

# Rigosertib Demonstrates Considerable Efficacy and Safety in the Treatment of Advanced/Metastatic Cutaneous Squamous Cell Carcinoma in Patients with Recessive Dystrophic Epidermolysis Bullosa

Martin Laimer MD<sup>1</sup>, Andrew P. South PhD<sup>2\*</sup>, Henry Y. Yang BSc<sup>3</sup>, Lauren Banner BSc<sup>3</sup>, Elisabeth Mayr PhD<sup>1</sup>, Sophie Kitzmueller MD<sup>1</sup>, Matthew Parris BSc<sup>4</sup>, Meena Arora MSc<sup>4</sup>, Johann W. Bauer MD<sup>1</sup>, Neda Nikbakht MD, PhD<sup>3</sup>

<sup>1</sup>Department of Dermatology and Allergology and EB House Austria, University Hospital of the Paracelsus Medical University, Salzburg, Austria; <sup>2</sup>Department of Pharmacology, Physiology and Cancer Biology, Thomas Jefferson University, Philadelphia, PA, USA; <sup>3</sup>Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA, USA; <sup>4</sup>Onconova Therapeutics Inc., Newtown, PA, USA  
\*Andrew.South@Jefferson.edu

## INTRODUCTION

- Recessive dystrophic epidermolysis bullosa (RDEB) is a rare and devastating genetic blistering disease caused by mutations in the COL7A1 gene encoding for type VII collagen.<sup>1</sup>
- Mutated type VII collagen results in numerous multisystem complications, most notably extreme skin fragility and generalized chronic blistering and wound formation which predispose afflicted individuals to the development of aggressive, recurrent, and fatal squamous cell carcinomas (SCC).<sup>2</sup>
- The average age of SCC onset in RDEB patients is 29.5 years and median survival is 2.4 years.<sup>3</sup>
- Beyond surgical excision, current strategies of anti-tumor therapy in advanced and/or metastatic RDEB-SCC, including conventional chemo-, radio- and targeted therapy, have not yet proven to provide a significant benefit.<sup>3-5</sup>
- Further, the tolerability of anti-tumor therapy is poor, exacerbated by RDEB associated disease burden and systemic morbidity.<sup>5-7</sup>
- To address the unmet need for effective and tolerable anti-tumor therapies in RDEB-SCC, two investigator-initiated open-label, single arm phase 2 studies are currently ongoing in the US and Austria to evaluate anti-tumor activity and safety of the polo-like kinase-1 (PLK1) inhibitor, rigosertib in RDEB patients diagnosed with locally advanced and/or metastatic SCCs that have failed prior standards of care [EudraCT No.: 2016-003832-19/NCT03786237; NCT04177498].
- Herein we report on the first three evaluable patients who have received rigosertib therapy.

## HYPOTHESIS

Oral or intravenous (IV) rigosertib treatment over will lead to demonstrable anti-tumor activity, as determined by overall response rate using Response Criteria in Solid Tumors Version 1.1 (RECIST1.1) for site assessment by imaging or RECIST plus clinical skin lesion measurements, in PDEB patients with SCC that have failed prior standards of care.

## METHODS

### Study Medication

- Rigosertib is a small molecule that interferes with multiple cellular pathways driving cancer cell growth (including the RAS/RAF/MEK pathway) and was originally identified as an inhibitor of PLK1.<sup>8-10</sup>
- The ability of rigosertib to inhibit the growth of cancer cells correlates with PLK1 expression in hepatocellular<sup>11</sup> and retinoblastoma cancers,<sup>12</sup> and was the basis of identifying rigosertib in RDEB-SCC preclinical studies.<sup>10</sup>

### Intervention

- RDEB patients with treatment-resistant, advanced SCC received rigosertib either IV (1800 mg/24-hours as a 72-hour continuous IV infusion on Days 1-3 of each 14-day cycle for 8 cycles, then on Days 1-3 of 28-day cycles until 1-year of treatment) or orally (560 mg BID on days 1-21 of each 28-day cycle for a total of 12 cycles).
- The primary objective was to assess anti-tumor activity determined by overall response rate using Response Criteria in Solid Tumors Version 1.1 (RECIST1.1) for site assessment by imaging or RECIST plus clinical skin lesion measurements.
- Safety was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 based on a medical review of adverse event reports and results of vital sign measurements, physical examinations, and clinical laboratory tests.

