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SURVIVAL OF PATIENTS WITH ADVANCED MELANOMA ACCORDING TO FIRST LINE TREATMENT AND KEY PROGNOSTIC FACTORS: REAL-WORLD DATA FROM GEM1801 STUDY

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BACKGROUND

Targeted therapy (TT) and immune-check-point inhibitors (CPi) have improved the survival of patients with advanced melanoma. Real-world data for these treatments add value, confirming the results of clinical trials, expanding evidence in underrepresented populations and detecting new areas of research.

The GEM-1801 study is a collaboration among 37 centers affiliated to Spanish Melanoma Group (GE**M**) to collect prospective data in order to obtain an image of the reality of patients who debut with advanced melanoma in Spain.

OBJECTIVES

- To define the profile of patients with advanced melanoma, based on a representative sample of patients treated following the routine clinical practice in Spanish centers.
- To analyze treatment choices and their health outcomes.

METHODS

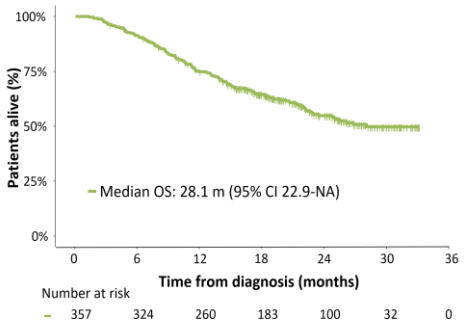
GEM1801 is a prospective observational, epidemiological and multicentric study including 400 pts with resected stage III and advanced/metastatic melanoma diagnosed since 2018 in Spain.

All pts are ≥18 years and provided written informed consent.

We report results of the advanced melanoma group (n=357). Patients were included since August 2018 to October 2019.

Age (range), years	**65.2 (23.3-95.2)**
Sex, n (%)	
Male	**200 (56)**
Female	**157 (44)**
ECOG performance status, n (%)	
0	**190 (53.2)**
1	**116 (32.5)**
2	**40 (11.2)**
3	**7 (2)**
UK	**4 (1.1)**
Type of melanoma, n (%)	
Cutaneous	**239 (67)**
Mucosal	**21 (5.9)**
Acral	**20 (5.6)**
Uveal	**10 (2.8)**
UK	**67 (18.8)**
***BRAF* mutation status, n (%)**	
***BRAF*-wt**	**168 (47.1)**
***BRAF*^{V600}-mut**	**180 (50.4)**
UK	**9 (2.5)**
Tumor stage AJCC8th ed. at study entry, n (%)	
III B	**6 (1.7)**
III C	**21 (5.9)**
III D	**6 (1.7)**
IV A	**89 (24.9)**
IV B	**51 (14.3)**
IV C	**124 (34.7)**
IV D	**60 (16.8)**
Number of affected organs, n (%)	
1	**122 (34.2)**
2	**95 (26.6)**
≥ 3	**124 (34.7)**
Lactate dehydrogenase level, n (%)	
Normal (≤ULN)	**185 (51.8)**
Elevated (>1x <2x ULN)	**91 (25.5)**
Elevated (>2x ULN)	**26 (7.3)**
UK	**55 (15.4)**
Previous adjuvant therapy, n (%)	
Targeted therapy	**5 (1.5)**
CPi	**53 (14.8)**
Number of treatment lines, n (%)	
1	**196 (54.9)**
≥ 2	**138 (38.7)**

Table 1. Patients´ characteristics (n=357); UK (unknown); wt (wild type); mut (mutated)

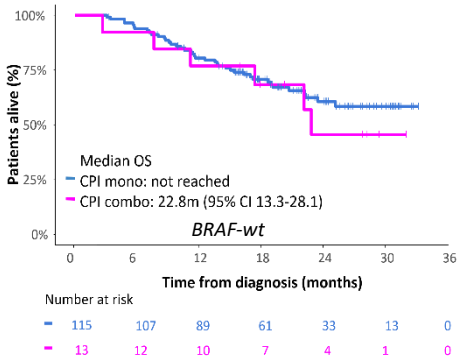


Estimated cumulative survival; % (95% CI)	All patients
At 12 months	74.8 (70.4-79.5)
At 18 months	64.5 (59.7-69.8)

Figure 1. OS stage III irresecable or IV

Patients with first line systemic treatment	*BRAF*-wt n = 156	*BRAF*^{V600}-mut n = 170
Immunotherapy, n (%)	**148 (94.9)**	**42 (24.7)**
CPi monotherapy	**115 (73.7)**	**36 (21.2)**
Anti PD-1 (pembrolizumab)	**57 (36.5)**	**12 (7.1)**
Anti PD-1 (nivolumab)	**58 (37.2)**	**24 (14.1)**
CPi combo	**13 (8.3)**	**6 (3.5)**
Targeted Therapy (BRAF - MEK i), n (%)	**0 (0)**	**109 (64.1)**
Vemurafenib + Cobimetinib	**0 (0)**	**13 (7.6)**
Dabrafenib + Trametinib	**0 (0)**	**96 (56.5)**
Chemotherapy	**1 (0.6)**	**2 (1.2)**
Fotemoustine	**1 (0.6)**	-
Platine	-	**2 (1.2)**
Clinical trials (CT)	**27 (17.3)**	**17 (10)**
CPi (CT)	**20 (12.9)**	**9 (5.3)**
TT +CPi (CT)	**7 (4.5)**	**7 (4.1)**
UK	-	**1 (0.6)**

