Results 66 patients (63% women, average age 45.6 ± 12.2 years) were included, 100% receiving off-label use. Indication and LE, describing benefit/no benefit/harm: relapsing–remitting multiple sclerosis (RRMS), LE: 2, no benefit (34 patients, 52,3%); primary/secondary progressive multiple sclerosis (PMS), LE: 2, no benefit (6 patients, 9,2%); optic neuromyelitis (ONM), LE: 4, benefit (7 patients, 10,8%); myasthenia gravis (MG), LE: 4, benefit (6 patients, 9,2%); demyelinating inflammatory chronic polyradiculoneuropathy (DICP), LE: 4, benefit (1 patient, 1,5%). Optic neuritis (4 patients); isolated CNS vasculitis (2 patients), other neurological disorders or syndromes (5 patients). Literature review found no good quality evidence for these last diseases.

Rituximab was firstline immunomodulatory treatment for all ONM, MG and DICP patients. 21 patients (52.5%) with RRMS and PMS received it rituximab as, at least, thirdline therapy. Most habitual dosage regimen was: 500–1000 mg for the first month (days 1 and 15, repeated 6 months later) with a maintenance dose of 500–1000 mg every 6–12 months.

Four patients had infusion related reactions. 12 infections: respiratory (6), urinary (5) and dermic (1), and 1 case of breast cancer were reported.

Average cost per patient was 6366€ during the first year and 2546€ each following year. 78% of this cost was spent in treating pathologies for which rituximab has shown poor evidence.

Conclusion and relevance Off-label rituximab is extensively used in neurological pathologies with no strong evidence. As many adverse events have been observed, close monitoring of patients is suggested. The high economic impact makes it necessary to rationalise rituximab prescriptions and optimise the efficiency of sanitary resources.

REFERENCES AND/OR ACKNOWLEDGEMENTS

Conflict of interest No conflict of interest

4CPS-305 EFFECTIVENESS AND SAFETY OF BRAF/MEK INHIBITORS IN ADVANCED OR METASTATIC MELANOMA IN TWO TERTIARY HOSPITALS

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Background and importance Dabrafenib/trametinib and vemurafenib/cobimetinib significantly increased progression free survival (PFS) and overall survival (OS) in patients with advanced or metastatic melanoma with BRAF mutations, in phase III clinical trials (CT).

Aim and objectives To assess the effectiveness and safety of vemurafenib/cobimetinib and dabrafenib/trametinib in patients with locally advanced or metastatic melanoma in real life.

Material and methods We performed a retrospective, multicentre, observational study of patients with BRAF mutated melanoma treated with vemurafenib/cobimetinib or dabrafenib/trametinib until 30 September 2020. Variables collected were: sex, age, stage, performance status (PS), previous treatments, duration of treatment and response, dose received and dose adjustments. Variables evaluated were: PFS, OS, adverse events (AE), withdrawal rate and reason for withdrawal.

Results We included 42 patients (27 men, mean age 62.4 ± 15.2 years). 81% had metastatic melanoma and 19% had locally advanced melanoma. 20 patients received vemurafenib/cobimetinib, 13 dabrafenib/trametinib, 1 dabrafenib and 8 received both drugs. 14 patients presented PS=0, 24 PS=1 and 13 PS $\geq$ 2. 71.4% and 14.3% of patients treated with vemurafenib/cobimetinib and dabrafenib/trametinib, respectively, received the drug as firstline treatment.

Effectiveness and safety variables were evaluated in 38 patients (n=4 loss to follow-up):

- median PFS was 9.71 (95% CI 5.77 to NA) and median OS was 18.5 (95% CI 11.9 to NA) in vemurafenib/trametinib treated patients, while in those who received dabrafenib/cobimetinib, median PFS was 10.1 (95% CI 7.7 to NA) and OS was not reached.
- median duration of treatment with vemurafenib/cobimetinib and dabrafenib/trametinib was 99 (IR 20–243) and 198 (IR 73–632) days, respectively.
- 14.8% and 26.3% of patients treated with vemurafenib/cobimetinib and dabrafenib/trametinib, respectively, showed complete response, 33.3% and 26.3% partial response, 11.1% and 15.8% progressed and 33.3% and 15.8% were not assessable (early toxicity or recent onset).

All patients treated with vemurafenib/cobimetinib presented with AE during treatment (85.2% dermatological and 74.1% gastrointestinal) and in 26% treatment was withdrawn. In patients treated with dabrafenib/trametinib, 94.7% showed AE (52.6% dermatological, 68.4% gastrointestinal and 57.9% low grade fever/discomfort), and in 15.8% treatment was withdrawn due to toxicity.

Conclusion and relevance The effectiveness observed in our patients was slightly lower than that seen in the pivotal CT (COBRIM-b) in vemurafenib/cobimetinib patients. In contrast, it was similar to that seen in other pivotal CTs (COMBI-v and COMBI-d) in patients treated with dabrafenib/trametinib.

The toxicity profile of both drugs was similar to the pivotal CTs. Dabrafenib/trametinib was better tolerated than vemurafenib/cobimetinib.

