Honoraria (self), Advisory/Consultancy, Travel/Accommodation/Expenses: Roche/Genentech; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (self), Research grant/Funding (institution), Travel/Accommodation/Expenses: Novartis; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony: Merck Sharp & Dohme; Honoraria (self), Advisory/Consultancy, Travel/Accommodation/Expenses: Merck Serono; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Amgen; Honoraria (self), Advisory/Consultancy: Immunocore; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony: Incyte; Honoraria (self), Advisory/Consultancy: 4SC; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony: Pierre Fabre; Advisory/Consultancy: Sanofi/Regeneron; Travel/Accommodation/Expenses: Merck; Honoraria (self): Agenus; Honoraria (self): Array BioPharma; Honoraria (self): Pfizer; Honoraria (self): Philogen; Honoraria (self): Regeneron; Advisory/Consultancy: Nektar; Advisory/Consultancy: Sandoz. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.1227

1105P Estimating long-term survivorship in patients with advanced melanoma treated with immune-checkpoint inhibitors: Analyses from the phase III CheckMate 067 trial

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Background: Immune-checkpoint inhibitors nivolumab (NIVO) and ipilimumab (IPI), alone and in combination, have demonstrated durable long-term survival patterns in previously untreated patients with advanced melanoma in the CheckMate 067 trial (NCT01844505). Plateaus in overall survival (OS) and progression-free survival (PFS) data can be attributed to survival heterogeneity, which can be better captured by mixture models.

Methods: We assumed that a subset of patients can be classified as long-term survivors (LTSs) and that their survival trend follows that of the general population, with no excess mortality due to melanoma. A cohort-level background survival distribution was derived using mortality rates from the World Health Organization and demographic information from CheckMate 067. After assessing the suitability of mixture models by comparing hazard functions for the 5-year data in the entire trial population and the general population, we fit mixture models to the OS and PFS data to estimate the proportion of LTSs in each treatment arm. Time-to-event outcomes of non-LTSs were modeled by parametric survival functions, the forms of which were varied to obtain a range for the proportions of LTSs and to test the robustness of the results.

Results: Regardless of the data source (OS or PFS), ranges of estimated proportions of LTSs did not overlap across the treatment arms. Based on OS analyses, ranges of estimated proportions of LTSs were 38—46% for NIVO, 49—54% for NIVO+IPI, and 16—26% for IPI. Based on PFS analyses, ranges were 29—33% for NIVO, 38—40% for NIVO+IPI, and 9—13% for IPI. As these ranges represent only a span of point estimates of LTSs across model choices, a formal statistical assessment of the significance of LTSs among the treatment arms would require a comparison of confidence intervals.

Conclusions: Mixture models adequately captured the survival plateaus in CheckMate 067 and suggested a higher proportion of LTSs with NIVO and NIVO+IPI than with IPI. These methods may be used in the indirect estimation of auxiliary outcomes, such as time to subsequent treatment and impact of subsequent treatments on LTSs.

Legal entity responsible for the study: Bristol-Myers Squibb Company.

Funding: Bristol-Myers Squibb Company.