Table 2. Treatment disposition (n=326). CT (clinical trial); UK (unknown)

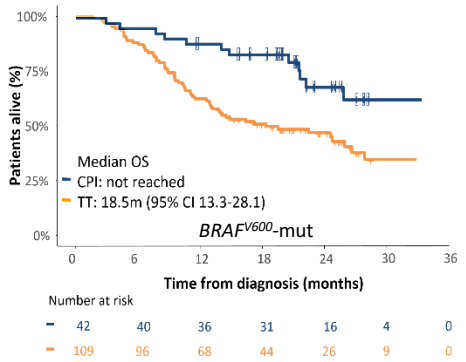


Estimated cumulative survival; % (95% CI)	CPi Mono	CPi combo
At 12 months	80.5 (73.5-88.2)	76.9 (57.1-100)
At 18 months	70.8 (62.8-79.9)	68.4 (46.9-99.7)

Figure 2. OS for *BRAF*-wt. The curves are for descriptive purpose only

	Factor		n (%)	12 - 18 m OS (%)	*p* (Cox / log-rank)
***BRAF*^{V600} mut TT**	**ECOG**	**0-1**	**83 (77)**	**67.5 - 56.4**	**0.005**
		>1	**25 (33)**	**44 - 35**	
	LDH	**≤ULN**	**50 (53)**	**78 – 63**	**0.024**
		>ULN	**45 (47)**	**46.7 - 39.8**	
	M1	**a-b**	**45 (41)**	**75.6 – 71**	**<0.0001**
		c-d	**64 (59)**	**53.1 - 37**	
***BRAF*^{V600} mut CPi**	**ECOG**	**0-1**	**41 (98)**	**90.2 - 85.2**	-
		>1	**1 (2)**	**NA**	
	LDH	**≤ULN**	**26 (72)**	**88.5 - 88.5**	**0.54**
		>ULN	**10 (28)**	**90 - 80**	
	M1	**a-b**	**19 (45)**	**84.2 - 84.2**	**0.42**
		c-d	**23 (55)**	**91.3 - 82.6**	
***BRAF*-wt CPi**	**ECOG**	**0-1**	**113 (89)**	**83.9 - 74.9**	**0.0027**
		>1	**14 (11)**	**46.2 - 30.8**	
	LDH	**≤ULN**	**71 (66)**	**89 – 82**	**<0.0001**
		>ULN	**36 (34)**	**61.1 - 43.3**	
	M1	**a-b**	**72 (56)**	**90.1 - 79.5**	**0.02**
		c-d	**56 (44)**	**67.3 - 59**	

Table 3. Factors associated with survival among vs therapies according to *BRAF* status



Estimated cumulative survival; % (95% CI)	CPi	TT
At 12 months	88.1 (78.8-98.5)	62.4 (53.9-72.2)
At 18 months	83.2 (72.6-95.4)	50.9 (42.3-61.3)

Figure 3. OS for *BRAF*^{V600}-mut. The curves are for descriptive purpose only.

n (%)	CPi	TT
Any G3-4 toxicity	**23 (9.3)**	**15 (8.7)**
Fever	**1 (0.4)**	**5 (2.9)**
Transaminase increase	**4 (1.6)**	-
Hepatitis	**3 (1.2)**	-
Diarrhea	**2 (0.8)**	**1 (0.6)**
Neumonitis	**2 (0.8)**	**1 (0.6)**
Colitis	**2 (0.8)**	-
Vomiting	-	**2 (1.2)**
Ocular events	-	**2 (1.2)**
Pancreatitis	**1 (0.4)**	**1 (0.6)**
Rash	**1 (0.4)**	**1 (0.6)**

Table 4. G3-4 Toxicity profile (a patient may have more than one treatment and/or toxicity)

RESULTS

Patients characteristics are summarized in **table 1**. 22 (6,2%) patients did not received first line systemic treatment (2 were unkown). Of the 333 (93,3%) patients treated with first line treatment, 44 (13,2%) were in a clinical trial and 289 (86,8%) in daily practice setting. **Table 2** summarizes these treatments for patients with known *BRAF* status (N=326).

With a median follow up of 18,3 months (95% CI 17.1-19.6) **figure 1** reflects the overall survival of the whole cohort.

For the 289 patients that received daily practice treatment, **figure 2** and **3** reflect the overall survival for immunotherapy and targeted therapy according to *BRAF* mutation status. **Table 3** analyzes the patients` characteristics that could influence survival outcomes.

Finally, **table 4** summarizes the toxicity profile of the different treatments that patients have receive until cutt off (November 17th 2020).

CONCLUSIONS

- Survival of patiens with advanced melanoma in "real-world" is similar to reported in clinical trials
- For *BRAF-wt* the preferred choice was anti-PD-1 monotherapy, with no apparent differences in survival when compared to the combination with anti-CTLA4.
- First line TT was chosen for aprox 2/3 *BRAF*^{V600}-mut cases while aprox 1/3 were treated with CPi.
- The apparent descriptive difference in OS curves in patients treated with CPi vs TT in *BRAF*^{V600}-mut group may be due to selection bias since patients with TT had worse baseline prognostic factors.
- Toxicity for CPi and TT has a similar profile than those described in clinical trials.

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