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European Society for Medical Oncology

European consortium study on the availability of anti-neoplastic medicines

Alexandru ENIU, MD, PhD

Chair, Emerging Countries Committee

Department of Breast Tumors

Head, Day Hospital Unit

Cancer Institute Ion Chiricuţă

Cluj-Napoca, Romania

Nathan I Cherny

Norman Levan Chair in Humanistic Medicine

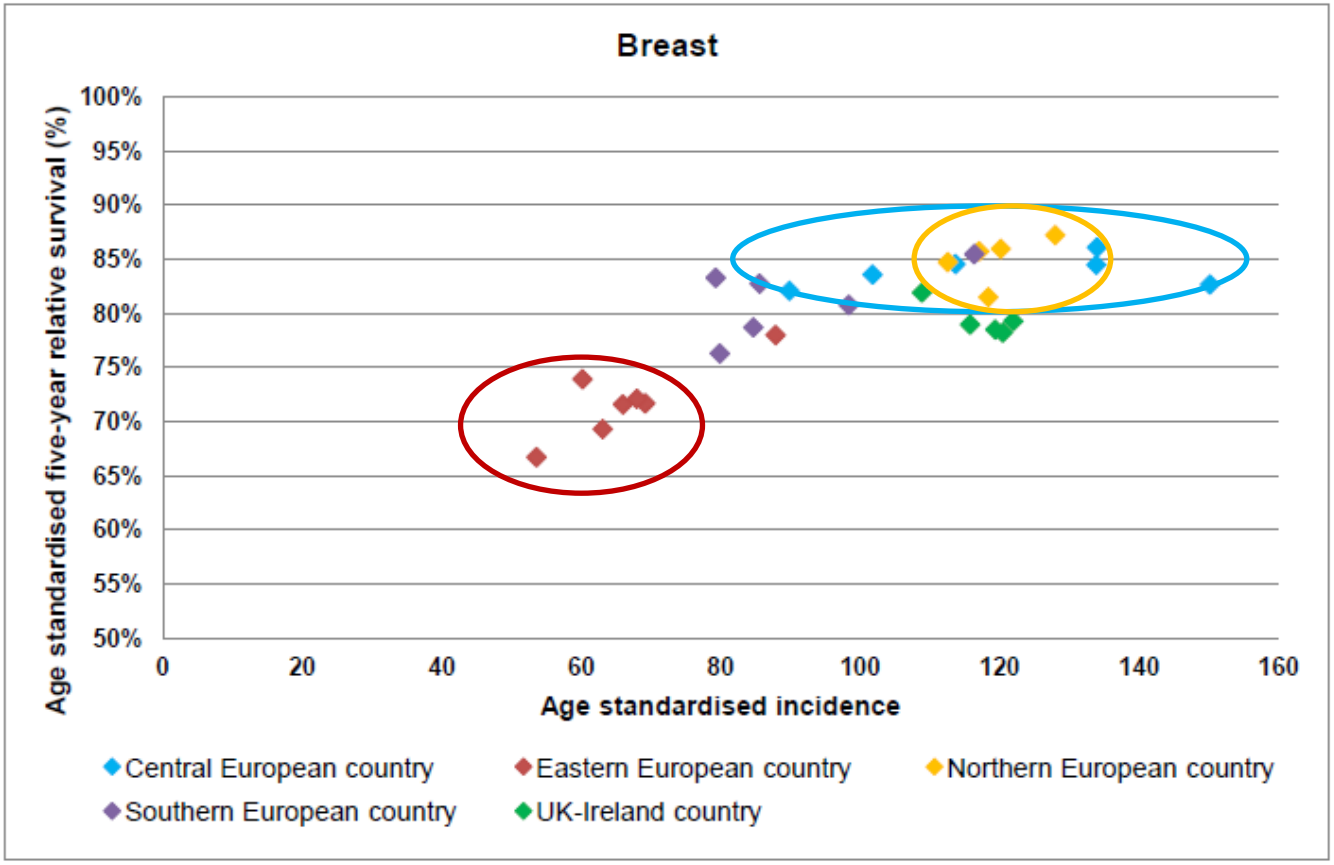
Dept Oncology

Unit Head: Cancer pain and palliative Medicine

Shaare Zedek Medical Center

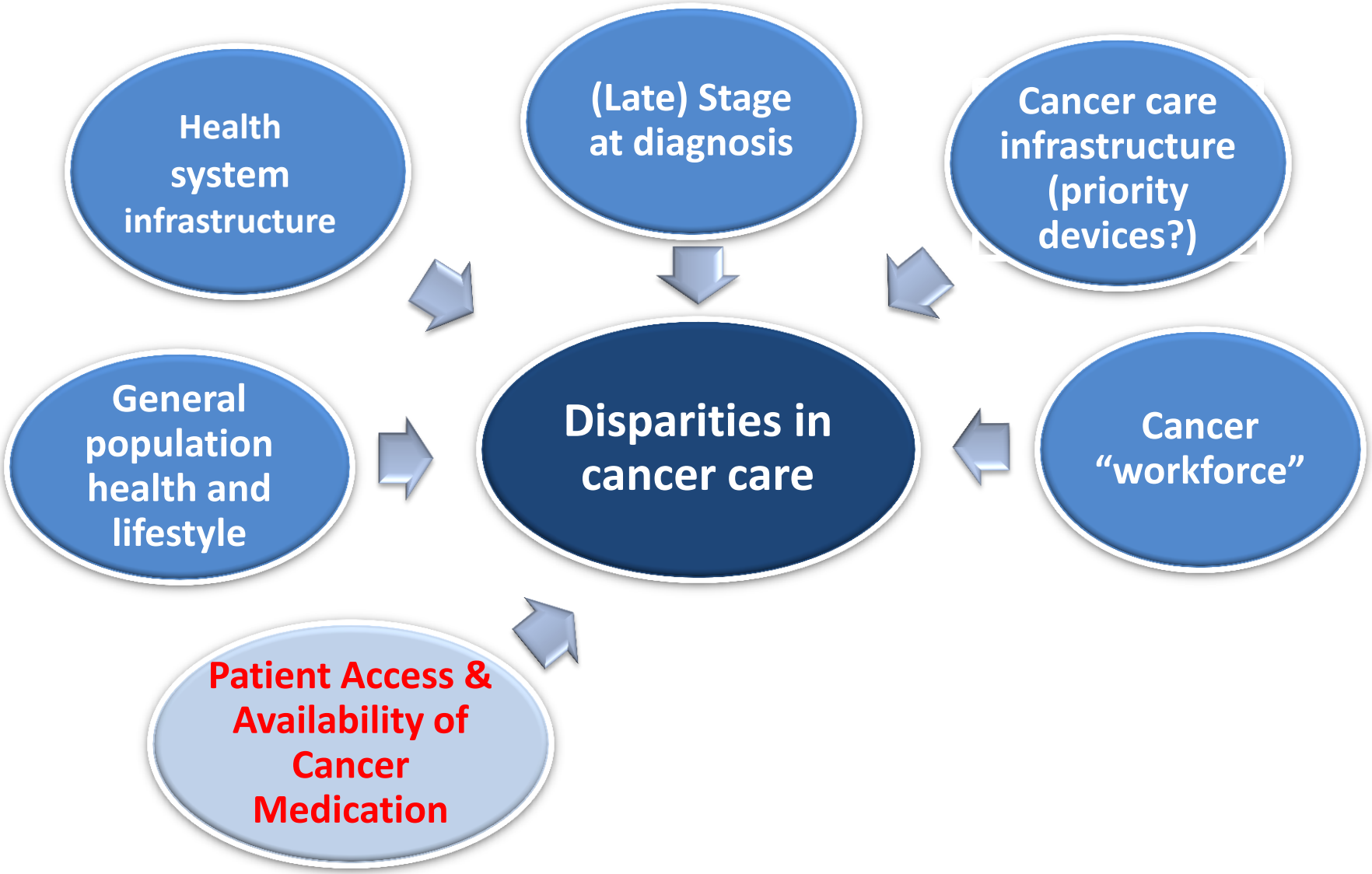
Disparities in cancer outcomes (survival) across Europe

Figures 2: Age-standardised incidence (rates per 100,000 person-year) vs. age-standardised five-year relative survival (%) for cancers of breast (women), prostate, skin melanoma by European region. Period of diagnosis 2000-2007. Countries represented by dots.



