NOVINKY Z LETOŠNÍHO NEJVÝZNAMNĚJŠÍHO SETKÁNÍ ONKOLOGŮ

Shrnutí ze sekce melanomu a kožních nádorů

Ivana Krajsová
Kožní klinika 1. LF UK a VFN v Praze

The Anti–PD-1 Antibody Spartalizumab in Combination With Dabrafenib and Trametinib in Advanced *BRAF* V600–Mutant Melanoma: Efficacy and Safety Findings From Parts 1 and 2 of the Phase III COMBI-i Trial

Georgina V. Long,[1] Celeste Lebbé,[2] Victoria Atkinson,[3] Mario Mandalà,[4] Paul Nathan,[5] Ana Arance,[6] Erika Richtig,[7] Naoya Yamazaki,[8] Caroline Robert,[9] Dirk Schadendorf,[10] Hussein Abdul-Hassan Tawbi,[11] Paolo Antonio Ascierto,[12] Antoni Ribas,[13] Keith Flaherty,[14] Neha Pakhle,[15] Aisha Masood,[16] Eduard Gasal,[16] Reinhard Dummer[17]

[1]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; [2]APHP Dermatology and CIC, U976, Université de Paris, Paris, France; [3]Greenslopes Private Hospital, Gallipoli Medical Research Foundation, University of Queensland, Greenslopes, QLD, Australia; [4]Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; [5]Mount Vernon Cancer Centre, Northwood, UK; [6]Hospital Clinic of Barcelona, Barcelona, Spain; [7]Medical University of Graz, Graz, Austria; [8]National Cancer Center Hospital, Tokyo, Japan; [9]Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; [10]University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; [11]The University of Texas MD Anderson Cancer Center, Houston, TX; [12]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy; [13]University of California, Los Angeles, Los Angeles, CA; [14]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA; [15]Novartis Healthcare Private Limited, Hyderabad, India; [16]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [17]University Hospital Zürich Skin Cancer Center, Zürich, Switzerland

Background

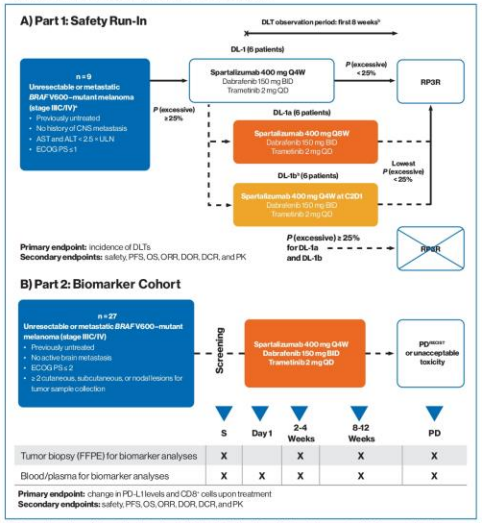
- Although immune checkpoint inhibitors and BRAF + MEK inhibitor targeted therapies have substantially improved outcomes in patients with metastatic melanoma, only ≈ 30% to 50% of patients are alive at 5 years with current treatments, highlighting a continued unmet need[1-5]
- The combination of anti–programmed death receptor 1 (PD-1) antibodies with dabrafenib plus trametinib (D+T) demonstrated promising efficacy in early-phase clinical trials (KEYNOTE-022; TRIDeNT)[6,7]
- Recent results from the Phase III IMspire150 trial showed that an anti–programmed death ligand 1 (PD-L1) antibody (atezolizumab) in combination with BRAF + MEK inhibitors (vemurafenib plus cobimetinib) significantly improves progression-free survival (PFS) over BRAF + MEK inhibition alone[8]

Objective

- Here we report updated efficacy and safety findings from part 1 (safety run-in; **Figure 1A**) and part 2 (biomarker cohort; **Figure 1B**) of the ongoing Phase III COMBI-i study (NCT02967692) of the anti–PD-1 antibody spartalizumab (S; formerly PDR001) at 400 mg every 4 weeks in combination with D+T at 150 mg twice daily plus 2 mg once daily in treatment-naive patients with *BRAF* V600–mutant metastatic melanoma

Methods

Figure 1. Study Designs for COMBI-i Parts 1 and 2



ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; C2D1, cycle 2 day 1; CNS, central nervous system; DCR, disease control rate; DL, dose level; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed, paraffin-embedded; ORR, objective response rate; OS, overall survival; *P* (excessive), probability of excessive toxicity; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP3R, recommended Phase III regimen; S, screening; ULN, upper limit of normal.

[a]BRAF V600 mutation will be assessed using a validated testing method, such as bioMérieux THxID-BRAF. [b]DL-1b: DLT observation period starts at C2D1 (day 29). Patients who do not tolerate dabrafenib and/or trametinib and discontinue during the first 4 weeks will be replaced due to insufficient exposure.

- Safety and efficacy analyses are based on the pooled patient population (N = 36) from parts 1 (n = 9) and 2 (n = 27) of COMBI-i, with a data cutoff of August 19, 2019
  - Both parts 1 and 2 enrolled patients with stage IIIC/IV *BRAF*-mutant melanoma and no prior systemic therapy for unresectable/metastatic disease, but additional key inclusion/exclusion criteria differed:
  - In part 1, patients had no history of central nervous system (CNS) metastasis and had alanine and aspartate aminotransferase levels < 2.5 times the upper limit of normal and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
  - Part 2 excluded only patients with active CNS metastases, and patients with an ECOG PS of 2 were also permitted; there was an additional requirement for sufficient tissue for biomarker sample collection
- Treatment with S+D+T was continued until disease progression, death, unacceptable toxicity, loss to follow-up, or withdrawal of consent
- Treatment beyond progression[9] was permitted if protocol-specific criteria were met

Results

Patients

- At the time of data cutoff, median follow-up was 24.3 months (range, 20.8-29.5 months), and treatment was ongoing in 10 patients

Table 1. Baseline Characteristics

	Part 1 (n = 9)	Part 2 (n = 27)	Parts 1 and 2 (N = 36)
Age, median (range), years	45 (35-69)	61 (23-76)	55.5 (23-76)
Age < 65 years, n (%)	7 (78)	18 (67)	25 (69)
Male, n (%)	7 (78)	15 (56)	22 (61)
White, n (%)	9 (100)	24 (89)	33 (92)
ECOG PS, n (%)			
0	7 (78)	19 (70)	26 (72)
1	2 (22)	8 (30)	10 (28)
AJCC 7 stage, n (%)			
IIIC	0	2 (7)	2 (6)
IV M1a	2 (22)	6 (22)	8 (22)
IV M1b	3 (33)	3 (11)	6 (17)
IV M1c with elevated LDH levels	2 (22)	11 (41)	13 (36)
IV M1c with normal LDH levels	2 (22)	5 (19)	7 (19)
***BRAF* mutation status, n (%)[a]**			
V600E	8 (89)	21 (78)	29 (81)
V600K	1 (11)	3 (11)	4 (11)
V600 other	0	3 (11)	3 (8)
LDH levels, n (%)[b]			
< 1 × ULN	6 (67)	13 (48)	19 (53)
≥ 1 to < 2 × ULN	3 (33)	6 (22)	9 (25)
≥ 2 × ULN	0	6 (22)	6 (17)
Sum of target lesion diameters, median (range), mm	42 (10-133)	61 (10-255)	57 (10-255)
No. of organ sites with disease, n (%)			
< 3	4 (44)	12 (44)	16 (44)
≥ 3	5 (56)	15 (56)	20 (56)

AJCC 7, American Joint Committee on Cancer, 7th edition; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

[a]*BRAF* mutation status was reported based on local testing. A V600K mutation in the presence of another V600 mutation, including V600E, could be combined into the "V600K" category. The "V600 other" category includes V600 mutations other than V600E or V600K. [b]LDH levels from 2 patients were not available.

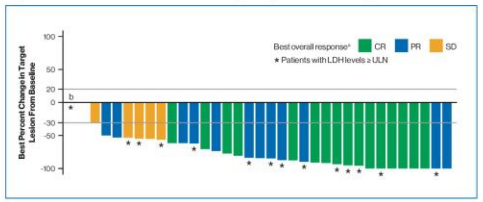
Objective Response Rate

Table 2. Objective Response Rate

Patients With Measurable Disease at Baseline	N = 36
Best overall response, n (%)	
CR	16 (44)
PR	12 (33)
SD	6 (17)
PD	1 (3)
Unknown	1 (3)
Confirmed ORR (CR + PR), n (%) [95% CI]	28 (78) [61-90]
DCR (CR + PR + SD), n (%) [95% CI]	34 (94) [81-99]
DOR, median (95% CI), months	NR (17-NR)
24-Month DOR rate (95% CI), %	53 (29-73)

CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Waterfall Plot of Best Overall Response per Local Investigator Review

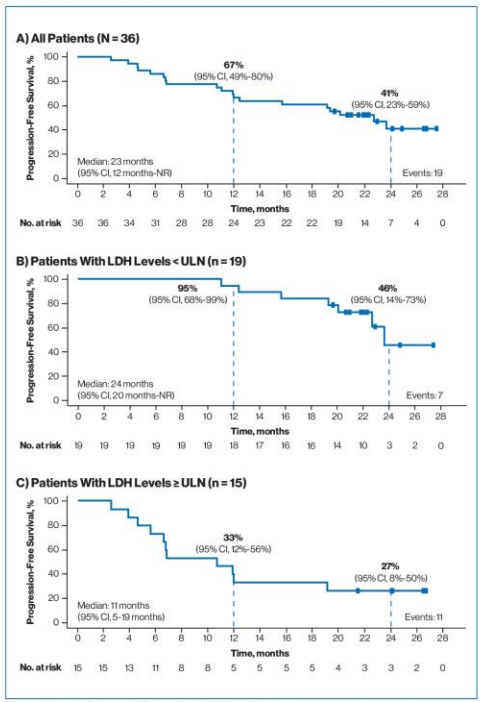


CR, complete response; LDH, lactate dehydrogenase; PR, partial response; SD, stable disease; ULN, upper limit of normal.

[a]One patient with SD had a best percent change of 0% in the target lesion, while best percent change could not be calculated for 1 patient because best overall response was unknown. [b]Best percent change in the target lesion was not available for 1 patient with progressive disease.

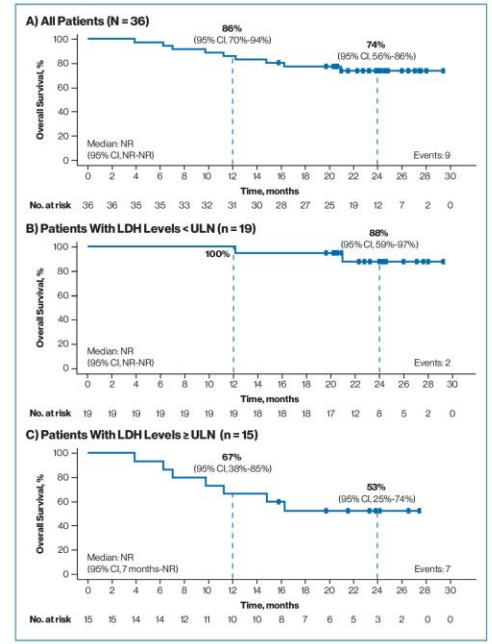
Time-to-Event Endpoints

Figure 3. Kaplan-Meier Estimates of PFS (per local investigator review)



LDH, lactate dehydrogenase; NR, not reached; PFS, progression-free survival; ULN, upper limit of normal.

Figure 4. Kaplan-Meier Estimates of OS



LDH, lactate dehydrogenase; NR, not reached; OS, overall survival; ULN, upper limit of normal.

Safety

Table 3. Summary of Safety

AEs	All Grades	Grade ≥ 3
Any AEs, n (%)	36 (100)	29 (81)
Treatment-related AEs	36 (100)	26 (72)
AEs requiring treatment with immunosuppressant	30 (83)	19 (53)
Treatment-related AEs leading to discontinuation, n (%)[a]		
Dabrafenib	11 (30)	
Trametinib	12 (33)	
Spartalizumab	11 (30)	
Spartalizumab + dabrafenib + trametinib	6 (17)	
Treatment-related AEs leading to dose interruption, n (%)		
Dabrafenib	34 (94)	
Trametinib	34 (94)	
Spartalizumab	23 (64)	
Treatment-related deaths, n (%)[b]	0	
Exposure to study drug, median (range), months		
Dabrafenib	13 (0.8-29)	
Trametinib	13 (0.8-29)	
Spartalizumab	9 (0.9-29)	

AE, adverse event.

[a]Patients who discontinued all 3 study drugs include those who discontinued spartalizumab plus dabrafenib plus trametinib due to the same AE, which included immune-mediated hepatitis, paresthesia, hypokalemia, interstitial lung disease, increased alanine and aspartate aminotransferase levels, increased γ-glutamyltransferase, and generalized exfoliative dermatitis. [b]One patient died of cardiac arrest that was not considered treatment related.

Table 4. Overview of Treatment-Related AEs[a]

Preferred Term, n (%)	All Grades	Grade ≥ 3
Any treatment-related AE	36 (100)	26 (72)
Pyrexia	31 (86)	6 (17)
Arthralgia	16 (44)	2 (6)
Chills	15 (42)	0
Rash	15 (42)	1 (3)
Fatigue	13 (36)	0
Vomiting	11 (31)	0
Anemia	10 (28)	1 (3)
Headache	10 (28)	0
Myalgia	10 (28)	0
Alanine aminotransferase increased	9 (25)	1 (3)
Asthenia	9 (25)	0
Blood creatine phosphokinase increased	9 (25)	3 (8)
Diarrhea	9 (25)	1 (3)
Amylase increased	7 (19)	2 (6)
Lipase increased	6 (17)	4 (11)
Neutropenia	6 (17)	4 (11)
γ-Glutamyltransferase increased	5 (14)	3 (8)
Lymphopenia	5 (14)	2 (6)
Hypophosphatemia	4 (11)	2 (6)
Transaminase increased	4 (11)	2 (6)
Pancreatitis	2 (6)	2 (6)

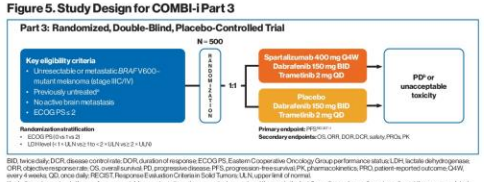
AE, adverse event.

[a]Any-grade treatment-related AEs observed in ≥ 20% of patients or grade ≥ 3 in > 5%.

Conclusions

- S+D+T exhibited an ORR of 78%, including a promising CR rate of 44%, in 36 patients with unresectable or metastatic *BRAF*-mutant melanoma
  - Among patients with elevated LDH levels, 27% achieved a CR
- S+D+T may be associated with a high frequency of durable responses, with 24-month PFS and OS rates of 41% and 74%, respectively
- No new safety signals were observed; AEs were consistent with the individual toxicity profiles of each study drug
- The AE profile of S+D+T was manageable, and many AEs were reversible, as only 17% of patients discontinued all 3 study drugs
- Limitations of these results from the single-arm parts 1 and 2 of COMBI-i include the small patient number and lack of an active comparator
  - The global, placebo-controlled, randomized part 3 is ongoing (**Figure 5**)

Figure 5. Study Design for COMBI-i Part 3



BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

*Including prior systemic therapy for unresectable or metastatic melanoma, prior locoregional therapy in the last 6 months, and neoadjuvant or adjuvant therapy completed within 6 months. [a]Treatment beyond PD[RECIST v1.1] is permitted if all the following criteria are met: (1) patient provides informed consent for treatment beyond progression; (2) the treatment will not delay an imminent intervention to prevent serious complications; (3) the treatment is tolerable, and (4) patient performance status remains stable.

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COMBI-i is registered at ClinicalTrials.gov (NCT02967692) and conducted in accordance with Study Protocol CPDR001F2301.

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Cílem bylo prokázat, zda cílená léčba BRAF a MEK inhibitory v kombinaci s imunoterapií anti PD-1 protilátkou může zvýšit účinnost léčby proti samotné imunoterapii či samotné cílené léčbě při akceptovatelné toxicitě

Spartalizumab (anti PD-1) 400 mg à čtyři týdny, dabrafenib 150 mg dvakrát denně, trametinib 2 mg jednou denně

Hodnocení 36 pacientů proběhlo k srpnu 2019 při mediánu sledování 24,3 měsíce

ORR dosáhly 78 %, z toho CR byla 44 % a PR 33 %

Mediánu DOR nebylo dosaženo

24 měsíců přetrvávaly ORR u 53,4 % pacientů

Medián PFS byl 22,7 měsíce a 24 měsíců bylo bez progrese 41,4 % pacientů

Mediánu OS nebylo dosaženo a 24 měsíců přežívalo 74,1 % pacientů

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Pacienti s elevací LDH	ORR 67 %, z toho CR byla 27 %
	Medián PFS 10,7 měsíce
	Mediánu OS nebylo dosaženo
	Odhadovaná četnost 24měsíčního PFS byla 26,7 % a OS 52,5 %

Nejčastějšími nežádoucími účinky byly pyrexie, elevace lipázy, neutropenie, elevace CK a GGT

U 17 % pacientů bylo pro toxicitu ukončeno podávání všech tří léků

Závěr: výsledky potvrzují vysokou účinnost kombinace imunoterapie s cílenou léčbou jak v četnosti léčebných odpovědí, tak v délce jejich trvání, a to i u pacientů s nepříznivou prognózou

Effect of First-Line Spartalizumab + Dabrafenib + Trametinib on Immunosuppressive Features Detected in Peripheral Blood and Clinical Outcome in Patients With Advanced *BRAF* V600–Mutant Melanoma

Reinhard Dummer,[1] Kelly Biette,[2] Daniel Gusenleitner,[2] Radha Ramesh,[3] Celeste Lebbé,[4] Victoria Atkinson,[5] Mario Mandalà,[6] Paul Nathan,[7] Ana Arance,[8] Erika Richtig,[9] Naoya Yamazaki,[10] Caroline Robert,[11] Dirk Schadendorf,[12] Hussein Abdul-Hassan Tawbi,[13] Paolo Antonio Ascierto,[14] Antoni Ribas,[15] Keith T. Flaherty,[16] Eduard Gasal,[17] Jan C. Brase,[18] Georgina V. Long[19]

[1]University Hospital Zürich Skin Cancer Center, Zürich, Switzerland; [2]Novartis Institutes for BioMedical Research, Inc, Cambridge, MA; [3]Oncology Precision Medicine, Novartis, Cambridge, MA; [4]APHP Dermatology and CIC, U976, Université de Paris, Paris, France; [5]Greenslopes Private Hospital, Gallipoli Medical Research Foundation, University of Queensland, Greenslopes, QLD, Australia; [6]Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; [7]Mount Vernon Cancer Centre, Northwood, UK; [8]Hospital Clinic of Barcelona, Barcelona, Spain; [9]Medical University of Graz, Graz, Austria; [10]National Cancer Center Hospital, Tokyo, Japan; [11]Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; [12]University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; [13]The University of Texas MD Anderson Cancer Center, Houston, TX; [14]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy; [15]University of California, Los Angeles, Los Angeles, CA; [16]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA; [17]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [18]Novartis Pharma AG, Basel, Switzerland; [19]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Background

- Although immune checkpoint inhibitors and targeted therapy demonstrated long-term survival in patients with unresectable or metastatic melanoma, most patients subsequently experience disease progression[1-5]
- Early trials suggested that combining anti–programmed death receptor 1 (PD-1) antibodies with BRAF and MEK inhibitors could induce a high frequency of rapid and durable responses in patients with *BRAF* V600–mutant melanoma[6,7]
- COMBI-i is a 3-part Phase III trial (NCT02967692) evaluating anti–PD-1 antibody spartalizumab plus dabrafenib plus trametinib in patients with *BRAF* V600–mutant melanoma[8,9]
- Results from part 1 (safety run-in) and 2 (biomarker cohort) of COMBI-i showed[8,9]:
  - Objective response rate of 78% (28 of 36 patients), including complete responses (CRs) in 44%
  - Median progression-free survival (PFS) of > 2 years
  - Immunosuppressive tumor microenvironment (TME) at baseline associated with a lack of CR and shorter PFS
- Here we analyze peripheral blood biomarkers in patients enrolled in parts 1 and 2 of COMBI-i to assess whether liquid markers can also predict response and clinical outcome with spartalizumab plus dabrafenib plus trametinib

Methods

- Biomarker analysis was conducted in the pooled patient population (N = 36) from parts 1 (n = 9; **Figure 1A**) and 2 (n = 27; **Figure 1B**) of COMBI-i, based on a data cutoff of August 19, 2019
  - Blood and tissue samples were collected at baseline, during treatment with spartalizumab plus dabrafenib plus trametinib after 2 to 4 weeks and 8 to 12 weeks, and at disease progression
- Blood-based markers were assessed by cytokine profiling (N = 45; **Table 1**) and RNA sequencing (RNA-Seq; 114 signatures) in all 36 patients
  - Cytokines in plasma were quantified with multiplexed sandwich immunoassays using electrochemiluminescence (Meso Scale Diagnostics)
- Tissue samples were prepared as formalin-fixed, paraffin-embedded slides with DNA/RNA coextracted from each available sample and extracted RNA used for RNA-Seq
- Patients were divided into 2 groups based on:
  - PFS of > 1 year (n = 24) vs < 1 year (n = 12)
  - Presence of CR vs partial response/stable disease/progressive disease (no CR)

Figure 1. Study Designs for COMBI-i Parts 1 and 2

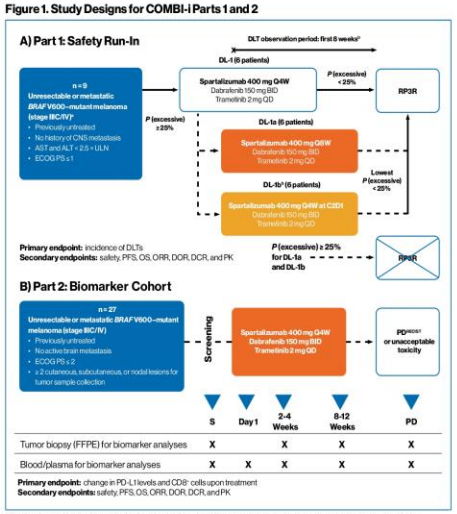

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Table 1. Cytokines Profiled (N = 45) in Blood Biomarker Analysis

bFGF	IFN-γ	IL-8	IL-18	SAA1
CCL13	IL-1α	IL-8 (HA)[a]	MCP-1	sVEGFR1
CCL17	IL-1β	IL-10	MDC	TIE-2
CCL26	IL-1RA	IL-12p40	MIP-1α	TNF-α
CRP	IL-2	IL-12p70	MIP-1β	TNF-β
CXCL10	IL-4	IL-13	MMP-1	VCAM-1
Eotaxin-1	IL-5	IL-15	MMP-3	VEGF-A
GM-CSF	IL-6	IL-16	MMP-9	VEGF-C
ICAM-1	IL-7	IL-17A	PlGF	VEGF-D

bFGF, basic fibroblast growth factor; CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; IL-1RA, IL-1 receptor antagonist; MCP-1, monocyte chemoattractant protein-1; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; PlGF, placenta growth factor; SAA1, serum amyloid A-1 protein; sVEGFR, serum VEGF receptor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor.
[a]Increased sensitivity for detection.

