Use of a natural multicomponent mouthwash plus oral hygiene vs oral hygiene alone to prevent everolimus-induced stomatitis: the STOP multicenter, randomized trial

Camillo Porta1,2, Elena Verzoni3, Silvia Zai4, Caterina Messina5, Vittorio Ferrari6, Nicole Gri1,2 and Giuseppe Procopio3

Abstract

Background: Stomatitis is highly prevalent in patients with cancer treated with the mammalian target of rapamycin inhibitor everolimus; it usually has an early onset and may compromise treatment dose intensity and patients’ quality of life. Within the randomized controlled Stomatitis Prevention trial (STOP, ISRCTN14568888), we investigated the possibility of using a commercial natural multicomponent mouthwash (Orasol Plus®) to prevent the development of stomatitis of any grade in patients with advanced renal cell carcinoma (RCC) treated with everolimus.

Methods: Overall, 62 patients were randomized to receive either Orasol Plus in addition to oral hygiene or oral hygiene alone (31 patients per treatment arm).

Results: In the whole study population, 28 episodes of stomatitis were observed (41.9%); in only 2 patients, stomatitis occurred more than once (2 episodes). As expected, the episodes of stomatitis occurred early in the course of treatment with everolimus. Treatment with Orasol Plus prevented the onset of everolimus-induced stomatitis: only 8 episodes of stomatitis were observed in the treated group with Orasol Plus in addition to oral hygiene vs 20 episodes in the group treated with oral hygiene only (p = 0.0021). Also, a reduction in the average duration of mucositis in patients treated with Orasol Plus compared to patients treated with oral hygiene only was observed (8 days vs 11.2 days, p = 0.0416).

Conclusion: This study showed that the use of a natural multicomponent mouthwash coupled with regular oral hygiene was able to reduce the severity and duration of everolimus-induced stomatitis in patients with RCC.

Trial registration number: ISRCTN14568888

Keywords

Stomatitis, everolimus, prevention, natural multicomponent mouthwash, oral hygiene, renal cell carcinoma

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Introduction

Similarly to aphthous ulcers, stomatitis associated with mammalian target of rapamycin (mTOR) inhibitors such as everolimus is characterized by small, ovoid, grayish ulcers, surrounded by an erythematous ring, which affect the non-keratinized mucosa of the oral cavity.\(^1\,\,2\) Stomatitis is clinically distinct from oral mucositis, which is more often observed in patients with cancer treated with cytotoxic chemotherapy and/or radiation therapy, and usually presents as nonuniform erythematous and ulcerated lesions, which may extend to the upper aerodigestive tract.\(^1\,\,2\)

A recent meta-analysis,\(^2\) which included a total of 1455 patients treated with everolimus within randomized controlled trials conducted across different malignancies, showed that 973 patients (i.e. 67%) experienced stomatitis, with most of all first episodes (870, i.e. 89%) occurring within 8 weeks from the start of the oncologic treatment. Notably, of the 973 patients treated with everolimus who experienced an initial stomatitis event, 388 (40%) complained also of a second episode.\(^2\)

Although the overall incidence of stomatitis of any grade in the everolimus-containing arms of the studies considered in the meta-analysis was not trivial, most stomatitis events were grade 1 or 2, with grade 3 or 4 events having been reported in as few as 9% of patients (with only 1 patient experiencing grade 4 stomatitis, i.e. 0.1%).\(^2\) Still, stomatitis led to dose reductions and/or interruptions in 24% and 23% of patients complaining of the first and second episode, respectively, although, not surprisingly, they occurred more frequently in patients enrolled in breast cancer trials, in which everolimus was administered in combination with other anticancer agents,\(^2\) including cytotoxic agents.\(^3\)

Everolimus-induced stomatitis usually has an early onset, the rate of any-grade stomatitis being 60.8% at 2 months, and the median time to the first episode 0.8 months.\(^2\)

To date, no standard preventive measures for stomatitis have been suggested for patients with cancer who are candidates for everolimus treatment.

