

1. BDA Workshop

Market & Patient Access to New Oncology Products in Europe

Brussels, Belgium – 29 November 2007

2. BDA Workshop

Actual developments in European Regulatory and HTA Management – What does this mean for oncology in Europe?

Bonn, Germany – 9 March 2011

3. BDA Workshop

Access to Innovative Oncology Medicines in Europe

Bonn, Germany – 16 & 17 January 2014

4. CDDF Workshop

Access to Innovative Oncology Drugs in Europe

Madrid, Spain – 7 & 8 September 2017

Co-chairs:

- *Lothar Bergmann (Frankfurt University Hospital, Germany)*
- *Jorge Camarero (AEMPS, Spain)*
- *Francesco De Lorenzo (ECPC, Italy)*

ACCESS to INNOVATIVE Oncology Drugs in

Impact of Drug Access on Survival



Lothar Bergmann
Ambulantes Krebszentrum, Frankfurt (AKS)
und
Medizinische Klinik II
Goethe Universität Frankfurt
Germany



What are the relevant issues to be discussed?

- What is the current status in Europe?
- Is there a relation between access to oncology drugs and survival in cancer patients?
- What are the challenges to achieve equal access?
- What`s about oncology drugs without a confirmed benefit for survival?

UK cancer survival rates lag behind those of other European countries – study

Experts highlight need for earlier diagnosis and improved access to treatments, as figures show UK healthcare spend is lower than the European average



Previous research suggests that the UK survival rates for breast cancer are a decade behind countries such as France and Sweden. Photograph: Echo/Getty Images/Cultura RF

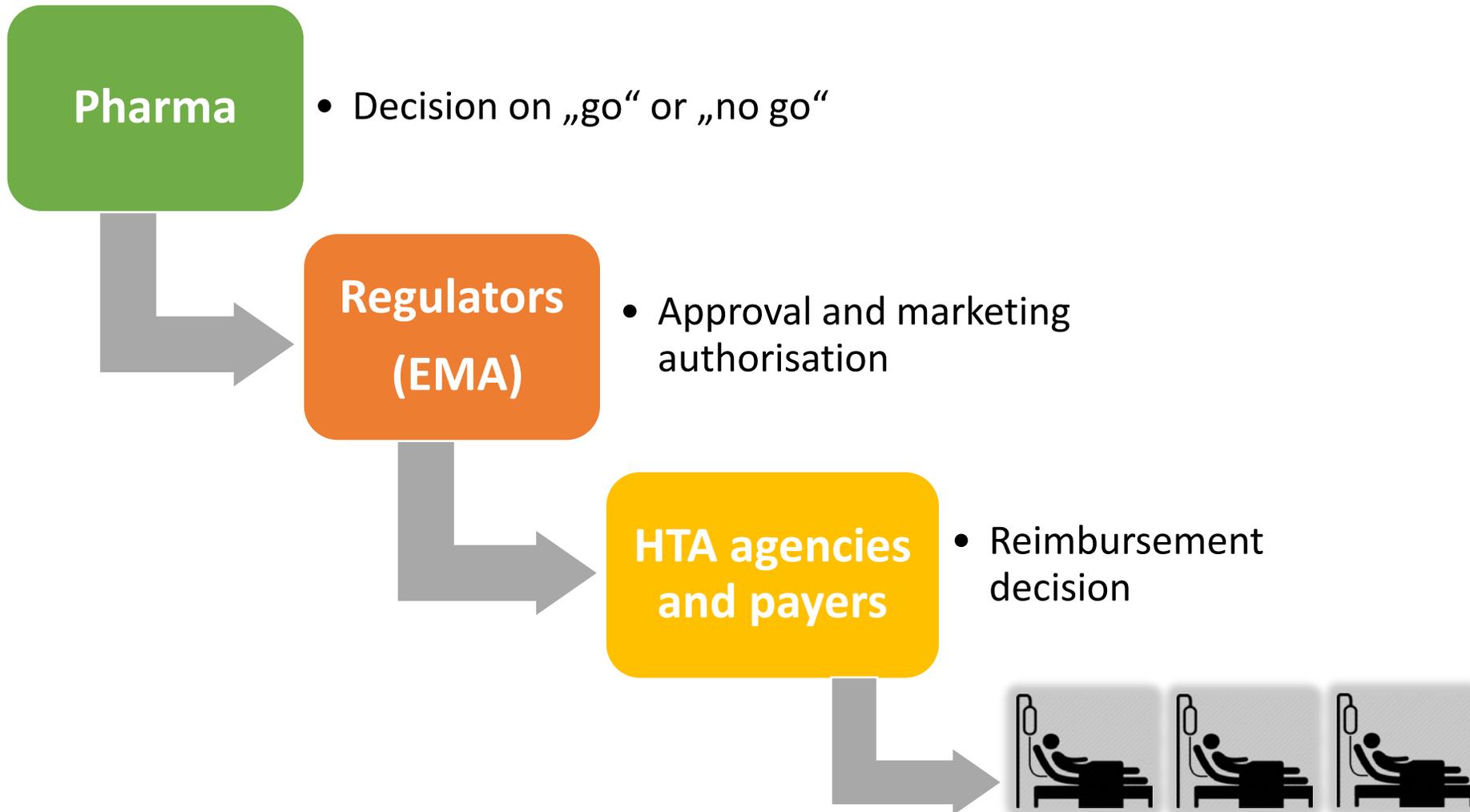
Comments in The Guardian

- The UK spent 9.1% of its GDP on healthcare in 2014, the European average was 10.1%
- Looking specifically at cancer spending, compared to countries including France, Denmark, Austria and Ireland the UK spent less on cancer per person, with Germany spending almost twice as much per head
- The UK is lagging behind other large European countries, including France and Germany, in the *uptake of new drugs*
- It is crucial to make sure that *new drugs* and other treatments are available and accessible to patients (*Emlyn Samuel*)
- The UK is slower at adopting innovative cancer medicines than other countries and that is a concern

GDP= Gross domestic product

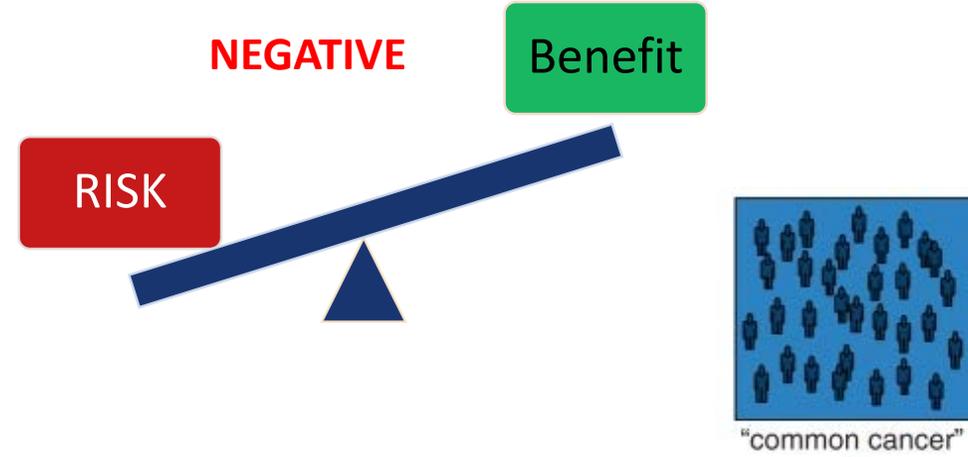
These issues apply for other European countries as well !

