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### **Hormone-immunotherapy in endocrine dependent metastatic breast cancer patients**

**H**ormone therapy is advised for ER+ metastatic breast cancer patients due to its efficacy concomitant with low toxicity. However, in most patients the occurrence of resistance is a not well yet understood hurdle to overcome. In these patients, during clinical benefit (CB) from conventional anti-estrogens, the addition of cycles of sequential immunotherapy could prolong the benefit and delay the arising of acquired hormone resistance. In order to validate this hypothesis, in 1992 we started an open exploratory clinical trial. Forty-two of these patients in CB during first line anti-estrogen salvage therapy also received beta-interferon (INF-beta) 3,000,000 IU i.m./day 3 days/week, weeks 1-4 and successively recombinant interleukin-2 (IL-2) 3,000,000 IU s.c./day 3 days/week, weeks 5-8 until progression. The immunotherapy cycle lasted 10 weeks and the patient continued anti-estrogen alone during weeks 9-10, the 11<sup>th</sup> week being the first week of the successive cycle. At each control visit, routine laboratory examinations and serum measurement of a CEA-TPA-CA15.3 tumor marker (TM) panel were carried out, and an immunological assessment was made (total lymphocytes, CD4+, CD8+, NK cells, T-reg, IL-6, IL-10, IL-12, TNF $\alpha$ , TGF $\beta$ 1 and IFN-gamma.) The addition of INF-beta-IL-2 sequence significantly prolonged clinical benefit and overall survival from conventional antiestrogens. During CB as opposed to progression, a significant immune stimulation was observed. During CB also a significant CEA, TPA, CA15.3 decrease occurred 24–72 h after interleukin-2 administration. At the progression a significant increase for CEA and for all 3 markers (standardized values) was found 24–72 h after interleukin-2 administration. In patients who survived less than 5 years, the Treg cell increase occurred at a significantly shorter time interval than in those who survived longer than 5 years (20 vs 45.5 months, respectively;  $P = 0.001$ ). To further confirm these promising results a multicenter prospective phase II trial is going to be launched by the Cancer Center Institute of Tuscany in Italy.

### **Biography**

Andrea Nicolini graduated (summa cum laude) at School of Medicine, University of Pisa in 1974. He received postgraduate diplomas at University of Pisa in Internal Medicine (1980), Pneumology (1984), and Nuclear Medicine (1986). His research interests include breast and gastrointestinal cancer and their metastases, tumour markers, post-operative follow-up, physiopathology, immunology and immunotherapy of cancer, and thyroid tumours.

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