Orasol Plus\(^6\) is a nutritional supplement, available in liquid form, containing a number of natural components (Table 1) with anti-inflammatory, analgesic, and cytoprotective properties. Notably, as per the product data sheet, Orasol Plus can be swallowed at the end of the rinsing, thus expanding its protective effect not only in the oral cavity, but also in the esophageal mucosa.

We report the results of the Stomatitis Prevention trial (STOP), aimed at investigating the possibility of using Orasol Plus in patients with advanced renal cell carcinoma (RCC) treated with everolimus, in order to prevent the development of stomatitis of any grade. The primary objective of the STOP study was to evaluate the efficacy of

<table>
<thead>
<tr>
<th>Table 1. Components present in Orasol Plus and their proposed properties.</th>
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</thead>
<tbody>
<tr>
<td><strong>Component</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
</tr>
<tr>
<td>Tabebuia avellanedae Lorentz ex Griseb (lapachone)</td>
</tr>
<tr>
<td>Green tea (Camellia sinensis L. Kuntze),</td>
</tr>
<tr>
<td>Calendula officinalis L.</td>
</tr>
<tr>
<td>Mauve (Malva sylvestris L.)</td>
</tr>
<tr>
<td>Erisimo (Sisymbrium officinale) L. Scop.</td>
</tr>
<tr>
<td>Plantain (Plantago major L.)</td>
</tr>
<tr>
<td>Propoli</td>
</tr>
</tbody>
</table>

All the plants contained in the solution and reported here can be found within the 2019 Italian Ministry of Health guidelines on physiologic effects of botanicals. Orasol Plus was approved for marketing by the Italian Ministry of Health in 2013, has been a registered trademark since 2014, and is commercially available across the European Union. Each lot utilized for the Stomatitis Prevention trial (STOP) has been released after quarantine with its analysis certificate (as any commercial lot).
Orasol Plus in addition to standard oral hygiene in the prevention of everolimus-induced stomatitis, while secondary objectives were evaluation of pain and the consequent need for analgesic (nonsteroidal anti-inflammatory drugs, major analgesics, steroids), evaluation of the incidence of infectious episodes in the oral cavity, and evaluation of nutritional status.

**Methods**

**Study design and primary endpoint**

STOP was a multicenter, randomized (1:1), open-label study aimed at comparing the incidence and duration of cases of mucositis of any grade (described both according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 functional criteria and morphologic criteria [Table 2]) in 2 groups of patients treated prophylactically with Orasol Plus in addition to standard oral hygiene, or with standard oral hygiene alone. The trial registration number is ISRCTN14568888.

**Secondary endpoints**

Beyond the incidence of stomatitis between the 2 groups, i.e. the primary endpoint of the study, we also evaluated variations of pain intensity and duration (by means of a 0- to 10-point visual analogue scale [VAS]), with particular attention paid to the type and dose of any analgesics used; incidence of infectious episodes; changes in body weight from baseline (at 1, 3, and 5 months from the start of treatment); and type and duration of any nutritional support, in case of severe dysphagia caused by stomatitis.

**Inclusion and exclusion criteria**

Inclusion criteria were the following: patients with locally advanced and/or metastatic RCC (of any histological subtype), for whom a second- or third-line treatment with everolimus was provided (as indicated by the Italian Medicines Agency [AIFA]); patients who received everolimus as part of experimental protocols were included in the present study only if everolimus was administered as monotherapy (not in combination) and if the protocol in question did not explicitly prohibit the use of food supplements; age over 18; written informed consent to join the study; and Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2.

Exclusion criteria were poor patient compliance and ongoing systemic or oral infections.

All patients signed an informed consent for study participation and for the publication of study results. The consent form was approved by the coordinating center’s institutional review board (IRB) as well as by all participating centers’ IRBs. No individual patient data are presented in this article.

**Enrollment and randomization**

Recruitment took place at the oncology units of the participating institutions under the sponsorship of the Italian Nephro-Oncology Group (Gruppo Italiano di Oncologia Nefrologica). A randomization list was generated, managed by the coordinating center; following the arrival of the screening sheets, each individual patient was randomized and the relative outcome of the randomization communicated directly by fax to the participating centers. The experimental product Orasol Plus was provided free of charge by the manufacturer (GAM Farma SrL, Milan, Italy) for all patients and for the whole duration of the study, in the absence of additional costs for the participating hospitals, as well as for the National Health System.