Disclosure: P. Mohr: Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Non-remunerated activity/ies: Pierre Fabre; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Non-remunerated activity/ies: GlaxoSmithKline; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Non-remunerated activity/ies: Merck Sharp & Dohme; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Non-remunerated activity/ies: Merk KGaA; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Non-remunerated activity/ies: Roche; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Non-remunerated activity/ies: Bristol-Myers Squibb Company; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Non-remunerated activity/ies: Novartis. J. Larkin: Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Bristol-Myers Squibb Company; Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Merck Sharp & Dohme; Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Novartis; Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Pfizer; Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Achilles; Research grant/Funding (self): Aveo; Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Roche; Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Nektar; Research grant/Funding (self): Covance; Research grant/Funding (self): Immunocore; Honoraria (self), Advisory/Consultancy: AstraZeneca; Honoraria (self), Advisory/Consultancy: Boston Biomedical; Honoraria (self), Advisory/Consultancy: Eisai; Honoraria (self), Advisory/Consultancy: EUSA Pharma; Honoraria (self), Advisory/Consultancy: GlaxoSmithKline; Honoraria (self), Advisory/Consultancy: Ipsen; Honoraria (self), Advisory/Consultancy: Imugene; Honoraria (self), Advisory/Consultancy: Incyte; Honoraria (self), Advisory/Consultancy: iOnctura; Honoraria (self), Advisory/Consultancy: Kymab; Honoraria (self), Advisory/Consultancy: Merck; Honoraria (self), Advisory/Consultancy: Pierre Fabre; Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Pfizer; Honoraria (self), Advisory/Consultancy: Secarna; Honoraria (self), Advisory/Consultancy: Vitaccess. V.F. Paly: Advisory/Consultancy, Full/Part-time employment, Employee of ICON Plc., which provides consulting and research services: ICON Plc. A. Remiro Azocar: Advisory/Consultancy, Full/Part-time employment: IQVIA; Advisory/Consultancy: ICON plc. G. Baio: Research grant/Funding (self): Merck Sharp & Dohme; Advisory/Consultancy: ICON plc.; Advisory/Consultancy: Parexel; Advisory/Consultancy: IQVIA. M. Kurt: Travel/Accommodation/Expenses, Shareholder/Stockholder/Stock options, Full/Part-time employment: Bristol-Myers Squibb Company; Full/Part-time employment: Merck. A. Amadi: Shareholder/Stockholder/Stock options, Full/Part-time employment: Bristol-Myers Squibb Pharmaceuticals Ltd. J.I. Rizzo: Shareholder/Stockholder/Stock options, Licensing/Royalties, Full/Part-time employment: Bristol-Myers Squibb Company. H.M. Johnson: Advisory/Consultancy, Full/Part-time employment: Bristol-Myers Squibb Pharmaceuticals Ltd. A. Moshyk: Shareholder/Stockholder/Stock options, Full/Part-time employment: Bristol-Myers Squibb Company. S. Kotapati: Leadership role, Research grant/Funding (self), Travel/Accommodation/Expenses, Shareholder/Stockholder/Stock options, Full/Part-time employment: Bristol-Myers Squibb Company. M. Middleton: Advisory/Consultancy: Amgen; Advisory/Consultancy, Research grant/Funding (institution): Roche; Research grant/Funding (institution): AstraZeneca; Advisory/Consultancy, Research grant/Funding (institution): GlaxoSmithKline; Advisory/Consultancy, Research grant/Funding (institution): Novartis; Research grant/Funding (institution): Millenium; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Immunocore; Advisory/Consultancy, Research grant/Funding (institution): Bristol-Myers Squibb Company; Research grant/Funding (institution), Non-remunerated activity/ies, Member of IDSMC: Eisai; Research grant/Funding (institution): Pfizer; Advisory/Consultancy, Research grant/Funding (institution), Non-remunerated activity/ies, Member of IDSMC: Merck/Merck Sharp & Dohme; Advisory/Consultancy, Research grant/Funding (institution), Acquired by Merck Sharp & Dohme: Rigontec; Research grant/Funding (institution): Regeneron; Advisory/Consultancy, Research grant/Funding (institution): BiolineRx; Advisory/Consultancy, Research grant/Funding (institution), Acquired by Pfizer: Array Biopharma; Research grant/Funding (institution), Travel/Accommodation/Expenses: Replimune; Advisory/Consultancy: Kineta; Advisory/Consultancy: Silicon Therapeutics.

https://doi.org/10.1016/j.annonc.2020.08.1228

1106P International experience of ipilimumab and nivolumab in patients with advanced melanoma

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Background: Immune checkpoint inhibition (ICI) combination therapy with ipilimumab (IPI) and nivolumab (NIVO), considered a standard of care for metastatic melanoma, has shown high rates of objective response rate (ORR), progression free survival (PFS) and overall survival (OS), but at a cost of significant toxicity. We aimed to analyse the efficacy and toxicity outcomes related to treatment with IPI and NIVO in routine practice in a multicentre cohort of patients (pts) with metastatic melanoma.

Methods: We conducted a retrospective review of medical notes of pts with advanced melanoma (unresectable Stage 3 or Stage 4) treated with IPI and NIVO between 2015 and 2020 at 6 centers across Europe, USA and Australia. Baseline characteristics were collected including the presence of brain metastases (BM). The primary endpoint was OS in the non-BM cohort. Secondary endpoints were PFS, ORR and immune-related adverse events (irAE) in the whole cohort and BM pts only.

