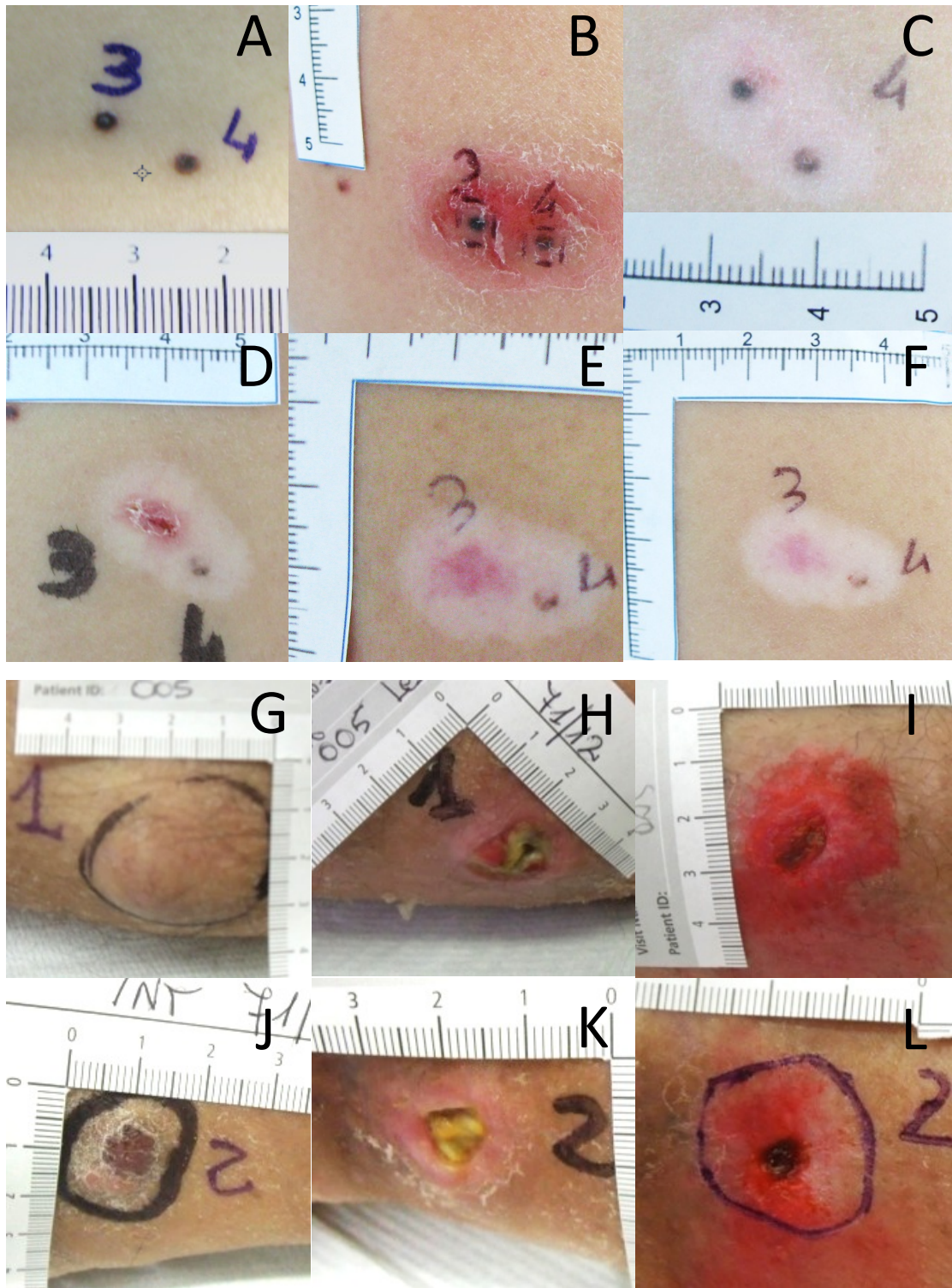


**Supplementary Table 1: Previous antineoplastic therapies**

| Patient number | Prior antitumor therapy | Treatment line | Active principle | Dose                   | Administration route | Start date | End date |
|----------------|-------------------------|----------------|------------------|------------------------|----------------------|------------|----------|
| 001            | Yes                     | 1              | NY-ESO           | NA                     | Intramuscular        | 26/03/12   | 04/06/12 |
|                |                         | 2              | Bleomycin (ECT)  | 30 mg                  | Intravenous bolus    | 24/07/12   | 24/07/12 |
|                |                         | 3              | Dacarbazine      | NA                     | Intravenous          | 02/08/12   | 02/10/12 |
| 002            | No                      |                |                  |                        |                      |            |          |
| 003            | Yes                     | 1              | Bleomycin (ECT)  | 30 mg                  | Intravenous bolus    | 01/03/12   | 01/03/12 |
| 004            | Yes                     | 1              | MAGE A3 + AS15   | 0.5 ml                 | intramuscular        | 21/06/11   | 11/07/11 |
| 005            | No                      |                |                  |                        |                      |            |          |
| 006            | Yes                     | 1              | Dacarbazine      | 1000 mg/m <sup>2</sup> | Intravenous          | 01/04/12   | 01/09/12 |
| 007            | Yes                     | 1              | Melphalan (ILP)  | 100 mg                 | Intravenous bolus    | 30/04/12   | 30/04/12 |
| 008            | No                      |                |                  |                        |                      |            |          |
| 009            | Yes                     | 1              | Dacarbazine      | 1600 mg/m <sup>2</sup> | Intravenous          | 12/09/12   | 28/12/12 |
| 010            | Yes                     | 1              | Dacarbazine      | 1000 mg/m <sup>2</sup> | Intravenous          | 05/09/12   | 27/09/12 |
|                |                         | 2              | Vemurafenib      | 960 mg b.i.d.          | Oral                 | 14/10/12   | 08/02/13 |
