Highlights in Oncology in 2010

J. De Grève, L. Duck, J. Vermorken, T. Feys, selected jointly by the board of the BSMO and the BJMO

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Advanced melanoma

Ipilimumab improves survival

Metastatic melanoma has a dismal prognosis, with current therapies only having palliative, but no life prolonging effects. In a phase III study, it was shown that ipilimumab, which blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) allowing an antitumour T-cell response, administered with or without a glycoprotein 100 (gp100) peptide vaccine improves survival compared to the vaccine alone.[1] The vaccine alone had no impact. The median overall survival was 10.0 months among patients receiving ipilimumab compared to 6.4 months among patients receiving no ipilimumab (hazard ratio (HR) for death 0.68; $p<0.001$) (*Figure 1*). The survival benefit is remarkably large compared to the objective response rate of only 10%. Classical criteria for assign response probably need to be adapted for immunological treatments as, among others, the interval between treatment initiation and response might be long. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment (including corticosteroids). Grade 3 or 4 immune-related adverse events occurred in 10-15% of patients treated with ipilimumab. These are mainly auto-immune effects in the skin, colon and pituitary gland. In contrast to ipilimumab, recombinant interleukin (rhIL)-2 has not been proven to improve survival, despite induction of remissions.[1]

BRAF targeting

Forty percent of melanoma carries an activating mutation known as V600E in the BRAF gene, encoding a serine-threonine kinase. One of the small molecules targeting BRAF, PLX4032, is highly active in metastatic melanoma carrying such mutations. No less than a cumulated 37/48 patients (77%) with such a mutation in their tumor achieved an objective response, including some complete responses (CR) and with a progression-free survival (PFS) of more than 7 months.[2] Future progress may reside in exploring combined ipilimumab and BRAF targeting.

Lung cancer

EML-Alk fusion targeting

Targeted therapies have altered the clinical practice of advanced lung cancer treatment. Inhibitors (gefitinib and erlotinib) targeting the epidermal growth factor receptor (EGFR) have a major impact in patients whose lung cancer carries a mutant EGFR and have become standard first or second line treatment for such patients. An even smaller proportion (2-7%) of all lung cancers (with a similar phenotype as EGFR mutant lung cancer) has a chromosomal rearrangement leading to an activated ALK kinase. Crizotinib, a specific ALK inhibitor, produced dramatic response rates in such patients (*Figure 2*, page

Authors: J. De Grève, MD PhD, Department of Medical Oncology, Oncologisch Centrum, UZ Brussel, L. Duck, MD PhD, Department of Internal Medicine, Onco-Hematology Unit Clinique St-Pierre, Ottignies, J. Vermorken, MD PhD, Antwerp University Hospital, Department of Oncology, Edegem, Belgium, T. Feys, Ariez Medical Publishing, Amsterdam.

Please send all correspondence to: J. De Grève, Oncologisch Centrum UZ Brussel, Department of Medical Oncology, Laarbeeklaan 101, 1090 Brussels, Belgium, E-mail: jacques.degreve@uzbrussel.be