Results: 696 pts with median follow-up of 13 months (m) were included. Median age was 58 years, 400 (57%) were male, 678 (97%) had PS- ECOG 0-1. Primary site was cutaneous in 487 pts (70%), unknown in 133 pts (20%) and other (acral, mucosal and uveal) in 77 pts (10%). 352 pts (50.5%) had a BRAF mutation, 516 pts (74%) were treatment naive, 241 pts (35%) had BM, of which 131 (18%) were untreated. 277 pts (40%) had elevated LDH. ORR was 48% (95% CI, 45-52). Median PFS (mPFS) was 6m (95% CI, 4.3-7.6), median OS (mOS) was 38m (95% CI, 26.6-49.3) for the entire cohort. mOS in non-BM pts was 52 m (95% CI, NR-NR) and 14m (95% 5-23) in BM pts. Intracranial (IC) ORR was 43% (95% CI, 37-49) and IC disease-control-rate was 56% (95% CI, 49-62). 253 pts (36%) started maintenance NIVO. Any irAE occurred in 76% of pts; grade 3/4 in 44%, hospital admission rate was 36%, and 4 (0.7%) treatment-related deaths (1 pneumonitis, 2 myocarditis and 1 colitis) were recorded.

Conclusions: The findings on this large cohort of pts support efficacy and provide insights into pts characteristics and outcomes associated with IPI and NIVO treatment for a heterogeneous population with advanced melanoma and are comparable with those of previously reported pivotal trial, Checkmate 067. Further analysis of the data including prognostic factors is ongoing.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: N. Cook: Advisory/Consultancy, scientific advisory board: Redx Pharmaceutical; Advisory/Consultancy, Research grant/Funding (institution), scientific advisory board: Tarveda Pharmaceuticals; Advisory/Consultancy, scientific advisory board: Neomed pharmaceuticals; Advisory/Consultancy, Research grant/Funding (institution), scientific advisory board: Roche Pharmaceuticals; Research grant/

Funding (institution): Novartis; Research grant/Funding (institution): Redx; Research grant/Funding (institution): Astrazeneca; Research grant/Funding (institution): Boehringer; Research grant/Funding (institution): Taiho; Research grant/Funding (institution): UCB; Research grant/Funding (institution): Eisai; Research grant/Funding (institution): Milenium; Research grant/Funding (institution): Starpharma; Research grant/Funding (institution): Orion; Non-remunerated activity/ies, scientific advisory board: Roche; Leadership role: Experimental Cancer Medicine Centre (ECMC) Strategy group, UK. D.M. Graham: Honoraria (self): Clinigen; Honoraria (self): McCann Health; Research grant/Funding (institution): Pfizer. A. 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https://doi.org/10.1016/j.annonc.2020.08.1229

1107P Clinical outcomes to checkpoint inhibitors in NRAS mutated metastatic melanoma (MM) compared with wild type BRAF/NRAS: An Italian Melanoma Intergroup (IMI) study

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Background: At present, the standard treatment for NRAS mutated MM is the same as for BRAF wild type MM with immune checkpoint inhibitors (ICIs) used as first line. It is thought that NRAS mutation is associated with better outcomes to immunotherapy. Nevertheless, retrospective studies reported controversial findings. To better understand the predictive role of NRAS mutation to ICIs, we assessed retrospectively clinical outcomes in two cohorts of pts homogeneously treated with ICIs as first line therapy: NRAS mutated/BRAF wild type MM (mut/wt) and NRAS wild/BRAF wild type MM (wt/wt).

Methods: A total of 331 pts including 163 mut/wt and 168 wt/wt were recruited in 11 Centres in Italy. The main evaluated pts features included: sex, age, origin and characteristics of primary cancer, previous adjuvant therapy, ECOG PS, M stage, metastatic sites, lactate dehydrogenase (LDH) level, basal count of white blood cells, lymphocyte and platelet, and subsequent therapies. In the wt/wt population, 35 pts received ipilimumab, 131 antiPD-1or antiPD-L1 and 2 the combination of both. In the cohort mut/wt, 45 patients received ipilimumab, 115 antiPD-1 and 3 the combination.

