhibitors may exert part of their action by limiting the destructive remodelling of lung structure. In one study, the potent papain-line cysteine protease, cathepsin-K, was found to be strongly expressed in all investigated cases of lymphangioleiomyomatosis cells, a disease in which the mTOR pathway is also deregulated [36].

So far, no patient-related or context-related risk factors have been identified in cohort studies.

**Incidence of mTOR inhibitor-associated NIP in patients with solid tumours**

We searched Medline (until June 2010) and EMBASE (1996–2010) using as keywords mammalian target of rapamycin inhibitor (or the common denomination of the inhibitor), renal cell carcinoma (or solid tumour), and a list of keywords related to pulmonary toxicity (see Supplementary data, available at *Annals of Oncology* online) in order to review published cases of mTOR inhibitor-associated NIP in cancer patients. Our core search retrieved 108 references, which,
however, included many reviews on mTOR inhibitors and few original research articles. Relevant citations were identified in the selected references. Published abstracts of recent congresses were perused.

Studies reporting cases of pulmonary toxicity in patients with solid tumours receiving mTOR inhibitors are summarised in Table 3. The significance of the incidence of NIP in many of these studies (last column) is difficult to gauge as only full case-by-case descriptions would provide the information required. The wide variation in incidence (2%–36%) may be due to a variety of factors including history (e.g. pre-existing pulmonary dysfunction or prior radiotherapy), choice of drug, length of drug exposure, dose, frequency and type of imaging studies during follow-up, problems of differential diagnosis, and whether the AE is truly drug related. In addition, many of the studies in Table 3 include too few patients to be able to accurately assess the incidence of a relatively rare AE.

symptoms and radiological findings of mTOR inhibitor-associated NIP in patients with mRCC

At onset, symptomatic patients usually present with non-productive cough and/or dyspnoea. These occur in about a quarter of patients with mRCC receiving either everolimus or temsirolimus (see Table 2). Systemic symptoms such as fever and fatigue may also occur. However, many patients are asymptomatic despite presenting signs of the complication on radiography or HRCT [43, 48].

According to the literature and author experience, early radiological signs are unobtrusive and non-specific. The most common on HRCT scans are ground-glass opacities, inter/intra lobular septal linear thickening, and, in more advanced cases, multifocal areas of parenchymal lung consolidation with a basilar predominance. They occur predominantly at the lung base and periphery, are often asymmetric, and tend to be bilateral though at first they may affect a single lung. At times, they are migratory and poorly delineated. A less common radiological sign, most frequently observed in organ transplant patients, is pleural effusion, especially during the early stages of mTOR inhibitor treatment. Very few cases of granulomatous interstitial lung disease (ILD), desquamative interstitial pneumonia, alveolar haemorrhage or pulmonary alveolar proteinosis pattern, pulmonary vasculitis, or necrosis have been reported [43].

The relationship between clinical symptoms and radiographic findings has been investigated in several retrospective reviews of serial chest HRCT scans (see Supplementary Data, available at Annals of Oncology online). These reviews highlighted the following: NIP diagnosis was based mostly on clinical symptoms but radiological evidence was often present before clinical symptoms became manifest; radiological signs may or may not worsen during mTOR inhibitor treatment; they often resolved on dose reduction or drug discontinuation (Figure 1) [43]; two patients developed NIP after successive treatment with either temsirolimus or ridaforolimus, thus supporting the hypothesis of a class effect [43, 53]; the correlation between HRCT and chest X-ray findings increased with increasing NIP severity (from 50% for grade 1 to 71.4% for grade 3) [43]; there was, however, no correlation between radiological findings and baseline lung function tests or the presence of lung metastases [44]; the most common grade was grade 1 NIP (according to the NCI–CTCAE classification); patients with grade 2 NIP tended to fall into two fairly distinct severity categories (low and high).