The path to patients



Turn a negative risk/benefit balance into a positive one

Regulatory decision for new drug asked for a wide target population



Regulatory decision for a restricted subpopulation only

Subpopulation defined by biological criteria, genetics, etc. (CDx)



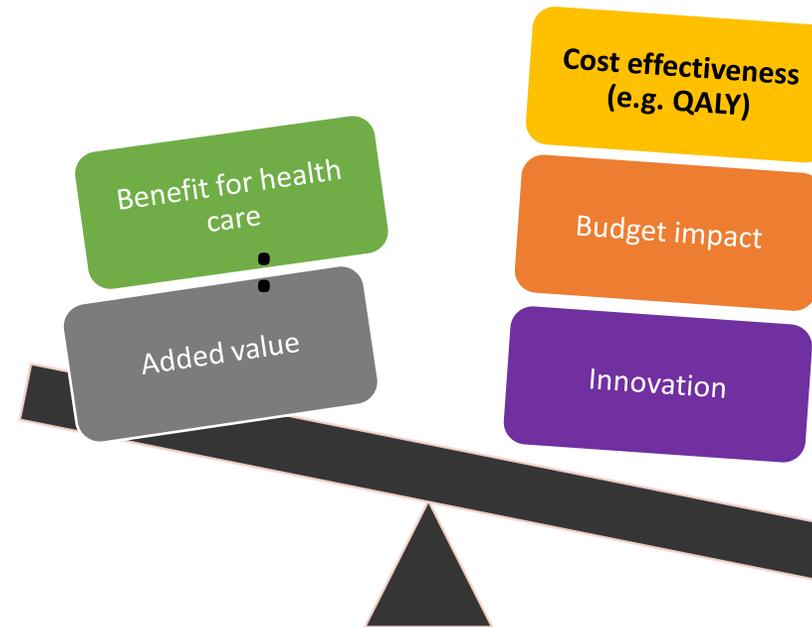
Different Methods for Assessments of new Anticancer Drugs by HTAs in Europe

National HTAs

e.g.

UK	NICE
France	HAS
Germany	IQWiG
Spain	OSTEBA
Finland	FinOHTA

Decisions made on national or even regional level usually based on a formal assessment of HTA bodies.



- 40 national and/or regional HTAs
- Different assessment methods
- Different health economy
- Different reimbursements
- **Different availability for patients**

Different assessment methods for health technology agencies (HTA)

Cost-effectiveness (e.g. NICE, England)

$$\frac{\text{cost}_{\text{new}} - \text{cost}_{\text{current}}}{\text{health gain}_{\text{new}} - \text{health gain}_{\text{current}}}$$

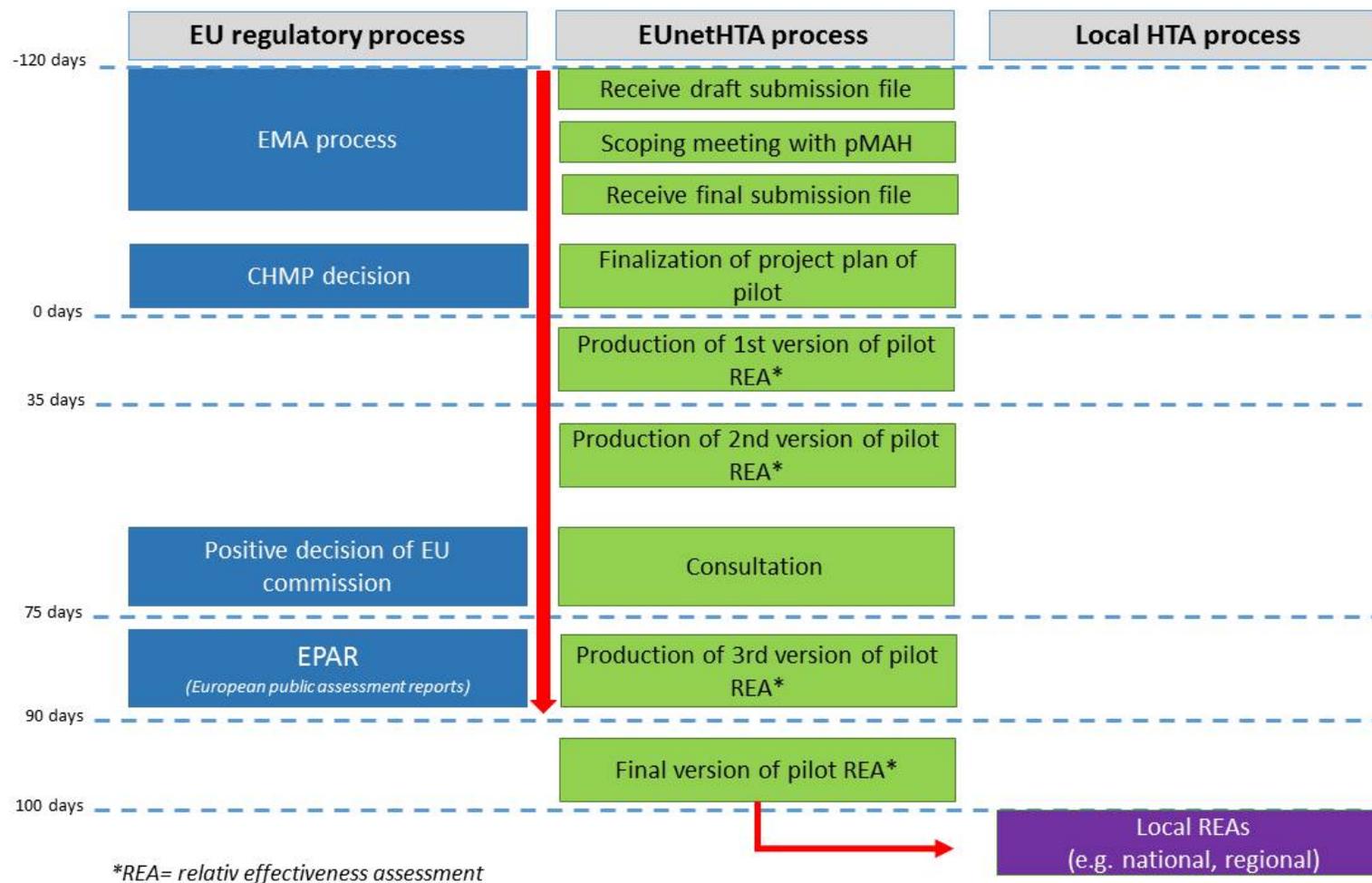
Health gain expressed as quality adjusted life years (QALYs)
→ **Cost per QALY gained**

Added value (e.g. GBA in Germany)

Extend of benefit:

- major
- considerable
- minor
- not quantifiable
- no additional benefit
- benefit less than alternative

