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Access to melanoma drugs in Spain: a cross-sectional survey

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	consulted about the real access to new drugs in each hospital. The responses were collected anonymously and analyzed according to several variables, including the AACC. Results: The survey was answered by 50 physicians in 15 AACC. No major differences on access between AACC were observed for indications that are reimbursed by the Spanish Health Care System (adjuvant immunotherapy for stage IIIC-IIID and resected stage IV melanoma). Important differences in drug access were observed among AACC and among centers within the same AACC, for most of the EMA indications that are not reimbursed (adjuvant immunotherapy for stages IIB-IIC-IIIA-IIIB) or that are not fully reimbursed (ipilimumab plus nivolumab in advanced stage). Homogeneously, access to adjuvant targeted drugs, TIL therapy and TVEC, is extremely low or non-existing in all AACC. Conclusions: For most indications that reimbursement is restricted out of the EMA indication, a great diversity on access was found throughout the different hospitals in Spain, including heterogeneity intra AACC.
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Title: Access to melanoma drugs in Spain: a cross-sectional survey

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ABSTRACT

Background: The development of highly active drugs has improved the survival of melanoma patients, but elevated drug prices place a significant burden on health care systems. In Spain, the public health care system is transferred to the 17 autonomous communities (AACC). The objective of this study is to describe the situation of drug access for melanoma patients in Spain and how this decentralized system is affecting equity.

Methods: From July to September 2023 a cross-sectional survey was sent to members of the Spanish Multidisciplinary Melanoma Group (GEM Group). The questionnaire consulted about the real access to new drugs in each hospital. The responses were collected anonymously and analyzed according to several variables, including the AACC.

Results: The survey was answered by 50 physicians in 15 AACC. No major differences on access between AACC were observed for indications that are reimbursed by the Spanish Health Care System (adjuvant immunotherapy for stage IIIC-IIID and resected stage IV melanoma). Important differences in drug access were observed among AACC and among centers within the same AACC, for most of the EMA indications that are not reimbursed (adjuvant immunotherapy for stages IIB-IIC-IIIA-IIIB) or that are not fully reimbursed (ipilimumab plus nivolumab in advanced stage). Homogeneously, access to adjuvant targeted drugs, TIL therapy and TVEC, is extremely low or non-existing in all AACC.

Conclusions: For most indications that reimbursement is restricted out of the EMA indication, a great diversity on access was found throughout the different hospitals in Spain, including heterogeneity intra AACC.

HIGHLIGHTS

- Access to new melanoma drugs is restricted in many countries due to their high cost.
- Access in Spain to new drugs for melanoma treatment is highly heterogenous inter regions and intra regions.
- Adjuvant anti PD-1 for melanoma stages IIB to IIIB was only available in less than one third of centers.
- Full access to the combination of ipilimumab plus nivolumab was observed only in 38% of centers.

RESEARCH IN CONTEXT

Evidence before this study

In Spain only 28% of the cancer drugs approved by the EMA between 2018 and 2021 are reimbursed by its public health system. Inequality on drug access for cancer patients across the different regions of the country has been previously reported by the Spanish Society of Oncology (SEOM), patients' associations and by several scientific societies. There were no data about the specific situation of access to new drugs for Spanish patients with melanoma.

Added value of this study

Our results confirm a low rate of access and inequality not only between different regions in Spain, but also between different centers into the same region.

Implications of all the available evidence

These results could enable pragmatic measures in the country to increase access to drugs for melanoma treatment according to EMA approvals.

INTRODUCTION

In the last decade, novel and expensive drugs have been approved for the treatment of melanoma[1,2]. The challenge in gaining access to these therapies, once they are approved by EMA, is a hard issue for most European countries [3-5]. According to "EFPIA Patients W.A.I.T. Indicator Survey", only 28% of the cancer drugs approved by EMA between 2018 and 2021 are fully available in Spain[6].

In Spain, the Health System is mainly public and universal. It is organized in 17 regional health ministries, one per every autonomous community (AACC). The regulation of the drug reimbursement is decided at the national level by the Spanish Agency of Medicines and Medical Devices (AEMPS) and the Inter-Ministerial Commission for Medicines Pricing (CIPM). Finally, it is each AACC who decides and pays, with capacity of restriction over the general decision from the AEMPs. This decentralized system results in wide differences in access to treatment for Spanish patients, according to their place of residence. This situation has been previously reported by the Spanish Society of Oncology (SEOM)[7], patients associations[8] and by scientific societies[9]. Until now, no record has been made about the specific situation of access to new drugs for melanoma.

In this study we present the results of a cross-sectional survey answered by physician members of the Spanish Melanoma Group between June and September 2023. Additionally, the Spanish public reimbursement status of every drug is reviewed in parallel with the real access for prescription.

METHODS

Study population and survey design

The cross-sectional survey was developed by investigators of the Spanish Melanoma Group. All members of the Spanish Melanoma Group (GEM), from 154 hospitals across all the AACC in Spain, were invited to answer the electronic questionnaire in an anonymous way. Only those physicians who deliver systemic anticancer therapy were eligible to participate in the full questionnaire. The survey captured information on demographics and clinical practice setting. The first set of questions was related to hospital characteristics, AACC, and physician data as sex, age, and specialty. The second set of questions was related to access out of clinical trials, to anti PD-1 antibodies (Ab) and BRAF-MEK inhibitors in the adjuvant setting, neoadjuvant treatment, combination of ipilimumab plus nivolumab in advanced stage, tumor infiltrating lymphocytes (TIL) therapy, and TVEC.

Statistical Analysis

Every survey item was analyzed according to different factors, including differences by AACC. The descriptive analysis results are presented. The analysis was performed using the statistical analysis software SAS version 9.4.

RESULTS

The survey was answered by 50 physicians of GEM, representing 50 hospitals from 15 AACC. Most centers were public hospitals (92%), while most participants were medical oncologists (80%). The median number of centers that participated per AACC was two (range from 1 to 12) (Table 1). In nine AACC, there were two or more centers participating (Table 1). There were not significant differences on drug access according

to the age or sex of the prescriber physician, nor to the type of hospital or to the city population *(Supplementary Figure 1-3).*

1. Adjuvant anti PD-1 Abs

Adjuvant treatment for resected stage III- IV melanoma with anti PD-1 Ab is currently a standard of care, based on the demonstrated improvement in terms of relapse free survival (RFS) and distant metastases free survival (MFS) demonstrated in several phase III trials (Keynote 054 tested pembrolizumab in stage IIIA/B/C[10], S1404 tested pembrolizumab in stage IIIA/B/C/IV [11], CheckMate 238 tested nivolumab in stages IIIB/C/IV)[12,13]. In 2018 EMA approved the indication of adjuvant pembrolizumab for stage III melanoma and nivolumab for resected stage III and IV melanoma. In Spain, from January 2022 until the time of this survey, adjuvant treatment for stage III/IV melanoma was reimbursed only for stages IIIC/D/IV.

The results of the survey demonstrated a high homogeneous access to adjuvant anti PD-1 Ab for stages IIIC/IIID/IV. For the non-reimbursed indications (stage IIIA/B), there was a great heterogeneity. For stage IIIB there were 15 (30%) centers with full access to anti PD-1 Abs, 13 (26%) with a relative restriction and 22 (44%) without access. There were seven AACC where all centers had some type of access. Of the nine AACC with two or more centers participating in the study, only two AACC had homogeneous access (Canary Islands and Cantabria). There were six AACC with heterogeneous intracommunity access (Madrid, Andalusia, Galicia, Murcia, Aragon and Valencia). In Catalonia, none of the four public hospitals had access.

For stage IIIA, there were 8 (16%) hospitals that had full access to anti PD-1 Abs, 10 (20%) had a relative restriction, and 32 (64%) had no access. There were four AACC where all centers had some type of access. Of the nine AACC with two or more centers, one had no access in a homogeneous way (Galicia). There were seven AACC with heterogeneous responses (Madrid, Andalusia, Murcia, Aragon, Canary Islands, Cantabria and Valencia). In Catalonia, none of the public centers had access (Figure 1a-d).

2. Adjuvant anti PD-1 Abs in stage IIB/IIC

Adjuvant treatment with pembrolizumab and nivolumab has been approved by EMA in years 2022 and 2023, respectively, based on the significant benefit demonstrated in terms of RFS and MFS in the phase III trials Keynote 716[14] and Check Mate76k[15]. In Spain reimbursement is not approved for these indications.

Our results demonstrate that for stage IIC there were 16 (32%) hospitals with full access, 10 (20%) with some restrictions, and 24 (48%) without access. For stage IIB, 15 (30%) hospitals had full access, 10 (20%) had some restrictions and 25 (50%) had no access. There were seven AACC where all centers had some type of access to adjuvant treatment for stage II. From nine AACC with two or more centers participating in the study, two AACC had no access in any center (Murcia and Valencia). There was one AACC with homogeneous access (Aragon). There were five AACC with heterogeneous responses (Andalusia, Madrid, Canary Islands, Cantabria and Galicia). In Catalonia none of the four public hospitals had access (Figure 2a-b).

3. Adjuvant dabrafenib plus trametinib in stage III

In 2018 EMA approved the adjuvant treatment with the combination of the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib for resected stage III melanoma with BRAFV600 mutation, based on the results of the phase III trial combi-AD that demonstrated improved RFS and MFS in stages IIIA/IIIB/IIIC melanoma with BRAFV600E or BRAV600K mutation[16]. In Spain the decision in 2021 was no reimbursement.
According to our survey there were only two (4%) centers in Spain (one in Canary Islands and the second one in Valencia) with full access for this indication (Figure 3). Five (10%) centers had a restricted access in stages IIIC/IIID (Figure 3c); three (6%) centers had access with restrictions for stage IIIB (Figure 3b) and four (8%) centers for stage IIIA (Figure 3a). In the four private hospitals there was no access through private insurance, only as private patients.
Adjuvant treatment with dabrafenib plus trametinib after resection of a local relapse during anti PD-1 adjuvant treatment, has no approved indication by EMA. According to the survey, in Spain there were 13 (26%) centers with full access to the indication, 6 (12%) with relative restrictions and 31 (62%) centers with no access (Figure 3d).
From nine AACC with two or more centers participating in the study, for stage IIIA six AACC had homogeneously no access (Murcia, Galicia, Andalusia, Catalonia, Cantabria and Valencia). There were three AACC with heterogeneous responses (Madrid, Canary Islands and Aragon). (Figure 3a). For stage IIIB/C/D five AACC had homogeneously no access (Murcia, Galicia, Andalusia, Catalonia and Cantabria). There were four AACC with heterogeneous responses (Madrid, Canary Islands, Valencia and Aragon) (Figure 3b and 3c). Access to adjuvant treatment with dabrafenib plus trametinib after resection of a local relapse was heterogenous in the nine AACC that had more than one center per region (Figure 3d)

4. Neoadjuvant immunotherapy

Recent data from a phase II randomized study showed superior activity of pembrolizumab as neoadjuvant treatment versus adjuvant for stages IIIB/IIIC/IIID melanoma with clinically detectable nodes or resectable stage IV[17]. There is no EMA approval for this indication.
According to the survey, in Spain there were 13 (26%) centers with full access to the indication of neoadjuvant treatment for clinically detectable locoregional disease of debut, 18 (36%) centers had access when disease was a locoregional relapse and it increased to 23 (46%) for resectable stage IV.
There were five and six AACC where all centers had some type of access to neoadjuvant treatment for stage III of debut and for local relapse/resectable stage IV, respectively (Figure 4).
Of the nine AACC with two or more centers, for stage III of debut, there was one AACC that had homogeneous access (Galicia) and three AACC where no center had access (Aragon, Canary Islands and Cantabria). There were five AACC with heterogeneous responses (Madrid, Andalusia, Murcia, Catalonia and Valencia) (Figure 4a). In the case of stage III at relapse and resectable stage IV, there were two AACC with homogeneous access (Galicia and Aragon) and seven AACC with heterogeneous responses (Madrid, Andalusia, Murcia, Catalonia, Cantabria, Canary Islands and Valencia) (Figure 4b and 4c).

5. Talimogene Laherparepvec (T-VEC)

T-VEC was the first oncolytic viral immunotherapy approved for intralesional therapy of advanced melanoma. Results from a phase III trial in stage IIIB/IIIC/IVM1a-b-c demonstrated benefit in terms of response duration and survival, but mainly in treatment naïve patients with stages III to IVM1a[18]. The drug was approved by EMA in 2015 for treatment of melanoma IIIB/IIIC/IVM1a.

The evaluation in Spain was performed in 2018, and the decision was not to grant reimbursement for this indication.

According to the present survey, access to T-VEC was homogenously restricted in Spain. Only one center in Canary Islands had full access, while two private centers in Madrid, and one public center in Extremadura, answered that they had access in special circumstances.

6. Ipilimumab plus nivolumab advanced stage

The combination of nivolumab plus ipilimumab demonstrated high activity at the first line setting in the phase III trial CheckMate 067[19,20]. Later on, other studies, including a prospective randomized phase II study[21], suggested that this combination could also be superior to ipilimumab after progression to anti PD-1 Ab.

In 2016, the EMA approved the combination for the treatment of unresectable or metastatic melanoma, regardless of BRAF mutational status.

In Spain, the initial decision in 2018 was reimbursement only for patients with brain metastases or metastatic uveal melanoma. More recently, in 2021, the decision was expanded to advanced melanoma with PD-L1 expression below 1%.

The present study shows that only 12 (24%) out of 50 centers prescribed the combination according to the reimbursed indication. Six (12%) centers had access only in cases of brain metastases and uveal melanoma. In addition, four (8%) centers had access only in cases with low PD-L1. Three (6%) centers had no access. On the other hand, there were 19 (38%) centers with full access (Figure 5a).

For those AACC with two or more centers, for the indication at first line setting only Galicia had homogeneous access according to the funded indication, the remaining AACC were highly heterogeneous (Figure 5a). In the case of the indication for patients after progression to anti PD-1 Ab, only in Cantabria all the centers had access for cases evaluated by an Institutional board, the remaining AACC had high heterogenous situation of access between the intraregional centers (Figure 5b)

7. TIL advanced stage

Although TIL therapies do not yet have EMA approval, they are under evaluation. Given the positive results from a phase III trial demonstrating longer survival with TIL therapy versus ipilimumab after progression to PD-1 Ab, and multiple phase II studies that have uniformly demonstrated long responders, there is a great interest in TIL therapy. In Spain there is no reimbursement for this indication, nor any formal regulation for defining access in private centers. Only one private center in Madrid answered that had access to TIL therapy.

DISCUSION

In recent years we have witnessed the development of new and expensive therapies with high effectiveness in cancer. Most of these treatments are based on the activation of the immune response or are inhibitors of molecular targets. In countries where the public system assumes the costs of oncological treatments, it constitutes a great challenge for reimbursement [3,22,23]. Reimbursement of cancer drugs in Spain covers only 28% of the drugs approved for marketing in Europe[6]. The complexity of the evaluation system in our country and the decentralization of final decisions can generate differences in access between regions.

The results of the current study show for non-reimbursed indications, mainly adjuvant immunotherapy for stages IIB-IIC-IIIA-IIIB and ipilimumab plus nivolumab combination in advanced disease, a high heterogeneity between different regions, but also intra-regions.

The indication with the highest heterogenicity among different AACC and centers, was ipilimumab plus nivolumab. In Spain the reimbursement for this treatment was recently expanded to melanomas with low PD-L1 expression, in addition to the previous reimbursement that had been approved for cases with brain metastases, and metastatic uveal melanoma. Only 24% of centers responded that they strictly adapted to these indications, while 38% responded that they had free access to the combination according to the criteria of the treating physician.

For TIL therapy, out of clinical trials, there is no access in Spain. Probably the main barrier for access to TIL therapy lies in the lack of regulatory approval by the EMA [25]. Spanish AEMPs have communicated that only centers with active clinical trials with a TIL product can ask for a compassionate use. But at the time of the present study, there were only two academic clinical trials opened in four centers at three AACC in Spain.

In the same manner, for other drugs without reimbursement in Spain, as adjuvant dabrafenib with trametinib, and TVEC in advanced stage, the heterogeneity is low as most centers had no access.

Regarding neoadjuvant therapy, although there are data from a randomized phase 2 study suggesting superior survival using anti PD-1 Ab before and after surgery, with no impact on costs compared with adjuvant treatment, less than 50% of centers in the country had access, probably due to the lack of regulation by authorities.

The main limitations of this study are two: first that it is an anonymous survey without a data audit and second, the inherent potential non-responses bias. Moreover, although the representation of the Spanish territory in the survey is adequate, with 15 of the 17 AACC represented, there are only nine AACC with two or more participating hospitals, so the intra-community heterogeneity evaluation is limited.

According to our data, melanoma patients in Spain have different treatment opportunities within the public system according to their residence and to the public hospital to which they are referred. These findings suggest that there are other factors, in addition to the transferred health system to 17 AACC, that contribute to inequity. Ideally, access to new therapies should be broader, including all the EMA approvals. To reach this goal, greater efforts and deep changes must be made, including the consideration of a simplified regulatory framework at the international level, and simplified processes at a national level.

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TABLES

Table 1. Participant characteristics. Characteristics of physicians that answered the questionnaire and their centers

Total 50	
Physician Speciality, n (%)	
Dermatology	10 (20.00)
Medical Oncology	40 (80.00)
Physician Sex, n (%)	
Men	22 (44.00)
Women	27 (54.00)
No answer	1 (2.00)
Physician Age, median (range)	43 (32 to 64)
Hospital Type, n (%)	
Private	4 (8.00)
Public	46 (92.00)
Hospital Complexity, n (%)	
Comunitary	5 (10.00)
Terciary	45 (90.00)
Number of participant centers per AACC, n (%)	
Andalusia	11 (22.00)
Aragon	2 (4.00)
Asturias	1 (2.00)
Basque Country	0 (0.00)
Canary Islands	3 (6.00)
Cantabria	2 (4.00)
Castile la Mancha	1 (2.00)
Castile Leon	1 (2.00)
Catalonia	6 (12.00)
Extremadura	1 (2.00)
Galicia	2 (4.00)
Madrid	11 (22.00)
Murcia	3 (6.00)
Navarre	1 (2.00)
Valencia	5 (10.00)
Number of participant centers according to city inhabitants, n (%)	
200.000 a 500.000 inhabitants	19 (38.00)
More than 500.000 inhabitants	26 (52.00)
Less than 200.000 inhabitants	5 (10.00)

FIGURE LEGENDS

Figure 1. Access to adjuvant immunotherapy in stage III-IV by AACC. a. Access to adjuvant treatment for stage IIIA. **b**. Access to adjuvant treatment for stage IIIB. **c**. Access to adjuvant treatment for stage IIIC. **d**. Access to adjuvant treatment for stage IIID/IV. *Percentage of centers in every AACC were marked in red when there was no access, grey when there was full access in public centers, blue when there was full access in private centers, green when there was access only in cases with node tumor deposits of more than 1.00 mm in size and yellow when there was access only for exceptional cases. pu: public hospital. pr: private hospital*

Figure 2. Access to adjuvant treatment for stage II by AACC. a. Access to adjuvant treatment for stage IIB. **b**. Access to adjuvant treatment for stage IIC. *Percentage of centers in every AACC were marked in red when there was no access, grey when there was full access and yellow when there was access only for exceptional cases. pu: public hospital. pr: private hospital*

Figure 3. Access to adjuvant dabrafenib plus trametinib by AACC. a. Access to adjuvant treatment for stage IIIA of debut. **b**. Access to adjuvant treatment for stage IIIB of debut. **c.** Access to adjuvant treatment for stage IIIC/D of debut. **d.** Access to adjuvant treatment for regional relapse during adjuvant immunotherapy. *Percentage of centers in every AACC were marked in red when there was no access in public hospitals, gray when there was full access, yellow when there was access only for exceptional cases. pu: public hospital. pr: private hospital*

Figure 4. Access to neoadjuvant immunotherapy by AACC. a. Access to neoadjuvant treatment for stage III of debut. **b**. Access to neoadjuvant treatment for regional relapse. **c.** Access to neoadjuvant treatment for resectable stage IV. *Percentage of centers in every AACC were marked in red when there was no access in public hospitals, blue when there was full access in public centers, yellow when there was access for exceptional cases. pu: public hospital. pr: private hospital*

Figure 5. Access to the combination of ipilimumab plus nivolumab in stage IV by AACC. a. Access for first line treatment. **b**. Access for second line treatment after progression to anti PD-1 Ab. *Percentage of centers in every AACC were marked in red when there was no access, gray when there was evaluated by an internal Institunional board, blue only for melanoma with PD-L1 expression <1%, orange for melanomas with PD-L1*

expression<1% or brain metastases or metastatic uveal melanoma (the theoretical reimbursed conditions in Spain), green when there was access for melanomas with brain metastases or metastatic uveal melanoma, yellow when there was full access. pu: public hospital. pr: private hospital

Figure 1

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Figure 1. Access to adjuvant immunotherapy in stage III-IV by AACC

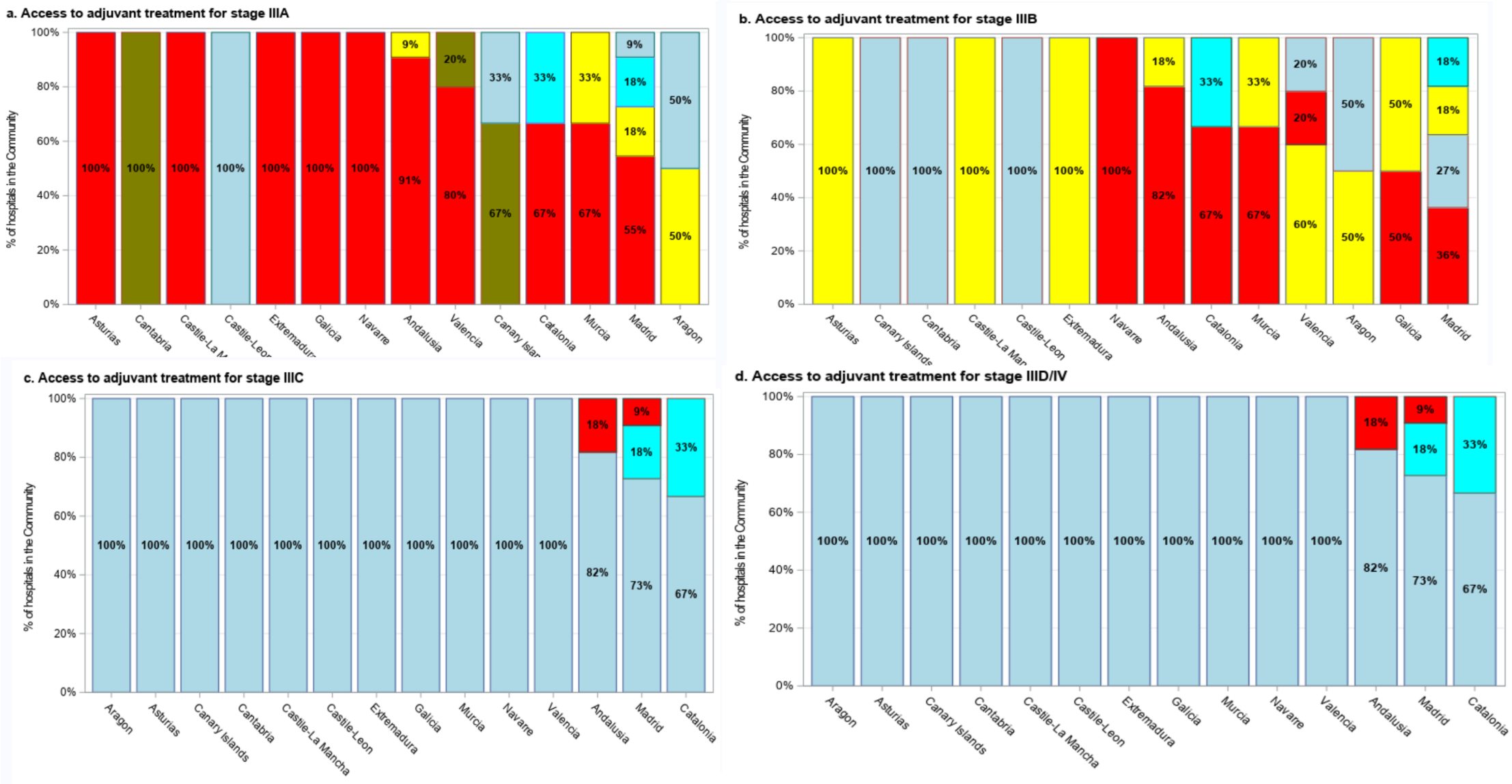

Figure 2

Click here to access/download;colour figure;FIGURE 2.pptx

Figure 2. Access to adjuvant treatment for stage II by AACC

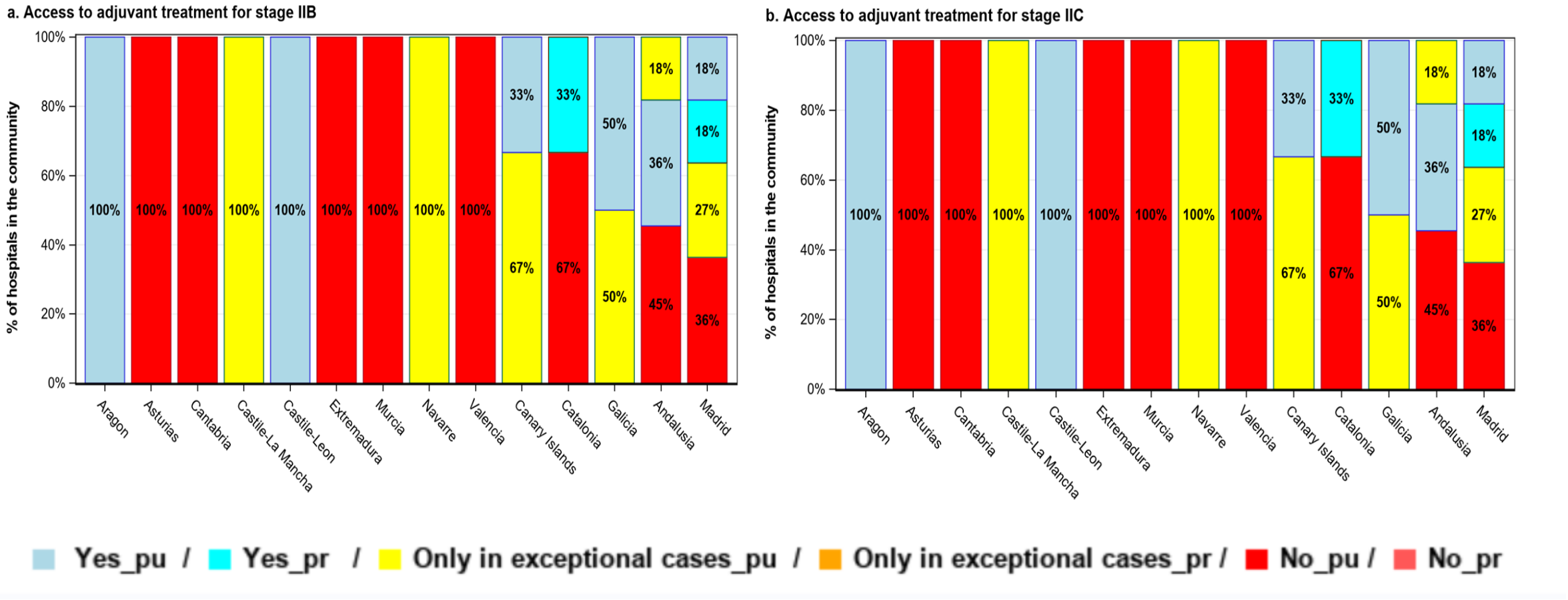

Figure 3

Click here to access/download;colour figure;Figure 3.pptx

Figure 3. Access to adjuvant dabrafenib plus trametinib by AACC

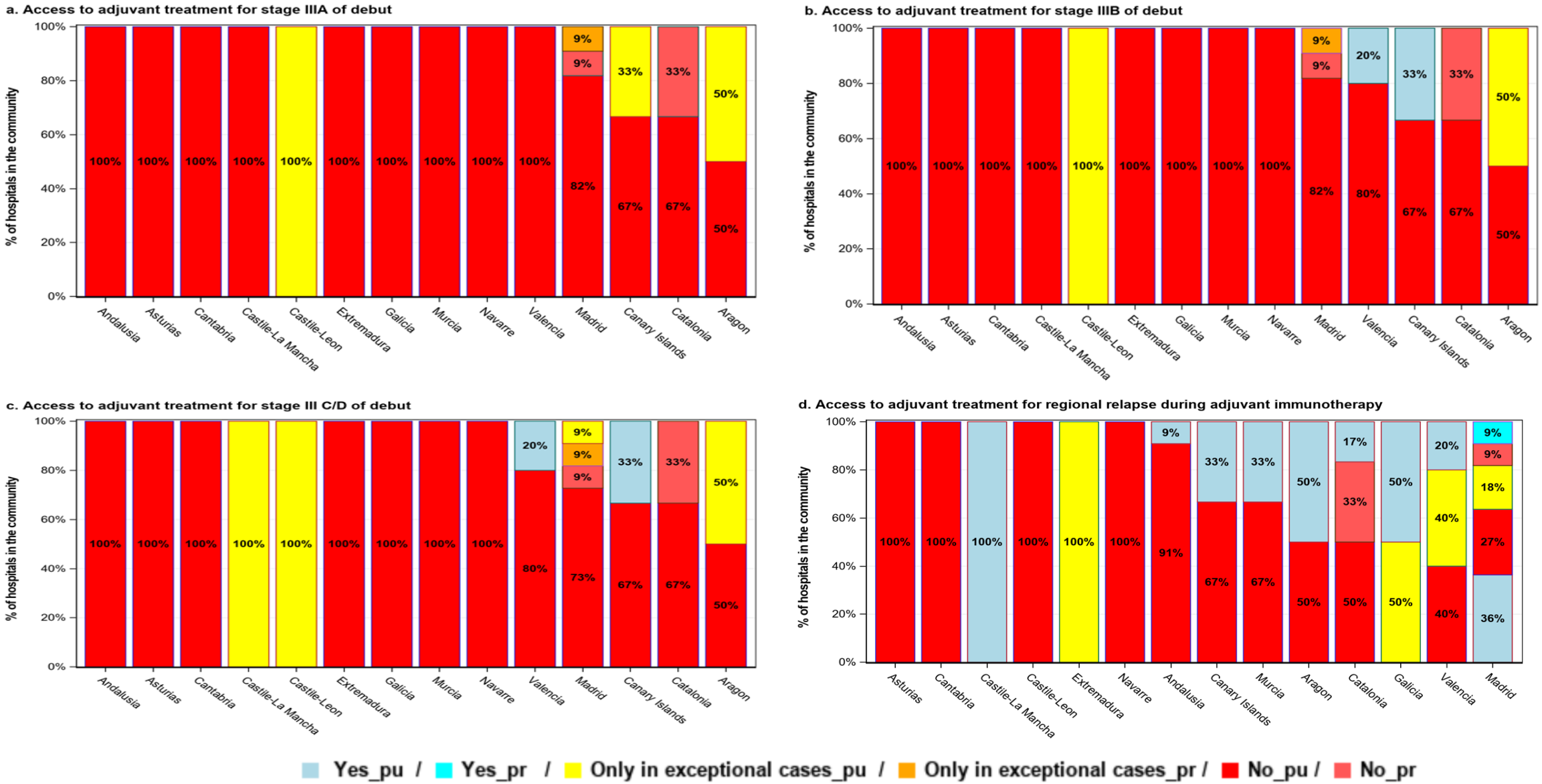

Figure 4

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Figure 4. Access to neoadjuvant immunotherapy by AACC