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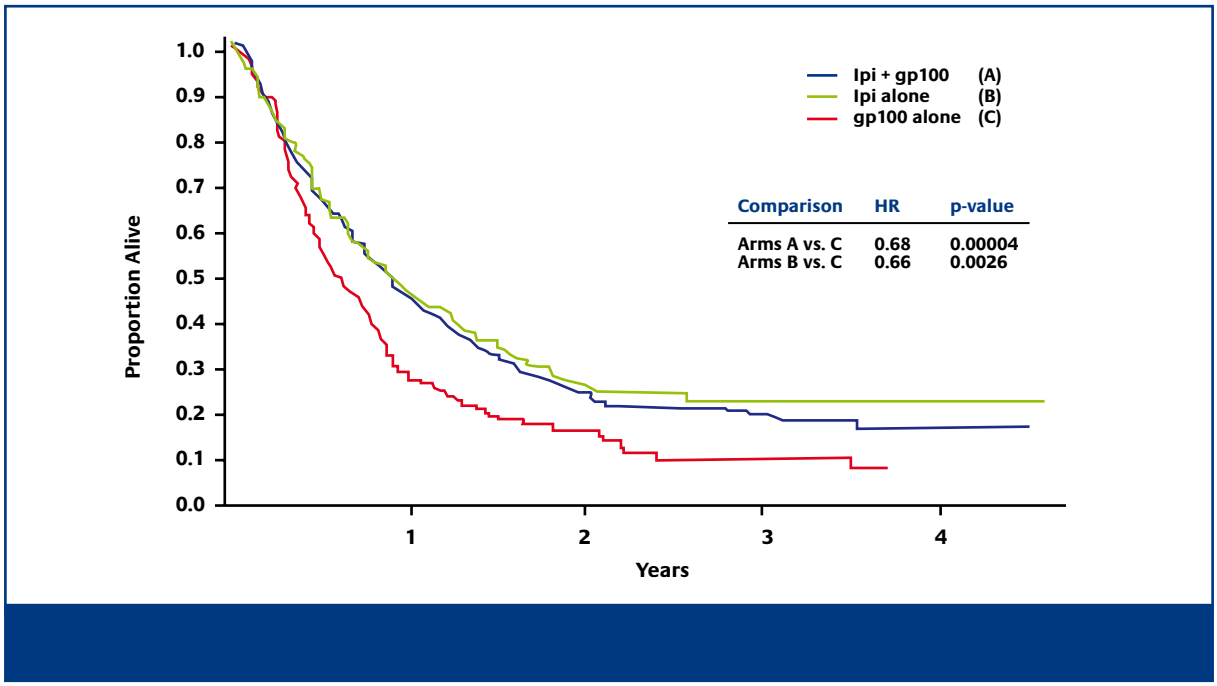

Figure 1. Overal survival analysis (Kaplan-Meier analysis) in melanoma patients treated with ipilimumab, gp100 or the combination.[1]

40). The overall response rate was 57%, including a rare CR, and the estimated probability of 6-month PFS was 72%, with no median for the study reached. The drug resulted in only grade 1 or 2 (mild) gastrointestinal side effects.

Elderly patients (>70 years)

Elderly patients with advanced lung cancer are often considered too frail for receiving standard chemotherapy used in younger patients. As a consequence many clinicians use only single-agent chemotherapy. A French phase III clinical trial in patients aged 70-89 however indicates that doublet chemotherapy leads to a significant superior survival (10.3 versus 6.2 months) compared to single agent gemcitabine or vinorelbine (*Figure 3*, page 40). The toxicity is increased, but acceptable.[4] A major conclusion is that, also in lung cancer, treatment proposals should not be driven by age alone, but only by co-morbidities and patient preferences.

Breast cancer: HER2 targeting

Current targeting of oncogene products only partially shuts down the oncogenic activity of the targets. The same is true for HER2 targeted with trastuzumab. At the last San Antonio Breast Cancer Symposium (SABCS) impressive results were shown with dual targeting by adding either pertuzumab or lapatinib to trastuzumab leading to doubling of response rates.[5,6] Both combinations have differential toxicities that might influence their respective use in the future.[5,6] The expense of combining these drugs will also have to be addressed.

Prostate cancer

For prostate cancer patients progressing after docetaxel-based chemotherapy for hormone-refractory prostate cancer, two new treatments emerged.

In the TROPIC trial, patients with ECOG performance status 0-2, progressing during or after docetaxel (cumulative dose ≥225 mg/m^2) were randomized to receive 10 mg/day of prednisone with either 3-weekly mitoxantrone 12 mg/m^2 or cabazitaxel 25 mg/m^2. In the primary analysis based on the intent to treat population, patients receiving cabazitaxel demonstrated a statistically significantly longer overall survival (OS) com-

