

2015 EUROPEAN CANCER CONGRESS

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SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European Cancer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinary as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

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MELANOMA

Baseline genetic heterogeneities do not alter superior clinical benefit seen with cobimetinib/vemurafenib over sole vemurafenib in advanced BRAFV600-mutated melanoma: Updated results from co-BRIM

Grant McArthur, Peter MacCallum Cancer Centre in Melbourne, Australia reported updated efficacy results from the ongoing phase III placebo-controlled coBRIM study of patients with advanced BRAFV600-mutated melanoma, together with findings from an analysis of outcome according to individual mutations present in tumour tissue taken prior to treatment. Cobimetinib is an extremely selective allosteric small molecule inhibitor of MEK that was used with vemurafenib, which targets BRAF, to achieve co-inhibition of BRAF and MEK. Findings from coBRIM previously reported [ESMO 2014] showed treatment-naïve BRAFV600 mutation-positive patients with advanced melanoma receiving cobimetinib plus vemurafenib demonstrated significant improvement in progression-free survival (PFS) and objective response rate (ORR).

Results presented at the ECC from an analysis done at 14.2 months of follow-up also favoured cobimetinib/vemurafenib over vemurafenib monotherapy; the median PFS was 12.3 months with combination compared to 7.2 months with sole vemurafenib, HR 0.58. The ORR was 70% versus 50%, and the complete response (CR) rates were 16% versus 11% with cobimetinib/vemurafenib versus vemurafenib, respectively.

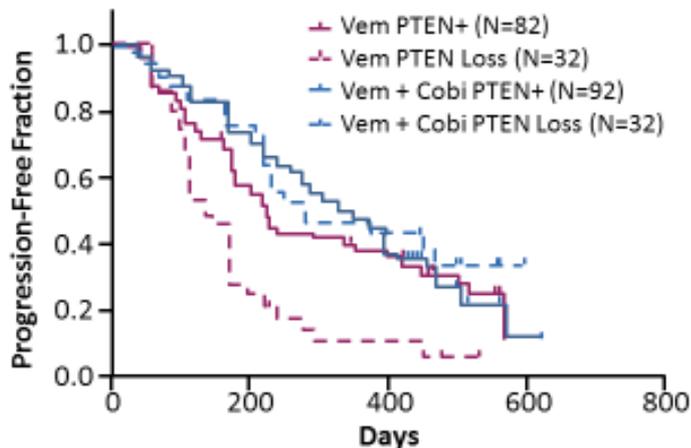
The impact of baseline tumour heterogeneity, including BRAFV600 copy number, RAS and other genetic sequence variants that could drive resistance, on clinical outcome was also evaluated. Tumour samples collected prior to treatment were analysed by targeted deep-sequencing to a median coverage of 3600×. Variant allele frequency was calculated as a ratio of the variant allele to total read depth at the V600 codon and hotspots in 17 additional oncogenes.

Immunohistochemistry (IHC) was used to assay PTEN loss and Cox proportional hazards modelling was used to determine the association between biomarker parameters and PFS that was observed until the data cut-off of 16 January 2015. This analysis showed that the advantage seen with combination treatment was consistent across several mutation types, those that might be predicted to induce resistance. Cobimetinib/vemurafenib showed clinical benefit across every patient subgroup evaluated, including patients with BRAFV600K and BRAFV600E mutation, where median PFS was 12.4 months, HR 0.52 (95% CI 0.27, 1.02) and 10.6 months, HR 0.64 (95% CI 0.49, 0.83), respectively.



Addition of Cobimetinib to Vemurafenib Overcomes the Negative Impact of PTEN Loss on PFS

Progression-Free Survival Based on PTEN Expression



PTEN+: H-score ≥ 50
PTEN Loss: H-score < 50

HR, Vem PTEN loss v Vem + Cobi
1.6; 95% CI, 0.96-2.8

Caption: *coBRIM – Addition of cobimetinib to vemurafenib overcomes the negative impact of PTEN loss on progression-free survival.*

