Rigosertib for locally advanced/metastatic EB-associated SCC

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Introduction

Recessive dystrophic epidermolysis bullosa (RDEB) is a severe genodermatosis caused by mutations in the COL7A1 gene encoding type VII collagen. The latter protein represents a major component of anchoring fibrils that provide stability to the dermal-epidermal adhesion. Consequently, RDEB is characterized by generalized mucocutaneous blistering. Aggressive metastasizing squamous cell carcinomas (SCCs) typically arising in areas of chronic skin wounding and inflammation are the primary cause of death in this cohort, with a cumulative risk of death of 70 % and 78.7% by age 45 and 55, respectively [1,2]. These neoplasms show limited response rates of mostly short duration to conventional chemo- and radiotherapy as well as targeted therapy with epidermal growth factor (cetuximab, panitumumab) and tyrosine kinase inhibitors (gefitinib, erlotinib) [1, 3]. Likewise, high quality evidence on the therapeutic impact and immunomodulatory effects of programmed death receptor-1 (PD-1) blocking antibodies on EB-SCCs as well as disease-specific local and systemic inflammatory states, susceptibility to skin infections and microbial burden is hitherto lacking. Against this background preclinical models (1) demonstrated that RDEB SCC keratinocytes are specifically sensitive to PLK1 reduction by siRNA treatment compared to normal primary keratinocytes and (2) further identified the PI3K/PLK1 inhibitor Rigosertib as having the best specificity by demonstrating the largest therapeutic window separating tumor and normal cells [4]. Rigosertib is currently investigated for anti-neoplastic activity also in patients with myelodysplastic syndrome and other hematological malignancies as well as advanced solid tumors.

Methods

Here we report on early preliminary data of an investigator-initiated "first in EB" phase II, open-label trial evaluating the preclinically observed anti-tumor activity and safety of Rigosertib in RDEB patients diagnosed with locally advanced/metastatic SCCs that have failed prior standard of care (EudraCT No.: 2016-003832-19). The treatment schedule includes 72h CIV infusions of 1800 mg/24h on days 1-3 of a two week-cycle for 8 cycles and then on days 1-3 of a 4 week cycle thereafter. Efficacy is assessed by determining the Objective Response Rate (ORR) using Response Criteria in Solid Tumors Version 1.1 (RECIST1.1) per site assessment up to 52 weeks by PET-CT/MR scan.

Results

In a 24-year-old RDEB patient with history of multiple, unresectable cutaneous SCCs unresponsive to prior treatments including Cemiplimab, administration of Rigosertib led to sustained clinical and histological remission of all target lesions without signs of metastatic disease as assessed after completion of currrently 12 treatment cycles. Explorative analyses with molecular profiling of tumors before, during and after treatment are ongoing. Safety and tolerability have been good. Hitherto observed adverse events comprise rigosertib induced CTCAE grade II irritative cystitis, nausea and alopecia as well as recurrent episodes of bacteriaemia with predominantly Staphylococcus aureus and Pseudomonas aeruginosa (most probably due to chronic skin wounding and indwelling catheters for CIV administration of rigosertib, however without cardiovascular compromise). Notably, neuropathic pain was reported as intensified during IP-administration with striking restriction to target lesion areas.

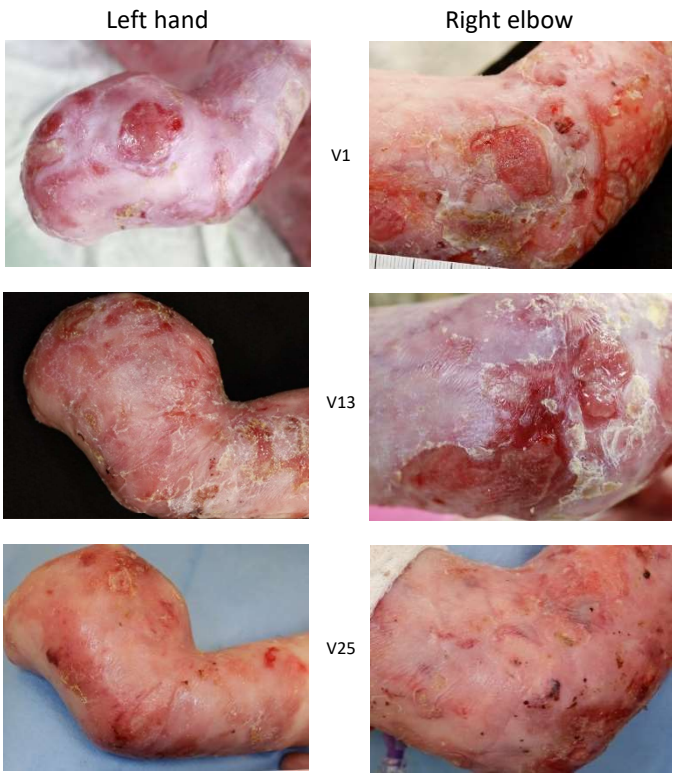

Figure 1. Clinical photography of two target lesions (i) left hand and (ii) right elbow at V1 (day1), V13 (day 85-91) and V25 (day 169-175). At V25 after 11 cycles, both lesions display clinical and histological remission. Concurrent staging has revealed no signs of metastatic disease.

References: 1. PMID: 26302137, DOI: 10.1111/bjd.14104; 2. PMID: 19026465, DOI: 10.1016/j.jaad.2008.09.035; 3. PMID: 32113942, DOI: 10.1016/j.ejca.2020.01.008; 4. PMID: 30846478, DOI: 10.1158/1078-0432.CCR-18-2661

Conclusion

This initial single patient data indicate anti-tumor activity and acceptable safety profile of Rigosertib in the setting of EB-associated SCC with usually fatal prognosis. Additional patients are anticipated to be enrolled into the study in Salzburg, AT, London, UK and Philadelphia, PA/USA.

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