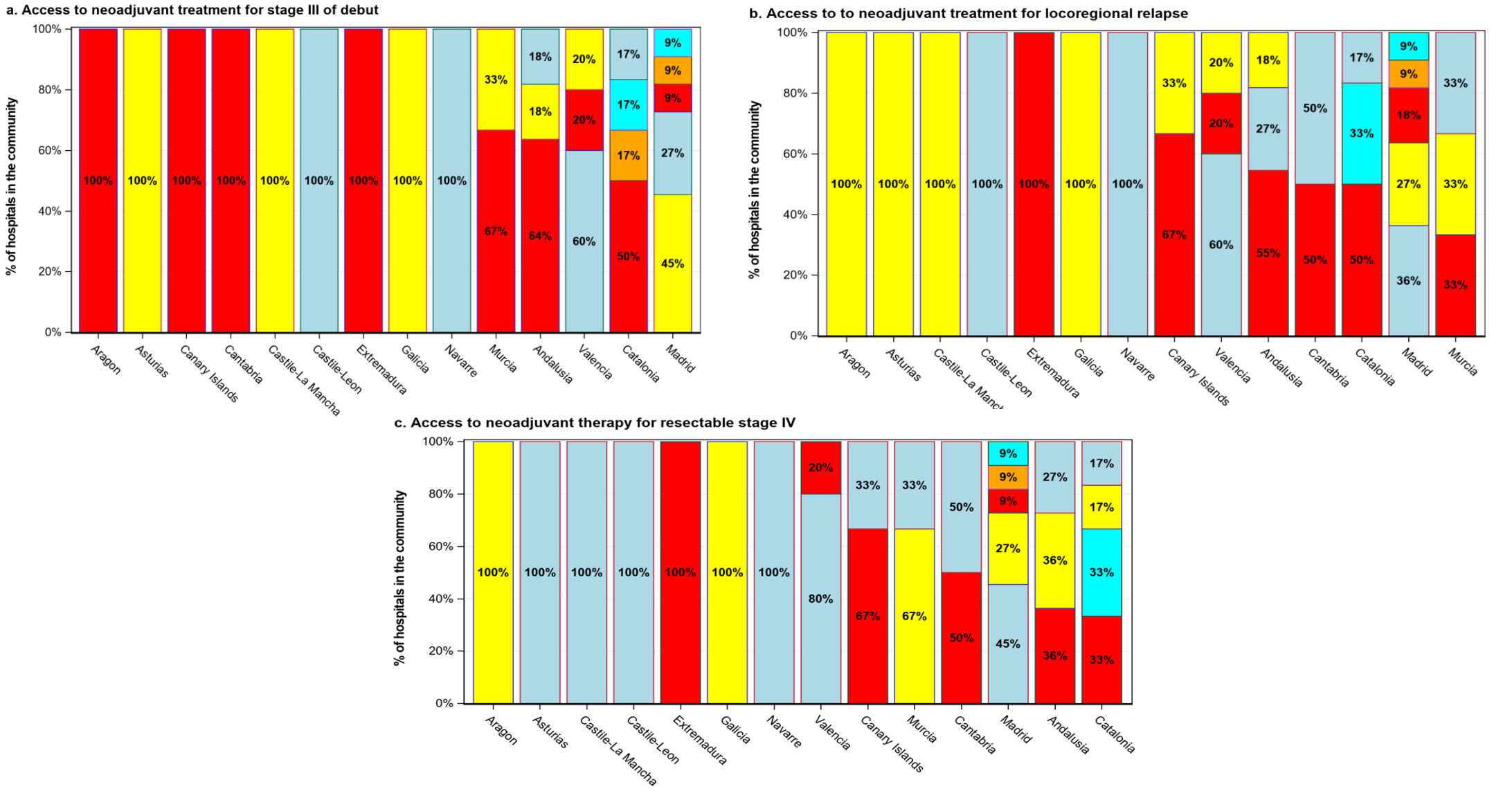
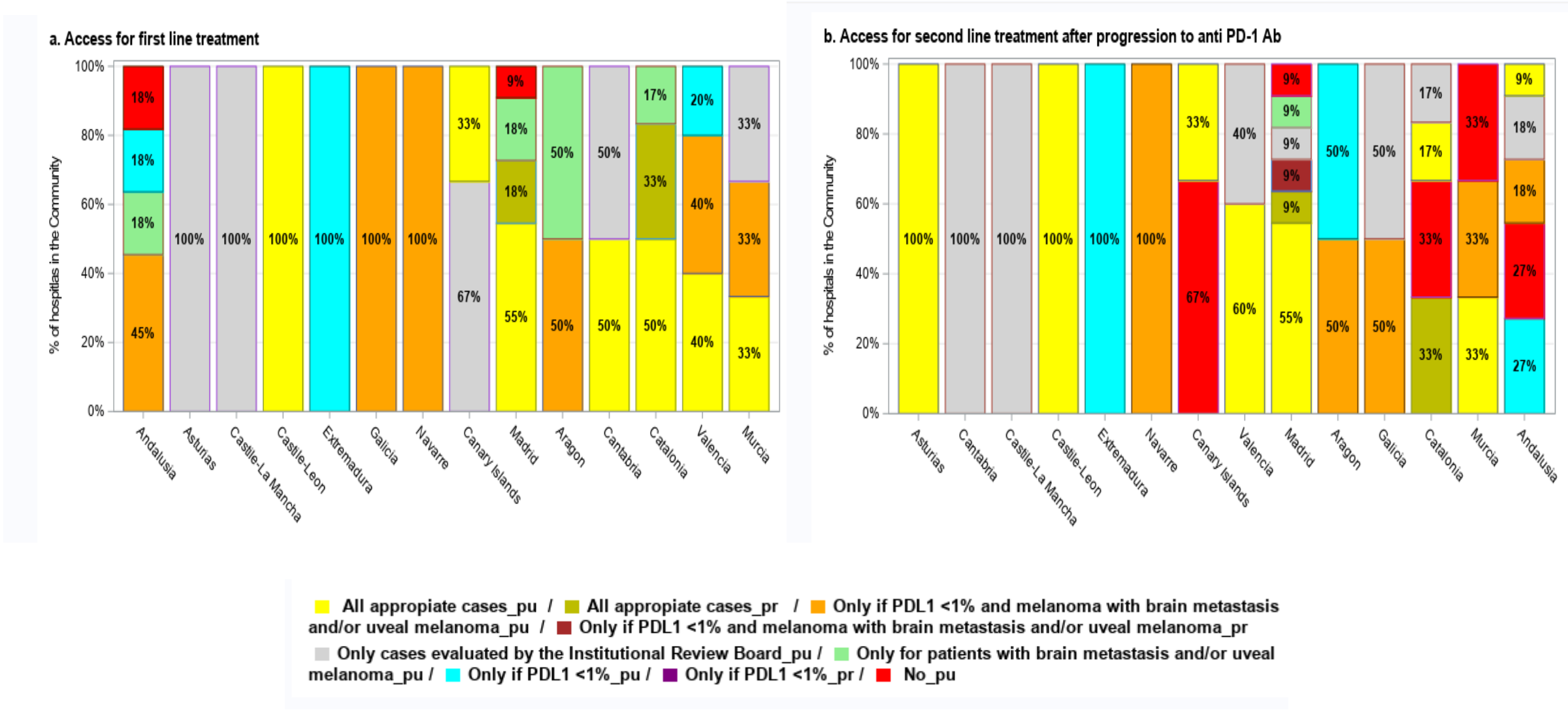


Figure 5

Click here to access/download;colour figure;Figure 5.pptx

Figure 5. Access to the combination of ipilimumab plus nivolumab in stage IV by AACC



Supplemental Online Content

Gonzalez-Cao M, et al. **Access to melanoma drugs in Spain: a cross-sectional survey**

SUPPLEMENTAL FIGURE LEGENDS

SUPPLEMENTAL FIGURES

This appendix has been provided by the authors to give readers additional information about their work

SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1. Distribution of drug access according to the age of prescriber physician. Two groups are defined based on the median age (43 years) of physicians.

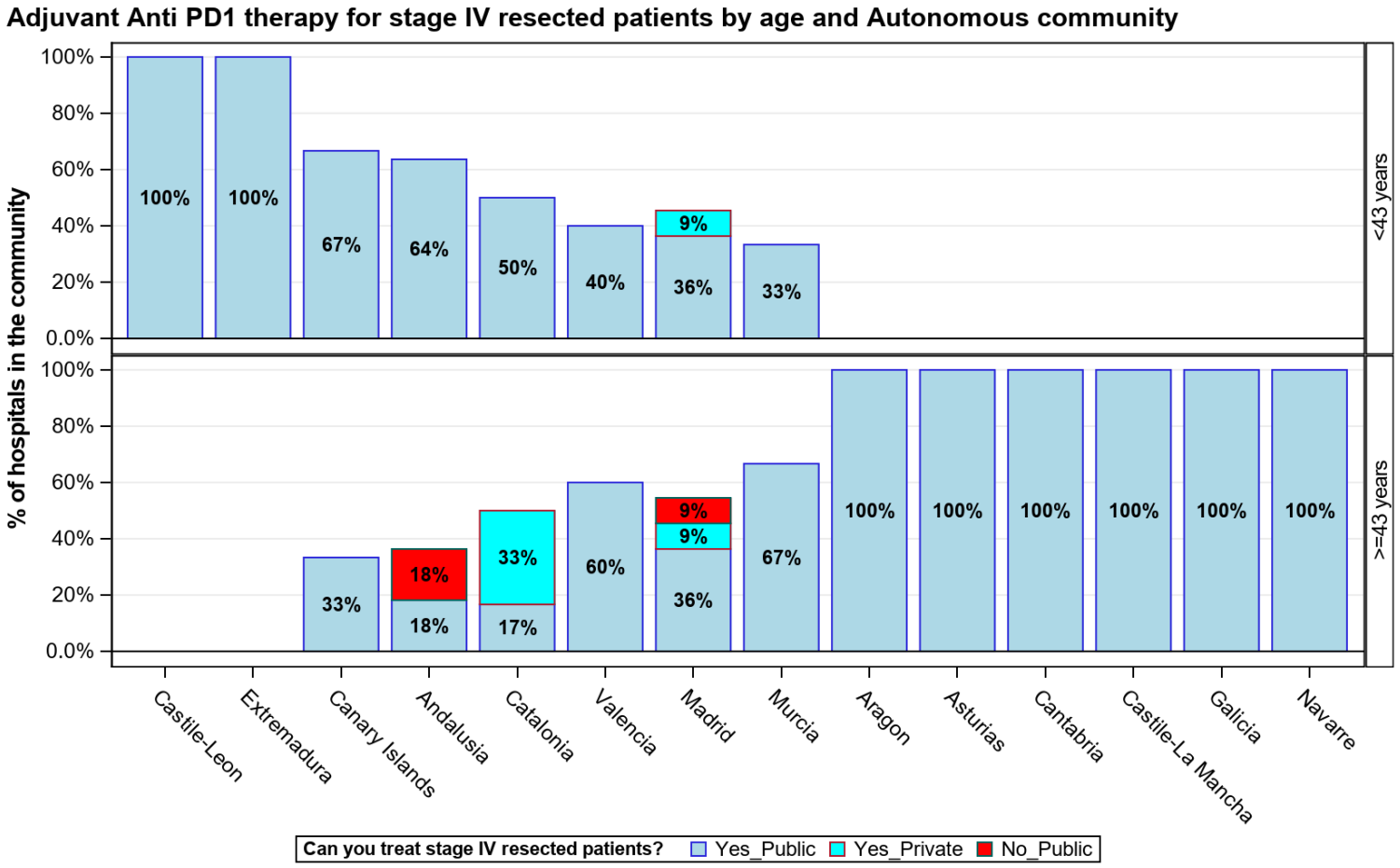
Supplemental Figure 2. Distribution of drug access according to the sex of prescriber physician

Supplemental Figure 3. Distribution of drug access according to the size of the area of influence of the hospital. Hospitals are grouped based on the size of the area of influence: <200.000; 200.000-500.000; >500.000 inhabitants.

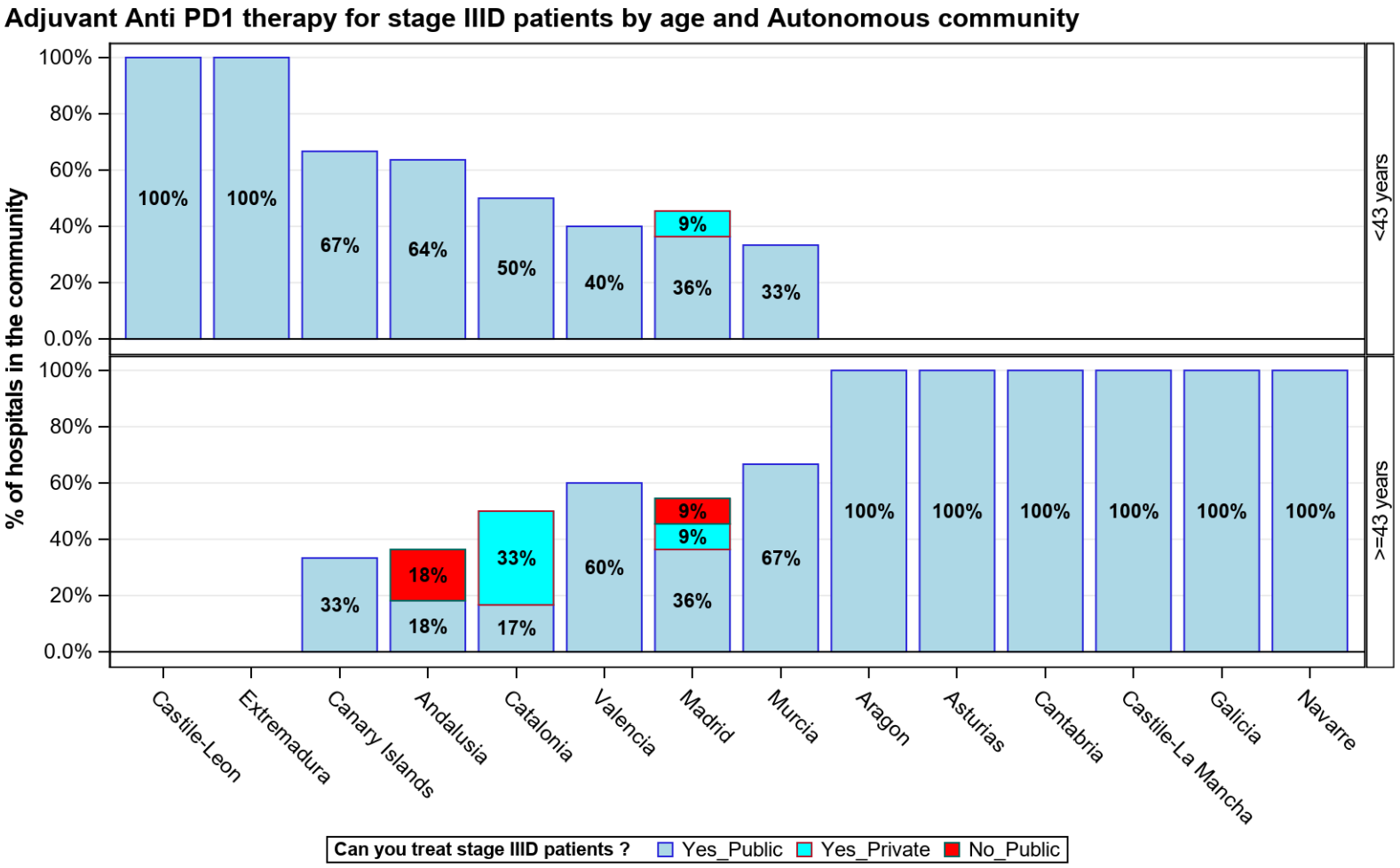
SUPPLEMENTAL FIGURES

Supplemental Figure 1. Distribution of drug access according to the age of prescriber physician

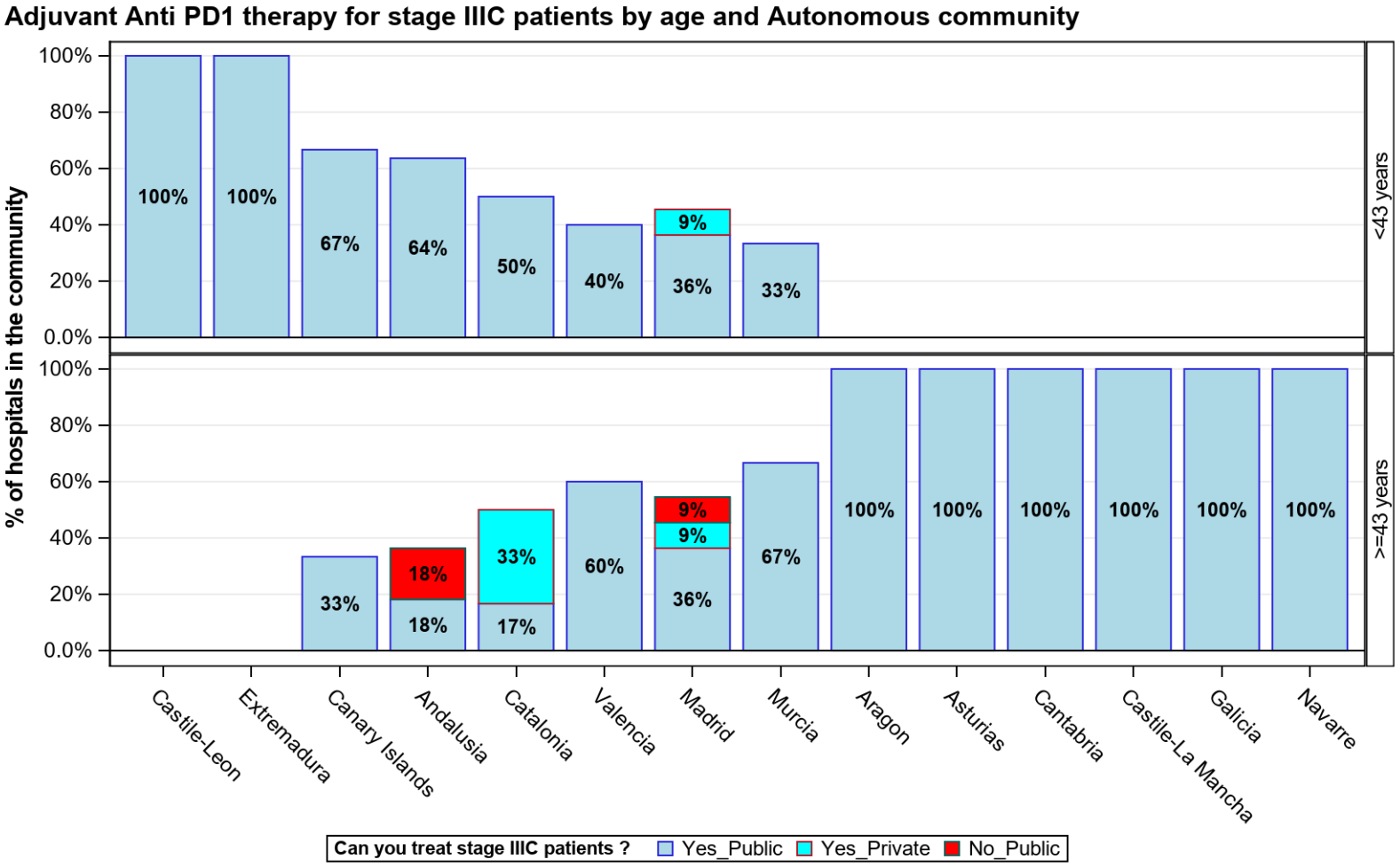
Supplemental Figure 1. 1. Adjuvant Anti PD1 therapy for stage IV resected patients by physician´s age and Autonomous Community



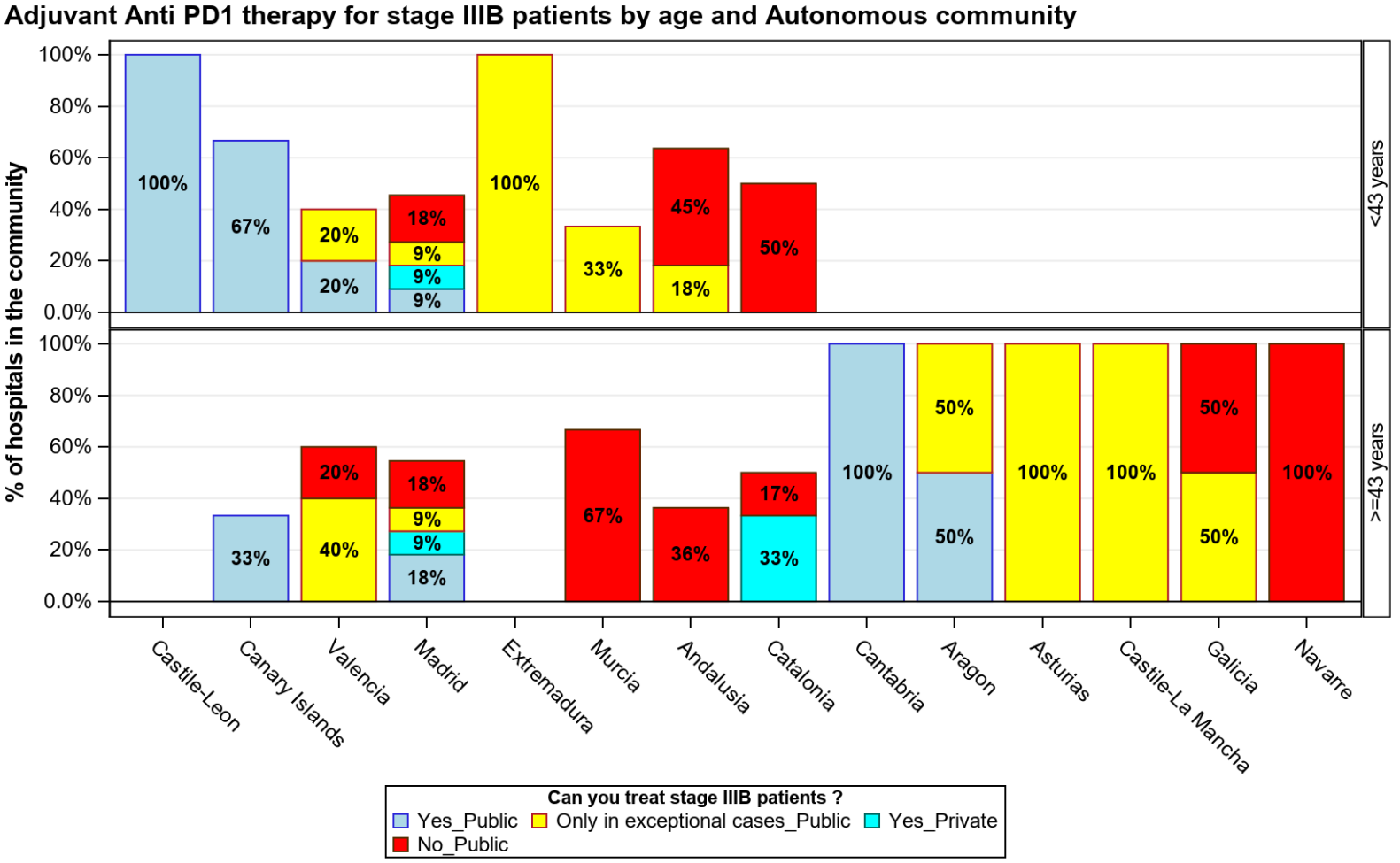
Supplemental Figure 1.2. Adjuvant Anti PD1 therapy for stage IIID patients by physician´s age and Autonomous community



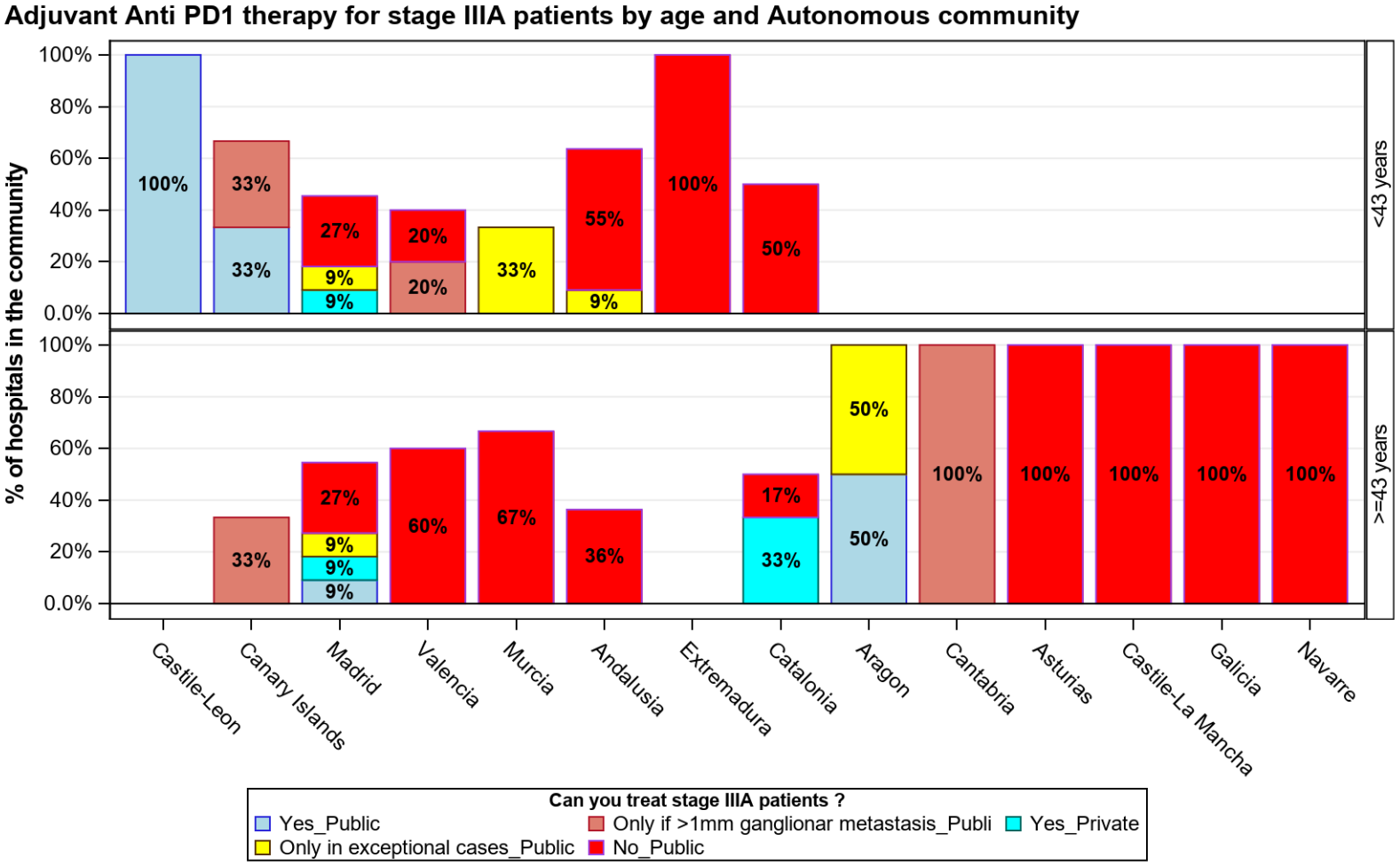
Supplemental Figure 1.1 Adjuvant Anti PD1 therapy for stage IIIC patients by physician´s age and Autonomous community



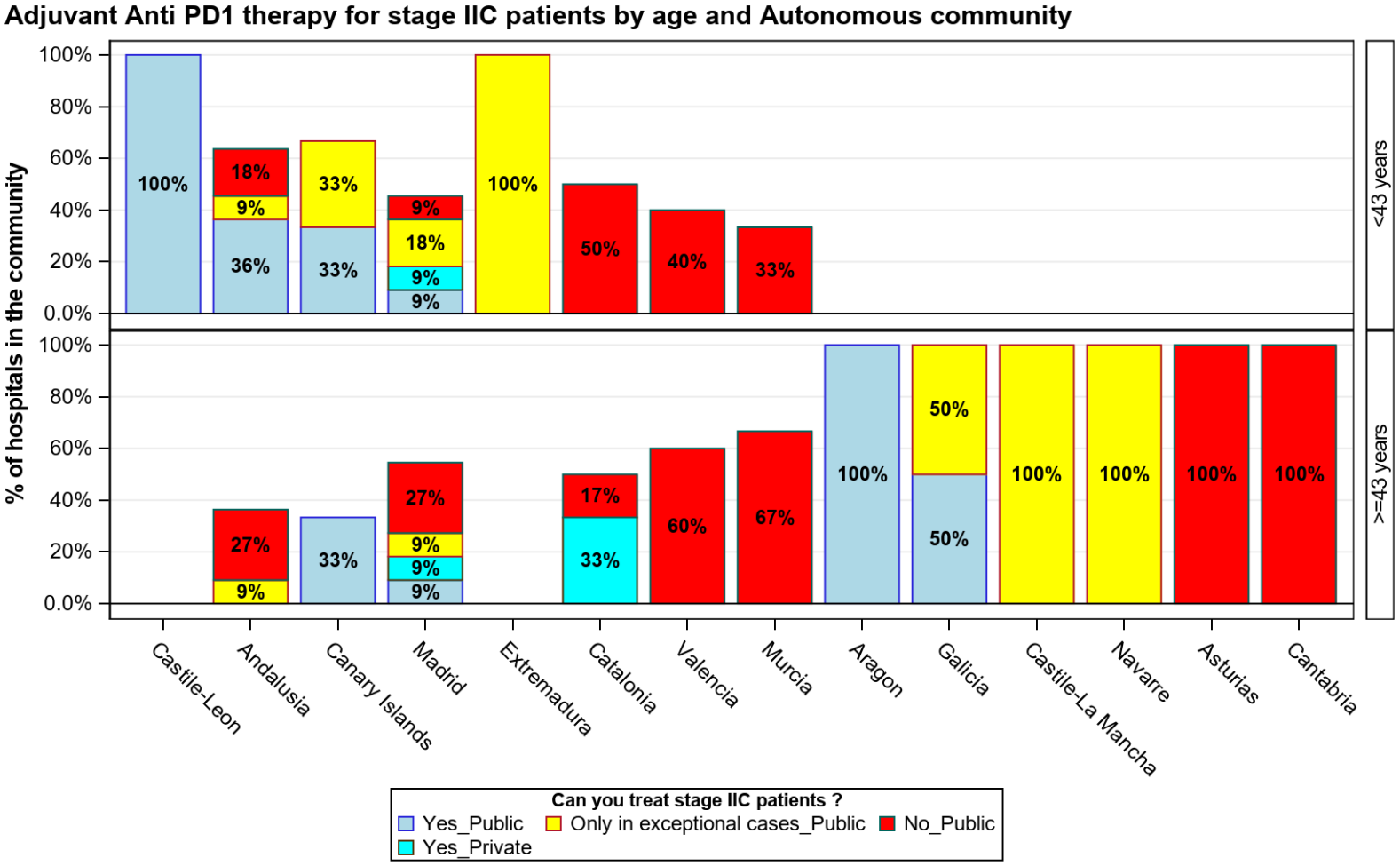
Supplemental Figure 1.2 Adjuvant Anti PD1 therapy for stage IIIB patients by physician´s age and Autonomous community



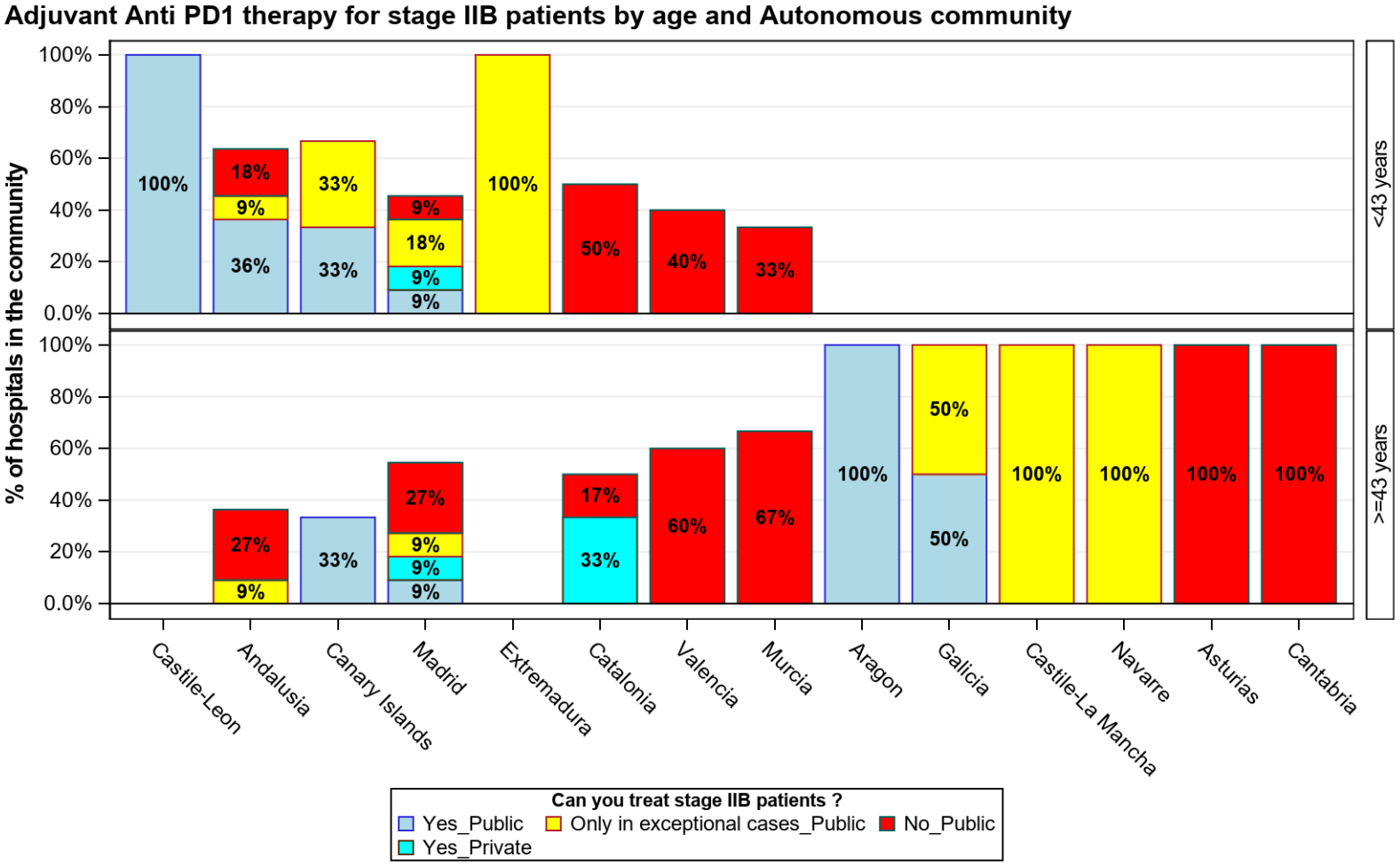
Supplemental Figure 1.5 Adjuvant Anti PD1 therapy for stage IIIA patients by physician´s age and Autonomous community



