Table SI. *Characteristics of included studies*

Study	Trial design and phase	Patients, *n*	Study duration	Treatment[a] (*n*)	Inclusion criteria: Age (years)	Lesions, *n*	Location of lesions	Lesion size/ total lesion area	Lesion description/ type/diagnosis	Other	Exclusion criteria
5-FU/SA											
Stockfleth, et al. (2011) (22)	DB, PG, Ph III study	470	Until lesions completely cleared or a maximum of 12 weeks, with 8 weeks' follow-up	Arm 1: 5-FU/SA (*n* = 187) Arm 2: diclofenac (*n* = 185) Arm 3: 5-FU/SA vehicle (*n* = 98)	≥ 18 and ≤ 85	4–10	Face, forehead or bald scalp	≥ 0.5 and ≤ 1.5 cm in diameter	Olsen et al. (1991) (10) grade I or grade II Histologically confirmed diagnosis	Fitzpatrick skin type I–IV No treatment within treatment area in previous 3 months	NR
Stockfleth, et al. (2012) (17)	Ph III study observational follow-up of all treated population from (22)	435	12-month follow-up after end of treatment	Arm 1: 5-FU/SA (*n* = 173) Arm 2: diclofenac (*n* = 169) Arm 3: 5-FU/SA vehicle (*n* = 93)	≥ 18 and ≤ 85	4–10	Face, forehead or bald scalp	≥ 0.5 and ≤ 1.5 cm in diameter	Olsen et al. (1991) (10) grade I or grade II Histologically confirmed diagnosis	Fitzpatrick skin type I–IV No treatment within treatment area in previous 3 months	NR
Ingenol mebutate											
Spencer (2010) (23)	Multicentre, DB, PG	265	2–3 days' treatment with follow-up at 57 days	Arms 1 & 5: PEP005 gel 0.005% (NR) Arms 2 & 6: PEP005 gel 0.01% (NR) Arms 3 & 7: PEP005 gel 0.015% (NR) Arms 4 & 8: vehicle (NR)	NR	NR	Face or scalp	NR	NR		NR
Weiss & Zibert (2013) (15)	NR	NR	3 days' treatment with 54 days' follow-up	Arm 1: ingenol mebutate 150 µg/g (*n* = 277) Arm 2: vehicle (NR)	NR	4–8[b]	NR	NR	"Typical" AK lesions		NR
Lebwohl et al. (2012) (18)	DB, PG, Ph III study	547 (head region)	3 days' treatment with 54 days' follow-up	Arm 1: ingenol mebutate 0.015% once daily for 3 days (*n* = 277) Arm 2: vehicle once daily for 3 days (*n* = 270)	> 18	4–8[b]	Face or scalp	NR	"Clinically typical, visible and discrete" AK lesions		See note 1
Berman et al. (2012) (24)	DB, PG, Ph III study	547	3 days' treatment with follow-up after 54 days	Arm 1: ingenol mebutate 0.015% once daily for 3 days (*n* = 277) Arm 2: vehicle once daily for 3 days (*n* = 270)	> 18	4–8[b]	Face or scalp	NR	"Clinically typical, visible and discrete" AK lesions		See note 1
Lebwohl et al. (2012) (25)	DB, PG, Ph III study	545 (head region)	3 days' treatment with follow-up after 54 days	Arm 1: ingenol mebutate 0.015% once daily for 3 days (*n* = 274) Arm 2: vehicle once daily for 3 days (*n* = 271)	> 18	4–8[b]	Face or scalp	NR	"Clinically typical, visible and discrete" AK lesions		See note 1
Lebwohl et al. (2013) (16)	Ph III observational follow-up study to (18)	108	12-month follow-up after end of treatment	Ingenol mebutate 0.015% once daily for 3 days (*n* = 108 entered follow-up)	NR	NR	NR	NR	NR	Complete clearance in prespecified 25 cm^2 area at day 57 of the original study	NR

Table SI contd.

Siller et al. (2009) (21)	DB, PG, Ph IIa study at six centres in Australia	58	A: treatment on days 1 and 2; B: treatment on days 1 and 8. Results pooled. Follow-up at day 85	Arm 1: ingenol mebutate 0.0025% once daily (n = 15) Arm 2: ingenol mebutate 0.01% once daily (n = 16) Arm 3: ingenol mebutate 0.05% once daily (n = 15) Arm 4: vehicle once daily (n = 12)	> 18	≥ 5	Arms, shoulders, chest, face and/or scalp	3–15 mm in diameter	Clinically diagnosed		See note 2
Imiquimod 2.5%/3.75%										
Hanke et al. (2010) (19)	DB, PG, Ph III study at 26 centres in the USA	490	9 weeks: two 3-week treatment cycles separated by a 3-week no-treatment interval. 8-week follow-up (all treated population) after treatment	Arm 1: imiquimod 2.5% once daily (n = 164) Arm 2: imiquimod 3.75% once daily (n = 162) Arm 3: vehicle once daily (n = 164)	"Adults"	5–20	Face or balding scalp, but not both	Total lesion coverage area > 25 cm^2	"Visible or palpable"	See note 3
Swanson et al. (2010) (20)	DB, PG, Ph III study at 25 centres in the USA	479	6 weeks: two 2-week treatment cycles separated by a 2-week no-treatment interval. 8-week follow-up (all treated population) after treatment	Arm 1: imiquimod 2.5% once daily (n = 160) Arm 2: imiquimod 3.75% once daily (n = 160) Arm 3: vehicle once daily (159)	"Adults"	5–20	Face or balding scalp, but not both	Total lesion coverage area > 25 cm^2	"Visible or palpable"	See note 3

[a]Unless otherwise stated 5-FU/SA dosages are 0.5%/10.0% and diclofenac dosages are 3% in hyaluronic acid. [b]Within a single 25 cm^2 area.

Exclusion criteria:

1: ·Treatment area within 5 cm of an incompletely healed wound or within 10 cm of a suspected BCC or SCC; ·Previous treatment with ingenol mebutate gel; ·Target area contained hypertrophic or hyperkeratotic lesions, cutaneous horns, or lesions that had not responded to cryosurgery; ·Recently used medications/other treatments that could interfere with evaluation of treatment area.

2: ·Recurrent lesions; ·Prior or concomitant therapy, immunosuppression, use of topical corticosteroids; ·Lesions that were markedly hyperkeratotic on clinical evaluation or had atypical histology.

3. No significant condition in the treatment area that might impair evaluation; ·Atypical AK, e.g., > 1 cm^2 in size; ·Prior therapy[c] (within 1 year – imiquimod 5% on the head; within 90 days – interferon (inducers), cytotoxic drugs, immunomodulators, immunosuppressants, oral or parenteral corticosteroids, topical corticosteroids > 2 g/day, dermatological procedures or surgeries in the treatment area, and any AK therapy in the target treatment area; and within 30 days – imiquimod outside of the head, and topical prescription drugs).

AK: actinic keratosis; BCC: basal cell carcinoma; DB: double blind; FU: fluorouracil; NR: not reported; PG: parallel group; Ph: phase; SA: salicylic acid; SCC: squamous cell carcinoma.