**Sample size and statistical design of the study**

Considering a percentage of patients with mucositis of 40% in the oral hygiene only group, and 10% in those treated with Orasol Plus, with 31 patients per group, the study had a potency of 81%; the calculation was made using a 2-tailed test with pooled variance, and a 5% α error.

Statistical analyses were conducted using descriptive and inferential statistical methods appropriate to the sample size and to the study variables. The primary endpoint was evaluated with the chi-square test for the incidence of

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**Table 2. Morphologic (Common Terminology Criteria for Adverse Events v4.0) and functional criteria used to evaluate stomatitis severity within the Stomatitis Prevention trial (STOP).**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain, not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Morphologic</td>
<td>Mucosal erythema</td>
<td>Patchy ulcerations or pseudomembranes</td>
<td>Confluent ulcerations or pseudomembranes; bleeding from minor trauma</td>
<td>Necrosis with significant spontaneous bleeding; life-threatening</td>
<td>Death</td>
</tr>
</tbody>
</table>
mucositis episodes and with the Student t test for independent data regarding their duration.

The primary efficacy analysis was performed according to an intention to treat approach; all randomized patients were included in the analysis, regardless of whether the treatment program was completed or not. This choice was inevitable in a setting such as the second or third line of a highly lethal carcinoma such as RCC. A p value of <0.05 was considered statistically significant.

**Allocation and treatments**

After randomization, 31 patients (group A) received experimental prophylactic treatment (oral mouth rinses with Orasol Plus mouthwash) plus standard oral hygiene, while the other 31 patients (group B) followed only standard oral hygiene.

Based on the Orasol Plus data sheet, the patients performed 3 mouth rinses within 24 hours (at least 3 hours apart from each other), using for each rinsing a measure of undiluted mouthwash: the patient rinsed for at least 30 seconds and then swallowed the product. In order to standardize how the rinses were performed, during the screening visit, the patient was carefully instructed in this regard and performed 2 test rinses (with water) in the presence of the physician who proposed the protocol.

As far as standard oral hygiene, according to the National Association of Italian Dentists (ANDI) guidelines, the correct oral hygiene that all patients enrolled in the protocol were required to follow and that was adequately explained to them included the following:

1. Brush teeth twice a day and use dental floss daily
2. Use fluoride-containing toothpaste

In particular, correct use of the toothbrush involved the following steps:

- Place the toothbrush at an angle of 45° against the gingival margin and brush or rotate away from the gingival margin
- Gently brush the outside, the inside, and the surface of each tooth with fast forward and backward movements
- Gently brush the tongue to remove bacteria and refresh the breath

Correct use of dental floss involved the following steps:

- Use about 45 cm of thread, rolling it around the middle finger of both hands and leaving a few centimeters to work with
- Gently follow the curves of the teeth
- Be sure to clean under the gum line

These suggestions, together with explanatory photographs, were obtained from the ANDI website (www.andipg.it, accessed at the time of study conduction), and given to all participating patients.

**Follow-up**

Considering the average duration of treatment with everolimus in RCC, predictable based on the results of the RECORD-1 trial, the STOP study had a maximum duration of 150 days; patients who discontinued prior to the 150-day treatment term, for whatever reasons (either inefficacy or toxicity of the oncologic treatment), were included in the analysis.

**Outcome assessment**

Study outcomes were evaluated through objective examination and accurate anamnesis by the study physician, as well as patient self-report evaluation of pain intensity using a VAS. The presence of stomatitis was evaluated by means of both CTCAE and functional criteria at baseline and then at days +15, +30, +90, and +150 (and whenever necessary) during everolimus treatment.

The general objective examination included an evaluation of the condition of the oral cavity, with particular attention to the localization (at the labial, cheeks, tongue, soft palate, or hard palate) of any stomatitis lesions, as well as their relative severity (both in accordance with the CTCAE v4.0 criteria and with the morphologic grading scale) and extension.