Results: As regard the primary, mut/wt was more frequently ulcerated (p.0038) and arose more frequently on the trunk (p.003) with respect wt/wt. At the onset of advanced stages, mut/wt had a higher M1c rate (p.001) involving less frequently lung (p.007) and brain (p.011) and progressing less to the brain if case be so (p.011). There was no significant difference in ORR, PFS and OS between the two groups (41.4%, 11 months [6-20, 95% CI] and 32 months [23-61, 95% CI] in mut/wt and 36,1%, 9 months [6-17, 95% CI] and 27 months [16-35, 95% CI] in wt/wt). Univariate analysis across the entire population showed a better ORR significatively associated with normal LDH, <3 sites of metastases, N/L ratio under 2.5 and the use of antiPD-1 than antiCTLA-4. A longer PFS and OS were also correlated with normal LDH, <3 sites of metastases, N/L ratio $<2,5$, lower platelet count and the use of antiPD-1 than antiCTLA-4.

Conclusions: We provide evidence that ICIs used as first line therapy are equally effective in mut/wt and wt/wt MM.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: M. Guida: Advisory/Consultancy: Merck Sharp & Dohme; Advisory/Consultancy: Novartis; Advisory/Consultancy: Pierre Fabre; Advisory/Consultancy: for Bristol-Myers Squibb. P. Quaglino: Speaker Bureau/Expert testimony: Bristol-Myers Squibb; Speaker Bureau/Expert testimony: Merck Sharp & Dohme; Speaker Bureau/Expert testimony: Pierre Fabre; Speaker Bureau/Expert testimony: Novartis; Speaker Bureau/Expert testimony: Roche. A.M. Di Giacomo: Advisory/Consultancy: Bristol-Myers Squibb; Advisory/Consultancy: Merck Sharp & Dohme; Advisory/Consultancy: GSK; Advisory/Consultancy: Pierre Fabre; Advisory/Consultancy: Sanofi. A.M. Minisini: Advisory/Consultancy: Novartis; Advisory/Consultancy: Merck Sharp & Dohme; Advisory/Consultancy: Pierre Fabre. P. Queirolo: Advisory/Consultancy: Bristol-Myers Squibb; Advisory/Consultancy: Merck Sharp & Dohme; Advisory/Consultancy: GSK; Advisory/Consultancy: Pierre Fabre; Advisory/Consultancy: Sanofi. F. Spagnolo: Honoraria (self): BMS; Honoraria (self): Roche; Honoraria (self), Advisory/Consultancy: Novartis; Honoraria (self), Advisory/Consultancy: MSD; Honoraria (self): Sanofi; Honoraria (self): Merck; Honoraria (self), Advisory/Consultancy: Sunpharma; Honoraria (self), Advisory/Consultancy: Pierre-Fabre. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.1230

1108P Real world (RW) sequencing outcomes with immunotherapy and targeted therapy (TT) in BRAF+ metastatic melanoma (The NOBLE study series)

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Background: Initial treatment decision-making for BRAF+ Metastatic Melanoma (MM) patients remains complex. TT with BRAF-MEK inhibition is associated with high ORR but are thought to be of limited duration, while checkpoint inhibitors (IO) are associated with lower ORR but can be more durable. In absence of head-to-head clinical trial data, it is unclear which treatment sequence (1L IO to 2L TT vs 1L TT to 2L IO) provides maximum benefit to patients. This study compares outcomes in the RW across the two treatment sequences.

Methods: The study included BRAF+ MM patients (n=358) who received both 1L and 2L therapies (IO and TT) according to the NCCN guidelines from Jan 1, 2014 up to Dec 31, 2018. Data was obtained from academic and community sites in the US using a RW registry (NOBLE study). Patient characteristics were analyzed descriptively. Kaplan-Meier curves and Cox regression model were used to compare progression free survival (PFS) and 2-year overall survival (OS) across the two treatment sequences. Differences in patient characteristics including disease severity across the two sequences were adjusted using inverse probability of treatment weighting (IPTW).

Results: Patients who received the TT to IO sequence vs IO to TT sequence were more likely to have elevated LDH (30.2% vs 17.7%) and 3+ organ sites of metastasis (47.4% vs 36.5%). Regardless of treatment sequence, patients progressed relatively rapidly through both 1L and 2L therapies (combined PFS of 13.2m for TT-IO and 12m for IO-TT). The 2-year OS was 76% for the TT-IO sequence compared to 77% for IO-TT. Adjusted Cox regression model found no statistical difference in outcomes across the two sequences.

Conclusions: RW data suggests that half of BRAF+ MM patients, regardless of initial treatment choice, are likely to progress through both 1L and 2L treatments within 12 months. Pending the results of randomized clinical trials, this RW study found no