NIP onset and resolution

According to author experience, NIP usually occurs within the first 6 months of treatment. It has been detected by HRCT as early as the first evaluation at 2 months after everolimus administration [44]. In some patients, radiological signs and symptoms of previous ILD are already present at baseline [43]. The median time to onset was 108 days (range, 24–257 days) in a study of 37 patients experiencing clinical NIP on everolimus treatment in the RECORD 1 trial [6, 43]. For temsirolimus, the estimated cumulative probability of radiologically identified drug-related pneumonitis was 21% [95% confidence interval (CI) 15–28] at 8 weeks, 31% [95% CI 24–40] at 16 weeks, and 45% [95% CI 36–57] at 13 months in patients with mRCC [54].

The beginnings of a relationship between NIP onset and treatment efficacy have been observed in patients from one centre of the RECORD 1 trial on everolimus but this was not confirmed in an analysis of the entire population [43, 44]. Recent preliminary data on 44 patients with mRCC treated by either everolimus or temsirolimus in two other centres do however suggest that NIP may be a marker of therapeutic efficacy [55].

In the RECORD-1 trial on everolimus, among the 18 patients with grade 2 NIP, complete resolution was obtained in 11 patients and 1 patient improved to grade 1, as a result of either corticosteroid therapy (10/18), dose adjustment (12/18), and/or discontinuation (3/18). Among the 10 patients with grade 3 NIP, complete resolution was obtained in 6 patients and 1 patient improved to grade 1, after steroid therapy (6/10), dose adjustment (6/10), and/or drug discontinuation (7/10). One grade 3 patient experienced persistent NIP. Two patients died of complications that may have been related to grade 3 NIP. One was a patient with recurrent Candida sepsis, alveolar haemorrhage, and lung infiltration who died with a picture of acute respiratory distress syndrome (ARDS). The other was a non-everolimus-related death from progressive metastatic disease and ARDS [6]. In the pivotal trial of temsirolimus, a patient whose NIP progressed from grade 3 to grade 5 was reported to have died of progressive underlying disease; yet, the persistent NIP may have contributed to death [26].