Credit: Grant McArthur

The presence of co-mutation in oncogene hotspots and tumour suppressor genes known to mediate resistance to BRAF or MEK inhibition, including RAS, RTK, and PTEN, at allele frequencies of $>3\%$ (median 8.6%) had no impact on PFS in either arm, with the exception of PIK3CA mutation or PTEN loss. Loss of PTEN expression was associated with shorter PFS in patients receiving vemurafenib monotherapy, as compared to patients with intact PTEN; HR 1.6 (95% CI 0.96, 2.8). However, loss of PTEN did not affect PFS in patients receiving cobimetinib/vemurafenib. The authors suggest these data support the combination of cobimetinib/vemurafenib as the new standard of care for patients with advanced BRAFV600-mutated melanoma. NCT01689519. Mc Arthur et al. Abstract 25LBA.

Practice point and future research opportunities

The most common mechanism of acquired resistance to the BRAF inhibitor vemurafenib is reactivation of cell growth via the MAPK pathway through MEK; administering a BRAF inhibitor and

MEK inhibitor together in the first-line setting turns off both proteins, thereby increasing pathway inhibition and delaying the development of resistance that is observed with BRAF inhibition alone. This updated data from co-BRIM shows that simultaneous inhibition with cobimetinib/vemurafenib improved progression-free survival over BRAF inhibition with vemurafenib and also was unaffected by baseline genetic heterogeneities. These results may represent practice changing findings in patients with advanced BRAF V600 mutation-positive melanoma.

Promising clinical benefit with ribociclib and binimetinib combination in patients with NRAS-mutant melanoma confirmed in dose finding study

Promising preliminary anti-tumour activity has been reported from a simultaneous blockade of activation of the MAPK signalling pathway by targeting MEK with binimetinib and CDK4/6 with ribociclib in advanced NRAS-mutant melanoma [Sosman et al. ASCO 2014], leading Carla Van Herpen, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands and colleagues to conduct this phase Ib/II, open-label study of ribociclib plus binimetinib in patients with NRAS-mutant melanoma. The phase Ib segment aimed to determine the maximum-tolerated dose (MTD)/recommended phase 2 dose (RP2D) of the combination and secondary objectives included safety, pharmacokinetics, and preliminary efficacy. Ribociclib/binimetinib doses up to 300/45 mg have been assessed and 450/45 mg is currently being tested; 2 dosing schedules were assessed, a 28-day cycle of ribociclib once daily (QD) for 21 days plus binimetinib twice daily (BID) continuously and a 21-day cycle of ribociclib QD plus binimetinib BID for 14 days per cycle.

Regarding the 28 day cycle, 22 patients with ECOG PS 0/1/2 in 41%, 50%, and 9% of patients received one of 4 ribociclib/binimetinib combination dose levels: 9 patients received DL1 of 200/45 mg, 3 patients had DL2 of 250/45 mg, 4 patients received DL3 at 300/30 mg, and 6 patients received DL4 of 300/45 mg. The MTD for the 28-day cycle was determined to be DL1, based upon the following dose limiting toxicities: One patient in the DL1 cohort experienced grade 3 acute renal injury, and one patient at DL3 suffered fatal intracranial bleeding. In the DL4 cohort one patient each had grade 4 anaemia, grade 4 asymptomatic creatinine phosphokinase elevation (CPK), and grade 3 oedema plus grade 4 atrial fibrillation. Overall, the safety profile following exposure to this combination was consistent with single-agent results; the most commonly reported treatment-related toxicities included elevated CPK, anaemia, rash, nausea, oedema, diarrhoea, elevated creatinine, elevated phosphate, neutropenia, and vomiting.

Promising efficacy results were reported, with 5 (23%) patients achieving partial response (PR), and 4 (18%) patients achieving unconfirmed PR. Stable disease occurred in 9 (41%) patients.

Preliminary median progression-free survival was estimated at 6.2 (95%CI 3.7, NE) months. Several patients reported early tumour shrinkage that was accompanied by major symptomatic improvement. No patients currently remain on the 28-day treatment cycle treatment and assessment of the 21-day cycle is ongoing in 22 patients with an MTD as yet undetermined. Van Herpen et al. Abstract 3300.