De Angelis, et al: Cancer survival in Europe 1999–2007 by country and age: EUROCARE-5 Lancet Oncol, 2013

Factors accounting for cancer outcomes disparities



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ESMO Anti-Neoplastic Medicines Survey

Perception survey to **map access to cancer medicines**, including WHO Essential Medicines, reporting on:

- **Approval status (yes/no) across Europe**
  - Informative for new drugs
- **Reimbursement (yes/no)**
  - Highlight differences in cancer policies
  - Residual (out of pocket) cost to patients
  - Delays in access due to special authorization
- **Actual availability**
  - Drug shortage for old drugs
  - Unavailability in the pharmacy (parallel export) for expensive drugs

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Coordinating & Collaborating Partners

- **Coordinating Organization**
  - ESMO

- **Collaborating Project Partners**

1. World Health Organization (WHO), Geneva, Switzerland
2. Union for International Cancer Control (UICC), Geneva, Switzerland
3. Institute of Cancer Policy, Kings College, London, UK
4. European Society of Oncology Pharmacists

- Breast Cancer
- Lung Cancer
- Colorectal Cancer
- Prostate Cancer
- Ovarian Cancer
- Sarcoma
- Pancreatic cancer
- Germ cell Tumors
- Renal cell Cancer
- GIST
- Urothelial Cancers
- Gastric and esophageal cancer
- Melanoma

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Example of form :Metastatic Breast Cancer

BREAST CANCER (METASTATIC)

	Is it permitted to prescribe the medication for this indication?		Is the medicine reimbursed for this indication?		Does reimbursement require pre-authorisation?		Does the pre-authorisation process delay treatment by more than 4 weeks?		Cost of medication to patients (What proportion of the full retail price does the AVERAGE PATIENT have to pay?)					Actual availability when needed for most patients in your country (Can patients actually get the medication when it is prescribed?)					If the medication is not always available, what are the reasons for this (one or more)?				
	Yes	No	Yes	No	Yes	No	Yes	No	Free	<25% cost	25-50% cost	Discount <50%	Full cost	Always	Usually	Half the time	Occasionally	Never	No / unreliable supplier	No commercial motive *	Parallel export **	Manufacturing problems	Budget capitation ***
Albumin-bound paclitaxel	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Anastrozole	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Bevacizumab	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Capecitabine	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Carboplatinum	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Cisplatinum	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Cyclophosphamide IV	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Cyclophosphamide (tablets)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Denosumab	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Docetaxel	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Doxorubicin	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Epirubicin	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐
Eribulin	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	☐	☐	☐	☐	☐

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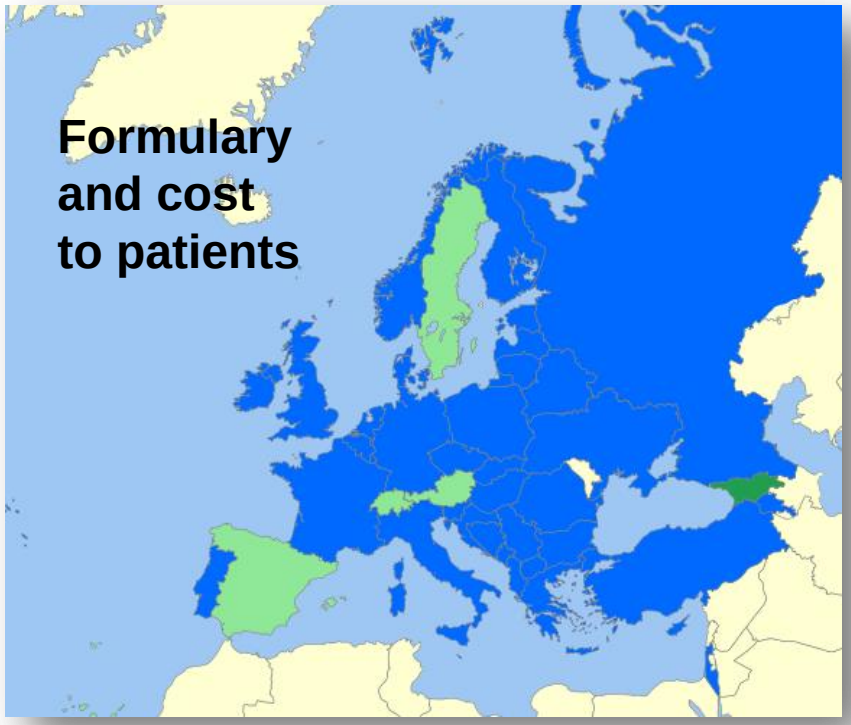
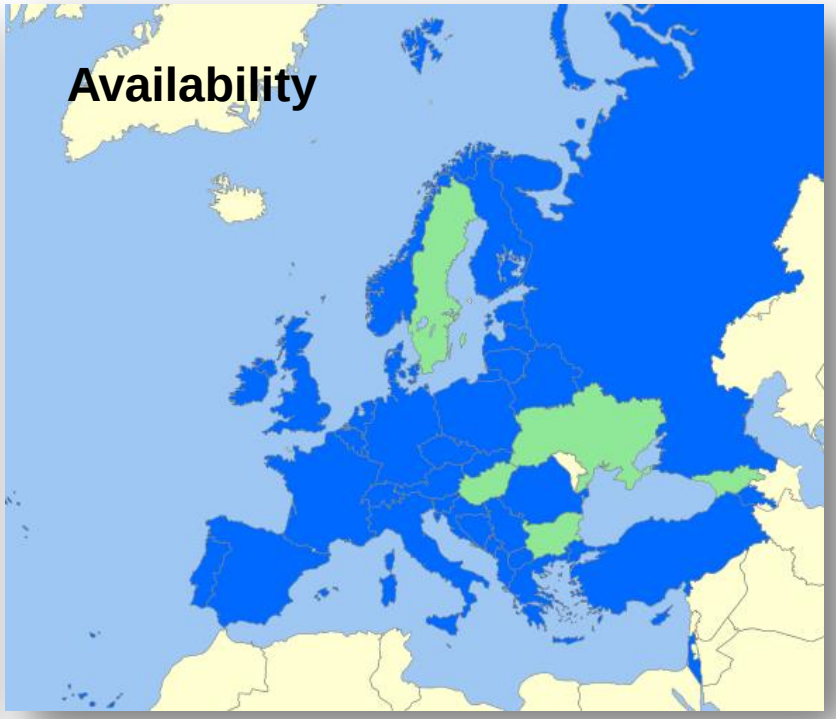
Data reporters

- National representatives
- Known credible professionals nominated by coordinating and collaborating partners
- Minimum of 2 reporters for each country nominated
- Total 185 from 49 countries
- 102/185 responses from 46/49 countries
- Respondents
  - 25 oncology pharmacists (22 countries)
  - 77 oncologists
  - 74 Academic cancer centers or hospitals

Adjuvant breast cancer: : formulary inclusion and availability : TAMOXIFEN





- **Drug shortages affect several essential, old and inexpensive drugs** (tamoxifen, doxorubicin, cisplatin, 5-FU, bleomycin…)
- Not an issue of resources!

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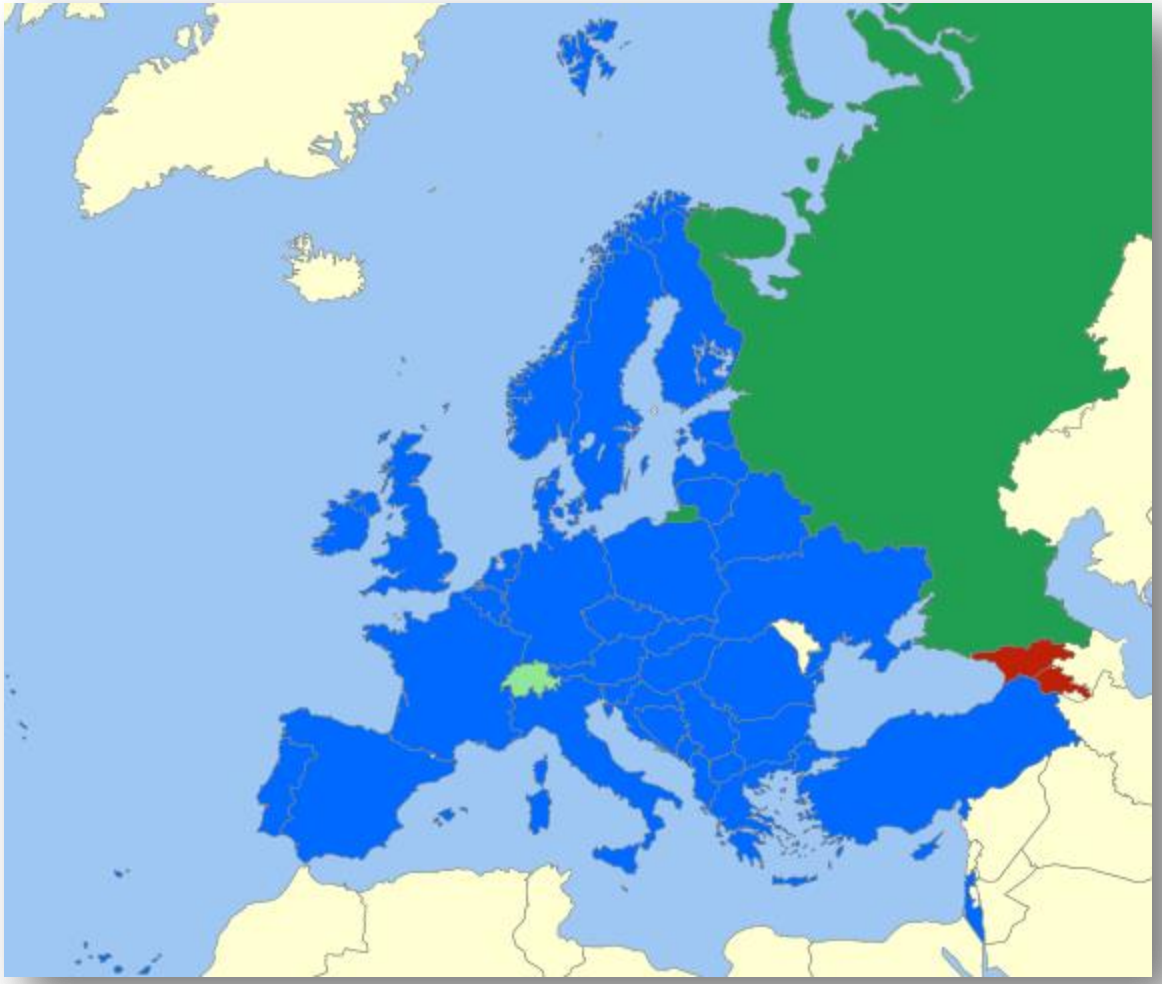
Adjuvant breast cancer: formulary inclusion and cost to patients - TRASTUZUMAB