Results

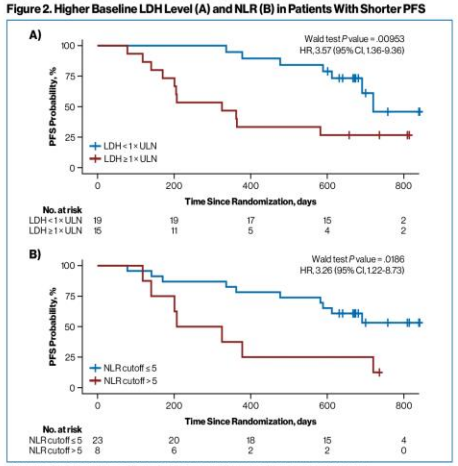
- As shown in **Table 2**, analysis of pretherapeutic blood biomarkers in patients treated with spartalizumab plus dabrafenib plus trametinib revealed:
  - High lactate dehydrogenase (LDH) level, neutrophil to lymphocyte ratio (NLR), and neutrophil count were most associated with PFS < 1 year (**Figure 2**; **Figure 3A** and **B**)
  - High lymphocyte count and albumin level were most associated with PFS > 1 year

Table 2. Blood Biomarkers Associated With PFS > 1 Year

Parameter	Ratio of Median Level for PFS > 1 year vs PFS < 1 year[a]	*P* Value[b]
LDH level	0.50	.0029
NLR	0.56	.0049
Percentage of neutrophils	0.87	.0057
Percentage of lymphocytes	1.65	.0093
Albumin level	1.10	.0150

LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PFS, progression-free survival.
[a]Wilcoxon test. [b]All *P* values are nominal.

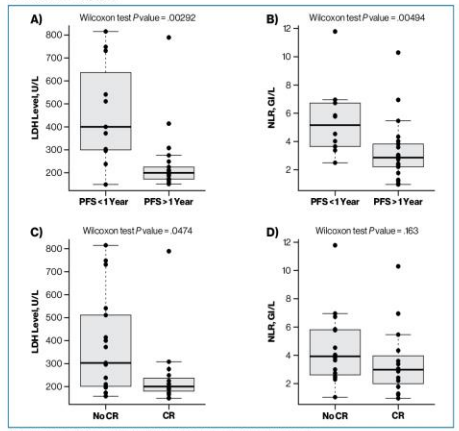
Figure 2. Higher Baseline LDH Level (A) and NLR (B) in Patients With Shorter PFS



HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PFS, progression-free survival; ULN, upper limit of normal.

- Higher LDH level and NLR at baseline showed moderate trends associated with a lack of CR (**Figure 3C** and **D**)

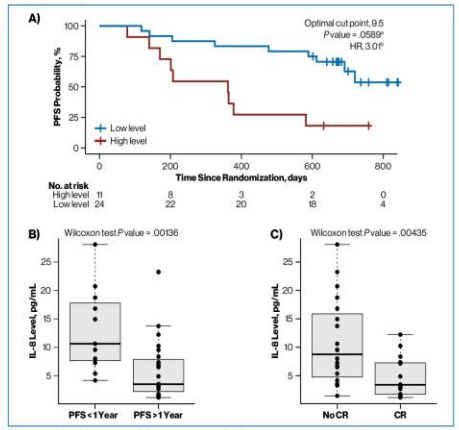
Figure 3. Higher Baseline LDH Level and NLR in Patients With PFS < 1 Year (A, B) and/or a Lack of CR (C, D)



CR, complete response; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PFS, progression-free survival.

- Profiling of 45 cytokines in patient blood samples revealed that interleukin 8 (IL-8) level at baseline was the biomarker most associated with both PFS and CR status
- Lower baseline IL-8 level was associated with:
  - Achieving longer PFS (**Figure 4A** and **B**)
  - Achieving a CR (**Figure 4C**)

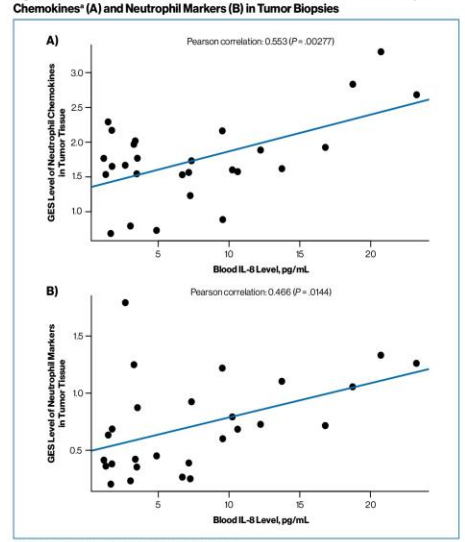
Figure 4. Lower Baseline IL-8 Level Associated With Improved PFS (A), PFS > 1 Year (B), and CR (C)



CR, complete response; HR, hazard ratio; IL-8, interleukin 8; PFS, progression-free survival.
[a]*P* value is corrected to avoid overfitting. [b]The HR is based on the optimal cut point.

- Analysis of pretherapeutic tumor biopsies showed that the gene expression signatures (GES) that correlated with baseline blood IL-8 level included immunosuppressive features, such as neutrophil markers
  - Patients with high circulating IL-8 levels were characterized by high levels of neutrophil chemokine signaling (ρ = 0.553; **Figure 5A**) and neutrophil markers (ρ = 0.466; **Figure 5B**) in GES in tumor tissue as measured by RNA-Seq

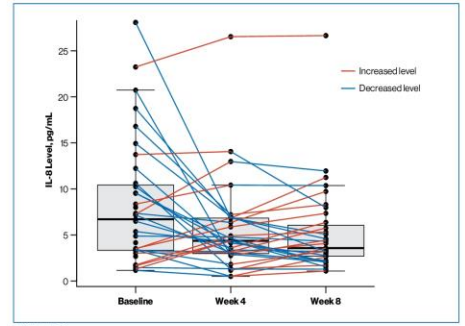
Figure 5. Correlation of Baseline IL-8 Level With Baseline GES Level of Neutrophil Chemokines[a] (A) and Neutrophil Markers (B) in Tumor Biopsies



GES, gene expression signature; IL-8, interleukin 8; NFKBIZ, NF-kappa-B inhibitor zeta.
[a]CXCL1, CXCL2, CXCL3, CXCL5, NFKBIZ, CCL20.

- Circulating IL-8 levels decreased from baseline upon treatment with spartalizumab plus dabrafenib plus trametinib (**Figure 6**)

Figure 6. Modulation of IL-8 Level With Spartalizumab Plus Dabrafenib Plus Trametinib



IL-8, interleukin 8.

Conclusions

- Blood biomarker analysis supports recent findings from tissue samples from patients enrolled in COMBI-i, which demonstrated that immunosuppressive features at baseline may preclude a CR and are associated with poor survival outcomes[8]
- Here we show that in addition to LDH level, lower NLR at baseline was associated with longer PFS, as reported with other therapies[10]
- Of the 45 serum cytokines assessed at baseline, we identified IL-8 as a prognostic indicator for both PFS and CR, and baseline IL-8 levels appeared to be associated with an immunosuppressive TME
  - A decrease in IL-8 levels was reported upon treatment with spartalizumab plus dabrafenib plus trametinib, as previously reported with targeted therapy alone[11]
  - IL-8 may add prognostic value to other blood markers, including LDH and NLR, but further validation is required
- The randomized part 3 of COMBI-i evaluating spartalizumab plus dabrafenib plus trametinib vs placebo plus dabrafenib plus trametinib is ongoing and includes efficacy, safety, and biomarker analyses

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COMBI-i is registered at ClinicalTrials.gov (NCT02967692) and conducted in accordance with Study Protocol CPDR001F2301.

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Effect of First-Line Spartalizumab + Dabrafenib + Trametinib on Immunosuppressive Features Detected in Peripheral Blood and Clinical Outcome in Patients (pts) With Advanced BRAF V600–Mutant Melanoma

Reinhard Dummer, Kelly Biette, Daniel Gusenleitner, Radha Ramesh, Celeste Lebbe, Victoria Atkinson, Mario Mandalà, Paul D. Nathan, Ana Arance, Erika Richtig, Naoya Yamazaki, Caroline Robert, Dirk Schadendorf, Hussein Abdul-Hassan Tawbi, Paolo Antonio Ascierto, Antoni Ribas, Keith Flaherty, Eduard Gasal, Jan C. Brase, Georgina V. Long

J Clin Oncol 38: 2020 (suppl; abstr 10034)

Již předchozí analýzou ve studii COMBI-i bylo prokázáno, že nemocní, u kterých vyvolala kombinovaná léčba spartalizumab + dabrafenib + trametinib CR, měli většinou nízké hladiny imunosupresivních faktorů v nádorovém mikroprostředí

Tato současná práce byla zaměřena na hodnocení krevních biomarkerů ve stejné kohortě pacientů s cílem zjistit, zda i „tekuté markery“ mohou predikovat klinickou účinnost léčby

U 36 pacientů byly odebírány tkáňové vzorky i krev při zahájení terapie, ve 2.–3. a 8.–12. týdnu a dále při progresi onemocnění

Hodnoceny byly mimo jiné hladina LDH, poměr neutrofilů a lymfocytů (NLR) a hladina plazmatického IL-8 (pIL-8)

Závěr: pravděpodobnost příznivé odpovědi a prodloužení PFS predikují nízká hladina LDH, nízké NLR a také snížená hladina IL-8

Randomizovaná 3. část studie COMBI-i ověřuje nyní tato pozorování na větším souboru pacientů

Long-Term Benefit of Adjuvant Dabrafenib + Trametinib (D+T) in Patients (pts) With Resected Stage III *BRAF* V600–Mutant Melanoma: Five-Year Analysis of COMBI-AD.

Axel Hauschild, Reinhard Dummer, Mario Santinami, Victoria Atkinson, Mario Mandalà, John M. Kirkwood, Vanna Chiarion Sileni, James M. G. Larkin, Marta Nyakas, Caroline Dutriaux, Andrew Mark Haydon, Caroline Robert, Laurent Mortier, Jacob Schachter, Kohinoor Dasgupta, Eduard Gasal, Monique Tan, Georgina V. Long, Dirk Schadendorf

J Clin Oncol 38: 2020 (suppl; abstr 10001)

COMBI-AD patří mezi nejvýznamnější adjuvantní studie s cílenou léčbou BRAFi a MEKi u pacientů po operaci pokročilého melanomu stadia III

V primární analýze byla hodnocena data z tříletého sledování, která ukázala významně vyšší účinnost D + T proti placebu – RFS 58 % proti 39 % (HR 0,47)

Na ASCO®20 Virtual byla prezentována data z pětiletého sledování

Mediánu RFS nebylo dosaženo

Z pacientů léčených D + T čtyři roky přežívalo bez relapsu 55 %,
pět let přežívalo bez relapsu 52 %

Z pacientů s placebem to bylo 38 % / 36 %

Long-Term Benefit of Adjuvant Dabrafenib + Trametinib (D+T) in Patients (pts) With Resected Stage III *BRAF* V600–Mutant Melanoma: Five-Year Analysis of COMBI-AD.

Axel Hauschild, Reinhard Dummer, Mario Santinami, Victoria Atkinson, Mario Mandalà, John M. Kirkwood, Vanna Chiarion Sileni, James M. G. Larkin, Marta Nyakas, Caroline Dutriaux, Andrew Mark Haydon, Caroline Robert, Laurent Mortier, Jacob Schachter, Kohinoor Dasgupta, Eduard Gasal, Monique Tan, Georgina V. Long, Dirk Schadendorf

J Clin Oncol 38: 2020 (suppl; abstr 10001)

Přínos adjuvantní léčby D + T byl patrný ve všech podskupinách pacientů: HR u IIIA 0,61 / IIIB 0,50 / IIIC 0,48

Mediánu DMFS nebylo dosaženo ani u D + T, ani u placeba, ale příznivější trend byl pozorován u D + T (HR 0,55)

OS dosud nebylo hodnoceno, je nezbytné vyčkat dostatečného počtu událostí

Závěr: pětiletá analýza potvrzuje dlouhodobý přínos adjuvantní terapie D + T pro pacienty po operaci melanomu stadia III s pozitivní BRAFV600E/K mutací

#402: Risk of disease progression (PD) following discontinuation of BRAF±MEK targeted therapies for reasons other than PD in patients (pts) with metastatic or unresectable melanoma

Francesca Corti[1*], Giovanni Randon[1*], Marta Bini[1], Alessandra Raimondi[1], Sara Manglaviti[1], Emma Zattarin[1], Ilaria Bisogno[1], Irene Vetrano[1], Carolina Cimminiello[1], Filippo G. de Braud[1,2], Michele Del Vecchio[1], Lorenza Di Guardo[1]
*These Authors contributed equally to this work
1. Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy // 2. Oncology and Hemato-Oncology Department, University of Milan, Milan, Italy

Background

In pts with *BRAF* V600 mutated metastatic melanoma achieving durable responses on BRAF ± MEK inhibitors, outcomes following discontinuation for reasons other than PD are largely unknown.

Methods:

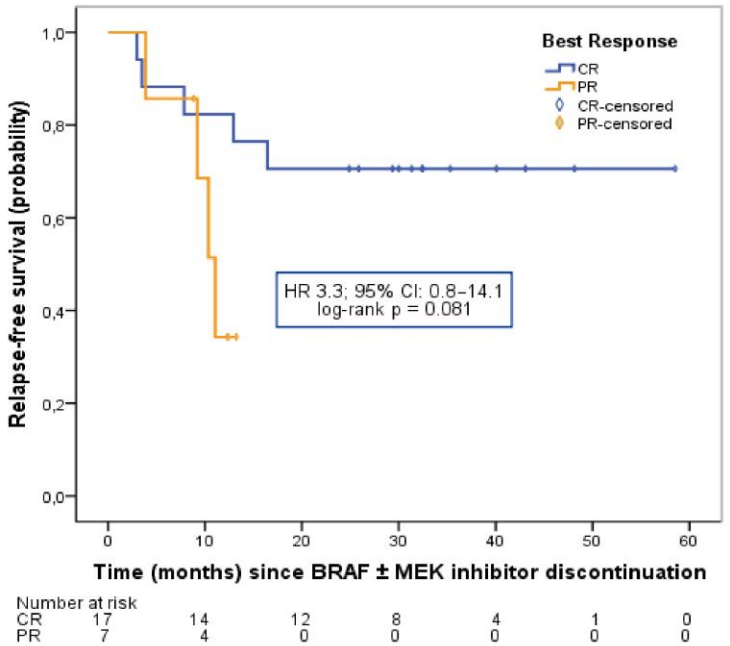
We identified all patients (n=24) with *BRAF* mutated metastatic/unresectable melanoma treated with targeted therapy at a single Institution, who interrupted BRAF±MEK inhibitors for unacceptable toxicity or consent withdrawal after obtaining a complete (CR) or partial response (PR).

Results

- Median treatment duration was 59 (range 12-88) months
- At the time of discontinuation, 17 (71%) and 7 (29%) pts had achieved CR and PR respectively.
- **Nine (37.5%) pts experienced PD** at a median follow up of 31 (range 8-59) months after treatment discontinuation.
- Median time to PD after treatment discontinuation was 9 (range 3-16) months
- After PD, 6 pts resumed BRAF+MEK inhibitors with a response rate of 100% and 3/6 pts achieving CR

Risk of PD following discontinuation	
12 months	31%
24 months	45%

- There was a non-significant trend towards a higher risk of relapse for patients interrupting treatment with residual disease compared to those who achieved CR [HR 3.3; 95%CI (0.8–14.1); log-rank p = 0.081].



Conclusions and future directions

- In a subset of metastatic melanoma patients with sustained sensitivity to BRAF±MEK inhibitors and favorable disease behavior, treatment discontinuation was associated with relevant risk of relapse (~30% within one year)
- Biomarker studies are needed to identify pts who might safely discontinue therapy in case of sustained toxicity, especially after achieving CR.

ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI
Francesca.Corti@istitutotumori.mi.it
Lorenza.DiGuardo@istitutotumori.mi.it

Risk of disease progression (PD) following discontinuation of BRAF±MEK targeted therapies for reasons other than PD in patients (pts) with metastatic or unresectable melanoma

Francesca Corti, Giovanni Randon, Marta Bini, Alessandra Raimondi, Sara Manglaviti, Emma Zattarin, Ilaria Bisogno, Irene Vetrano, Carolina Cimminiello, Filippo G. De Braud, Michele Del Vecchio, Lorenza Di Guardo

J Clin Oncol 38: 2020 (suppl; abstr 10053)

Retrospektivně hodnoceno 24 pacientů léčených monoterapií BRAFi či kombinací BRAFi a MEKi

Všichni měli při zahájení léčby LDH v normě a ECOG 0

U 79 % pacientů byla důvodem ukončení terapie toxicita a 21 % nemocných odvolalo souhlas s léčbou

V době ukončení terapie bylo 71 % v CR a 29 % v PR

Při mediánu sledování 31 měsíců (8–59) po ukončení léčby došlo u 37,5 % k PD, z toho u 22 % v dosud nepostiženém orgánu

Medián doby do progrese od ukončení terapie byl 9 měsíců (3–16)

Risk of disease progression (PD) following discontinuation of BRAF±MEK targeted therapies for reasons other than PD in patients (pts) with metastatic or unresectable melanoma

Francesca Corti, Giovanni Randon, Marta Bini, Alessandra Raimondi, Sara Manglaviti, Emma Zattarin, Ilaria Bisogno, Irene Vetrano, Carolina Cimminiello, Filippo G. De Braud, Michele Del Vecchio, Lorenza Di Guardo

J Clin Oncol 38: 2020 (suppl; abstr 10053)

Riziko progrese bylo 12 měsíců po ukončení léčby 31 % a 24 měsíců po ukončení léčby 45 %

Nebyl zaznamenán žádný signifikantně významný znak, který by ukazoval na riziko PD, pouze určitý trend, že nemocní s PR měli vyšší riziko než nemocní v CR

U všech šesti pacientů, kteří byli pro PD léčeni opět BRAFi a MEKi, byla popsána léčebná odpověď a u 3/6 došlo k CR

Nicméně závěry studie ukazují, že i u pacientů s dobrou prognózou onemocnění a významnou léčebnou odpovědí je riziko relapsu po ukončení terapie vysoké a že zatím neznáme biomarkery, které by nám označily nemocné, u nichž je možné podávání BRAFi a MEKi po dosažení CR ukončit

Poster 10012

Update on Overall Survival in COLUMBUS: A Randomized Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) vs Vemurafenib (VEM) or ENCO in Patients With BRAF V600–Mutant Melanoma

Helen J. Gogas [1], Paolo A. Ascierto,[2] Keith T. Flaherty,[3] Ana Arance,[4] Mario Mandala,[5] Gabriella Liszkay,[6] Claus Garbe,[7] Dirk Schadendorf,[8] Ivana Krajsova,[9] Ralf Gutzmer,[10] Jan Willem B. de Groot,[11] Caroline Dutriaux,[12] Carmen Loquai,[13] Ashwin Gollerkeri,[14] Michael D. Pickard,[14] Caroline Robert,[15] Reinhard Dummer,[16]

1. Department of Internal Medicine, National and Kapodistrian University of Athens, Laikon Hospital, Athens, Greece; 2. Melanoma Unit, Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; 3. Cancer Center, Massachusetts General Hospital, Boston, MA, USA; 4. Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain; 5. Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; 6. Department of Dermatology, National Institute of Oncology, Budapest, Hungary; 7. Department of Dermatology, University Hospital Tuebingen, Tuebingen, Germany; 8. Department of Dermatology, University Hospital Essen, Essen, Germany, and German Cancer Consortium, Heidelberg, Germany; 9. Department of Dermato-oncology, University Hospital Prague and Charles University First Medical Faculty, Prague, Czech Republic; 10. Department of Dermatology and Allergy, Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany; 11. Department of Medical Oncology, Isala, Zwolle, Netherlands; 12. Department of Oncologic Dermatology, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France; 13. Department of Dermatology, University Medical Center Mainz, Mainz, Germany; 14. Pfizer Inc., NYC, NY, USA; 15. Service of Dermatology, Department of Medicine and Paris-Sud University, Gustave Roussy, Villejuif, France; 16. Department of Dermatology, University Hospital Zürich Skin Cancer Center and University Zürich, Zürich, Switzerland

Introduction

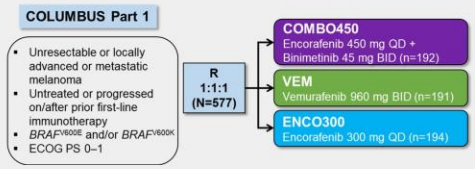
- Based on improved overall survival and manageable tolerability relative to BRAF inhibitor monotherapy, combination of BRAF/MEK inhibitor therapy is now the standard of care in *BRAF* V600–mutant locally advanced or metastatic melanoma[1-3]
- The phase 3 COLUMBUS study (NCT01909453) compared ENCO 450 mg once daily (QD) + BINI 45 mg twice daily (BID) vs ENCO 300 mg QD or vemurafenib 960 mg BID in patients with *BRAF* V600E/K–mutant melanoma[4,5]
  - The combination extended median progression-free survival compared with vemurafenib (14.9 vs 7.3 months) and median overall survival (33.6 vs 16.9 months)
- In an effort to provide landmark analyses of progression-free survival (PFS) and overall survival (OS), as well as analyses of some prognostic subgroups from the COLUMBUS study, a 4-year updated, post-hoc analysis with additional follow-up from the COLUMBUS trial was conducted

Materials and Methods

STUDY DESIGN

- COLUMBUS was a two-part, multicenter, randomized, open-label, phase 3 study with patients enrolled from 162 hospitals in 28 countries. Enrollment occurred between December 2013, and November 2015
- In Part 1 of COLUMBUS, 577 patients with advanced/metastatic *BRAF* V600E/K–mutant melanoma that was untreated or progressed after first-line immunotherapy were randomized 1:1:1 to ENCO 450 mg QD + BINI 45 mg BID (COMBO450) vs VEM 960 mg BID (VEM) or ENCO 300 mg QD (ENCO300) (**Figure 1**)
- Details on the study design have been previously published[10,11]

Figure 1. Study Design



Stratified by AJCC stage, ECOG PS, BRAF mutation status/prior first-line immunotherapy[a]

AJCC=American Joint Committee on Cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; a: Prior first-line immunotherapy replaced BRAF mutation status as a stratification factor after protocol amendment 2.[10,11]

Results

PATIENTS

- A total of 577 patients were randomized in part 1 of the COLUMBUS study (COMB450:192; ENCO300: 194 and VEM: 191)
- Baseline characteristics were well balanced between treatment groups and consistent with advanced/metastatic *BRAF*V600-mutant melanoma (Table 1)

Table 1. Baseline Characteristics

Characteristic	COMBO450 n=192	ENCO300 n=194	VEM n=191
Median age (range), years	57 (20–89)	54 (23–88)	56 (21–82)
Male	60%	56%	58%
ECOG performance status 0	71%	72%	73%
LDH > Upper Limit Normal	29%	24%	27%
LDH ≤ Upper Limit Normal	71%	76%	73%
***BRAF* mutation status (*BRAF*V600E/*BRAF*V600K)**	89%/11%	89%/10%	88%/12%
Tumor stage at study entry			
IIIB/IIIC	5%	3%	6%
IVM1a	14%	15%	13%
IVM1b	18%	20%	16%
IVM1c	64%	62%	65%
Number of organs involved			
1	25%	29%	24%
2	30%	27%	31%
≥3	45%	44%	46%

In the COLUMBUS trial, Results for Updated PFS and OS with Encorafenib and Binimetinib Continue to Demonstrate Long-Term Benefits in Patients with *BRAF* V600–Mutant Melanoma

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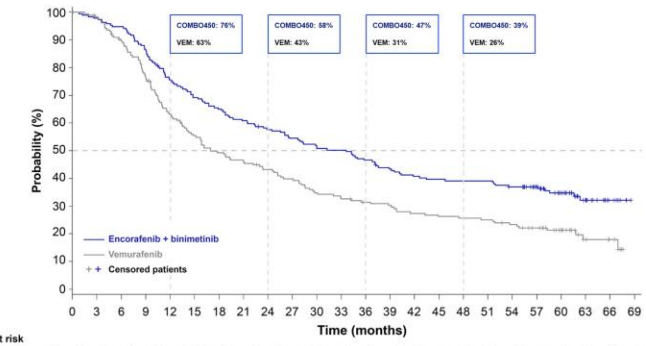
EFFICACY

- At data cutoff (November 2019), overall survival events had occurred in 65%, 59%, and 75% of patients and progression-free survival events had occurred in 62%, 60%, and 62% of patients in the COMBO450, ENCO300, and VEM treatment arms, respectively.

Figure 2. Overall Survival and 4-Year Landmark Analysis COMBO vs VEM



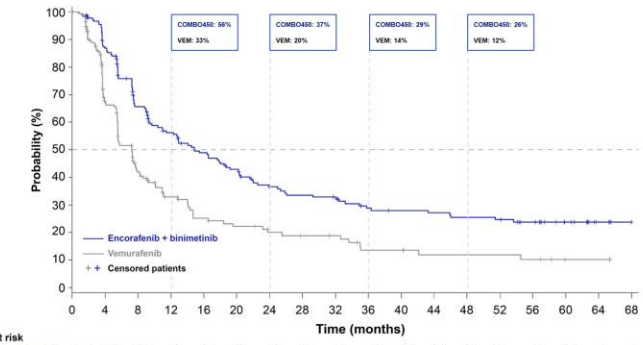
Patients at risk

Encorafenib + binimetinib	192	188	182	166	144	132	124	116	109	103	96	95	88	81	76	74	73	73	68	56	40	21	7	0
Vemurafenib	191	184	166	141	115	100	89	83	77	71	62	58	54	52	47	45	44	43	39	33	23	9	6	0

EFFICACY *(continued)*

- Across arms, median follow-up for OS was 60.6 months (mo), with median OS of 33.6 mo (95% CI, 24.4–39.2) for COMBO450, 23.5 mo (95% CI, 19.6–33.6) for ENCO300, and 16.9 mo (95% CI, 14.0–24.5) for VEM (Figure 2). Compared to VEM, COMBO450 decreased the risk of death by 39% (HR, 0.61 [95% CI, 0.48–0.78])

Figure 3. PFS and 4-Year Landmark Analysis: COMBO450 vs VEM (BICR)



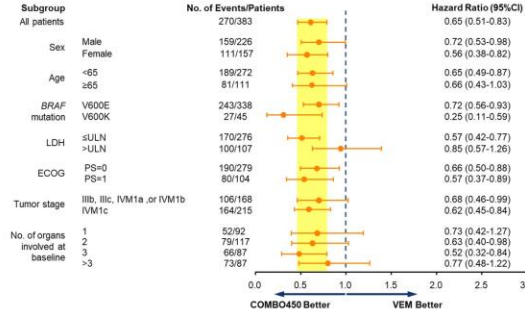
Patients at risk

Encorafenib + binimetinib	192	151	108	87	73	63	50	45	43	35	33	32	30	29	24	13	5	0
Vemurafenib	191	98	55	36	26	22	18	16	15	10	10	7	7	7	6	2	2	0

EFFICACY *(continued)*

- A landmark analysis showed a higher rate of OS for COMBO450 at each year analyzed, with rates at 4 years of 39% (95% CI, 32-46), 37% (95% CI, 30-44), and 26% (95% CI, 19-32) for COMBO450, ENCO300, and VEM, respectively (Figure 2)
- Confirmed overall response by blinded independent central review was observed in 64% of patients for COMBO450, 52% for ENCO300, and 41% for VEM
- A landmark analysis showed a higher rate of PFS for COMBO450 at year 4 of 26% (95% CI, 19-33), 22% (95% CI, 15-29), and 12% (95% CI, 6-20) for COMBO450, ENCO300, and VEM, respectively (Figure 3). Updated median PFS was the same as previously reported
- In general, subgroup analyses for the comparison COMBO450 with VEM showed point estimates in favor of COMBO450 (Figure 4)

Figure 4. Overall Survival Subgroups: COMBO vs VEM*



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; PS=performance status; ULN=upper limit of normal; VEM=vemurafenib 960 mg BID. *Subgroup analysis is not stratified.

SAFETY

- A summary of adverse events are presented in Table 3.

Table 3. Adverse Events Occurring in ≥20% of Patients

Event	COMBO450 n=192 Median Duration of Exposure: 51 weeks		ENCO300 n=192 Median Duration of Exposure: 31 weeks		VEM n=186 Median Duration of Exposure: 26 weeks	
	All Grades	Grade 3/4	All Grades	Grade %	All Grades	Grade 3/4
Total	98%	70%	100%	70%	100%	66%
Nausea	44%	2%	39%	4%	35%	2%
Diarrhea	39%	3%	15%	2%	34%	3%
Vomiting	32%	2%	29%	5%	16%	1%
Fatigue	30%	2%	26%	1%	31%	2%
Arthralgia	29%	1%	45%	9%	46%	6%
Blood Creatine Phosphokinase Increased	27%	6%	2%	1%	2%	0%
Headache	26%	2%	29%	3%	20%	1%
Constipation	25%	0%	17%	0%	7%	1%
Asthenia	22%	2%	22%	3%	19%	4%
Pyrexia	20%	4%	17%	1%	29%	0%
Dry Skin	17%	0%	30%	1%	23%	0%
Myalgia	16%	0%	29%	10%	18%	1%
Rash	17%	2%	21%	2%	30%	3%
Hyperkeratosis	15%	1%	40%	4%	29%	0%
Alopecia	15%	0%	56%	0%	38%	0%
Pruritus	15%	1%	22%	1%	11%	0%
Pain in Extremity	13%	1%	23%	1%	15%	1%
Decreased Appetite	10%	0%	21%	1%	19%	1%
Palmoplantar Keratoderma	10%	0%	27%	2%	18%	1%
Palmar-Plantar Erythrodysaesthesia Syndrome	6%	0%	52%	14%	14%	1%
Keratosis Pilaris	5%	0%	17%	0%	23%	0%
Photosensitivity Reaction	4%	1%	4%	0%	25%	1%

Conclusions

- Landmark analyses show improved OS and PFS for COMBO450 vs VEM at year 1, 2, 3 and 4
- Results were similar across a broad range of subgroups
- Safety results were consistent with the known tolerability profile of COMBO450. No new safety concerns were noted in this update
- Updated results for COMBO450 from the COLUMBUS trial continue to represent new benchmarks for treatment of *BRAF* V600–mutated melanoma

Acknowledgements: We thank the patients, their families, and the sites that participated in this study. This study was sponsored by Array BioPharma Inc which was acquired by Pfizer Inc in July 2019. Editorial support was provided by Mayville Medical Communications and funded by Pfizer Inc. ‡If you do not have access to a smartphone, please access the poster via the following link: https://congress-download.pfizer.com/asco_2020_american_society_of_clinical_oncology_56th_annual_meeting_629_braftovi_gogas_h_10012.html BICR= blinded independent central review

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Presented at the 2020 Annual ASCO Meeting• May 29-31, 2020 • Chicago, IL USA

Update on Overall Survival in COLUMBUS: A Randomized Phase 3 Trial of Encorafenib (ENCO) plus Binimetinib (BINI) vs Vemurafenib (VEM) or ENCO in Patients With *BRAF* V600-Mutant Melanoma.

Helen Gogas, Paolo Antonio Ascierto, Keith Flaherty, Ana Arance, Mario Mandalà, Gabriella Liszkay, Claus Garbe, Dirk Schadendorf, Ivana Krajsova, Ralf Gutzmer, Jan Willem de Groot, Caroline Dutriaux, Carmen Loquai, Ashwin Gollerkeri, Michael D Pickard, Caroline Robert, Reinhard Dummer

J Clin Oncol 38: 2020 (suppl; abstr 10012)

Prezentována byla aktualizovaná data týkající se PFS, OS a ORR podle typu podávané léčby – COMBO 450, ENCO 300 a VEM

Při mediánu sledování 60,6 měsíce byl:

Medián OS
COMBO 450 – 33,6 měsíce
ENCO 300 – 23,5 měsíce
VEM – 16,9 měsíce

Medián PFS
COMBO 450 – 14,9 měsíce
ENCO 300 – 9,6 měsíce
VEM – 7,3 měsíce

Čtyři roky přežívalo
COMBO 450 – 39 % pacientů
ENCO 300 – 37 % pacientů
VEM – 26 % pacientů

Nebyly pozorovány žádné neočekávané nežádoucí účinky léčby

Závěr: výsledky potvrzují dlouhodobou účinnost COMBO 450 u pacientů s BRAFV600-pozitivním melanomem

Abstract #10049: Activity and safety of third-line BRAF targeted therapy (TT) following first line TT and second-line immunotherapy (IT) in advanced melanoma

Victoria Atkinson[1, 2,3], Kathleen Batty[4,6], Georgina V. Long[4,5,6], Matteo S. Carlino[4,5,7], Lauren Brown[7], Geoffrey Peters[8,9], Prachi Brave [10], Andrew Haydon[10], Maggie Moore[10], Wen Xu[1,2], Melissa Arneil[1], Megan Lyle[11,12] and Alexander M. Menzies[4,5,6]

1. Princess Alexandra Hospital, 2. University of Queensland,3. Greenslopes Private Hospital, 4. Melanoma Institute of Australia, 5. The University of Sydney, 6. Royal North Shore Hospital, 7.Department of Medical Oncology Westmead, and Blacktown. 8. Canberra Hospital. 9.Australian National University.
2. 10. Department of Medical Oncology Alfred Hospital. 11. Liz Plummer Cancer Centre Cairns Hospital. 12. James Cook University.

Background and Methods:

- Patients with advanced BRAF mutant melanoma who progress on 1st line TT and 2nd line IO have limited treatment options.
- The efficacy of re-challenge with third line TT is not well described.
- Data were collected and pooled from 6 centers in Australia from 2009-2018.
- Eligible patients had BRAF V600 mutant advanced melanoma, received first line therapy with a BRAF/MEK inhibitor, 2nd line therapy with immunotherapy (IO - ipilimumab, anti-PD-1/L1) and were then re-challenged with a BRAF and MEK inhibitor.

Results

- 90 patients were identified, with a median age of 61 years
- 78% were BRAF V600E, 14% V600K, 6% V600R, 1% V600M.

Table 1. Stage and Performance Status across lines of therapy

	Frequency (%)		
	1st line therapy (TT)	2nd line therapy (IO)	3rd line therapy (TT)
Stage (AJCC v8)			
IIIb	1 (1%)		
IIIc	6 (7%)	2 (2%)	1 (1%)
IIId	4 (4%)	1 (1%)	1 (1%)
IVa	8 (9%)	7 (8%)	4 (4%)
IVb	14 (16%)	8 (9%)	4 (4%)
IVc	39 (43%)	37 (41%)	31 (34%)
IVd	18 (20%)	35 (39%)	49 (54%)
LDH			
Normal	47 (52%)	51 (57%)	27 (30%)
Elevated	36 (40%)	34 (38%)	46 (51%)
ECOG			
0	52 (58%)	49 (54%)	24 (27%)
1	29 (32%)	32 (36%)	30 (33%)
2	4 (4%)	3 (3%)	21 (23%)
3	1 (1%)		3 (3%)
4			1 (1%)

Table 3. Reasons for stopping treatment and BORR at 1st and 2nd line treatment

Reason stopped	Frequency (%) 1st line (TT)	2nd line (IO)
Adjuvant	4 (4%)	
Completed 4 doses		1 (1%)
Neoadjuvant on trial	1 (1%)	
Progressive disease	62 (69%)	72 (80%)
Planned break		1 (1%)
Planned sequence to another Rx	14 (16%)	
Toxicity	8 (9%)	14 (16%)
BORR		
CR	18 (20%)	3 (3%)
PR	37 (41%)	9 (10%)
SD	15 (15%)	9 (10%)
PD	12 (13%)	63 (70%)

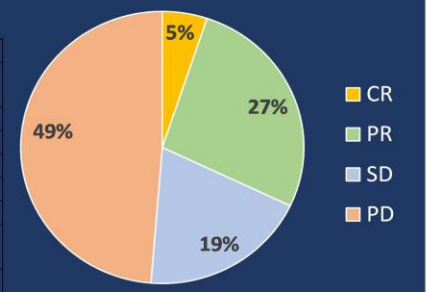

Figure 1: Third line BORR

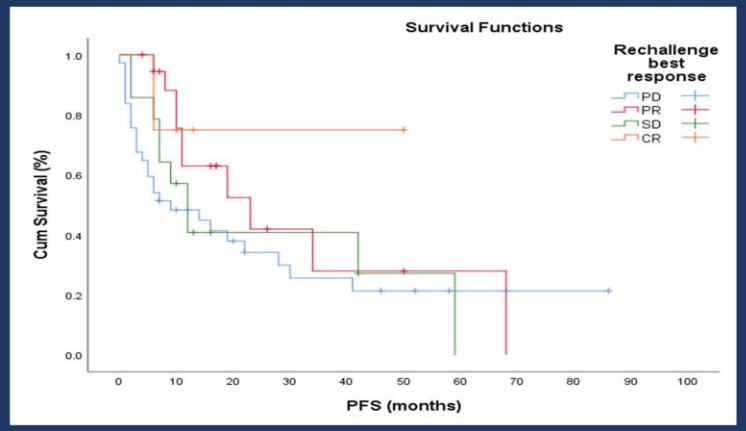

Figure 2: Kaplan-Meier curve PFS survival from time of re-challenge with TT

- In the patients who had a planned switch from 1st line TT to 2nd line IO (n=16), there were no response, only one patient had SD as BORR.
- The most common reason for ceasing 2nd line IO was progressive disease at 70%.
- There was no new safety signals with rechallenge (3rd line) targeted therapy, 15% developed rash and 7% fever.
- The median OS was 12 months, which is poor compared to the published data, this may reflect high proportion of CNS disease.