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## RESULTS

### Patient Summaries

- Patient 1 (IV)
  - 23-year-old female with a history of more than 29 cutaneous SCCs and progression after two cycles of cemiplimab therapy resulting in unresectable tumors, including target lesions on her left hand and wrist, and right elbow.
- Patient 2 (Oral)
  - 32-year-old female with a history of more than 6 cutaneous SCCs with nodal involvement previously treated with surgical excisions, 4 cycles of cetuximab, and 4 cycles of pembrolizumab.
  - Patient presented with active SCC on her left elbow and enlarged lymph nodes on imaging.
- Patient 3 (IV)
  - 21-year-old tumor cachectic female (height: 158 cm, weight: 25 kg), presenting with a massive, ulcerated cutaneous SCC on her right lower leg, which had previously been partially amputated, and additional tumor lesions on her right knee, ipsilateral groin and scalp as well as pre-diagnosed lung metastasis.
  - Prior treatment included lymph node dissection, radiotherapy (20 Gy), and 10 months of immunotherapy with cemiplimab.

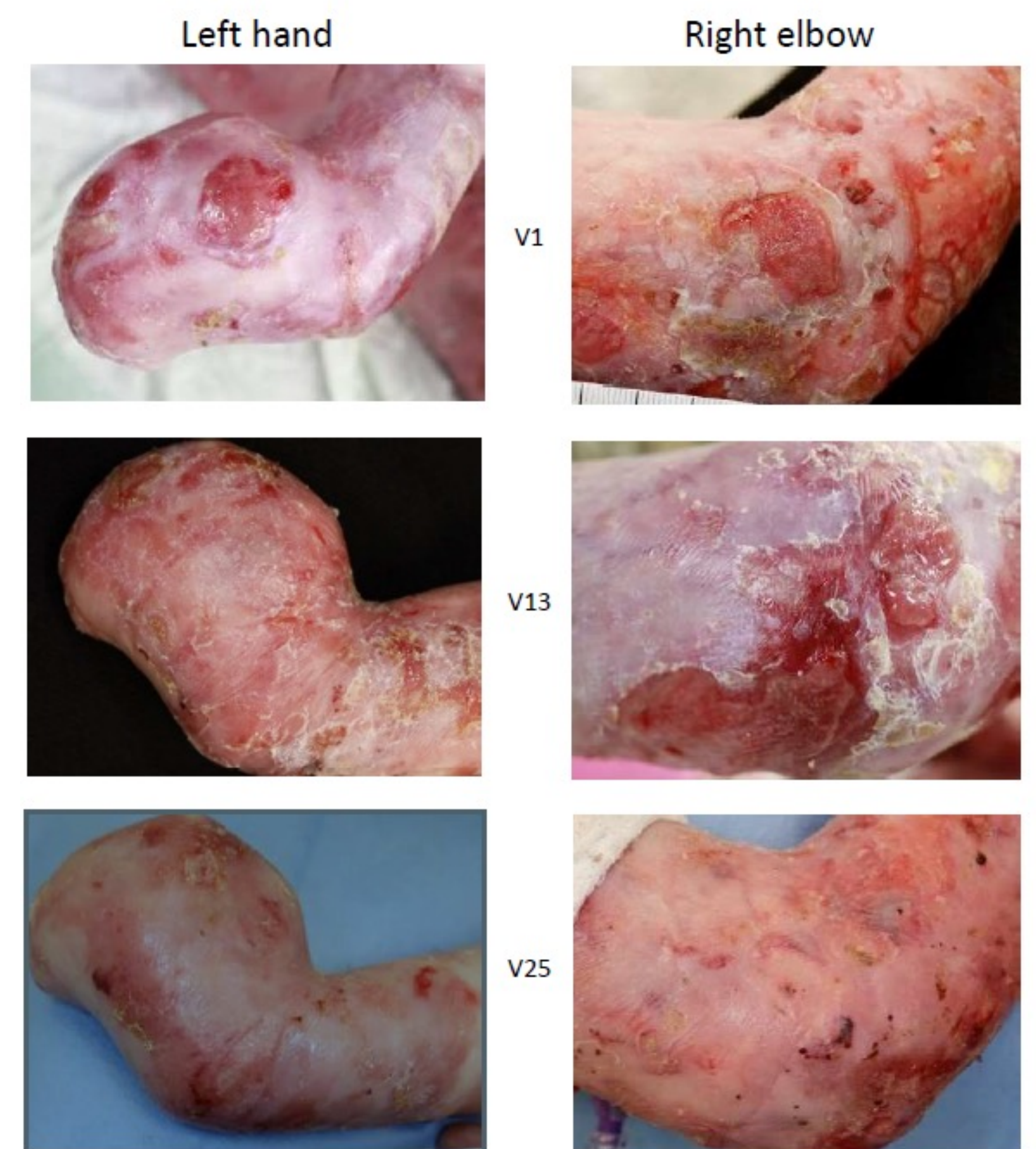
### Patient Results

- Patient 1 (IV)
  - Achieved clinical and histological remission with stable metabolic activity in PET-CT at week 12 of the study
  - Follow-up demonstrated:
    - No evidence of tumor/SCC disease during study treatment
