Interferon (IFN)-γ is the uppermost cytokine implicated in the immune system’s fight against cancer. With its cytostatic, pro-apoptotic and immune-provoking effects, IFN-γ plays a central role in the recognition and elimination of transformed cells. To protect the normal tissues from collateral damage and to facilitate the re-establishment of homeostasis, many regulatory pathways are as well induced by IFN-γ. Nevertheless, once the tumor cells adapt to survive despite the immune responses, they take the advantage of IFN-γ as an inducer of regulatory molecules such as PD-L1, PD-L2, FasL, CEACAM1, reactive oxygen species (ROS) and nitric oxide (NO), and indoleamine 2,3-dioxygenase (IDO). Under the influence of tumor-derived factors, the cells of myeloid origin including myeloid-derived suppressor cells (MDSCs) are also licensed by IFN-γ to perform regulatory actions. Today, evidence is accumulating on the immunomodulatory functions of IFN-γ in cancer, creating an alternative story to be told.