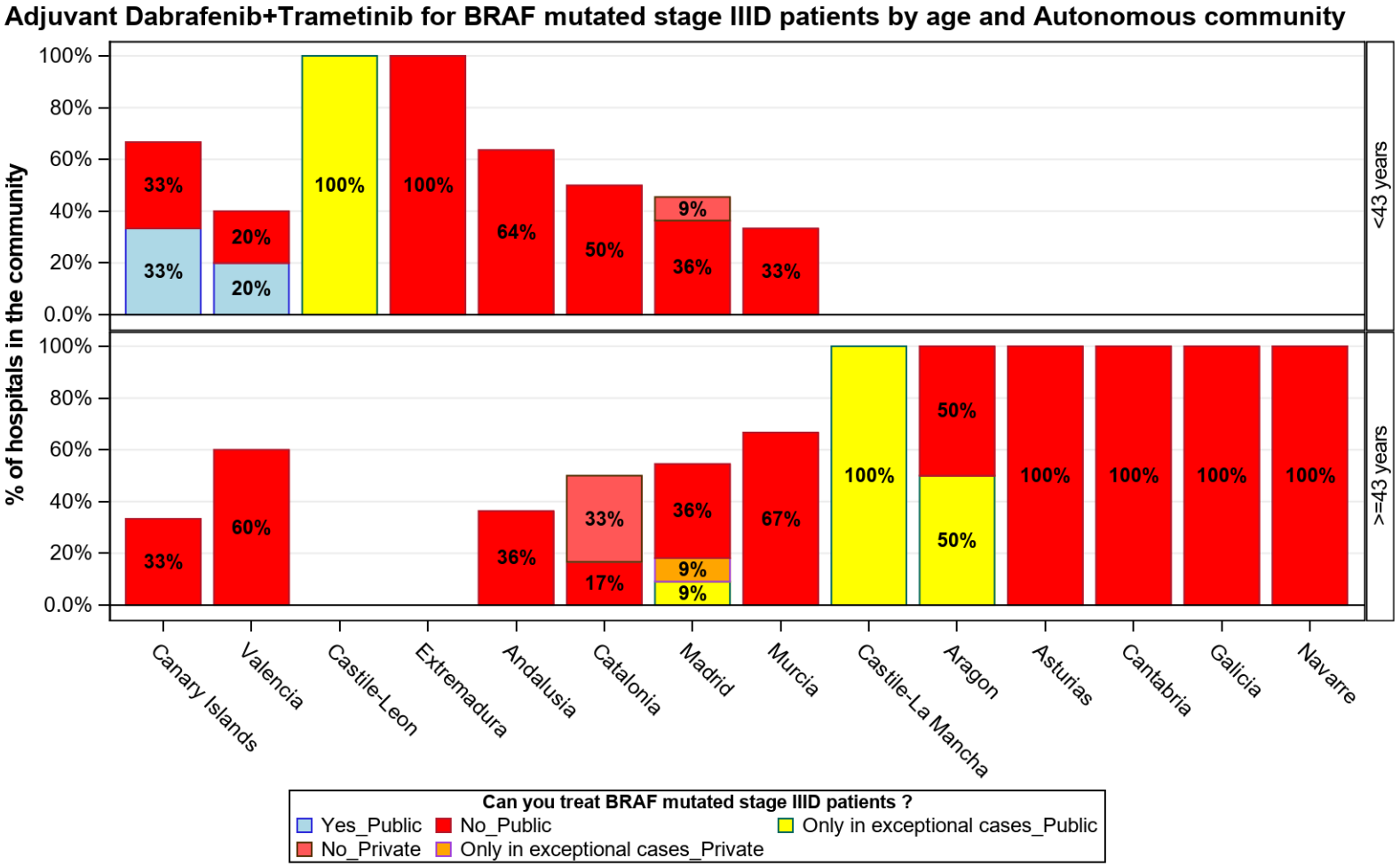
Supplemental Figure 1.3 Adjuvant Anti PD1 therapy for stage IIC patients by physician´s age and Autonomous community



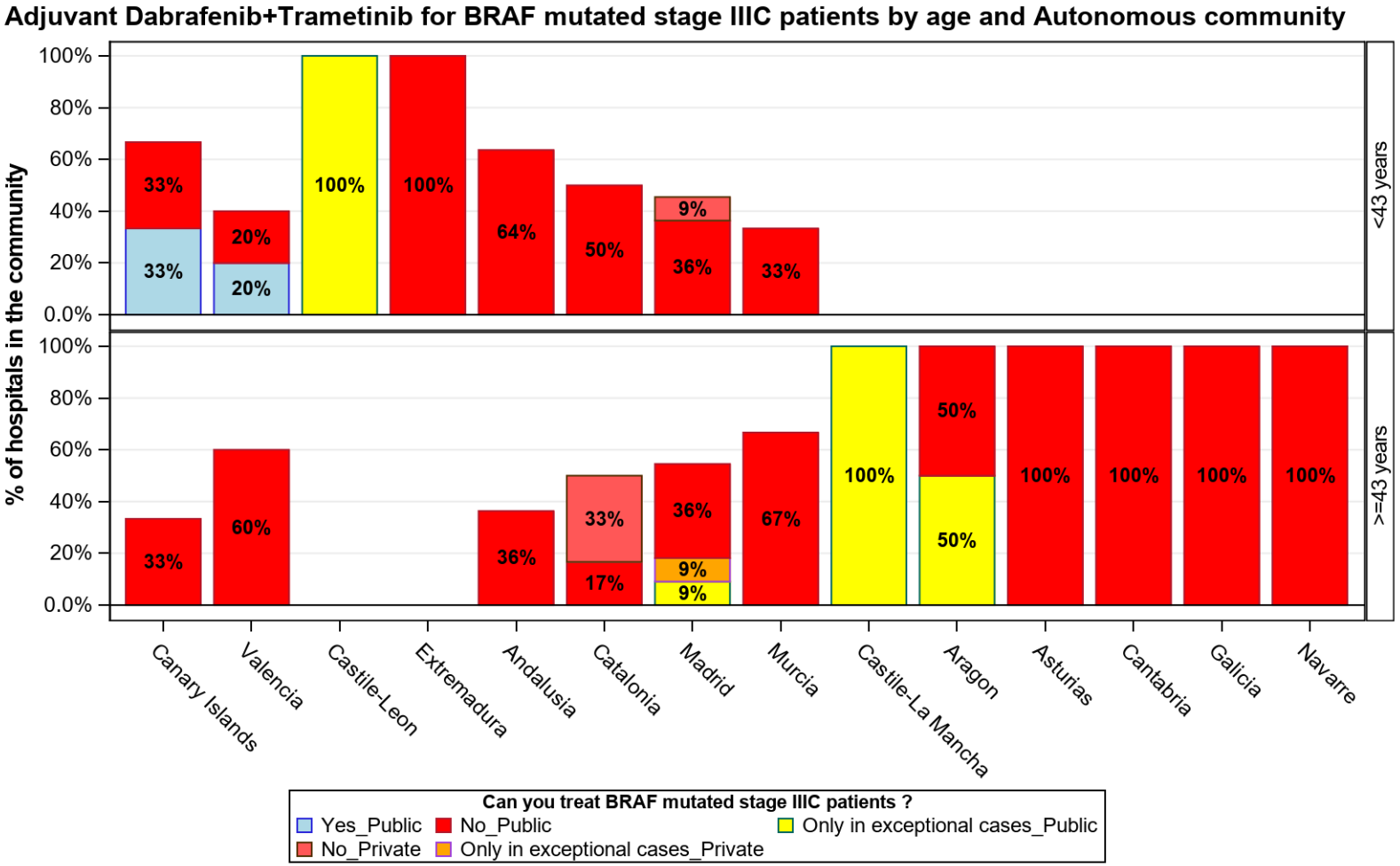
Supplemental Figure 1.4 Adjuvant Anti PD1 therapy for stage IIB patients by physician´s age and Autonomous community



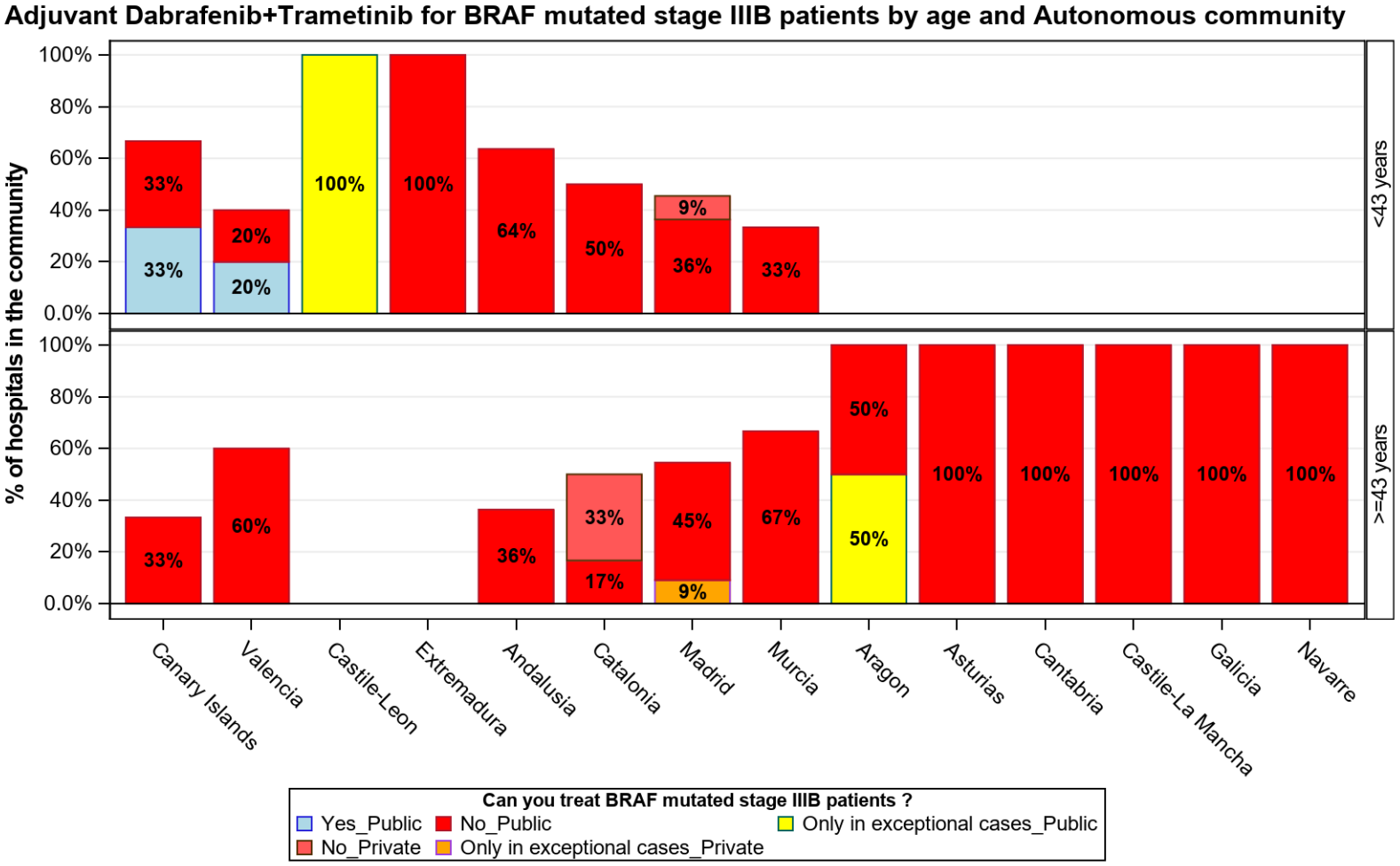
Supplemental Figure 1.5 Adjuvant Anti PD1 therapy for BRAF mutated stage IIID patients by physician´s age and Autonomous community



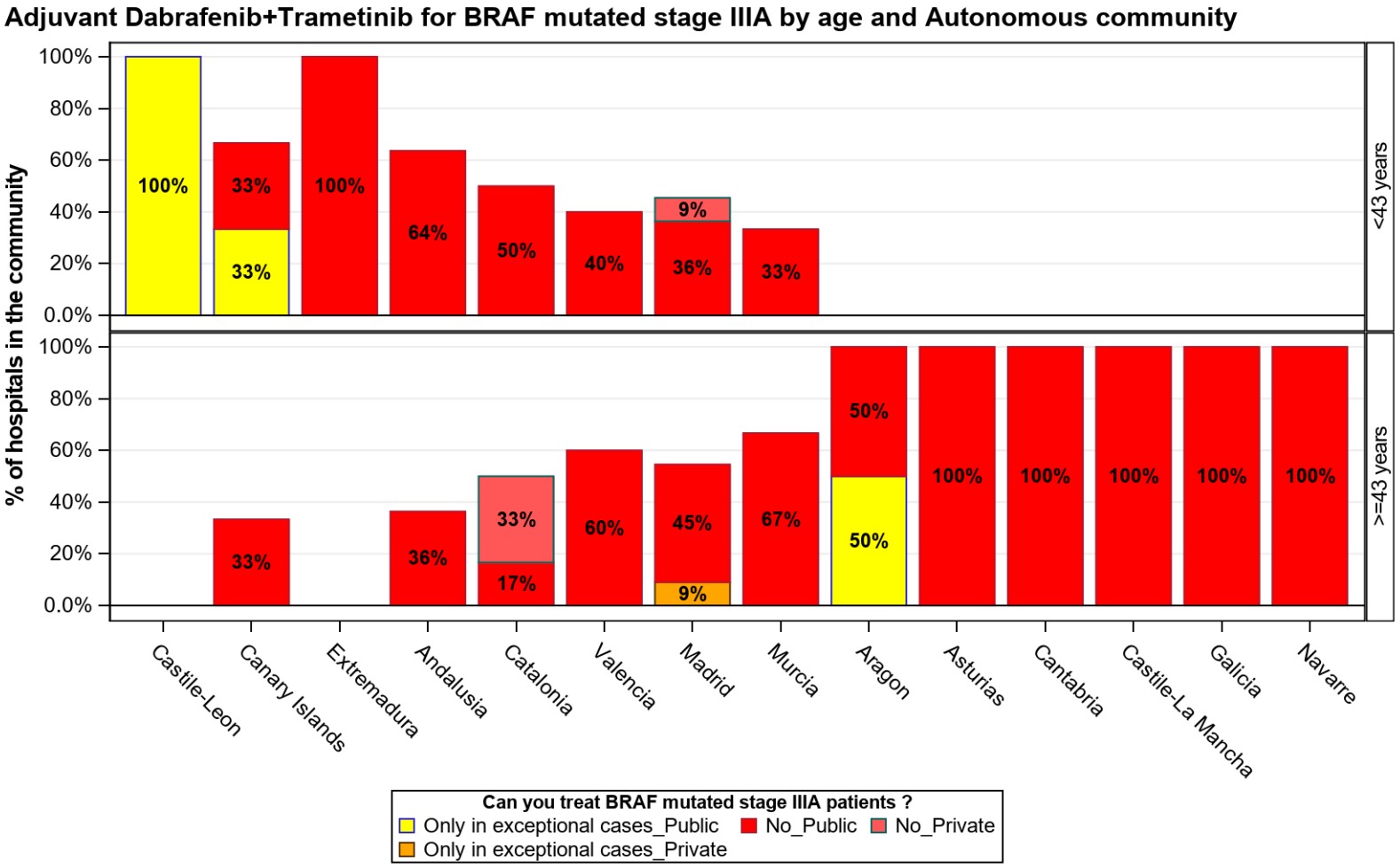
Supplemental Figure 1.6 Adjuvant Dabrafenib+Traemtinib therapy for BRAF mutated stage IIIC patients by physician´s age and Autonomous community



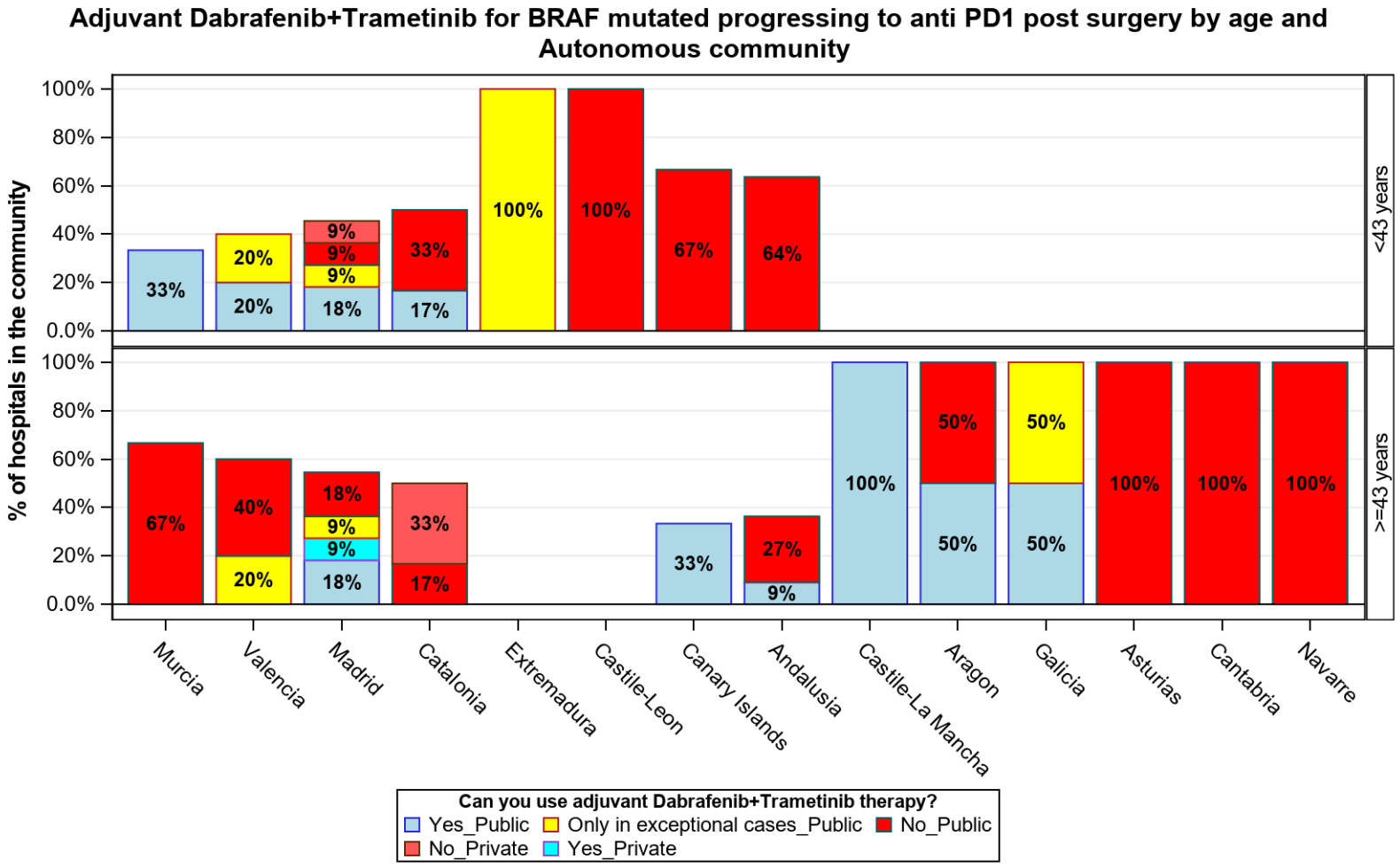
Supplemental Figure 1.7 Adjuvant Dabrafenib+Traemtinib therapy for BRAF mutated stage IIIB patients by physician´s age and Autonomous community



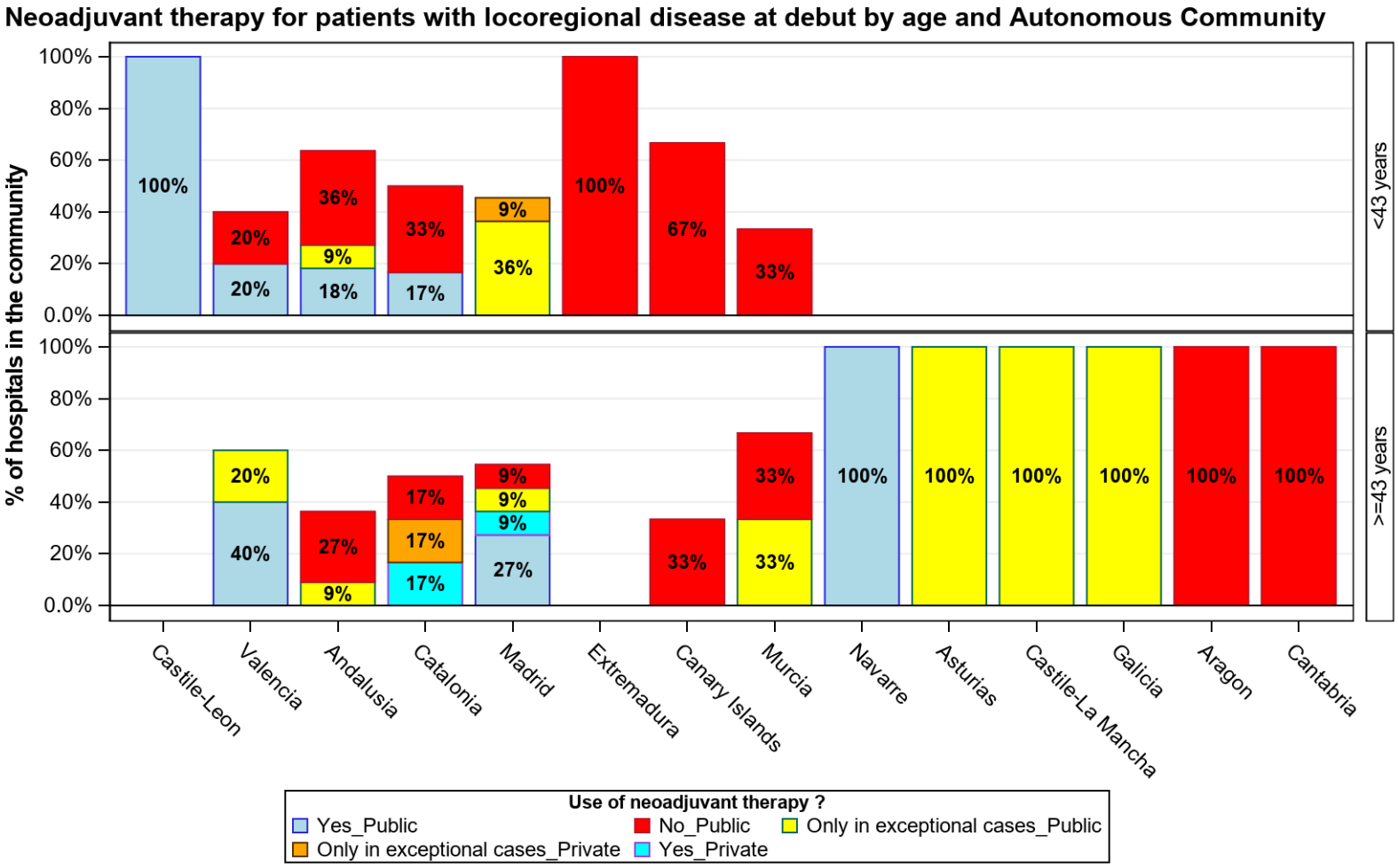
Supplemental Figure 1.8 Adjuvant Dabrafenib+Traemtinib therapy for BRAF mutated stage IIIA patients by physician´s age and Autonomous community



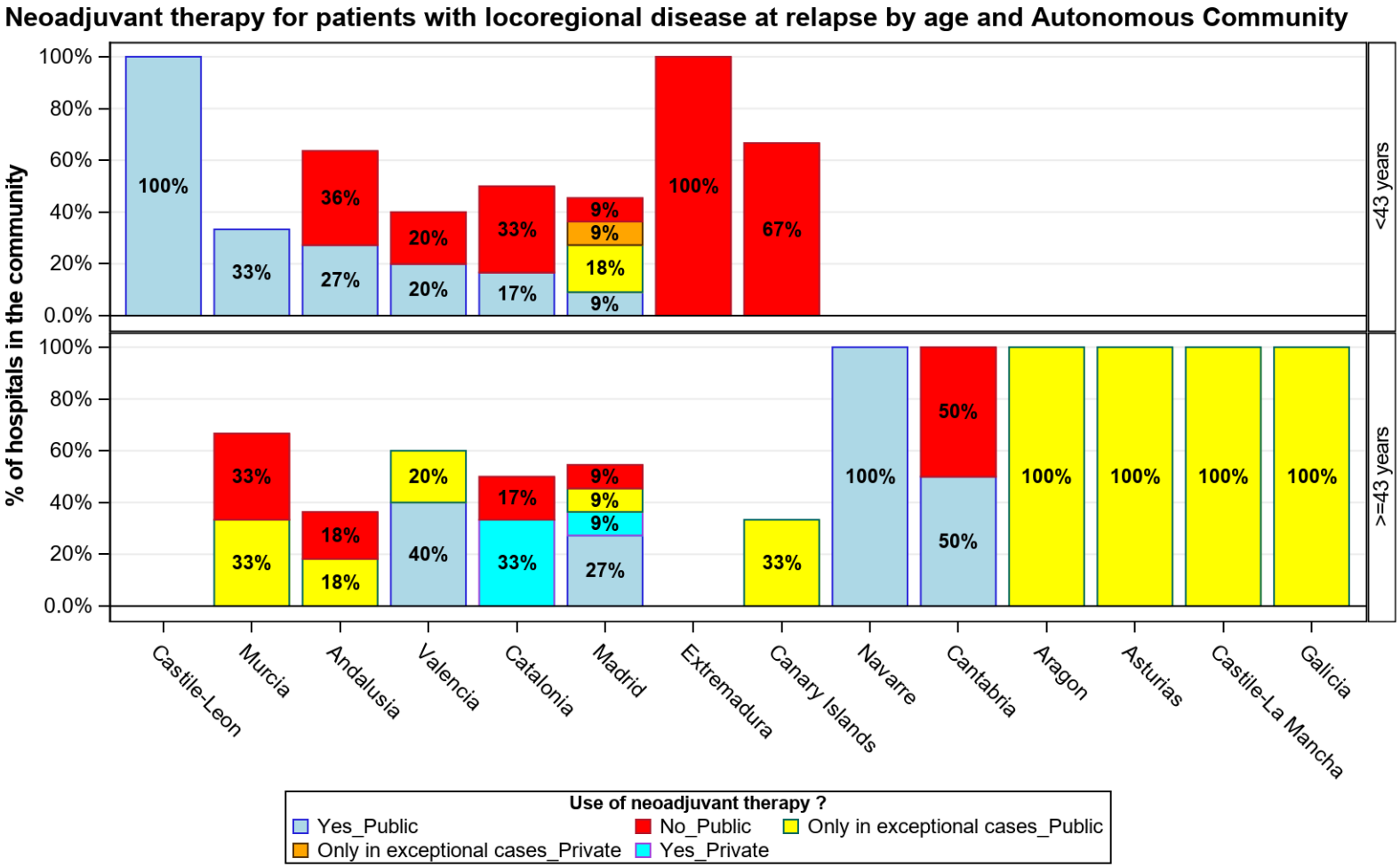
Supplemental Figure 1.9 Adjuvant Dabrafenib+Trametinib for BRAF mutated progressing to anti PD1 post surgery by physician´s age and Autonomous community



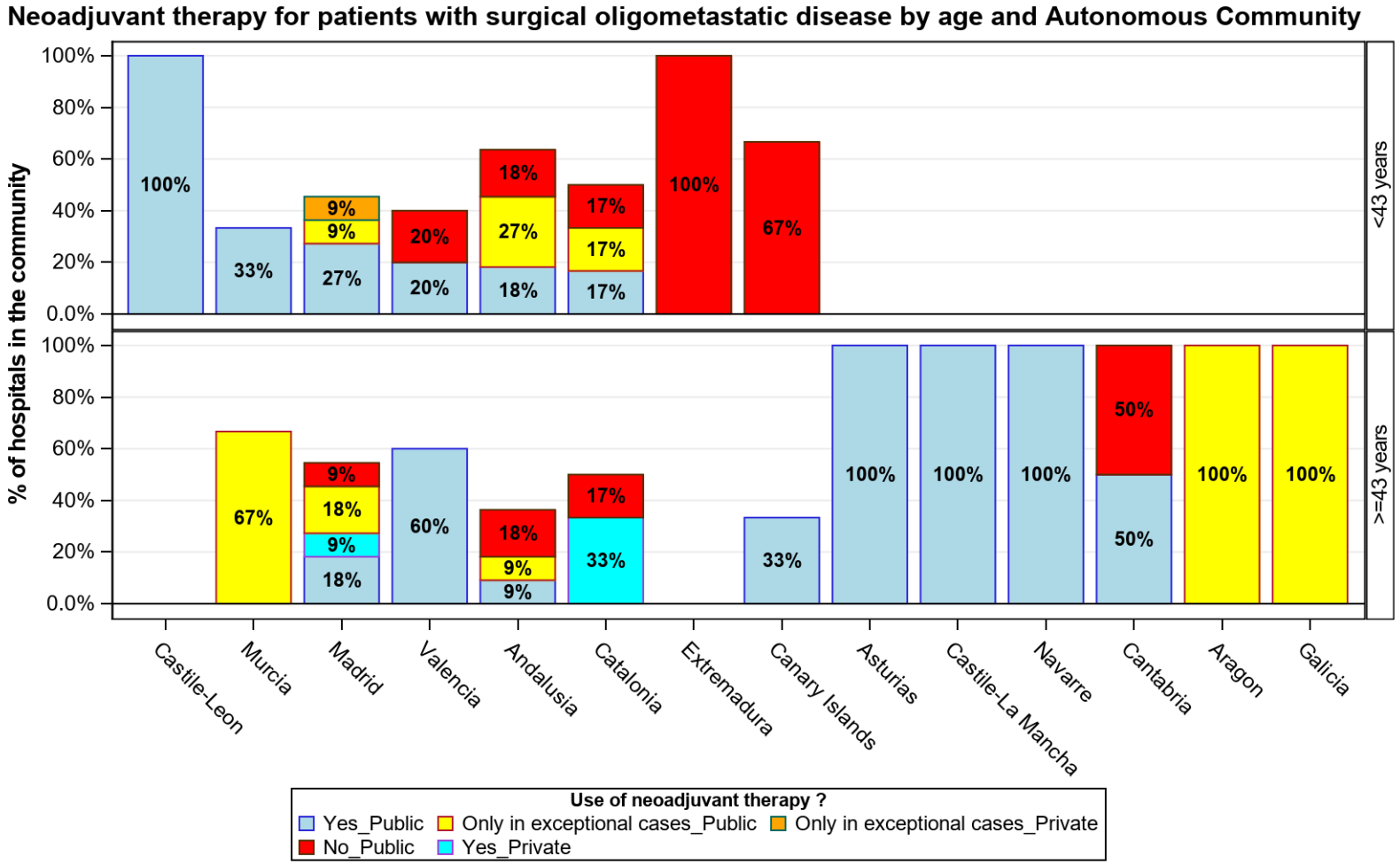
Supplemental Figure 1.13 Neoadjuvant therapy for patients with locoregional disease at debut by physician´s age and Autonomous Community