The anamnesis focused on reporting any episodes of stomatitis occurring between visits, and on their size and duration.

Blood chemistry tests were routinely performed on a monthly basis, and included at least 1 complete blood count.

Any adverse event (AE) possibly related to the experimental treatment was reported and monitored for the duration of the treatment and up to 1 month from the end of the same for each enrolled patient.

**Results**

**Patients**

Enrollment into the STOP study started on August 1, 2013, and lasted until June 30, 2016; the last follow-up visit for the last patient was performed on November 28, 2016.

Of the 62 patients enrolled in the study, 38 (61.3%) were male and 24 (38.7%) female, median age 68 years, with a range between 48 and 86 years, as expected on the basis of the epidemiology of this neoplasm. Regarding the treatment with everolimus, at the time of enrollment in the
STOP study, 32 patients (51.6%) received everolimus as a second treatment line vs 30 patients (48.4%) as a third line of therapy; everolimus was always used after 1 or 2 agents targeting the vascular endothelial growth factor receptors pathway.

The main characteristics of the population of patients enrolled in the STOP study are summarized in Table 3.

### Table 3. Characteristics of the population of patients with advanced renal cell carcinoma (RCC) at the time of enrollment in the Stomatitis Prevention trial (STOP).

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm A (standard oral hygiene + Orasol Plus)</th>
<th>Treatment arm B (standard oral hygiene alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>66.5</td>
<td>67.1</td>
</tr>
<tr>
<td>Median</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Range</td>
<td>48–74</td>
<td>52–86</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell RCC</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Non-clear cell RCC</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>ECOG Performance Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><strong>Treatment line with everolimus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Third</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td><strong>Previous or concomitant treatments (to STOP)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy on the head–neck or cervical spine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zoledronic acid or denosumab</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Patients recruited by each participating center</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pavia, IRCCS Policlinico San Matteo</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Milano, IRCCS Istituto Nazionale Tumori</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Alessandria, Ospedale Santi Antonio e Biagio e C. Arrigo</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Bergamo, Ospedale Papa Giovanni XXIII</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Brescia, Spedali Civili</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

ECOG: Eastern Cooperative Oncology Group.

All the patients discontinued treatment due to progression or death (the latter being a single patient, in whom the death was attributed by the treating physician to disease progression). Since all patients continued to perform mouthwashes until everolimus was stopped, or else until day +150 (whichever occurred first), mean time on study was equivalent to mean everolimus treatment duration.

A Consolidated Standards of Reporting Trials (CONSORT) diagram, summarizing study conduction, is provided in Figure 1.

### Toxicity of the experimental treatment

According to the treating physicians, no severe AEs were attributed to oral rinses with the experimental product, nor to the use of normal oral hygiene. We report only a modest proportion of patients (24.2%) who complained of episodes of burning in the oral cavity during the mouthwash with Orasol Plus, burning never higher than grade 1 and of the average duration of some minutes. No other data are available regarding these events (i.e. the total number of
episodes), as this information was not required by the protocol.

**Efficacy of the experimental treatment on everolimus-induced stomatitis**

Overall, in the patient population enrolled in the STOP study, 28 episodes of stomatitis were observed, equivalent to a percentage of 41.9%; in only 2 patients, stomatitis occurred more than once (2 episodes). As expected, the episodes of stomatitis occurred early in the course of treatment with everolimus, 17 episodes having been recorded in the first 15 days of therapy, and a further 5 within the first month; only 6 episodes of stomatitis were observed in the following months (4 between day 16 and day 90, and a further 2 between day 91 and day 150).

Treatment with Orasol Plus was shown to prevent the onset of everolimus stomatitis, since only 8 episodes of stomatitis were observed (4 within the first 15 days of treatment and 4 within the first month) in the treated group with Orasol Plus in addition to oral hygiene vs 20 episodes in the group treated only with oral hygiene (13 over the first 15 days, 1 over the first month, 4 over the first 90 days, and 2 within 150 days from the start of treatment) ($p = 0.0021$).