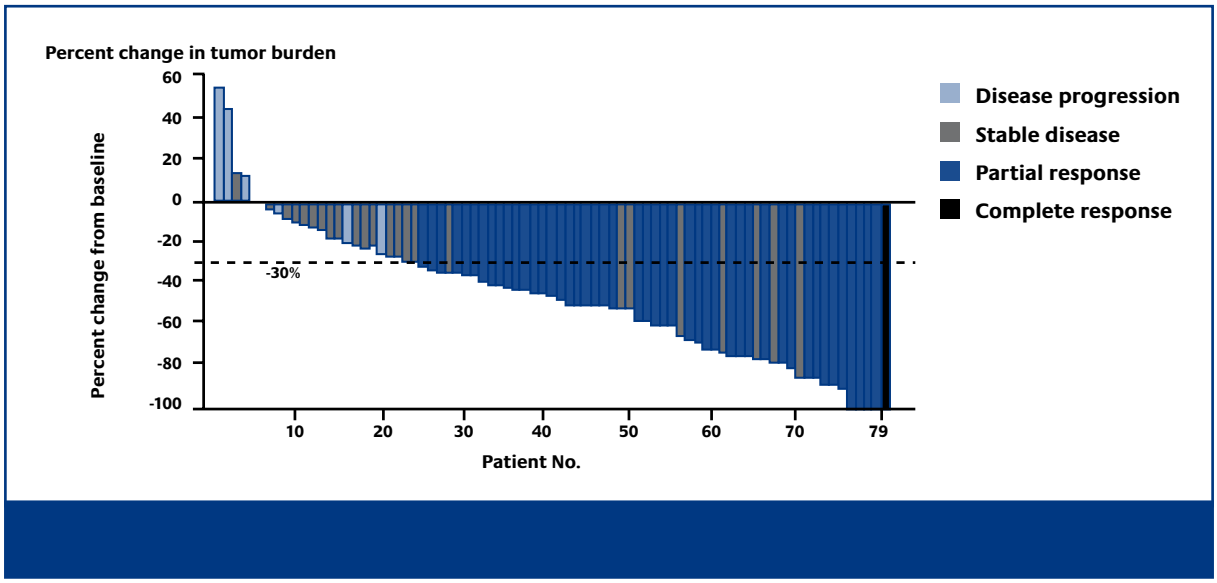

Figure 2. Overall response of lung cancer patients with an ALK kinase activating chromosomal rearrangement to crizotinib.

pared to mitoxantrone (HR 0.70; 95% CI 0.59-0.83; p<0.0001).[7] The median survival in the cabazitaxel group was 15.1 months compared to 12.7 months in the mitoxantrone group. The most frequent grade 3/4 toxicity was neutropenia observed in 81.7% of patients treated with cabazitaxel and 58.0% treated with mitoxantrone. Rates of febrile neutropenia were 7.5% and 1.3%, respectively.[7]

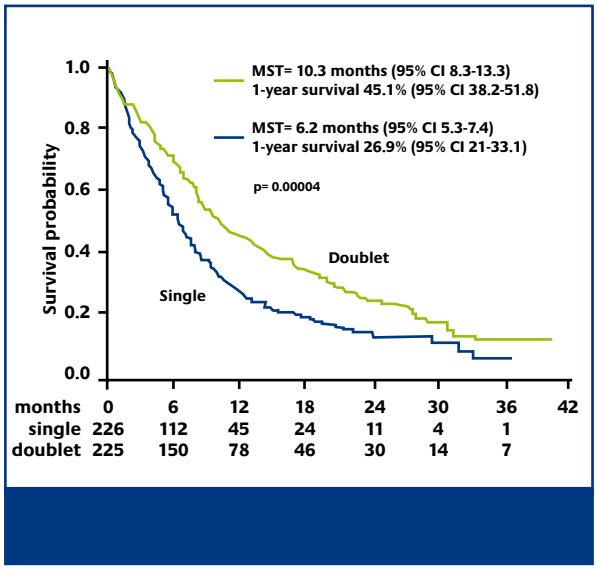

Figure 3. Overall survival data in elderly lung cancer patients (ITT population) treated with doublet chemotherapy or single agent gemcitabine or vinorelbine. MST=median survival time.

In a second phase III placebo-controlled trial 1,195 docetaxel pretreated patients were randomized 2:1 to abiraterone acetate (1,000 mg) plus low dose prednisone (n=797) versus placebo plus prednisone (n=398). An impressive 4 months gain in OS was shown with the addition of abiraterone (10.9 months versus 14.8 months, HR 0.65; p<0.0001), in this usually poor prognosis population.[8] Abiraterone acetate is a selective androgen biosynthesis inhibitor that acts by blocking CYP17 and potently inhibits persistent androgen synthesis from adrenal and intratumoral (autocrine/paracrine) sources. Mineralocorticoid-related adverse events (fluid retention, hypokalemia) were more frequent in the abiraterone arm.[8]

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