management of solid organ transplant patients with mTOR inhibitor-associated NIP

The studies included in our review were unable to ascertain with any confidence the influence of dose reduction, drug interruption, and/or corticosteroid therapy in the management of mTOR inhibitor-associated NIP. Some information on NIP management can be gleaned from
### Table 3. Review of mTOR inhibitor-associated pneumonitis in cancer patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients (N)</th>
<th>Prior therapy</th>
<th>Dose</th>
<th>Occurrence of pneumonitis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temsirolimus (i.v.)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atkins et al., 2004 [37]</td>
<td>Advanced refractory RCC 111</td>
<td>≥2 immunotherapy or chemotherapy regimens in 51% patients</td>
<td>25, 75, or 250 mg weekly</td>
<td>N = 6 (possible pneumonitis); 5 (75 mg) + 1 (25 mg)</td>
</tr>
<tr>
<td>Chan et al., 2005 [38]</td>
<td>Locally advanced or metastatic breast cancer 109</td>
<td>Included anthracylin or taxane</td>
<td>75 or 250 mg weekly</td>
<td>1 death from possibly drug-related pneumonia (75 mg)</td>
</tr>
<tr>
<td>Witzig et al., 2005 [39]</td>
<td>Relapsed or refractory mantle cell lymphoma 35</td>
<td>Median of 3 prior therapies</td>
<td>250 mg weekly</td>
<td>N = 1 (grade 3) (possibly drug-related) (Data for grades 1 or 2 not published)</td>
</tr>
<tr>
<td>Duran et al., 2006 [40]</td>
<td>Advanced NET or EC 22 (15 NET + 7 EC)</td>
<td>Prior chemotherapy (n = 9); prior radiotherapy (n = 5)</td>
<td>25 mg weekly</td>
<td>Radiological review; N = 8 (36%) (possibly drug-induced)</td>
</tr>
<tr>
<td>Smith et al., 2008 [41]</td>
<td>Relapsed or refractory lymphoma subtypes 82</td>
<td>Median of 2 prior regimens</td>
<td>25 mg weekly</td>
<td>N = 5 (removed from study)</td>
</tr>
<tr>
<td>Bellmunt et al., 2008 [26]</td>
<td>Advanced RCC 208</td>
<td>≥3 poor prognostic features; no prior systemic therapy</td>
<td>25 mg weekly</td>
<td>N = 4 (2%) (any grade); N = 1 (1%) (grades 3–4)</td>
</tr>
<tr>
<td>Kahn et al., 2010 [42]</td>
<td>Unspecified (any clinical trial at the centre) 77</td>
<td>Any dosage (i.v. or oral) to maximum tolerated dose</td>
<td></td>
<td>N = 4 (5%)</td>
</tr>
<tr>
<td><strong>Everolimus (oral)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White et al., 2010 [43]</td>
<td>mRCC 274</td>
<td>Progression on VEGF-targeted therapy</td>
<td>10 mg/day</td>
<td>Clinical pneumonitis: N = 37 (13.5%) (all grades); N = 9 (3.3%) (grade 1), 18 (6.6%) (grade 2), 10 (3.6%) (grade 3), 0 (grade 4); Serial radiological review: N = 95/245 (39.6%)</td>
</tr>
<tr>
<td>Albiges et al., 2009 [44]</td>
<td>Data for single centre participating in RECORD-1 trial: 39 patients</td>
<td>10 mg/day (n = 33) or 70 mg/week (n = 16)</td>
<td></td>
<td>36% incidence of radiological changes at 8 weeks</td>
</tr>
<tr>
<td>Ellard et al., 2009 [45]</td>
<td>Metastatic breast cancer 49 (33 assessable)</td>
<td>No or 1 prior chemotherapy</td>
<td></td>
<td>Daily schedule: N = 14 (all grades); N = 3 (grade ≥3); Weekly schedule: N = 3 (all grades); N = 0 (grade ≥3)</td>
</tr>
<tr>
<td>Amato et al., 2009 [46]</td>
<td>mRCC 41 (39 assessable)</td>
<td>No or 1 prior therapy</td>
<td>10 mg/day</td>
<td>31% (all grades); N = 2 (grade 1); N = 10 (grade 2); N = 7 (grade 3)</td>
</tr>
<tr>
<td>Soria et al., 2009 [47]</td>
<td>Non-small-cell lung cancer 85</td>
<td>1 or 2 prior chemotherapy regimens</td>
<td>10 mg/day, reduced to 5 mg/day if unacceptable toxicity</td>
<td>23% probably or possibly drug related (mainly grade 1 or 2)</td>
</tr>
<tr>
<td>White et al., 2009 [48]</td>
<td>64 patients assessable for independent radiological review of CT scans in above trial (every 4 weeks for 16 weeks, thereafter every 8 weeks)</td>
<td></td>
<td></td>
<td>N = 24 (37.5%) (all grades) but only 16 (25%) probably or possibly drug related; N = 18/24 (grade 1 or 2); N = 6/24 (grade ≥2) including 2 deaths</td>
</tr>
<tr>
<td>Doi et al., 2010 [49]</td>
<td>Metastatic gastric cancer 53</td>
<td>1 or 2 chemotherapy regimens</td>
<td>10 mg/day</td>
<td>N = 8 (15.1%) (grade 1 or 2)</td>
</tr>
<tr>
<td>Johnston et al., 2010 [50]</td>
<td>Relapsed Hodgkin lymphoma 19</td>
<td>Median of 6 prior therapies</td>
<td>10 mg/day</td>
<td>N = 4 (3 grade 3 pulmonary toxicity of whom 2 with dyspnoea and 1 with pleural effusion), 1 grade 4 (pneumonitis)</td>
</tr>
<tr>
<td>Yao et al., 2010 [51]</td>
<td>Metastatic pancreatic neuroendocrine tumours 160 of whom 45 on octeotride therapy</td>
<td></td>
<td>10 mg/day</td>
<td>N = 13 (grades 1 or 2)</td>
</tr>
</tbody>
</table>

*Continued*
studies of mTOR inhibitor use in solid organ transplant patients, although in this setting, doses and concomitant medications are different from those used in patients with solid tumours. In two studies of patients with renal and/or pancreas transplant rejection, the estimated incidence of interstitial NIP after sirolimus administration was 5% or 15% according to study [56, 57]. The first study, in 24 patients, found that dose reduction could provide transient clinical improvement in the 2 patients in whom this was attempted [56]. However, the drug had to be ultimately withdrawn in