Results (Continued)

Table 2. Lines of therapy across Stages

	Frequency (%) 1st line	2nd line	3rd line
Binimetinib, Encorafenib & Ribociclib	1 (1%)		
CombiDT + placebo	2 (2%)		
Dabrafenib	8 (9%)		1 (1%)
Dabrafenib & Trametinib	64 (71%)		44 (49%)
Dabrafenib & Trametinib/ Placebo	1 (1%)		
Encorafenib & Binimetinib			10 (11%)
Trametinib	1 (1%)		
Vemurafenib	7 (8%)		5 (6%)
Vemurafenib & Cobimetinib	4 (4%)		30 (33%)
Atezolizumab		1 (1%)	
Epacadostat/Placebo + pembrolizumab		2 (2%)	1 (1%)
Ipiluminab		13 (14%)	
Ipiluminab and Nivolumab		28 (31%)	
Ipiliuminab and Pembrolizumab		2 (2%)	
Nivolumab		8 (9%)	
Pembrolizumab		33 (37%)	
Pembrolizumab +/- TVEC trial		1 (1%)	

Discussion and Conclusions

- For patients who experience disease progression after 1st line TT and 2nd line IO, there are limited therapeutic options apart from supportive care and clinical trials pending availability.
- Rechallenge targeted therapy has been used in clinical practice but efficacy is not well reported.
- Rechallenge with TT demonstrated clinically meaningful palliation for this cohort of patients with a BORR of 27%, and little toxicity, although the duration of response was modest at a median of 81 days.
- TT rechallenge should be considered a viable option for palliation in patients with advanced BRAF mutant melanoma who have progressed on 1st and 2nd line therapy.
- This cohort had a poor outcome compared to modern data and this reflects the characteristics of this group-who had a high incidence of baseline CNS disease, progressed on TT and had limited response to 2nd line IO .

Activity and safety of third-line BRAF-targeted therapy (TT) following first-line TT and second-line immunotherapy (IT) in advanced melanoma

Victoria Atkinson, Kathleen Batty, Georgina V. Long, Matteo S. Carlino, Geoffrey David Peters, Prachi Bhave, Maggie A. Moore, Wen Xu, Lauren Julia Brown, Melissa Arneil, Megan Lyle, Alexander M. Menzies

J Clin Oncol 38: 2020 (suppl; abstr 10049)

V této práci byla hodnocena bezpečnost a účinnost cílené léčby BRAFi a MEKi ve 3. linii po předchozím selhání cílené léčby i imunoterapie

Zařazeno bylo 90 pacientů léčených v 1. linii cílenou léčbou (v 80 % D + T)

ORR v 1. linii: CR 20 %, PR 41 %, SD 17 % a PD 13 %. Medián trvání odpovědí 7,2 měsíce (0–33)

Druhá linie imunoterapie: 49 % monoterapie anti PD-1, 33 % kombinace anti PD-1 + anti CTLA-4, 14 % monoterapie anti CTLA-4

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J Clin Oncol 38: 2020 (suppl; abstr 10049)

Třetí linie léčby opět BRAFi a MEKi: 41 % D + T, 33 % V + C, 11 % E + B

Pacienti v pokročilém stadiu onemocnění: 34 % stadium IVc, 51 % ↑ LDH, ORR dosáhly 28 %, medián doby trvání 81 dnů

Medián OS 1,7 roku a 34 % přežívalo v době analýzy

Závěr: i přes progresi v předchozích dvou liniích léčby docházelo u pacientů při podání cílené léčby ve 3. linii k významné léčebné odpovědi

Estimating Treatment-Free Survival Over Extended Follow-up in Patients With Advanced Melanoma Treated With Immune Checkpoint Inhibitors: 5-Year Follow-up of CheckMate 067

Meredith M. Regan,[1,2] Charlene Mantia,[3] Lillian Werner,[1] Ahmad A. Tarhini,[4] Sumati Rao,[5] Andriy Moshyk,[5] Corey Ritchings,[5] Sandra Re,[5] Agnes Balogh,[5] Michael B. Atkins,[6] David F. McDermott[2,3]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Harvard Medical School, Boston, MA, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [5]Bristol Myers Squibb, Princeton, NJ, USA; [6]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA

This study was developed and conducted in collaboration with:

Dana-Farber Cancer Institute; Harvard Medical School; Moffitt Cancer Center; Beth Israel Deaconess Medical Center; Georgetown | Lombardi Comprehensive Cancer Center

Abstract #10043

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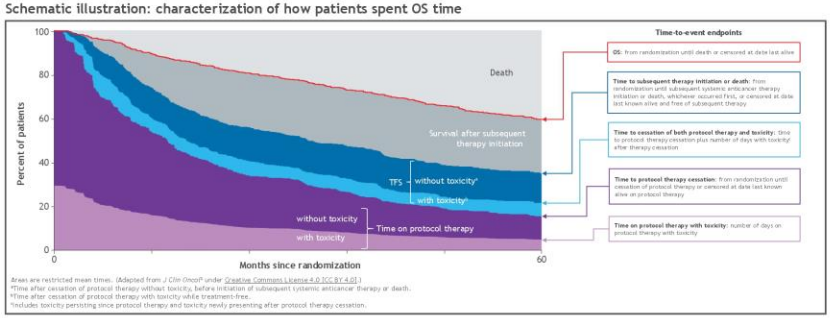
Background

- Immune checkpoint inhibitors (ICIs) produce unique patterns of antitumor response[1]
- Conventional measures, such as median progression-free survival, may characterize the antitumor response with ICIs suboptimally
- We previously defined a novel outcome, treatment-free survival (TFS), to characterize the time between ICI therapy cessation and subsequent therapy initiation or death[2]
  - TFS is part of an integrated analysis to comprehensively describe how patients spend overall survival (OS) time on and off treatment, with and without treatment-related toxicity
  - We initially reported survival states including TFS in ICI-treated patients with advanced melanoma in the phase 3 CheckMate 067 trial (NCT01844505) over the 36-month period since randomization
- A 5-year update of CheckMate 067 recently reported sustained long-term OS with no apparent loss of quality of life in patients who received nivolumab (NIVO)-containing ICI regimens[3]
- Here we present 5-year TFS results from CheckMate 067 to characterize how patients treated with ICI regimens spent OS time and to explore results of the integrated analysis when estimated at sequential analysis time points

Methods

- We analyzed data from 937 patients with advanced melanoma who initiated protocol therapy with NIVO plus ipilimumab (IPI), NIVO alone, or IPI alone in the randomized, placebo-controlled, double-blind phase 3 CheckMate 067 trial
  - NIVO+IPI was administered every 3 weeks (Q3W) for up to 4 doses, followed by NIVO every 2 weeks (Q2W) until disease progression or toxicity (n = 313)
  - NIVO was administered Q2W until disease progression or toxicity (n = 313)
  - IPI was administered Q3W for up to 4 doses (n = 311)
- The analysis population included all patients who initiated protocol ICI therapy
- How patients spent OS time over the 60-month period since randomization was comprehensively characterized by calculating the following (see schematic illustration below):
  - Kaplan-Meier (KM) estimates of time-to-event endpoints
  - Areas under each KM curve, as 60-month restricted mean times of endpoints
  - Areas between KM curves, as 60-month mean times in survival states
  - Between-group differences in mean survival state times, with bootstrapped 95% CIs
- **TFS (blue areas)** was:
  - Defined as the area between the KM curves of time to protocol ICI therapy cessation and time to subsequent therapy initiation or death
  - Partitioned with and without grade ≥ 3 treatment-related adverse events (TRAEs)
- Between-group differences in mean TFS and survival state times were also re-estimated by sequentially restricting follow-up to 24, 36, 48, or 60 months

Schematic illustration: characterization of how patients spent OS time



Results

- **Figure 1** summarizes TFS and survival states over the 60-month period since randomization by treatment regimen, revealing different patterns of time spent on each of the 3 regimens
  - Estimated mean times over the 60-month period and means as percentages of 60 months are provided in the inset table
  - Differences in mean times between NIVO+IPI and the monotherapies are also provided
- **Figure 2** presents TFS and survival state means as percentages of 60 months (using values from the **Figure 1** inset table), along with comparable percentages calculated over a 36-month period of follow-up
  - This illustrates how the times in survival states have shifted with extended follow-up
- **Figure 3** presents TFS and survival-state differences in mean times between NIVO+IPI and the monotherapies when re-estimated by restricting follow-up time to 24, 36, 48, or 60 months
  - In these analyses, mean times with and without toxicity were combined for TFS and for time on protocol therapy
  - These analyses provide insight into conclusions about treatment-group differences depending on time of analysis and how TFS and OS treatment differences compare

NIVO+IPI Versus NIVO

- Over the 60-month period since randomization, patients spent an average of 33% versus 17% of time treatment-free after receiving NIVO+IPI versus NIVO, respectively (**Figure 1A** and **1B**)
  - TFS represented a slightly greater percentage of the 60-month period than when initially estimated over 36 months (30% and 13%, respectively; **Figure 2**)
- In NIVO+IPI-treated patients, mean TFS was 19.7 months of the 60-month period versus 9.9 months in NIVO-treated patients (difference, 9.8 months; 95% CI, 6.7-12.8)
  - The difference in TFS after NIVO+IPI or NIVO was greater when measured over the 60-month than the 36-month period previously analyzed (**Figure 3A**)

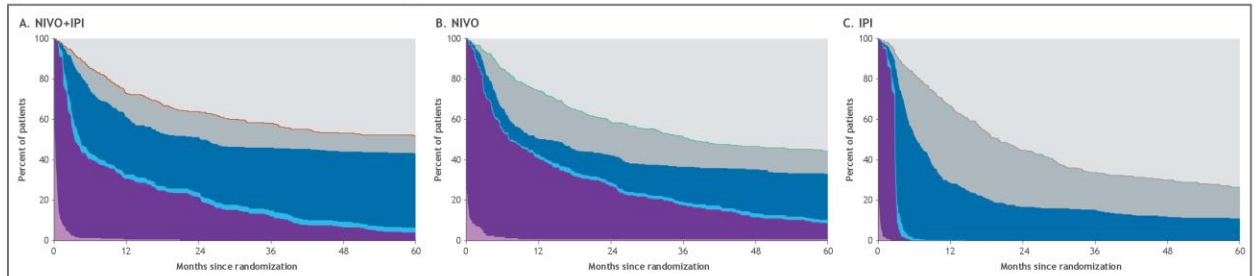
NIVO+IPI Versus IPI

- In contrast to NIVO-containing regimens, in patients treated with IPI, TFS represented a smaller percentage of the 60-month period (20%) than when initially estimated after 36 months of follow-up (25%; **Figure 2**)
- The mean TFS was 11.9 months of the 60-month period since randomization (**Figure 1C**)
- The difference in TFS after NIVO+IPI versus IPI was greater when estimated over the 60-month follow-up time (difference, 7.8 months; 95% CI, 4.6-11.0; **Figure 3B**)

Grade ≥ 3 TRAEs

- Mean TFS with grade ≥ 3 TRAEs remained a small proportion of the 60-month period at 3%, 2%, and < 1% after NIVO+IPI, NIVO, and IPI, respectively (**Figure 2**)

Figure 1. TFS and survival states over the 60-month follow-up period



Survival state	NIVO+IPI 60-mo mean time (mo)	NIVO+IPI Percent of 60-mo period	NIVO 60-mo mean time (mo)	NIVO Percent of 60-mo period	Difference (95% CI): NIVO+IPI vs NIVO (mo)	IPI 60-mo mean time (mo)	IPI Percent of 60-mo period	Difference (95% CI): NIVO+IPI vs IPI (mo)
Overall survival	38.6	64%	36.1	60%	2.5 (−1.1 to 6.2)	28.4	47%	10.2 (6.6 to 13.9)
Survival after subsequent therapy initiation	6.6	11%	9.3	15%	−2.7 (−4.9 to −0.4)	13.9	23%	−7.3 (−9.8 to −4.8)
TFS	19.7	33%	9.9	17%	9.8 (6.7 to 12.8)	11.9	20%	7.8 (4.6 to 11.0)
Without grade ≥ 3 TRAE	18.1	30%	9.0	15%	9.0 (6.1 to 12.0)	11.7	19%	6.4 (3.3 to 9.5)
With grade ≥ 3 TRAE	1.6	3%	0.9	2%	0.7 (−0.4 to 1.8)	0.2	< 1%	1.4 (0.5 to 2.3)
Time on protocol therapy	12.3	21%	16.9	28%	−4.6 (−7.3 to −1.8)	2.6	4%	9.8 (7.9 to 11.6)
Without grade ≥ 3 TRAE	11.8	20%	16.2	27%	−4.4 (−7.1 to −1.7)	2.5	4%	9.3 (7.5 to 11.1)
With grade ≥ 3 TRAE	0.5	1%	0.7	1%	−0.2 (−0.8 to 0.5)	0.1	< 1%	0.4 (0.2 to 0.6)

Figure 2. Percentage of mean times in survival states by follow-up period: 60 versus 36 months

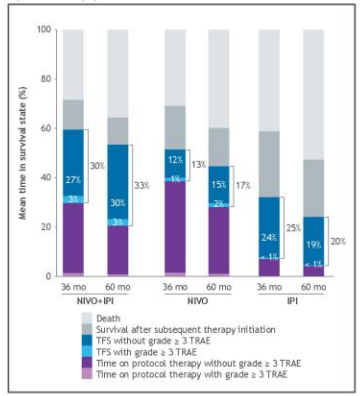
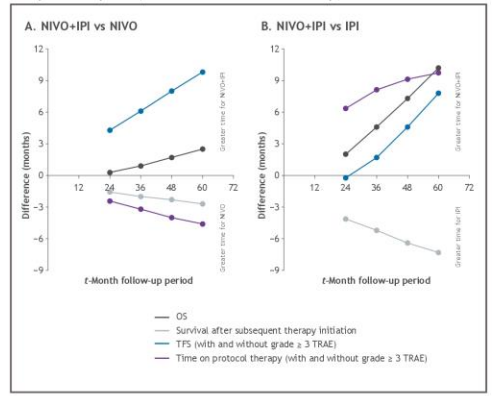


Figure 3. Differences in *t*-month TFS and survival state mean times by analysis time point (*t* = 24-60 months of follow-up)



Conclusions

- The sustained long-term OS benefit observed with NIVO-containing regimens compared with IPI was accompanied by sustained TFS, which represented an increasing percentage of time spent after NIVO+IPI and NIVO, but not after IPI
- On average, patients treated with NIVO+IPI have been treatment-free for one-third of the entire 5-year period since ICI initiation
- Patients treated with NIVO+IPI continued to have TFS twice as long as those treated with NIVO alone, due to earlier therapy cessation for toxicity and subsequent resolution of many of those toxicities without disease progression
- The majority of TFS time was spent without grade ≥ 3 TRAEs after all 3 treatment regimens

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2. Regan MM, et al. *J Clin Oncol* 2019;37:3350-3358.
3. Larkin J, et al. *N Engl J Med* 2019;381:1535-1546.

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MRegan@jimmy.harvard.edu

Estimating Treatment-Free Survival (TFS) Over Extended Follow-up in Patients (pts) With Advanced Melanoma (MEL) Treated With Immune Checkpoint inhibitors (ICIs): Five-Year Follow-up of CheckMate 067

Meredith M. Regan, Charlene Mantia, Lillian Werner, Ahmad A. Tarhini, Sumati Rao, Andriy Moshyk, Corey Ritchings, Jasmine I. Rizzo, Michael B. Atkins, David F. McDermott

J Clin Oncol 38: 2020 (suppl; abstr 10043)

V rámci studie CheckMate 067 (nivolumab + ipilimumab / monoterapie nivolumabem / monoterapie ipilimumabem) bylo mimo jiné hodnoceno také TFS (treatment free survival)

TFS je doba od ukončení imunoterapie do podání další následné léčby nebo úmrtí

Na ASCO®20 Virtual byl hodnocen tento ukazatel u nemocných ve studii CheckMate 067 po 60 měsících sledování

Analyzováno bylo 937 pacientů

TFS bylo rozděleno na TFS provázené nežádoucími účinky a TFS bez nežádoucích účinků léčby

Survival state	NIVO+IPI		NIVO		Difference (95% CI): NIVO+IPI vs NIVO (mo)	IPI		Difference (95% CI): NIVO+IPI vs IPI (mo)
	60-mo mean time (mo)	Percent of 60-mo period	60-mo mean time (mo)	Percent of 60-mo period		60-mo mean time (mo)	Percent of 60-mo period	
Overall survival	38.6	64%	36.1	60%	2.5 (−1.1 to 6.2)	28.4	47%	10.2 (6.6 to 13.9)
Survival after subsequent therapy initiation	6.6	11%	9.3	15%	−2.7 (−4.9 to −0.4)	13.9	23%	−7.3 (−9.8 to −4.8)
TFS	19.7	33%	9.9	17%	9.8 (6.7 to 12.8)	11.9	20%	7.8 (4.6 to 11.0)
Without grade ≥ 3 TRAE	18.1	30%	9.0	15%	9.0 (6.1 to 12.0)	11.7	19%	6.4 (3.3 to 9.5)
With grade ≥ 3 TRAE	1.6	3%	0.9	2%	0.7 (−0.4 to 1.8)	0.2	< 1%	1.4 (0.5 to 2.3)
Time on protocol therapy	12.3	21%	16.9	28%	−4.6 (−7.3 to −1.8)	2.6	4%	9.8 (7.9 to 11.6)
Without grade ≥ 3 TRAE	11.8	20%	16.2	27%	−4.4 (−7.1 to −1.7)	2.5	4%	9.3 (7.5 to 11.1)
With grade ≥ 3 TRAE	0.5	1%	0.7	1%	−0.2 (−0.8 to 0.5)	0.1	< 1%	0.4 (0.2 to 0.6)

Estimating Treatment-Free Survival (TFS) Over Extended Follow-up in Patients (pts) With Advanced Melanoma (MEL) Treated With Immune Checkpoint inhibitors (ICIs): Five-Year Follow-up of CheckMate 067

Meredith M. Regan, Charlene Mantia, Lillian Werner, Ahmad A. Tarhini, Sumati Rao, Andriy Moshyk, Corey Ritchings, Jasmine I. Rizzo, Michael B. Atkins, David F. McDermott

J Clin Oncol 38: 2020 (suppl; abstr 10043)

Studie CheckMate 067	Měsíce		
	Nivo + ipi	Nivo	Ipi
Trvání protokolové léčby	12,3	16,9	2,6
TFS	19,7	9,9	11,9
TFS bez nežádoucích účinků léčby ≥ 3	18,1	9,0	11,7
TFS s nežádoucími účinky léčby ≥ 3	1,6	0,9	0,2

Při srovnání 60měsíčního a 36měsíčního sledování je zřejmé, že nejvíce profitují pacienti léčení kombinací nivo + ipi, kteří mají TFS 2× delší než pacienti léčení monoterapií nivo

Jedním z důvodů je také časnější ukončení kombinované terapie pro toxicitu bez progrese onemocnění

Response to Immune Checkpoint Inhibitor (ICI) Rechallenge After High-Grade Immune Related Adverse Events (irAE) in Patients (pts) With Metastatic Melanoma (MM)

Payal Shah, Patrick Boland, Anna C. Pavlick

J Clin Oncol 38: 2020 (suppl; abstr 10045)

Současná doporučení omezují pokračování imunoterapie u pacientů se závažnými nežádoucími účinky

Retrospektivně hodnoceno 551 pacientů léčených v období od ledna 2014 do ledna 2020 imunoterapií: 180 pacientů (32,7 %) mělo závažné nežádoucí účinky, 91 pacientům (50,6 %) byla po odeznění nežádoucích účinků opakovaně podána imunoterapie

Medián vzniku prvních příznaků nežádoucích účinků po prvním podání imunoterapie byl 7,6 týdne

Většina pacientů (60 %) měla nežádoucí účinky stupně 3 a 40 % stupně 4

Nejčastěji se jednalo o kolitidu (27,5 %), hepatitidu (23,1 %), kožní toxicitu (22,0 %), dále hypofyzitidu (5,5 %) a adrenální insuficienci (5,5 %), neurologické potíže (4,4 %)...