EUnetHTA Activities



ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe

LUNG CANCER : Formulary and cost				
Country:	Erlotinib	Gefitinib	Afatinib	Crizotinib
Austria	Free	Free	Full cost	Free
Belgium	Free	Free	Full cost	Free
Cyprus	Free	Free	Full cost	Full cost
Denmark	Free	Free	Free	Free
Finland	Free	Free	Discount >50% and <100%	Free
France	Free	Free	Free	Free
Germany	Free	Free	Free	Free
Greece	Free	Free	Full cost	Free
Holland	Free	Free	Discount >50% and <100%	Free
Iceland	Free	Free	Free	Free
Ireland	Free	Free	<25% cost	Free
Israel	Free	Free	Free	Free
Italy	Free	Free	Full cost	Free
Luxembourg	Free	Free	Free	Free
Norway	Free	Free	Free	Free
Portugal	<25% cost	<25% cost	Free	Free
Spain	Free	Free	Free	Free
Sweden	Free	Free	Discount >50% and <100%	Free
Switzerland	<25% cost	<25% cost	Free	<25% cost
Turkey	Free	Full cost	Full cost	Free
United Kingdom	Free	Free	<25% cost	Free

Free
<25% cost
25–50% cost
Discount >50% and <100%
Full cost
Not available
Missing data

LUNG CANCER : Actual availability				
Country:	Erlotinib	Gefitinib	Afatinib	Crizotinib
Austria	Always	Always	Always	Always
Belgium	Always	Always	Usually	Always
Cyprus	Usually	Always	Never	Never
Denmark	Always	Always	Always	Always
Finland	Usually	Usually	Discount >50% and <100%	Usually
France	Always	Always	Always	Always
Germany	Always	Always	Always	Always
Greece	Usually	Usually	Occasionally	Half the time
Holland	Always	Always	Discount >50% and <100%	Always
Iceland	Always	Always	Always	Always
Ireland	Always	Always	Always	Always
Israel	Always	Always	Always	Always
Italy	Always	Always	Occasionally	Always
Luxembourg	Always	Always	Always	Always
Norway	Always	Always	Always	Always
Portugal	Usually	Usually	Always	Occasionally
Spain	Usually	Usually	Always	Occasionally
Sweden	Always	Always	Always	Always
Switzerland	Usually	Usually	Discount >50% and <100%	Usually
Turkey	Always	Always	Always	Always
United Kingdom	Always	Occasionally	Usually	Always

Always
Usually
Half the time
Occasionally
Never
Not available
Missing data

Cherny N, et al. Ann Oncol 2016; 27:1423-14443

ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe

costs

COLORECTAL CANCER : Formulary and cost		
Country:	Cetuximab	Panitumumab
Austria	Free	Free
Belgium	Free	Free
Cyprus	Free	Full cost
Denmark	Free	Free
Finland	Free	Free
France	Free	Free
Germany	Free	Free
Greece	Not available	Free
Holland	Free	Free
Iceland	Free	Free
Ireland	Free	Free
Israel	Free	Free
Italy	Free	Free
Luxembourg	Free	Free
Norway	Free	Free
Portugal	Free	Free
Spain	Free	Free
Sweden	Free	Free
Switzerland	<25% cost	<25% cost
Turkey	Free	Free
United Kingdom	Free	Free

Free
<25% cost
25–50% cost
Discount >50% and <100%
Full cost
Not available
Missing data

KRAS/RAF wild-type CRC

COLORECTAL: Actual availability		
Country:	Cetuximab	Panitumumab
Austria	Always	Always
Belgium	Always	Always
Cyprus	Always	Never
Denmark	Always	Always
Finland	Usually	Usually
France	Always	Always
Germany	Always	Always
Greece	Not available	Usually
Holland	Always	Always
Iceland	Always	Always
Ireland	Always	Always
Israel	Always	Always
Italy	Always	Always
Luxembourg	Always	Always
Norway	Always	Always
Portugal	Usually	Always
Spain	Always	Always
Sweden	Usually	Usually
Switzerland	Always	Always
Turkey	Always	Always
United Kingdom	Always	Always

Always
Usually
Half the time
Occasionally
Never
Not available
Missing data

KRAS/RAF wild-type CRC

Cherny N, et al. Ann Oncol 2016; 27:1423-14443

ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe

MELANOMA: Formulary and cost										
Country:	Interferon	DTIC	Fotemustine	High-Dose IL-2	TNF (intraarterial)	Temozolomide	Ipilimumab	Vemurafenib	Trametinib	Dabrafanib
Austria	Free	Free	Free	Free	Full cost	<25% cost	Free	<25% cost	Full cost	<25% cost
Belgium	Free	Free	Free	Free	Full cost	Full cost	Free	Free	Free	Free
Cyprus	Not available	Free	Not available	Free	Free	Not available	Free	Not available	Not available	Not available
Denmark	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Finland	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
France	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Germany	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Greece	Free	Free	Free	Free	Free	Free	Free	Not available	Not available	Not available
Holland	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Iceland	Free	Free	Not available	Free	Free	Free	Free	Free	Not available	Not available
Ireland	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Israel	Free	Free	Free	Free	Free	Free	Free	Full cost	Discount >50% and <100%	Discount >50% and <100%
Italy	Free	Free	Free	Free	Free	Free	Free	Not available	Free	Not available
Luxembourg	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Norway	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Portugal	Free	Free	Free	Free	Free	Free	Free	Free	Not available	Not available
Spain	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
Sweden	Free	Free	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available
Switzerland	<25% cost	<25% cost	<25% cost	<25% cost	<25% cost	<25% cost	<25% cost	<25% cost	<25% cost	<25% cost
Turkey	Free	Free	Free	Free	Free	Free	Free	Free	Free	Free
United Kingdom	Free	Free	Free	Full cost	Full cost	Free	Free	Free	Full cost	Free

	Free
	<25% cost
	25-50% cost
	Discount >50% and <100%
	Full cost
	Not available
	Missing data

DTIC=Decarbazine,IL-2+Interleukin-2, TNF= Tumorr necrosis factor

Cherny N, et al. Ann Oncol 2016; 27:1423-14443

ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe

MELANOMA: actual availability										
Country:	Interferon	DTIC	Fotemustine	High-Dose IL-2	TNF (intraarterial)	Temozolomide	Ipilimumab	Vemurafenib	Trametinib	Dabrafanib
Austria	Always	Always	Always	Always	Not available	Always	Always	Always	Always	Always
Belgium	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Cyprus	Always	Always	Not available	Always	Always	Always	Always	Always	Always	Always
Denmark	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Finland	Usually	Usually	Usually	Usually	Not available	Usually	Usually	Usually	Usually	Usually
France	Always	Always	Always	Always	Usually	Always	Always	Always	Usually	Always
Germany	Always	Always	Always	Always	Usually	Always	Always	Always	Usually	Always
Greece	Always	Usually	Usually	Always	Not available	Usually	Usually	Always	Always	Always
Holland	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Iceland	Always	Always	Not available	Always	Always	Always	Always	Always	Always	Always
Ireland	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Israel	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Italy	Always	Always	Always	Occasionally	Not available	Always	Always	Always	Always	Not available
Luxembourg	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Norway	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Portugal	Always	Always	Always	Always	Always	Always	Occasionally	Occasionally	Always	Always
Spain	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Sweden	Always	Always	Always	Always	Always	Always	Always	Always	Always	Always
Switzerland	Always	Always	Not available	Always	Always	Always	Always	Always	Not available	Always
Turkey	Always	Always	Always	Never	Occasionally	Always	Always	Always	Always	Always
United Kingdom	Always	Always	Always	Never	Occasionally	Always	Always	Always	Occasionally	Occasionally

