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1 **Ingenol Mebutate to Treat Lentigo Maligna of the Head (Face and Scalp): A Prospective**
2 **and Multicentre Single-Arm Phase 2 Trial indicates no benefit**

3 **Running title** Ingenol mebutate does not treat lentigo maligna

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40 *To the editor* Lentigo maligna (LM) is the most common subtype of melanoma *in situ*, arising
41 predominantly on chronically sun-damaged of elderly persons. The standard treatment
42 remains surgery.¹ Nevertheless, resectability, age, and patient preference can preclude surgical
43 resection. Alternative treatments (ie. imiquimod and radiation) are not always effective and
44 well tolerated.¹ Thus, there is a need for an effective and safe topical treatment.

45 Ingenol mebutate (IM) is indicated to treat actinic keratoses. It has been shown *in vitro* that
46 IM is able to induce apoptosis of melanoma cells.² But clinical data are missing, only one case
47 reporting its efficacy.³ We hypothesized that IM may have clinical and histological effect
48 against LM of the head and we conducted a prospective, multicentre, single-arm phase 2 trial
49 (NCT 02723721), planned according to Simon's optimal two-stage design⁴ for a total sample
50 size of 23 subjects. Patients were excluded if the LM had a surface area >25 cm², and/or were
51 previously treated with imiquimod. The primary endpoint was complete response (CR)
52 defined as a complete clearing of the LM at 2 months clinically and confirmed by a
53 centralized histological analysis in a blind fashion, by two independent pathologists.
54 Discordant cases were reviewed at multihead microscope. The intensity of short-term local
55 adverse events (AEs) was evaluated by the local skin reaction (LSR) score. Additionally, the
56 AEs were graded using the Common Terminology Criteria for Adverse Events version 4. The
57 concentration of 150 µg/g was chosen³ and IM was applied daily for 3 consecutive days (one
58 cycle). For patients with no CR or only partial remission at 2 months, a second cycle was
59 done.

60 Twelve patients were recruited, with a median age of 73 years (range, 62-96 years). The mean
61 size of LM was 2.52 ± 1.2 cm (min: 1; max: 5 cm), and the mean area to treat 9.6 ± 6.9 cm²
62 (min: 4; max: 25 cm²). The characteristics and outcome of the patients are detailed in [Table I](#).
63 The results of this trial are negative since only 2 patients had a CR (n°5 and 6; [Table I](#)), and
64 one of them (n°5) relapsed at 8 months. No correlation between IM-induced inflammation

65 and clinical/histologic clearance was observed (6/10 non responders had a strong IM-induced
66 reaction, [fig. 1](#)). In addition, the safety profile appears also a limitation, with a majority (66%)
67 of local AEs grade 3-4. All patients experienced, at least once, a LSR score ≥ 3 and the mean
68 maximum LSR score was 12 (min: 3 – max: 22, [Table 1](#)).

69 Because of a lack of effect and according to the study design⁴, the study ceased at the end of
70 step 1.

71 Our study should be interpreted with caution, because it has limitations, such as the lack of a
72 comparative arm and the heterogeneity of LM. Nevertheless, its design⁴ allows us to conclude
73 that IM at 150 $\mu\text{g/g}$ daily for 3 days (even after 2 cycles) is not a good option for treating LM
74 of the head. Its use with a more intense regimen would be limited by a poor safety profile.

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81 **TABLE I.** Patients' characteristics and use of IM gel