Free
<25% Cost
25%-50% Cost
Discount <50%
Full Cost
Not available
No Data

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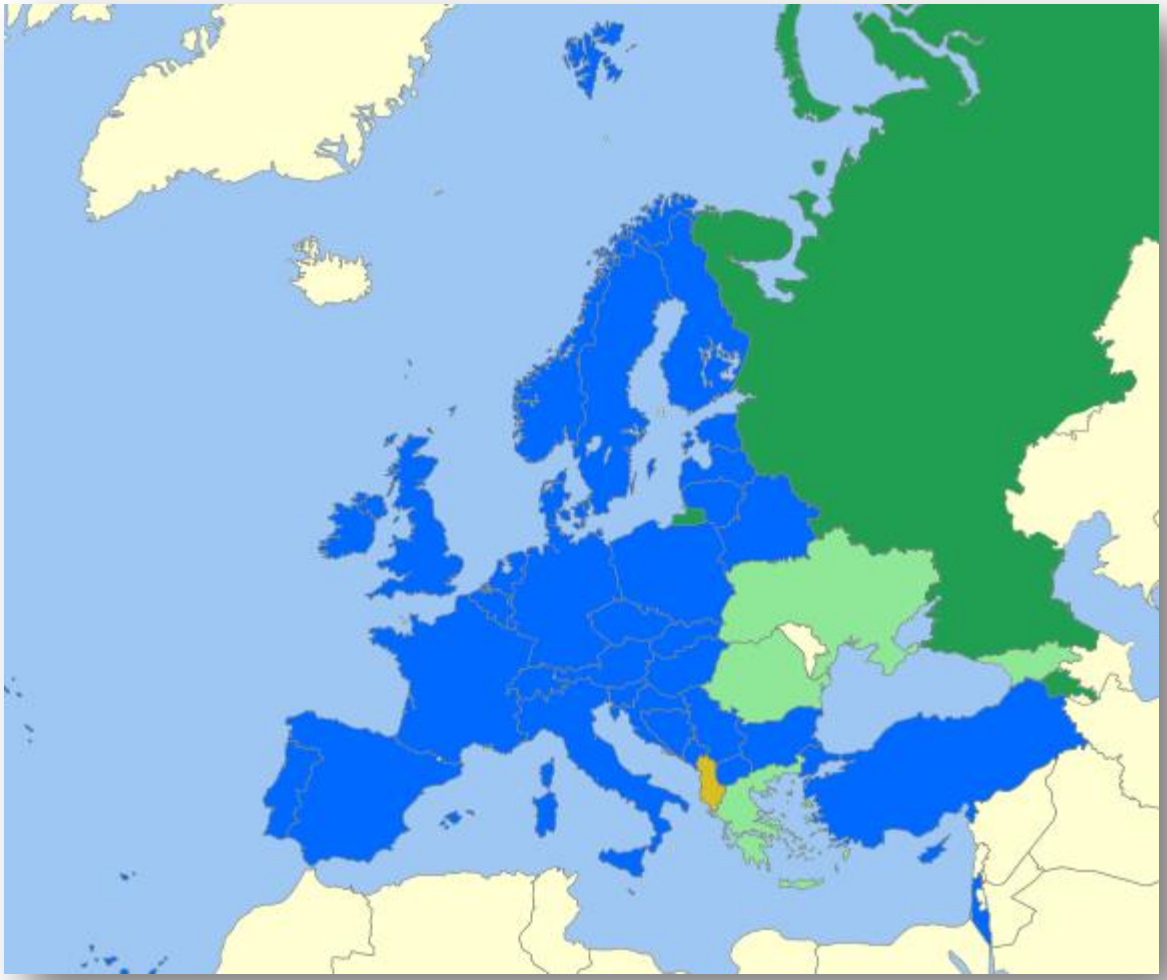
Adjuvant breast cancer: availability - TRASTUZUMAB



Always | Usually | Half the time | Occasionally | Never | Not available | No data

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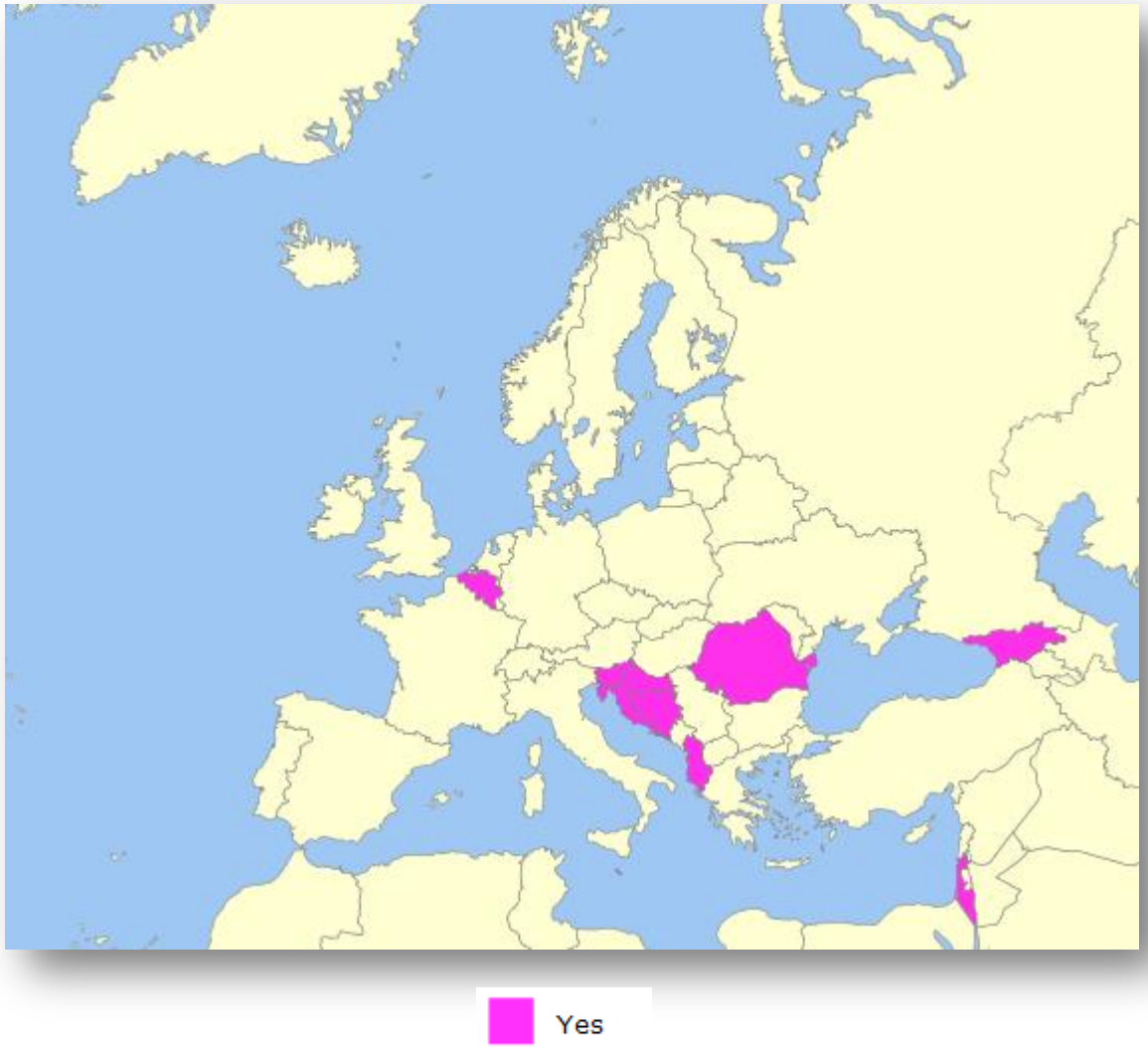
Adjuvant breast cancer: preapproval required: TRASTUZUMAB



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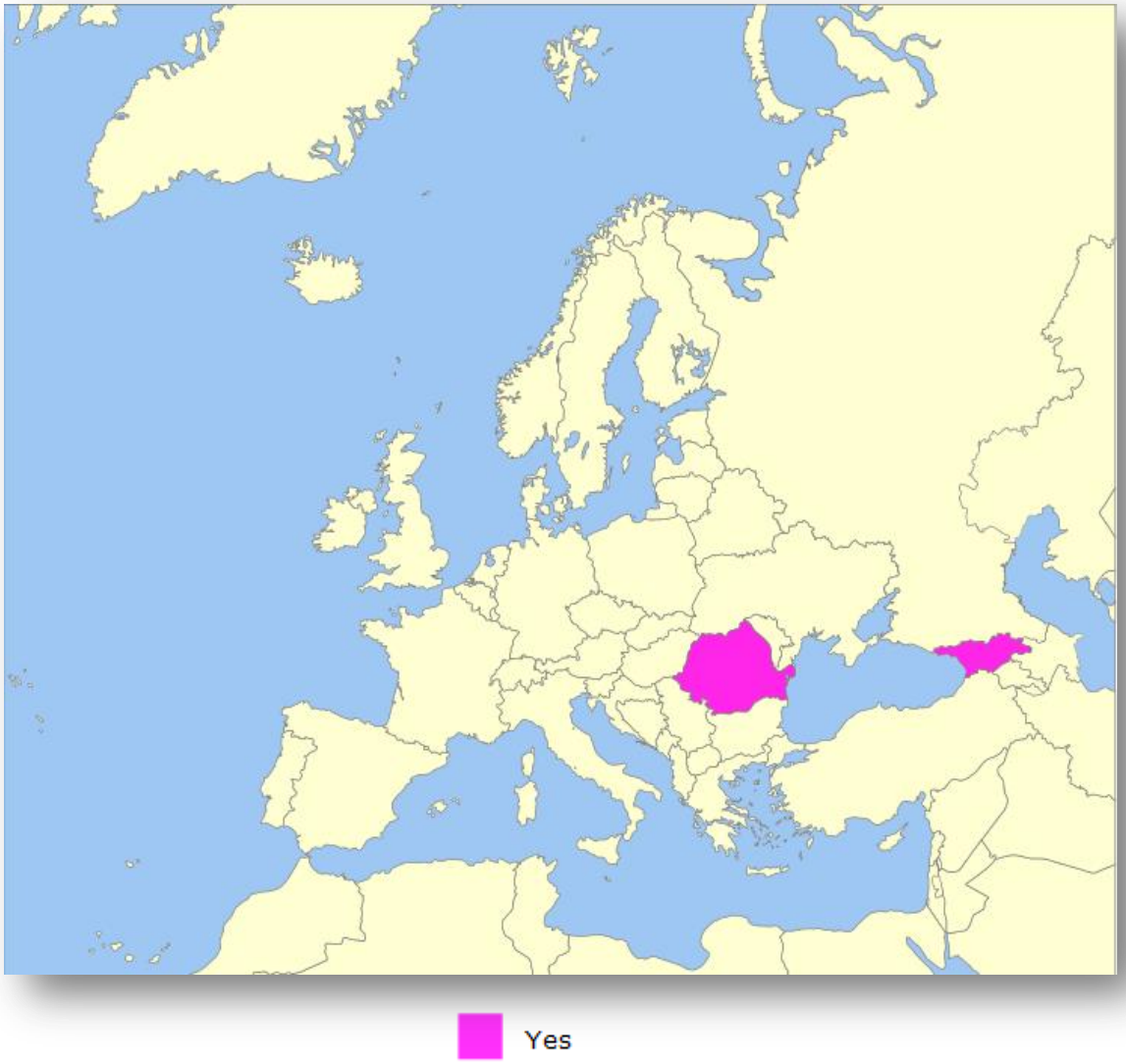
Adjuvant breast cancer