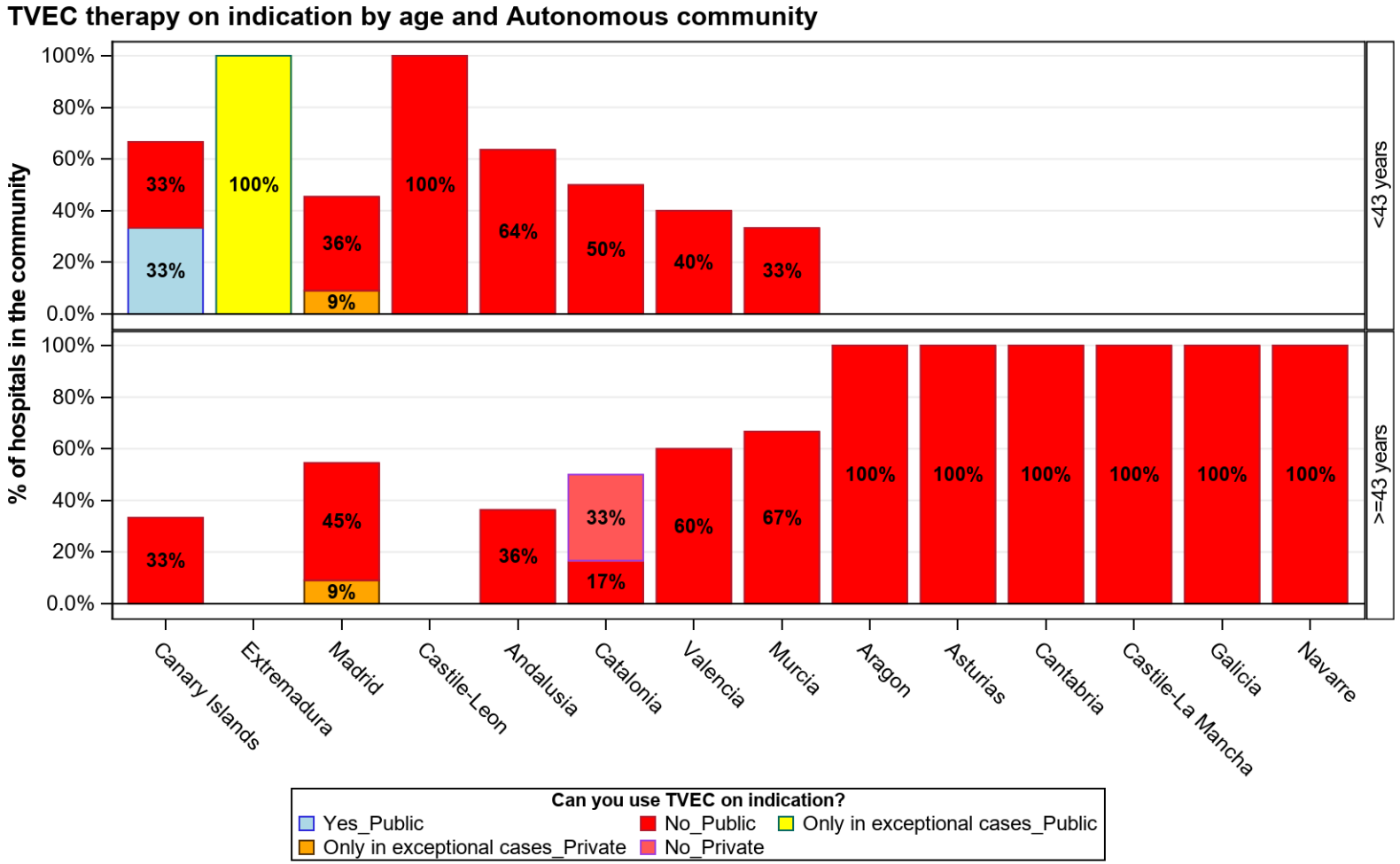
Supplemental Figure 1.10 Neoadjuvant therapy for patients with locoregional disease at relapse by physician´s age and Autonomous Community



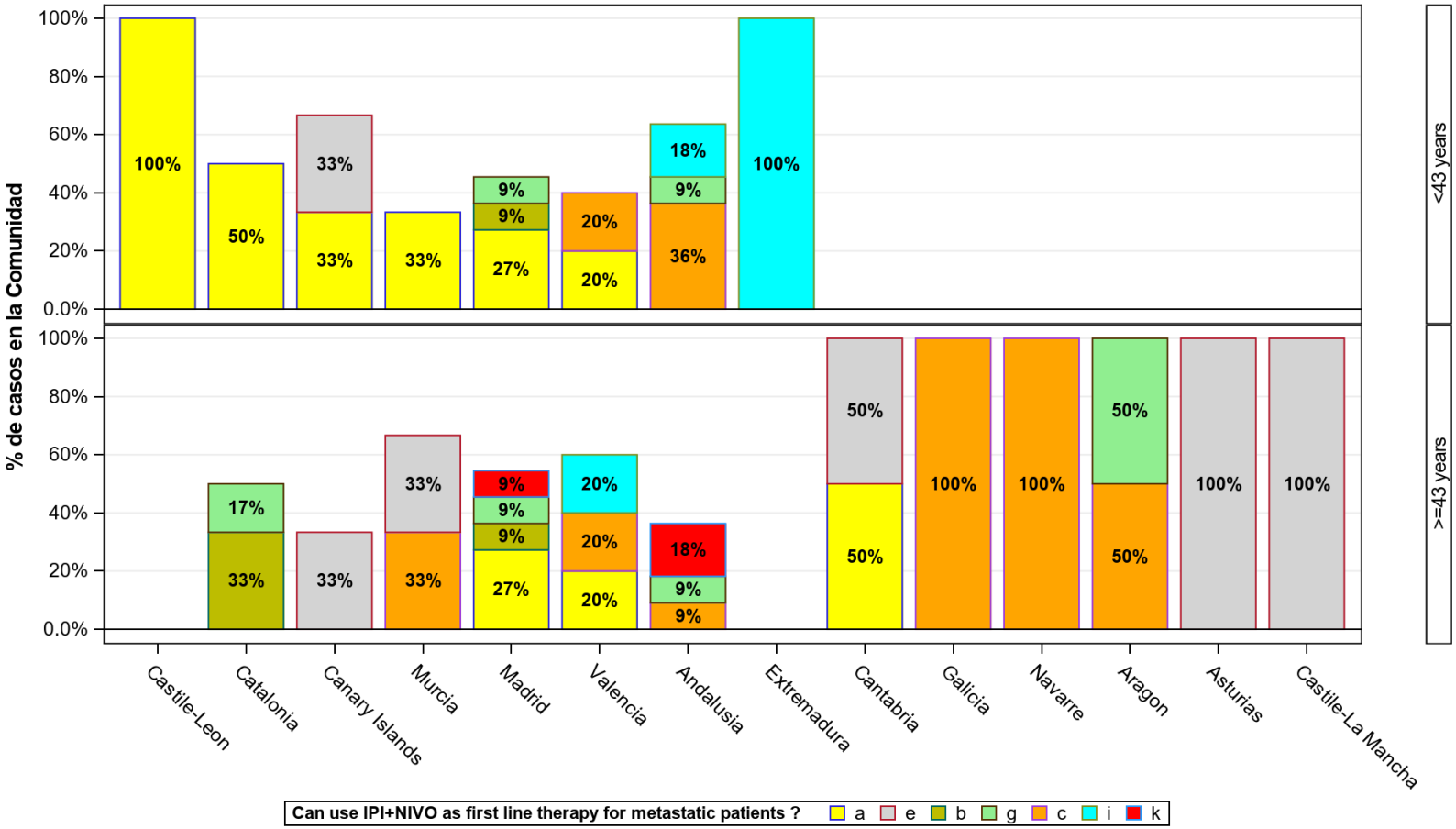
Supplemental Figure 1.11 Neoadjuvant therapy for patients with surgical oligometastatic disease by physician´s age and Autonomous Community



Supplemental Figure 1.12 TVEC therapy on indication by physician´s age and Autonomous community

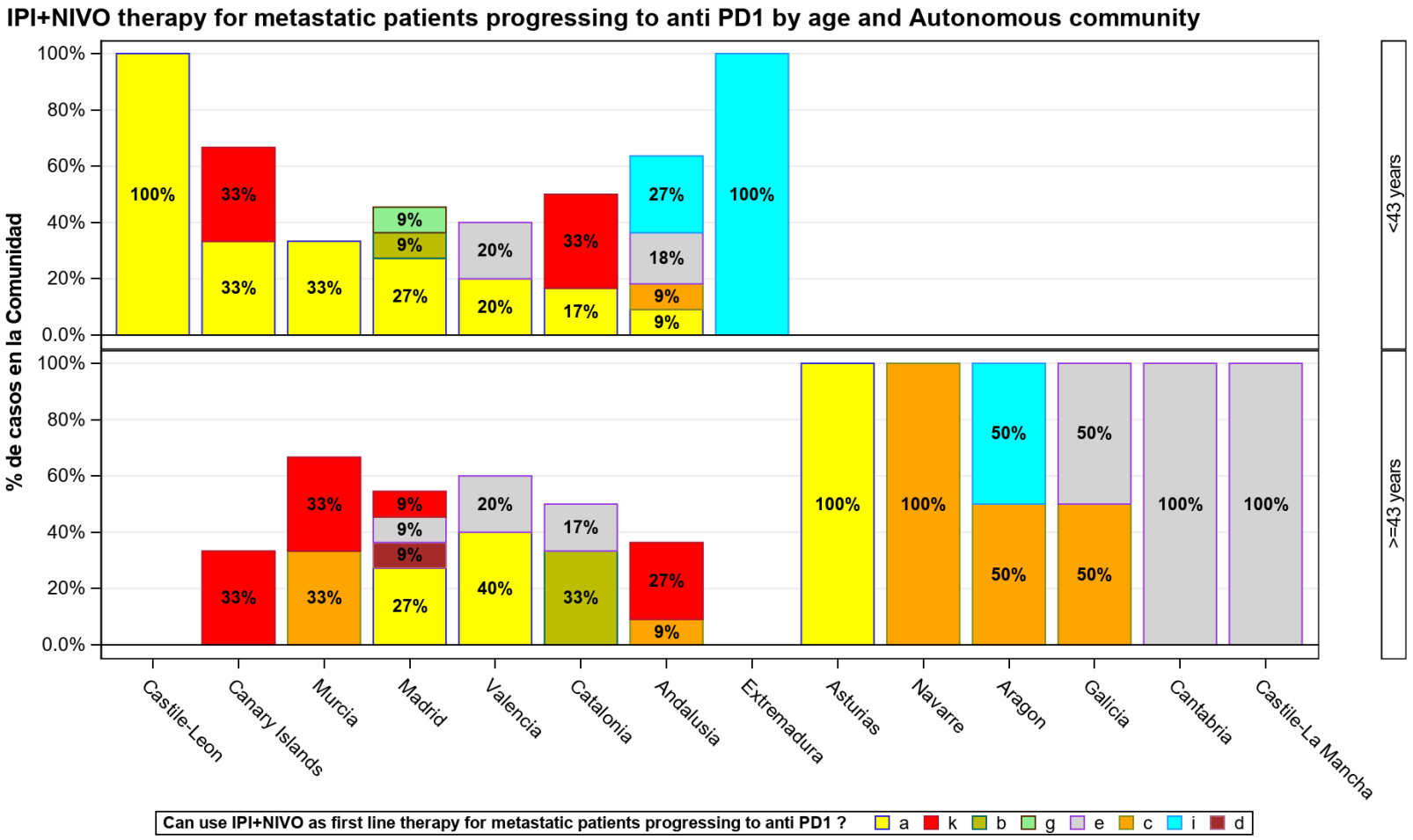


Supplemental Figure 1.13 IPILIMUMAB+NIVOLUMAB as first line for metastatic melanoma patients by physician´s age and Autonomous community



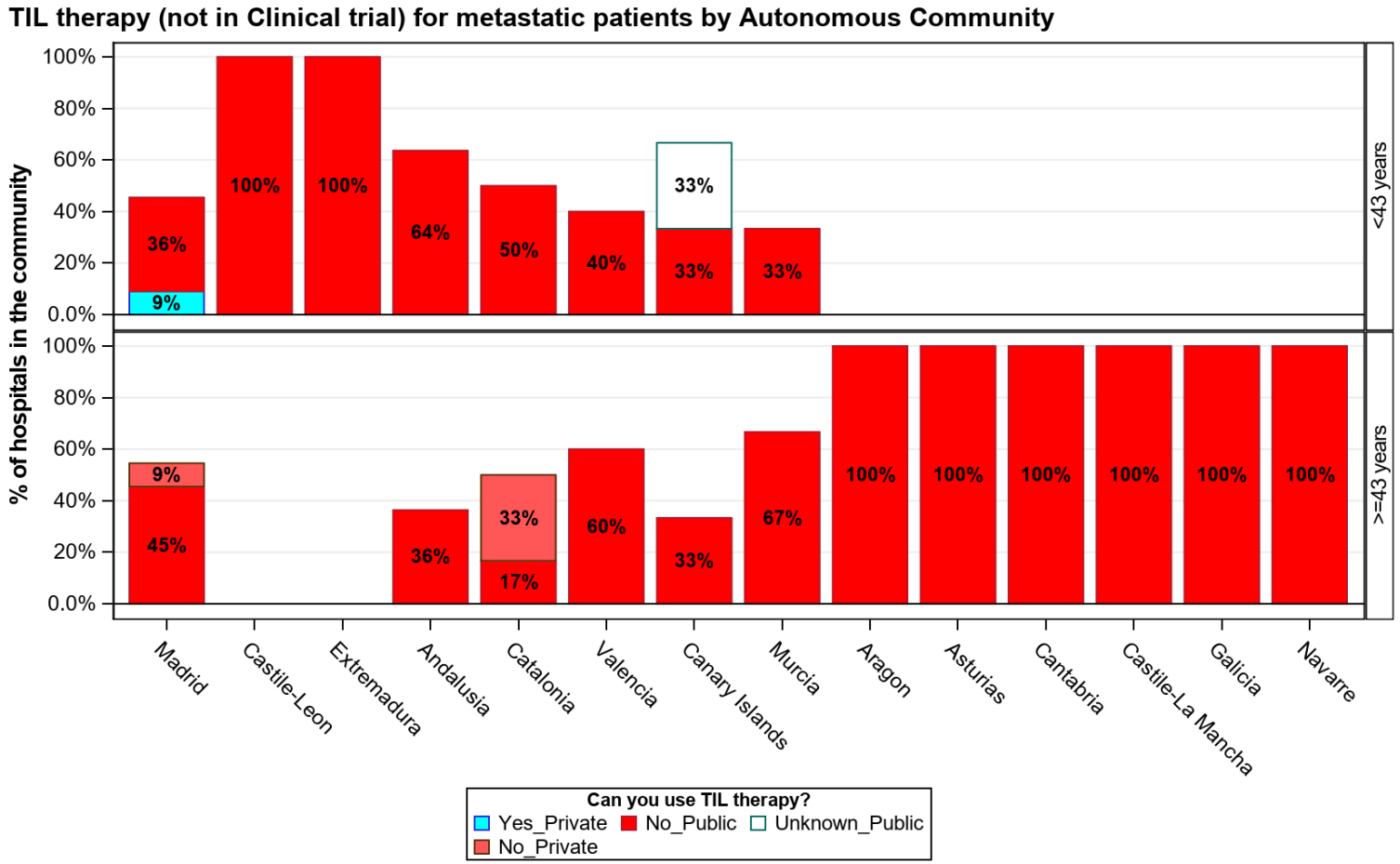
a=All appropiate cases_pu; b=All appropiate cases_pr; c=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pu; d=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pr; e=Only cases evaluated by the Institutional Review Board_pu f=Only cases evaluated by the Institutional Review Board_pr g=I g=Only for patients with brain metastasis and/or uveal melanoma_pu;h=Only for patients with brain metastasis and/or uveal melanoma_pr;i=Only if PDL1 <1%_pu; j=Only if PDL1 <1%_pr;k=No_pu;l=No_pr

Supplemental Figure 1.14 IPILIMUMAB+NIVOLUMAB at second line after progression to anti PD-1 Ab for metastatic melanoma patients by physician´s age and Autonomous community



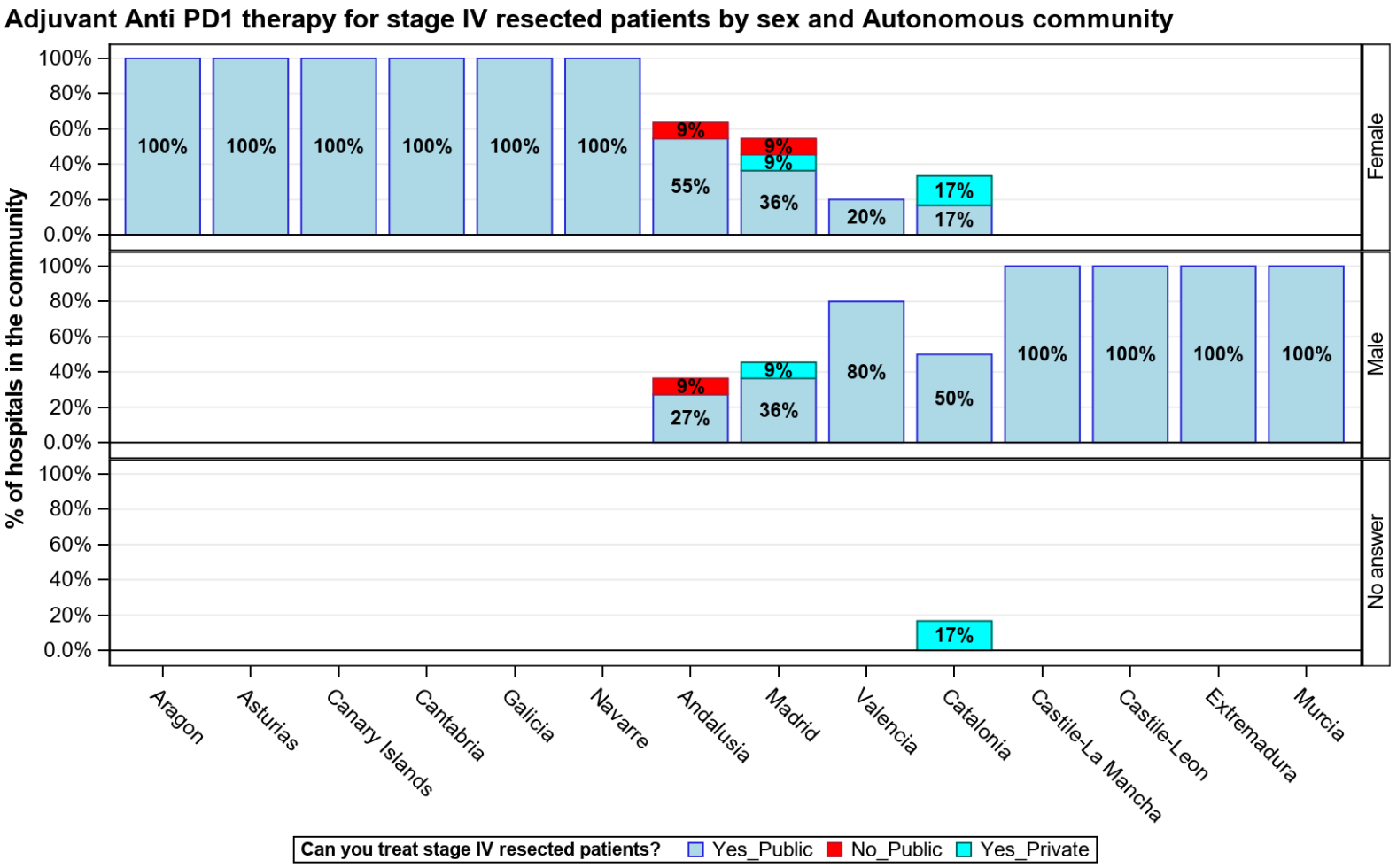
a=All appropiate cases_pu; b=All appropiate cases_pr; c=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pu; d=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pr; e=Only cases evaluated by the Institutional Review Board_pu f=Only cases evaluated by the Institutional Review Board_pr g=I g=Only for patients with brain metastasis and/or uveal melanoma_pu;h=Only for patients with brain metastasis and/or uveal melanoma_pr;i=Only if PDL1 <1%_pu; j=Only if PDL1 <1%_pr;k=No_pu;l=No_pr

Supplemental Figure 1.15 TIL therapy for metastatic patients by physician´s age and Autonomous Community

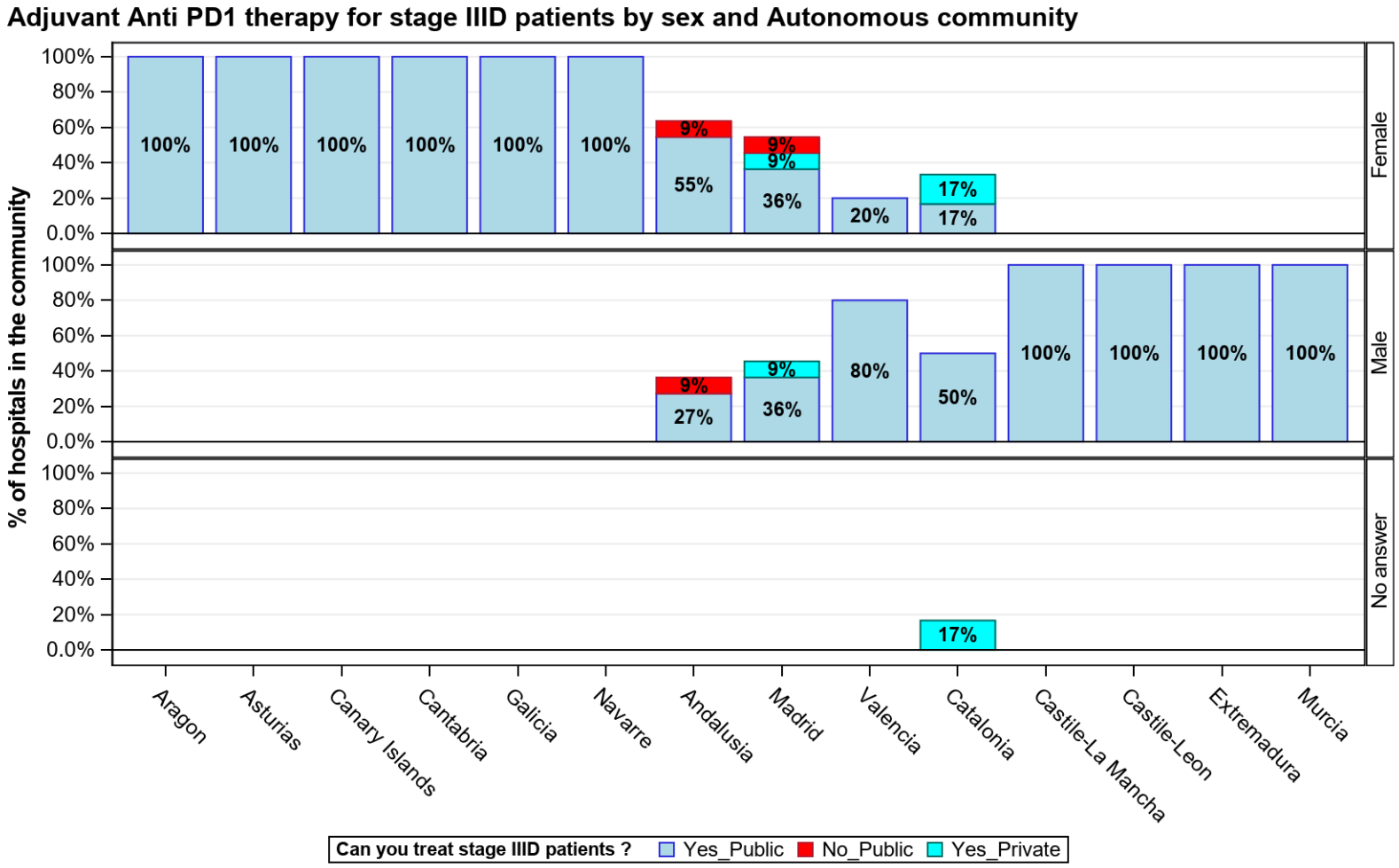


Supplemental Figure 2. Distribution of drug access according to the physician´s sex of prescriber physician

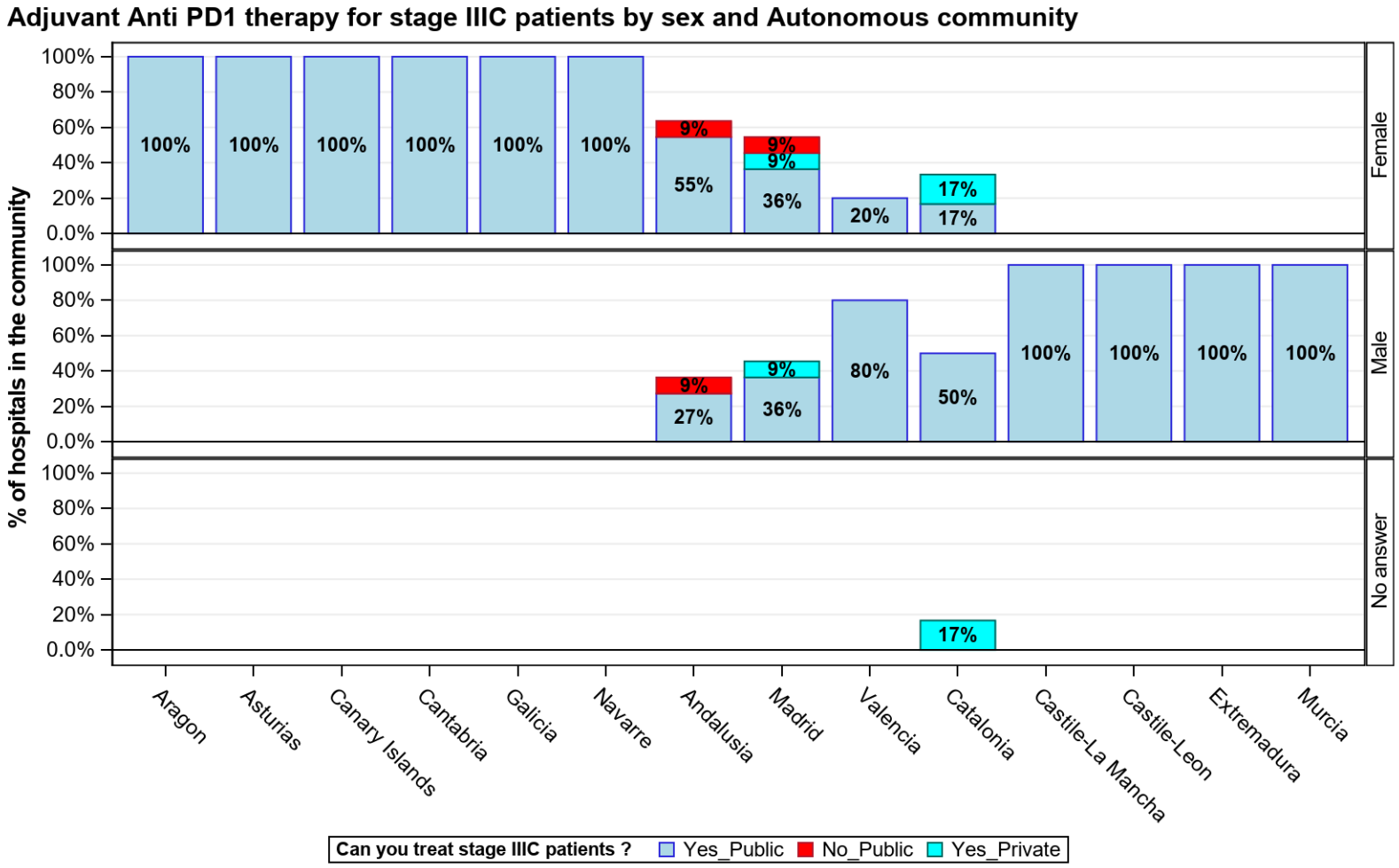
Supplemental Figure 2.1 Adjuvant Anti PD1 therapy for stage IV resected patients by physician´s sex and Autonomous community



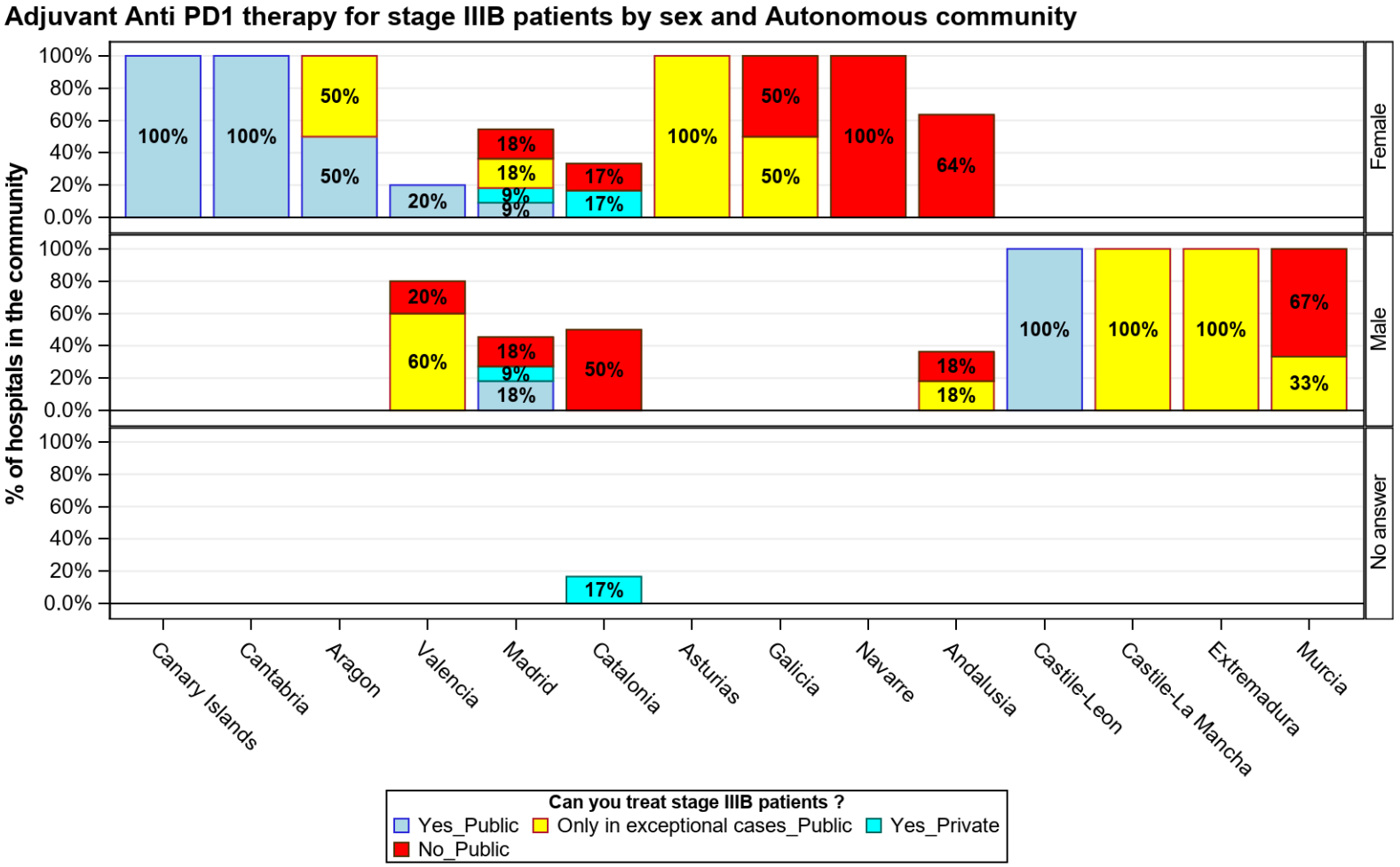
Supplemental Figure 2.16 Adjuvant Anti PD1 therapy for stage IIID patients by physician´s sex and Autonomous community