	Always
	Usually
	Half the time
	Occasionally
	Never
	Not available
	Missing data

DTIC=Decarbazine, IL-2+Interleukin-2, TNF= Tumorr necrosis factor

ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe

Prostate Cancer : Formulary and Cost						
Country:	Docetax.	Cabazitax.	Ketocon.	Abirat.	Enzalut.	Radium-223
Austria	Free	Free	Not available	<25% cost	<25% cost	Free
Belgium	Free	Free	Free	Free	Free	Free
Cyprus	Free	Full cost	Free	Free	Full cost	Full cost
Denmark	Free	Free	Free	Free	Free	Free
Finland	Free	Free	Free	Free	Free	Free
France	Free	Free	Free	Free	Free	Free
Germany	Free	Free	Free	Free	Free	Free
Greece	Free	Free	Free	Free	Free	Free
Holland	Free	Free	Free	Free	Free	Free
Iceland	Free	Free	Free	Free	Not available	Not available
Ireland	Free	Free	Free	Free	Free	Free
Israel	Free	Free	Full cost	Free	Full cost	Full cost
Italy	Free	Free	Full cost	Free	Full cost	Full cost
Luxembourg	Free	Free	<25% cost	Free	Full cost	Full cost
Norway	Free	Free	Free	Free	Free	Free
Portugal	Free	Free	Free	Free	Free	Free
Spain	Free	Free	<25% cost	Free	<25% cost	Free
Sweden	Free	Free	Not available	Free	Free	Free
Switzerland	<25% cost	<25% cost	<25% cost	Free	<25% cost	Free
Turkey	Free	Free	Free	Free	Free	Free
United Kingdom	Free	Free	Free	Free	Free	Free

Free
<25% cost
25-50% cost
Discount >50% and <100%
Full cost
Not available
Missing data

Docetax=Docetaxel, Carbzitx=Carbazitaxel, Ketocon=Ketoconazole, Abirat=Abiraterone, Enzalut=Enzalutamide

Prostate Cancer : Actual availability						
Country:	Docetax.	Cabazitax.	Ketocon.	Abirat.	Enzalut.	Radium-223
Austria	Always	Always	Usually	Always	Always	Always
Belgium	Always	Always	Always	Always	Always	Always
Cyprus	Always	Half the time	Usually	Usually	Occasionally	Never
Denmark	Always	Always	Always	Always	Always	Always
Finland	Always	Always	Always	Always	Always	Always
France	Always	Always	Always	Always	Always	Always
Germany	Always	Always	Always	Always	Always	Always
Greece	Always	Usually	Not available	Half the time	Not available	Occasionally
Holland	Always	Always	Always	Always	Always	Always
Iceland	Always	Always	Always	Always	Not available	Not available
Ireland	Always	Always	Always	Always	Always	Always
Israel	Always	Always	Always	Always	Always	Always
Italy	Always	Always	Always	Always	Always	Always
Luxembourg	Always	Always	Always	Always	Not available	Always
Norway	Always	Always	Always	Always	Always	Always
Portugal	Always	Always	Always	Always	Always	Always
Spain	Always	Always	Always	Always	Always	Always
Sweden	Always	Always	Not available	Usually	Always	Always
Switzerland	Always	Always	Always	Always	Always	Always
Turkey	Always	Always	Always	Always	Always	Always
United Kingdom	Always	Usually	Always	Usually	Usually	Usually

Always
Usually
Half the time
Occasionally
Never
Not available
Missing data

Docetax=Docetaxel, Carbzitx=Carbazitaxel, Ketocon=Ketoconazole, Abirat=Abiraterone, Enzalut=Enzalutamide

Cherny N, et al. Ann Oncol 2016; 27:1423-14443

Critical issues regarding benefit from new oncology drugs?

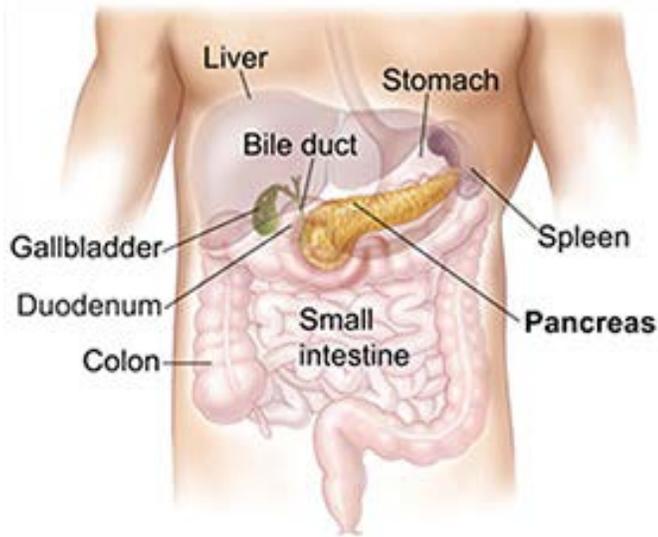
- What implies a delay in availability of new drugs for the patients?
 - Individual hope of a cancer patient to have a benefit for survival
 - Risk of not sufficiently collected data on side effect
 - Imbalances between European citizens due to different HTAs and payers

- How can we quantify the benefit for patients?
 - Improvement of OS
 - Improvement of PFS (does not imply a benefit for OS)
 - Life quality, symptom control

- Not all new oncology drugs prolong survival!

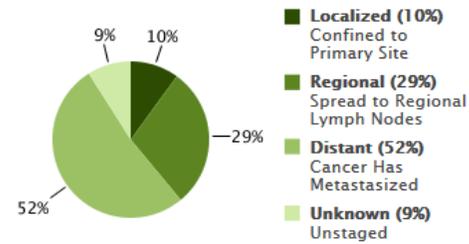
- What is affordable for the public health system?

Relative survival of pancreatic cancer patients

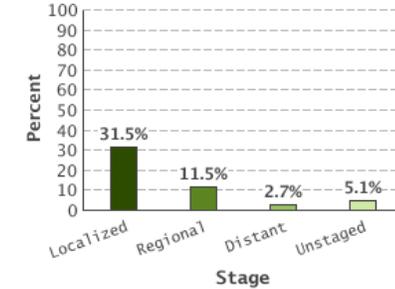


Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Pancreas Cancer

Percent of Cases by Stage



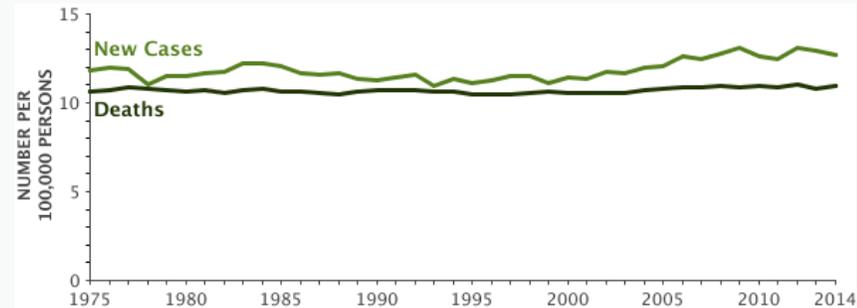
5-Year Relative Survival



SEER 18 2007-2013, All Races, Both Sexes by SEER Summary Stage 2000

New Cases, Deaths and 5-Year Relative Survival

[View Data Table](#)

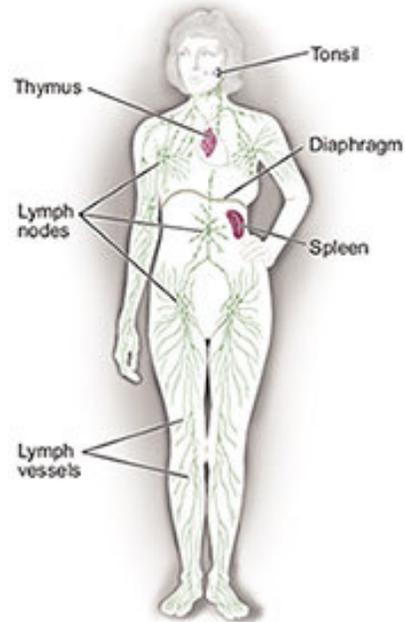


Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	3.0%	3.3%	3.2%	3.7%	3.6%	5.1%	6.2%	8.5%

SEER 9 Incidence & U.S. Mortality 1975-2014, All Races, Both Sexes. Rates are Age-Adjusted.

