Appendix S1

FEASIBILITY ASSESSMENT

Master network

The feasibility of performing a network meta-analysis (NMA) was assessed in the following steps: *(i)* the possibility of constructing a connected network of trials; (*ii*) the availability of data for each outcome of interest; (*iii*) a comparison of trial characteristics and clinical characteristics that could modify relative treatment effect for each outcome. Of the 75 randomized controlled trials (RCTs) included in the systematic literature review (SLR), 2 trials assessed non-approved and non-marketed interventions and 13 had no common comparator to be linked in the network diagram and could not contribute to the analysis.

The remaining 60 trials were further evaluated by applying the predefined eligibility criteria: trials must have included approved field-directed topical interventions administered as monotherapy and according to their summary of product characteristics (SPC). Trials involving prior treatment as part of their methodology were excluded. Of the 60 trials assessing licensed interventions, 17 did not meet SPC recommendations, 4 assessed laser/cryotherapy, 4 included prior treatment as part of their methodology, and 3 assessed combination therapy. In addition, one trial did not report data for key outcomes of interest for analysis and was excluded. Therefore, 31 trials were evaluated for feasibility assessment and contributed to the master network.

Across the 31 trials evaluated for feasibility analysis, high variability was observed in terms of treatment dose, frequency and duration across recommended doses. The variability in the duration of treatment was subsequently associated with the variation in the time-point of assessment. Some therapies included a lag phase prior to assessment, while for others immediate assessment after treatment was undertaken. The following assumptions were considered for analysis across trials meeting the recommendations: (*i*) if any trial investigated a treatment at different durations (all meeting SPC recommendations), the treatment group with the longest duration was included in the network; (*ii*) treatment arms within a trial were not pooled, except when the objective of the trial was assessment of bioequivalence of the interventions with results showing comparability of interventions; (*iii*) trial endpoints of each trial were taken into consideration for corresponding outcomes and sensitivity analyses were also conducted to restrict the evaluation time period to 4 weeks post-treatment (consistent with 5-FU 4% evaluation); (*iv*) across trials assessing multiple cycles of an intervention, results after 2 cycles of the treatments were considered for endpoint analysis; and (*v*) placebo and placebo-PDT were considered as different treatment regimens. Fig. 4A presents the master network, highlighting the possibility of analysis across RCTs.

Trials contributing to relevant network of each outcome

A second step was undertaken to conduct the assessment of variability and heterogeneity and defined relevant networks for each outcome of interest. Feasibility was evaluated based on potential differences in trial design, patient characteristics, outcome reporting and time-point of assessment that could potentially interfere with the relative treatment effects evaluation. The following methodological approach was adopted for this evaluation: (*i*) the possibility of constructing an interlinked network of trials based on data availability per outcome; (*ii*) evaluation of network heterogeneity by comparing trial designs, patient demographics that could modify the relative treatment effect followed by recommendations for appropriate analyses for each outcome.

A qualitative assessment of included evidence was undertaken to assess variation in trial population characteristics and to determine whether there exist any variables that may impact the results on pooling heterogenous trials.

Complete clearance

Of the 31 trials included for feasibility assessment, 27 trials (84.4%) reported complete clearance rate. Based on detailed heterogeneity and comparability assessment and the key characteristics, variability was observed across the trials. The variability factors that could lead to the heterogeneity across the trials included time-point of assessment, limited reporting of disease severity, sample size, blinding status and trial phase. Therefore, the following assumptions were undertaken: (*i*) trial endpoint would be considered for analysis, irrespective of variation from the time-point of assessment with the 5-FU 4% trial as it was considered methodologically and clinically relevant to use recommended treatment duration from the SPC; (*ii*) base-case analysis included trials reporting clinical clearance rate, irrespective of type of outcome assessed (primary, secondary or unclear) and patient populations with ≥ 5 lesions at baseline); and (*iii*) sensitivity analysis assessing any impact of observed key variables on the final results (types of clearance (clinical, histological, unclear); secondary outcome at endpoint (excluding secondary and unclear reporting); exclusion of open-label at endpoint; only trials reporting results 4 weeks post-treatment; only intent-to-treat population).

Based on these assumptions, 6 trials were excluded from the base-case analysis for the following reasons: method of assessment was unclear, clearance rate was assessed histologically, included patients that had 1 lesion each, and ambiguity in baseline lesion count. Therefore, a total of 21 trials contributed to base-case analysis of complete clearance rate, allowing comparisons among 13 interventions (Fig. 4B).

Partial clearance

Of the 31 trials included for feasibility assessment, 15 trials (46.9%) contributed to partial clearance rate. The same assumptions applied for complete clearance were followed for partial clearance. Of these 15 trials, 5 were excluded from the base-case analysis for the following reasons: no common comparator, did not meet the inclusion criterion as per definitions, published as a conference abstract with limited information pertaining to baseline characteristics, clearance rate was assessed histologically and ambiguity in baseline lesion count. Therefore, a total of 10 trials contributed to the base-case analysis of partial clearance rate, allowing comparisons among 10 interventions (Fig. 4C).

Withdrawals due to adverse events

Of the 31 trials evaluated for feasibility assessment, 18 (58.1%) reported data pertaining to trial withdrawals due to AEs. Of these 18 trials, one did not meet the lesion count criteria and was not considered for analysis. Based on the heterogeneity assessment of trials contributing to evidence network of withdrawals due to AEs, 2 trials were excluded as they did not provide baseline lesion count. In addition, 2 trials did not report the incidence of withdrawals due to AEs across all treatment groups and were excluded from the analysis. Therefore, a total of 9 trials contributed to the base-case analysis of partial clearance rate, allowing comparisons among 10 interventions (Fig. 4D).