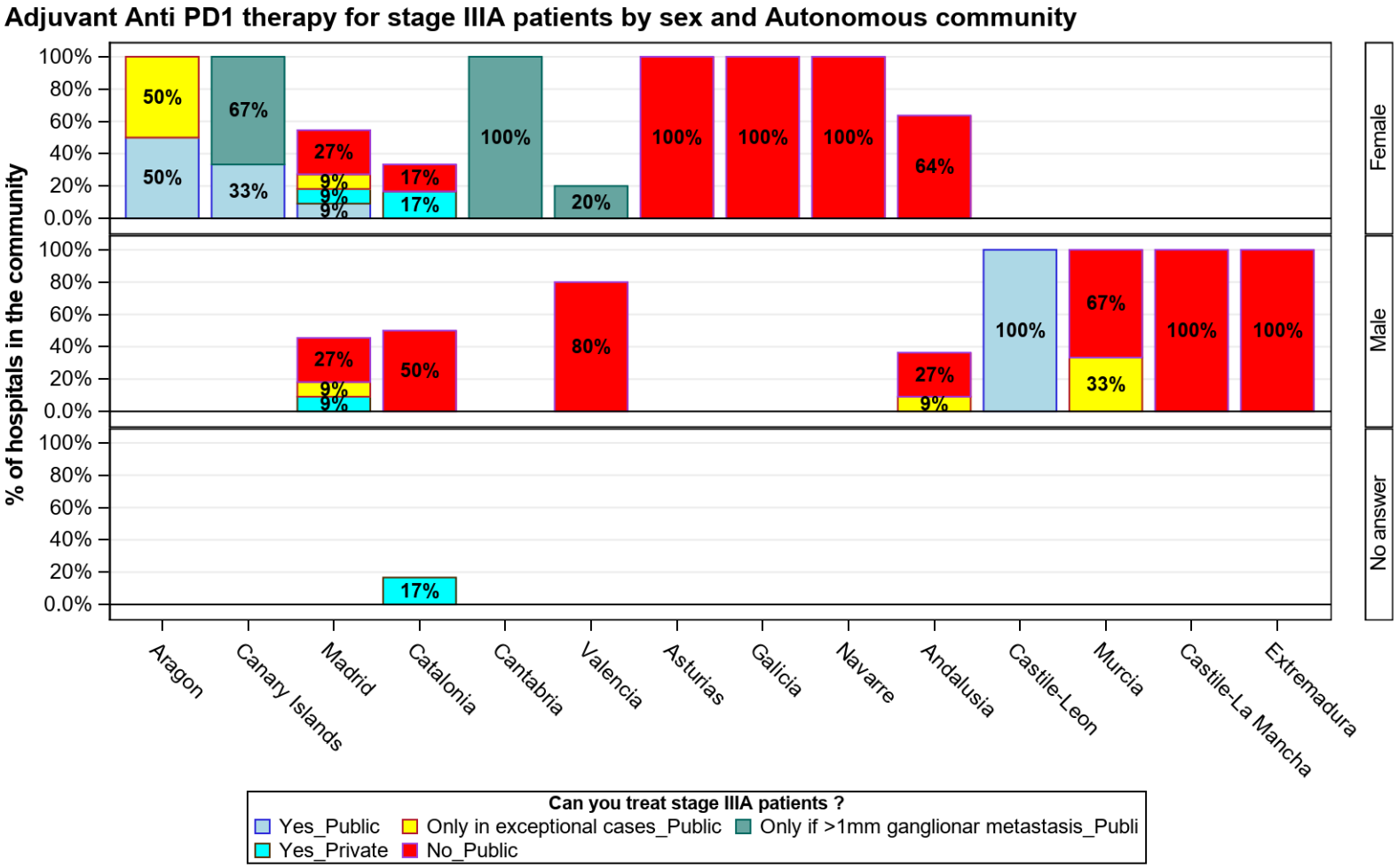
Supplemental Figure 2.17 Adjuvant Anti PD1 therapy for stage IIIC patients by physician´s sex and Autonomous community



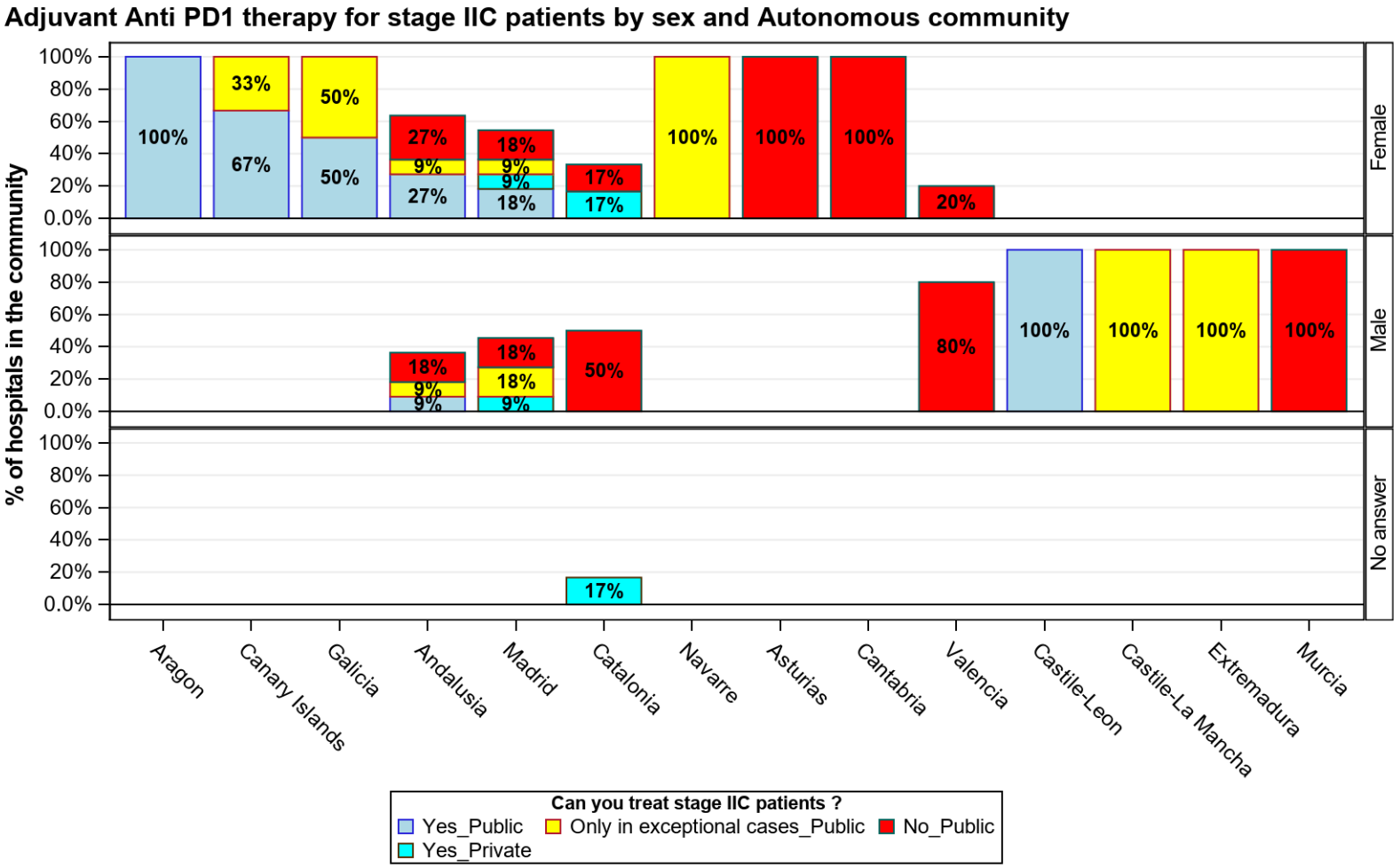
Supplemental Figure 2.18 Adjuvant Anti PD1 therapy for stage IIIB patients by physician´s sex and Autonomous community



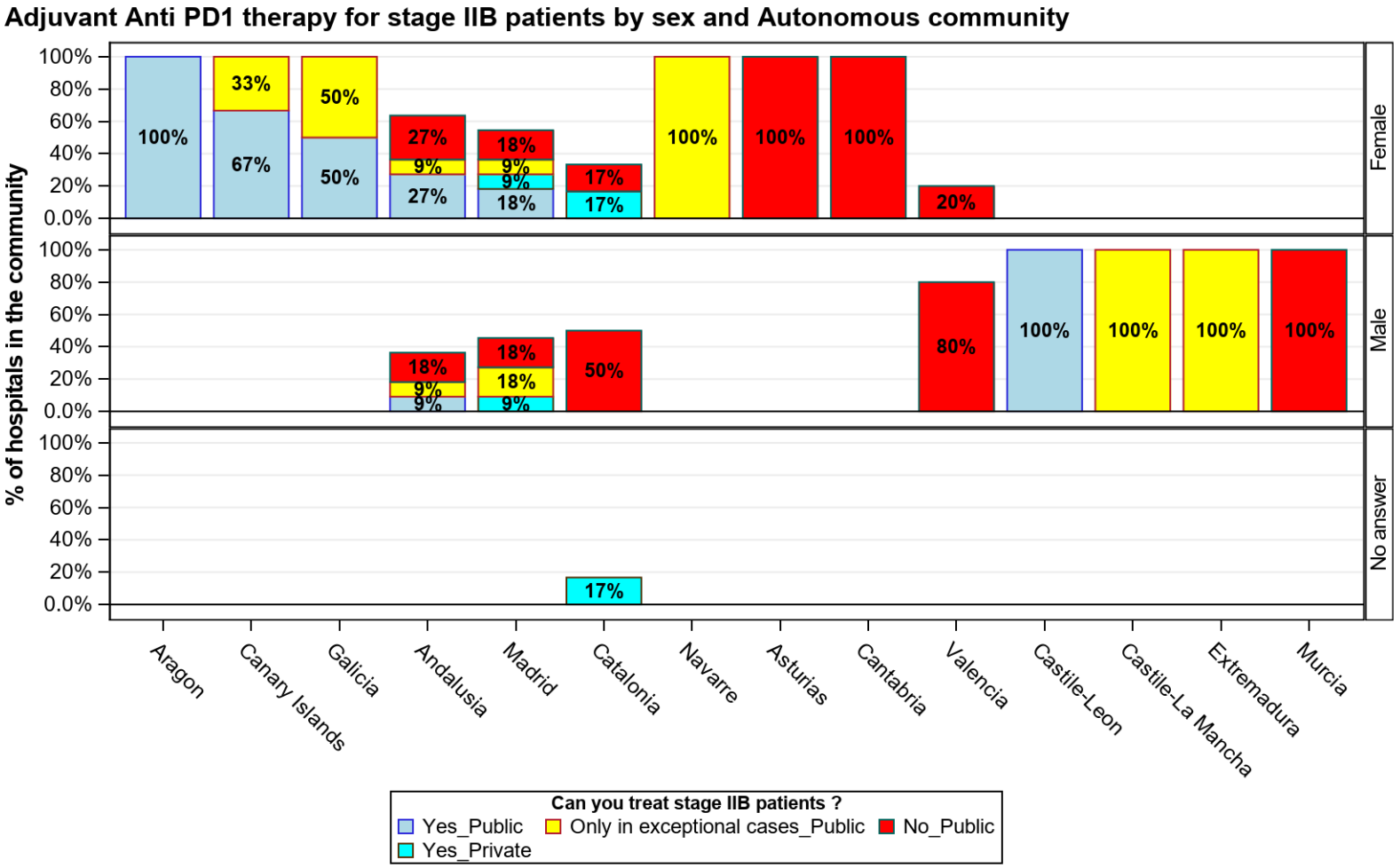
Supplemental Figure 2.19 Adjuvant Anti PD1 therapy for stage IIIA patients by physician´s sex and Autonomous community



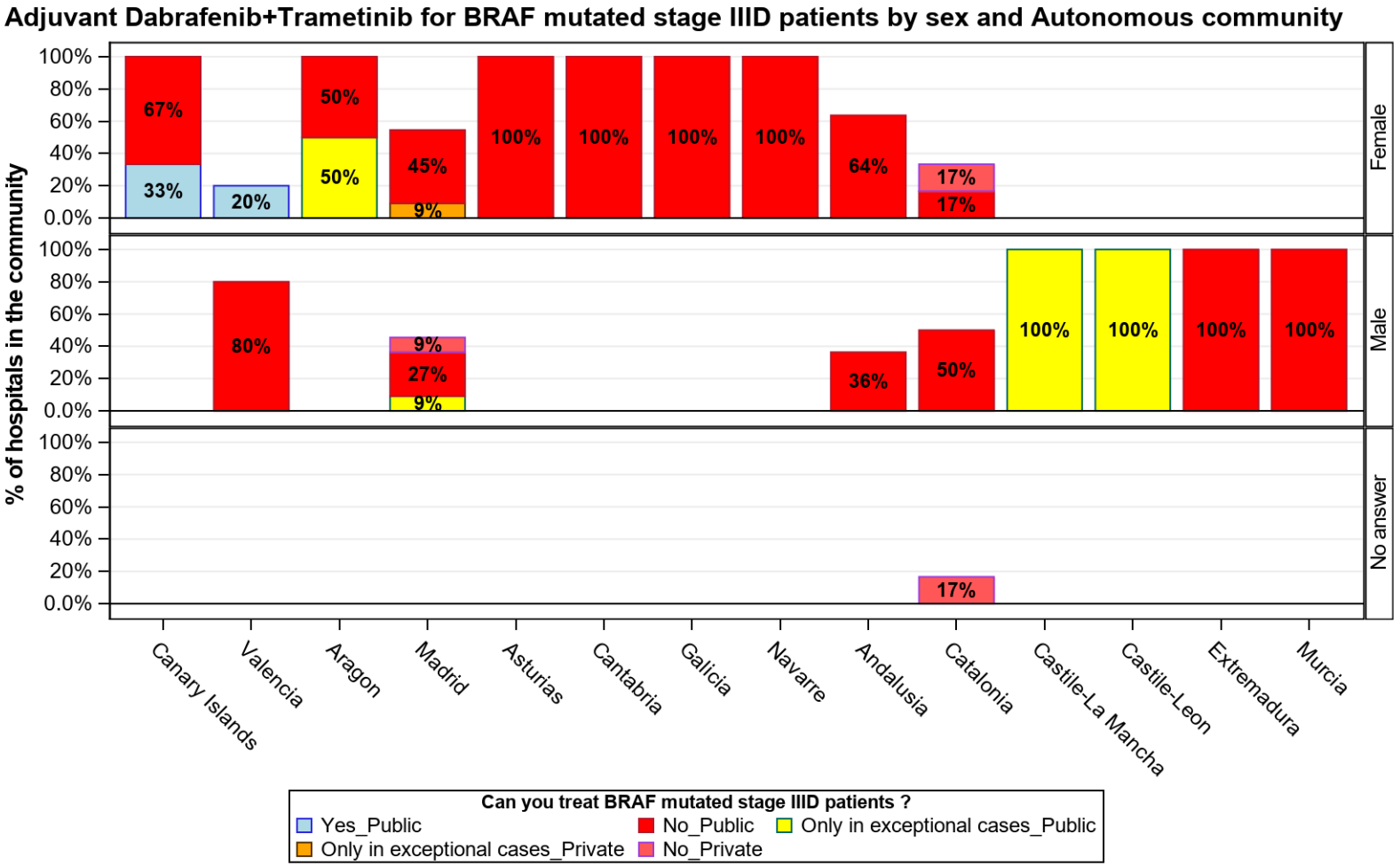
Supplemental Figure 2.20 Adjuvant Anti PD1 therapy for stage IIC patients by physician´s sex and Autonomous community



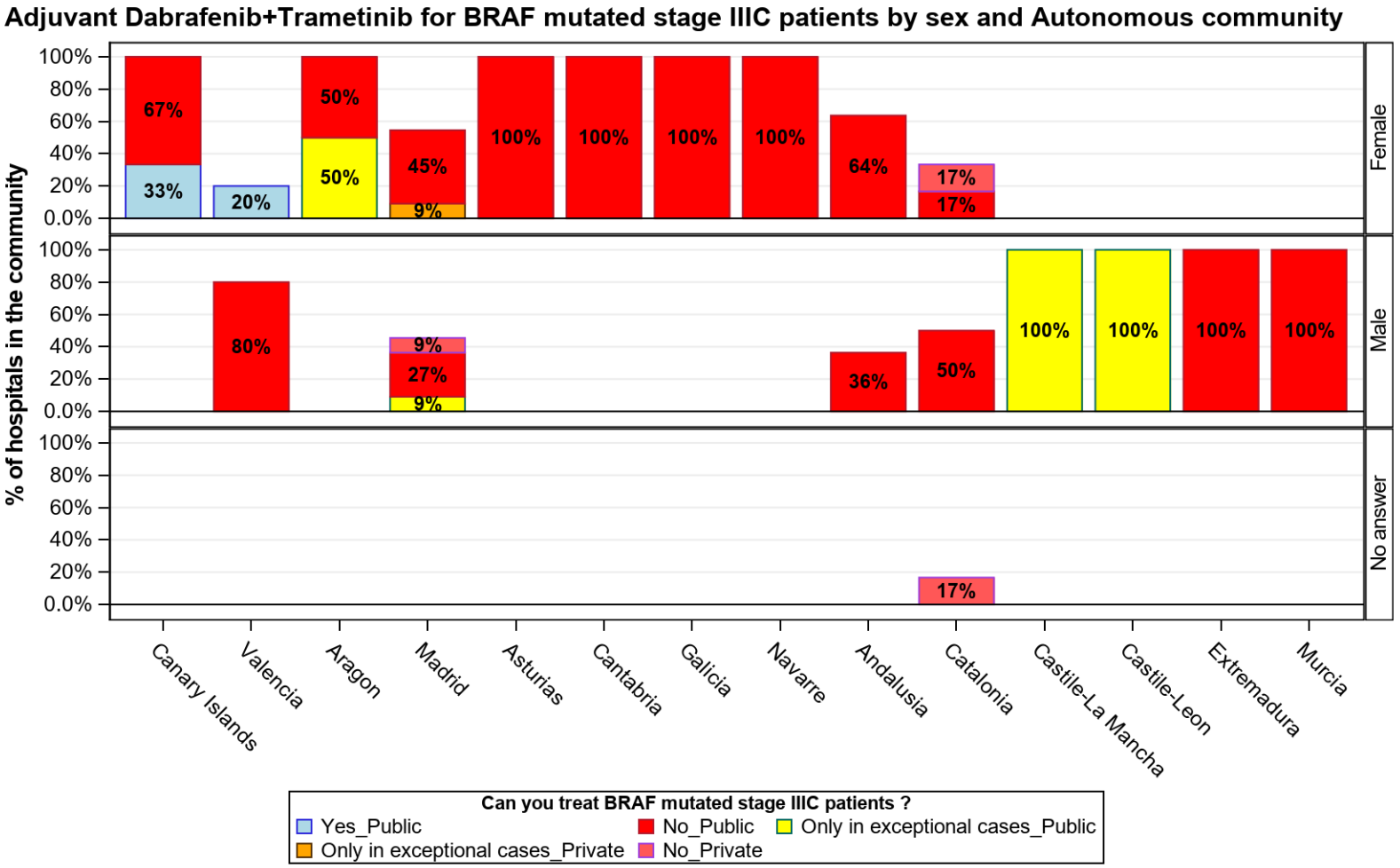
Supplemental Figure 2.21 Adjuvant Anti PD1 therapy for stage IIB patients by physician´s sex and Autonomous community



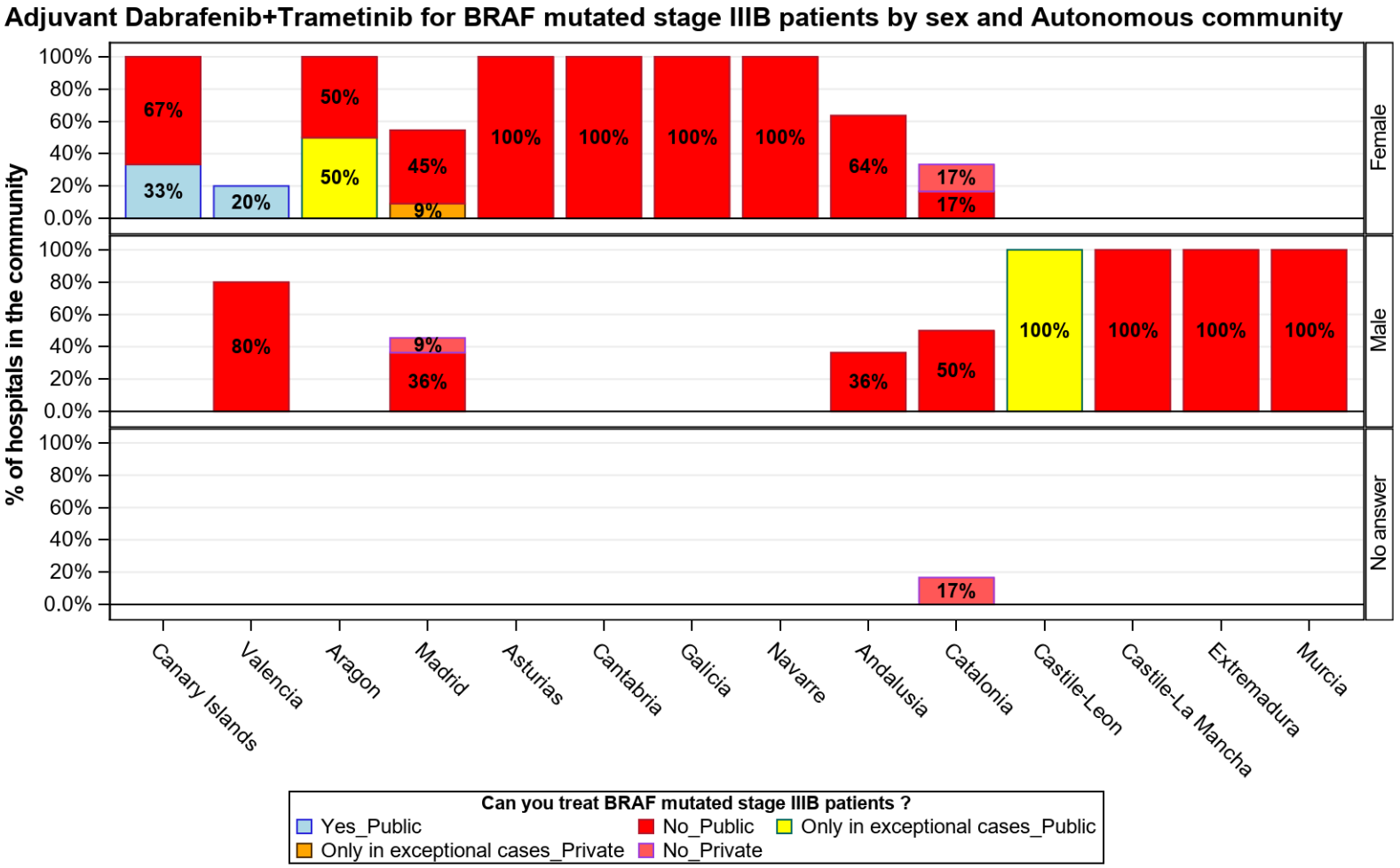
Supplemental Figure 2.22 Adjuvant Dabrafenib+Trametinib therapy for BRAF mutated stage IIID patients by physician´s sex and Autonomous community



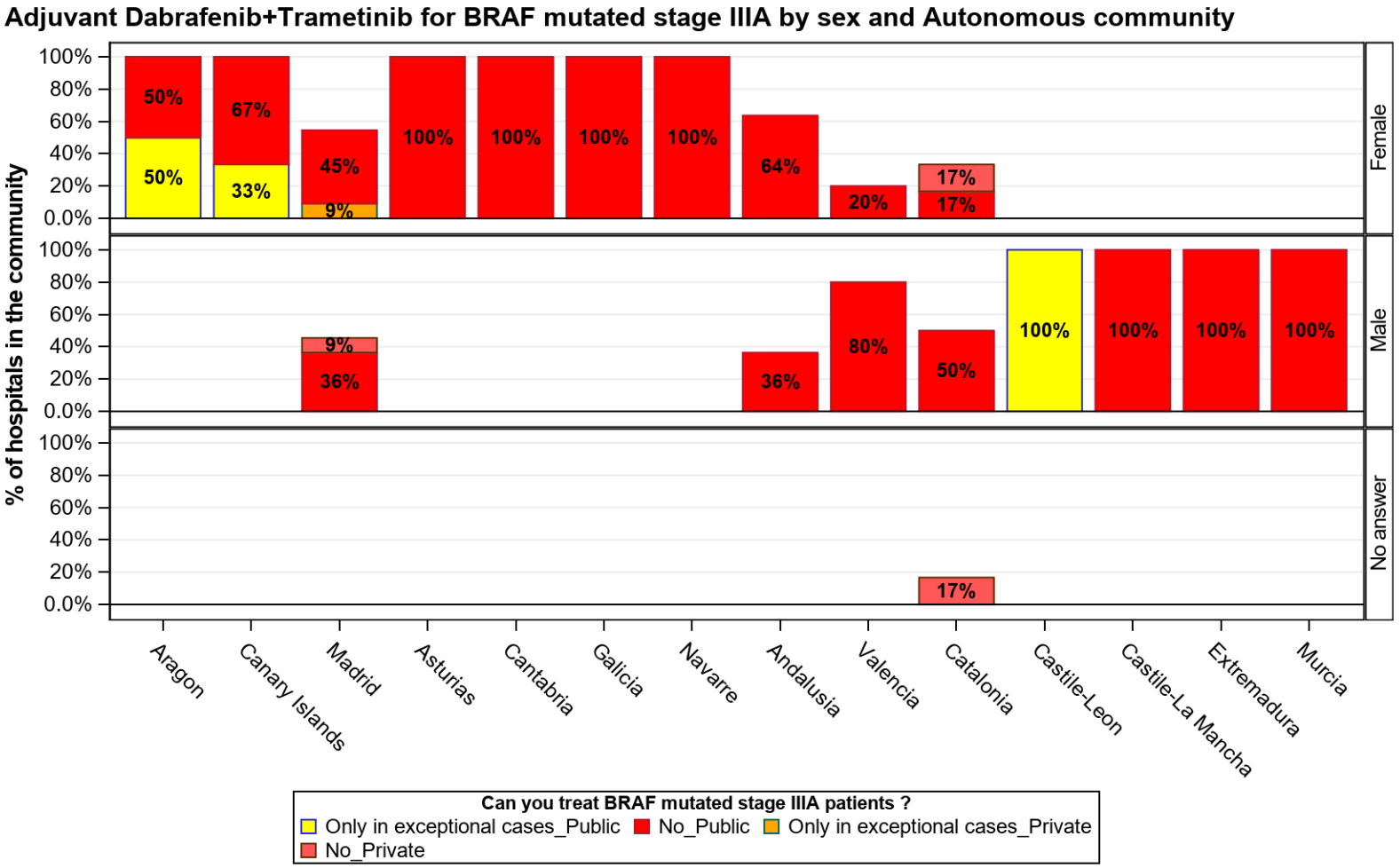
Supplemental Figure 2.23 Adjuvant Dabrafenib+Trametinib therapy for BRAF mutated stage IIIC patients by physician´s sex and Autonomous community



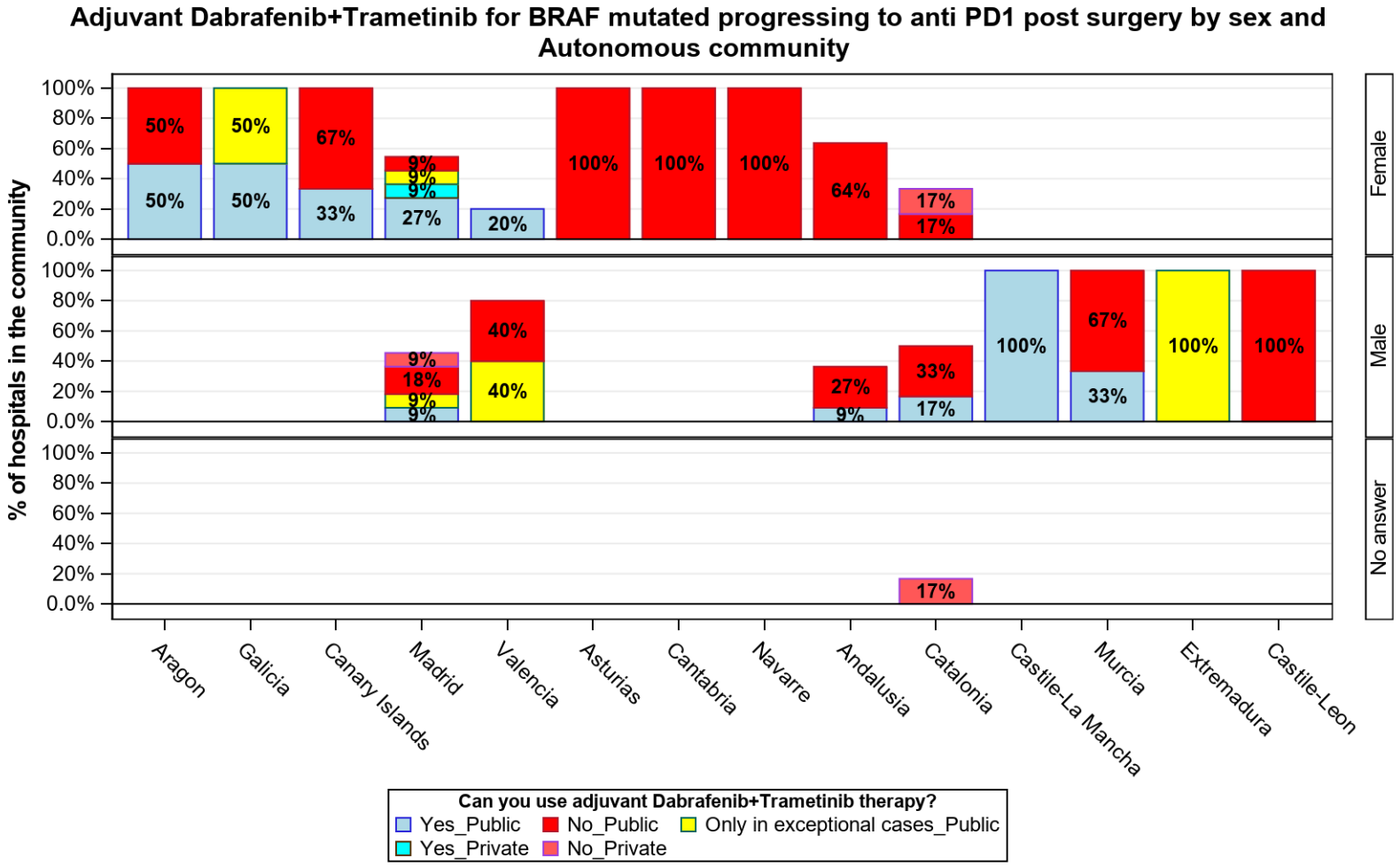
Supplemental Figure 2.24 Adjuvant Dabrafenib+Trametinib therapy for BRAF mutated stage IIIB patients by physician´s sex and Autonomous community