Response to Immune Checkpoint Inhibitor (ICI) Rechallenge After High-Grade Immune Related Adverse Events (irAE) in Patients (pts) With Metastatic Melanoma (MM)

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Medián doby od vzniku prvních nežádoucích účinků do nového podání imunoterapie byl 9,7 týdne

Z 56 pacientů primárně léčených kombinací bylo znovu léčeno kombinací 51,8 % (29) a 48 % (27) monoterapií

Z 35 pacientů primárně léčených monoterapií bylo znovu léčeno monoterapií 60 % (21) a 40 % (14) kombinací

Při mediánu sledování 21,1 měsíce se nežádoucí účinky objevily u 75,8 % (69/91) a z toho u 44,9 % se jednalo o jiný typ toxicity než při první imunoterapii a u 31,9 % se jednalo o závažnou toxicitu

Žádný pacient nezemřel na toxicitu léčby

U 60,4 % pacientů (55/91) došlo ke kontrole onemocnění: 40,7 % (37/91) mělo CR, 11 % (10/91) mělo PR a 8,8 % (8/91) mělo SD

Závěr: opakované podání imunoterapie po odeznění nežádoucích účinků předchozí imunoterapie může být bezpečné a nežádoucí účinky vzniklé při opakovaném podání imunoterapie mohou být odlišné od primární toxicity

Clinical outcomes with early-elective discontinuation of PD-1 inhibitors at one year in patients with metastatic melanoma

Abstract #10048

Rebecca Pokorny[1], Jordan P. McPherson[1], Kenneth F. Grossmann[2], Carolyn Luckett[2], Benjamin Newell Voorhies[3], Daniel S. Sageser[1], Jocelyn Wallentine[1], Zachary Tolman[1], Siwen Hu-Lieskovan[2], Umang Swami[2]
[1]Department of Pharmacy, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [3]Division of Oncology, Department of Medicine, Intermountain Healthcare, Salt Lake City, UT

Background

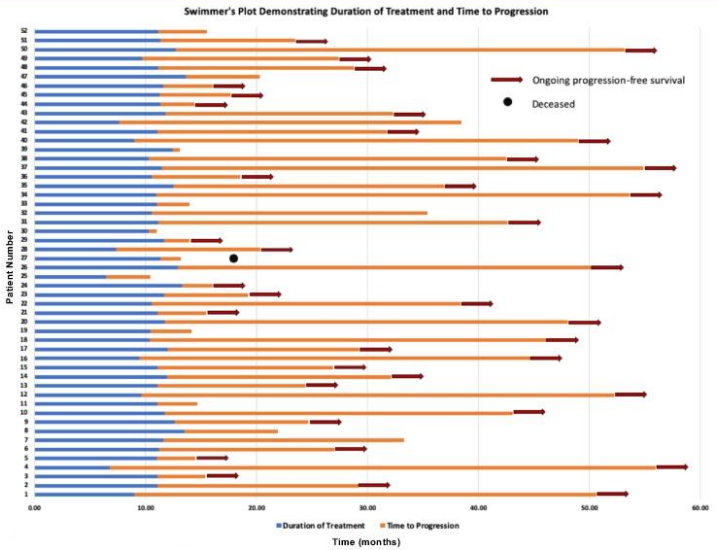
- Randomized trials investigating pembrolizumab and nivolumab in metastatic melanoma permitted treatment for 2 years or more, respectively[1-4]
- PD-1 inhibitors can lead to durable response, however the optimal duration of treatment is unknown
- At Huntsman Cancer Institute (HCI), many patients with advanced melanoma received PD-1 inhibitors and electively discontinued therapy after one year

Purpose: Investigate clinical outcomes of patients with advanced melanoma who electively discontinued PD-1 inhibitors at one year

Methods

- Real-world, retrospective cohort study
- Inclusion: Unresectable stage III or stage IV disease who received single agent PD-1 inhibitor for the first time (>6 mos and <18 mos)
- Exclusion: PD-1 inhibitor with other systemic therapy, discontinuation due to disease progression or immune-related adverse event, and PD-1 inhibitor in neoadjuvant, adjuvant, or clinical trial settings
- Data analysis: Best overall response (BOR) per RECIST 1.1 at PD-1 inhibitor discontinuation, PFS, and retreatment characteristics

In the largest continuous series of pts with advanced melanoma who electively discontinued PD-1 inhibitors after 1 year, the majority (75%) remained without progression at a median follow-up of 20.5 months



Future Directions

- Prospective validation of results in a randomized controlled trial

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@umangtalking Correspondence: Umang Swami at umang.swami@hci.utah.edu

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Clinical outcomes with early-elective discontinuation of PD-1 inhibitors (PDi) at one year in patients (pts) with metastatic melanoma (MM)

Rebecca Pokorny, Jordan P. McPherson, Kenneth F. Grossmann, Carolyn Luckett, Benjamin Newell Voorhies, Daniel S. Sageser, Jocelyn Wallentine, Zachary Tolman, Siwen Hu-Lieskovan, Umang Swami

J Clin Oncol 38: 2020 (suppl; abstr 10048)

Hodnoceno bylo 52 pacientů léčených monoterapií anti PD-1 protilátkami

Medián podávání terapie byl 11,1 měsíce: 25 % pacientů bylo v CR, 53,8 % mělo PR, 21,2 % SD

Při mediánu sledování 20,5 měsíce po ukončení léčby zůstávalo 75 % pacientů bez progrese

Ze 13 nemocných, kteří měli progresi, jich pět bylo léčeno znovu anti PD-1 protilátkami a u všech došlo ke kontrole onemocnění

Závěr: výsledky naznačují, že je možné uvažovat o zkrácení doby podávání anti PD-1 protilátek, aniž by došlo k významnému snížení účinnosti, ale došlo by ke snížení toxicity, která může léčbu provázet

Abstract 10054: Landmark Analysis of Immunotherapy Duration and Disease-Free Survival in Advanced Melanoma Patients with a Complete Response

Authors: Grayce N. Selig, Alexander Chan Chi Huang, Giorgos C. Karakousis, Wei Xu, Cathy Zheng, Mary Carberry, Lydia Giles, Kristin Kreider, Suzanne McGettigan, John Nicholas Lukens, Lynn Mara Schuchter, Ravi K. Amaravadi, Tara C. Mitchell

Department of Medicine, University of Pennsylvania, Philadelphia, PA; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

Perelman School of Medicine
University of Pennsylvania

Background

- Checkpoint blockade has improved survival in patients with advanced melanoma. A durable complete response has been observed.
- Based on protocol requirement from early clinical trails of PD-1 blockade, immunotherapy has typically been continued for 24 months in patients with a confirmed response (CR). However, if a CR was achieved early, patients and their physicians could decide stop treatment as early as 6 months assuming they had completed at least two cycles of treatment after CR was confirmed.
- Treatment durations of less then 24 months have not been adequately studied nor have outcomes been reported.
- Shorter treatment durations would not only reduce health care costs but would presumably decrease adverse events and improve quality of life.

Methods

- 45 patients with locally advanced stage III and IV melanoma who received immunotherapy and achieved a CR were identified from the Abramson Cancer Center patient pool.
- Disease-free survival (DFS), durable complete response (CR) and disease recurrence were analyzed in patients receiving greater than verse less then 7 months of therapy.
- DFS was defined as the time from CR until recurrence or date of data analysis.
- Seven months was selected as the cut off in order to capture patients who had an early complete response, confirmed by two scans 4 weeks apart, and elected to stop treatment early. Per prior protocol criteria, patients were eligible to terminate treatment after receiving at least 6 months of therapy plus two doses beyond their confirmed complete response. The median time to CR in these patients was 4.7 months. They then had to receive an additional 2 treatments.

Demographics		
Gender, N (%)	Male Female	31 (69) 14 (31)
Age, Median (range)		65.3 (34-98)
Cancer Stage, N (%)	Stage III Stage IV	8 (18) 37 (82)
BRAF Status, N (%)	WT Mutant Unknown	25 (55.5) 7 (15.5) 13 (29)
ECOG	0 1 2	36 (80) 8 (17.8) 1 (2.2)

Melanoma patients who stop ***immunotherapy*** prior to 7 months have a ***durable complete response without reduction*** in ***disease free survival*** or ***recurrence*** compared to those treated longer then 7 months

Correspondence: Grayce N. Selig, MD; grayce.selig@pennmedicine.upenn.edu

Penn Medicine

Results

- Patients who stopped treatment prior to 7 months, either due to CR or toxicity, had an equally durable CR compared to those treated for more then 7 months. These patients had no reduction in DFS.
- Patients who stopped therapy early due to toxicity (Treatment duration range: 1 day to 24.2 months) and subsequently achieved a CR, had no difference in DFS compared to those who were treated until CR (Treatment duration range: 4.8 to 20.3 months).
- There was no statistically significant difference in disease recurrence after achieving a CR in patients treated with longer treatment courses versus those who stopped therapy prior to 7 months.
  - Patients who were treated for less then 7 months and those who stopped treatment due to an adverse reaction, saw a fewer number of recurrences than those who were treated for over 7 months or stopped treatment due after a CR.

	# Patients	% Patients	Median Tx Duration (months)	Range of Tx	Time to CR (months)	Median DFS (months)	95% CI	Range of DFS (months)	# Patients Recurred
Tx <7 months (0-212d)	27	60	4.8	1d to 6.7m	4.7	30.4	23.7 to 37.2	2.9 to 65.7	2/27 (7.4%)
Tx >7 months (>212d)	18	40	12.4	7.5 to 24.2m	11.8	28	18.9 to 37	8.5 to 73.7	3/18 (16%)
Stopped Due to Toxicity	17	40	3.7	1d to 24.2m	4.7	30.4	20.7 to 40.1	2.9 to 65.7	1/17 (5.8%)
Stopped after CR	28	60	8.5	4.8 to 20.3m	5.8	27.6	21.2 to 34	7.2 to 73.7	4/28 (16%)
Overall	45	100	5.8	1d to 24.2m	5.6	28.6	23.3 to 34	2.9 to 73.7	5/45(11.1%)

Future Direction for Research

- Patients treated with shorter immunotherapy courses have an equally durable response compared to those treated with longer duration of therapy. We will continue to expand our panel size and monitor disease recurrence over a longer duration to expand our current data.
- We are currently evaluating quality of life metrics, including physical, emotional and social well-being in this patient population. We will look to see if quality of life improves in relation to therapy duration and treatment side effects

Landmark Analysis of Immunotherapy Duration and Disease-Free Survival in Advanced Melanoma Patients With a Complete Response

Grayce N. Selig, Alexander Chan Chi Huang, Giorgos C. Karakousis, Wei Xu, Cathy Zheng, Mary Carberry, Lydia Giles, Kristin Kreider, Suzanne McGettigan, John Nicholas Lukens, Lynn Mara Schuchter, Ravi K. Amaravadi, Tara C. Mitchell

J Clin Oncol 38: 2020 (suppl; abstr 10054)

Jak dlouho podávat imunoterapii zejména v případě dosažení CR, je stále nezodpovězená otázka

V této práci byla u 45 pacientů léčených imunoterapií (pembro, nivo, ipi + nivo) ukončena léčba po dosažení CR

Hodnocena byla doba přežití bez známek onemocnění (DFS)
(doba od dosažení CR do recidivy či data hodnocení)

Analýza DFS byla vztažena k celkové době podávání léčby, méně nebo více než sedm měsíců k důvodu ukončení léčby (toxicita či dosažení CR)

Doba léčby	CR	Medián DFS
≤ 7 měsíců	60 %	30,4 měsíce
> 7 měsíců	40 %	28,0 měsíce
Ukončení pro toxicitu		30,4 měsíce
Ukončení pro CR		27,6 měsíce

Závěr: Nebyl pozorován statisticky významný rozdíl mezi mediánem DFS a dobou podávání léčby ani důvodem jejího ukončení

CheckMate 067: Long-Term Outcomes in Patients With Mucosal Melanoma

10019

Alexander N. Shoushtari,[1] John Wagstaff,[2] Paolo A. Ascierto,[3] Marcus O. Butler,[4] Christopher D. Lao,[5] Iván Márquez-Rodas,[6] Vanna Chiarion-Sileni,[7] Reinhard Dummer,[8] Pier F. Ferrucci,[9] Paul Lorigan,[10] Michael Smylie,[11] Wim van Dijck,[12] Sandra Re,[12] F. Stephen Hodi,[13]* James Larkin[14]*

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]The College of Medicine, Swansea University, Swansea, United Kingdom; [3]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [4]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [5]University of Michigan, Ann Arbor, MI, USA; [6]General University Hospital Gregorio Marañón & CIBERONC, Madrid, Spain; [7]Oncology Institute of Veneto IRCCS, Padua, Italy; [8]Universitäts Spital, Zurich, Switzerland; [9]European Institute of Oncology IRCCS, Milan, Italy; [10]University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom; [11]Cross Cancer Institute, Edmonton, Alberta, Canada; [12]Bristol Myers Squibb, Princeton, NJ, USA; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom

*Contributed equally

Background

- Mucosal melanoma is a rare but aggressive malignancy with a poor prognosis and 5-year survival rates of 14%-25%, depending on the stages considered[1,2]
- Practice-changing clinical trial results led to the approval of checkpoint inhibitors in the treatment of metastatic melanoma, including nivolumab (NIVO) monotherapy and combination therapy with nivolumab plus ipilimumab (NIVO+IPI)
- Although response was lower than in the overall population, limited short-term data indicated clinical benefit with NIVO+IPI, NIVO, and IPI in patients with mucosal melanoma in a pooled study that included data from CheckMate 067[3]
- Other trials also showed activity of NIVO or pembrolizumab treatment in patients with mucosal melanoma, but without long-term follow-up[4-6]
- Here we report 5-year outcomes in the subgroup of patients with mucosal melanoma treated with NIVO+IPI, NIVO alone, or IPI alone in the phase 3 CheckMate 067 trial

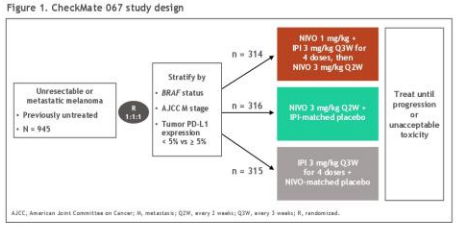
Objective

- The purpose of this analysis was to investigate long-term clinical outcomes with NIVO and IPI, alone or in combination, in patients with mucosal melanoma

Methods

- In CheckMate 067 (NCT01844505), patients with previously untreated stage III or stage IV melanoma were randomized 1:1:1 to receive NIVO+IPI, NIVO monotherapy, or IPI monotherapy (**Figure 1**)
- Co-primary endpoints were progression-free survival (PFS) and overall survival (OS) in the NIVO-containing arms versus IPI alone
  - Secondary endpoints included objective response rate (ORR) by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), correlation of programmed death ligand 1 (PD-L1) with survival endpoints, and safety
  - The study was not powered for a comparison between NIVO+IPI and NIVO
- Mucosal histology was not a stratification factor in the study
- Patients with mucosal melanoma were identified by investigators
- At the database lock on July 2, 2019, minimum follow-up was 60 months for all patients in the study

Figure 1. CheckMate 067 study design



AJCC, American Joint Committee on Cancer; M, metastasis; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized.

Results

Patients

- A total of 79 patients with mucosal melanoma were treated (**Figure 2**)
  - Patients in the NIVO group received the highest number of study treatment doses (median 7 doses)
  - The most common reason for discontinuing treatment was treatment-related adverse events (TRAEs) for patients treated with NIVO+IPI and disease progression for patients treated with NIVO or IPI monotherapy
- The mucosal melanoma population had generally poorer prognostic factors and a higher proportion of women compared to the intent-to-treat (ITT) population (**Table 1**)

Figure 2. Disposition and exposure of patients with mucosal melanoma

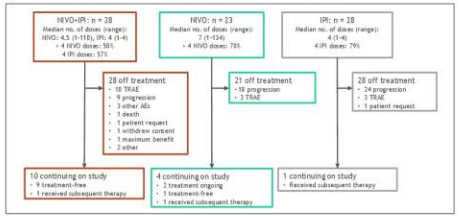


Table 1. Baseline characteristics in the mucosal and ITT populations

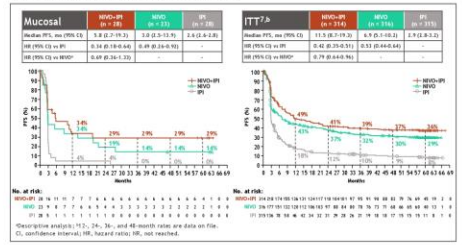
	NIVO+IPI		NIVO		IPI	
	Mucosal (n = 28)	ITT (n = 314)[a]	Mucosal (n = 23)	ITT (n = 316)[a]	Mucosal (n = 28)	ITT (n = 315)[a]
Median age, years (range)	64 (35-84)	61 (18-88)	61 (27-88)	60 (25-90)	61 (39-77)	62 (18-89)
Male, n (%)	13 (46)	206 (66)	11 (48)	202 (64)	15 (54)	202 (64)
ECOG PS 0, n (%)	18 (64)	208 (73)	17 (74)	237 (75)	19 (68)	224 (71)
***BRAF* mutation, n (%)**	2 (7)	101 (32)	0	100 (32)	3 (11)	97 (31)
LDH, n (%)						
≤ ULN	13 (46)	199 (63)	12 (52)	197 (62)	14 (50)	194 (62)
> ULN	15 (54)	114 (36)	11 (48)	112 (35)	13 (46)	115 (37)
> 2 × ULN	6 (21)	37 (12)	5 (22)	37 (12)	4 (14)	30 (10)
Not reported	0	1 (< 1)	0	7 (2)	1 (4)	6 (2)
PD-L1 expression, n (%)						
< 5%	21 (75)	210 (67)	16 (70)	208 (66)	21 (75)	202 (64)
≥ 5%	4 (14)	68 (22)	3 (13)	80 (25)	1 (4)	75 (24)
Not reported	3 (11)	36 (11)	4 (17)	28 (9)	6 (21)	38 (12)
History of brain metastases, n (%)	3 (11)	11 (4)	0	7 (2)	0	15 (5)
M stage, n (%)						
M0, M1A, or M1B	9 (32)	133 (42)	7 (30)	132 (42)	12 (43)	132 (42)
M1C	19 (68)	181 (58)	16 (70)	184 (58)	16 (57)	183 (58)
Sum of diameters of target lesions (mm), median (range)[b]	59 (10-153)	54 (10-372)	57 (10-200)	54 (10-384)	61 (14-240)	55 (10-283)
Number of lesion sites, n (%)						
1	4 (14)	89 (28)	5 (22)	80 (25)	10 (36)	84 (27)
2-3	18 (64)	165 (53)	13 (57)	176 (56)	15 (54)	170 (54)
> 3	6 (21)	60 (19)	5 (22)	59 (19)	3 (11)	61 (19)

[a]Primary site data were not collected.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Efficacy

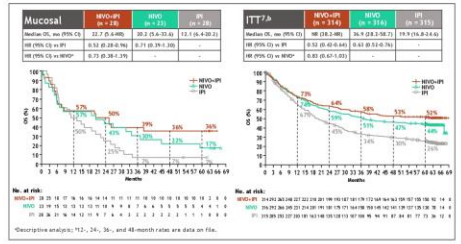
- In the mucosal melanoma population, NIVO+IPI treatment (compared with NIVO or IPI alone) was associated with
  - Higher 5-year PFS (29% vs 14% and 0%, respectively; **Figure 3**)
  - Higher 5-year OS (36% vs 17% and 7%; **Figure 4**)
- Although these trends were consistent with those of the ITT population, efficacy outcomes were generally less favorable overall in the mucosal melanoma population versus the ITT population
- In addition, differences between PFS and OS were less pronounced in the mucosal population for all treatment groups compared with the ITT population
- In patients with mucosal melanoma, ORR was higher for NIVO+IPI than for NIVO or IPI alone, similar to the ITT population (**Table 2**)
- ORR differences between the mucosal and ITT populations were similar for all treatment groups
  - ORR rates for the mucosal and ITT populations were 43% and 58% for NIVO+IPI, 30% and 45% for NIVO, and 7% and 19% for IPI, respectively
    - The difference in complete response (CR) rates between the mucosal and ITT populations was greater for NIVO-treated patients than for NIVO+IPI-treated patients (4% and 19% vs 14% and 22%, respectively)
- Median duration of response
  - Has not yet been reached for NIVO+IPI-treated patients with mucosal melanoma or the ITT population, nor for the NIVO-treated patients in the ITT population
  - Was 18.7 months for NIVO-treated patients with mucosal melanoma

Figure 3. PFS in the mucosal and ITT populations



*Descriptive analysis; †12-, 24-, 36-, and 48-month rates are data on file.
CI, confidence interval; HR, hazard ratio; NR, not reached.

