Skin immunity-related adverse events correlate with survival and response to anti-PD-1 treatment in patients with inoperable/metastatic melanoma.

Bożena Cybulska-Stopa[1#], Grażyna Kamińska-Winciorek[2#], Marcin Ziętek[3,4], Anna M. Czarnecka[5,6], Karolina Piejko[1], Robert Dziura[7], Łukasz Galus[8,9], Barbara Ziółkowska[10], Stanisław Kieszko[11], Natasza Kempa-Kamińska[12], Jacek Calik[12], Joanna Seredyńska[1], Kamila Gądek[1], Tomasz Zemełka[1], Paweł Teterycz[5], Wiesław Bal[13], Tomasz Kubiatowski[11], Rafał Suwiński[10], Jacek Mackiewicz[8,14], Piotr Rutkowski[5]

[1]Department of Clinical Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Cracow Branch, Poland; [2]Department of Bone Marrow Transplantation and Hematology-Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland; [3]Department of Surgical Oncology, Wroclaw Comprehensive Cancer Center, Wroclaw, Poland; [4]Department of Oncology, Wroclaw Medical University, Wroclaw, Poland; [5]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [6]Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland; 7Clinical Oncology Department,Holy Cross Cancer Center, Kielce, Poland; [8]Department of Medical and Experimental Oncology, University of Medical Sciences, Poznan, Poland; [9]Chemotherapy Department, Greater Poland Cancer Centre, Poznan, Poland; [10]II Clinic of Radiotherapy and Chemotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland; [11] Department of Clinical Oncology, Saint Jan of Dukla Oncology Centre of the Lublin Region, Lublin, Poland; [12]Department of Clinical Oncology, Lower Silesian Oncology Center, Wroclaw, Poland; [13]Department of Outpatients Chemotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland; [14]Department of Diagnostics and Cancer Immunology, Greater Poland Cancer Centre, Poznan, Poland

[#]Authors equally participated

Background

The impact of skin immune-related adverse events (irAE) on survival outcomes after single-agent immune checkpoint inhibitors (ICIs) remains unclear. We aimed to evaluate the association between skin irAEs and ICIs efficacy in melanoma patients. Our analysis is intended to contribute to the routine clinical practice-based knowledge on immunotherapy and its irAE's and, as such ultimately facilitate more watchful therapy monitoring.

Material and Methods

The analysis covered 593 patients with unresectable or metastatic melanoma treated with anti-PD-1 (nivolumab or pembrolizumab) in the first line between 01/2016 and 12/2019 in six major comprehensive cancer centers in Poland. We reviewed electronic medical records, including data on patient demographics, medical history, baseline disease parameters, and outcomes. The study's primary endpoint was to evaluate the correlation between skin immunity-related adverse events (irAE) and the median overall survival (OS), median progression-free survival (PFS), and response to treatment. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) assessed by the response evaluation criteria in solid tumors (RECIST) v. 1.1. The safety evaluation was done using the Common Terminology Criteria for Adverse Events (CTCAE) classification v. 4.03. Survival analyses were performed using the Kaplan-Meier method, log-rank test.

Characteristic		Patients with skin irAEs; n=31	Patients without skin irAEs; n=554
Age at the start of therapy	median (range)	69 (38-84)	66 (23-93)
	> 65 years	20 (65%)	329 (59%)
Gender	males	17 (55%)	263 (59%)
	females	14 (45%)	172 (41%)
BRAF mutation status	wild-type	24 (80%)	442 (80%)
	mutation	4 (20%)	108 (20%)
Location of the primary tumor	Skin	27 (83%)	499 (90%)
	mucosa	2 (7%)	32 (6%)
	unknown	0 (0%)	22 (4%)
ECOG	0	17 (55%)	218 (39%)
	1	14 (45%)	328 (59%)
	2	0 (0%)	8 (2%)
LDH level	normal	22 (71%)	326 (59%)
	> normal	9 (29%)	225 (41%)
Skin or subcutaneous tissue metastasis	Yes	11 (35%)	212 (38%)
Lymph nodes metastasis	Yes	10 (32%)	323 (58%)
Lung metastasis	Yes	15 (48%)	288 (52%)
Liver metastasis	Yes	7 (23%)	114 (21%)
Brain metastasis	Yes	2 (6%)	103 (18%)
Other locations of meta	Yes	7 (23%)	183 (33%)
TNM stage (AJCC 8th Edition)	III	4 (13%)	26 (5%)
	M1a	5 (16%)	120 (22%)
	M1b	7 (23%)	124 (22%)
	M1c	13 (42%)	181 (33%)
	M1d	2 (6%)	103 (18%)
Number of metastatic sites	≤2	28 (90%)	364 (66%)
	>2	3 (10%)	155 (34%)
Type of therapy	nivolumab	15 (48%)	344 (62%)
	pembrolizumab	16 (52%)	170 (38%)

LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group (performance status); irAEs, immune-related adverse events; TNM, tumor, node, metastasis (staging system); AJCC, American Joint Committee on Cancer.