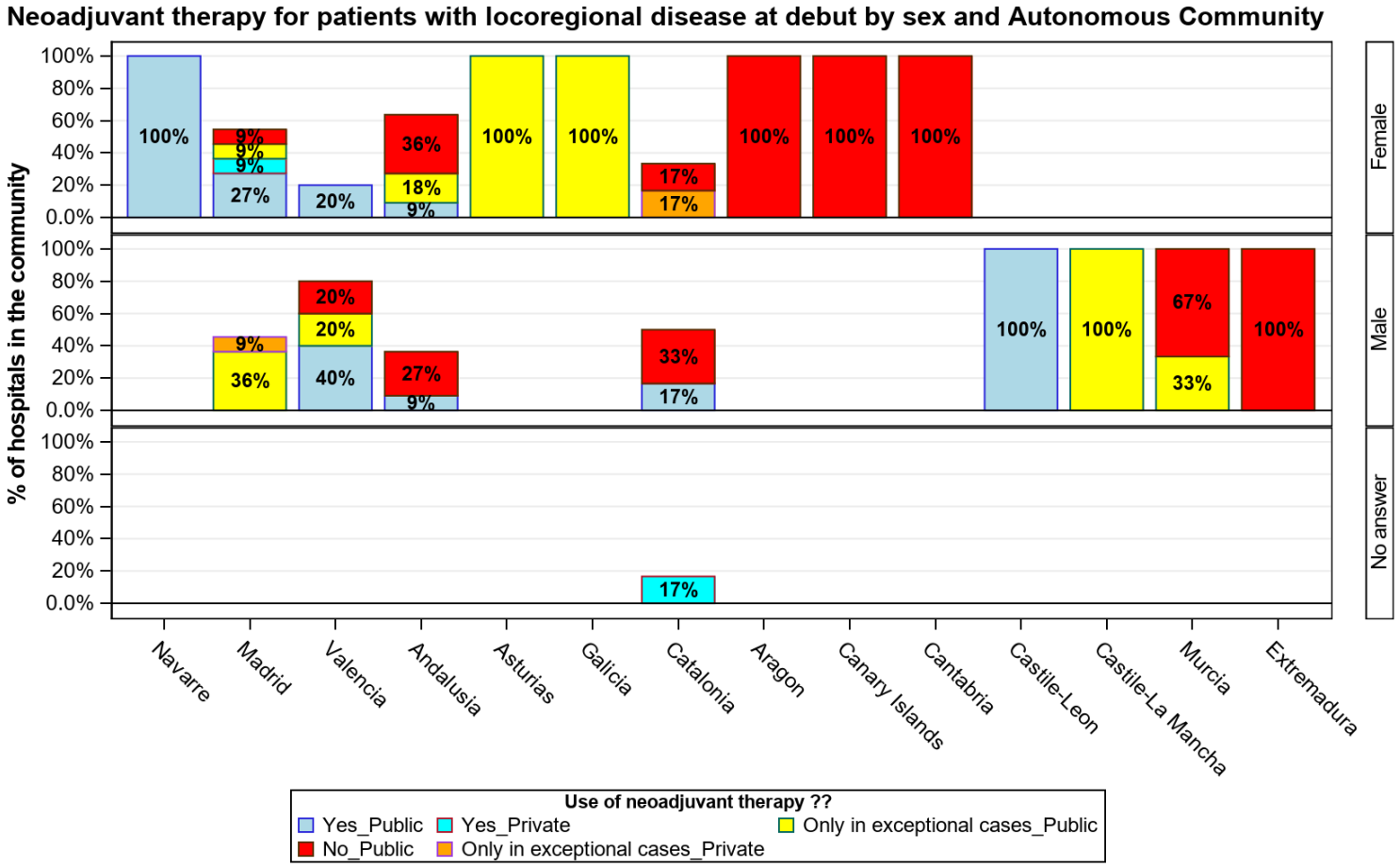
Supplemental Figure 2.25 Adjuvant Dabrafenib+Trametinib therapy for BRAF mutated stage IIIA by physician´s sex and Autonomous community



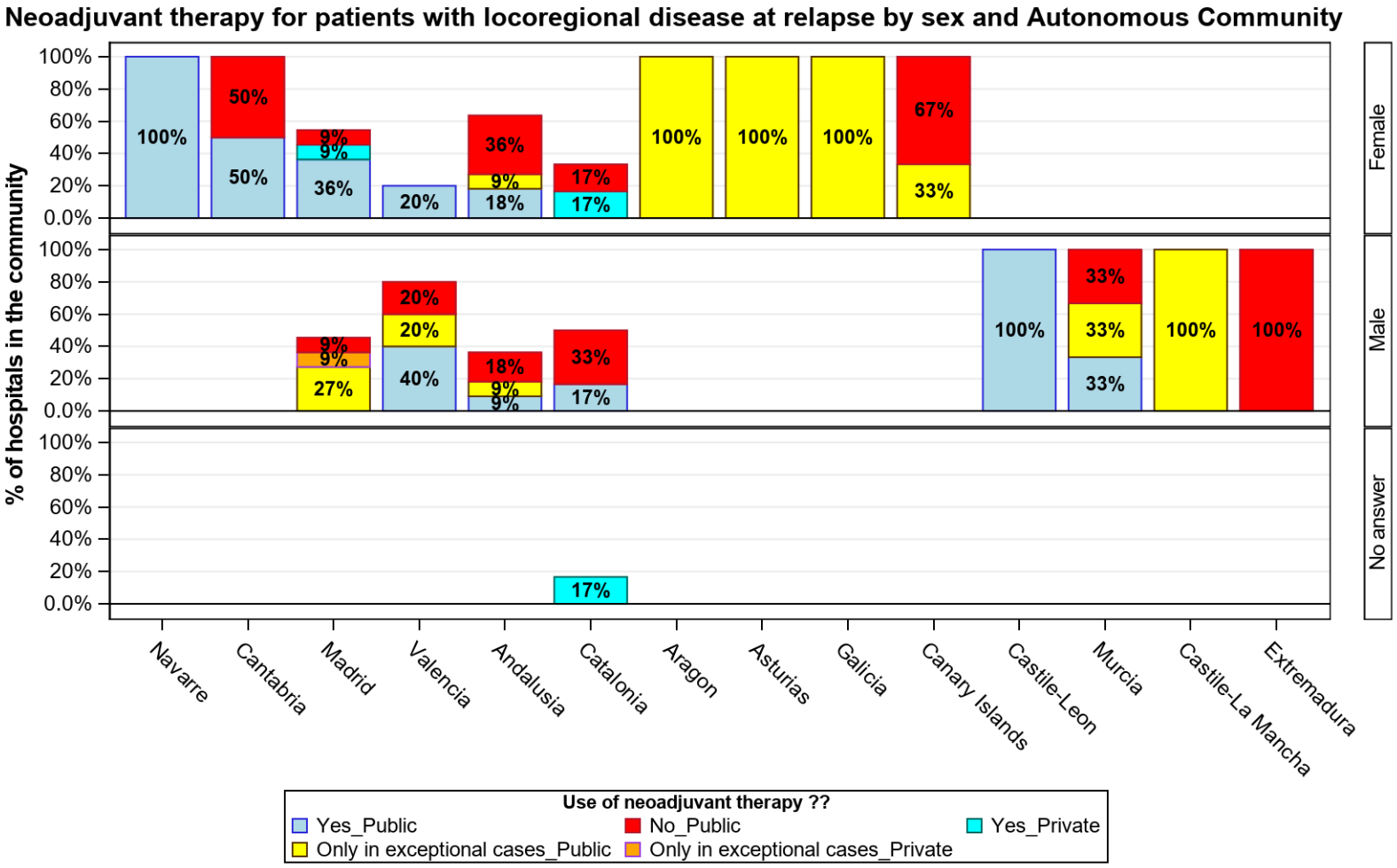
Supplemental Figure 2.26 Adjuvant Dabrafenib+Trametinib therapy for BRAF mutated progressing to anti PD1 post-surgery by physician´s sex and Autonomous community



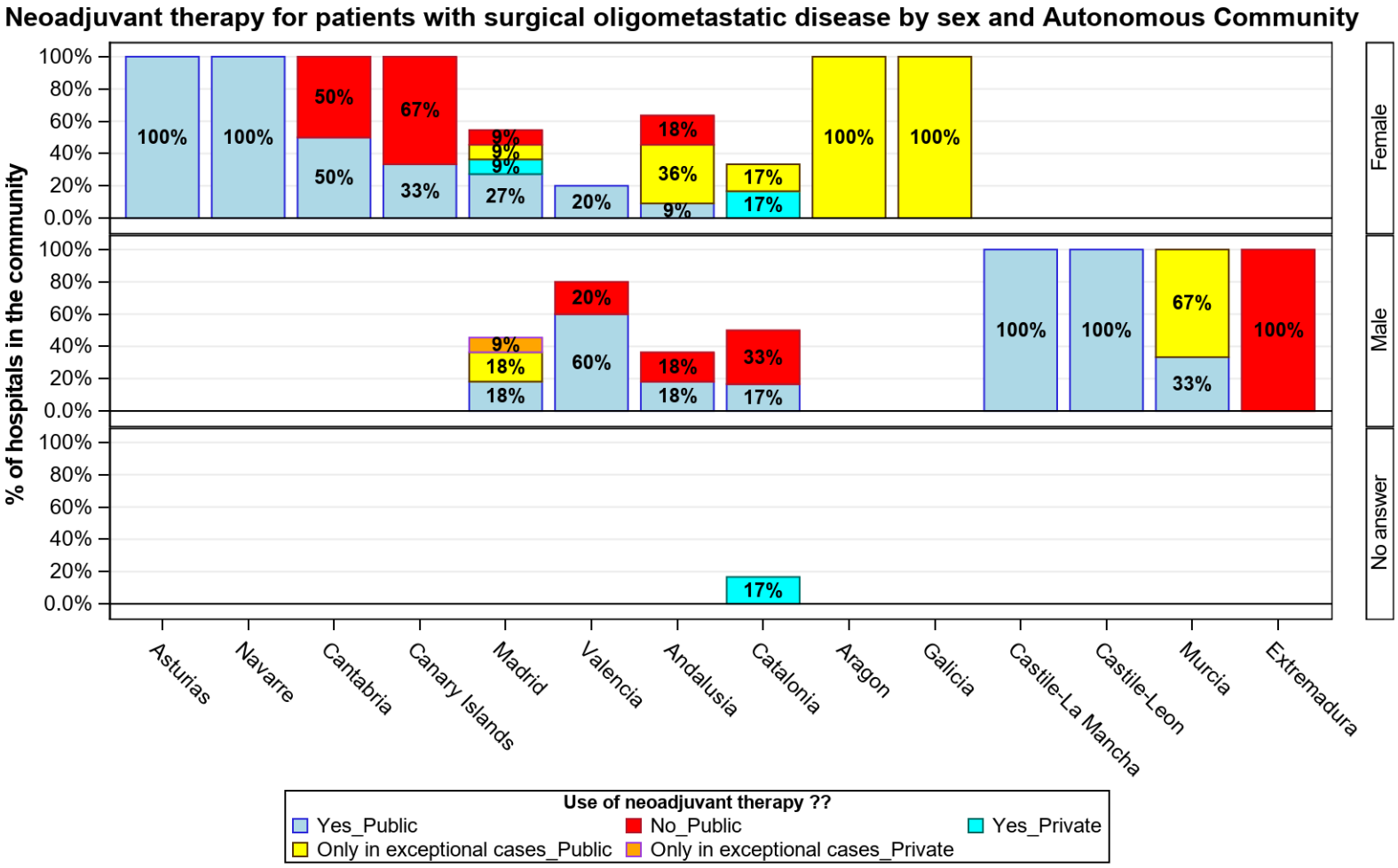
Supplemental Figure 2.27 Neoadjuvant therapy for patients with locoregional disease at debut by physician´s sex and Autonomous Community



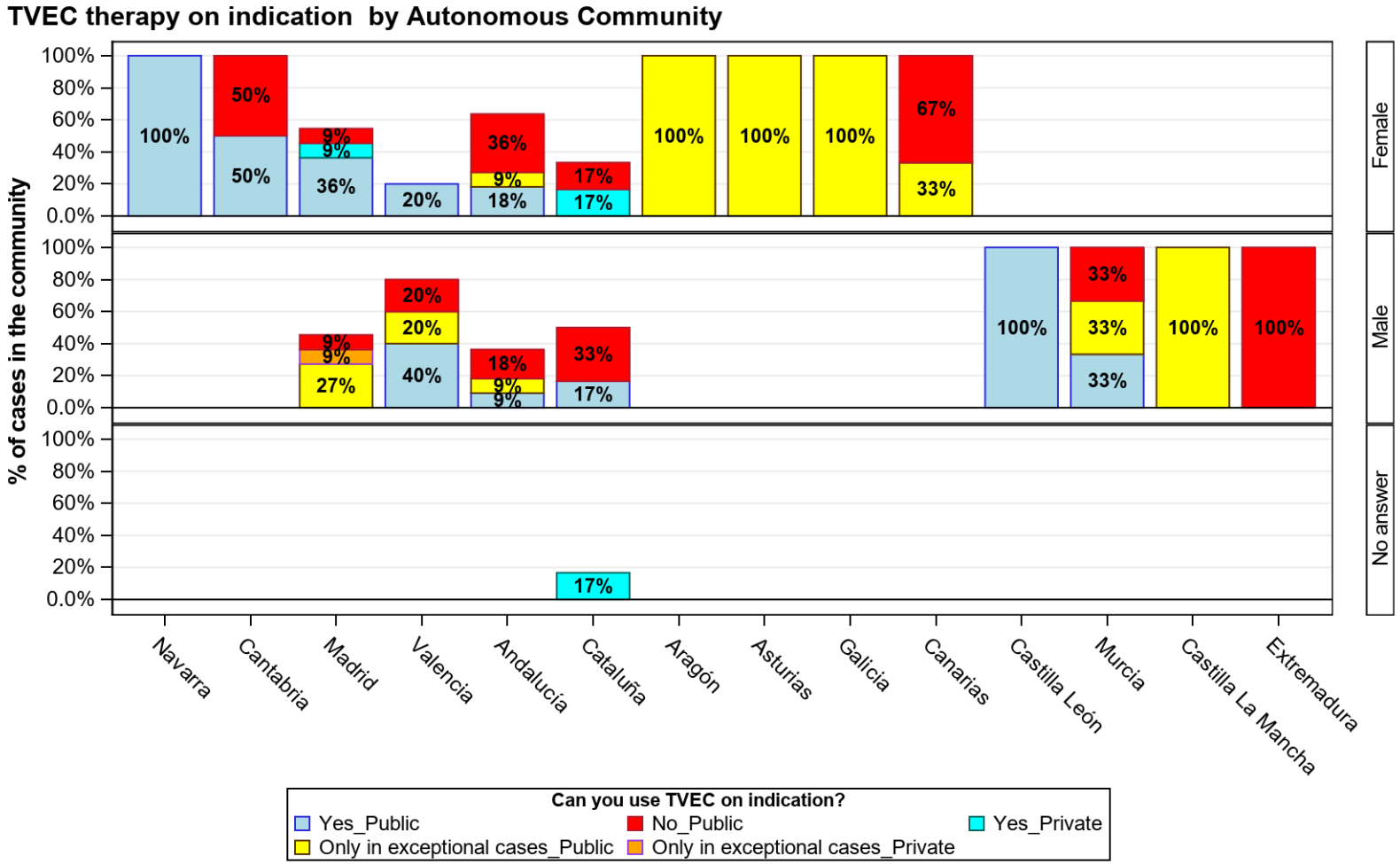
Supplemental Figure 2.28 Neoadjuvant therapy for patients with locoregional disease at relapse by physician´s sex and Autonomous Community



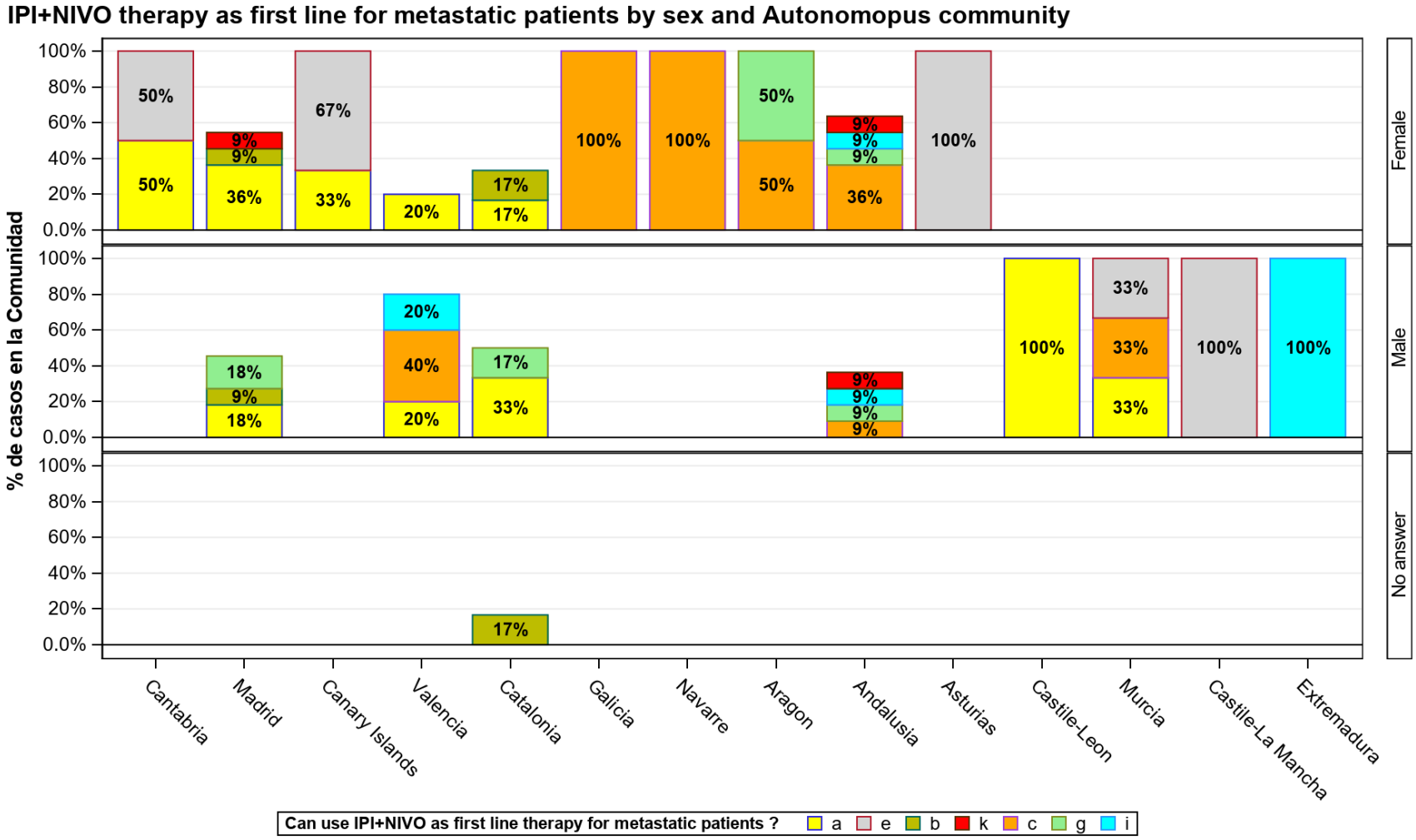
Supplemental Figure 2.29 Neoadjuvant therapy for patients with surgical oligometastatic disease by physician´s sex and Autonomous Community



Supplemental Figure 2.30 TVEC therapy on indication by physician´s sex and Autonomous community

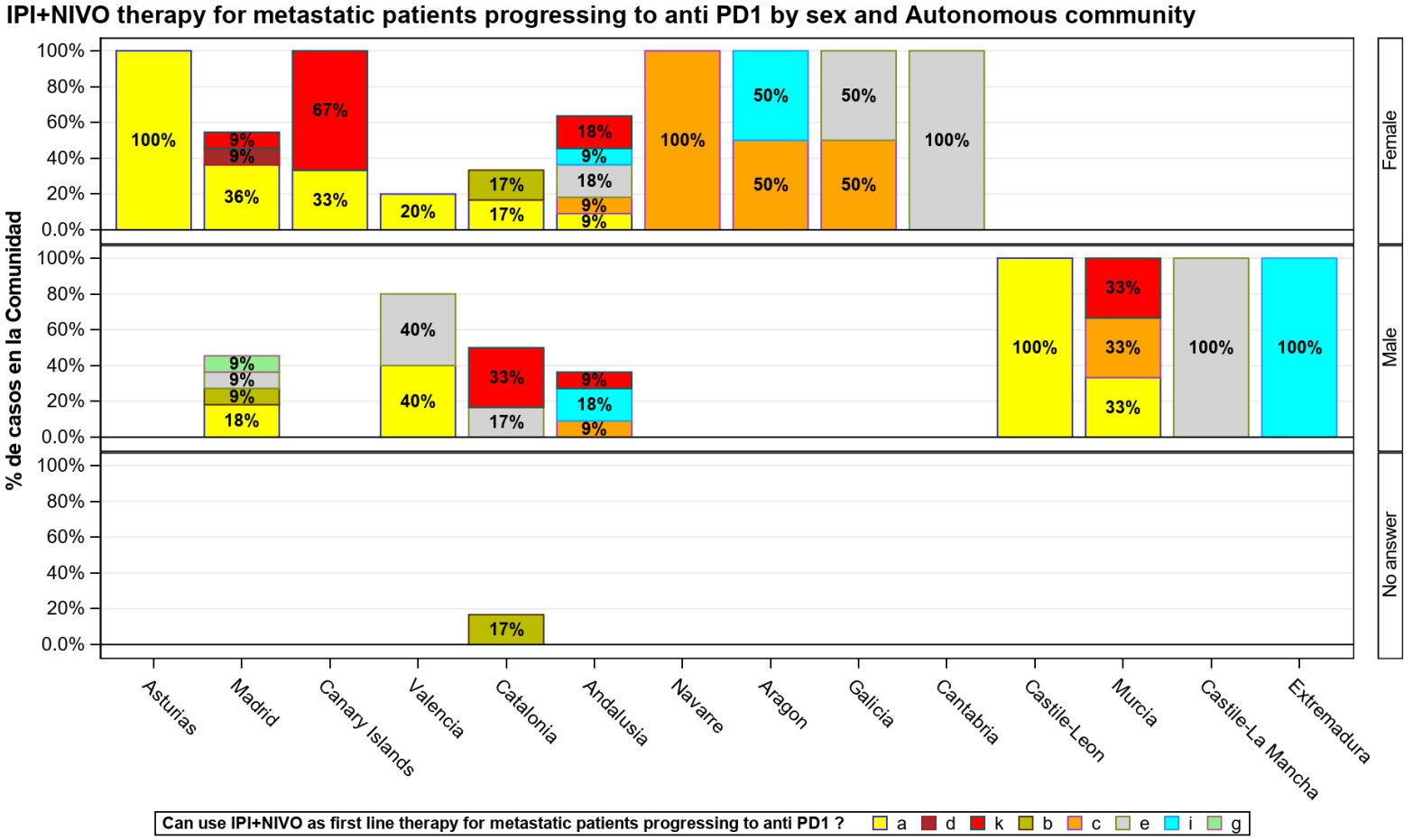


Supplemental Figure 2.31 IPI+NIVO therapy as first line for metastatic patients by physician´s sex and Autonomous community.



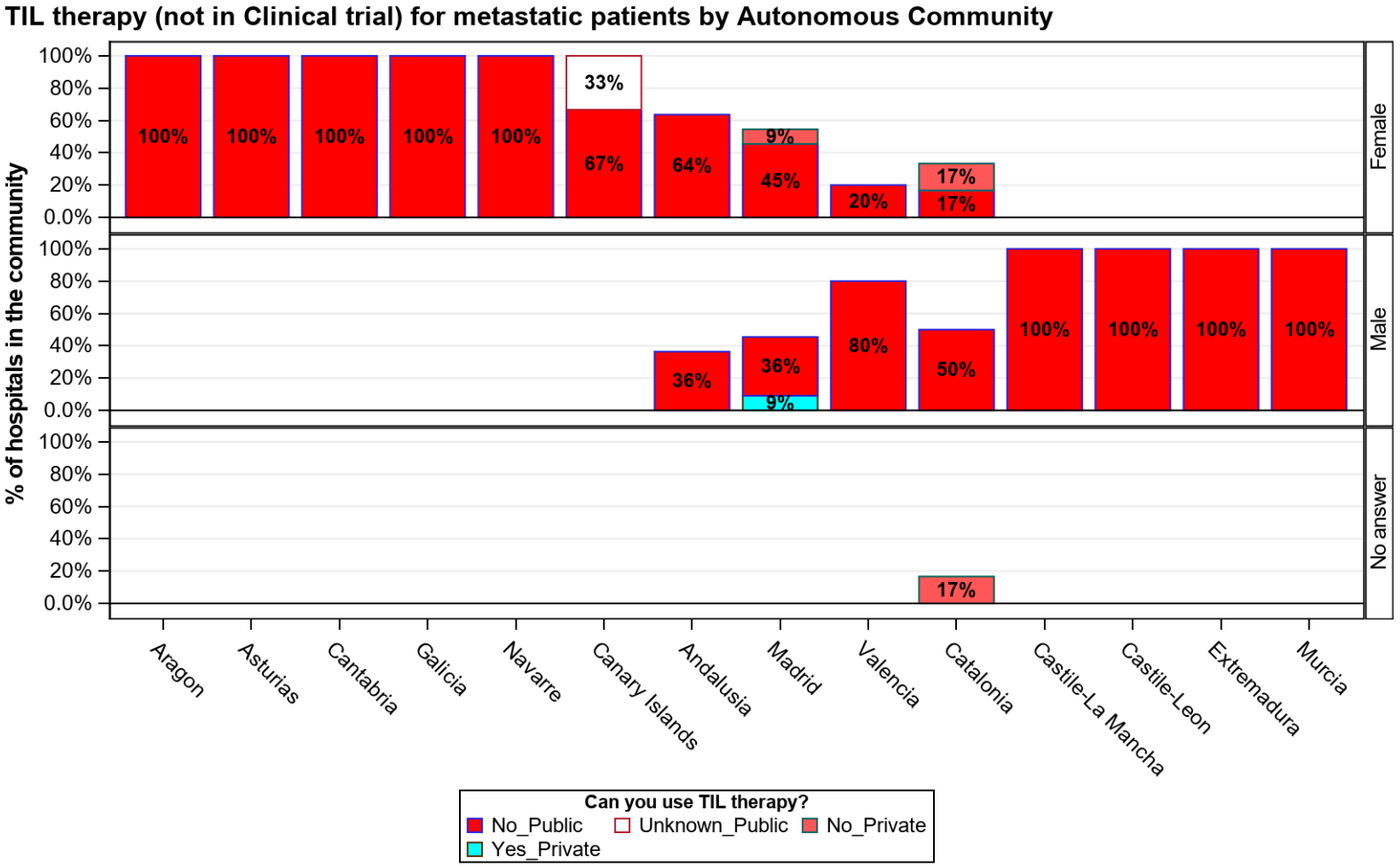
a=All appropiate cases_pu; b=All appropiate cases_pr; c=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pu; d=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pr; e=Only cases evaluated by the Institutional Review Board_pu f=Only cases evaluated by the Institutional Review Board_pr g=I g=Only for patients with brain metastasis and/or uveal melanoma_pu;h=Only for patients with brain metastasis and/or uveal melanoma_pr;i=Only if PDL1 <1%_pu; j=Only if PDL1 <1%_pr;k=No_pu;l=No_pr

Supplemental Figure 2.32 IPI+NIVO therapy for metastatic patients progressing to anti PD1 by physician´s sex and Autonomous community



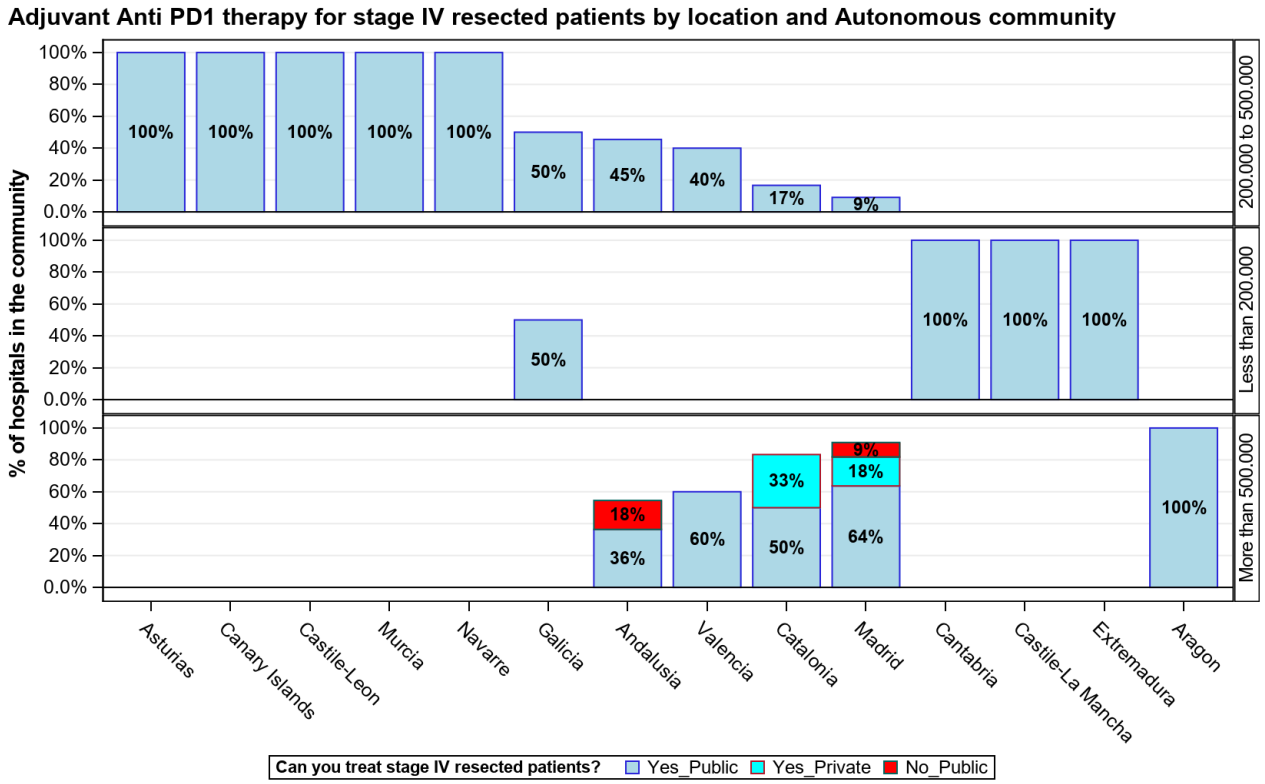
a=All appropiate cases_pu; b=All appropiate cases_pr; c=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pu; d=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pr; e=Only cases evaluated by the Institutional Review Board_pu f=Only cases evaluated by the Institutional Review Board_pr g=I g=Only for patients with brain metastasis and/or uveal melanoma_pu;h=Only for patients with brain metastasis and/or uveal melanoma_pr;i=Only if PDL1 <1%_pu; j=Only if PDL1 <1%_pr;k=No_pu;l=No_pr

Supplemental Figure 2.33 TIL therapy for metastatic patients by physician´s sex and Autonomous community

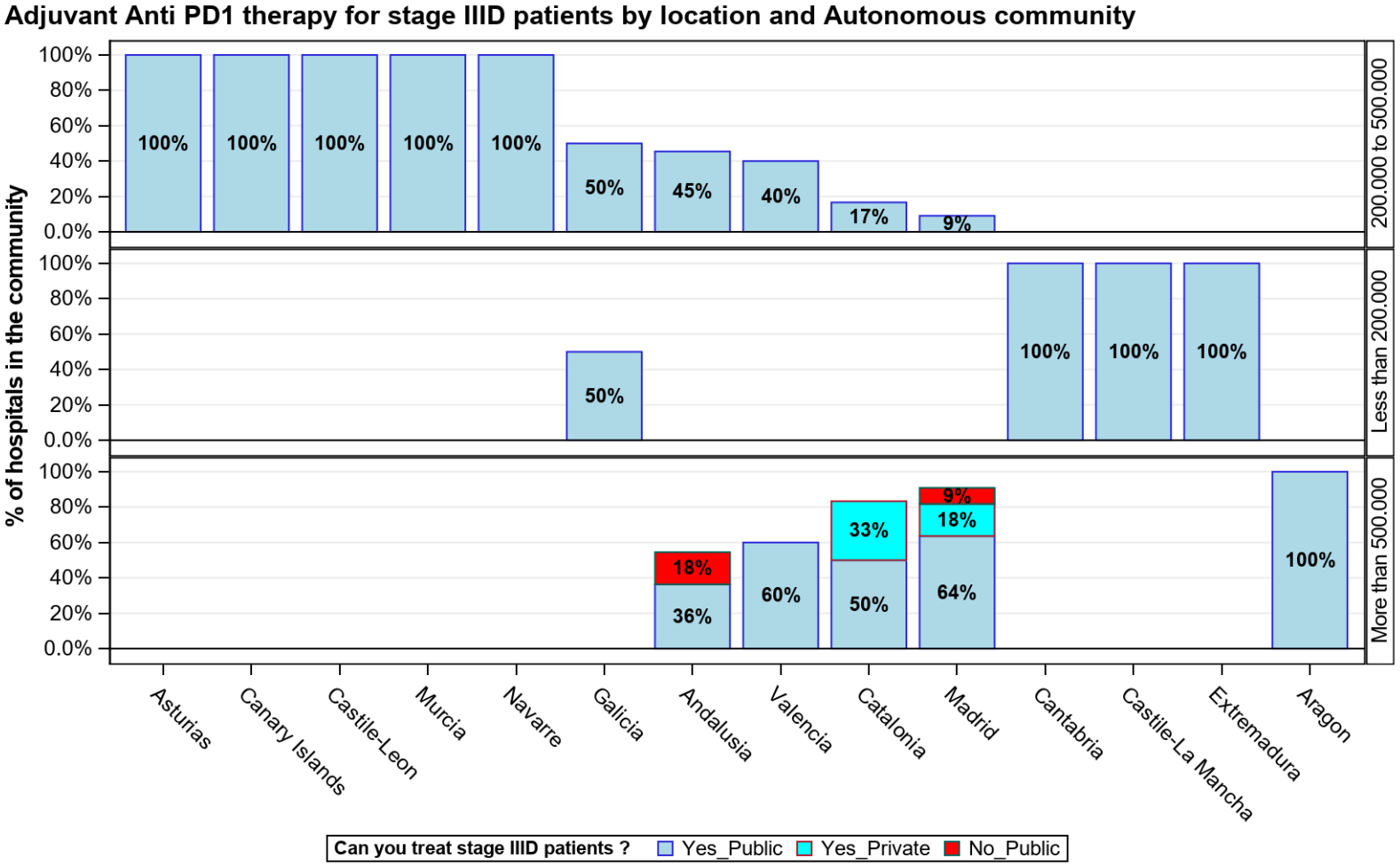


Supplemental Figure 3. Distribution of drug access according to the size of the area of influence of the hospital. Hospitals are grouped based on the size of the area of influence: <200.000; 200.000-500.000; >500.000 inhabitants.