Figure 4. OS in the mucosal and ITT populations



*Descriptive analysis; †12-, 24-, 36-, and 48-month rates are data on file.

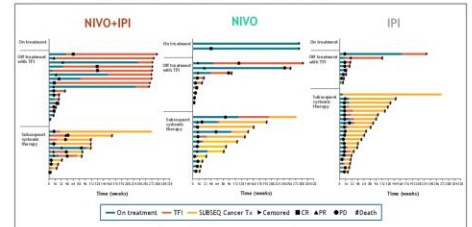
Table 2. Response in the mucosal and ITT populations

	NIVO+IPI		NIVO		IPI	
	Mucosal (n = 28)	ITT[a] (n = 314)	Mucosal (n = 23)	ITT[a] (n = 316)	Mucosal (n = 28)	ITT[a] (n = 315)
ORR, % (95% CI)	43 (24-63)	58 (53-64)	30 (13-53)	45 (39-50)	7 (1-24)	19 (15-24)
Best overall response, n (%)						
Complete response	4 (14)	69 (22)	1 (4)	60 (19)	0 (0)	18 (6)
Partial response	8 (29)	114 (36)	6 (26)	81 (26)	2 (7)	42 (13)
Stable disease	4 (14)	38 (12)	2 (9)	30 (9)	1 (4)	69 (22)
Progressive disease	9 (32)	74 (24)	11 (48)	121 (38)	25 (89)	159 (50)
Unknown	3 (11)	19 (6)	3 (13)	24 (8)	0 (0)	27 (9)
Median duration of response, mo (95% CI)	NR (7.6-NR)	NR	18.7 (2.8-NR)	NR (50.4-NR)	11.1 (3.0-19.2)	14.4 (8.3-53.6)
Median time to response, mo (range)	2.9 (1.9-9.9)	2.8 (1.1-27.8)[a]	2.8 (2.4-6.9)	2.8 (2.3-42.9)[a]	4.6 (2.6-6.6)	2.9 (2.5-49.7)[a]

[a]Data on file.

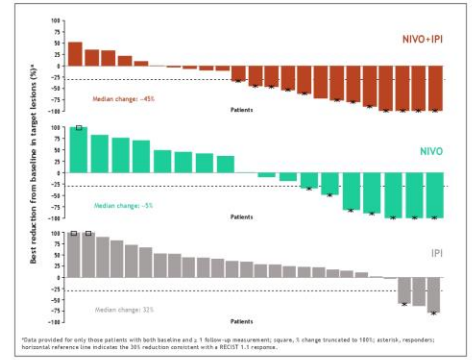
- Responses were durable in patients with mucosal melanoma (**Figure 5**)
  - 9 patients in the NIVO+IPI group who have discontinued treatment and have not started subsequent systemic therapy (thus, were treatment-free) were still alive and being followed at 60 months, including 3 who were treated for ≤ 16 weeks
  - In the NIVO group, 4 patients were alive and being followed at 60 months, including 2 patients who remained on treatment and 1 patient who had discontinued treatment at 48 weeks and remained treatment-free
- Patients with mucosal melanoma treated with NIVO+IPI had the greatest decrease in tumor burden, with a median change of -45% (**Figure 6**)

Figure 5. Time to and duration of response in the mucosal population



PD, progressive disease; PR, partial response; SUBSEQ Cancer Tx, subsequent systemic therapy; TFI, treatment-free interval.

Figure 6. Tumor burden change from baseline in the mucosal population



*Data provided for only those patients with both baseline and ≥ 1 follow-up measurement; square, % change truncated to 100%; asterisk, responders; horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response.

Safety

- Both the incidence of any-grade and grade 3/4 TRAEs was similar in patients in the mucosal subgroup and the ITT population (**Table 3**)

Subsequent therapy

- In patients with mucosal melanoma, fewer patients in the NIVO+IPI group received subsequent therapy than in the NIVO or IPI monotherapy groups, similar to that observed in the ITT population (**Table 4**)
- The proportion of patients who received any subsequent therapy was similar for the mucosal compared with the ITT population for both NIVO+IPI- and IPI-treated patients
  - For NIVO-treated patients, the proportion of patients with any subsequent therapy was higher in the mucosal compared with the ITT population (70% vs 59%, respectively); there was also a greater proportion of patients who received subsequent radiotherapy (39% vs 29%, respectively)
- Subsequent anti-programmed death (PD)-1 therapy or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) therapy was received by 17% and 39% of NIVO-treated patients and 50% and 11% of IPI-treated patients, respectively
- Of patients alive and being followed at 5 years treated with NIVO+IPI, 1 of 10 have received subsequent systemic therapy and 9 of 10 were treatment-free

Table 3. Safety summary

	NIVO+IPI, n (%)		NIVO, n (%)		IPI, n (%)	
	Mucosal (n = 28)	ITT[a] (n = 313)	Mucosal (n = 23)	ITT[a] (n = 313)	Mucosal (n = 28)	ITT[a] (n = 311)
Any-grade TRAEs	27 (96)	300 (96)	19 (83)	271 (87)	22 (79)	268 (86)
Grade 3/4 TRAEs	15 (54)	186 (59)*	6 (26)	73 (23)*	7 (25)	86 (28)*
Increased lipase	4 (14)	34 (11)	2 (9)	18 (6)	3 (11)	12 (4)
Diarrhea	2 (7)	30 (10)	2 (9)	9 (3)	1 (4)	18 (6)
Increased amylase	2 (7)	9 (3)	0	7 (2)	2 (7)	4 (1)
Increased aspartate aminotransferase	2 (7)	19 (6)	0	3 (1)	0	2 (1)
Colitis	1 (4)	26 (8)	1 (4)	3 (1)	2 (7)	24 (8)
Fatigue	1 (4)	13 (4)	1 (4)	3 (1)	0	3 (1)
Pruritus	1 (4)	6 (2)	0	1 (< 1)	0	1 (< 1)
Rash	1 (4)	10 (3)	0	1 (< 1)	0	5 (2)
Hypophysitis	0	5 (2)	0	1 (< 1)	0	5 (2)
Increased alanine aminotransferase	0	27 (9)	0	4 (1)	1 (4)	5 (2)
Maculopapular rash	0	6 (2)	0	2 (1)	0	1 (< 1)
Nausea	0	7 (2)	0	0	0	2 (1)
Vomiting	0	7 (2)	0	1 (< 1)	0	1 (< 1)

*Individual grade 3/4 TRAEs are those occurring in ≥ 2% patients in the ITT population.

Table 4. Subsequent therapy in the mucosal and ITT populations

	NIVO+IPI, n (%)		NIVO, n (%)		IPI, n (%)	
	Mucosal (n = 28)	ITT[a] (n = 314)	Mucosal (n = 23)	ITT[a] (n = 316)	Mucosal (n = 28)	ITT[a] (n = 315)
Any subsequent therapy*	13 (46)	143 (46)	16 (70)	185 (59)	23 (82)	237 (75)
Subsequent systemic therapy	11 (39)	109 (35)	12 (52)	152 (48)	20 (71)	207 (66)
Subsequent immunotherapy	7 (25)	55 (18)	9 (39)	105 (33)	15 (54)	149 (47)
Anti-PD-1 agents[b]	6 (21)	39 (12)	4 (17)	49 (16)	14 (50)	144 (46)
Anti-CTLA-4 agents[b]	2 (7)	21 (7)	9 (39)	91 (29)	3 (11)	16 (5)
BRAF inhibitor[c]	0	43 (14)	1 (4)	60 (19)	2 (7)	72 (23)
MEK/NRAS inhibitor[c]	0	33 (11)	1 (4)	43 (14)	1 (4)	42 (13)
Subsequent radiotherapy	3 (11)	66 (21)	9 (39)	93 (29)	12 (43)	126 (40)
Subsequent surgery	5 (18)	65 (21)	4 (17)	72 (23)	8 (29)	94 (30)

*Patients may have received > 1 subsequent therapy; †May include patients treated with anti-PD-1+anti-CTLA-4 combination; ‡May include patients treated with BRAF+MEK inhibitor combination.

Conclusions

- This 5-year analysis showed that patients with mucosal melanoma in CheckMate 067 had similar safety outcomes but poorer long-term efficacy versus the ITT population
- Patients with mucosal melanoma treated with NIVO+IPI demonstrated more favorable survival outcomes than those treated with NIVO or IPI alone
  - 5-year PFS (29%, 14%, and 0, respectively)
  - 5-year OS (36%, 17%, and 7%)
- The addition of IPI to NIVO treatment in patients with mucosal melanoma appeared to increase the rate of CRs and the duration of response compared with NIVO alone
  - 9 of 28 patients in the NIVO+IPI group (32% of the total group) discontinued treatment and remained treatment-free at 60 months from randomization
- In the mucosal patient population, PFS appeared to be an appropriate surrogate for OS
- While NIVO+IPI demonstrated the highest long-term efficacy in this study, novel therapies are needed to further improve benefit in patients with mucosal melanoma

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Collaborations:
- Dako, an Agilent Technologies, Inc. company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay (Santa Clara, CA)
- Bristol-Myers Squibb Company (Princeton, NJ) and ONO Pharmaceutical Company Ltd. (Osaka, Japan)

CheckMate 067: Long-Term Outcomes in Patients With Mucosal Melanoma

Alexander Noor Shoushtari, John Wagstaff, Paolo Antonio Ascierto, Marcus O. Butler, Christopher D. Lao, Ivan Marquez-Rodas, Vanna Chiarion-Sileni, Reinhard Dummer, Pier F. Ferrucci, Paul Lorigan, Michael Smylie, Wim van Dijck, Jasmine I. Rizzo, F. Stephen Hodi, James M. G. Larkin

J Clin Oncol 38: 2020 (suppl; abstr 10019)

Slizniční melanom patří mezi vzácné klinické varianty, ale má většinou velmi závažnou prognózu

V rámci studie CheckMate 067 bylo léčeno 79 pacientů se slizničním melanomem

Pětiletá analýza ukázala, že nejvyšší účinnost u nemocných s tímto typem melanomu měla kombinovaná imunoterapie nivo + ipi

ORR: 43 % u kombinace proti 30 % u monoterapie nivo a 7 % u monoterapie ipi (CR 14 % / 4 % / 0 %)

Bez progrese bylo při minimálním sledování 60 měsíců 29 % pacientů u kombinace proti 14 % u monoterapie a 0 % u monoterapie ipi

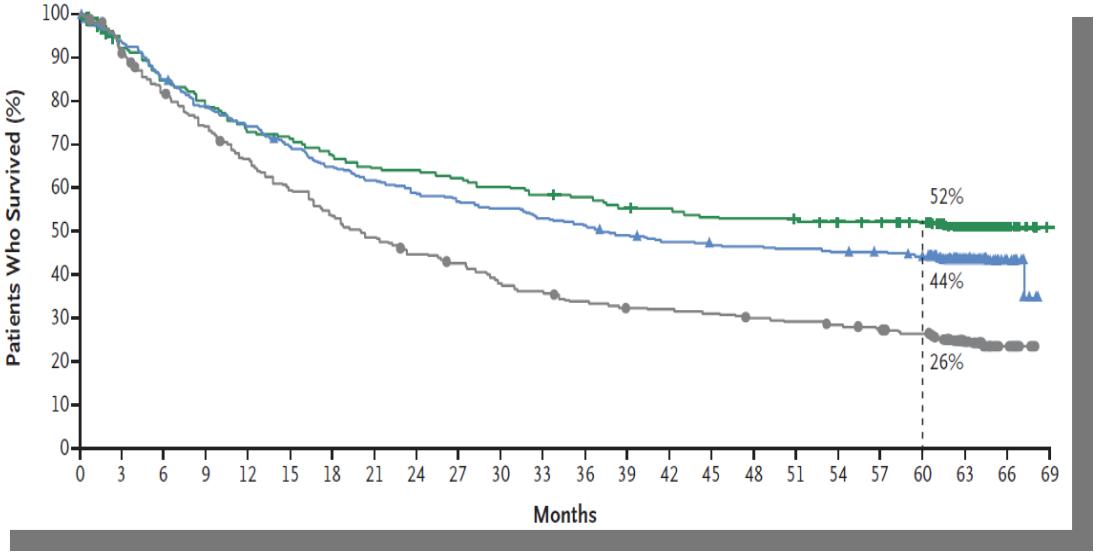
CheckMate 067: Long-Term Outcomes in Patients With Mucosal Melanoma

Alexander Noor Shoushtari, John Wagstaff, Paolo Antonio Ascierto, Marcus O. Butler, Christopher D. Lao, Ivan Marquez-Rodas, Vanna Chiarion-Sileni, Reinhard Dummer, Pier F. Ferrucci, Paul Lorigan, Michael Smylie, Wim van Dijck, Jasmine I. Rizzo, F. Stephen Hodi, James M. G. Larkin

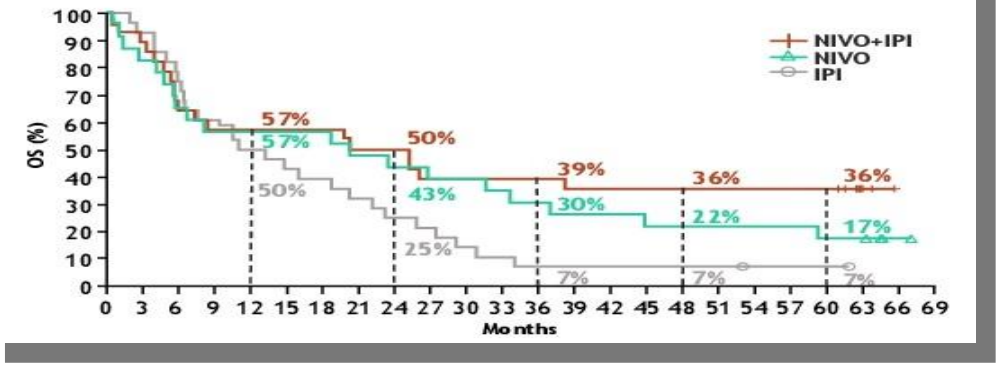
J Clin Oncol 38: 2020 (suppl; abstr 10019)

Pět let přežívalo 36 % pacientů léčených kombinací, 17 % léčených monoterapií nivo, 7 % léčených ipi

Závěr: účinnost u slizničního melanomu byla nižší než u kožního melanomu, ale kombinovaná imunoterapie nivo + ipi prokázala výrazně vyšší účinnost než monoterapie



Mucosal	NIVO+IPI (n = 28)	NIVO (n = 23)	IPI (n = 28)
Median OS, mo (95% CI)	22.7 (5.6-NR)	20.2 (5.6-33.6)	12.1 (6.4-20.2)
HR (95% CI) vs IPI	0.52 (0.28-0.96)	0.71 (0.39-1.30)	-
HR (95% CI) vs NIVO[a]	0.73 (0.38-1.39)	-	-



Phase 2 Study of Cemiplimab in Patients with Advanced Cutaneous Squamous Cell Carcinoma (CSCC): Longer Follow-Up

Danny Rischin,[1] Nikhil I. Khushalani,[2] Chrysalyne D. Schmults,[3] Alexander Guminski,[4] Anne Lynn S. Chang,[5] Karl D. Lewis,[6] Annette M. Lim,[1] Leonel Hernandez-Aya,[7] Brett G.M. Hughes,[8] Dirk Schadendorf,[9] Axel Hauschild,[10] Elizabeth Stankevich,[11] Jocelyn Booth,[11] Suk-Young Yoo,[11] Zhen Chen,[12] Emmanuel Okoye,[13] Israel Lowy,[12] Matthew G. Fury,[12] Michael R. Migden[14]

[1]*Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia;* [2]*Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL, USA;* [3]*Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [4]*Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia;* [5]*Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA;* [6]*University of Colorado Denver, School of Medicine, Aurora, CO, USA;* [7]*Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA;* [8]*Royal Brisbane & Women's Hospital and University of Queensland, Brisbane, Australia;* [9]*University Hospital Essen, Essen and German Cancer Consortium, Essen, Germany;* [10]*Schleswig-Holstein University Hospital, Kiel, Germany;* [11]*Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA;* [12]*Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA;* [13]*Regeneron Pharmaceuticals, Inc., London, UK;* [14]*Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Background

- Cutaneous squamous cell carcinoma (CSCC) is the second most common cancer in the US and its incidence is increasing.[1]
- Most cases of CSCC are cured by complete surgical excision.[2,3] However, a small but substantial number of patients present with either metastatic CSCC (mCSCC) or locally advanced CSCC (laCSCC) not amenable to curative surgery or curative radiotherapy (collectively referred to as "advanced CSCC"), both of which have poor prognoses.[4–6]
- Historical data shows median overall survival (OS) of approximately 15 months with conventional chemotherapy or epidermal growth factor receptor inhibitors.[7]
- Cemiplimab is a high-affinity, highly potent human immunoglobulin G4 monoclonal antibody to the programmed cell death (PD)-1 receptor.[8]
- Cemiplimab monotherapy achieved clinically meaningful activity in patients with advanced CSCC and has a safety profile consistent with other anti–PD-1 inhibitors.[9–11]
- Based on initial data (median follow-up of 9.4 months in the pivotal study, NCT02760498), cemiplimab (cemiplimab-rwlc in the US) was approved for the treatment of patients with advanced CSCC.

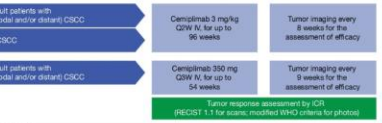
Objective

- The primary objective of the Phase 2 study was to evaluate the objective response rate (ORR) by independent central review (ICR) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) (for scans)[12] and modified World Health Organization (WHO) criteria (for photos).
- Key secondary objectives included ORR per investigator review (INV), duration of response (DOR) by ICR and INV, progression-free survival (PFS) by ICR and INV, OS, complete response rate by ICR, safety and tolerability, and assessment of health-related quality of life. Durable disease control rate, defined as the proportion of patients with response or stable disease for at least 105 days, was also examined.
  - Please see poster #382 for results on health-related quality of life data from this study.
- Here, we present up to 3-year follow-up (median duration of follow-up for all patients: 15.7 months) from the largest and most mature prospective data set in advanced CSCC.

Methods

- EMPOWER-CSCC-1 is an open-label, non-randomized, multicenter, international Phase 2 study of patients with advanced CSCC.
- Patients received cemiplimab 3 mg/kg every 2 weeks (Q2W) (Group 1; mCSCC; Group 2, laCSCC) or cemiplimab 350 mg every 3 weeks (Q3W) (Group 3, mCSCC) (**Figure 1**).
- The severity of treatment-emergent adverse events (TEAEs) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).
- The data cut-off was October 11, 2019.

Figure 1. Study design



ECOG, Eastern Cooperative Oncology Group; IV, intravenously; PD-L1, PD-ligand 1.

Results

Patients

- A total of 193 patients were enrolled (Group 1, n=59; Group 2, n=78; Group 3, n=56) (**Table 1**).

Table 1. Baseline demographics

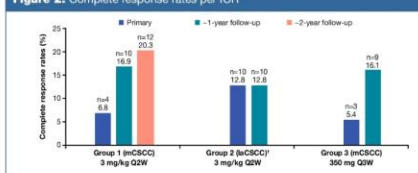
	Advanced CSCC (n=193)
Median age, years (range)	72.0 (38–96)
Male, n (%)	161 (83.4)
ECOG performance status, n (%)	
0	86 (44.6)
1	107 (55.4)
Primary CSCC site: head and neck, n (%)	131 (67.9)
mCSCC, n (%)	115 (59.6)
laCSCC, n (%)	78 (40.4)
Patients with cemiplimab as first-line therapy, n (%)	128 (66.3)
Patients with prior systemic therapy, n (%)[†]	65 (33.7)
Median duration of exposure to cemiplimab, weeks (range)	51.1 (2.0–109.3)
Median number of doses of cemiplimab administered (range)	18.0 (1–48)

[†]Settings for prior lines of therapy included metastatic disease, adjuvant, chemotherapy with concurrent radiation, or other and the most common types of prior systemic therapy were platinum compounds (n=46/65 [70.8%]) and monoclonal antibodies (n=18/65 [27.7%]).