| 011            | No                      |                |                  |                        |                      |            |          |
| 012            | No                      |                |                  |                        |                      |            |          |
| 013            | No                      |                |                  |                        |                      |            |          |
| 014            | Yes                     | Adjuvant       | Melphalan (ILP)  | 100 mg                 | Intravenous drip     | 07/03/12   | 07/03/12 |
| 015            | Yes                     | Adjuvant       | IFN              | High-dose              | Intravenous          | 26/08/13   | 09/10/13 |
| 016            | No                      |                |                  |                        |                      |            |          |
| 017            | Yes                     | Adjuvant       | IFN              | 3 MIU                  | Intravenous          | 01/04/00   | 01/10/01 |
|                |                         | 1              | Dacarbazine      | 800 mg/m <sup>2</sup>  | Intravenous          | 17/10/06   | 13/11/06 |
|                |                         | 1              | Thymosine        | 3.2 mg                 | Subcutaneous         | 17/10/06   | 13/11/06 |
|                |                         | 2              | Ipilimumab       | 10 mg/kg               | Intravenous          | 10/01/07   | 21/02/07 |
| 018            | Yes                     | 1              | Bleomycin (ECT)  | 27 mg                  | Intravenous bolus    | 24/09/13   | 24/09/13 |
| 019            | No                      |                |                  |                        |                      |            |          |
| 020            | Yes                     | Adjuvant       | Anti-BCG         | NA                     | Subcutaneous         | 01/08/10   | 12/08/10 |
| 021            | No                      |                |                  |                        |                      |            |          |
| 901            | Yes                     | Adjuvant       | IFN              | NA                     | Subcutaneous         | 01/12/12   | 01/11/13 |

NA = Not available; ECT = Electrochemotherapy; ILP = Isolated limb perfusion; IFN = Interferon; b.i.d. = twice a day