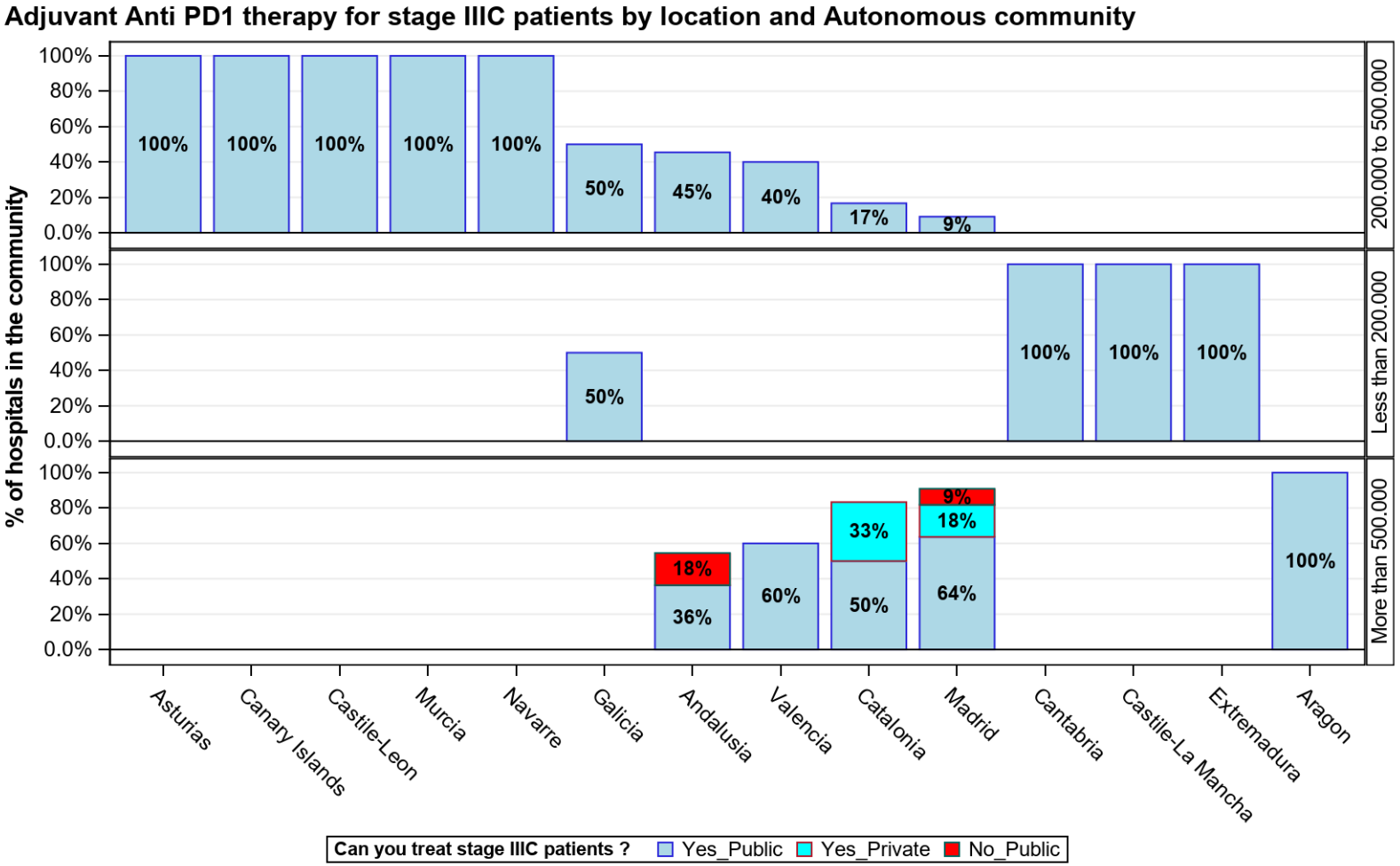
Supplemental Figure 3.34 Adjuvant Anti PD1 therapy for stage IV resected patients by number of inhabitants of the area of influence and Autonomous community



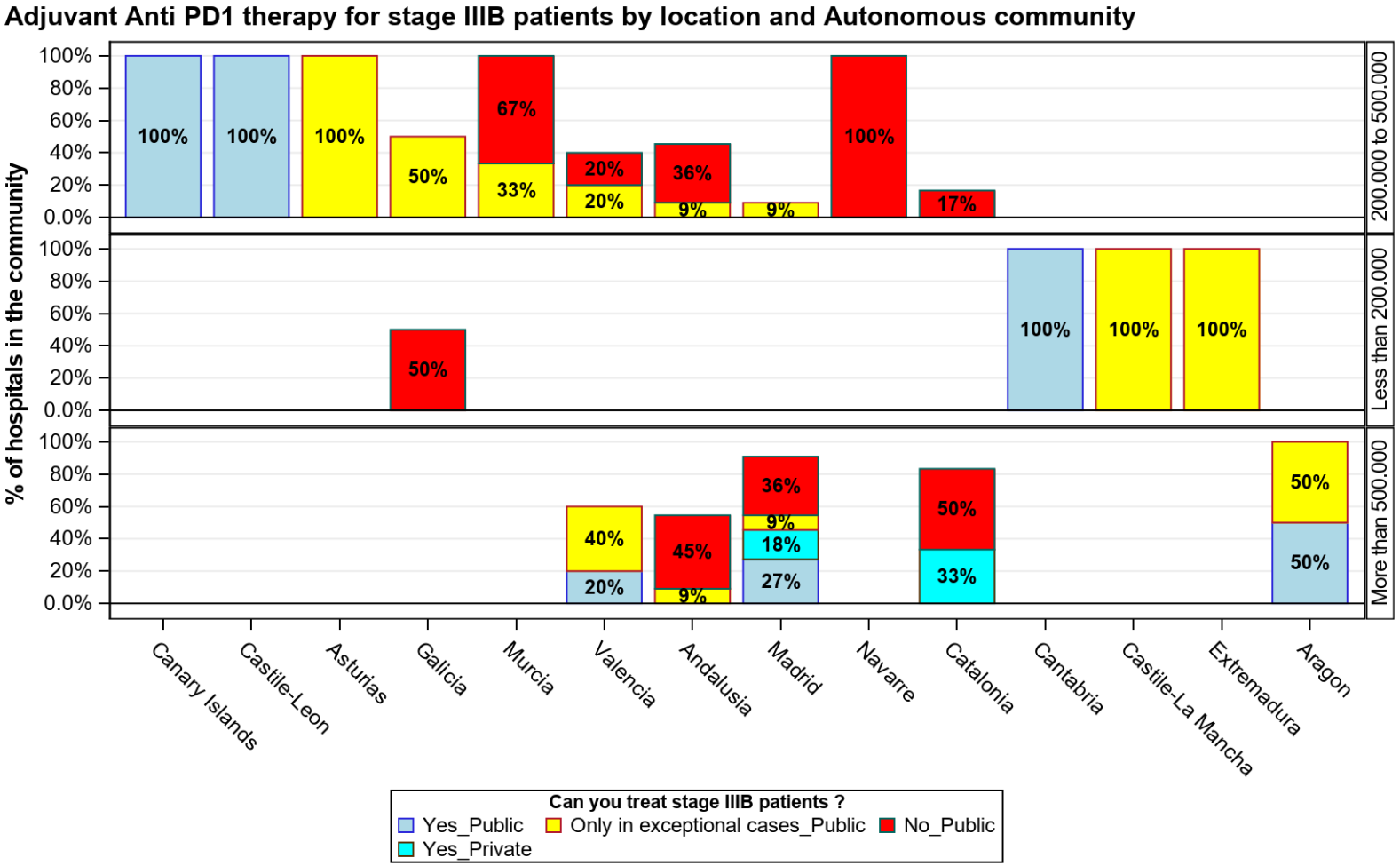
Supplemental Figure 3.2. Adjuvant Anti PD1 therapy for stage IIID patients by number of inhabitants of the area of influence and Autonomous community



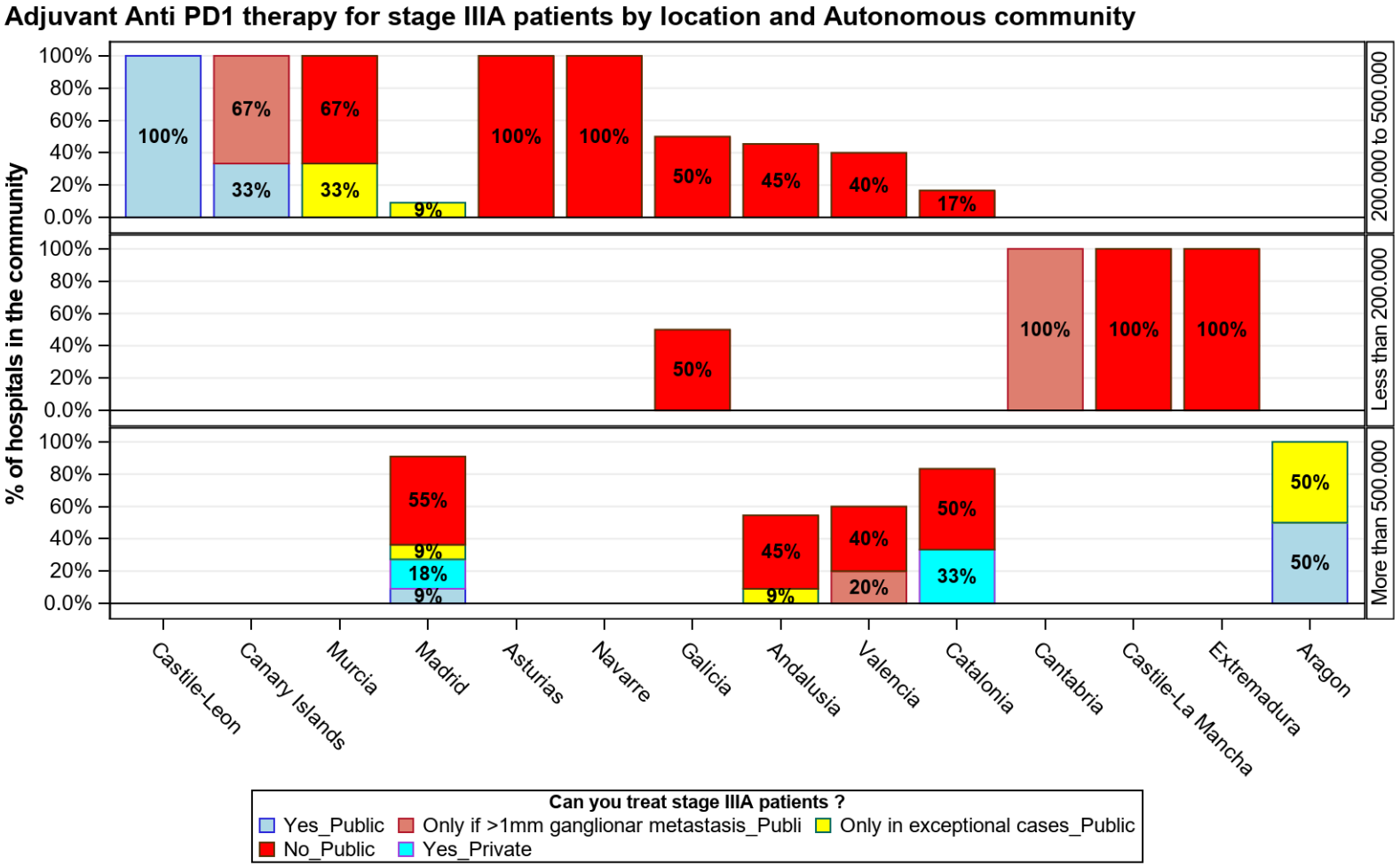
Supplemental Figure 3.35 Adjuvant Anti PD1 therapy for stage IIIC patients by number of inhabitants of the area of influence and Autonomous community



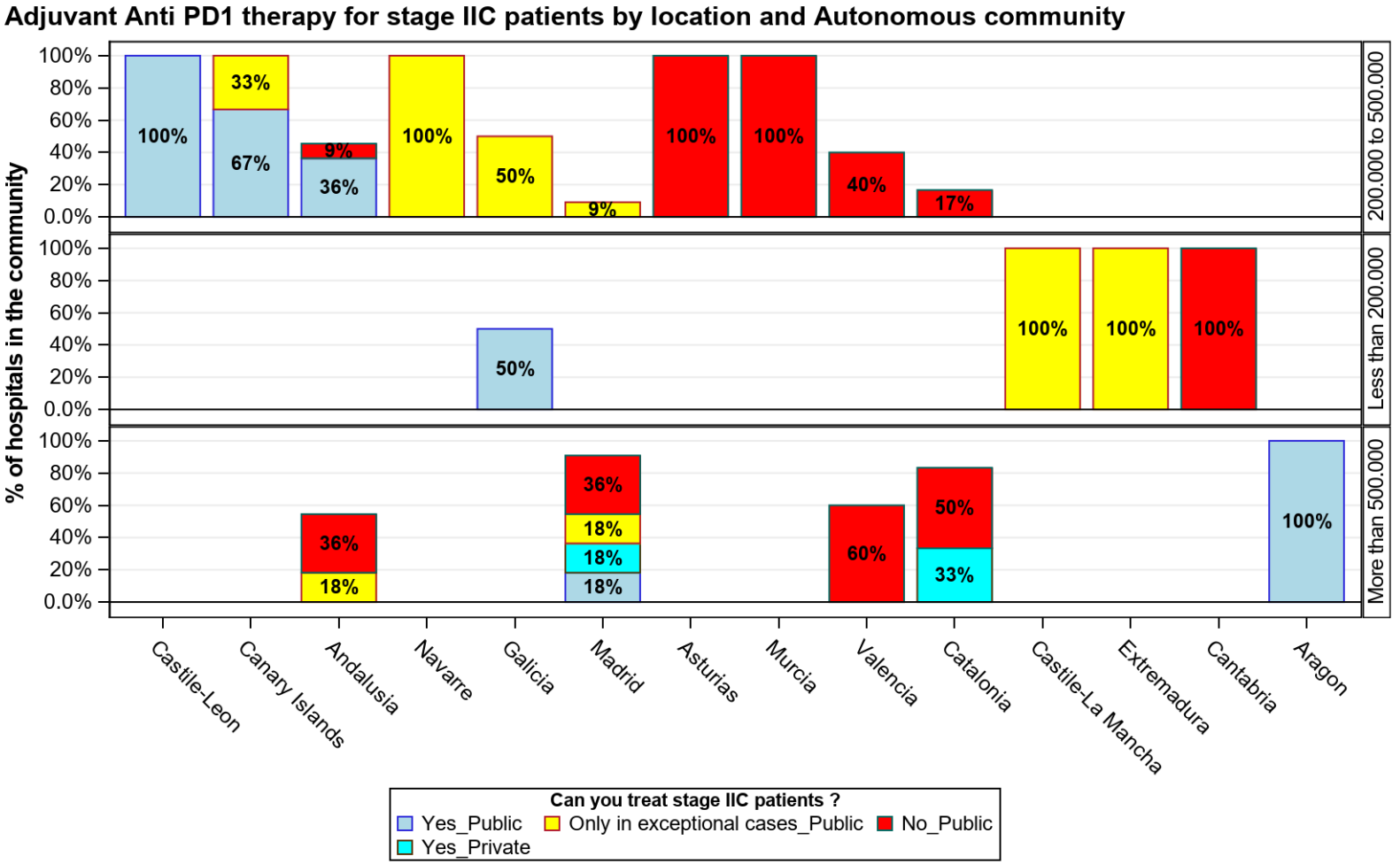
Supplemental Figure 3.36 Adjuvant Anti PD1 therapy for stage IIIB patients by number of inhabitants of the area of influence and Autonomous community



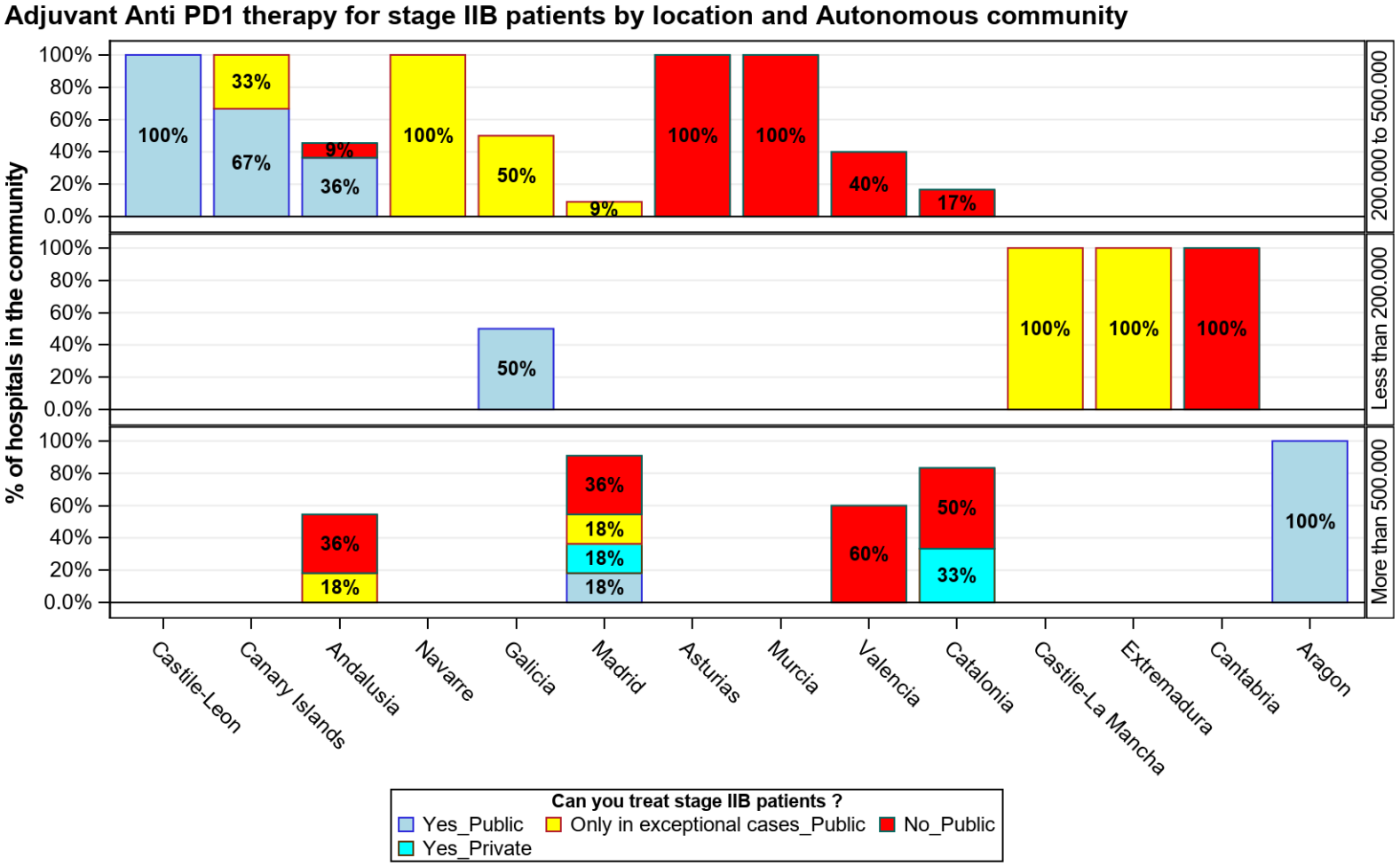
Supplemental Figure 3.37 Adjuvant Anti PD1 therapy for stage IIIA patients by number of inhabitants of the area of influence and Autonomous community



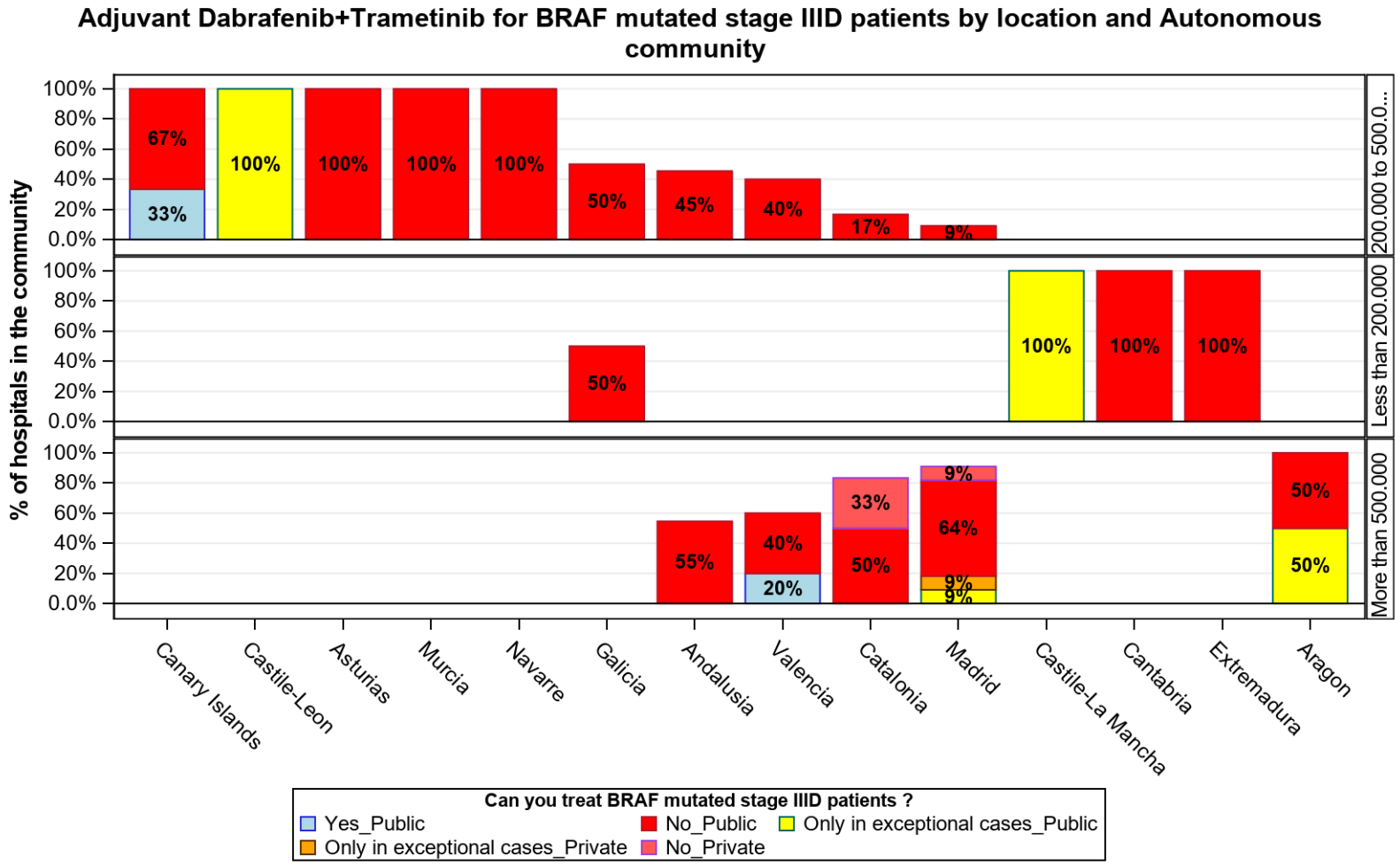
Supplemental Figure 3.38 Adjuvant Anti PD1 therapy for stage IIC patients by number of inhabitants of the area of influence and Autonomous community



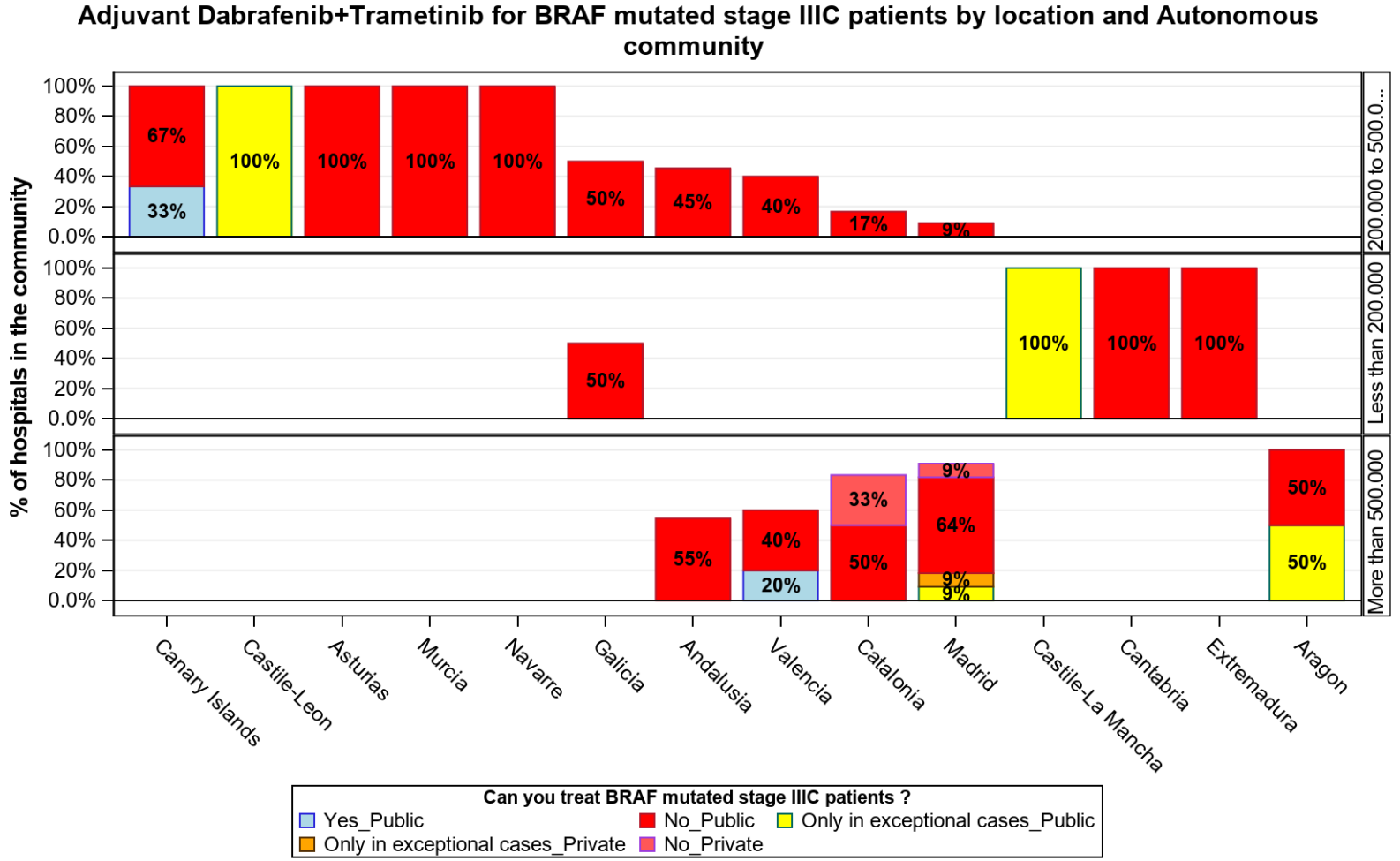
Supplemental Figure 3.39 Adjuvant Anti PD1 therapy for stage IIB patients by number of inhabitants of the area of influence and Autonomous community



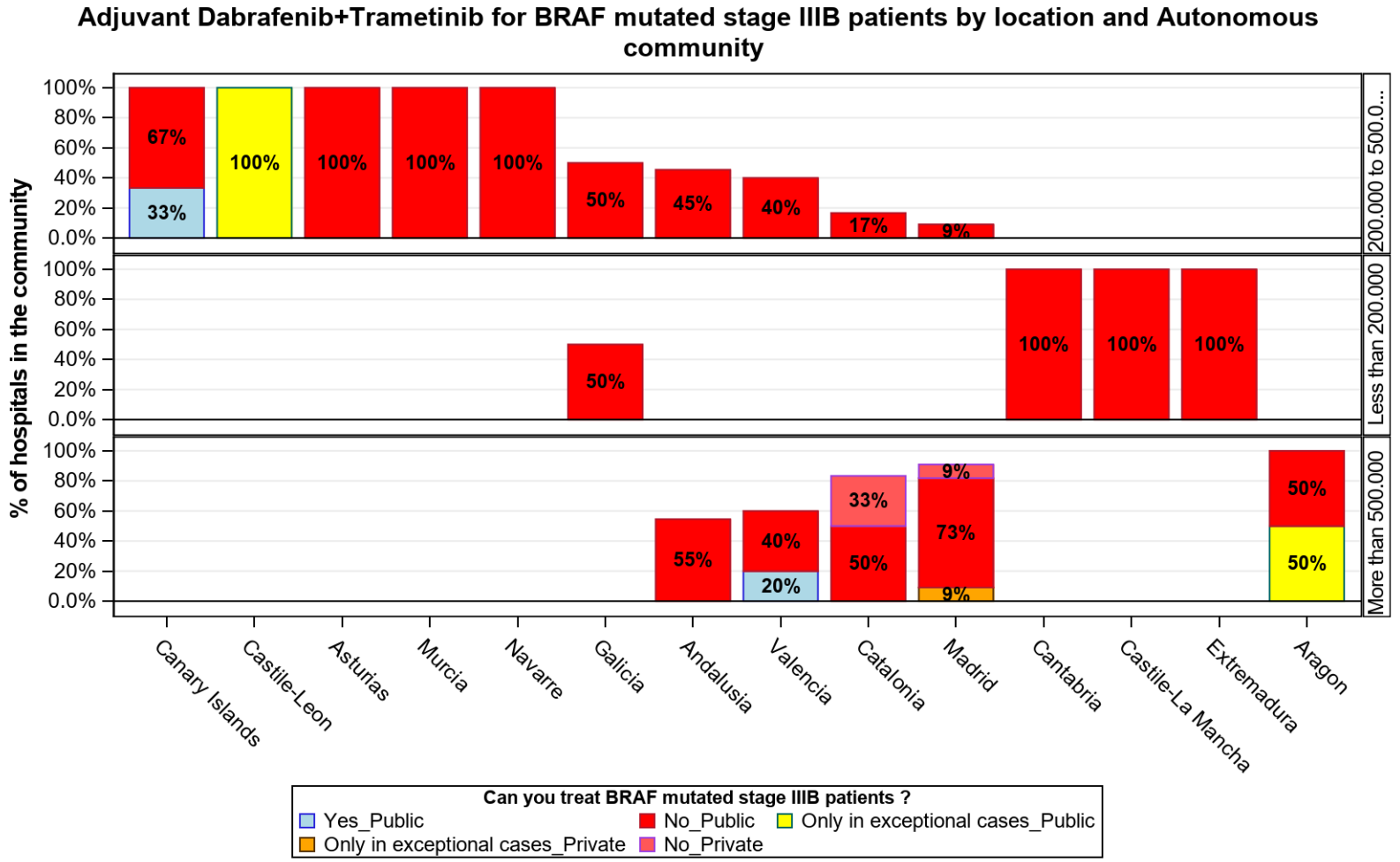
Supplemental Figure 3.40 Adjuvant Dabrafenib+Trametinib for BRAF mutated stage IIID patients by number of inhabitants of the area of influence and Autonomous community