Regarding the duration of episodes of stomatitis, there was a reduction in the average duration of mucositis in patients treated with Orasol Plus compared to patients treated with oral hygiene only (average duration of 8 days [range, 4–14] vs 11.2 days [range, 5–20], respectively) ($p = 0.0416$).

These results are summarized in Table 4.

Regarding the severity of the episodes of stomatitis, they never exceeded grade 2, both from a morphologic and functional point of view; in patients treated with Orasol Plus there were 5 episodes of G1 stomatitis, both morphologic and functional, and 3 episodes in which there was a discrepancy between the functional (G2) and the morphologic data (G1).

In patients treated with oral hygiene alone, 3 episodes of G2 (both morphologic and functional), 14 episodes of G1 (both morphologic and functional), and 3 cases in which there was a discrepancy between the functional (G2) and the morphologic data (G1) were observed.

These data are summarized in Table 5. Notably, none of the patients treated had to stop treatment due to stomatitis, regardless of its severity.

**Table 4.** Number of stomatitis episodes and average duration in patients treated with Orasol Plus and oral hygiene or oral hygiene alone within the Stomatitis Prevention trial (STOP).

<table>
<thead>
<tr>
<th></th>
<th>Treatment with Orasol Plus + oral hygiene</th>
<th>Treatment with oral hygiene alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stomatitis episodes, n</td>
<td>Average duration, d</td>
</tr>
<tr>
<td>Day +15</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Day +30</td>
<td>4</td>
<td>6.5</td>
</tr>
<tr>
<td>Day +90</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Day +150</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Difference between experimental arm and control arm due to the number of stomatitis episodes $p$ Value (chi-square test) = 0.0021

Difference between experimental arm and control arm for the average duration of stomatitis episodes $p$ Value (Student t test for independent data) = 0.0416
In no case did an episode of stomatitis require enteral or parenteral nutrition; moreover, no patient, due to stomatitis, lost more than 10% of his or her initial body weight.

Regarding the pain caused by stomatitis, neither treatment determined an improvement in the severity of pain in the oral cavity, or changed the need to take analgesics; however, the duration of the pain in patients treated with Orasol Plus was reduced, corresponding to the duration of the stomatitis itself (data not shown).

### Table 5. Morphologic (M) and functional (F) severity of single patient stomatitis episodes, time point (day [d] +15, +30, +90, and +150), and treatment arm (Orasol Plus + hygiene oral vs oral hygiene only).

<table>
<thead>
<tr>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>G1</td>
<td>GI</td>
<td>G1</td>
<td>G1</td>
<td>G1</td>
<td>G1</td>
<td>G1</td>
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<td>GI</td>
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<tr>
<td>GI</td>
<td>G1</td>
<td>GI</td>
<td>G2</td>
<td>_</td>
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<tr>
<td>GI</td>
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<td>G1</td>
<td>G1</td>
<td>G1</td>
</tr>
</tbody>
</table>

### Table 6. Treatments received by patients who, independently of the treatment arm within the Stomatitis Prevention trial (STOP), developed stomatitis.

- **Patients treated with Orasol Plus + oral hygiene who developed stomatitis (n = 8)**
  - Hyaluronic acid–containing topical gels (n = 4)
  - Rinses with Nystatin solution (n = 1)
  - Rinses with water and bicarbonate (n = 6)
  - Rinses with chlorhexidine solution (n = 4)

- **Patients treated with oral hygiene alone who developed stomatitis (n = 20)**
  - Rinses with Orasol Plus (n = 5)
  - Local applications of flumetasone + clioquinol (n = 3)
  - Hyaluronic acid–containing topical gels (n = 2)
  - Rinses with water and bicarbonate (n = 10)
  - Rinses with chlorhexidine solution (n = 10)

Some patients received more than 1 treatment.

### Discussion

Stomatitis is an AE typical of a number of anticancer therapies, often negatively impacting not only quality of life but also the possibility of continuing antitumor treatment with an adequate dose intensity. Indeed, severe grade stomatitis often requires therapeutic breaks and, in extreme cases, discontinuation of treatment.