(Pre-approval causing >4 weeks delay): TRASTUZUMAB



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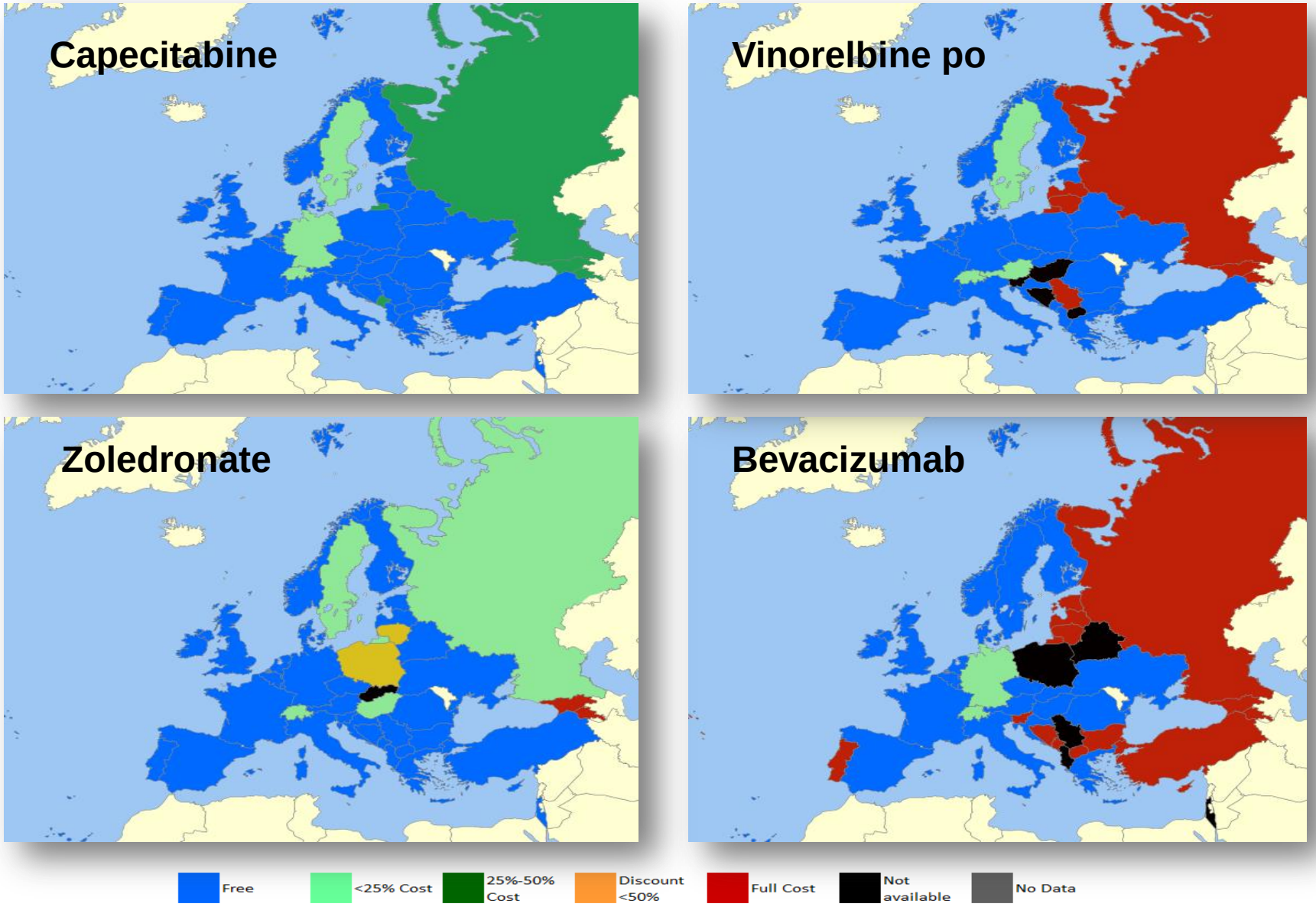
Metastatic breast cancer
(formulary inclusion & cost to patients)



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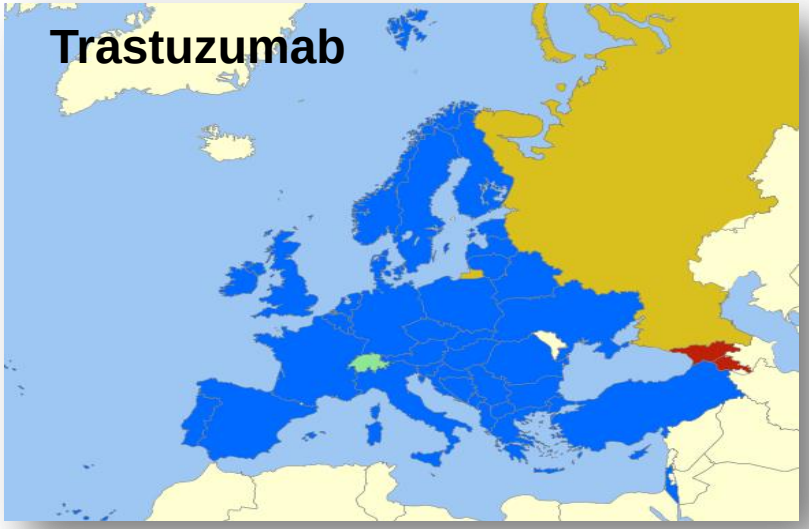
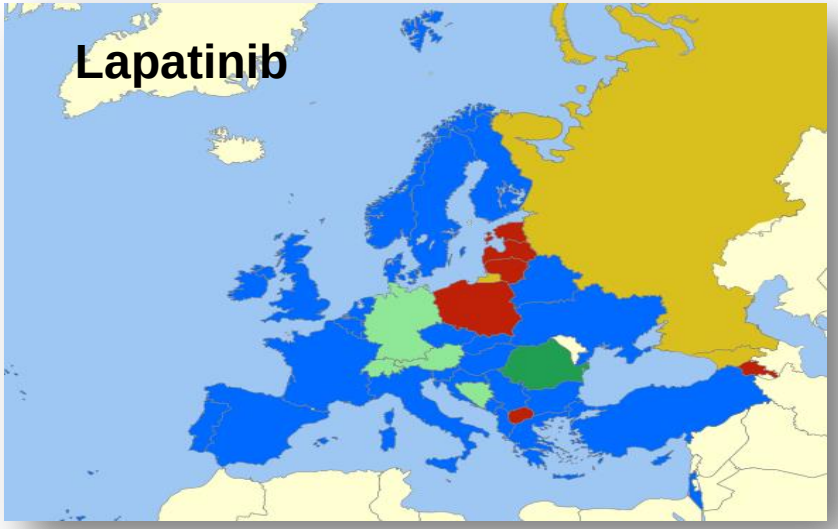
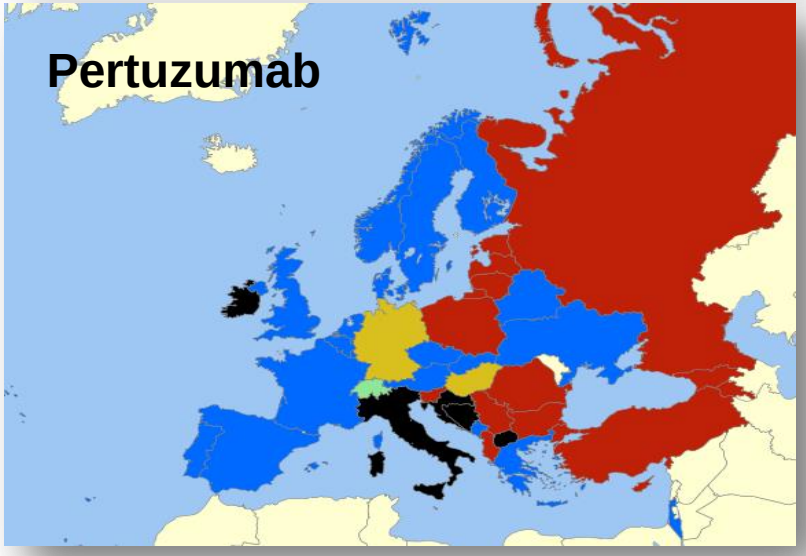
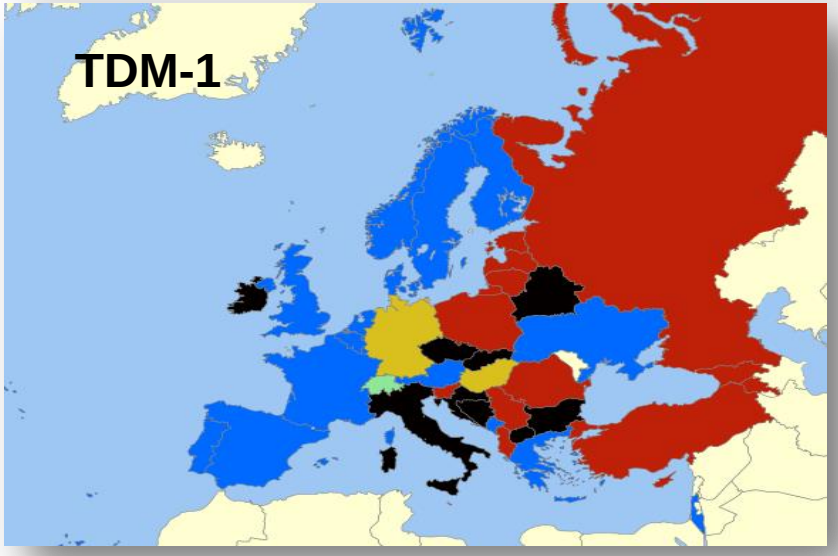
Metastatic breast cancer

