A Novel Approach to Oral Mucositis: An Unmet Medical Need in Head and Neck Cancer Patients

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ABSTRACT

Objective: Oral mucositis is a debilitating side effect of tumor treatment very common in head and neck cancer (HNC) patients. There is no approved treatment. SGX942 (dusquetide), a novel Innate Defense Regulator, reduces the duration of oral mucositis and may also prevent/treat infection and augment tumor control.

Method: A Phase 2 trial enrolled 111 patients receiving chemoradiation therapy (CRT) who were treated twice per week during radiation therapy and were followed for 12 months after CRT completion. Duration of severe oral mucositis, rate of infection and rate of tumor resolution were monitored.

Results: SGX942 is a first-in-class drug with a novel mechanism of action, modulating the innate immune system to decrease inflammation while enhancing bacterial clearance and tissue healing. CRT-associated oral mucositis has been linked to dysfunctional inflammation stimulated by the innate immune system. Incidence of severe oral mucositis (defined as the inability to eat and/or drink) is particularly high (>70%) HNC patients undergoing cancer treatment (an orphan clinical population).

A Phase 2 study (ClinicalTrials.gov Identifier: NCT02013050) evaluating a 4-minute IV infusion of SGX942 or placebo (saline) administered twice weekly after radiation therapy was completed. Compared to placebo patients, patients receiving 1.5 mg/kg of SGX942 had a 50% reduction in their duration of severe oral mucositis (SOM; 9 days versus 18 days; p=0.099) and a corresponding trend in reductions in incidence and area under the severity-time curve (AUC). In patients receiving aggressive cisplatin (80-100 mg/m^2 every 3rd week), SGX942 at 1.5 mg/kg decreased the duration of severe OM by 67% (p=0.04) and ulcerative OM (UOM) by 22% (p=0.099). Use of daily opioid pain medication was found to decrease in the 1.5 mg/kg SGX942 treatment group.

Potential effects on tumor progression rates both during treatment and for 12 months following treatment were also evaluated. The number of patients with a "complete tumor response" using the Response Evaluation Criteria in Solid Tumors (RECIST) score was increased at the initial follow-up visit and at the 12-month follow-up visit, which was consistent with an increased survival benefit in the SGX942 treated groups at the 12-month time point. 1-year mortality in the placebo group in this study was 19% compared to 7% in the SGX942 treatment group. These data indicate that SGX942 does not interfere with and may augment tumor treatment.

Reported infections during CRT of both fungal and non-fungal origin were also decreased with SGX942, in keeping with the nonclinical findings and mechanism of action.

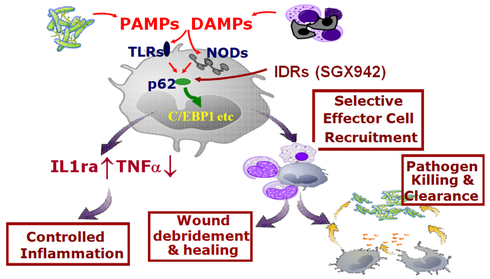
Conclusions: SGX942 (dusquetide) appears to be a promising treatment for SOM in HNC patients undergoing CRT and may offer ancillary benefits to infections, tumor clearance and, hence, mortality. Taken together, the reduced duration of oral mucositis, the reduced infection rate, coupled with the potential for accelerated tumor clearance and the trend towards reduced mortality, indicate that further studies are warranted.

A Phase 3 study evaluating SGX942 in the treatment of oral mucositis in HNC patients is actively recruiting in the United States and Europe (ClinicalTrials.gov Identifier: NCT03237325). The Phase 3 clinical trial design has been discussed with both US Food & Drug Administration (FDA) and the European Medicines Agency (EMA). The EMA has indicated that positive results from a single Phase 3 study may be sufficient for marketing approval. SGX942 has received FDA fast-track designation for the treatment of oral mucositis and Priority Innovative Medicine (PIM) designation in the United Kingdom.

Soligenix has received partial funding from National Institute of Dental and Craniofacial Research for its oral mucositis clinical studies. The Phase 2 study was supported with a Phase I Small Business Innovation Research (SBIR) grant (#R43DE024032) award, with the Phase 3 study startup activities being supported by a Phase II SBIR grant (#R44DE024032) award.

IDR MECHANISM

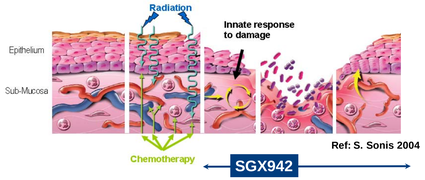
Dusquetide (a 5-amino acid peptide) specifically binds to the ZZ domain of p62 (Yu et al 2009) and selectively stabilizes TNFα-induced p62-RIP1 complex formation while having no effect on TNFα-induced p62-PKCξ complex formation. Dusquetide activates MAPK p38 and C/EBPβ, resulting in modulation of cytokine production and increased macrophage recruitment to the site of infection/damage (Yu et al 2009; North et al 2016).



ORAL MUCOSITIS

Mucositis is the clinical term for damage done to the mucosa by anticancer therapies. It can occur in any mucosal region, but is most commonly associated with the mouth, followed by the small intestine. It is estimated, based upon review of historic published studies and reports and an interpolation of data on the incidence of mucositis, that mucositis affects approximately 500,000 people in the US per year and occurs in 40% of patients receiving chemotherapy. Mucositis can be severely debilitating and can lead to infection, sepsis, the need for parenteral nutrition and narcotic analgesia. The gastrointestinal damage causes severe diarrhea. These symptoms can limit the doses and duration of cancer treatment, leading to sub-optimal treatment outcomes.