REFERENCES AND/OR ACKNOWLEDGEMENTS

Conflict of interest No conflict of interest

4CPS-306 DAROLUTAMIDE, ENZALUTAMIDE AND APALUTAMIDE: PLACE IN THERAPEUTICS OF CASTRATION RESISTANT NON-METASTATIC PROSTATE CANCER

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Background and importance Apalutamide, enzalutamide and darolutamide have recently been approved for treating castration resistant non-metastatic prostate cancer (nmCRPC). The lack of direct comparisons makes the selection and positioning of these drugs in this new scenario difficult. Taking into account the social and economic importance, it is essential to develop studies that provide answers to this lack of information.

Aim and objectives The aim of this study was to compare the relative efficacy of darolutamide versus apalutamide and enzalutamide using clinical trial data to determine the positioning of new antiandrogenic drugs in the treatment of nmCRPC.

Material and methods We performed adjusted indirect comparisons using Bucher's method. We selected the main clinical trial for each drug (ARAMIS, PROSPER and SPARTAN trials). The three studies had a similar design and included populations with similar characteristics. The main outcome used was metastasis free survival (MFS). MFS was demonstrated to be an adequate surrogate variable for overall survival.¹ The variable used for darolutamide in the darolutamide versus enzalutamide IC was progression free survival (PFS) due to the PROSPER design. MFS and PFS were compared with placebo in the three studies.

Results The three drugs were superior to placebo for the end-points analysed. In the comparison between enzalutamide (MFS=36.6 months (m) vs 14.7 m) versus darolutamide (PFS=36.8 m vs 14.8 m), HR calculated using Bucher's method favoured enzalutamide (0.76 (IC 0.59–0.98); p=0.037). In the IC darolutamide (MFS=40.4 m vs 18.4 m) versus apalutamide (MFS= 40.5 m vs 14.7 m) HR favoured apalutamide (1.41 (IC 1.07–1.87); p=0.015). Both IC yielded a statistically significant result.

Conclusion and relevance While indirect comparisons had limitations, this analysis showed the slight superiority in HR in delaying the appearance of metastases for enzalutamide and apalutamide. Despite the data obtained, the inferiority of darolutamide cannot be assured. The biases involved in the comparison may have influenced the results. Real world data are needed to expand our knowledge of castration resistant non-metastatic prostate cancer treatment.

REFERENCES AND/OR ACKNOWLEDGEMENTS

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4CPS-307 SAFETY EVALUATION OF NEW ANTIANDROGENIC DRUGS IN CASTRATION RESISTANT NON-METASTATIC PROSTATE CANCER

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Background and importance Apalutamide, enzalutamide and darolutamide have recently been approved for treating castration resistant non-metastatic prostate cancer (nmCRPC). The three drugs demonstrated efficacy over placebo in clinical trials, but the lack of direct comparisons, particularly with regard to safety, makes the selection and positioning of these drugs in this new scenario difficult.

Aim and objectives The aim of this study was to compare the relative safety of darolutamide versus apalutamide and enzalutamide using clinical trial data to determine the positioning and objective differences in security profiles of new antiandrogenic drugs in the treatment of nmCRPC.

Material and methods We performed adjusted indirect comparisons using Bucher's method. We used security data from the main clinical trials for each drug (ARAMIS, PROSPER and

SPARTAN trials). The three studies had a similar design and included populations with similar characteristics. We calculated risk differences and number needed to harm (NNH) for each relevant outcome and selected those with statistically significant difference.

Results The results are shown in tables 1 and 2.

Abstract 4CPS-307 Table 1

Adverse event (AE)	Risk differences darolutamide vs placebo (95% CI)	Risk differences enzalutamide vs placebo (95% CI)
AE	6.3% (2.1% to 10.6%)	9.5% (5.1% to 13.8%)
AE grades 3–4	5.2% (1.0% to 9.5%)	8% (3.1% to 12.8%)
Serious AE	4.8% (0.5% to 9.1%)	6% (1.6% to 10.5%)
AE leading to discontinuation	0.2% (–2.7% to 3.2%)	3.3% (0.5% to 6.2%)

Abstract 4CPS-307 Table 2

Adverse event	Risks differences darolutamide vs placebo (95% CI)	Risk differences apalutamide vs placebo (95% CI)
AE	6.3% (2.1% to 10.6%)	3.3% (0.5% to 6.1%)
AE grades 3–4	5.2% (1.0% to 9.5%)	10.9% (5.1% to 16.7%)
Serious AE	4.8% (0.5% to 9.1%)	1.7% (–3.4% to 6.8%)
AE leading to discontinuation	0.2% (–2.7% to 3.2%)	3.6% (0.3% to 6.8%)

No statistically significant difference was found using Bucher's method for any outcome so the NNH was not calculated.

Conclusion and relevance There were no differences in the safety profiles of the drugs evaluated, although the number of patients for some variables was small. According to preclinical studies, darolutamide does not cross the blood–brain barrier. This could explain the similar incidence of AE in the darolutamide and placebo groups in the ARAMIS trial. Data on larger patient samples are needed to determine differences.

REFERENCES AND/OR ACKNOWLEDGEMENTS

Conflict of interest No conflict of interest

4CPS-308 EXPERIENCE WITH TERIFLUNOMIDE TREATMENT FOR MULTIPLE SCLEROSIS IN A UNIVERSITY HOSPITAL

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Background and importance Teriflunomide (TRF) is a once daily oral immunomodulatory drug approved in over 80 countries for multiple sclerosis (MS). It is indicated in young adults and contraindicated in pregnant women or women of reproductive age because of the potential for fetal harm. TRF