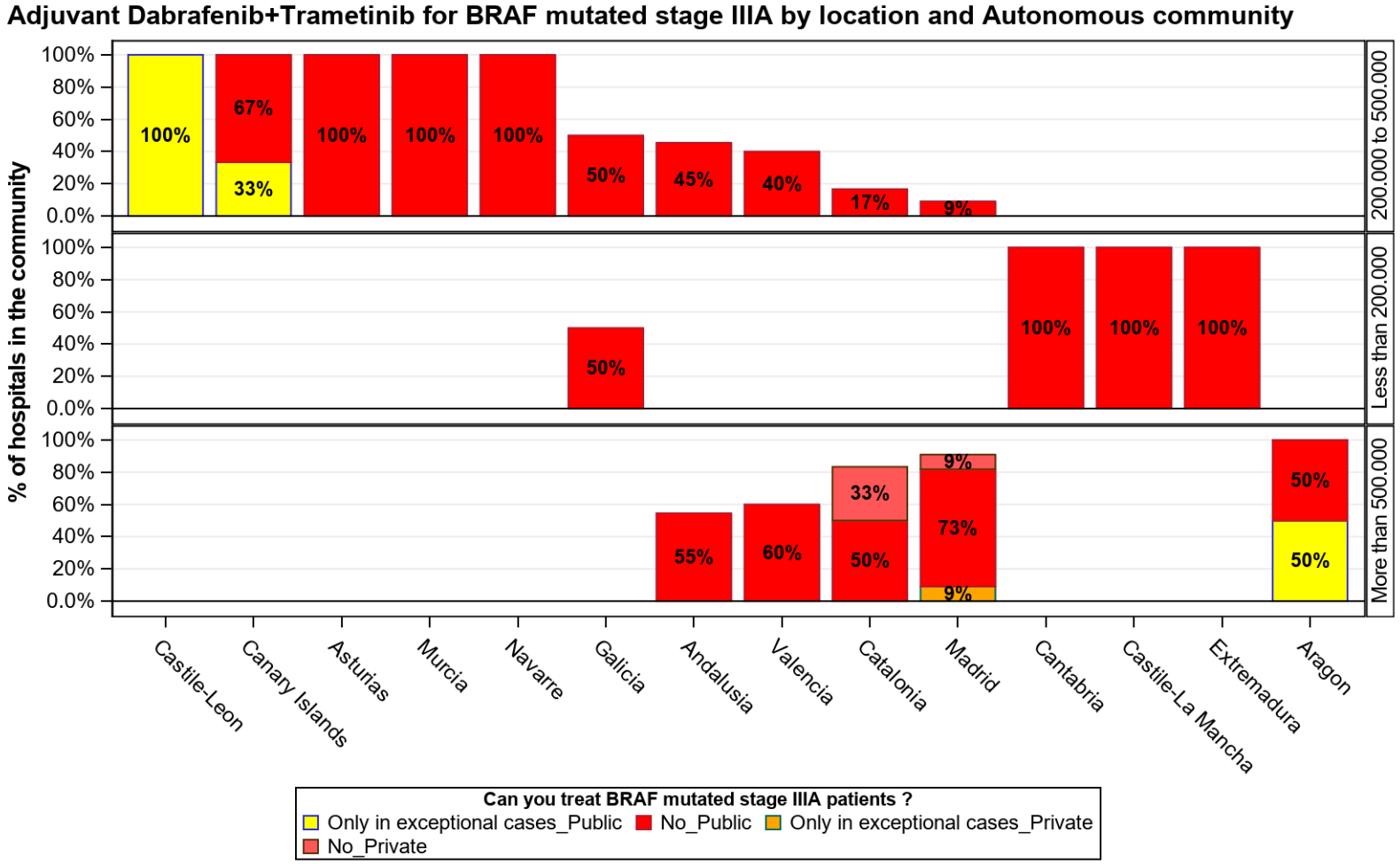
Supplemental Figure 3.41 Adjuvant Dabrafenib+Trametinib for BRAF mutated stage IIIC patients by number of inhabitants of the area of influence and Autonomous community



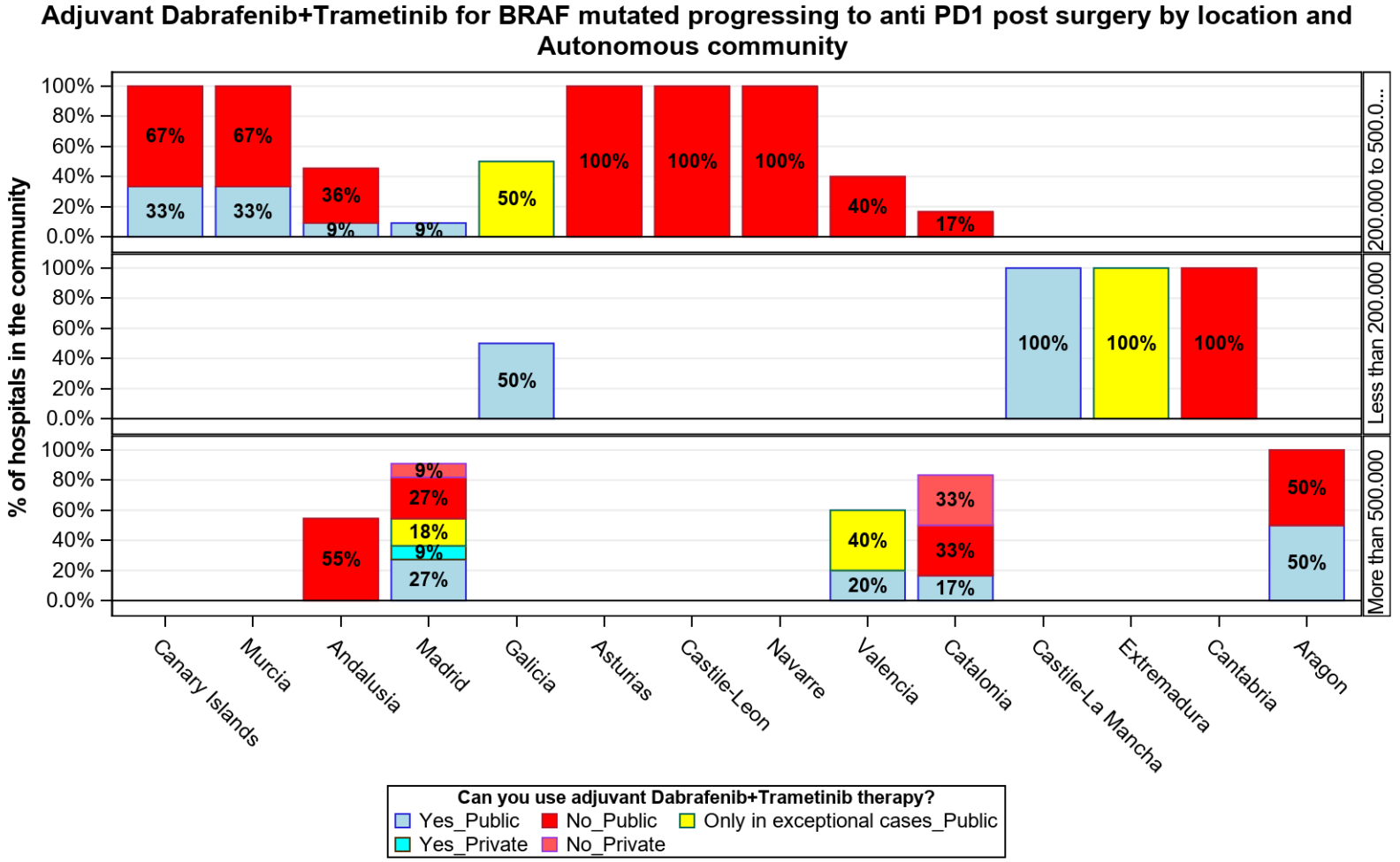
Supplemental Figure 3.42 Adjuvant Dabrafenib+Trametinib for BRAF mutated stage IIIB patients by number of inhabitants of the area of influence and Autonomous community



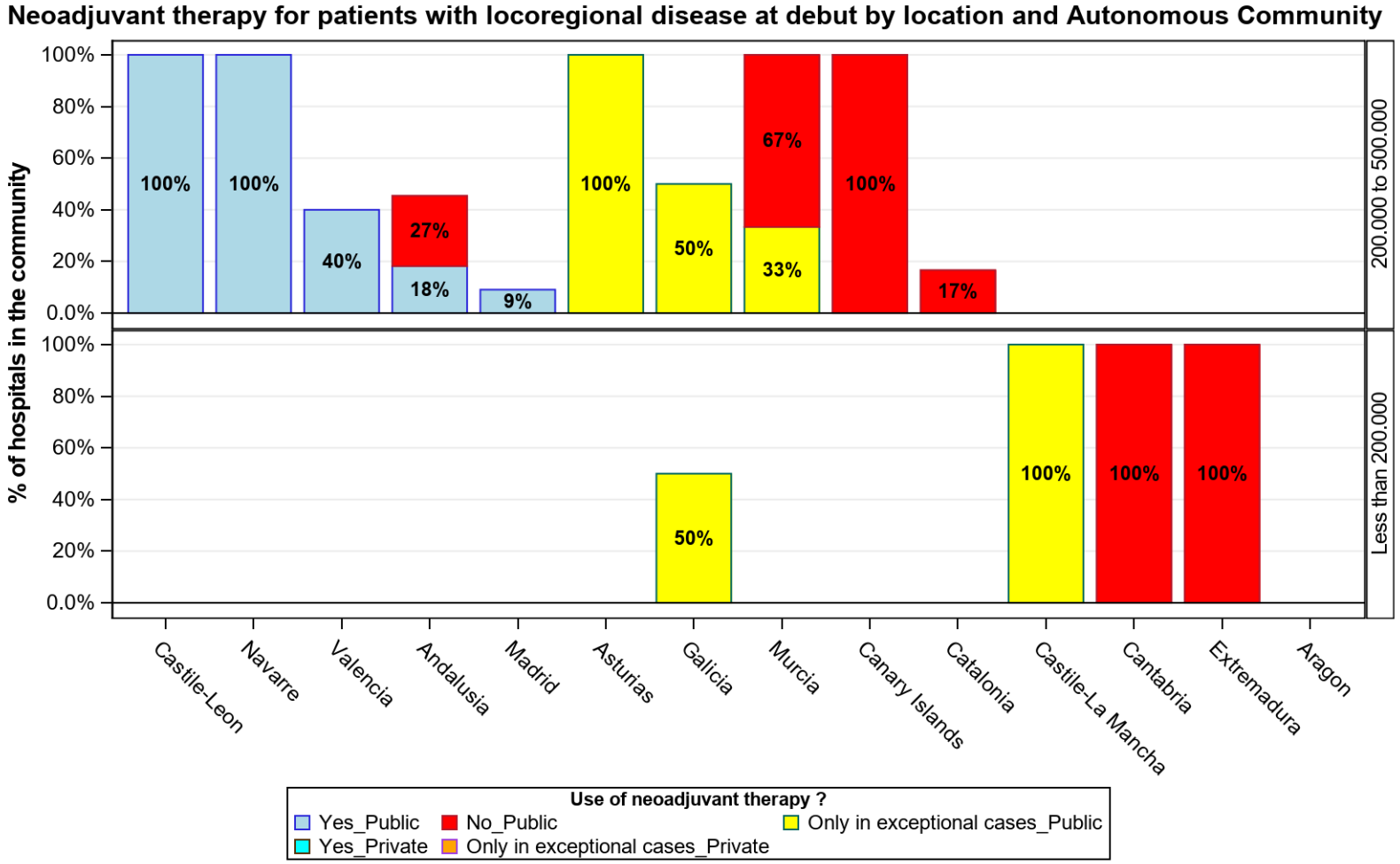
Supplemental Figure 3.43 Adjuvant Dabrafenib+Trametinib for BRAF mutated stage IIIA by number of inhabitants of the area of influence and Autonomous community



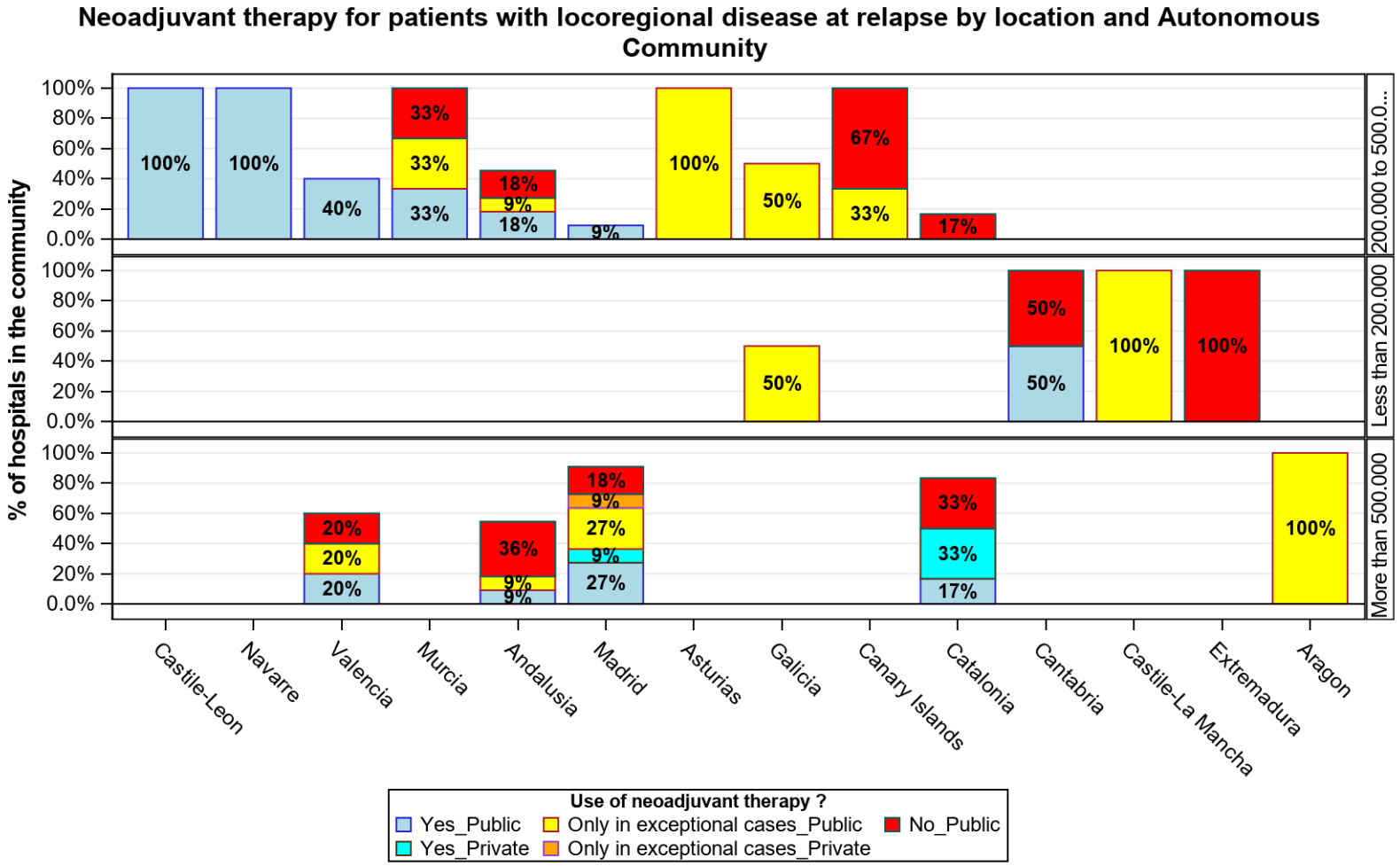
Supplemental Figure 3.44 Adjuvant Dabrafenib+Trametinib for BRAF mutated progressing to anti PD1 post-surgery by number of inhabitants of the area of influence and Autonom



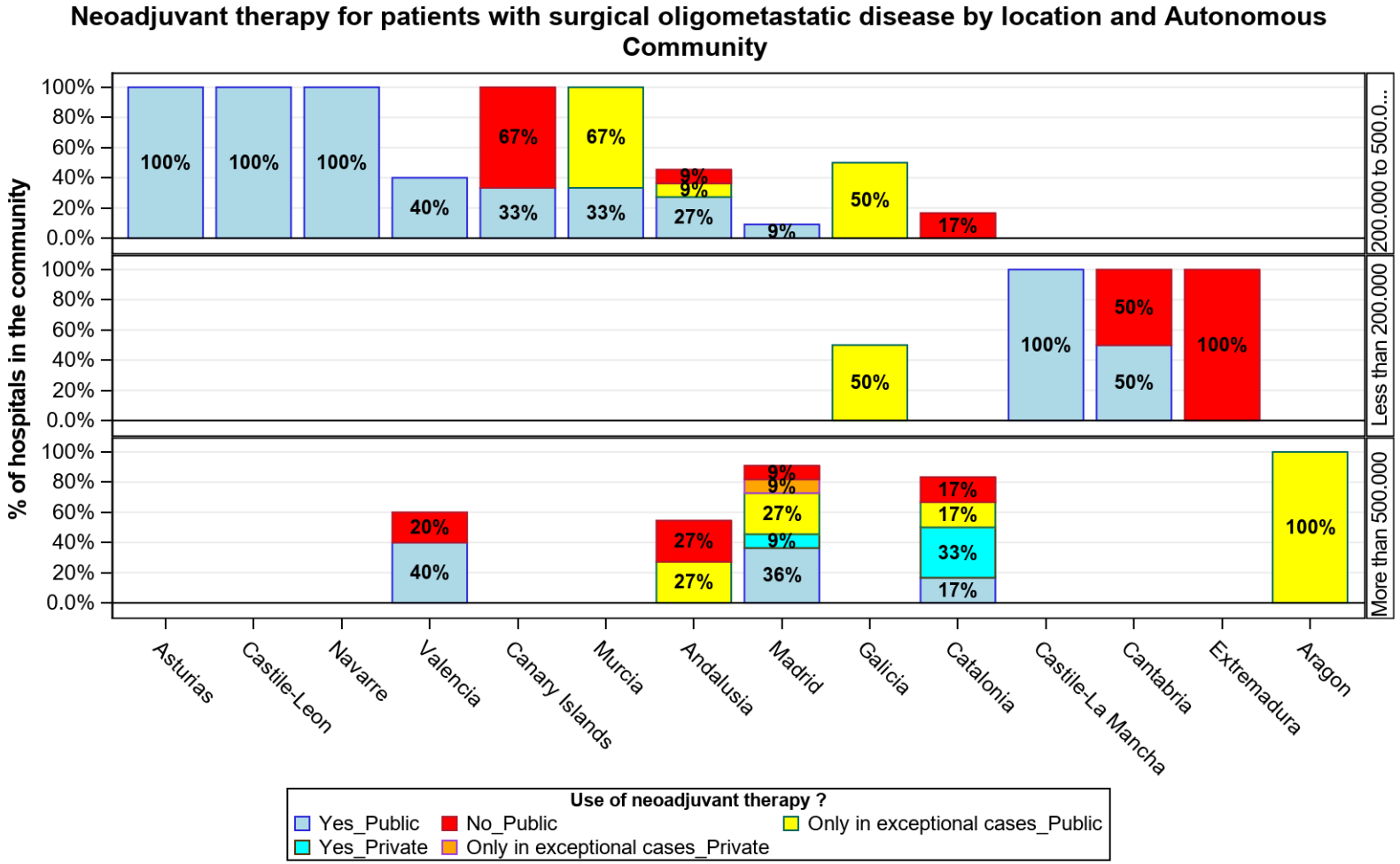
Supplemental Figure 3.45 Neoadjuvant therapy for patients with locoregional disease at debut by number of inhabitants of the area of influence and Autonomous Community



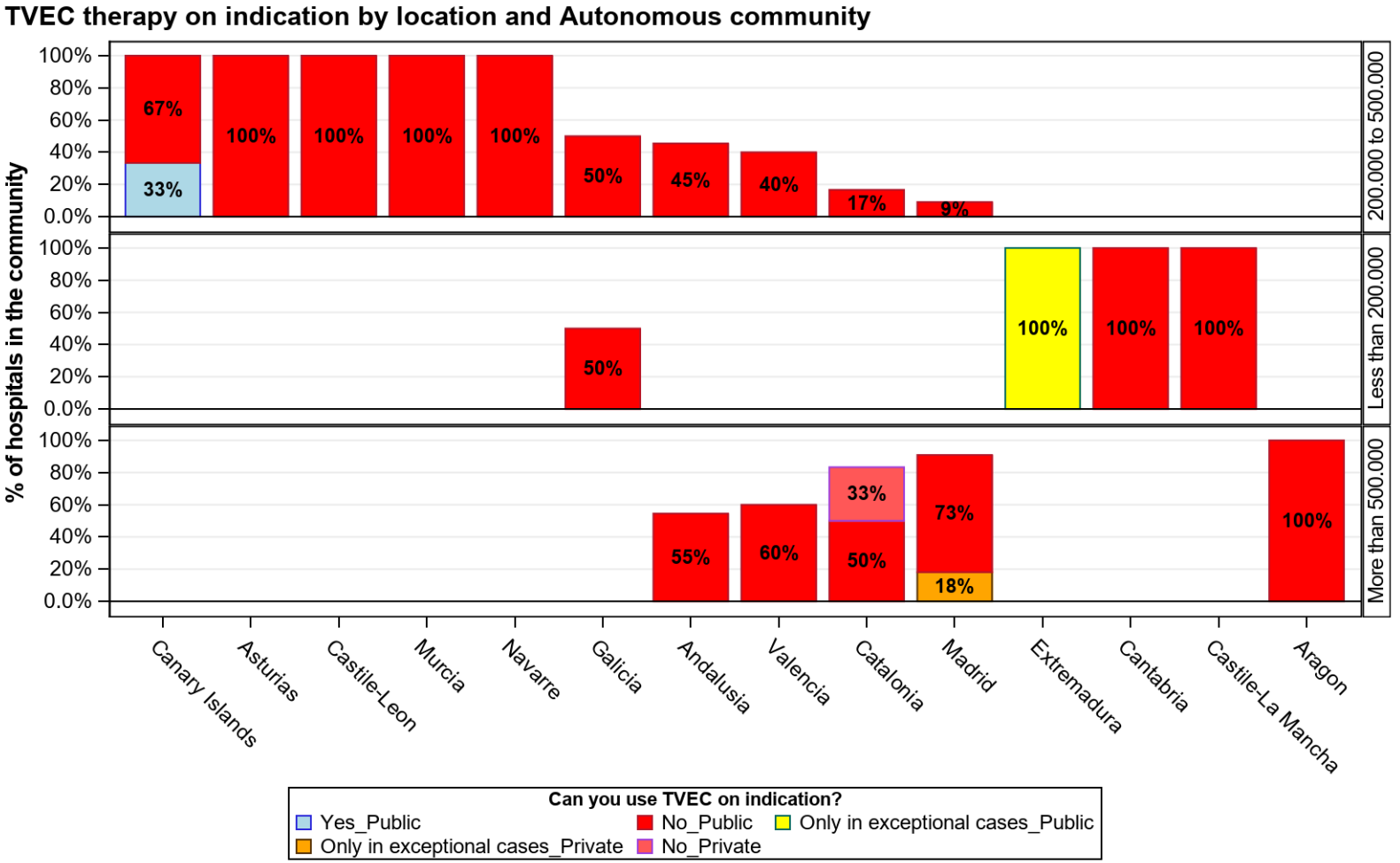
Supplemental Figure 3.46 Neoadjuvant therapy for patients with locoregional disease at relapse by number of inhabitants of the area of influence and Autonomous Community



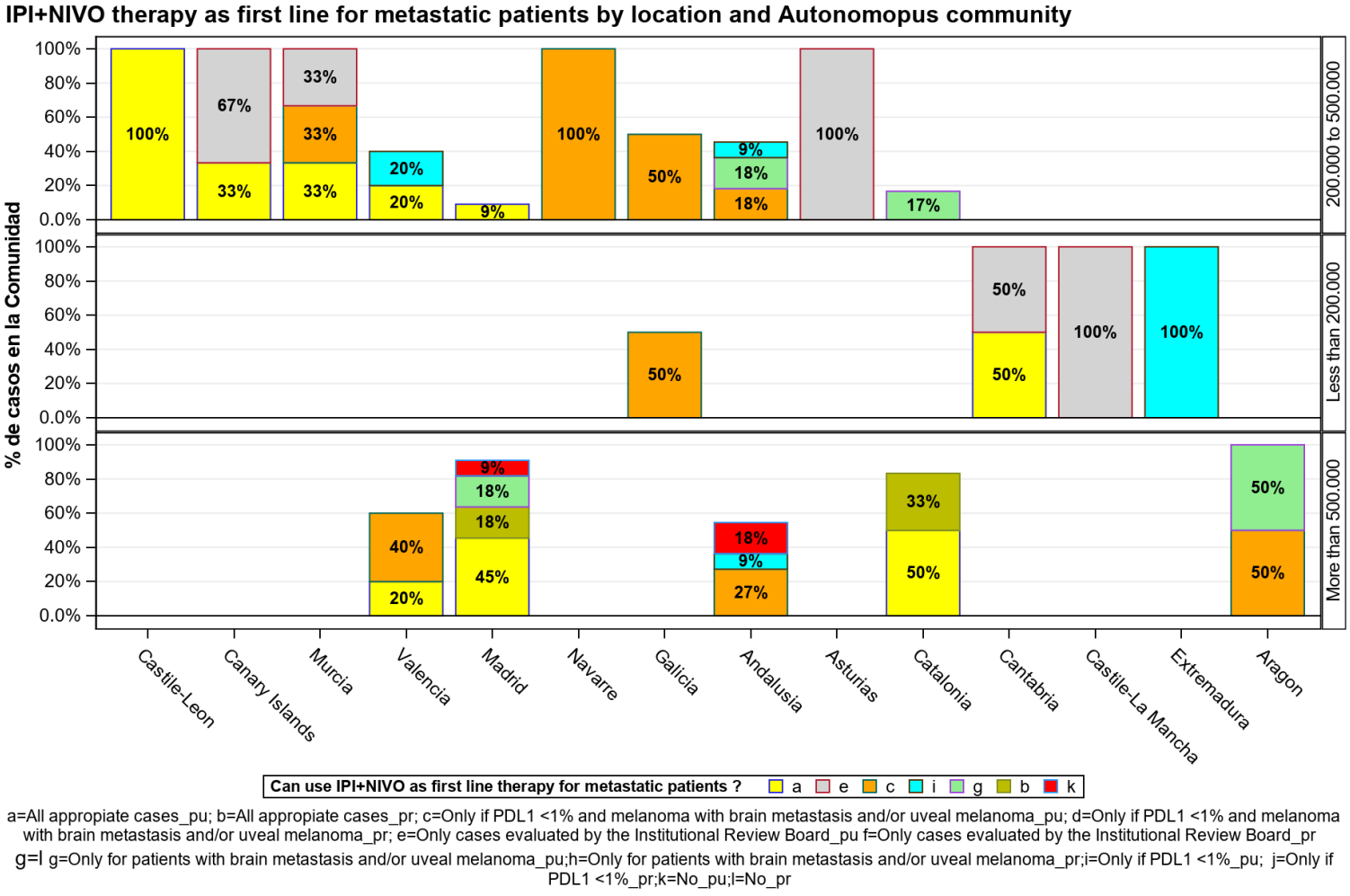
Supplemental Figure 3.15 Neoadjuvant therapy for patients with surgical oligometastatic disease by number of inhabitants of the area of influence and Autonomous community



Supplemental Figure 3.47 TVEC therapy on indication by number of inhabitants of the area of influence and Autonomous community

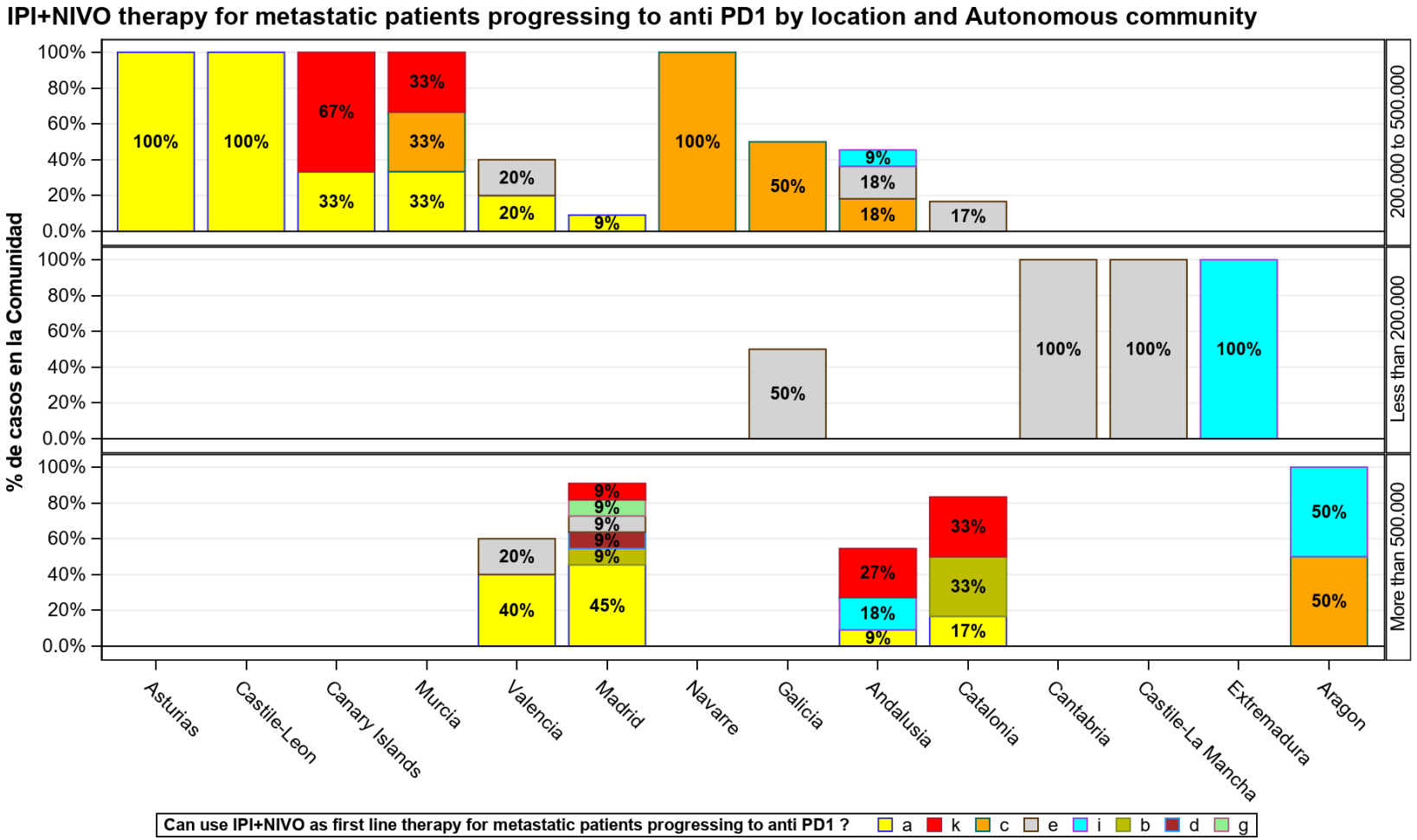


Supplemental Figure 3.48 IPI+NIVO therapy as first line for metastatic patients by number of inhabitants of the area of influence and Autonomopus community



a=All appropiate cases_pu; b=All appropiate cases_pr; c=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pu; d=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pr; e=Only cases evaluated by the Institutional Review Board_pu f=Only cases evaluated by the Institutional Review Board_pr g=I g=Only for patients with brain metastasis and/or uveal melanoma_pu;h=Only for patients with brain metastasis and/or uveal melanoma_pr;i=Only if PDL1 <1%_pu; j=Only if PDL1 <1%_pr;k=No_pu;l=No_pr

Supplemental Figure 3.49 PI+NIVO therapy for metastatic patients progressing to anti PD1 by number of inhabitants of the area of influence and Autonomous community



a=All appropiate cases_pu; b=All appropiate cases_pr; c=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pu; d=Only if PDL1 <1% and melanoma with brain metastasis and/or uveal melanoma_pr; e=Only cases evaluated by the Institutional Review Board_pu f=Only cases evaluated by the Institutional Review Board_pr g=I g=Only for patients with brain metastasis and/or uveal melanoma_pu;h=Only for patients with brain metastasis and/or uveal melanoma_pr;i=Only if PDL1 <1%_pu; j=Only if PDL1 <1%_pr;k=No_pu;l=No_pr

Figure Error! No text of specified style in document.**-50 TIL therapy (not in Clinical trial) for metastatic patients by location and Autonomous Community**