Clinical activity

- Complete response rates at primary analysis, ~1 year follow-up for Groups 1, 2, and 3, and ~2 year follow-up for Group 1 are shown in **Figure 2**.
- Among 89 responders, median time to complete response was 11.2 months (interquartile range [IQR], 7.4–14.8).

Figure 2. Complete response rates per ICR



†Among 23 laCSCC patients who were included in the pre-specified Group 2 interim analysis, there were no complete responses.

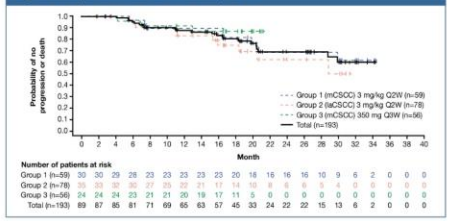
Table 2. Duration of follow-up and tumor response to cemiplimab per ICR

	Group 1 (mCSCC) 3 mg/kg Q2W (n=59)	Group 2 (laCSCC) 3 mg/kg Q2W (n=78)	Group 3 (mCSCC) 350 mg Q3W (n=56)	Total (n=193)
Median duration of follow-up, months (range)	18.5 (1.1–36.1)	15.5 (0.8–35.6)	17.3 (0.6–26.3)	15.7 (0.6–36.1)
ORR, % (95% CI)	50.8 (37.5–64.1)	44.9 (33.6–56.6)	42.9 (29.7–56.8)	46.1 (38.9–53.4)
Complete response, n (%)	12 (20.3)	10 (12.8)	9 (16.1)	31 (16.1)
Partial response, n (%)	18 (30.5)	25 (32.1)	15 (26.8)	58 (30.1)
Stable disease, n (%)	9 (15.3)	27 (34.6)	10 (17.9)	46 (23.8)
Non-complete response/non-progressive disease, n (%)	3 (5.1)	0	2 (3.6)	5 (2.6)
Progressive disease, n (%)	10 (16.9)	10 (12.8)	14 (25.0)	34 (17.6)
Not evaluable, n (%)	7 (11.9)	6 (7.7)	6 (10.7)	19 (9.8)
Disease control rate, % (95% CI)	71.2 (57.9–82.2)	79.5 (68.8–87.8)	64.3 (50.4–76.6)	72.5 (65.7–78.7)
Durable disease control rate,[†] % (95% CI)	61.0 (47.4–73.5)	62.8 (51.1–73.5)	57.1 (43.2–70.3)	60.6 (53.3–67.6)
Median observed time to response, months (IQR)[‡]	1.9 (1.8–2.0)	2.1 (1.9–3.8)	2.1 (2.1–4.2)	2.1 (1.9–3.7)
Median observed time to complete response, months (IQR)	11.1 (7.5–18.4)	10.5 (7.4–12.9)	12.4 (8.2–16.6)	11.2 (7.4–14.8)
Median DOR, months (range)[§]	NR (20.7, NE)	NR (18.4, NE)	NR (NE, NE)	NR (28.8, NE)
Kaplan–Meier 12-month estimate of patients with ongoing response, % (95% CI)	89.5 (70.9–96.5)	83.2 (64.1–92.7)	91.7 (70.6–97.8)	87.8 (78.5–93.3)
Kaplan–Meier 24-month estimate of patients with ongoing response, % (95% CI)	68.8 (46.9–83.2)	62.5 (38.4–79.4)	NE (NE, NE)	69.4 (55.6–79.6)

[†]Defined as the proportion of patients without progressive disease for at least 105 days.
[‡]Based on number of patients with confirmed complete or partial response.
ORR per INV was 54.4% (95% CI: 47.1–61.6) for all patients; 50.8% (95% CI: 37.5–64.1) for Group 1, 56.4% (95% CI: 44.7–67.8) for Group 2, and 55.4% (95% CI: 41.5–68.7) for Group 3. ORR per INV was 57.8% (95% CI: 48.8–66.5) among treatment-naïve patients and 47.7% (95% CI: 35.1–60.5) among previously treated patients.
CI, confidence interval; NE, not evaluable; NR, not reached.

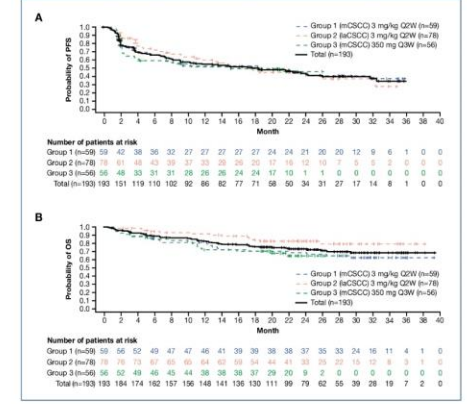
- ORR per ICR was 46.1% (95% CI: 38.9–53.4) among all patients; 50.8% (95% CI: 37.5–64.1) for Group 1, 44.9% (95% CI: 33.6–56.6) for Group 2, and 42.9% (95% CI: 29.7–56.8) for Group 3 (**Table 2**).
- Per ICR, ORR was 48.4% and 41.5% among those who had not received prior anticancer systemic therapy (n=128) and those who had received prior anticancer systemic therapy (n=65), respectively.
- Overall, the observed time to response was 2 months for 41 (46.1%) patients, 2–4 months for 29 (32.6%) patients, 4–6 months for eight (9.0%) patients, and >6 months for 11 (12.4%) patients.
- Median DOR has not been reached (observed DOR range: 1.9–34.3 months). In responding patients, the estimated proportion of patients with ongoing response at 24 months was 69.4% (95% CI: 55.6–79.6) (**Figure 3**).

Figure 3. Kaplan–Meier curves of DOR per ICR



- Estimated median PFS was 18.4 months (95% CI: 10.3–24.3) for all patients. The Kaplan–Meier estimated progression-free probability at 24 months was 44.2% (95% CI: 36.1–52.1) (**Figure 4A**).
- Median OS has not been reached. The Kaplan–Meier estimated probability of OS at 24 months was 73.3% (95% CI: 66.1–79.2) (**Figure 4B**).

Figure 4. Kaplan–Meier curves for A) PFS per ICR and B) OS



Treatment-emergent adverse events

- In total, 192 (99.5%) patients experienced at least one TEAE of any grade regardless of attribution (**Table 3**).
- Overall, the most common TEAEs of any grade were fatigue (n=67, 34.7%), diarrhea (n=53, 27.5%), and nausea (n=46, 23.8%).
- Grade ≥3 TEAEs regardless of attribution occurred in 94 (48.7%) of patients. The most common Grade ≥3 TEAEs were hypertension (n=9; 4.7%) and anemia and cellulitis (each n=8; 4.1%).

Table 3. TEAEs regardless of attribution

n (%)	Advanced CSCC (n=193)	
	Any grade	Grade ≥3
Any	192 (99.5)	94 (48.7)
Led to discontinuation	19 (9.8)	14 (7.3)
Most common[†]		
Fatigue	67 (34.7)	5 (2.6)
Diarrhea	53 (27.5)	2 (1.0)
Nausea	46 (23.8)	0
Pruritus	41 (21.2)	0
Rash	32 (16.6)	1 (0.5)
Cough	32 (16.6)	0
Arthralgia	28 (14.5)	1 (0.5)
Constipation	26 (13.5)	1 (0.5)
Vomiting	24 (12.4)	1 (0.5)
Actinic keratosis	23 (11.9)	0
Maculopapular rash	23 (11.9)	1 (0.5)
Anemia	22 (11.4)	8 (4.1)
Hypothyroidism	22 (11.4)	0
Headache	21 (10.9)	0
Upper respiratory tract infection	20 (10.4)	0

[†]TEAEs reported in ≥10% of patients, ordered by frequency of any grade.

- Grade ≥3 treatment-related adverse events (TRAEs) were reported in 33 (17.1%) patients, with the most common being pneumonitis (n=5, 2.6%), autoimmune hepatitis (n=3; 1.6%), anemia, colitis, and diarrhea (all n=2; 1.0%).
- No new TEAEs resulting in death were reported compared to previous reports.[9–11]

Conclusions

- For patients with advanced CSCC, cemiplimab achieved ORR of 46.1%.
- Patients had deepening responses over time as evidenced by increasing complete response rates.[9–11] Overall, the complete response rate is now 16.1% and median time to complete response was 11.2 months.
- DOR and OS are longer than what has been previously described with other agents.[7]
- With median DOR not reached after an additional 1 year of follow-up, this analysis indicates an increasing, clinically meaningful DOR with cemiplimab.
- The discontinuation rate, regardless of attribution, was low and most TRAEs were Grades 1–2.

See poster #382 reporting post hoc analysis of health-related quality of life in the same patient population presented in this poster. Also see poster #433 that provides the design and rationale of a Phase 3, randomized, double-blind study of adjuvant cemiplimab versus placebo post-surgery and radiation in patients with high-risk CSCC.

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For any questions or comments, please contact Dr Danny Rischin, Danny.Rischin@petermac.org

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Phase 2 Study of Cemiplimab in Patients (pts) with Advanced Cutaneous Squamous Cell Carcinoma (CSCC): Longer Follow-Up

Danny Rischin, Nikhil I. Khushalani, Chrysalyne D. Schmults, Alexander David Guminski, Anne Lynn S. Chang, Karl D. Lewis, Annette May Ling Lim, Leonel Fernando Hernandez-Aya, Brett Gordon Maxwell Hughes, Dirk Schadendorf, Axel Hauschild, Elizabeth Stankevich, Jocelyn Booth, Siyu Li, Zhen Chen, Emmanuel Okoye, Israel Lowy, Matthew G. Fury, Michael Robert Migden

J Clin Oncol 38: 2020 (suppl; abstr 10018)

Hodnocení tříletého sledování pacientů léčených cemiplimabem pro inoperabilní nebo pro radioterapii nevhodný CSCC

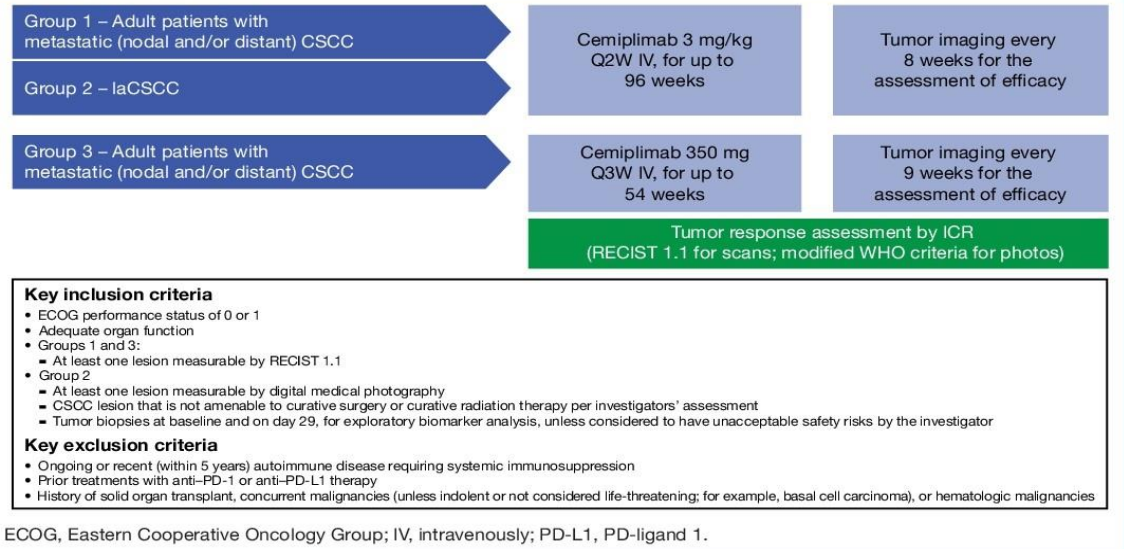
Zařazeno bylo 193 pacientů

Pacienti byli léčeni cemiplimabem v dávce 3 mg/kg nebo 350 mg

ORR při hodnocení ICR: 46,1 % (50,8 % / 44,9 % / 42,9 %)

ORR: cemiplimab v 1. linii 48,4 %, v dalších liniích 41,5 %

Figure 1. Study design



Phase 2 Study of Cemiplimab in Patients (pts) with Advanced Cutaneous Squamous Cell Carcinoma (CSCC): Longer Follow-Up

Danny Rischin, Nikhil I. Khushalani, Chrysalyne D. Schmults, Alexander David Guminski, Anne Lynn S. Chang, Karl D. Lewis, Annette May Ling Lim, Leonel Fernando Hernandez-Aya, Brett Gordon Maxwell Hughes, Dirk Schadendorf, Axel Hauschild, Elizabeth Stankevich, Jocelyn Booth, Siyu Li, Zhen Chen, Emmanuel Okoye, Israel Lowy, Matthew G. Fury, Michael Robert Migden

J Clin Oncol 38: 2020 (suppl; abstr 10018)

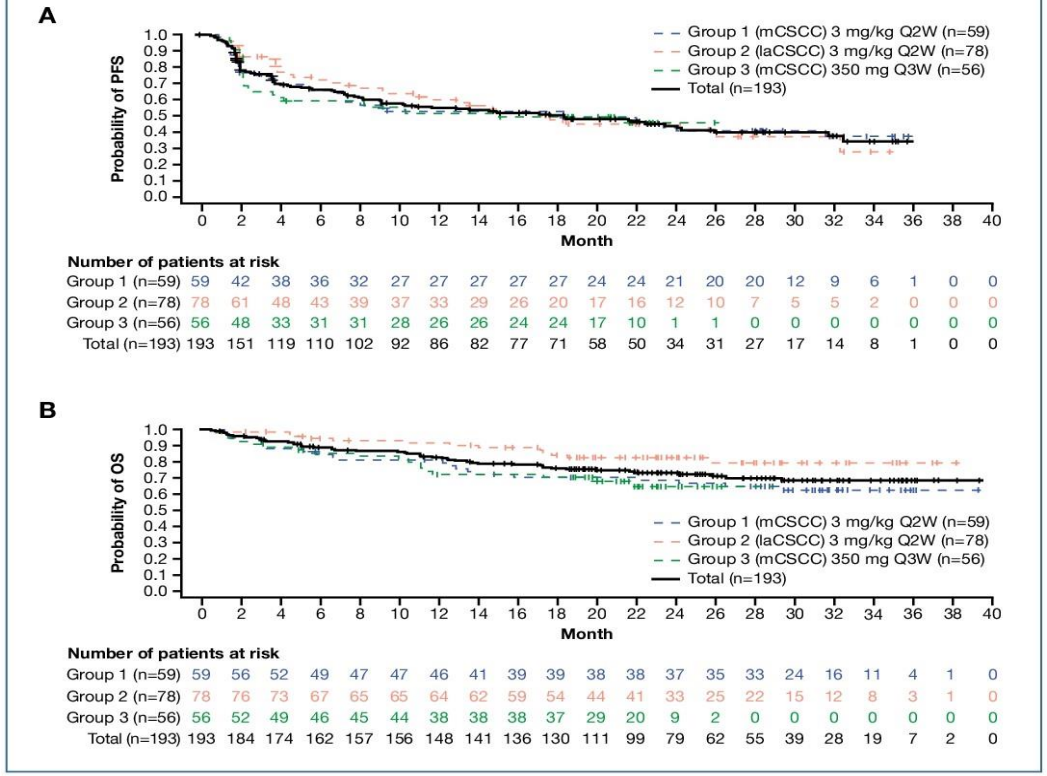
Doba do objevení léčebné odpovědi:
2 měsíce u 46,1 % pacientů
2–4 měsíce u 32,6 % pacientů
4–6 měsíců u 9 % pacientů
> 6 měsíců u 12,4 % pacientů

Mediánu trvání léčebné odpovědi (DOR) nebylo dosaženo, dva roky přetrvávala odpověď u 69,4 % pacientů

Medián PFS 18,4 měsíce / mediánu OS nebylo dosaženo, dva roky PFS 44,2 % pacientů / OS 73,3 % pacientů

Závěr: cemiplimab je účinnější než dosud používané léčebné metody

Figure 4. Kaplan–Meier curves for A) PFS per ICR and B) OS



Abstract 10065: Cemiplimab as First Intervention for Patients with Locally Advanced Cutaneous Squamous Cell Carcinoma

Authors: Jennifer Atlas MD[1], Marina Kanos NP[1], James Symanowski PhD[2], Daniel Brickman MD[3], Meghan Forster MD[4], Catherine Frenkel MD[3], Zvonimir Milas MD[3], Terry Sarantou MD[4], Richard White MD[4], Asim Amin MD PhD[1]

[1]Department of Medical Oncology, [2]Department of Cancer Biostatistics, [3]Head and Neck Surgery and [4]Surgical Oncology, Levine Cancer Institute, Atrium Health

Atrium Health Levine Cancer Institute

Background:

- Cutaneous squamous cell carcinoma is the second most common non-melanoma skin cancer.
- Early stage disease is managed with local intervention in the form of surgery or radiation and translates into cure for greater than 95% of the patients.
- Patients with high risk disease who have large primary lesions, neural, or nodal involvement are usually not amenable to cure with local intervention and may experience significant morbidity, disfigurement, or functional deficits.

Study Objectives:

We report the outcomes for upfront treatment with cemiplimab in locally advanced cSCC.
The primary end point was to ascertain the need for local intervention with surgery and/or radiation.

Methods:

- This is a single institution retrospective study of patients with locally advanced cSCC defined as those requiring more than simple excision and/or complex repair, or regional disease with nodal involvement who received at least two doses of cemiplimab between January 1, 2018 through January 17, 2020.
- Exclusion criteria – Less than or equal to 1 infusion of cemiplimab, metastatic disease
- Patients with radiologically measurable disease had response evaluated per RECIST criteria.
- Patients who had no measurable disease had their clinical response (complete resolution or healing of primary lesion) assessed per treating physician and need or lack of local intervention documented.
- Adverse event assessment per CTCAE criteria.
- Primary end point was to ascertain the need for local intervention.

Results/Graphs/Data:

- Thirty six patients were eligible.
- At the time of analysis, thirty-one patients had discontinued treatment. Twenty-six patients (84%) did not require local intervention with surgery and/or radiation. Five (16%) patients received local intervention.
- Three patients progressed on treatment.
- There was one treatment related death (Patient had myositis and hepatotoxicity).
- Five (14%) of thirty-six patients were still receiving cemiplimab and local intervention decision was pending at the time of data cutoff.
- The overall response rate (CR+PR) was 72% and the clinical benefit rate (CR+PR+SD) was 92%.
- The median duration of treatment was five months.
- The median number of doses received was eight.