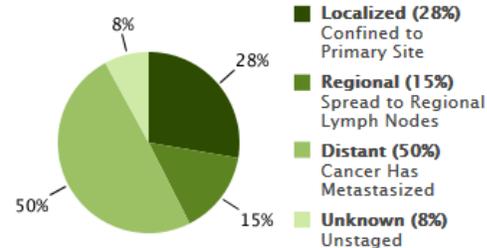
<https://seer.cancer.gov/statfacts/html/kidrp.html>

Relative survival of non-Hodgkin lymphoma patients

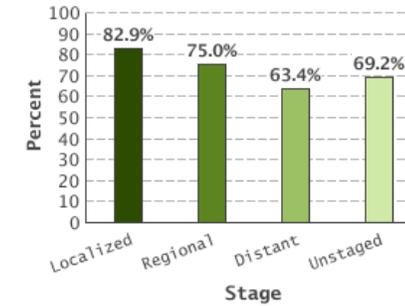


Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Non-Hodgkin Lymphoma

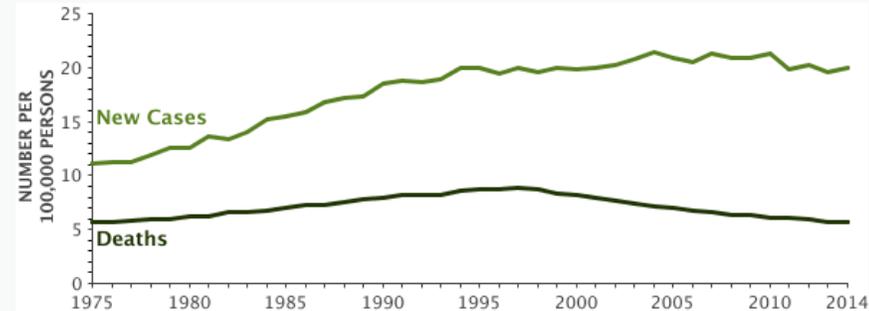
Percent of Cases by Stage



5-Year Relative Survival



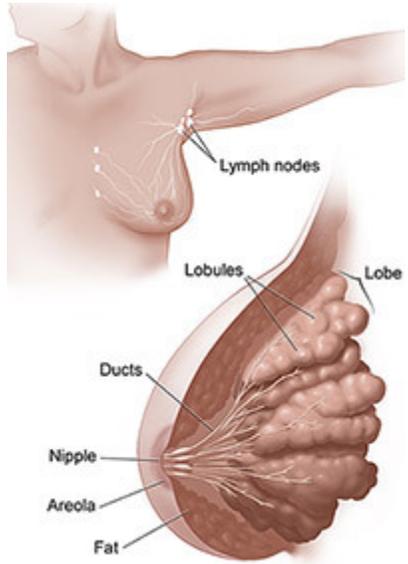
SEER 18 2007–2013, All Races, Both Sexes by SEER Summary Stage 2000



Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	45.7%	49.1%	52.4%	49.7%	51.9%	63.8%	71.6%	74.0%

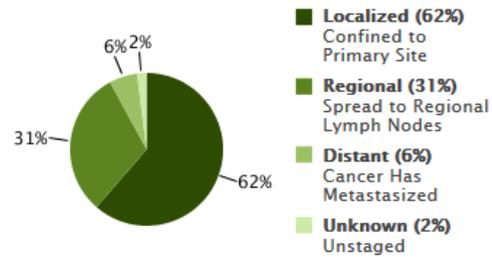
SEER 9 Incidence & U.S. Mortality 1975–2014, All Races, Both Sexes. Rates are Age-Adjusted.

Relative survival of breast cancer patients

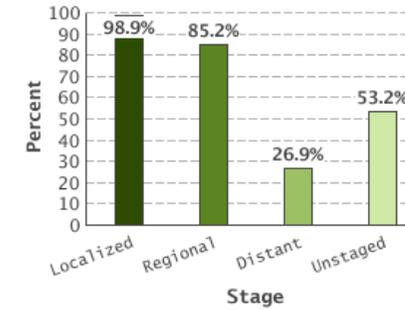


Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Female Breast Cancer

Percent of Cases by Stage



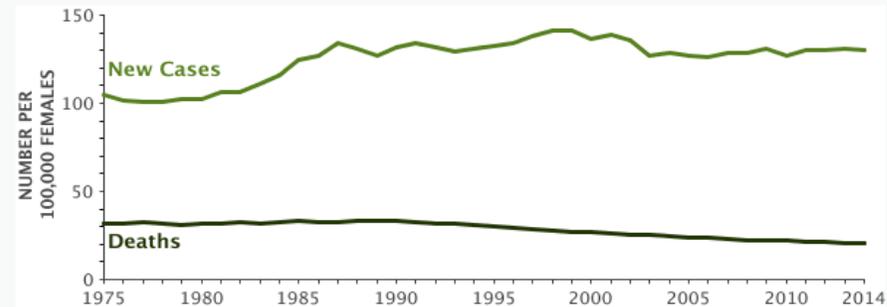
5-Year Relative Survival



SEER 18 2007-2013, All Races, Females by SEER Summary Stage 2000

New Cases, Deaths and 5-Year Relative Survival

[View Data Table](#)

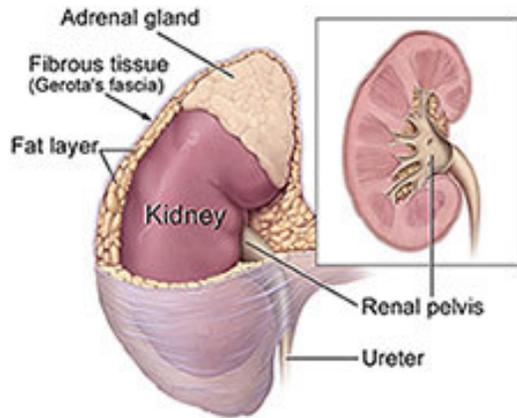


Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	75.2%	74.9%	78.4%	84.6%	86.8%	90.2%	90.5%	91.3%

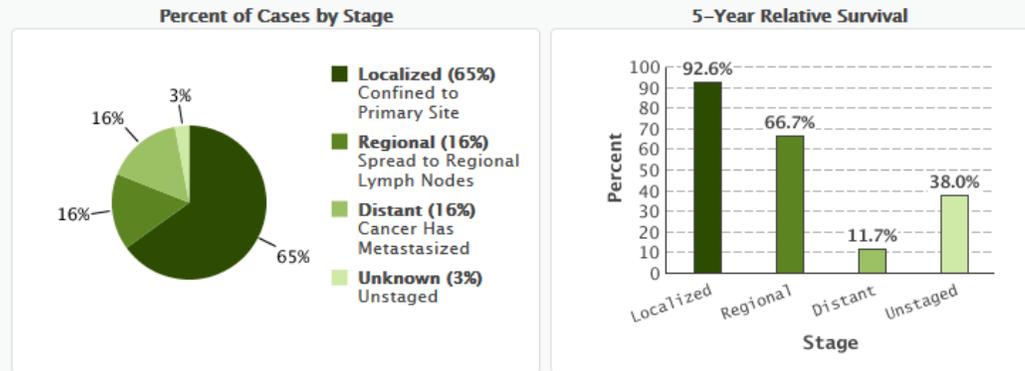
SEER 9 Incidence & U.S. Mortality 1975-2014, All Races, Females. Rates are Age-Adjusted.