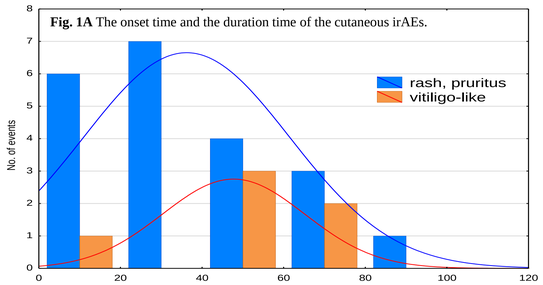


Fig. 1A The onset time and the duration time of the cutaneous irAEs.

Fig. 2A Overall survival: with skin irAE vs. without skin irAE

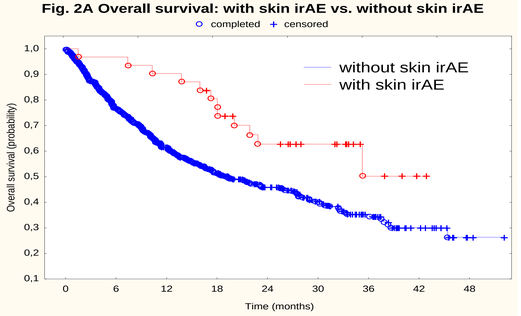
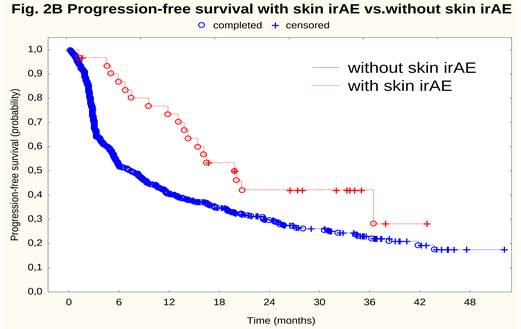


Fig. 2B Progression-free survival with skin irAE vs.without skin irAE



Results

At the time of analysis 585 patients were enrolled in the study. Among screened individuals eight patients were excluded due to missing data. The baseline patients characteristics was typical for melanoma patients treated in the routine clinical practice outside of clinical trials. Skin irAEs occurred in 31 patients, in 27 (83%) patients with grade (G) 1 or G2, and in 4 (13%) with G3. No skin irAEs were developed in G4. The most common skin irAEs were rash (24 patients) and vitiligo (7 patients). Stevens-Johnson syndrome occurred in two patients. The onset time and the duration time of the cutaneous irAEs are shown in Figure 1A. Statistically significant differences were demonstrated between the group of patients without and with skin irAE in median OS and PFS (p=0.0121, HR 2.1, 95% CI 1.2–3.7 and p=0.0169, HR 1.8, 95% CI 1.1–2.9, respectively) Fig. 2A, B. There was also a statistically significant correlation between skin irAEs and the response to anti-PD1 treatment (p=0.0039).

Conclusions

Our retrospective analysis includes more patients than enrolled in clinical trials and relies on evidence coming from real-world clinical practice. Skin irAEs were associated with longer OS, PFS, and more frequent radiological response to treatment (CR, PR, SD). More studies are required to characterize the surrogate biomarkers of anti-PD1 treatment efficacy as well as underlying pathomechanisms of toxicities. Multidisciplinary cooperation between clinical oncology and dermatology departments is needed towards more effective monitoring and clinical management of skin-related toxicities.

Disclosures
Grants and consultancies: PR – *BMS, Novartis, Roche and Merck; JM - BMS, MSD*
Fees and honoraria: AMC, PR, PRo, TK, JC – *Bristol-Myers Squibb, Novartis, Roche, Merck; BCS - BMS, Novartis, Roche, Pierre Fabre, MSD; RS* – BMS, MSD, Astellas Pharma; JM – BMS, GlaxoSmithKline, Roche, MSD, Novartis, Pierre-Fabre; BZ,TZ, JR, SK, NKK, MZ - none declared

Contact details for further information: bcybulskastopa@vp.pl