Stomatitis is particularly common in patients with cancer treated with mTOR inhibitors, and with everolimus in particular, irrespective of the specific malignancy and of the possible combination with other anticancer agents.

In a recent systematic review, 44 studies that enrolled a total of 2822 patients treated with temsirolimus (19 studies), everolimus (20 studies), and ridaforolimus (5 studies) for a wide range of solid malignancies were reviewed for the incidence of oral toxicity. Mucositis proved to be not only the most frequent AE (73.4%), as well as the third most frequent severe AE (20.7%) overall, accounting for 27.3% and 13.1% of dose reductions and treatment discontinuations, respectively, but was also the most frequent dose-limiting toxicity (52.5%).

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In no case did an episode of stomatitis require enteral or parenteral nutrition; moreover, no patient, due to stomatitis, lost more than 10% of his or her initial body weight.

Regarding the pain caused by stomatitis, neither treatment determined an improvement in the severity of pain in the oral cavity, or changed the need to take analgesics; however, the duration of the pain in patients treated with Orasol Plus was reduced, corresponding to the duration of the stomatitis itself (data not shown).

### Treatments of stomatitis arising during the course of preventive treatment

In both treatment arms, in those patients in whom the appearance of stomatitis was observed, various topical treatments were used, as shown in Table 6. It should be noted that the use of an antifungal agent such as Nystatin in oral solution was not chosen following the documentation of a fungal superinfection, but in an empirical manner.
In RCC, within the RECORD-1 trial, the incidence of all-grade stomatitis in the everolimus group was between 42% and 44%, and 3% to 4% of cases were grade 3, depending on the different subsequent reports of the study.5–7 The majority of patients developed stomatitis within the first 2 months of treatment, but most cases resolved spontaneously within 3 days. Although the majority of patients presented mild stomatitis, the impact of this AE on administration of therapy was substantial; of all the everolimus-treated patients who developed stomatitis, 13 required dose modifications or interruptions, 49 required supportive therapies, and 1 had to discontinue treatment. Of the 11 patients with grade 3 stomatitis, 2 continued treatment without dose adjustments, 8 continued on a reduced dose, and 1 discontinued.7

The pathogenesis of mTOR inhibitor–induced stomatitis has been proposed to follow a 2-hit model, with a direct epithelial injury, followed by a second inflammatory phase, characterized by the absence of microorganisms.8,9 Notably, the presence of a higher incidence of concomitant cutaneous AEs provides additional evidence supporting the peculiarity of mTOR inhibitor–related stomatitis, as compared to conventional stomatitis from other anticancer treatments.10

To date, there are no treatment protocols, especially in the prevention setting, for stomatitis that can be called evidence-based. Indeed, a series of Cochrane meta-analyses addressed the role of different interventions to prevent the onset of stomatitis in patients with cancer under treatment.

Evaluated interventions (either preventive or therapeutic) were acyclovir, allopurinol mouth rinse, amifostine, antibiotic pastille or paste, benzydamine, chamomile, chlorhexidine, clarithromycin, folinic acid, glutamine, GM-CSF, hydrolytic enzymes, ice chips, oral care, pentoxifylline, povidone, prednisone, propantheline, progastlandin, sucralfate, Traumeel, and keratinocyte growth factor (KGF). Only few of them showed some evidence of a benefit (albeit usually limited), especially in the preventive setting,11 which should be regarded as an unmet need.

It was clear that benefits were specific just for certain types of cancers and treatments.12,13 For example, oral cryotherapy led to large reductions in oral mucositis of all severities in adults receiving 5-fluorouracil (5-FU) for solid cancers,14 while the use of KGF proved to be beneficial in the prevention of oral mucositis in adults treated with radiotherapy to the head and neck combined with cisplatin or 5-FU, or with chemotherapy alone for mixed solid and hematologic cancers.15