<https://seer.cancer.gov/statfacts/html/kidrp.html>

Relative survival of renal cell cancer patients



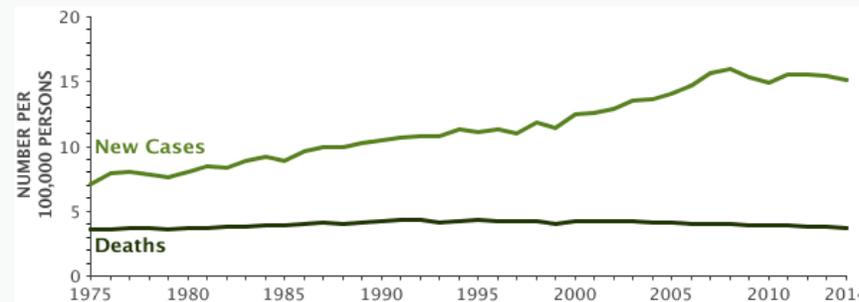
Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Kidney and Renal Pelvis Cancer



SEER 18 2007-2013, All Races, Both Sexes by SEER Summary Stage 2000

New Cases, Deaths and 5-Year Relative Survival

[View Data Table](#)

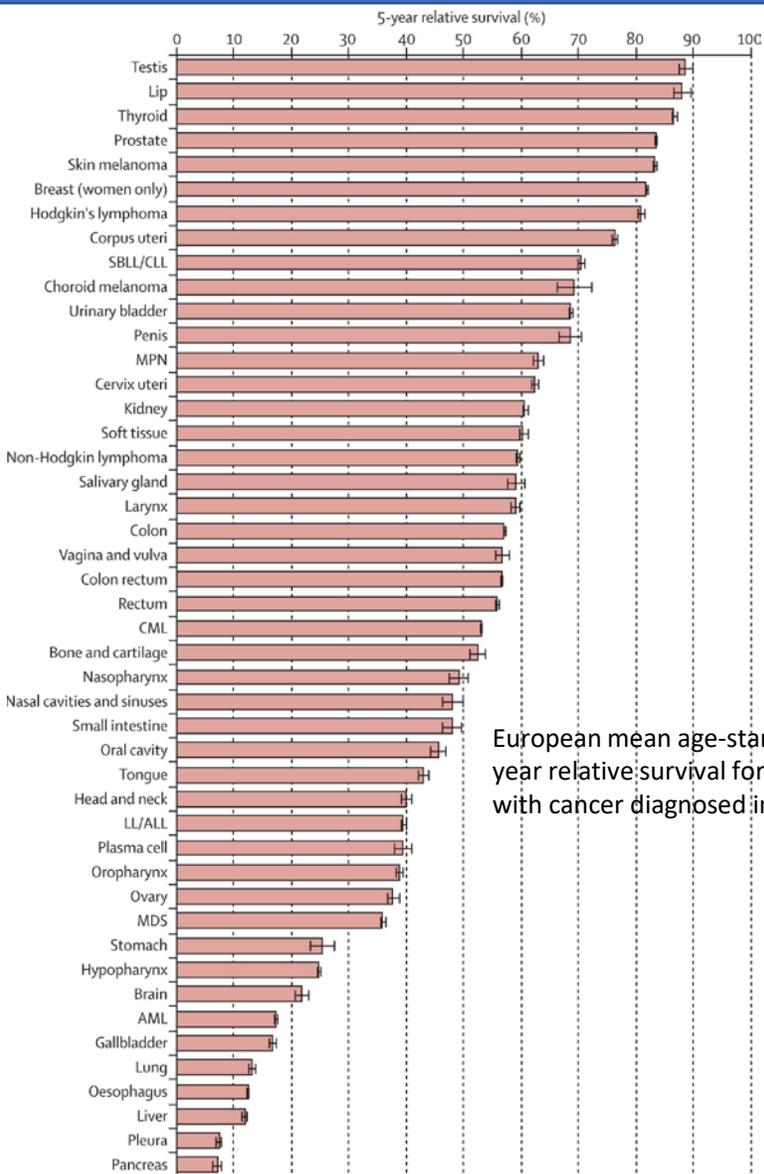


Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	52.1%	54.3%	55.2%	59.8%	61.4%	65.5%	74.5%	76.0%

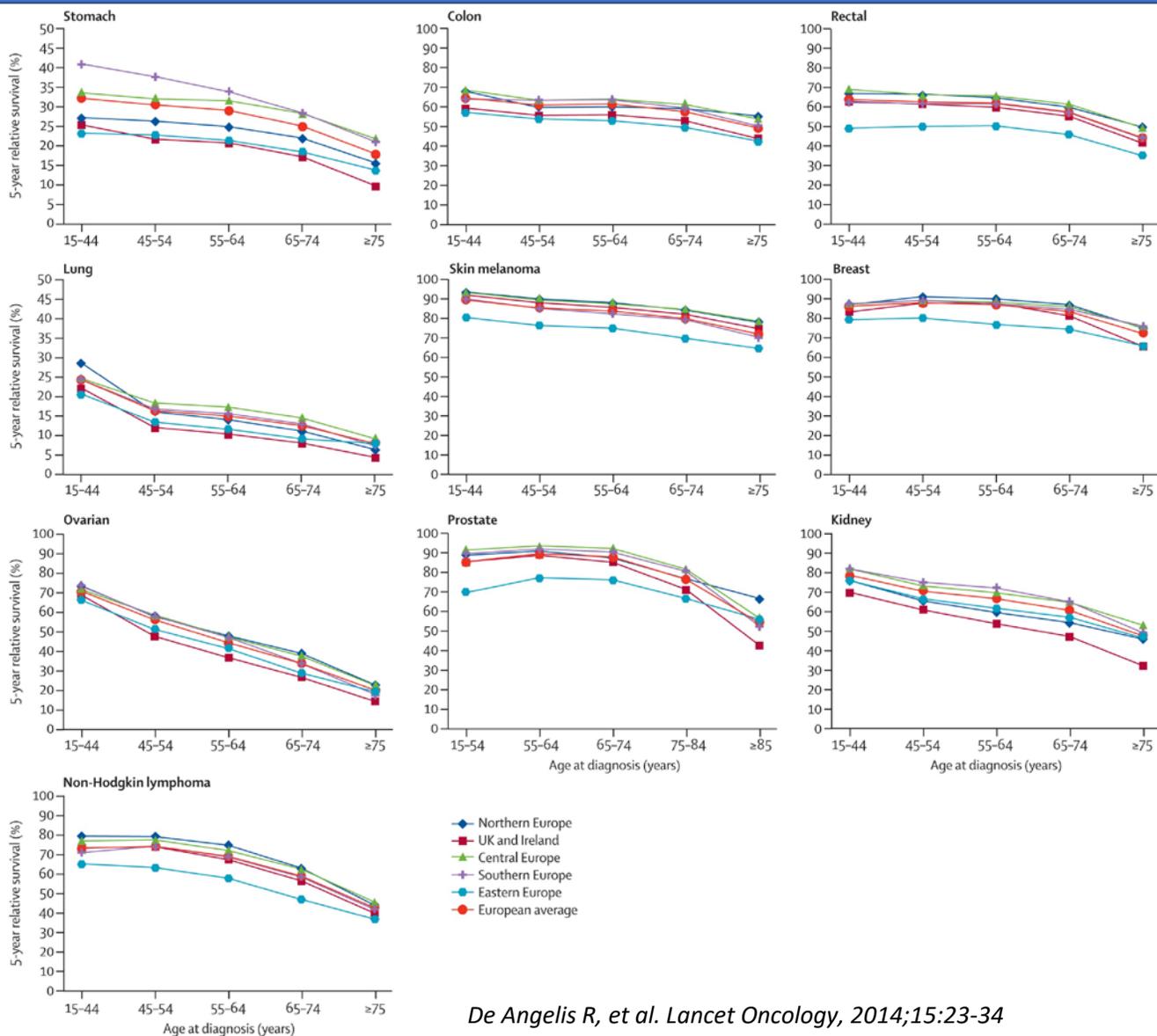
SEER 9 Incidence & U.S. Mortality 1975-2014, All Races, Both Sexes. Rates are Age-Adjusted.

