Impact on survival of early discontinuation of immune checkpoint inhibitors after objective response in melanoma

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Inge Mansfield Noringriis[1], Rebecca Schou Jurlander[1], Karijn Suijkerbuijk[2], Nethanel Asher[3], Dirk Schadendorf[4], Joanna Mangana[5], Krešimir Blažičević[6], Friedegund Meier[7], Paolo A. Ascierto[8], Jovana Pavlica[9], Peter Mohr[10], Aleksandar Popović[11], Helen Gogas[12], Imke von Wasielewski[13], Berna C. Özdemir[14], Henrik Schmidt[15], Lars Bastholt[16], Michael Weichenthal[17], Eva Ellebaek[1], Inge Marie Svane[1]

[1]National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology, Copenhagen University Hospital, Herlev, Denmark; [2]UMC Utrecht, Utrecht, The Netherlands; [3]Skin Cancer and Melanoma Center at Davidoff Cancer Center, Rabin Medical Center, Petach Tikva, Israel; [4]Department of Dermatology, Venereology and Allergology, University Hospital Essen, Essen, Germany; [5]University Hospital of Zurich, Switzerland; [6]University Hospital Center Zagreb, Zagreb, Croatia; [7]Department of Dermatology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [8]Department of Melanoma, Cancer Immunotherapy and Development Therapeutics - Istituto Nazionale Tumori ;IRCCS Fondazione "G. Pascale", Napoli, Italy; [9]Military Medical Academy Belgrade, Belgrade, Serbia; [10]Dermatologic Center Buxtehude, Buxtehude, Germany; [11]University Clinical Center Nis, Nis, Serbia; [12]First Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [13]Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany; [14]Department of Medical Oncology, Inselspital Bern, Bern University Hospital, Bern, Switzerland; [15]Department of Oncology, Aarhus University Hospital, Denmark; [16]Department of Oncology, Odense University Hospital, Denmark; [17]Skin Cancer Center Kiel, University Hospital Schleswig-Holstein, Kiel, Germany

BACKGROUND

- The optimal treatment duration for immune checkpoint inhibitor (ICI) therapy in melanoma remains unknown.
- Official ESMO guidelines support considering ICI discontinuation after confirmed complete response (CR), while continuation until 2 years is otherwise recommended.
- Danish national guidelines recommend response-based discontinuation after confirmed CR, or six months following best partial response (PR).
- Recent results from the prospective Dutch Safe-Stop trial[1] and the **Danish Metastatic Melanoma Database (DAMMED)**[2] report excellent survival following early, elective discontinuation after confirmed objective response (OR).

OBJECTIVES

- To compare survival outcomes among patients with melanoma who achieve an OR to ICI therapy and either discontinue treatment early based on response or continue treatment, using Danish real-world data and a European control cohort.

METHODS

- The study retrospectively analyzed patients who received 1L ICI treatment between 2019 and 2024 with a best overall response (BOR) of CR or PR before end of treatment (EoT) in Denmark (**Denmark**) and European countries (**Other countries**).
- Data was retrieved from the **European Melanoma Registry (EUMelaReg).**
- 1:1 matching was conducted using inverse propensity score matching, including age, sex, ECOG PS, LDH status, AJCC substage, BRAF status, and number of metastatic sites.
- Endpoints included progression-free survival (PFS), overall survival (OS), melanoma-specific survival (MSS), time on treatment, follow-up and differences in endpoints between matched cohorts.

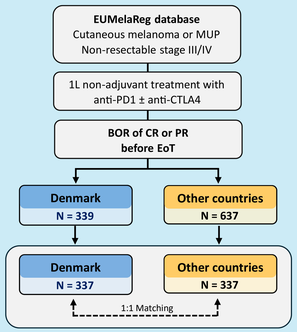


Figure 1: Flow chart illustrating the selected populations for analysis using real-world data from EUMelaReg. N, number of patients; MUP, melanoma of unknown primary; 1L, first line; BOR, best overall response; CR complete response; PR, partial response; EoT, end of treatment. 1:1 matching was performed with an optimal matching algorithm using inverse propensity score matching.