Table 3. Continued

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients (N)</th>
<th>Prior therapy</th>
<th>Dose</th>
<th>Occurrence of pneumonitis a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ridaforolimus</td>
<td>Mia et al. 2008 [52]</td>
<td>Various advanced malignancies</td>
<td>32</td>
<td>From no to over 4 antitumour regimens</td>
</tr>
<tr>
<td>Ridaforolimus</td>
<td>Kahn et al., 2010 [42]</td>
<td>Unspecified (any clinical trial at the centre)</td>
<td>122</td>
<td>Any dosage (iv or oral) to maximum tolerated dose</td>
</tr>
</tbody>
</table>

Figure 1. Computed tomography (CT) scans of representative cases showing resolution of non-infectious pneumonitis. (A) A 74-year-old man with metastatic renal cell carcinoma (mRCC) developed a cough ∼4 months after starting everolimus (10 mg). Top left panel: Chest radiograph showed slight increase in markings in addition to metastases. Top right panel: Subsequent chest CT showed stable metastatic nodules but increased interstitial markings with septal thickening. Bottom left panel: Improving infiltrates with holding everolimus and 2-week course of steroids. Bottom right panel: Resolved infiltrates being maintained on reduced dose (5 mg) of everolimus. (B) A 63-year-old man with mRCC developed cough and dyspnoea ∼3 months after starting everolimus (10 mg) with need for supplemental oxygen. Left panel: Bilateral ground glass opacities with mild reticular interstitial disease, predominantly in the lower lobes. Right panel: After discontinuation of everolimus and high-dose corticosteroids, symptoms and infiltrates cleared. (Reprinted from [43] with permission of the American Thoracic Society. Copyright© American Thoracic Society.)
all patients. All had a complete recovery within 6 months. The second study found that NIP frequency was significantly lower on de novo than second-line sirolimus use (4% vs 14%) maybe because impaired renal function or sensitisation might constitute a risk factor on second-line use and that NIP may occur even at low trough levels and after dose reduction [57]. It concluded that sirolimus discontinuation was the safest option.

An overview of cases of mTOR inhibitor-related NIP in organ transplant recipients for whom sufficient data on management and outcome were available (104 sirolimus and 9 everolimus cases) reported that sirolimus was withdrawn in 87/104 patients, with complete resolution in 82 patients, partial resolution in 1 patient, and 4 deaths [58]. Of the 13/104 patients who continued sirolimus at a reduced dose, 8 showed complete resolution and the remaining 5 either had persistent symptoms or relapsed. All five patients had complete resolution on drug discontinuation. Among the nine patients treated by everolimus, drug was withdrawn in eight patients and continued at a reduced dose in one patient. Eight received concomitant corticosteroids. All experienced complete recovery. In 4/104 patients, a switch from sirolimus to everolimus provided short-term complete resolution, although one patient developed relapsing pneumonitis on follow-up [58]. Recovery after switching from sirolimus to everolimus has also been reported by others [59]. The explanation offered was that everolimus is more hydrophilic than sirolimus.

**outstanding issues on the management of mTOR inhibitor-associated NIP in patients with mRCC**

The non-specific appearance and often low clinical impact of mTOR inhibitor-associated NIP in patients with solid tumours may lead to underreporting and partly explain why many issues on NIP diagnosis, management, and surveillance remain unsolved. Recently published management guidelines for AEs occurring during targeted therapies for advanced RCC have relied mostly on toxicity data from pivotal trials [29, 43, 60, 61]. We used the information retrieved from our review (see Supplementary Data, available at *Annals of Oncology* online) to derive eight questions on outstanding issues for consideration (‘expert panel consensus’) in order to draft recommendations and a decision tree.
question 1: what are the differential diagnosis procedures for mTOR inhibitor-associated NIP?
Diagnosis is especially difficult in patients with a history of lung disease who present clinical symptoms due to lung metastases. In these patients, sudden changes in radiological patterns may constitute a warning sign. Most importantly, diagnosis needs to differentiate NIP from other incidental ILDs. The most problematic in the context of malignancy is onset of carcinomatous lymphangitis, which is characterized by irregular septal thickening, presence of multiple small nodules, and pleural effusion. Next to be considered are early signs of infection (e.g. viral pneumonia [62]) and of other interstitial diseases (e.g. onset of acute pulmonary oedema, drug-induced hypersensitivity). Other differential diagnoses pose fewer problems (e.g. Pneumocystis jiroveci, typical acute lobar pneumonia, and lung mediastinal lymph node and/or pleural metastases secondary to mRCC).