Eurocare-5

European mean age-standardised 5-year relative survival for adult patients with cancer diagnosed in 2000–2007



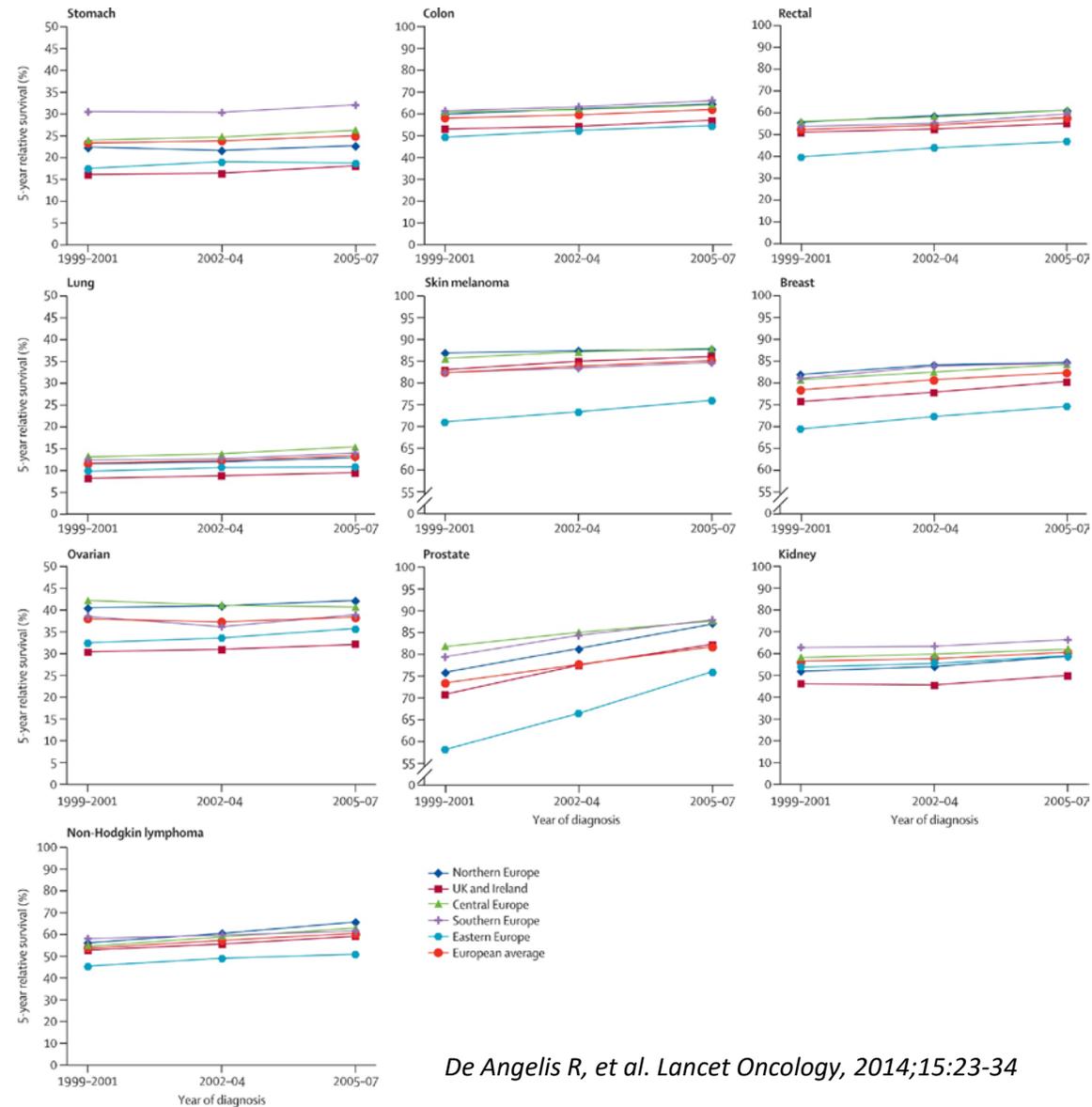
European mean age-standardised 5-year relative survival for adult patients with cancer diagnosed in 2000–2007



De Angelis R, et al. *Lancet Oncology*, 2014;15:23-34

Eurocare-5

Age-standardised 5-year relative survival for adult cancer patients followed up in 1999–2001, 2002–04, and 2005–075-year survival data



