What is new in melanoma after European Cancer Congress 2017?

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The recent European Cancer Congress (ECCO 2017, Amsterdam, The Netherlands) focused mainly on oncopolicy and the results from possibly practice changing trials.

The incidence of melanoma is still increasing worldwide and the number of patients dying from metastatic disease continues to rise [1]. Moreover, because of aging and increasing population, the age of death with melanoma will steadily increase; with predictions assuming that the numbers of melanoma deaths will keep increasing until 2030–2035 above levels suggested by changes in age-adjusted rates [1]. Surgery still is the cornerstone of treatment for patients with stage II and III melanoma, but recent developments in targeted therapy and immunotherapy, which significantly changed the landscape of melanoma therapy in metastatic setting, give hope for effective adjuvant and neoadjuvant treatment in high risk loco-regionally advanced disease [2–5].

Neoadjuvant treatment

Neoadjuvant therapy has been attributed to several potential clinical benefits such as facilitating resectability, decreasing surgical morbidity, providing better local control, prevention of micrometastases, personalization of adjuvant therapy based on the response

to pre-operative therapy and opportunity for evaluation of mechanism of action and resistance to the drugs (by collection of biospecimens). A significant number of presentations and discussions during ECCO 2017 discussed the key topic of neoadjuvant therapy of locally advanced melanomas. These included, but were not limited to, promising preliminary results of trials with BRAF and MEK inhibitors as well as immunotherapies. The summary of these initial results is shown in [Table 1](#).

Dr John Haanen (Netherlands Cancer Institute, The Netherlands) presented preliminary results of Reductor trial (Cytoreductive Treatment of Dabrafenib Combined with Trametinib to Allow Complete Surgical Resection in Patients with *BRAF* Mutated, Prior Unresectable Stage III or IV Melanoma; Registered in the Dutch Trial Register NTR4654) on 13 patients with initially unresectable or bulky disease (with high chance of positive margins) *BRAF*-positive stage IIIC melanoma [6]. Patients were treated with dabrafenib and trametinib for 8 weeks; 11 patients underwent surgery (lymph node dissection) with 9 R0 resections achieved. Of these 9 patients (with a median follow-up of 9 months; range 3–22 months), 6 patients recurred, and three remain disease-free.

KEYWORDS

- adjuvant • anti-CTLA-4
- anti-PD-1 • BRAF inhibitor
- immunotherapy • MEK inhibitor • melanoma
- metastases • neoadjuvant

Table 1. Preliminary results of trials with neoadjuvant therapy in loco-regionally advanced melanoma.

Study (presenter)	Number of patients and study population	Pre-operative therapy	Percentage of radical resections, responses	Reported trial outcomes, recurrences	Ref.
Reductor trial (Haanen <i>et al.</i>)	13 patients with stage IIIC, <i>BRAF</i> V600E/K mutated, bulky, irresectable or with high probability R+ resection nodal metastases	Dabrafenib + trametinib for 8 weeks pre-operatively	9 R0 resections (69%), 2 progressions during pre-operative treatment	6 of 9 patients recurred (with 9 months follow-up), 4 recurrences managed by surgery	[6]
Long <i>et al.</i>	30 patients with <i>BRAF</i> -mutated stage III bulky disease resectable melanoma	Dabrafenib + trametinib for 12 weeks pre-operatively and post-operatively up to 52 weeks	Pathological and PET-FDG metabolic complete response in 50%, no progressions during pre-operative treatment	9 patients (30%) recurred during follow-up with median time to recurrence 51 weeks	[7]
Amaria <i>et al.</i>	21 patients with locally advanced <i>BRAF</i> -mutated resectable stage IIIC melanoma	14 patients treated with neoadjuvant (8 weeks) and adjuvant (44 weeks) dabrafenib and trametinib vs 7 patients with standard upfront surgery	In 12 assessed patients after neoadjuvant therapy – 7 complete pathological responses (pCR; 58%), 77% RECIST response rate during neoadjuvant therapy, no RECIST disease progressions	Neo-/adjuvant therapy significantly improved relapse-free survival over upfront standard surgery arm ($p < 0.0001$), HR 62.5 (95% CI: 6.9–8302), patients with pCR had improved relapse-free survival as compared with those without pCR ($p = 0.04$)	[8]
OpACIN trial (Blank <i>et al.</i>)	10 patients with stage IIIC locally advanced melanoma in neo-adjuvant arm	Pre-operative immunotherapy with two cycles of ipilimumab + nivolumab with next two cycles post-operatively; 2nd arm with adjuvant therapy only	80% response rate	Very high percentage of grade 3–4 adverse events	[9]

HR: Hazard ratio.