(formulary inclusion and cost to patients): Anti-Her2 therapy









Free
<25% Cost
25%-50% Cost
Discount <50%
Full Cost
Not available
No Data

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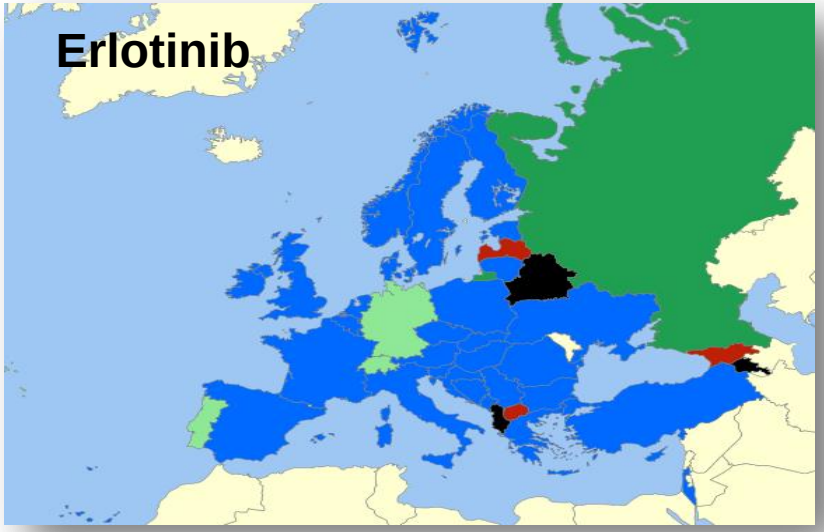
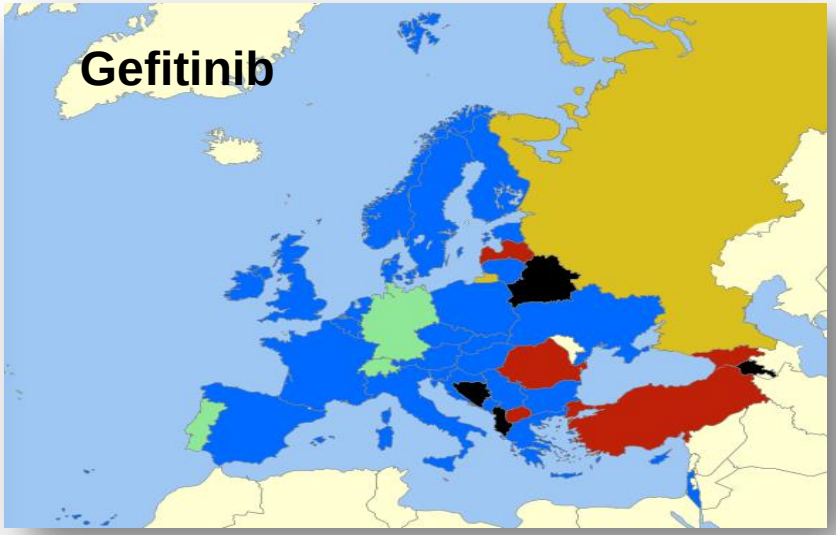
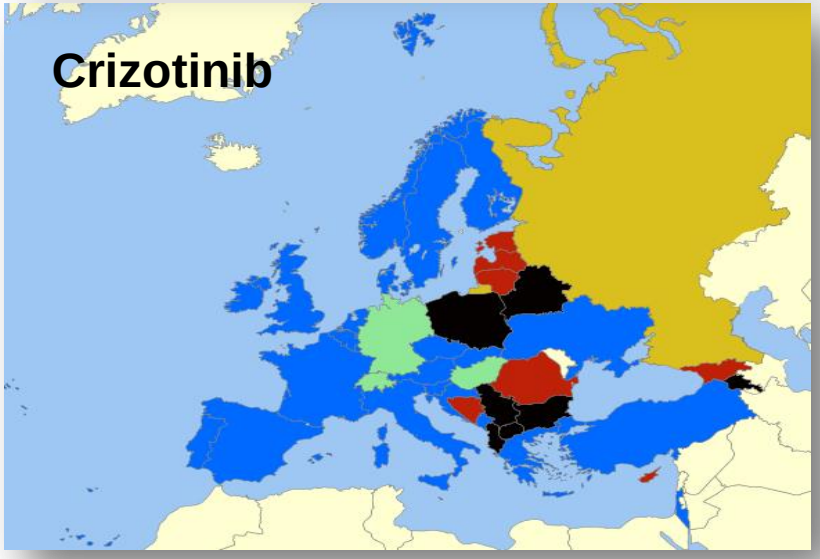
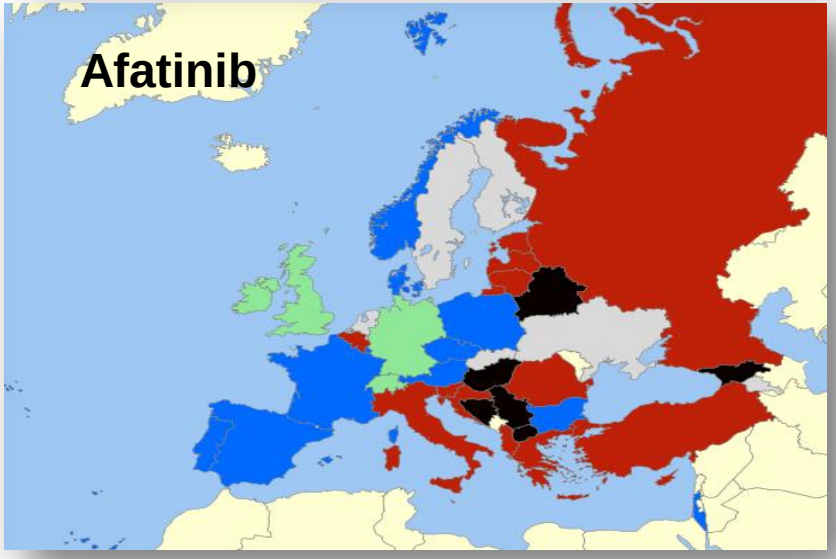
Lung cancer :formulary inclusion and cost to patients:

Targeted therapy









Free | <25% Cost | 25%-50% Cost | Discount <50% | Full Cost | Not available | No Data

