From a historical point of view, treatment of neoplastic disease can be considered one of the clearest examples of the importance of combination strategies. In fact, a combination of surgery, radiotherapy and chemotherapy, is the best approach for the treatment of certain cancers such as breast cancer, ovarian and head and neck cancer.

However, not only cancer may benefit from combination therapy. Tuberculosis is a classical example of this concept [1]. After the discovery of Streptomycin in 1944, a new era for the treatment of tuberculosis dawned with further detection of Isoniazid, the first oral mycobactericidal drug in 1952 and Rifamycins in 1957. Sanatoria closed and truly effective public health measures became possible. Treatment was also increasingly expanded to include those with latent tuberculous infections. Furthermore, the introduction of Rifampicin in 1970 revolutionized the treatment of tuberculosis as, with its use in the context of combination strategies, the therapy of this infectious disease changed. In fact, use of antituberculosis drugs in monotherapy, including those of first choice, is strictly proscribed, since it might be easy to select spontaneously resistant germs. For this reason, drug regimens include associations of 3 or more drugs, variously alternated in relation to the clinical and developmental stages of tuberculosis (Table 1). Another aim of using drugs in combination was to eliminate bacterial subpopulations in various stages of metabolic activity and at different locations.

In the era of targeted therapy and development of novel therapies, the most important example in the context of combination therapies is Human Immunodeficiency Virus Syndrome (HIV). In fact, the discovery of several classes of drugs that act at different levels of the HIV virus, has caused a dramatic change in the prognosis of these patients. With the Highly Active Anti Retroviral Therapy (HAART), the famous drug cocktail, the definition of this disease has changed from incurable to a chronic illness [2].

From a historical point of view, the introduction of target agents trastuzumab in 1998 and imatinib in 2001 led to the era of targeted therapy in oncology. More than 10 years have since passed and more and more innovative treatment details have been reached. Ipilimumab is a further example of what has been said. The use of a target agent that, through an indirect action on the immune system, shows antineoplastic activity against cancers such as melanoma, prostate cancer and NSCLC, was not even imaginable a few years ago. In March of this year FDA approved the ipilimumab in the treatment of advanced melanoma and in June it was published the positive results of the combination dacarbazine + ipilimumab as first line treatment of advanced melanoma [3]. This could be considered the start of the combination approach in melanoma therapy.

The failure of first approaches to vaccine therapy [4] and the controversial role of interferon in some cancers (melanoma and renal cancer cell) have made the world of oncology skeptical about immunotherapy. The year 2010, from this point of view, has been a fantastic year. In fact, this was the year in which the first vaccine therapy showed effectiveness in oncology: Sepueleucel-T in the treatment of prostate cancer (the first anti-cancer vaccine which received FDA approval) [5]. Furthermore, the first phase III study demonstrated a survival advantage in malignant melanoma through the use of ipilimumab, even if second line [6]. Moreover, year 2010 brought news not only in the field of immunotherapy. Vemurafinib (well known as PLX4032), or the specific inhibitor of BRAF V600E in the mutated form, was another important achievement in the field of oncology [7]. In fact, considering that 50% of patients with melanoma has V600E mutation in BRAF protein, resulting in a proliferation signal always active, having found an agent that could inhibit the activity of this kinase could be the beginning of a new era for the treatment of melanoma.

For several years, sorafenib, a multi-kinase inhibitor, kindled hopes of a breakthrough in the treatment of melanoma. The phase II study published by Flaherty [8] showed a median progression free survival (PFS) of 8.8 months in combination with carboplatin and paclitaxel compared with 1.7 months for historical controls [9]. Unfortunately, subsequent phase II–III studies have not confirmed the initial data of the study of Flaherty [10–12]. However, considering the positive

### Table 1: Adapted from Treatment of tuberculosis: guidelines for national programmes. Fourth edition. World Health Organization. http://www.who.int/tb/features_archive/new_treatment_guidelines_may2010/en/index.html

| Drug used in Standard regimens for new TB patients | Intensive phase treatment | Continuation phase |
|---------------------------------------------------|--------------------------|-------------------|
| (presumed, or known, to have drug-susceptible TB) | 2 months | 4 months |
| HRZE regimen | HR regimen |
| Isoniazid (H) | Isoniazid (H) |
| Rifampicin (R) | Rifampicin (R) |
| Pyrazinamide (Z) | |
| Ethambutol (E) | |
| streptomycin | |
| In tuberculous meningitis, ethambutol should be replaced by streptomycin. | |
| (in settings where the level of isoniazid resistance among new TB cases is high and isoniazid susceptibility testing is not done) | |
| (or results are not available) before the continuation phase begins | |
| Intensive phase treatment | Continuation phase |
| 2 months | 4 months |
| HRZE regimen | HRE regimen |
| isoniazid | isoniazid |
| rifampicin | rifampicin |
| pyrazinamide | ethambutol |
| Ethambutol | |

Corresponding author: Paolo Antonio Ascierto, Unit of Medical Oncology and Innovative Therapies, Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione “G. Pascale”, Napoli, Italy. E-mail: paolo.ascierto@gmail.com