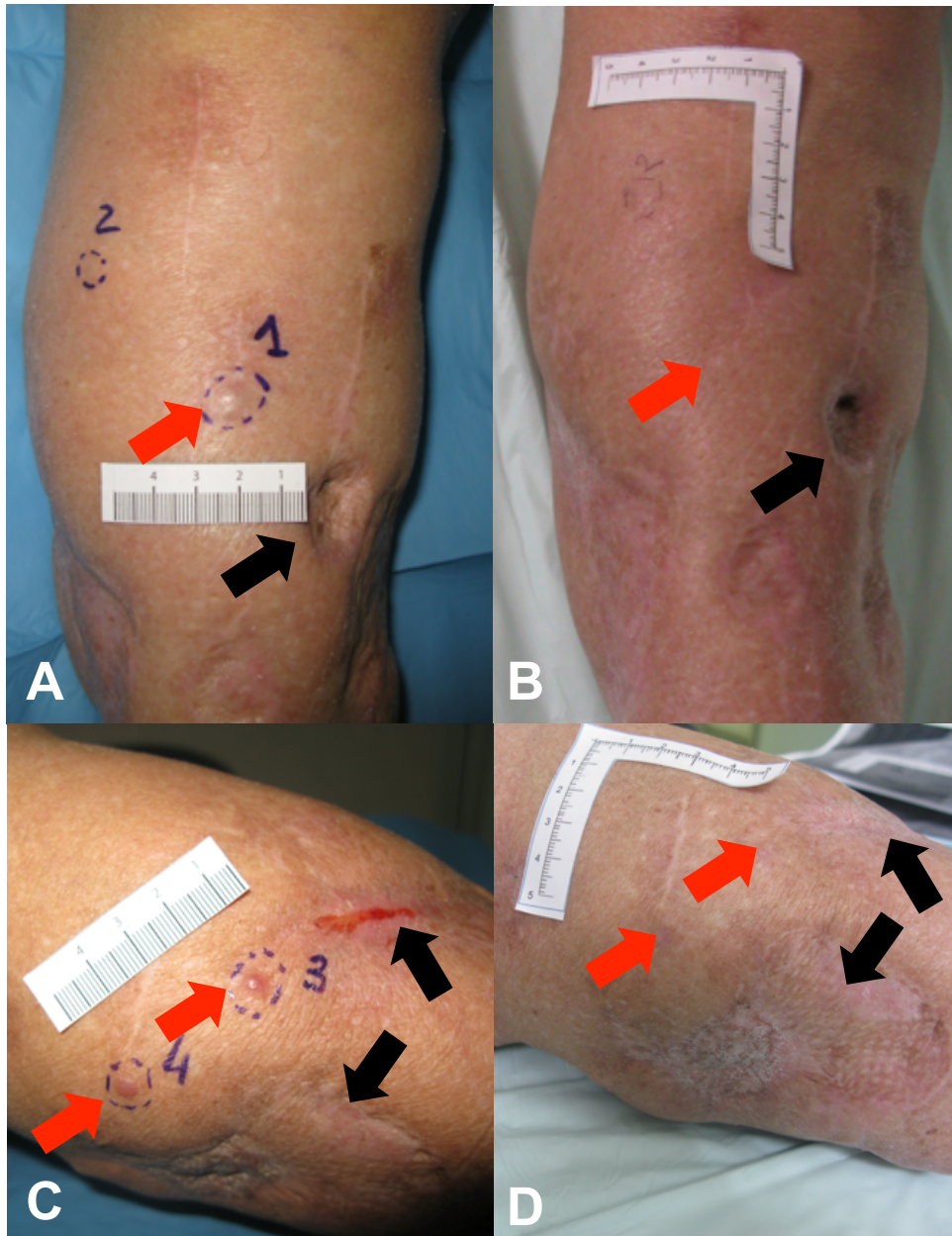


Supplementary Figure 1.

***Supplementary Figure 1. Examples of responses of injected cutaneous/subcutaneous metastases.***

**A to F.** Two cutaneous lesions present at baseline (**A**) in this patient (patient 23.003.S.005) were injected with L19-IL2/L19-TNF. After last injection (day 22) the injected area appears erythematous and lesions less surelevated (**B**). At tumor assessment 2 at week 12 (day 85), lesions appear reduced in size and surrounded by a vitiligo-like, discoloured skin area (**C**). At tumor assessment 3 (week 24, day 168) a crusty scar is visible in the place of lesion 3 (**D**). At the following assessment (week 36) and at follow-up 1 (week 52), lesion 3 has disappeared while lesion 4 has become not measurable, leaving behind a hyperpigmented rim (**E** and **F**).

**G to L.** Two large subcutaneous lesions present at baseline in patient 14.004.S.008 (**G** and **J**) were treated with the immunocytokine combination. After 6 weeks, both lesions appeared necrotic and ulcerated (**H** and **K**). At tumor assessment 2 (week 12, day 85), lesions appear to have considerably shrunk (**I** and **L**). Three weeks later, the patient underwent surgical resection of the residual measurable lesion (lesion 1) and was withdrawn from the study because considered NED.



Supplementary Figure 2.

*Supplementary Figure 2. Comparison between intralesional treatment with L19IL2/L19TNF and surgery.*

**A and C.** Two patients with cutaneous metastases at baseline (red arrows), who had previously received surgical exeresis of several other skin lesions (black arrows), were treated with L19IL2/L19TNF as per protocol. At tumor assessment at week 12, all treated lesions appeared to have disappeared leaving behind little scars (**B and D**). The immunocytokine treatment is less disfiguring than surgery, with better cosmetic results and no margin problems, thus improving patient's quality of life.