The Cost of Metastatic Colorectal Cancer Patients with BRAF^{V600E} Mutations in Greece

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Introduction

- Tumors harboring BRAF mutation are among the most aggressive forms of metastatic colorectal cancer (mCRC), with an estimated incidence of 8-12% of mCRC cases in Europe.[1]
- Within BRAF-mutations in mCRC, BRAF^{V600E} accounts for more than 90%.[2]
- BRAF^{V600E} mutation leads to the activation of BRAF kinase and sustains the RAS/RAF/MEK/ERK pathway signalling, resulting in increased cell growth and proliferation.[3]
- Patient population with BRAF^{V600E}-mutant metastatic CRC (BRAF^{V600E}-MT mCRC) has the shortest overall survival (OS) compared to other types of mCRC mutation subgroups.[4]
- In Greece, about 10% of mCRC patients are found with BRAF mutation, leading to around 210 patients per year with BRAF^{V600E} mutated tumors.

Objective

- The aim of this study was to explore the treatment strategy and economic burden of mCRC patients with BRAF ^{V600E} mutation in Greece.

Methods

- The methodology followed was based on a two-step approach. First, the local treatment pathways and associated resource use were identified emerging from a panel of experts. Secondly, the total costs for each pathway were estimated, by assigning unit costs to resource use items.

Local treatment pathway and resource use

- An expert panel of 6 medical oncologists of public and private sector with expertise in mCRC was convened, in order to map the current local treatment algorithm and associated health care resource use.
- The treatment phases studied were: pre-progression, disease progression and terminal care.
- Data collection was performed during an expert panel and the data elicitation method was a three-round Delphi technique.[5]

Cost estimation for each pathway

- Unit costs were retrieved from publicly available sources, ministerial gazette, DRG costs and other healthcare sources[6-8]. The perspective adopted was from the Greek National Services Organization (EOPYY).
- The micro-costing method was followed for costs estimation. Only direct medical costs were considered, which consisted of oncology drug costs, costs of resource utilization associated with medical consultations, home care, hospital visits, laboratory tests, imaging examinations and procedures. The cost analysis in this study is presented on monthly and annual basis.
- According to expert panel the cost of progression was allocated as follows: 1st line - 1 relapse, 2nd average of 1.25 relapses, 3rd line average of 1.75 relapses.
- To estimate pharmaceutical costs, the average price per mg was calculated based on the hospital prices per package, for all packages marketed in Greece. Prices were taken from the latest Price Bulletin.[7]
- In order to take into account, the dosage changes and patients' compliance for the regimens, relative dose intensity (RDI) was used in all treatment categories.
- The cost of relapses were also added in the annual cost estimation. 1 relapse for the 1st line, 1.25 relapse for 2nd line and 1.75 relapse at 3rd line.
- The cost of pharmaceuticals is presented at hospital prices minus 5% (EOPYY & Hospital purchase price) without taking into consideration any other discounts ie. Rebate, clawback or price negotiations between pharmaceutical companies and negotiation committee, as this is information is confidential and not published. Pharmaceutical prices are presented in Table 1.

Table 1: Pharmaceutical cost

	Hospital prices – 5%, Unit cost (€)	Cost per mg (€)
Irinotecan	147.31	0.47
Folinic acid	11.2	0.03
Fluorouracil	14.14	0.0028
Cetuximab	132.26	1.32
Panitumumab	1,100.28	2.75
Bevacizumab	204.52	2.05
Aflibercept	250.27	2.50
Oxaliplatin	19.82	0.40
Capecitabine	10.66	0.002
Nivolumab	2,106.87	8.78
Pembrolizumab	2,229.89	22.30
Encorafenib	1,046.92	0.33
Tas102 (Trifluridine-tiporacil)	445.92	1.05
Regorafenib	1,884.71	0.56
Mitomycin-C	15.91	0.84

Results

- At 1st line 60% of patients receive combination of Bevacizumab and chemotherapy and 40% combination chemotherapy.
- At 2nd line 25% of patients receive targeted therapy of Encorafenib & Cetuximab, 45% receive combination of chemotherapy and biological therapies, 20% chemotherapy and 10% immunotherapies.
- At 3rd line 50% of patients receive targeted therapy of Encorafenib & Cetuximab, 10% Regorafenib and 40% TAS102
- At Table 2 the pharmaceutical treatment options are presented at 1st, 2nd and 3rd line for all mutations.

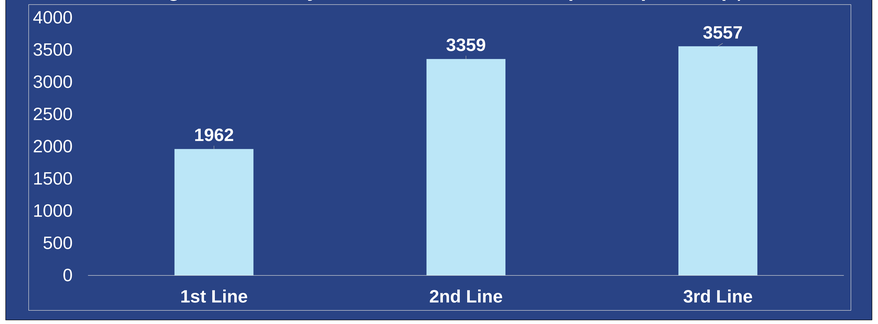
Table 2. Treatment options of BRAF Mutation ^{v600E} per line (% of patients)

	BRAF MUTATED		
	1st line	2nd line	3rd line
Folfiri	10	20	
Folfiri & Bevacizumab	15	25	
Folfiri & Aflibercept		10	
Folfox	10		
Folfox & Cetuximab		10	
Folfox & Bevacizumab	5		
Folfoxiri	20		
Folfoxiri & Bevacizumab	30		
CapOX & Bevacizumab	10		
Tas102			40
Regorafenib			10
Encorafenib & Cetuximab		25	50
Immunotherapies		10	
TOTAL	100	100	100

Monthly & Annual Cost Per Line of mCRC BRAF^{V600E} patient

- In Figure 1 the monthly cost of mCRC patient with BRAF^{V600E} mutation per line is presented.
- The respective annual total cost for the 1st line patients has been estimated at €24,127.29, for the 2nd line at €41,036.84 and for the 3rd line the annual total cost has been estimated at €43,705.32.
- Experts agreed that in the 2nd and 3rd line hospitalization and day hospital visits increase with an immediate impact on 2nd and 3rd line cost. More specifically, the cost of management for the 2nd line per month was estimated at €188.21 and for the 3rd line at €203.81.

Figure 1. Monthly cost of mCRC BRAF^{V600E} patient per line (€)



Discussion

- Patients with mCRC have a 5-year survival rate accounting, less than 10%, which is accompanied also with poor quality of life.[9,10]
- The present study investigated and provided an overall view of the resource use and associated costs required to treat metastatic CRC BRAF^{V600E} patients in Greece.
- BRAF^{V600E} accounts for more than 90% of BRAF mutations in CRC and a new targeted therapy[2], currently approved for 2nd line, for this mutation has been recently introduced in the Greek market (Encorafenib plus Cetuximab).
- The direct cost of mCRC patient was estimated on monthly and annual basis, without taking into consideration the survival rate of each treatment, which is an important parameter for the choice of medical decision makers and the anticipating reason for the choice of targeted therapies as well as immunotherapies.

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