Professor Georgina Long (University of Sydney, Australia) presented results of trial with neoadjuvant and adjuvant dabrafenib + trametinib combination in *BRAF*-mutated stage III bulky disease resectable melanoma patients, who were treated pre-operatively for 12 weeks and post-operatively up to 52 weeks (Neoadjuvant dabrafenib + trametinib for AJCC Stage IIIB–C *BRAF* V600 mutation-positive melanoma; NCT01972347) [7]. In the 30 assessed patients, after 12 weeks of therapy, pathological and PET-FDG metabolic complete response was achieved in 50%. Disease recurrences were observed in 9 patients (30%) during median follow-up time of 51 weeks.

Long also presented the design for a neoadjuvant sequencing study with three arms: pre-operative BRAF + MEK inhibitors followed by anti-PD-1 therapy pre- and post-operatively; combination of BRAF + MEK inhibitors + anti-PD-1 pembrolizumab therapy simultaneously pre- and

post-operatively; and anti-PD-1 monotherapy pre- and post-operatively.

Dr Rodabe Amaria (MD Anderson, TX, USA) discussed the trial with neoadjuvant (8 weeks) + adjuvant (44 weeks) therapy with dabrafenib and trametinib versus standard upfront surgery (Neoadjuvant and Adjuvant Dabrafenib and Trametinib in Patients with Clinical Stage III Melanoma [Combi-Neo]; NCT02231775) [8]. In 21 patients, neoadjuvant and adjuvant dabrafenib/trametinib (14 patients) significantly improved relapse-free survival over standard arm (7 patients; $p < 0.0001$). Among 12 patients assessed following pre-operative therapy, complete pathological response was observed (58%) in seven. The OpACIN trial (Study to Identify the Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab in Resectable Stage III Melanoma Patients; NCT02437279) with neoadjuvant and adjuvant combined immunotherapy (ipilimumab

+ nivolumab) was also mentioned, where 10 patients analyzed, presented with an overall response rate of 80% though this was accompanied by high toxicity [9]. A OPACIN-NEO trial with three arms of neoadjuvant combination of ipilimumab and nivolumab at different doses is being planned as a follow-up trial.

Adjuvant therapy

One of the most important issues were the discussions on the long-term results of European Organization for Research and Treatment of Cancer (EORTC) 18071 trial with adjuvant ipilimumab versus placebo after complete lymph node dissection in stage III melanoma (Efficacy Study of Ipilimumab vs Placebo to Prevent Recurrence After Complete Resection of High Risk Stage III Melanoma; NCT00636168) [10]. The final results of this first trial that used immune-checkpoint inhibitor after radical lymphadenectomy showed significant increase compared with placebo both in recurrence-free survival and overall survival (OS; 5-year RFS rates 40.8 vs 30.3%, hazard ratio [HR] 0.76 and 5-year OS rates 65.4 vs 54.4%; HR: 0.72, respectively) [10]. Clear benefits of a reduced risk of death with the use of adjuvant ipilimumab may be controversial taking into account significant adverse event rates that resulted. In fact, only 42% of patients received more than four doses of ipilimumab and grade 3–4 immune-related adverse events occurred in 41.6% of patients treated with ipilimumab as compared with 2.7% in placebo arm. Moreover, 5 patients (1.1%) died due to immune-related adverse events [10]. Nevertheless, recently published additional data on health-related quality-of-life demonstrated that despite increased toxicity, especially during the induction phase of ipilimumab administration, overall health-related quality of life, measured by the EORTC QLQ-C30, was similar between ipilimumab- and placebo-treated groups, and no clinically relevant differences in global health status scores were observed during or after induction [11].

The ‘hot debates’ concerned the ipilimumab duration of treatment and dosage and as well as patients’ selection. Ongoing trials with targeted therapy and anti-PD-1 drugs may redefine the adjuvant therapy landscape within the next 2–3 years.