Practice point and future research opportunities

Determination of the recommended phase 2 dose and optimal dosing schedule is ongoing for the combination of ribociclib and binimetinib, which continues to show promising preliminary antitumour activity in patients with NRAS-mutant melanoma.

Anti-PD-1 combined safely with radiotherapy in patients with metastatic melanoma

Previous reports suggest that radiotherapy may induce an abscopal immune response, possibly mediated by the release of tumour antigens and subsequent immune recognition, which could be enhanced by immunotherapy. Therefore, Elizabeth Liniker, Melanoma Institute Australia, Sydney, Australia and colleagues evaluated data from 32 patients with unresectable stage III/IV melanoma who received PD1 therapy, consisting of either nivolumab or pembrolizumab, and current or sequential radiotherapy to determine the safety and clinical outcomes of patients having immunotherapy plus radiotherapy. At the start of PD1 therapy, 16 patients had a median of 4 brain metastases, 21 (54%) had an elevated LDH, and 29 (74%) patients had M1c disease. Various radiotherapy regimens were delivered, including radiotherapy to extracranial sites in 27 (69%) patients, 4 (10%) patients had stereotactic radiotherapy to brain metastases, 4 (10%) patients underwent whole brain radiotherapy, and 4 (10%) patients received a combination of these treatments. After beginning PD1 therapy, the median time to radiotherapy was 8.5 (range: 28 to 185) days.

Although no complete response (CR) by RESIST was observed, 9 patients achieved partial response (PR), and 5 patients had stable disease. A total of 82 metastases were irradiated; of these, 25 were clinically or radiologically progressing on PD1 therapy at the start of radiotherapy; subsequently, 3 (12%) of these patients achieved CR, 7 (28%) achieved PR, and 5 (20%) patients experienced progression. In the cohort of patients with brain metastases, the median progression-free survival (PFS) was 2.5 months and overall survival (OS) was 6.8 months, whereas patients without brain metastases had PFS of 4.1 months and OS of 16.4 months.

The investigators concluded that radiotherapy plus PD1 therapy does not increase acute extracranial toxicity; however, since one patient with multiple small asymptomatic brain metastases receiving PD1 therapy and concurrent whole brain radiotherapy experienced potential delayed neurotoxicity, they suggest that potential neurotoxicity with cerebral radiotherapy requires investigation. One patient experienced cerebral radionecrosis 3 months after stereotactic radiotherapy that responded to bevacizumab and steroids. One patient had disproportionate cerebral oedema. The investigators are continuing to evaluate irradiated and non-irradiated lesion-specific and site-specific (intracranial and extracranial) response rates. Liniker et al. Abstract 3302.

Practice point and future research opportunities

These results suggest that radiotherapy may be effective for patients with lesions that progress on PD1 therapy and that they can be safely co-administered. Although no excess acute extracranial toxicity was observed in this small study, the potential for neurotoxicity with cerebral radiotherapy requires further investigation.

Analysis of key patient subgroups in CheckMate 067 shows consistent superior progression-free survival with combined nivolumab plus ipilimumab versus sole nivolumab or ipilimumab in treatment-naive patients with advanced melanoma

Lead author James Larkin, Royal Marsden Hospital, London, UK, presented an analysis of predefined key subgroups that included patients with poor prognostic factors from the phase III CheckMate 067, which demonstrated significantly improved progression-free survival (PFS) with combined ipilimumab and nivolumab over either as monotherapy in advanced melanoma. CheckMate randomised 945 treatment-naive patients to receive nivolumab at 3 mg/kg plus placebo, or nivolumab at 1 mg/kg plus ipilimumab at 3mg/kg Q3W for 4 weeks followed by nivolumab at 3mg/kg Q2W, or sole ipilimumab at 3mg/kg Q3W for 4 weeks plus placebo until disease progression or unacceptable toxicity.

The analysis demonstrated enhanced patient outcome with combination treatment across all subgroups, according to BRAF mutation status, age, disease stage, and baseline LDH levels. In the overall population, median PFS was 11.5 months with combination nivolumab/ipilimumab, versus 2.9 months with ipilimumab, HR 0.42 ($p < 0.00001$), and 6.9 months with nivolumab, HR 0.57 versus ipilimumab ($p < 0.00001$).

