PCN 101

Cost-effectiveness of ipilimumab for previously untreated patients with advanced melanoma in Spain

Aceituno S.[1], Canal C.[2], Paz S.[1], González P.[2], Márquez-Rodas I.[3]

[1] Outcomes'10, Spain; [2] Bristol-Myers Squibb, Spain; [3] Instituto de Investigación Sanitaria Gregorio Marañón, Spain

Introduction

- Melanoma is a public health concern because of the aggressiveness and high mortality in the advanced stage. In Spain, the incidence adjusted per 100,000 inhabitants is 5.5 for men and 5.3 for women[1], with approximately 850 deaths every year[2].
- No approved chemotherapy agents for advanced melanoma have provided an additional survival benefit as compared to the standard of care for most patients (dacarbazine) in the past 30 years[3] being 6.2 months the median overall survival (OS) for advanced melanoma patients on treatment[4].
- Ipilimumab obtained CHMP positive opinion in 2011 and has improved the OS in a number of studies[5-9]. Therefore, it is necessary to evaluate the overall costs and survival benefits associated to ipilimumab with respect to the standard of care for most patients (dacarbazine) in advanced melanoma patients.

Objective

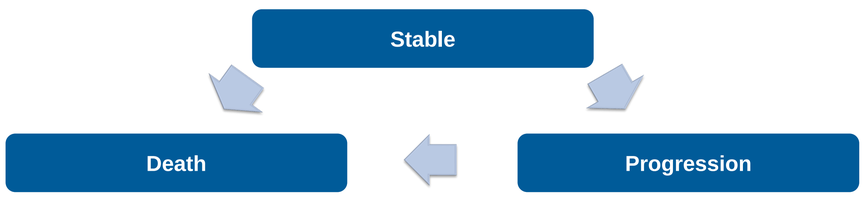
- **To determine the cost-effectiveness of ipilimumab (3 mg/kg) compared to dacarbazine as first-line treatment in patients with advanced melanoma in Spain.**

Methods

Model description

- A 3-health states Markov model (Figure 1) with 3-week cycles was developed. All patients started in stable state. Transition probabilities were based on progression-free survival (PFS) and OS data from clinical trials.

Figure 1. Health states



- The time horizon considered in the base-case was 30 years, time by which 99% of patients were estimated to have died (patient lifetime horizon).
- The model takes the perspective of the Spanish Healthcare System. Costs and benefits were discounted at an annual rate of 3%.
- The main outputs were incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) based on the following outputs: life years gained (LYG), quality adjusted life years (QALYs) and therapy costs [drugs, disease and adverse events (AEs) management].
- Key assumptions, inputs and methodology applied in the model were validated by key opinion leaders (KOLs) involving health economics experts and clinicians experienced in the treatment of melanoma from various European countries.

Survival data

- The survival data for ipilimumab was obtained from a pooled dataset of chemotherapy naive patients (n=78) from three phase II studies (CA184-004, CA184-022, MDX010-08) and a phase III study (MDX010-20)[5], and was compared with an adjusted arm of the CA184-024 trial[10] for dacarbazine (single arm comparison method). Parametric extrapolation methods were used to project survival over lifetime.
- Second-line drug efficacy was not considered.

Health utilities

- Utility values were taken from the CA184-024 trial (0.84 'stable', 0.83 'progression')[10]. AEs related utility decrements were not included in the base-case.

Costs estimation

- Direct costs included: drug acquisition and administration, disease and AEs management. Unit costs were derived from Spanish healthcare cost databases (€, 2013)[11-14].

Drug acquisition and administration

- First- (ipilimumab, dacarbazine) and second-line (dacarbazine, paclitaxel, temozolomide, fotemustine, vemurafenib, ipilimumab) drug costs were considered (Table 1). The costs of second-line drugs were added to each treatment arm by taking a weighted average cost based on market share.

Table 1. Cost per model cycle (21 days)

Drug (dose)	Target dose* (mg)	Drug cost† (€)	Administration cost (€)	Total cost (€)
Ipilimumab (3mg/kg)	210	16,511	268	16,779
Dacarbazine (850 mg/m^2)	1,530	22	268	290
Paclitaxel‡ (260 mg/m^2)	468	1,039	268	1,307
Temozolomide (200 mg/m^2)	360	589	0.00§	589
Fotemustine (100 mg/m^2)	180	759	604	1,363
Vemurafenib (240 mg)	1,920	6,410	0.00§	6,410

* Mean patient weight: 70 kg; mean patient body surface area: 1.79 m^2. No drug wastage and no dose reduction was assumed.
† A mandatory -7.5% (ipilimumab; vemurafenib; paclitaxel; temozolomide) or -15% (fotemustine) rebate was applied.
‡ Abraxane® cost (other paclitaxel formulations are not used in clinical practice in Spain).
§ No administration costs (oral therapy).

- For drugs with a double-pricing system (like ipilimumab), costs were based upon the official notified prices in Spain.