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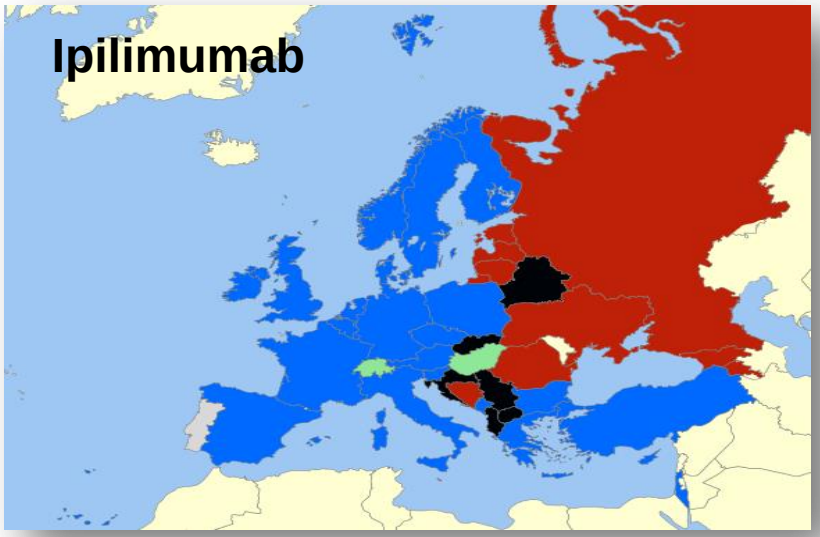
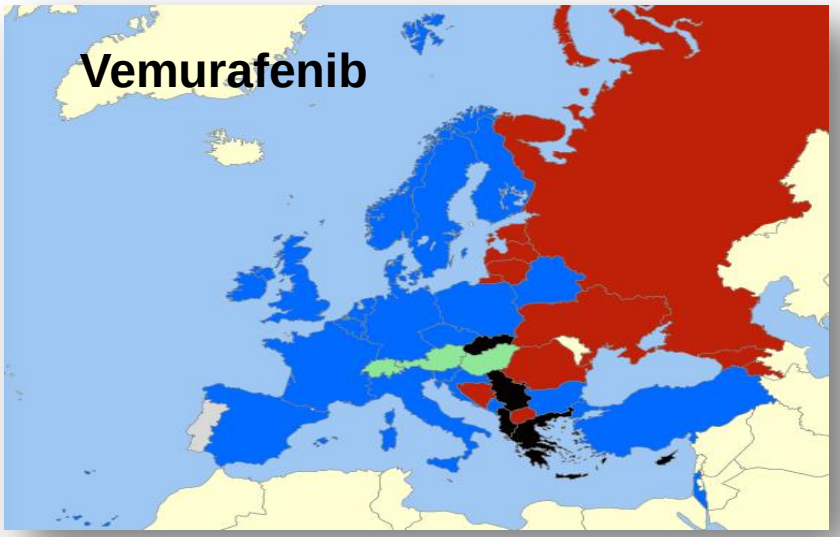
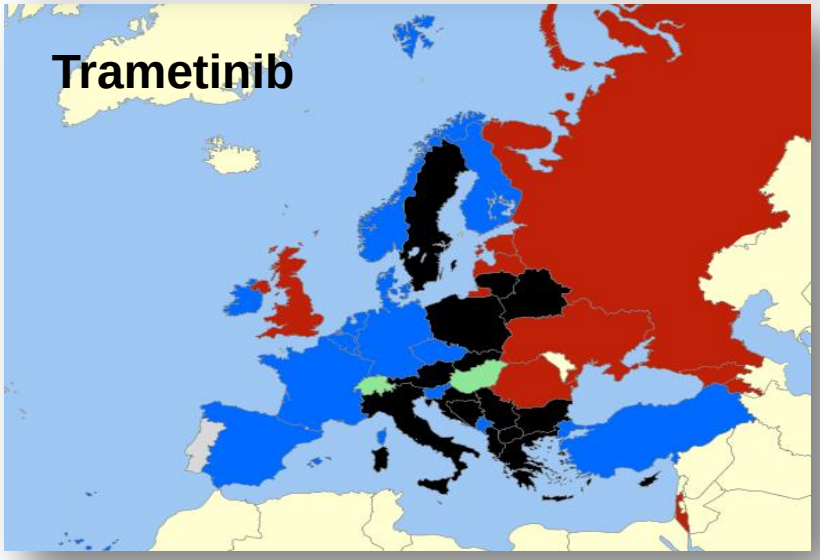
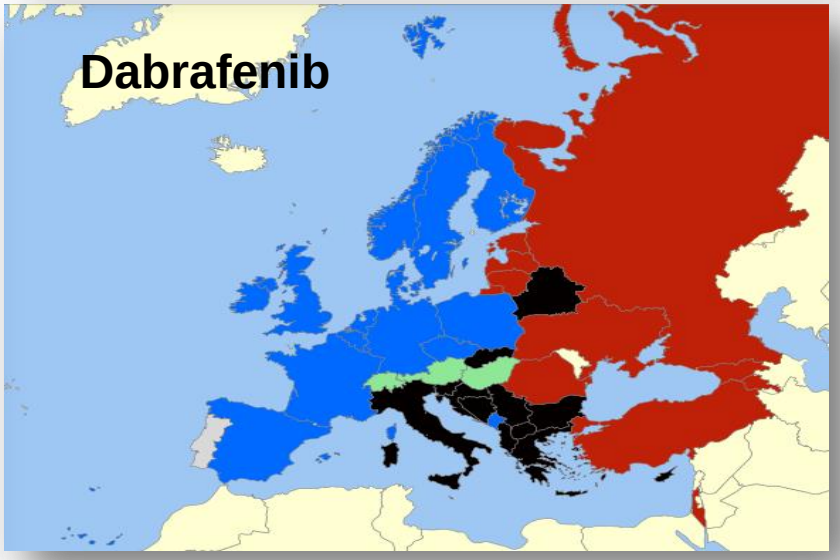
Melanoma : formulary inclusion and cost to patients









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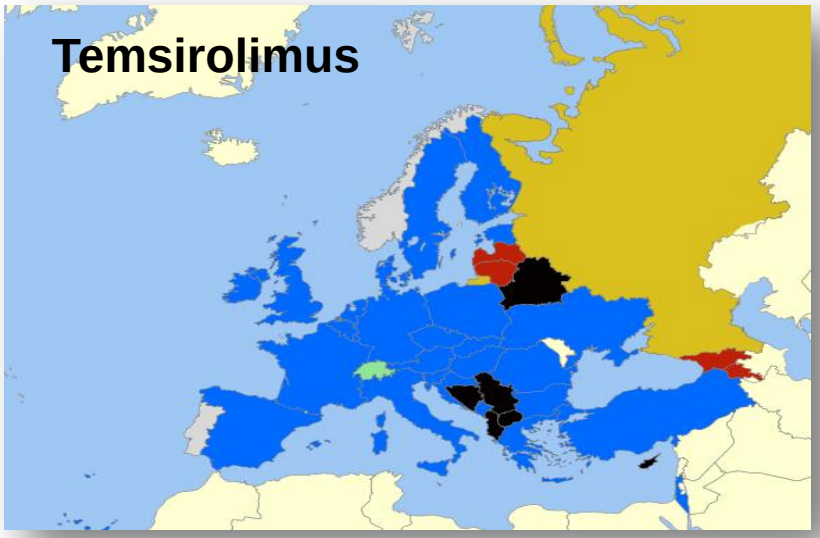
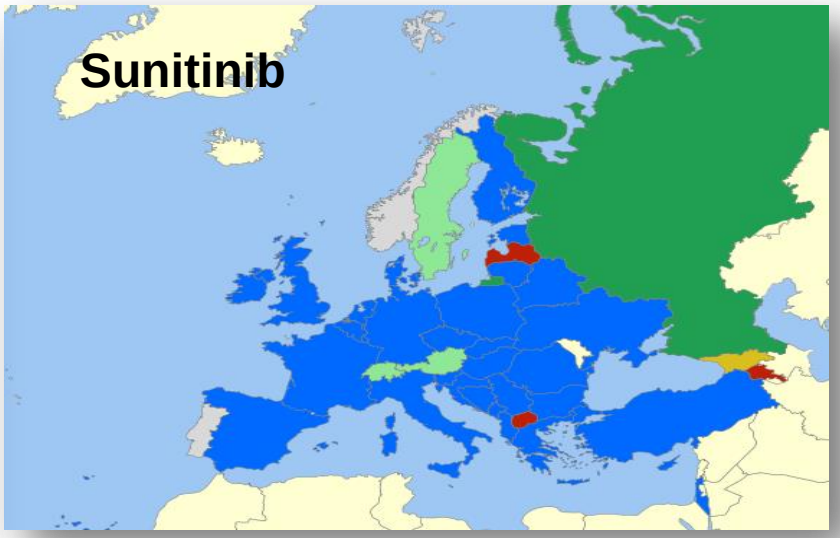
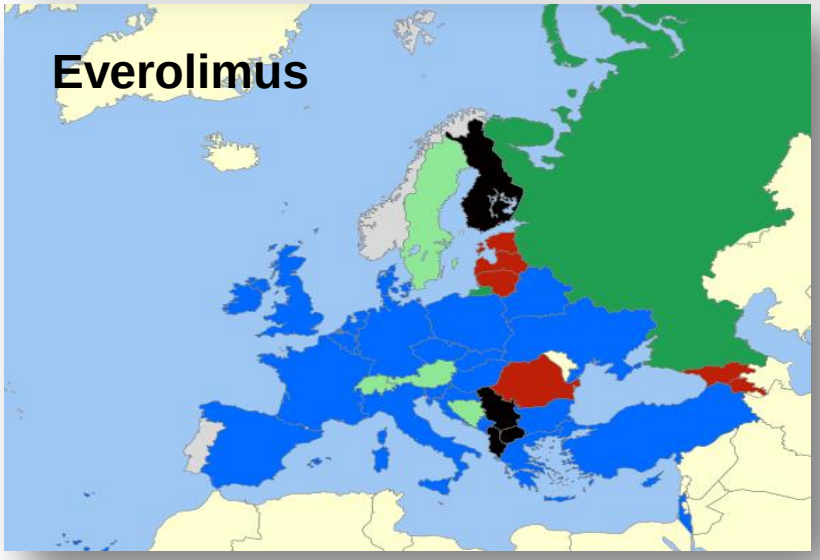
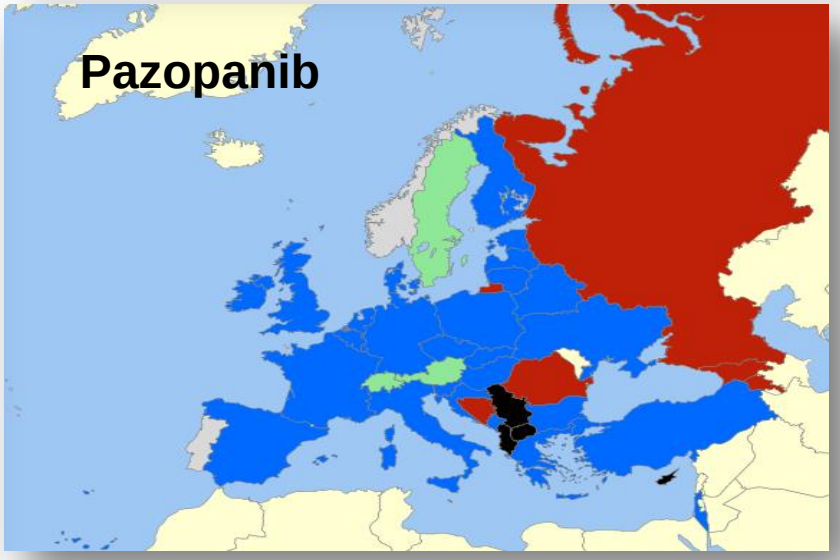
Renal Cancer : formulary inclusion and cost to patients