Consistently longer PFS was seen combined nivolumab plus ipilimumab or with nivolumab monotherapy than with ipilimumab in subgroups defined by BRAF mutation status. Median PFS was 11.7 months with the combination among patients with a BRAF mutation and 11.2 months among patients with wild-type BRAF compared with 7.9 versus 5.6 with nivolumab and 2.8 versus 4.0 months with ipilimumab in BRAF mutated and BRAF wild-type, respectively. In patients less than 65 years, PFS was 11.7, 5.5, and 2.8 months in the combination, nivolumab, and ipilimumab cohorts, respectively. Median PFS was 11.1, 12.7 and 2.9 months in the 65 to 75 year cohort, versus not reached, 5.3, and 4.0 months in patients over 75 years with combination, nivolumab, and ipilimumab, respectively. Regarding disease stage, patients with tumours staged M0/M1a/M1b demonstrated median PFS of 15.5, 9.3, and 4.2 months versus patients with M1c tumours, wherein median PFS was 8.5, 5.4, and 2.8 months with combination, nivolumab, and ipilimumab, respectively. Analysis of treatment according to baseline LDH showed patients below the ULN had median PFS of 14.0, 10.2, and 4.0 versus patients with measurements above ULN, who benefited the least from all treatments, by demonstrating median PFS of 4.2, 2.8, and 2.6 months with combination, nivolumab and ipilimumab, respectively.

The safety profile across subgroups was consistent with that observed in the overall safety population; the overall incidence of drug-related adverse events grade 3/4 was 55.0% with combined nivolumab/ipilimumab, 16.3% with nivolumab, and 27.3% with ipilimumab. Larkin et al. Abstract 3303.

Practice point and future research opportunities

The combination of nivolumab and ipilimumab showed prolonged progression-free survival in patients with previously untreated advanced melanoma that was consistent across key subgroups that included patients with poor prognostic factors, such as increased baseline LDH. The safety profile with the combination therapy suggests that it may be used safely in a broad range of clinical settings.

The majority of lesions are metabolically inactive in patients with metastatic melanoma receiving long-term anti-PD-1 therapy

Ben Kong, Westmead Hospital, Sydney, Australia presented findings on behalf of colleagues from an analysis of metabolic activity in individual lesions from patients with metastatic melanoma following long-term treatment with the anti-PD1 antibodies, nivolumab or pembrolizumab. In all, 27 patients received computed tomography (CT) or 18-F Fluorodeoxyglucose positron emission tomography (FDG-PET) scans after one year of treatment (median 15.2, range: 9.5 to 35.0

months). The best overall radiological response (ORR) and response rates at time of PET scanning was determined using standard immune related response criteria (irRC) and classification of the presence of FDG-PET metabolic activity was done by visual inspection, with lesions subsequently being characterised as PET positive or negative based upon the metabolic activity of individual lesions identified on CT. Unexpected PET positive foci were included in the lesion-specific analysis even if not visible on prior CT and biopsy or surgery was performed where clinically indicated to investigate the cause of unexpected or atypical lesions.

Following anti-PD1 treatment, the best ORR was complete response (CR), which was seen 9 (33%) patients; 11 (41%) patients achieved partial response (PR), 6 (22%) patients had stable disease (SD) and one (4%) patients experienced progressive disease (PD). At the time PET scans were taken, 8 (29.6%) patients were in complete CT response and achieved CR, another 8 (29.6%) showed PR, 4 (14.8%) patients had SD and 7 (25.9%) showed PD.

CT scans taken prior to PET scanning identified 62 individual lesions, of which 34 (55%) lesions were PET positive and 28 (45%) were PET negative; 5 additional PET positive lesions were identified by PET which were not noted on CT. Patients demonstrating a response who had not progressed per irRC demonstrated lesions that were negative by PET in 63% of cases. However, just 14% of lesions were negative by PET in patients showing PD. In the cohort of 8 patients achieving CR, 6 (75%) had negative PET scans, whereas 2 (25%) patients had PET positive scans; however biopsies excluded melanoma in both cases and instead confirmed lymphocytic infiltrate and granuloma. In the cohort of 8 patients having PR, 4 (50%) patients had no PET positive lesions. The authors concluded that PET may be no more sensitive than CT for recurrence detection in patients with a radiological complete response, and suggested that false positive results on PET may be due to treatment related granulomatous reactions, and biopsies of unexpected or atypical lesions should be considered to confirm or exclude disease progression. Kong et al. Abstract 3304.