question 2: which of the following are required for diagnosis: chest X-ray, HRCT scan, pulmonary function tests, BAL?
A baseline pretreatment chest HRCT scan is recommended in order to be able to detect possible onset of drug-associated NIP and the background presence of any lung or mediastinal lymph node metastases, and in order to monitor disease progression. If the patient presents with clinical symptoms during the course of mTOR inhibitor treatment, prompt imaging (either chest X-ray or HRCT-scan, whichever is the more readily available) is needed to exclude differential diagnoses such as significant tumour progression or pleural effusion. A negative X-ray, however, does not rule out a diagnosis of NIP and should be followed by an HRCT scan, especially in patients with dyspnoea. The subsequent monitoring schedule depends on the clinical course. If the patient is asymptomatic, the chest HRCT scans from routine follow-up of metastatic disease progression should be carefully examined for any signs of NIP and, in cases of doubt, the interval between successive imaging tests should be reduced. Overall radiation exposure has to be taken into account.

If the patient presents radiological signs of NIP and has fever and/or if an infection is suspected, BAL should be considered depending upon NIP grade (see below). If facilities for BAL are lacking, empiric antibiotic treatment should be discussed.

There is no solid evidence for pretreatment pulmonary function tests [e.g. spirometry, diffusion capacity, pulse oxymetry (SaO₂) at rest]. The development of NIP has not been found to be associated with more impaired baseline spirometry results [43, 44], although such tests are considered in patients with significant lung disease who might warrant closer surveillance during follow-up [61]. Nor have any relationships been found between the results of such tests and the presence of lung metastases [44]. However, if NIP is diagnosed, SaO₂ at rest and, if need be, on exertion may be used to help assess impact on lung physiology. Prompt action including possible drug withdrawal should be taken to prevent further lung damage and worsening of the patient’s condition.

Biomarkers facilitating diagnosis are sorely needed.

question 3: are there any preventive actions to be taken?
Before treatment initiation, patients should be made aware of this rare, but potentially serious, complication and should be strongly encouraged to contact their physician should they develop new or unexplained cough and/or dyspnoea or should baseline symptoms worsen [63]. Cough and dyspnoea may not necessarily be due to NIP but may be signs of underlying metastatic disease or of incidental seasonal viral infections. The meaning and import of these symptoms could be explained in a patient information leaflet or during a therapeutic education programme for patients and health professionals.

question 4: how well do the National Cancer Institute Common Terminology Criteria for Adverse Events (v 4.0) apply to mTOR inhibitor-associated NIP?
The CTCAE v4.0 classification is as follows: Grade 1 (asymptomatic): clinical or diagnostic observations only, intervention not indicated; Grade 2 (symptomatic): limiting instrumental activities of daily living (ADL), medical intervention indicated; Grade 3 (severe symptoms): limiting self-care ADL, oxygen indicated; Grade 4 (life-threatening): respiratory compromise, urgent intervention indicated (e.g. tracheotomy or intubation); Grade 5: death.

Patients on mTOR inhibitor therapy presenting grade 2 NIP constitute a clinically non-uniform category. They display symptoms of differing severity, often depending on their pretreatment respiratory status. We therefore recommend that, for mTOR inhibitors, this category should be subdivided into grade 2a patients (close to grade 1), whose symptoms are minor, non-threatening, and do not impact on ADL (slight-to-moderate cough), and grade 2b patients (close to grade 3), whose symptoms are more severe and begin to impact on ADL (severe cough, dyspnoea on exertion with or without hypoxemia on exertion). Grade 2b patients should be monitored more closely in case they progress to a higher grade (grade 3) and require more aggressive management.