Disease management

- Resource use was derived from a physicians' survey on resource use associated with the treatment of melanoma in Europe. Disease management, best supportive care, terminal care and home care costs were included considering medical visits, hospital stay, laboratory tests, radiology tests and pain control drugs.

AEs management

- Grade 3-4 AEs (ipilimumab and dacarbazine: infection, sepsis, thrombocytopenia, anemia, neutropenia, diarrhea, vomiting, pain, nausea, leukopenia, fatigue, rash, hypothyroidism, pyrexia; ipilimumab: colitis, stomatitis, intestinitis, hypopituitarism, hypophysitis, adrenal insufficiency, hepatitis) frequencies from observational CA184-338 study[7] were considered.
- The proportion of in-patient versus out-patient was estimated by the clinicians. The in-patient cost was based on the resource use estimated by clinicians multiplying by unit costs; the out-patient cost was based on aggregated costs.

Sensitivity analysis

- One-way (OWSA) and probabilistic sensitivity analysis (PSA) were performed to test the impact of uncertainty on the model. Explored parameters were:
  - OWSA: survival data, utility values, AEs related utility decrements, second-line treatment cost, ipilimumab administration costs, stable patients cost, discount rate, time horizon, and management of long-term survivors.
  - PSA: drugs dose, frequency of resources use (gamma distribution); proportion of patients using each resource and utility values (beta distribution).

Results

- The ICER was 34,566 €/LYG and the ICUR was 41,459 €/QALY for ipilimumab compared to dacarbazine (Table 2).

Table 2. Cost-effectiveness results

	Cost per patient (€)	LYG	QALYs	ICER	ICUR
Ipilimumab	124,816	2.58	2.15	34,566	41,459
Dacarbazine	55,217	0.57	0.47	-	-
Difference	69,598	2.01	1.68	-	-

Sensitivity analysis

OWSA

- The use of different utility values from alternative data sources and the non inclusion of second-line drug costs had the greatest impact on the ICUR and ICER, respectively (Figure 2 and 3).

Figure 2. Tornado diagram (ICER)

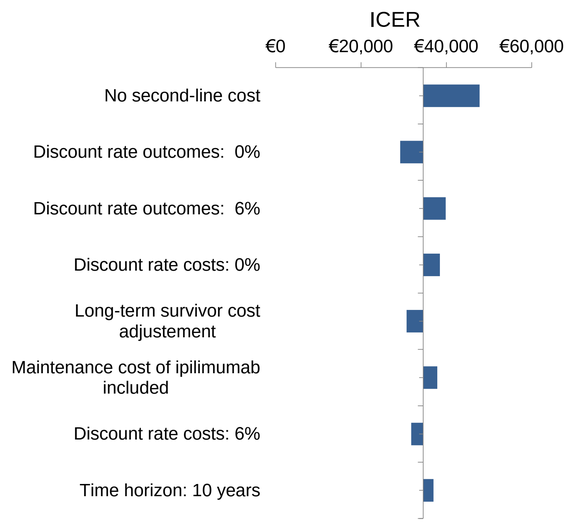
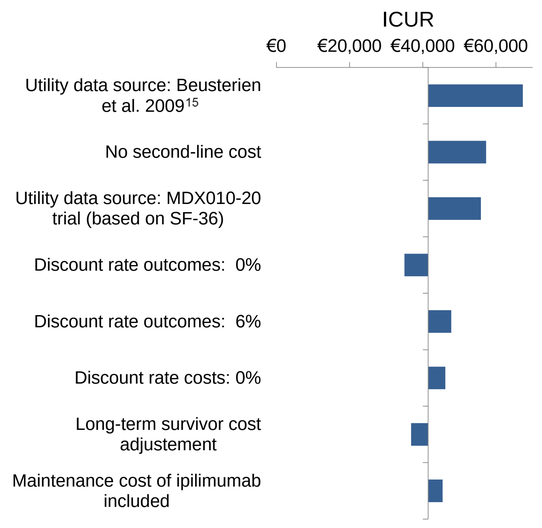


Figure 3. Tornado diagram (ICUR)



PSA

- The cost-effectiveness plane for the cost per LYG (Figure 4) and cost per QALY (Figure 5) shows that ipilimumab is more effective and more costly than dacarbazine.