Practice point and future research opportunities

Findings from this study show that the majority of residual disease on CT is metabolically inactive in patients with melanoma who show a prolonged response to anti-PD1 therapy. In this series, PET was no more sensitive than CT in lesion detection. Lesions detected on PET but not CT should be biopsied.

MASTERKEY-265 safety data reveals no dose limiting toxicities with talimogene laherparepvec and pembrolizumab in unresectable stage IIIB-IV melanoma and supports phase III trial

Findings presented by lead investigator Georgina V. Long, University of Sydney in Sydney, Australia revealed that the combination of the attenuated oncolytic virus talimogene laherparepvec (T-VEC) and the immune checkpoint inhibitor pembrolizumab passed an early safety evaluation for the treatment of unresectable melanoma. PD-1/PD-L1 inhibitors, such as pembrolizumab, have previously demonstrated activity in advanced melanoma, and T-VEC is an oncolytic herpes simplex virus type 1 that has been engineered to replicate selectively in tumour cells and express human GM-CSF.

Safety was assessed using data from phase Ib of the MASTERKEY-265 study, which enrolled 21 treatment-naive patients with unresectable stage III/IV melanoma and injectable lesions; patients with clinically active brain metastases, active herpetic skin lesions, or a history of herpetic infection complications were excluded. An intralesional T-VEC injection at doses up to 4 mL per treatment was injected into cutaneous, subcutaneous, or nodal lesions at 106 PFU/mL (day 1), 108 PFU/mL (day 22), then Q2W. Pembrolizumab was added from day 36 at 200 mg i.v. Q2W. Treatment continued until complete response (CR) or progressive disease (PD) occurred, no injectable lesions (T-VEC only) remained, or for up to 2 years. The primary endpoint was dose-limiting toxicities (DLTs), which were assessed during weeks 0 to 6. Data cut-off was 6 weeks after the last patient had the first pembrolizumab dose. The 21 patients enrolled from December 2014 to March 2015 had a median age of 8.0 years, 62% were female, 90% of patients had ECOG PS 0, 48% had stage IIIB-IVM1a, 52% had stage IVb/c, and approximately 20% had BRAF-positive melanoma.

All patients received one or more doses of both T-VEC and pembrolizumab. No DLTs were reported over a treatment duration of median 13.1 weeks that included a median 7 of doses of T-VEC, and treatment duration was median 10.1 weeks that included a median 5 doses of pembrolizumab. No patients discontinued therapy due to an adverse event. All patients experienced a treatment-emergent adverse event (TEAE) that was mostly grades 1/2; the grade 3 TEAE rate was 29% and no grade 4 TEAEs occurred. The only grade 3 TEAEs occurring in more than one 1 patient were anaemia and rash, each occurring in 2 patients; rash occurred following the first pembrolizumab. The most common TEAEs were rash (57%), pyrexia (38%), fatigue (29%), chills (24%), nausea (19%), pruritis (19%), diarrhoea (19%), vomiting (14%), headache (14%), and

arthralgia (14%). One patient had a grade 1 TEAE of cytokine release syndrome. One patient died of shock related to progressive disease and not to treatment. NCT02263508. Long et al. Abstract 24LBA.

Practice point and future research opportunities

T-VEC and pembrolizumab have favourable and non-overlapping adverse event profiles and the combination was well tolerated at full dose with no dose limiting toxicities in patients with unresectable stage IIIB-IV melanoma. Efficacy data are not yet available but the combination may have favourable anti-tumour activity. The phase Ib study supports the initiation of the randomised phase III part of the study evaluating the efficacy and safety of the combination compared with pembrolizumab monotherapy.

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AFFILIATION AND DISCLOSURE

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Disclosure

No conflicts of interest to disclose.

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