As far as everolimus-induced stomatitis, recently a multicenter, single-arm, phase 2 stomatitis prevention study16 was conducted in postmenopausal, metastatic, hormone receptor–positive, HER2-negative patients with breast cancer. Together with the oncologic treatment, consisting of everolimus 10 mg plus exemestane 25 mg daily, patients performed oral rinses with 10 mL of alcohol-free dexamethasone 0.5 mg/5 mL oral solution, 4 times daily for 8 weeks; after 8 weeks, patients were allowed to continue the preventive treatment for up to 8 additional weeks at the discretion of the clinician and patient. The primary endpoint was incidence of grade 2 or worse stomatitis by 8 weeks, as compared to historical controls from the everolimus BOLERO-2 trial.17 Of the 85 patients evaluable for efficacy, the incidence of grade 2 or worse stomatitis by 8 weeks was 2% (vs 33% in the 482 historical controls). However, the experimental treatment was hindered by not negligible toxicities, episodes of grade 3 and 4 hyperglycemia, rash, dyspnea, and pneumonia in the treated patients.16

When mTOR inhibitor–related mucositis occurs, oral hygiene together with benzydamine- or dexamethasone-containing mouthwash is often recommended,9 although the relative level of evidence remains low.

We investigated the hypothesis that treatment with Orasol Plus, a mouthwash based on natural products each endowed with potential favorable properties (anti-inflammatory, lenitive, antifungal), could be useful in preventing stomatitis in patients with advanced RCC treated with everolimus. This product proved useful in preventing or reducing oral mucositis during radiotherapy for head and neck cancer.15

Orasol Plus was effective in preventing stomatitis from everolimus, reducing stomatitis events from the 20 observed in the group treated with oral hygiene alone to only 8 observed in the group with preventive treatment with the addition of the experimental mouthwash. The duration of episodes of stomatitis was also shorter in patients treated prophylactically with Orasol Plus: 8 vs 11.2 days.

The figures relative to stomatitis duration were unexpected, given the average duration of the episodes of stomatitis observed in the RECORD-1 study, which were significantly lower; this could be due to the particular attention given to the detection of stomatitis by those patients participating in our study.

No differences were observed in terms of incidence of dysgeusia and dysphagia, changes in pain in the oral cavity, consequent assumption of analgesics, changes in body weight, or occurrence of infectious episodes localized to the oral cavity. This is realistically due to the absence of episodes of severe stomatitis (G3 or even G4), demonstrating that even a trivial approach, such as the systematic application of oral hygiene protocols, can contribute to reduction of the severity of episodes of stomatitis.

A strength of our study is its randomized design. Limitations should also be acknowledged. First, since it was academically driven, and thus not supported economically, it was not placebo-controlled or double-blinded. Second, the duration of the observation period was
relatively short (although in line with the expected duration of everolimus treatment in the second- and third-line setting) and could have missed late episodes of stomatitis. Third, due to the evolution of RCC treatment, during study conduction the number of patients receiving everolimus dramatically decreased, making enrollment into the protocol complex and thus longlasting. Furthermore, 69.4% of the patients enrolled in the STOP study dropped out of it (with less than a month of difference between the 2 arms in terms of treatment duration) due to early everolimus discontinuation because of progression or death, as expected in a population with a poor prognosis.5 Finally, results achieved in patients with RCC treated with everolimus may not translate completely into the clinical reality of other malignancies, such as breast cancer, as highlighted by Aapro et al.19

Nevertheless, this study showed that the use of a natural multicomponent mouthwash, coupled with regular oral hygiene, was able to reduce the severity and duration of everolimus-induced stomatitis in patients with RCC.

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Author contributions

Camillo Porta, as the Principal Investigator of the study, designed and wrote the protocol, examined study data, and wrote the manuscript. All coauthors enrolled patients into the study, reviewed, commented, and approved this study report.

Declaration of conflicting interests

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Ethics approval and trial registration

The STOP study was approved by the coordinating center’s IRB on 6 May 2013 (resolution number: 3DG0764) and subsequently by all participating centers’ IRBs. Orasol Plus is a nutritional supplement (not a drug). The STOP study was registered on July 15, 2019 (with the number ISRCTN14568888), when we decided to publish the results of the study.

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Data availability

Study data are stored at the coordinating center, as well as at each participating center, and are available from the corresponding author on reasonable request.

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