Figure 4. Cost-effectiveness plane (cost/LYG)

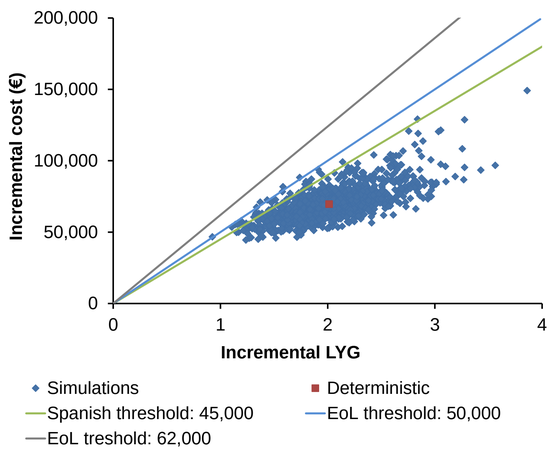
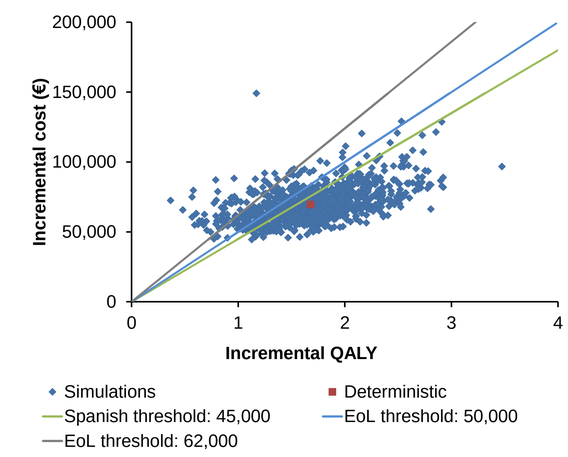
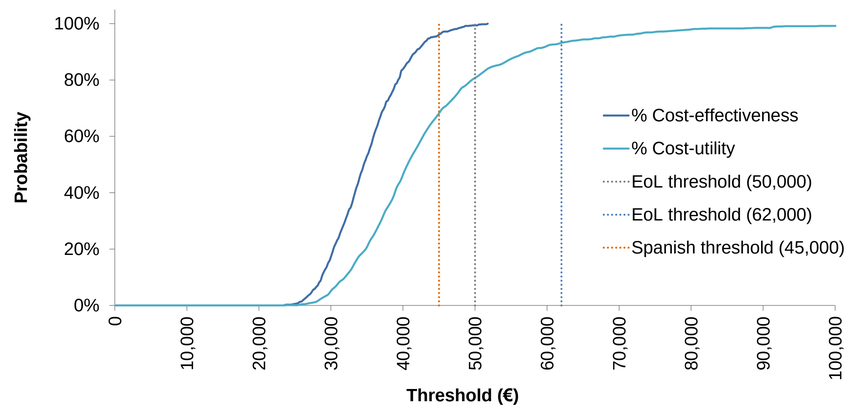


Figure 5. Cost-effectiveness plane (cost/QALY)



- PSA showed that ipilimumab is up to 99-100% and 81-93% likely to be cost-effective at the threshold established by the NICE for oncology drugs that meet 'End-of-Life' (EoL) criteria (50,000-62,000)[16] for ICER and ICUR (Figure 6), respectively. Additionally, at the threshold acceptable in Spain (45,000)[17] the likelihood of ipilimumab being cost-effective is up to 96% and 66% for ICER and ICUR, respectively.

Figure 6. Cost-effectiveness and cost-utility acceptability curves



Conclusions

Ipilimumab is a cost-effective alternative compared with dacarbazine for previously untreated patients with advanced melanoma in Spain providing an additional two-years survival benefit related to dacarbazine over the model time horizon.

References

1. *Asociación Española Contra el Cáncer* (AECC). Available at: https://www.aecc.es. [Accessed: August, 2012]; **2.** GLOBOCAN 2008. Available: http://globocan.iarc.fr/ [Accessed: October, 2013]; **3.** Gimotty PA, *et al*. J Clin Oncol. 2008;26:517-18; **4.** Korn EL, *et al.* J Clin Oncol. 2008;26:527-34; **5.** CHMP. EPAR - Assessment report variation. Yervoy (ipilimumab); **6.** Patt D, *et al.* European Cancer Congress; 2013. Amsterdam; **7.** Margolin KA, *et al.* European Cancer Congress; 2013. Amsterdam; **8.** Hodi FS, *et al.* N Engl J Med. 2010;363:711-23; **9.** Schadendorf D, *et al.* European Cancer Congress. 2013. Amsterdam; **10.** Robert C, *et al.* N Engl J Med. 2011;364:2517-26; **11.** *Nomenclator.* Available at: http://www.msssi.gob.es/profesionales/nomenclator.do [Accessed: December, 2013]; **12.** Botplusweb. Available at: https://botplusweb.portalfarma.com/ [Accessed: July, 2013]; **13.** *Ministerio de Sanidad, Política Social e Igualdad*. CMBD 2011. Available at: http://pestadistico.msc.es [Accessed: July, 2013]; **14.** eSalud. Oblikue consulting. Available at: http://www.oblikue.com/bddcostes/ [Accessed: September, 2013]; **15.** Beusterien KM, *et al.* Br J Cancer. 2009;101:387-9; **16.** Longson C, *et al.* NICE. 2009; **17.** De Cock E, *et al*. Pharmacoeconomics SRA. 2007;4:97-107.

ISPOR 17TH ANNUAL EUROPEAN CONGRESS
Amsterdam, November 8th-12th, 2014

Bristol-Myers Squibb