RESULTS

- We identified **339 Danish and 637 European patients** who achieved OR before discontinuation of first-line ICI for any cause.
- Danish patients were slightly older, with higher proportion being BRAF-positive, having poor performance status, and had ≥2 metastatic sites.

Table 1. Patient demographics for full and matched cohorts in Denmark and Other countries

	FULL COHORTS			MATCHED COHORTS		
	Denmark N = 339	Other Countries N = 637	P-value	Denmark N = 337	Other Countries N = 337	P-value
Age (years)			0.03			0.97
Mean (SD)	69 (14)	67 (14)		69 (13)	69 (13)	
Sex			0.37			0.88
Female	136 (40%)	236 (37%)		135 (40%)	132 (39%)	
BRAF status			<0.0001			<0.0001
Positive	142 (42%)	211 (33%)		141 (42%)	136 (40%)	
ECOG			<0.0001			0.03
0	215 (64%)	473 (74%)		215 (64%)	239 (71%)	
1	96 (28%)	105 (17%)		96 (28%)	86 (25%)	
≥2	28 (8%)	13 (2%)		26 (8%)	12 (4%)	
TNM stage			<0.0001			0.57
III-NR/IV-M1a	82 (24%)	176 (28%)		81 (24%)	81 (24%)	
IV-M1b	62 (18%)	175 (28%)		62 (18%)	71 (21%)	
IV-M1c	146 (43%)	174 (27%)		145 (43%)	129 (38%)	
IV-M1d	49 (15%)	112 (18%)		49 (15%)	56 (17%)	
No. of metastatic sites			<0.0001			0.13
≥2	245 (72%)	368 (58%)		244 (72%)	225 (67%)	
Treatment regimen			0.02			0.25
Anti-PD1	239 (70%)	402 (63%)		237 (70%)	222 (66%)	
Anti-PD1/CTLA4	100 (30%)	235 (37%)		100 (30%)	115 (34%)	

N, number of patients; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; NR, non-resectable; No, number.

- More Danish patients were discontinued due to applicable guidelines (39% vs 29%) and toxicity (25% vs 13%).
- Fewer Danish patients had BOR of CR (53% vs 59%).

Table 2. Outcome of full and matched cohorts in Denmark and Other countries

	FULL COHORTS			MATCHED COHORTS		
	Denmark N = 339	Other Countries N = 637	P-value	Denmark N = 337	Other Countries N = 337	P-value
Cause of discontinuation			<0.0001			<0.0001
Regular ended	134 (39%)	187 (29%)		133 (39%)	93 (28%)	
Progression/Death	61 (18%)	112 (18%)		61 (18%)	59 (17%)	
Toxicity	84 (25%)	85 (13%)		83 (25%)	53 (16%)	
Ongoing at data cutt-off	16 (5%)	84 (13%)		16 (5%)	46 (14%)	
Other	44 (13%)	169 (27%)		44 (13%)	86 (25%)	
Best overall response						
CR	181 (53%)	377 (59%)	0.09	180 (53%)	182 (54%)	0.94
PR	158 (47%)	260 (41%)		157 (47%)	155 (46%)	

CR, complete response; PR, partial response.

Time on treatment was significantly shorter for Danish patients compared to Other countries (p<0.0001).

Figure 2: Kaplan-Meier curves of time on treatment for patients in Denmark (blue line) and Other countries (yellow line). TOT, time on treatment; CI, confidence interval.

- **PFS** was comparable between the cohorts, with a trend towards improved long-term PFS for Danish patients (p=0.07).
- Analysis performed on **matched cohorts** showed similar results (PFS: p=0.37)

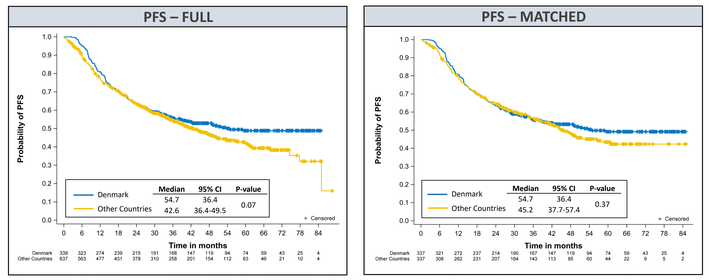


Figure 3A: Kaplan-Meier curves of PFS for full cohort (left side) and matched cohort (right side) for patients from Denmark (blue line) and Other countries (yellow line). PFS, progression-free survival.