Free | <25% Cost | 25%-50% Cost | Discount <50% | Full Cost | Not available | No Data

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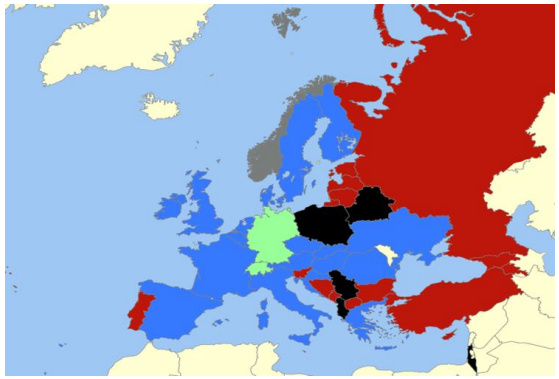
The present scenario

The pharmaceutical company requests marketing authorization
Evaluation by EMA (high degree of transparency!)
Approval by the European Commission

Time 0: the new drug is effective and safe – valid for whole EU

Europe explodes into 28 different countries…



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The nightmare of the cancer medicines journey

- Many national commissions and expert committees-replicating at a lower level the same assessment done at the EMA stage
- A few HTA bodies
  - Working on few and weak data
  - With limited consultive value
- Fruitless sessions of negotiation, looking for creative/desperate strategies

The problem: *JUSTUM PRETIUM* is utopia

- The price proposed by pharmaceutical companies is
  - dramatically increasing
  - frequently **unrelated to the size of the benefit produced by the new medicine**
- Little transparency (if any) in the way the price is decided

European Journal of Cancer (2014) **50**, 3089–3097

An exploratory analysis of the factors leading to delays in cancer drug reimbursement in the European Union: The trastuzumab case

Felipe Ades [a], Chistelle Senterre [b], Dimitrios Zardavas [e], Evandro de Azambuja [a], Razvan Popescu [c], Florence Parent [d], Martine Piccart [a,*]

Fig. 1. Time periods for trastuzumab approval/reimbursement in the adjuvant and metastatic settings across European Union (EU) countries.

Therefore development of an ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)

ESMO

- **Recognizes**
  - the need for clear and unbiased statements regarding the magnitude of clinical benefit from new therapeutic approaches supported by credible research

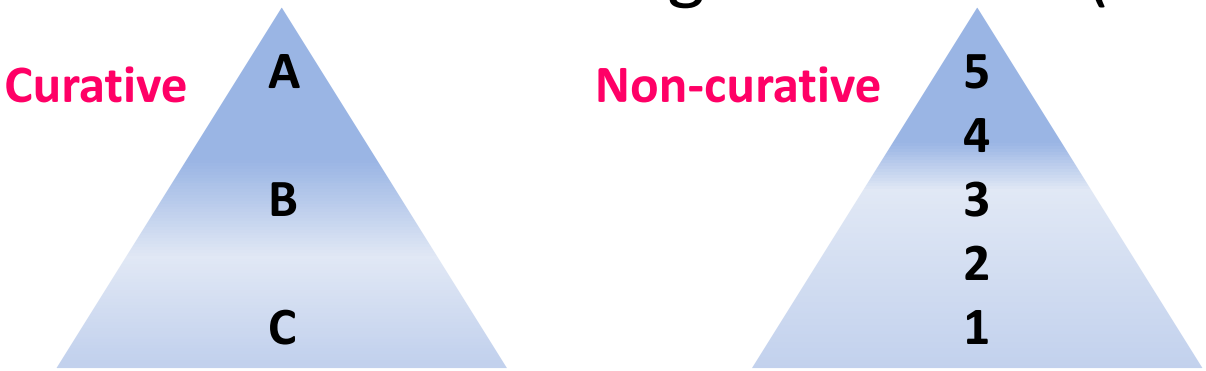
- **Wants to**
  - highlight treatments which bring substantial improvements to the duration of survival and/or the QoL of cancer patients
  - use the scale for accelerated:
    - registration
    - reimbursement evaluation incorporating ESMO-MCBS, value and cost effectiveness considerations

Cherny, N et al, Ann Oncol epub 30 May 2015

How will the ESMO-MCBS be used?

- When a new anticancer drug is EMA approved, its benefit will be «scaled» by a dedicated ESMO committee

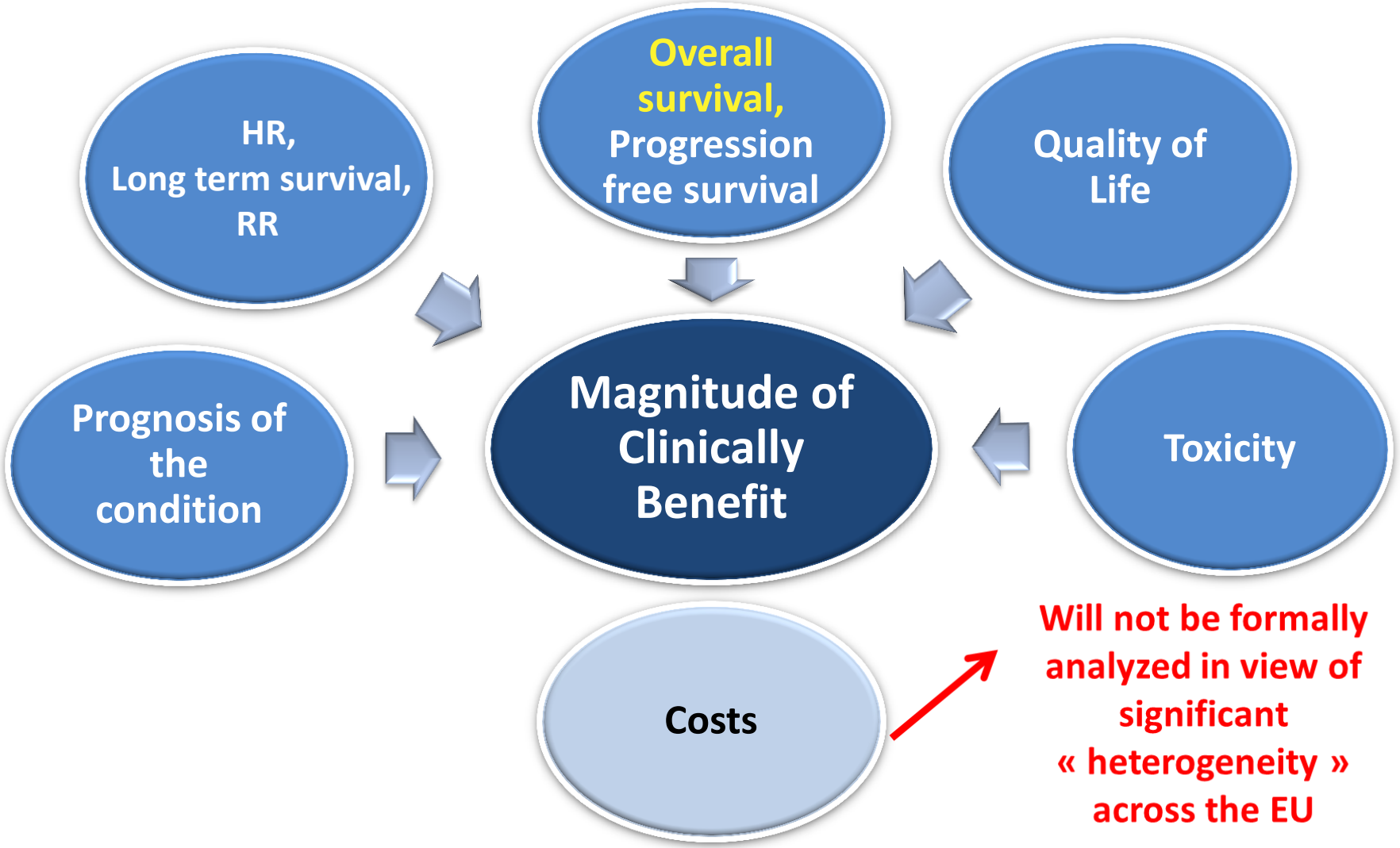
- Drugs which obtain the highest scores (A&B or 5&4):



1. will be highlighted in the ESMO guidelines
2. represent the highest priority for rapid endorsement by national bodies across Europe

Cherny, N et al, Ann Oncol epub 30 May 2015

Factors taken into account for ESMO-MCBS



Cherny, N et al, Ann Oncol epub 30 May 2015

Evaluation form 1:

for adjuvant and other treatments with curative intent

	Mark with X if relevant
Grade A	
>5% improved survival at ≥ 3 years follow-up	
Improvement in DFS alone (primary endpoint) (HR < 0.65) in studies without mature survival data	
Grade B	
≥ 3% but ≤ 5% improvement at ≥ 3 years follow-up	
Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	
Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	
Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	
Grade C	
< 3% improvement at ≥ 3 years follow-up	
Improvements in DFS alone (primary endpoint) (HR > 0.8) in studies without mature survival data	