Patient No.	Age/sex (years/F or M)/ Phototype	Localization of LM	Number of biopsy(ies) to confirm diagnosis	Size of LM (cm)/ and surface area to treat (cm²)	Number of cycle	LSR score D1/D2/D3/D8/M1/M2 †	Number of biopsy(ies) to confirm the response or not after 1st/2nd cycle	LSR score D86/D87/D88/M3/M5 †	Follow-up Every 3 months - Response or not	Outcome of patients
1	96/F III	cheek	1	3/16	2	0/8/19/7/3/0	1/NA	Not available	NA NR after 1 cycle	Lost to follow-up after the second cycle
2	81/F II	cheek	1	5/25	2	0/5/7/3/2/1	2/2	0/3/9/6/1/0	NA NR after 2 cycles	Surgery confirming persistence of LM with micro-invasive component
3	73/H II	cheek	3	2/12	2	6/9/10/3/0/0	1/2	0/9/15/1/0	NA NR after 2 cycles	Surgery confirming persistence of LM with micro-invasive component
4	68/F III	cheek	1	3/13	2	0/11/13/7/2/0	1/2	0/14/17/5/1	NA NR after 2 cycles	Surgery confirming persistence of LM after failure of radiotherapy (42 Gray in six times)
5	62/H II	ear lobe	1	1/4	2	1/12/6/3/2/0	1/1	0/13/12/22/6/0	PR after 1 cycle, CR after 2 cycles then clinical and histological relapse at M8	Surgery revealing again LM

6	70/H II	ear lobe	1	1.8/5.5	1	15/20/18/12/ 0/0	1/not applicable	Not applicable	CR at M18 after 1 cycle	CR at M18
7	73/F II	cheek	1	3/4.5	2	4/5/7/6/1/0	1/1	4/4/6/5/1/0	NA NR after 2 cycles	Imiquimod; clinical clearance
8	81/F II	cheek	1	4,5/16.6	2	12/13/15/3/2/ 2	1/1	8/14/12/11/4/1	NA NR after 2 cycles	Surgery confirming persistence of LM
9	73/H II	cheek	1	1,4/4	2	3/3/3/10/1/0	1/1	1/2/3/1/0/0	NA NR after 2 cycles	Surgery confirming persistence of LM
10	85/F III	nose	1	2/3.8	2	5/4/6/4/0/0	1/1	2/5/4/8/0/0	NA NR after 2 cycles	Refused any further treatment
11	62/F III	cheek	1	2/6	2	8/9/9/9/1/0	1/1	9/10/12/10/1/0	NA NR after 2 cycles	Surgery confirming persistence of LM
12	77/H III	nose	1	1.5/5	1	5/13/14/6/0/0	1/not available	Not available	NA NR after 1 cycle	Lost to follow-up after the first cycle

82 *F*; Female, *M*; male, NA; not applicable, *CR*; complete response, *PR*; partial response, *NR*; no response. †LSR; local skin response score. To
83 ensure uniform reporting, LSRs were assessed quantitatively using a grading scale and photographic guide images, a method similar to that used
84 in published studies with IM. The following responses were assessed on a scale that ranged from 0 to 4 (with higher numbers indicating more
85 severe reactions): swelling, vesiculation or pustulation, erosion or ulceration, flaking or scaling, crusting, and erythema. The composite LSR
86 score was defined as the sum of the 6 individual scores (maximum composite score = 24). Patients were assessed on days 1, 2, 3, and 8 and at
87 months 1 and 2. If a second cycle of IM was done, the LSR score was evaluated on days 86, 87, and 88 and at months 3 and 5.

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91 **Fig. 1** Lentigo maligna. Clinical photographs of patient 1, who failed to respond to ingenol
92 mebutate (IM) after 1 cycle despite a brisk, quick (8 days after IM) and inflammatory
93 reaction, with erosion [grade 2], and apparent effect with clearance of pigmentation.

94 * Corresponding to the site of biopsy.

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110 **Author Contributions**

111 Drs Lacour, Le Duff, and Montaudié had full access to all of the data in the study and take
112 responsibility for the integrity of the data and the accuracy of the data analysis. Concept and
113 design: Drs Lacour, Le Duff, Montaudié. Acquisition, analysis, or interpretation of data: All
114 authors. Statistical analysis: Dr Fontas et Roger. Histopathology analysis: Drs Butori and
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116 Drafting of the manuscript: Lacour and Montaudié. Critical revision of the manuscript for
117 important intellectual content: All authors. 

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