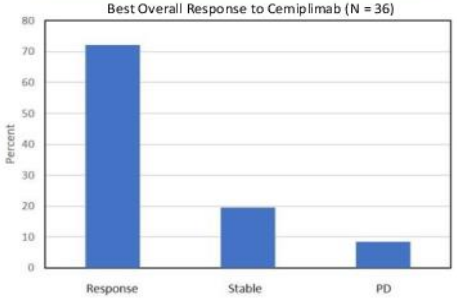
Table 1. Baseline Patient Demographics and Characteristics (N = 36)

Median Age, Years (Range)	77 (56 - 91)
Sex, n(%)	
Male	28 (77.8)
Female	8 (22.2)
Primary Location, n(%)	
Face, Head/Neck	28 (77.8)
Trunk	2 (5.6)
Extremity	5 (13.9)
Face, Head/Neck and Extremity	1 (2.8)
Nodal Metastasis, n(%)	14 (38.9)
Prior Surgery, n(%)	22 (61.1)
Prior Radiotherapy, n(%)	7 (19.4)
Prior Systemic Therapy, n(%)	2 (5.6)
Pre-existing autoimmune condition, n(%)	7 (19.4)

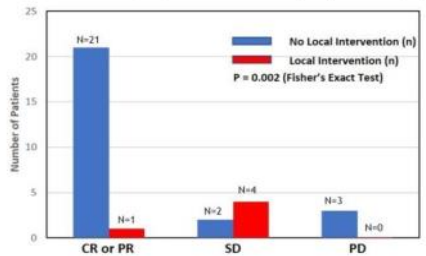
Table 2. Efficacy Outcomes (N=36)

Best Overall Response, n(%)	
Complete Response/Partial Response	26 (72.2)
Stable Disease	7 (19.4)
Progressive Disease	3 (8.3)
Discontinued Treatment, n(%)	31 (86.1)
Received local intervention, n(%)	5/31 (16.1)

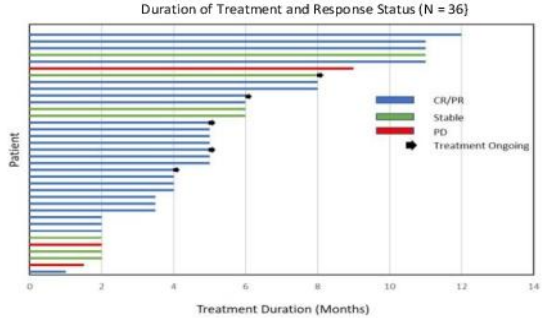
Best Overall Response to Cemiplimab (N = 36)



Number of Patients requiring Local Intervention by Response Category (N=31)



Duration of Treatment and Response Status (N = 36)



Safety Results:

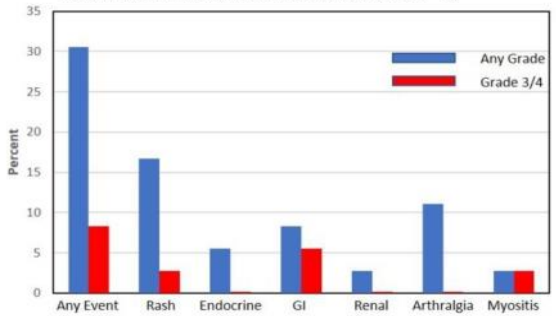
- Adverse events occurred in 31% of patients.
- Grade 3/4 adverse were observed in <9% of all reported adverse events.

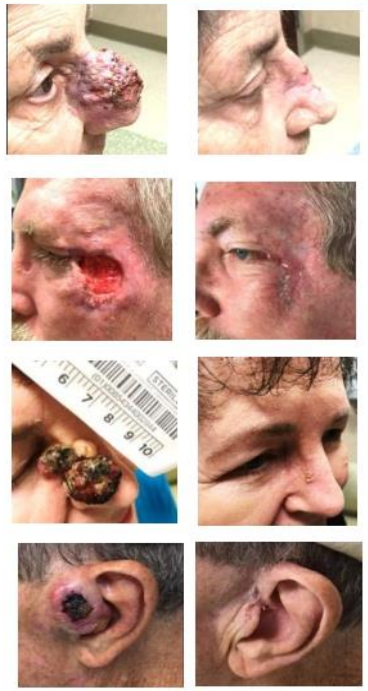
Table 3. Summary of Treatment-Related Selected AEs by Maximum Grade (N=36)

	All Grades		Grades 3 or 4	
Adverse Event Type	Number	Percent	Number	Percent
Any Adverse Event*	11	30.6	3	8.3
Rash	6	16.7	1	2.8
Endocrine	2	5.6	0	0
GI	3	8.3	2	5.6
Renal	1	2.8	0	0
Arthralgia	4	11.1	0	0
Myositis**	1	2.8	1	2.8

* Eleven of the thirty six patients developed at least one autoimmune AE; six of the eleven patients developed 2 AEs.
**There was one treatment related death. Patient developed myositis and hepatotoxicity.
A total of 5 patients discontinued cemiplimab due to development of autoimmune AEs.

Treatment-Related Adverse Events by Maximum Grade (N = 36)





Conclusions:

- Upfront treatment with cemiplimab in patients with locally advanced cSCC obviated need for disfiguring/complex surgery or radiation in majority of patients.
- Cemiplimab showed encouraging antitumor activity in locally advanced cSCC, with a manageable toxicity profile
- No new safety signals were noted with cemiplimab when compared with other anti-PD1 antibodies.
- Cemiplimab warrants further investigation to determine its optimal use in locally advanced cSCC. A phase II neoadjuvant study is currently underway.

Acknowledgements: The Patients and their families.

Disclosures:
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Correspondence: JenniferAtlas MD at Jennifer.Atlas@AtriumHealth.org

Cemiplimab as First Intervention for Patients with Locally Advanced Cutaneous Squamous Cell Carcinoma

Jennifer Lynn Atlas, Marina Kanos, James Thomas Symanowski, Daniel Brickman, Meghan Forster, Catherine Frenkel, Zvonimir Milas, Terry Sarantou, Richard L. White, Asim Amin

J Clin Oncol 38: 2020 (suppl; abstr 10065)

Většina CSCC (cca 90–95 %) je léčitelná a vyléčitelná chirurgickým zákrokem a radioterapií

V 5–10 % se ale jedná o pokročilé rozsáhlé nádory, které způsobují devastaci okolních tkání, mohou se šířit podél nervů, do uzlin i zakládat vzdálené metastázy

Chirurgická léčba je často mutilující

V této práci byli retrospektivně hodnoceni pacienti s lokálně pokročilým CSCC nebo pacienti s uzlinovým postižením, kteří byli primárně léčeni místo chirurgie či radioterapie cemiplimabem

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Hodnoceno bylo 36 nemocných, kteří dostali minimálně dvě dávky cemiplimabu

Cílem studie bylo zjistit, zda i při této léčbě bude nutná následná lokální terapie

U 84 % nebyla nutná následná chirurgická léčba či radioterapie, tři pacienti měli progresi, 14 % pacientů stále dostává léčbu a ještě nebylo rozhodnuto, zda bude nutná lokální intervence

ORR dosáhly 72 %, DCR (CR + PR + SD) 92 %

Medián podávání léčby byl pět měsíců, medián počtu dávek osm

Nežádoucí účinky se objevily u 31 % pacientů, jeden pacient zemřel (myozitida + hepatotoxicita)

Autoři uzavírají, že podání cemiplimabu u pokročilých CSCC před chirurgickou léčbou sníží potřebu mutilujících náročných chirurgických zákroků či radioterapie

433

A Phase 3, Randomized, Double-Blind Study of Adjuvant Cemiplimab Versus Placebo Post-Surgery and Radiation in Patients with High-Risk Cutaneous Squamous Cell Carcinoma (CSCC)

Danny Rischin,[1] Matthew G. Fury,[2] Israel Lowy,[2] Elizabeth Stankevich,[3] Siyu Li,[2] Hyunsil Han,[2] Sandro V. Porceddu[4]

[1]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [3]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [4]School of Medicine, University of Queensland, Herston, Queensland, Australia; Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia.

C-POST

Background

Cutaneous squamous cell carcinoma (CSCC)

- CSCC is the second most common skin cancer with an estimated incidence of around 1 million cases per year in the US.[1] Worldwide, reports show an annual rise in incidence of 3–7% in most countries.[2]
- While the surgical cure rate for CSCC is approximately 95%, a proportion of patients are considered to be at high risk for recurrence as assessed by immune status, primary disease stage, extent of nodal involvement, presence of extracapsular extension, and prior treatment.[3,4]
- Post-operative radiation is recommended for some patients with CSCC after surgery, but locoregional or distant recurrence can still occur.
- POST, the largest prospective randomized adjuvant CSCC study, provided new insights into risk factors for CSCC recurrence.[5]

Cemiplimab

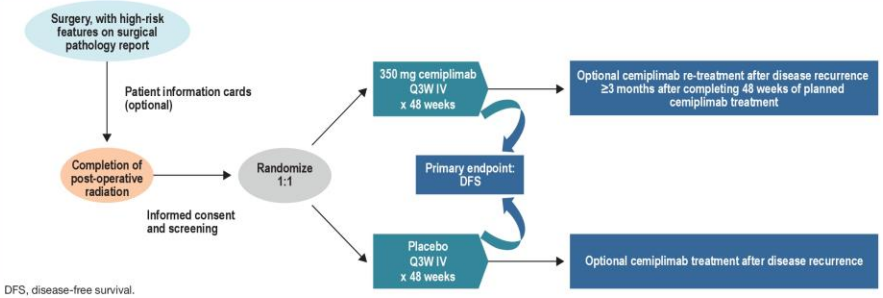
- Cemiplimab is a high-affinity, highly potent human monoclonal antibody directed against the programmed cell death (PD)-1 receptor.[6,7]
- In Phase 1 and Phase 2 trials (NCT02383212 and NCT02760498, respectively), cemiplimab exhibited antitumor activity with a safety profile comparable to those of other anti–PD-1 inhibitors in patients with advanced malignancies, including CSCC.[7–9]
  - For the latest data from the Phase 2 study of cemiplimab in patients with advanced CSCC, please see poster 367 reporting longer follow-up data and poster 382 reporting post hoc analysis of health-related quality of life.
- Cemiplimab (cemiplimab-rwlc in the US) is the only therapy approved by the US Food and Drug Administration and the European Commission for treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.[10,11]
- While the clinical activity of cemiplimab as monotherapy has been established in patients with advanced CSCC who are not candidates for curative surgery or curative radiation, this study aims to evaluate its benefit as an adjuvant treatment following surgery and post-operative radiation in patients with CSCC at high risk for recurrence.

Methods

Study design

- This randomized, placebo-controlled, double-blind, multicenter Phase 3 trial (C-POST) is evaluating the clinical activity of adjuvant cemiplimab versus placebo in patients with high-risk CSCC, after surgery and post-operative radiation (NCT03969004).
- The study consists of two parts:
  - Part 1: Double blind, randomized, placebo-controlled
    - Study treatment: 30-minute infusions of cemiplimab 350 mg or placebo intravenously (IV) every 3 weeks (Q3W) for up to 48 weeks or until unacceptable toxicity, disease recurrence, death, or withdrawal of consent
    - Duration: A screening period of up to 28 days prior to randomization, a treatment period of up to 48 weeks, and a follow-up period of up to disease recurrence or end of study (**Figure 1**).

Figure 1. C-POST study design



DFS, disease-free survival.

  - Part 2: Optional open-label
    - Treatment: Cemiplimab IV 350 mg Q3W
    - Duration of treatment: Up to 96 weeks in Part 2 or until disease progression, unacceptable toxicity, withdrawal of consent, death, or loss to follow-up.

Outcome measures

- The primary objective of the study is to compare DFS of patients with high-risk CSCC treated with adjuvant cemiplimab versus placebo after surgery and post-operative radiation.
- The secondary objectives of the study are to compare the following measures with cemiplimab versus placebo after surgery and post-operative radiation in the aforementioned patient population:
  - Overall survival (OS)
  - Freedom from locoregional recurrence
  - Freedom from distant recurrence
  - Cumulative incidence of second primary CSCC tumors
  - Safety.
- The exploratory objectives of the study are:
  - To evaluate patterns of failure in patients treated with cemiplimab or placebo
  - To explore geographic/regional variations in administration of post-operative radiation in patients treated with cemiplimab or placebo
  - To compare health-related quality of life in patients treated with cemiplimab versus placebo
  - To explore associations between clinical activity of cemiplimab and molecular features in pre-treatment tumor samples.

Patient eligibility

- Adult patients with high-risk CSCC who have undergone surgical resection followed by radiation are eligible for study enrollment (**Tables 1 and 2**).

Table 1. Key inclusion criteria

- ≥18 years old (in Japan only: ≥21 years old)
- Resection of pathologically confirmed CSCC (primary CSCC lesion only, or primary CSCC with nodal involvement, or CSCC nodal metastasis with known primary CSCC lesion previously treated within the draining lymph node echelon) with macroscopic gross resection of all diseased area
- High-risk CSCC, defined by at least one of the following:
  - Nodal disease with extracapsular extension, defined as extension through the lymph node capsule into the surrounding connective tissue with or without associated stromal reaction, and at least one node of >20 mm on the surgical pathology report[3]
  - In-transit metastases, defined as skin or subcutaneous metastases of >2 cm from the primary lesion but are not beyond the regional nodal basin[12]
  - T4 lesion, including head and neck lesions and non-head-and-neck lesions[3,13]
  - Perineural invasion, defined as clinical and/or radiologic involvement of named nerves[13]
  - Recurrent CSCC, defined as CSCC that arises within the area of the previously resected tumor, plus at least one of the following additional features[3]:
    - ≥N2b disease associated with the recurrent lesion
    - Nominal ≥T3 (recurrent lesion of ≥4 cm in diameter, minor bone erosion, or deep invasion of >6 mm measured from the granular layer of normal adjacent epithelium)
    - Poorly differentiated histology and recurrent lesion of ≥20 mm diameter
- Completion of curative-intent post-operative radiation within 2 to 6 weeks of randomization
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate hepatic, renal and bone marrow functions

Table 2. Key exclusion criteria

- Squamous cell carcinoma arising from non-cutaneous sites
- Concurrent malignancy other than localized CSCC and/or history of malignancy other than localized CSCC within 3 years of date of randomization, except for tumors with negligible risk of metastasis or death
- Hematologic malignancies
- History of distantly metastatic CSCC (visceral or distant nodal), unless disease-free interval is ≥3 years
- Ongoing or recent (within 5 years) autoimmune disease that requires treatment
- Participation in a study of an investigational agent or an investigational device within 4 weeks of the randomization date or five half-lives
- Prior systemic anti-cancer immunotherapy for CSCC
- Receipt of immunosuppressive corticosteroid (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab or placebo
- Anticancer systemic therapy within 4 weeks or lack of recovery from any acute toxicities
- Prior allogeneic stem cell transplantation, or autologous stem cell transplantation
- Any infection requiring hospitalization and/or intravenous antibiotic therapy within 2 weeks of the randomization date
- Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C virus; or diagnosis of immunodeficiency
- History of immune-related pneumonitis within 5 years
- History of documented allergic reactions or acute hypersensitivity reaction attributed to any antibody treatment
- History of solid organ transplant except corneal transplant(s)
- Breastfeeding women
- Women of childbearing potential or sexually active men who are unwilling to practice highly effective contraception

Statistical assumptions and analysis

- The primary clinical hypothesis of the study is that cemiplimab prolongs DFS as compared with placebo.
- The primary analysis of DFS will be performed with a 2-sided alpha at 0.05 overall significance level for the following null and alternative statistical hypotheses:
  - H_0: The survival curve of DFS for cemiplimab is the same as that for placebo
  - H_1: The survival curve of DFS for cemiplimab is not the same as that for placebo.
- The full analysis set will include all randomized patients (intent-to-treat population) and will be used for analyses of efficacy endpoints.
- The safety analysis set will include all randomized patients who received any study drug (as-treated population) and will be used for analyses of all safety variables.
- The primary endpoint of DFS will be tested by stratified log-rank test at 2-sided 0.05 significance level.

Summary

- Patients with high-risk CSCC often experience relapse with locoregional recurrence or distant metastases despite initial treatment with surgery and post-operative radiation.
- Cemiplimab, a PD-1 monoclonal antibody, has demonstrated clinical activity with a safety profile comparable to those of other anti–PD-1 agents in advanced malignancies, including CSCC.
  - Cemiplimab (cemiplimab-rwlc in the US) is the only therapy approved by the US Food and Drug Administration and the European Commission for treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.
- This study will provide insight into the clinical activity of cemiplimab versus placebo as an adjuvant treatment in patients with CSCC at high risk for recurrence, after surgery and post-operative radiation.
- This study is ongoing and is actively enrolling patients.

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For any questions or comments, please contact Dr Danny Rischin, Danny.Rischin@petermac.org.

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A phase 3, Randomized, Double-Blind Study of Adjuvant Cemiplimab versus Placebo Post-Surgery and Radiation Therapy (RT) in Patients (pts) with High-Risk Cutaneous Squamous Cell carcinoma (CSCC)

Danny Rischin, Matthew G. Fury, Israel Lowy, Elizabeth Stankevich, Hyunsil Han, Sandro Porceddu; Peter MacCallum

J Clin Oncol 38: 2020 (suppl; abstr TPS10084)

Cílem této studie je posoudit účinnost cemiplimabu proti placebu v adjuvantním podání po operaci primárního nádoru a po pooperační radioterapii

Jedná se o dvojitě zaslepenou, placebem kontrolovanou studii fáze 3

Zařazováni mohou být nemocní po kompletním chirurgickém odstranění nádoru a pooperační radioterapii, kteří splňují minimálně jedno z kritérií (extrakapsulární šíření uzlinových metastáz, intranzitní metastázy, T4 klasifikace primárního nádoru s perineurální invazí nebo recidivující CSCC) s minimálně jedním dalším rizikovým faktorem

Pacienti v imunosupresi nemohou být zařazeni

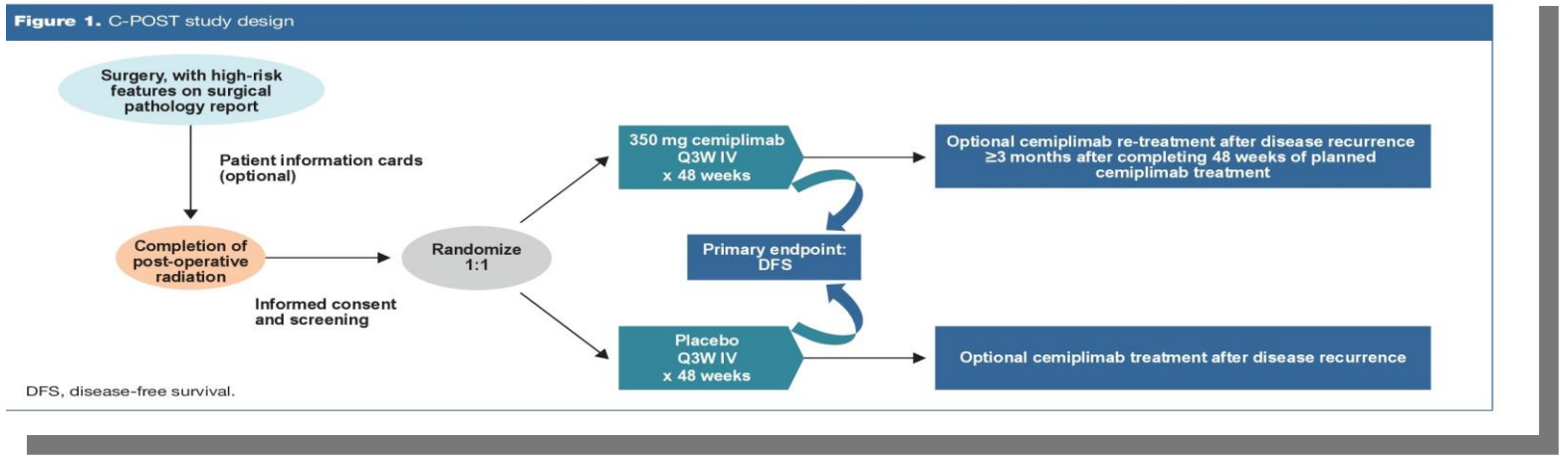
A phase 3, Randomized, Double-Blind Study of Adjuvant Cemiplimab versus Placebo Post-Surgery and Radiation Therapy (RT) in Patients (pts) with High-Risk Cutaneous Squamous Cell carcinoma (CSCC)

Danny Rischin, Matthew G. Fury, Israel Lowy, Elizabeth Stankevich, Hyunsil Han, Sandro Porceddu; Peter MacCallum

J Clin Oncol 38: 2020 (suppl; abstr TPS10084)

V zaslepené části 1 jsou pacienti randomizováni 1 : 1 na terapii cemiplimabem 350 mg nebo placebo podávané à tři týdny po celkovou dobu 48 týdnů

V odslepené části 2 mohou být pacienti, kteří dostávají placebo nebo u nich dojde k progresi za tři a více měsíců po ukončené terapii cemiplimabem, znovu léčeni cemiplimabem, a to po dobu 96 týdnů



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Primárním cílem je hodnocení DFS

Sekundárními cíli je OS, doba přežití bez lokoregionálního relapsu, doba přežití bez vzdálených metastáz a bezpečnost léčby

Studie probíhá a jsou do ní zařazováni pacienti v Severní Americe, Evropě a asijsko-pacifické oblasti

Děkuji za pozornost!