Received August 24, 2011; Accepted August 05, 2011; Published August 07, 2011

Citation: Ascierto PA (2011) The Future of Melanoma Therapy is the Combination Approach. J Mol Biomark Diagn 2:102e. doi:10.4172/2155-9929.1000102e

Copyright: © 2011 ASCIERTO PA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
example of melanoma. In fact, after 30 years of disappointments and almost non-existent care, this disease has been going through a plethora of treatment possibilities (Table 2). Ipilimumab and vemurafinib represent the starting point for more effective melanoma treatment. Considering the currently available drugs with activity against melanoma, it would be desirable to somehow repeat what happened in the treatment of HIV with HAART. In fact, we should learn from the HAART, a combination of three or four different antiretroviral drugs (reverse transcriptase and protease inhibitors) often referred to as “drug cocktail”, used to treat patients with HIV infection (see Table 3A-B). HAART inhibits HIV replication, keeps the HIV offspring low and reduces the chances of HIV mutation because each drug attacks HIV through a different mechanism. A similar approach for the therapy of melanoma using drugs with different mechanisms of action, for example on MAPK pathway, P313-mTOR pathway, apoptosis pathway and immunological monoclonal antibodies, could be considered. A multi-target therapy could combine novel agents with standard therapy (Dacarbazine, Temozolomide, other chemotherapeutic agents). Sequential administration of different agents may inhibit cancer cell growth at different check points, while other agents may inhibit neoangiogenesis, survival of malignant cells or metastatization, converting melanoma into a chronic disease [14,15].

Possibly, it would be better to interfere simultaneously on various pathways involved in melanoma progression. Comparing the number of path ways to parallel electric circuits, it is unlikely that single on off switch will be sufficient. It is likely that several triggers may constitutively activate different and complex processes which could then give different characteristics to the malignant cell [14,15].

Melanoma can become a model in cancer therapy. Today we have these two drugs (ipilimumab and vemurafinib) that have different characteristics and effectiveness, one (vemurafinib) that acts immediately, with a median latency of 6-7 months before developing resistance, the other (ipilimumab) with a slower (months) but more lasting (years) action. The first step is, of course, the combination of these two agents, but the real challenge is to bypass the mechanisms of resistance and improve the effectiveness of ipilimumab. In addition, we need to identify combined approaches for those patients (representing another 50%) who do not have the BRAF mutation. New molecular studies will certainly give us some important news for this subset of patients.

The toxicity will surely be a high price to pay. In fact, it is known that the combination of different compounds can amplify the side effects of every single drugs. The HAART is an example of toxicity from the combination of several drugs [16]. However, this could be the price for turning melanoma from an incurable disease into a manageable disease.

In the past year, Dr Donald Morton from the John Wayne Cancer Institute of Santa Monica (USA) had sentenced that surgery was the watchword was "Surgery, surgery, surgery". I think that it's started a new era with a new watchword: “Combine, combine, combine”.

**References**

1. Daniel TM (2006) The history of tuberculosis. Resp Med 100: 1862–1870.
2. Montaner JS, Lima VD, Banrios R, Yip B, Wood E, et al. (2010) Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet 376: 532–539.
3. Robert C, Thomas L, Bondarenko I, O’Day S, M D JW, et al. (2011) Ipilimumab
plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 364: 2517-2526.

4. Eggermont AM (2009) Immunostimulation versus immunosuppression after multiple vaccinations: the woes of therapeutic vaccine development. Clin Cancer Res 15:6745-6747.

5. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, et al. (2010) IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363: 411-422.

6. Hodi FS, O’Day SJ, McDermott DF, Weber RW, Sosman JA, et al. (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363: 711-723.

7. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, et al. (2010) Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809-819.

8. Flaherty KT, Schiller J, Schuchter LM, Liu G, Tuveson DA, et al. (2008) A phase I trial of the oral, multikinase inhibitor sorafenib in combination with carboplatin and paclitaxel. Clin Cancer Res 14: 4838-4842.

9. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, et al. (2008) Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 26: 527-534.

10. McDermott DF, Sosman JA, Gonzalez R, Hodi FS, Linette GP, et al. (2008) Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group. J Clin Oncol 26: 2178-2185.

11. Hauschild A, Agarwala SS, Trefzer U, Hogg D, Robert C, et al. (2009) Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. J Clin Oncol 27: 2823-2830.

12. Phase III Trial of Nexavar® in Chemotherapy-Naive Patients with Advanced Melanoma Does Not Meet Primary Endpoint. Study stopped based on interim analysis (2009) http://viva.vita.bayerhealthcare.com/scripts/pages/en/press/news_details_page.php/13136/2009-0198?print=1&print=1. 4-27.

13. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, et al. (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364: 2507-2516.

14. Ascierto PA, Streicher HZ, Sznol M (2010) Melanoma: a model for testing new agents in combination therapies. J Transl Med 8: 38.

15. Ascierto PA, Marincola FM (2011) Combination therapy: the next opportunity and challenge of medicine. J Transl Med 9:115.

16. Liu X, Ma Q, Zhang F (2010) Therapeutic drug monitoring in highly active antiretroviral therapy. Expert Opin Drug Saf 9:743-758.