The patient’s underlying disease, including metastatic and respiratory status, have to be taken into account when allocating subgrade.

question 5: what is the recommended management of mTOR inhibitor-associated NIP according to grade?
A suggested decision tree for the recommended management of mTOR inhibitor-associated NIP according to grade is presented in Figure 2. Patients with grade 1 NIP may continue mTOR inhibitor treatment without any dose adjustment at the physician’s discretion. However, patients should be informed of any signs of worsening to look out for, which would require contacting their physician.

Patients with grade 2a NIP (see above) may continue treatment without dose adjustment. This is especially desirable if the drug has shown demonstrable efficacy in the patient.
Alternatively, dose may be reduced temporarily at the physician’s discretion on the basis of a benefit/risk assessment. Close monitoring, whether clinical (to look out for worsening of symptoms, especially cough) and/or radiological, is indicated.

Patients with grade 2b NIP pose a conundrum: can the standard dose be continued for optimal antitumour activity as in grade 2a NIP patients or should the dose be adjusted to reduce the risk of NIP progressing to grade 3, even though there is no firm evidence showing that grade 2b cases systematically progress to grade 3. Reducing the dose depends on the clinical situation, the rapidity of NIP onset and its clinical impact, the underlying lung or mediastinal tumour disease, and at what moment during therapy NIP was diagnosed. The more rapid NIP onset and the greater its clinical impact, the more reason there is to reduce drug dose. However, in some cases of late NIP onset where there is evidence of mTOR inhibitor efficacy with an overall acceptable level of toxicity, continuation of long-term treatment at the standard dose may be attempted.

In the case of everolimus, the recommended daily oral dose of 10 mg should be reduced to 5 mg. Temsirolimus treatment can be withheld for 1–2 injections. Should symptoms persist 2–3 weeks after dose reduction, further tests are needed. Fiberoptic bronchoscopy and BAL should be considered. Depending on the clinical impact of NIP, its impact on gas exchange in the lungs, and any improvement observed on dose reduction, corticosteroid administration may be considered provided that infection has been satisfactorily ruled out (see ‘Question 6’ below).

In patients with grade 3 NIP, treatment should be interrupted and corticosteroids should be administered after ruling out infection. Fiberoptic bronchoscopy and BAL are strongly recommended. Diffuse alveolar haemorrhage, which may be a sign of a worse prognosis, needs to be identified and is best diagnosed using BAL. mTOR inhibitor treatment may be reintroduced later at a reduced dose, on downgrade to grade 1, provided that the treatment has shown—or is expected to show—therapeutic benefit. If the reduced dose does not prevent disease progression, re-escalation of dose may be considered provided that corticosteroids are administered and NIP-related clinical symptoms do not recur. A pulmonologist should be consulted.

In patients with grade 4 NIP, treatment should be withdrawn without delay. Signs of infection should be sought by fiberoptic bronchoscopy and/or BAL. In their absence, corticosteroids should be prescribed to help hasten recovery and improve outcomes. Switching to another mTOR inhibitor is not recommended because there is a risk of recurrence as the complication is class related [35, 58, 59].

Grade 3 and 4 cases of NIP should be reported to the Drug Regulatory Authorities’ pharmacovigilance programme.

question 6: when and for how long should corticosteroids be prescribed?
Corticosteroids may only be administered after all tests to rule out a coincidental infection have been carried out. Use depends on symptoms and radiological findings. As indicated above, they should be considered for grade 2b NIP and prescribed for grades 3 and 4. We recommend 0.75–1 mg/kg oral prednisolone once daily. In cases of severe NIP (grade 3 or more), i.v. methylprednisolone (2–5 mg/kg/day in two divided doses) may be required during the first few days.

Corticosteroids should be continued until a response is achieved and then tapered according to symptom alleviation (grades 1 or 2a). Temporary administration of corticosteroids (≤0.5 mg/kg) on mTOR inhibitor reintroduction in patients who have experienced grades 2b or 3 NIP may be considered.

