**Materials and Methods**

*Study Design and Patients*

The study was designed as a single-center, prospective, randomized, double-blind, placebo-controlled trial, conducted between December 2011 and January 2017. The trial included cancer patients (all tumor types) ≥18 years, attending the outpatient clinic at the Institute of Oncology of Davidoff Cancer Center, who were planned to initiate EGFRI treatment (cetuximab, panitumumab, erlotinib, or gefitinib), with/without concomitant chemotherapy. Exclusion criteria included a known hypersensitivity to any of the investigated agents, prior use of topical (facial) or systemic antibiotic or anti-inflammatory drugs during the 2 weeks prior to study initiation, and a skin rash 2 weeks prior to or at randomization.

Informed consent was obtained from all participants. The study was approved by the institutional review board at Rabin Medical Center and was registered at ClinicalTrials.gov (study identifier: NCT01256437).

*Treatment*

Eligible patients were randomized in a 1:1:1 ratio. Randomization was computerized to receive topical treatment with either CHL 3% + PRED 0.5% ointment (lot: 2001-09-45/2), CHL 3% ointment (lot: 2001-09-45/3), or aqua cream (AQUA; lot: 2001-09-45/4), all provided by Super-Pharm Professional-compounding pharmacy (Fig. 1).
All tubes containing topical treatments were similar, marked only with a study number code, and given to eligible patients prophylactically by a dermatologist (I.A.-L. or H.P.-N.).

For all patients, the topical treatment and the EGFRI treatment were initiated on the same day (day 0). Patients were instructed to apply a thin layer of the assigned topical treatment to their face once daily for 3 weeks and every other day thereafter to complete a total overall treatment of 30 days. Patients were instructed to avoid all other topical applications except for a potent sunscreen when outdoors.

Cultures from intranasal sites for *S. aureus* colonization were randomly obtained on day 0, from 28 patients, by placing a cotton bud swab in the anterior nares, applying gentle pressure, and rotating the swab.

*Evaluation*

Baseline clinical evaluation (day 0) consisted of taking medical history including medication list and history of drug reactions, skin examination by an expert dermatologist (I.A.-L. or H.P.-N.), and standardized digital photography of the face. Follow-up evaluations, including skin examination (±digital photography of the face, utilizing the same standard poses as at baseline), were performed on days 14 and 30 from study initiation.

Rash severity was assessed by using the CTCAE version 4.03 and by approximating the number of papulopustular lesions (NOL) in the face (conducted by I.A.-L. or H.P.-N.). As papulopustular rash of the face always involves less than 10% of the body surface area, CTCAE grading was used as follows: grade 1 = mild papular and/or pustular rash, which may or may not be associated with symptoms of pruritus/tenderness; grade 2 = moderate papular and/or pustular rash which may or may not be associated with symptoms of pruritus/tenderness and may be associated with psychosocial impact; grade 3 = moderate to severe papular and/or pustular rash which may or may not be associated with symptoms of pruritus/tenderness, associated with local superinfection with oral antibiotics indicated; and above grade 3 = severe papular and/or pustular rash of the face. The NOL approximation was used to categorize patients into the following groups: 0 ≤ NOL < 10, 10 ≤ NOL < 20, 20 ≤ NOL < 30, and NOL ≥30. Our clinical experience suggested that NOL ≥10 is perceived as a quality of life issue by patients and was therefore considered a protocol-specified significant rash. In the CTCAE-based assessment we investigated the incidence of ≥grade 3 rash.

*Statistical Analysis*

The primary end points were the incidence of CTCAE ≥grade 3 rash on days 14 and 30, and a subanalysis was conducted for the incidence of the protocol-specified significant rash (NOL ≥10) at the same time points.

As this was a proof-of-concept study, we applied a per-protocol analysis (rather than intention-to-treat analysis). Nevertheless, we provide detailed information on patients who discontinued the study protocol before day 30.

The study was designed according to the hypothesis that in the control group (AQUA) the incidence of papulopustular rash (end points) will be 80%, and in the treatment group (CHL-PRED) will be 45%, with greater than 0.8 power and 0.05 significance, leading to sample sizes of 30 patients in each treatment arm.

For analysis of continuous end points, a general linear model was used, and for dichotomous end points, a logistic procedure was used. A correlation measure between the 2 scoring systems was calculated. All analyses were performed with SAS version 9.4 (SAS Institute Inc., 2016).