Cherny, N et al. Ann Oncol epub 30 May 2015

Evaluation form 2a: treatments with non-curative intent, primary endpoint OS

IF median OS with the standard treatment is ≤ 1 year

	Mark with X if relevant
Grade 4	
HR ≤ 0.65 AND Gain ≥ 3 months	
Increase in 2 year survival alone ≥ 10%	
Grade 3	
HR ≤ 0.65 AND Gain 2.5-2.9 months	
Increase in 2 year survival alone 5- <10%	
Grade 2	
HR > 0.65-0.70 OR Gain 1.5-2.4 months	
Increase in 2 year survival alone 3- <5%	
Grade 1	
HR > 0.70 OR Gain < 1.5 month	
Increase in 2 year survival alone < 3%	

Cherny, N et al, Ann Oncol epub 30 May 2015

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Field testing Breast Cancer

EXAMPLE

Medication	Trial	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	ESM0 MCBS
Chemo +/- **trastuzumab**	HERA	(Neo)Adjuvant HER-2 positive tumors	DFS	2 y DFS 77.4%	8.4%	0.54 (0.43-0.67)					**A**
T-DM1 vs capecitabine + lapatinib	EMILIA	2nd line metastatic after trastuzumab failure	PFS & OS	6.4 m	3.2 m	0.65 (0.55-0.77)	25 m	6.8 m	0.68 (0.55-0.85)	Later deterioration	**5**
Trastuzumab + chemo +/- **pertuzumab**	CLEOPATRA	1st line metastatic	PFS	12.4 m	6 m	0.62 (0.52-0.84)	40.8 m	15.7 m	0.68 (0.56-0.84)	~	**4**
Lapatinib +/- trastuzumab	EGF 104900	3rd line metastatic	PFS	2 m	1 m	0.73 (0.57-0.93)	9.5 m	4.5 m	0.74 (0.57-0.97)		**4**
Capecitabine +/- **lapatinib**	Geyer, 2006	2nd line metastatic after trastuzumab failure	PFS	4.4 m	4 m	0.49 (0.34-0.71)			NS		**3**
Eribulin vs other chemo	EMBRACE	3rd line metastatic after anthracycline & taxane	OS				10.6 m	2.5 m	0.81 (0.66-0.99)		**2**
Paclitaxel +/- **bevacizumab**	Miller, 2007	1st line metastatic	PFS	5.9 m	5.8 m	0.6 (0.51-0.70)			NS	~	**2**
Exemestane +/- **everolimus**	BOLERO-2	Metastatic after failure aromatase inhibitor+PFS >6 m	PFS	4.1 m	6.5 m	0.43 (0.36-0.54)			NS	~	**2**

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Field testing Lung Cancer (1)

Medication	Trial	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS HR	QoL	Toxicity	ESM0 MCBS
Erlotinib vs carboplatin gemcitabine	OPTIMEL, CTONG-0802	1st line stage 3b/4 non-squamous + EGFR mutation	PFS	4.6 m	8.5 m	0.16 (0.10-0.26)				12% < serious adverse events	**4**
Erlotinib vs Pt-based chemo doublet	EURTAC	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	5.2 m	4.5 m	0.37 (0.25-0.54)	19.5 m	NS		15% < severe adverse reactions	**4**
Gefitinib vs carboplatin + paclitaxel	IPASS	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	6.3 m	3.3 m	0.48 (0.34-0.67)			↑	< toxicity	**4**
Afatinib vs cisplatin + pemetrexed	LUX Lung 3	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	6.9 m	4.2 m	0.58 (0.43-0.78)			↑		**4**
		Del19/L858R		6.9 m	6.7 m	0.47 (0.34-0.65)			↑		**4**
Crizotinib vs chemo	Shaw 2013	1st line stage 3b/4 non-squamous + ALK mutation	PFS, crossover allowed	3.0 m	4.7 m	0.49 (0.37-0.64)			↑	1% > toxic death	**4**
Crizotinib vs cisplatin + pemetrexed	Solomon 2014	1st line stage 3b/4 non-squamous + ALK mutation	PFS	7.0 m	3.9 m	0.45 (0.35-0.60)			↑		**4**

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Field testing Renal Cell Cancer version light

Medication	Trial	Setting	ESM0-MCBS
Pazopanib vs sunitinib	COMPARZ	1st line metastatic with clear cell component	**4**
Temsirolimus vs interferon vs combined	Hudes, 2007	1st line poor-prognosis metastatic	**4**
Sunitinib vs interferon	Motzer 2007 & 2009	1st line metastatic	**4**
Axitinib vs sorafenib	AXIS	Previously treated metastatic	3
Everolimus vs placebo	RECORD1	2nd or 3rd line after TKI metastatic	**3**
Pazopanib vs placebo	Sternberg 2010	2nd line locally advanced or metastatic	**3**
Interferon +/- **bevacizumab**	AVOREN	1st line metastatic with clear cell	**3**
Interferon +/- **bevacizumab**	CALGB 90206	1st line metastatic with clear cell	**1**

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Field testing Melanoma (1) version light

Medication	Trial	Setting	ESM0-MCBS
Ipilimumab +/- glycoprotein 100 vaccine vs vaccine alone	Hodi 2010	Previously treated metastatic	**4**
Vemurafenib vs dacarbazine	BRIM-3	1st line or 2nd line after IL-2 metastatic + BRAF V600E mutation	**4**
Trametinib vs dacarbazine or paclitaxel	METRIC	Unresectable or metastatic + BRAF V600E mutation	**4***
Dabrafenib +/- **trametinib**	Flagerty 2012	1st line unresectable or metastatic + BRAF V600E mutation	**4**
Dabrafenib vs dacarbazine	Hauschild 2012 Grob 2014	1st line unresectable or metastatic + BRAF V600E mutation	**4**

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Example of using MCBS data: Lung cancer, Romania

Medication	Setting	Primary outcome	ESMO-MCBS
Erlotinib vs carboplatin gemcitabine	1st line stage 3b/4 non-squamous + EGFR mutation	PFS	4
Erlotinib vs Pt-based chemo doublet	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	4
Gefitinib vs carboplatin + paclitaxel	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	4
Afatinib vs cisplatin + pemetrexed	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	4
Crizotinib vs chemo	1st line stage 3b/4 non-squamous + ALK mutation	PFS, crossover allowed	4
Crizotinib vs cisplatin + pemetrexed	1st line stage 3b/4 non-squamous + ALK mutation	PFS	4
Cisplatin pemetrexed vs **c**isplatin gemcitabine	1st line 3b/4 (non-squamous)	PFS	**4**
Erlotinib vs placebo	Stage 3b/4 disease	PFS	1

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Example of using MCBS data: Renal cancer, Romania

Medication	Setting	Primary outcome	ESM0-MCBS
Pazopanib vs sunitinib	1st line metastatic with clear cell component	PFS non inferiority	4
Temsirolimus vs interferon vs combined	1st line poor-prognosis metastatic	OS	4
Sunitinib vs interferon	1st line metastatic	PFS, crossover allowed	4
Axitinib vs sorafenib	Previously treated metastatic	PFS	3
Everolimus vs placebo	2nd or 3rd line after TKI metastatic	PFS, crossover allowed	3
Pazopanib vs placebo	2nd line locally advanced or metastatic	PFS, crossover allowed	3
Interferon +/- **bevacizumab**	1st line metastatic with clear cell	PFS	3
Interferon +/- **bevacizumab**	1st line metastatic with clear cell	PFS	1

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Example of using MCBS data: Melanoma , Romania

Medication	Setting	Primary outcome	ESM0-MCBS
Ipilimumab +/- glycoprotein 100 vaccine vs vaccine alone	Previously treated metastatic	OS	**4**
Vemurafenib vs dacarbazine	1st line or 2nd line after IL-2 metastatic + BRAF V600E mutation	PFS and OS	**4**
Trametinib vs dacarbazine or paclitaxel	Unresectable or metastatic + BRAF V600E mutation	PFS (crossover allowed)	**4***
Dabrafenib +/- **trametinib**	1st line unresectable or metastatic + BRAF V600E mutation	Toxicity, PFS	**4**
Dabrafenib vs dacarbazine	1st line unresectable or metastatic + BRAF V600E mutation	PFS (crossover allowed)	**4**

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Example of using MCBS data: Breast cancer, Romania

Medication	Setting	Primary outcome	ESMO-MCBS
Chemotherapy +/- trastuzumab	(Neo)adjuvant HER-2 positive tumours	DFS	**A**
T-DM1 vs lapatinib + capecitabine	2nd line metastatic after trastuzumab failure	PFS and OS	**5**
Trastuzumab + chemotherapy +/- pertuzumab	1st line metastatic	PFS	**4**
Lapatinib +/- trastuzumab	3rd line metastatic	PFS	**4**
Capecitabine +/- lapatinib	2nd line metastatic after trastuzumab failure	PFS	**3**
Eribulin vs other chemotherapy	3rd line metastatic after anthracycline and taxane	OS	**2**
Paclitaxel +/- bevacizumab	1st line metastatic	PFS	**2**
Exemestane +/- everolimus	Metastatic after failure of aromatase inhibitor (with PFS > 6 mth)	PFS	**2**

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Conclusions

- Disparities exist across Europe in access to cancer medicines
- Drug shortages affect several “essential”, old and inexpensive drugs
  - THIS SHOULD BE UNACCEPTABLE !
- Inequalities exist in availability and patient costs, especially for newer, more expensive drugs, across Europe
- The **ESMO Magnitude of Benefit Scale**, applied on the availability data (**ESMO Antineoplastic Medicines Survey)** can inform the process of prioritization access to medicines, when resources are limited