When pneumonitis is diagnosed but an infectious cause cannot be ruled out because facilities for fiberoptic bronchoscopy with BAL are not available, empiric treatment with antibiotics should be considered, concomitantly with corticosteroids.

question 7: what is the recommended surveillance of patients on mTOR inhibitors with regard to NIP?
Patients should be warned of the possible occurrence of pulmonary AEs (see ‘Question 3’). Surveillance should address clinical symptoms (cough and dyspnoea) and imaging findings.

Patients with grade 1 NIP should be advised to contact their physician if they experience cough and/or dyspnoea. Clinical evaluation at 2 weeks and imaging at 4 weeks should be considered (optional). The images obtained on routine chest X-ray or HRCT scan to evaluate malignant disease progression (every 8 weeks) have to be examined with special attention to any radiological pneumonitis. No data are available on the likelihood of grade 1 NIP worsening to grade 2.

Patients with grade 2a NIP should be advised to contact their physician as soon as they experience any worsening of symptoms and should undergo a first clinical examination at 2 weeks and imaging at 8 weeks. Thereafter, a routine clinical examination may be carried out every 4 weeks. An HRCT scan should be carried out every 6–8 weeks. The images should be reviewed with special attention to pneumonitis.

Patients with grade 2b NIP should undergo a clinical examination at 1 week and imaging at 2 weeks, followed by a clinical examination every 2–3 weeks until grade 2b symptoms resolve. An HRCT scan without injection of contrast agent is recommended at 4 weeks and should be repeated until symptom resolution.

Patients with grade 3 NIP need to be admitted to hospital for monitoring and treatment of their symptoms. An HRCT scan for monitoring NIP resolution should be carried out at 4 weeks. Specific clinical and radiological (standard X-ray) surveillance should be pursued every 2–3 weeks until recovery to grade 2a or 1. Thereafter, a control HRCT scan may be carried out every 4–6 weeks.

Patients with grade 4 NIP may require emergency ventilatory support. An HRCT scan at 4 weeks to monitor NIP resolution is recommended.

question 8: is mTOR inhibitor-associated NIP reversible and what is the risk of recurrence on reintroduction of mTOR inhibitor?
On dose reduction or treatment withdrawal, or on corticosteroid administration, mTOR inhibitor-associated NIP
may be alleviated or resolve, though this may take a few weeks [61]. Clinical symptoms tend to resolve before any evidence of resolution appears on imaging. If radiological signs persist or worsen, another cause should be sought for the pneumonitis. If there is incomplete resolution or sequelae are suspected after drug-induced NIP, pulmonary function tests should be carried out and SaO₂ monitored. Some cases of grades 1 or 2 NIP may resolve despite treatment continuation.

After alleviation to grade 1, re-escalation of dose may be envisaged (from 5 mg to 10 mg for everolimus), provided corticosteroids are given (0.5 mg/kg/day) but there is a risk of recurrence on reintroduction of the same or even another mTOR inhibitor, regardless of dose. However, short-term resolution has been documented on switching from sirolimus to everolimus in transplant patients [58, 59]. Little is known on the frequency and seriousness of recurrence.

closepclusions
The key aspects of our proposed guidelines for the management of mTOR inhibitor-associated NIP are summarised in the decision tree of Figure 1. These guidelines differ in one major aspect from existing proposals, namely, the subdivision of grade 2 pneumonitis into grades 2a and 2b. This subdivision is important because it takes into account the nature and severity of clinical symptoms that are potentially related to NIP, either the onset of new symptoms or the worsening of existing symptoms, and thus determines the type and frequency of follow-up. It thus also helps to identify a subgroup of patients in whom treatment, if effective, may be continued without dose adjustment.

The above proposals concern the management of NIP induced by the mTOR inhibitors in current use. However, they may also prove relevant to new drugs and new drug combinations under development. Current mTOR inhibitors (‘rapalogs’) inhibit the rapamycin-sensitive mTOR complex only (namely mTORC1). Dual inhibitors that inhibit the kinase activity of both mTORC1 and mTORC2 by competitive inhibition of their ATP binding domain are under development. Treatment combinations under consideration are combinations of mTORC1 inhibitors with inhibitors of mTORC2 but also of other targets within the PI3K/Akt/mTOR pathway [64]. These recommendations might therefore be of value in the development of new therapies and also in the production of recommendations for solid tumours other than RCC.

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references