    - PET-CT revealed decreased uptake in target lesions classifiable as “partial response” as per RECIST criteria
  - Adverse events (AEs) included:
    - Irritative cystitis (Grade 3) – prompted dose reduction to 1350 mg/24-hours as a 72-hour continuous infusion from cycle 13 until cycle 15 and then 900 mg/24-hours as a 72-hour continuous infusion from cycle 16 onwards for relief
    - Nausea and vomiting, increased lesion pain, amenorrhea, and hair loss
- Patient 2 (Oral)
  - Achieved complete clinical and histological remission of the skin lesions with oral rigosertib after 6 cycles of treatment until the end of the study (cycle 12)
  - No lymph nodes qualified as RECIST target lesions
  - Continued to remain in remission post-trial completion until 3 months post-treatment completion
  - AEs included:
    - Hematuria (Grade 3)
    - Urinary frequency and urgency
    - irritative cystitis
    - Proteinuria (Grade 2)
    - Fatigue (Grade 1)
- Patient 3 (IV)
  - The primary lesion showed a significant size reduction based on clinical assessment after two cycles
  - IV therapy reduced to 900 mg/24-hours from cycle 4 onwards due to poor clinical condition
  - Therapy stopped at cycle 5 due to PET-CT confirmed metastatic progression of disease
  - AEs: nausea and lesion pain during administration