Immunotherapy in metastatic disease

The survival of advanced unresectable metastatic melanoma has been greatly improved within the

last few years, which can be related to the introduction of two different therapeutic strategies: targeted therapy with BRAF and MEK inhibitors and immune checkpoint inhibitors with antibodies against CTLA-4 and PD-1. An Australian group of researchers presented data of 2-year survival of all advanced melanoma patients treated with ipilimumab (any line of therapy) in Australia in the period 2013–2014 [12]. Among 910 analyzed patients two years after treatment, 24% of patients (218) were alive, 52.3% were confirmed dead and the others were lost for follow-up. These results are important in terms of clinical outcomes of ipilimumab therapy, because they confirm the positive results from previous clinical trials [12]. Similarly, European researchers presented data from EURO-VOYAGE study on effectiveness and safety of ipilimumab administered during an expanded access program in 1043 patients with advanced melanoma after failure of at least one line of therapy [13]. With a median follow-up time of 4.5 years, 3- and 4-year OS rates were measured at 11 and 8%, respectively. 12% of patients experienced severe or life-threatening treatment-related colitis/diarrhea [13]. The important studies presented during ECCO 2017 regarded the efficacy of anti-PD-1 immunotherapy in subgroups of patients with poorer prognoses; analysis of the pivotal KEYNOTE-006 trial with pembrolizumab versus ipilimumab focused on the outcomes of patients with elevated baseline lactate dehydrogenase (LDH) levels [14]. Progression-free survival (PFS) was more favorable for pembrolizumab in patients with normal LDH (median 7.0 vs 2.9 months) and in patients with elevated LDH (median 2.8 vs 2.5 months) compared with ipilimumab. OS was also improved in both the normal (median not reached in either group) and elevated LDH groups (median 14.7 vs 6.2 months) treated with pembrolizumab, but generally survival in the increased LDH group (especially more than 2× upper limit norms) on anti-PD-1 monotherapy was unsatisfactory. The other analysis regarded patients with advanced mucosal melanoma, who received pembrolizumab in three studies KEYNOTE-001 (NCT01295827), KEYNOTE-002 (NCT01704287) and KEYNOTE-006 (NCT01866319) [15]. They had achieved a median PFS of 2.8 months and median OS of 11.3 months, worse than for nonmucosal melanoma patients, despite the activity of anti-PD-1 observed in this subgroup of patients. It can be viewed in the light of recently published pooled analysis of mucosal melanoma patients

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treated in clinical studies with nivolumab monotherapy (n = 86) and nivolumab combined with ipilimumab (n = 35) [16]. In patients who received nivolumab monotherapy, median PFS was 3 months (95% confidence interval [CI], 2.2–5.4 months) for mucosal melanoma and 6.2 months (95% CI: 5.1–7.5 months) for cutaneous melanoma, and objective response rates were also lower for mucosal origin melanomas (23.3%) than for melanomas originating from skin (40.9%). Median PFS in patients on nivolumab combined with ipilimumab was 5.9 months (95% CI: 2.8 months to not reached) for mucosal melanoma and 11.7 months (95% CI: 8.9–16.7 months) for cutaneous melanoma, and, similarly objective response rate was 37.1% (vs 60.4%, respectively). The safety profile of immunotherapy was similar between the two melanoma subtypes. These studies clearly indicate that in metastatic disease new strategies are needed for patients with poorer prognostic factors such as higher LDH activity or mucosal origin or the malignancy.

The other analyzed aspect of immunotherapy was the study on activity of ipilimumab administered following pembrolizumab failure in

advanced melanoma patients, which was a pivotal part of the KEYNOTE-006 trial. Ipilimumab was used as a subsequent therapy for 129 patients initially treated with pembrolizumab (in 97 analyzed patients ipilimumab was the first poststudy therapy) [17]. The reported overall response rate for ipilimumab was 14% with additional 33% of stabilization of disease. Subsequent disease progression occurred in 40% of patients with partial remission and in 48% of patients with disease stabilization. This study confirms the activity of ipilimumab after failure on anti-PD-1 monotherapy making it a viable therapeutic option in this clinical situation.

Financial & competing interests disclosure

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