- **OS and MSS** were poorer for Danish patients with a separation of the curves around 18 months following ICI initiation (OS: p=0.005 and MSS: p=0.01, respectively).
- Analyses performed on **matched cohorts** showed similar results (OS: p=0.02, MSS: p=0.02).

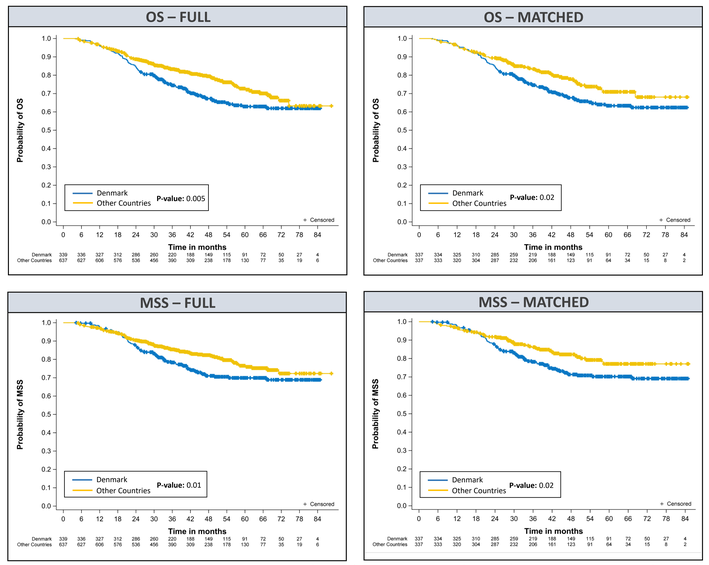


Figure 3B: Kaplan-Meier curves of OS and MSS for full cohort (left side) and matched cohort (right side) for patients from Denmark (blue line) and Other countries (yellow line). OS, overall survival; MSS, melanoma specific survival; CI, confidence interval.

- **Follow-up** was significantly longer for Danish patients compared to Other countries (p<0.0001).

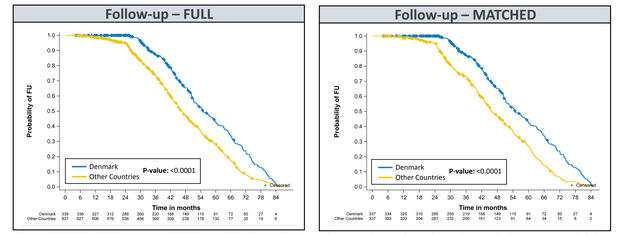


Figure 4: Kaplan-Meier curves of follow-up for full and matched cohort for patients from Denmark (blue line) and Other countries (yellow line).

DISCUSSION

- Similar PFS between cohorts suggests that early discontinuation following OR does not compromise response rate and durability.
- OS and MSS were poorer in the Danish cohort, which might be explained by differences in follow-up duration.
- Follow-up was significantly longer in the Danish cohort, reflecting continuous survival-status updates via linkage of electronic patient records and the Danish Central Person Register.
- In the control cohort, censoring began around 18 months after ICI initiation, coinciding with OS curve separation.
- Control cohort OS curves plateaued later than those of the Danish cohort and did not follow the characteristic shape seen for post-ICI survival.

SUMMARY AND CONCLUSION

- Danish patients with ICI-induced OR were discontinued earlier than patients of the pan-European control cohort.
- Danish patients and the European control cohort showed similar PFS.
- Comparability of OS was compromised by a shorter FU in the control cohort.
- Findings confirm that early discontinuation following OR can be pursued without compromising durability of response.

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Correspondence: Inge Mansfield Noringriis (inge.mansfield.noringriis@regionh.dk) or Inge Marie Svane (inge.marie.svane@regionh.dk)

European Melanoma Registry (EUMelaReg; www.eumelareg.org): This registry is a multi-center database run by a cross-national consortium of academic groups in Europe collecting and evaluating real-world melanoma cases with non-resectable stage III or metastatic stage IV melanoma. Data has been captured since 2018 entered voluntarily into the system by participating centers.



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