## CONCLUSIONS

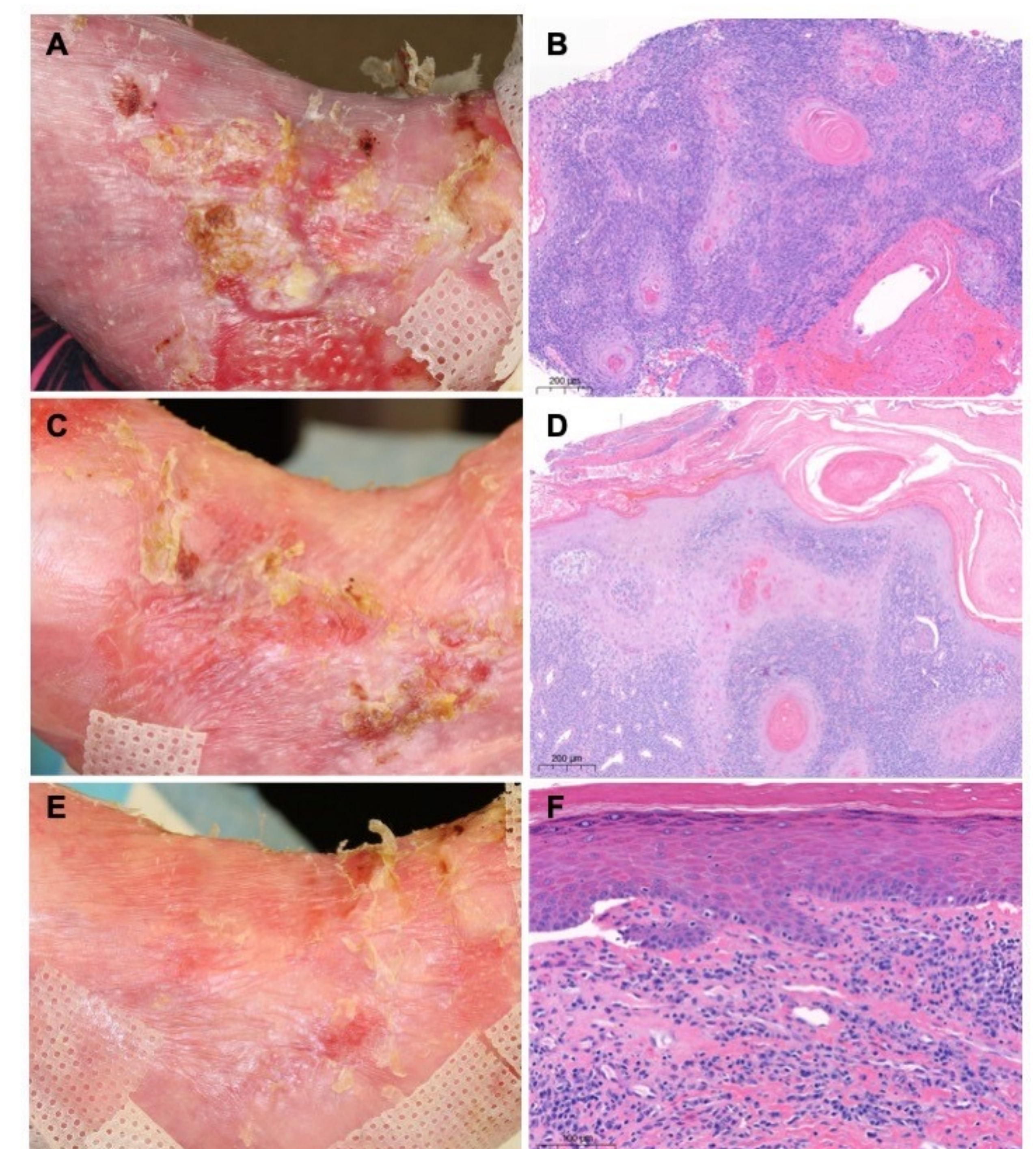
- Open-label treatment with rigosertib, a PLK1 inhibitor, in three patients with advanced RDEB-SCC led to complete remission of skin lesions in two patients and a substantial reduction in primary tumor volume in the third.
- A confirmatory Phase II trial to corroborate this impact in RDEB-cSCC is currently in preparation.

**Figure 1: Clinical Photography of Two Target Lesions of Patient 1**



**Figure 1.** Left hand and right elbow at visit 1 (V1, Day 1), V13 (Days 85-91) and V25 (Days 169-175). At V25 after 11 cycles, both lesions display clinical and histological remission. Concurrent staging has revealed no signs of metastatic disease.

**Figure 2: Clinical and Histopathological Evaluation of Patient 2 Left Elbow Lesion**



**Figure 2.** (A, B) Clinical and histopathological images at baseline (A) a friable, ulcerated, and crusted plaque of the left elbow measuring 1045 mm2 (B) dermal invasion by atypical keratinocytes and squamous eddies layered in a pearl-like fashion, H&E, 40x (C, D) clinical and histopathological images after 4 months (Cycle 4) of oral rigosertib treatment (C) resolving erythematous and crusted plaque measuring 248 mm2 (D) regressing squamous cell carcinoma with a prominent lymphocytic infiltrate, H&E, 40x (E, F) clinical and histopathological images after 6 months (Cycle 6) of oral rigosertib treatment (E) resolved lesion (F) scar with no residual neoplasm, H&E, 100x