The mechanisms of mucositis have been extensively studied and have been recently linked to the interaction of chemotherapy and/or radiation therapy with the innate defense system. Bacterial infection of the ulcerative lesions is now regarded as a secondary consequence of dysregulated local inflammation triggered by therapy-induced cell death, rather than as the primary cause of the lesions.



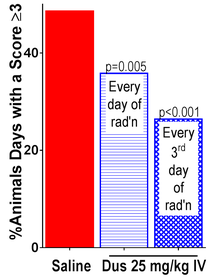
Ref: S. Sonis 2004

NONCLINICAL RESULTS

Extended Pharmacodynamics

As expected for a peptide, dusquetide has a rapid pharmacokinetic half-life in plasma (mean residence time <10 minutes). Despite this, the effect on the responses of the innate immune system are enduring. Anti-infective studies demonstrated no added benefit to repeated dusquetide administration within a 24-48 hour window, suggesting a pharmacodynamic response of 48-72 hours (North et al 2016). Studies in oral mucositis, similarly supported dosing every 3rd day.

Radiation-Induced Oral Mucositis: Fractionated radiation was administered to the everted cheek pouch of Golden Syrian hamsters on Days 0, 1, 2, 3, 6, 7, 8 and 9. Dusquetide ("Dus"; SGX942) was administered on the days indicated and 2 hours after radiation if applicable. OM was monitored by blinded scoring by 2 independent observers every second day throughout a 35 day window with OM reaching peak severity around Day 19.



CLINICAL RESULTS

Phase 2 Study Design

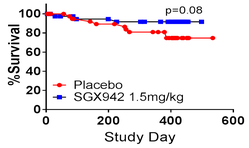
- Enrolled 111 HNC patients planned to receive at least 55 Gy radiation and either weekly (30-40 mg/m^2) or every 3rd week (80-100 mg/m2) cisplatin
  - 96 patients received at least 55 Gy irradiation and constituted the primary modified intent-to-treat (mITT) analysis population
- Dose escalating: Placebo, 1.5, 3.0 and 6.0 mg/kg administered twice weekly
  - 1.5 mg/kg was the most effective dose, consistent with preclinical and Phase 1 results
- Key efficacy endpoints: incidence and/or duration of severe OM
- Key safety endpoints: Adverse Events (AEs), serious AEs (AES), labs

Safety Findings

- SGX942 was well-tolerated in HNC patients undergoing CRT
  - No differences in the nature or severity of AEs and SAEs between treatment groups
  - No significant shifts in laboratory values
  - No impact on tumor resolution
- Consistent with 84-subject Phase 1 study in healthy volunteers

12-Month Survival Post-Radiation

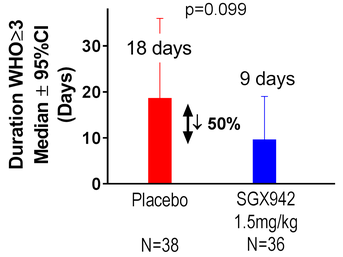
LONG TERM SURVIVAL



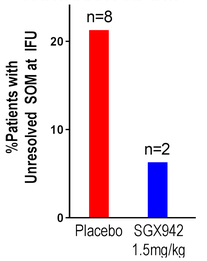
CLINICAL RESULTS

Clinically Significant Findings

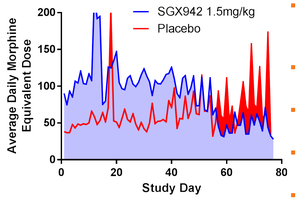
Duration Severe OM



%Unresolved OM

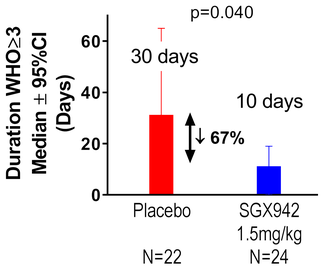


Average Daily Pain Medication Use



More Disease = Bigger Drug Effect

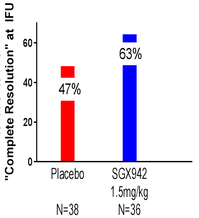
Duration Severe OM: Chemo Every 3rd Week



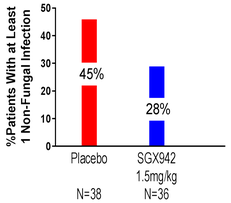
CLINICAL RESULTS

Ancillary Benefits

%"Complete" Tumor Resolution at 1 month post EOT



%Non-Fungal Infection



CONCLUSIONS

- Dusquetide (SGX942) modulates the response of the innate immune system to a broad spectrum of triggers including tissue damage, secondary inflammation and infection.
- IDRs have an extended pharmacodynamic impact and a clinically convenient 4-minute IV infusion twice-weekly of 1.5 mg/kg SGX942 is effective in reducing the median duration of oral mucositis.
- SGX942 (1.5 mg/kg) decreased SOM 50% and 67% in patients at highest risk for SOM.
- Consistent with the primary endpoints, secondary endpoints such as pain medication were reduced.
- Consistent with preclinical work, SGX942 reduced incidence of infection.
- SGX942 did not interfere with tumor treatment, also consistent with preclinical xenograft studies.
  - Some evidence of "accelerated" tumor resolution.
- SGX942 was safe and well-tolerated in HNC patients, including through 12-months post-radiation.
  - Reduced mortality over 12 months and sustained tumor resolution.
- A high degree of clinical translation was observed in recent Phase 1 and Phase 2 studies. A Phase 3 study in oral mucositis is currently recruiting.

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