De Angelis R, et al. *Lancet Oncology*, 2014;15:23-34

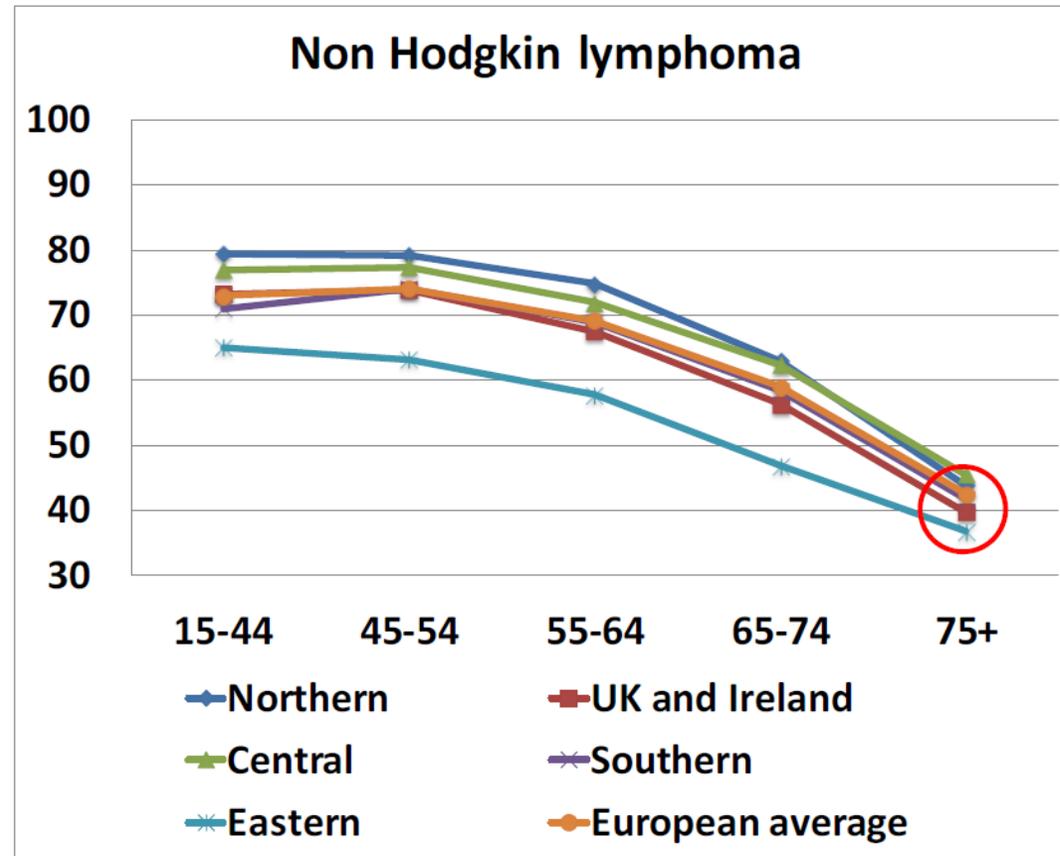


Survival differences by age

age-specific 5-y relative survival 2000-07

Eastern countries

- survival gap is wider in younger ages
- almost no differences in the elderly



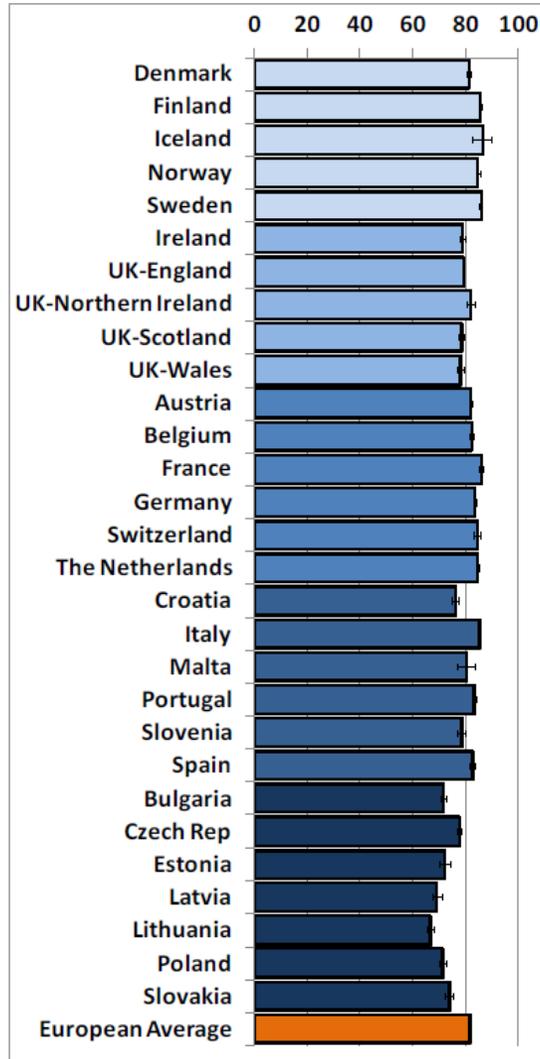
Eurocare-5

Period 2000-2007

deAngelis R, et al

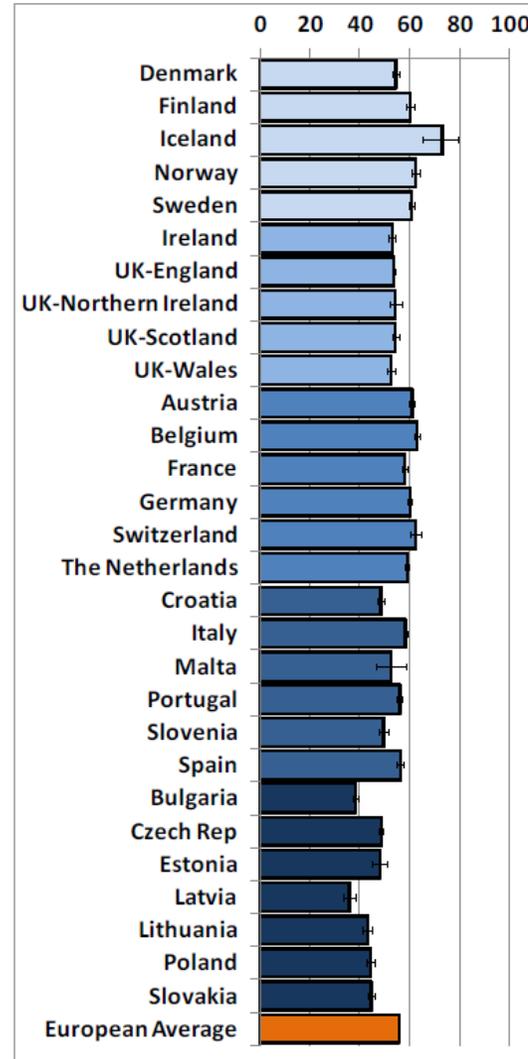
Breast

5-y relative survival 2000-07



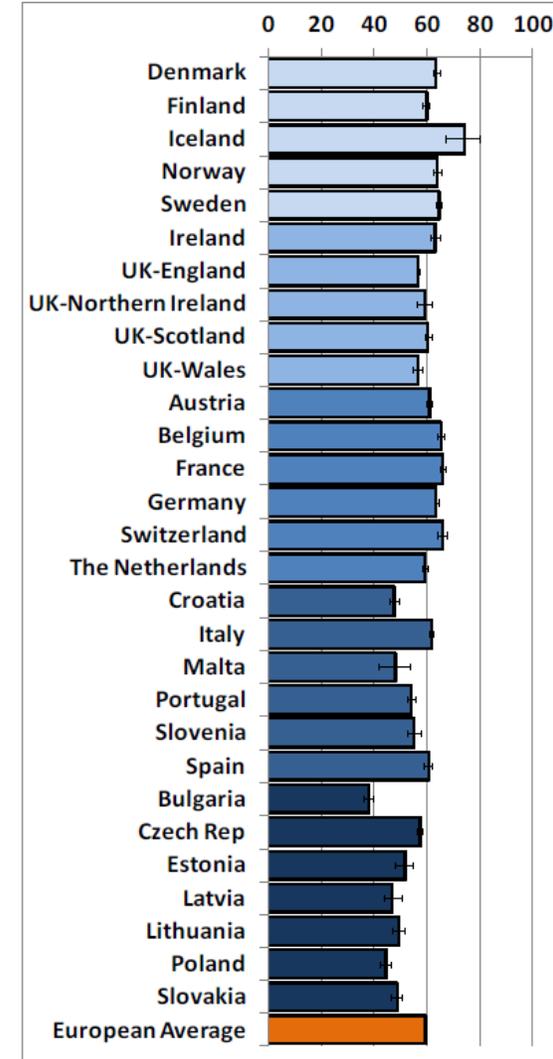
Rectal

5-y relative survival 2000-07



NH lymphomas

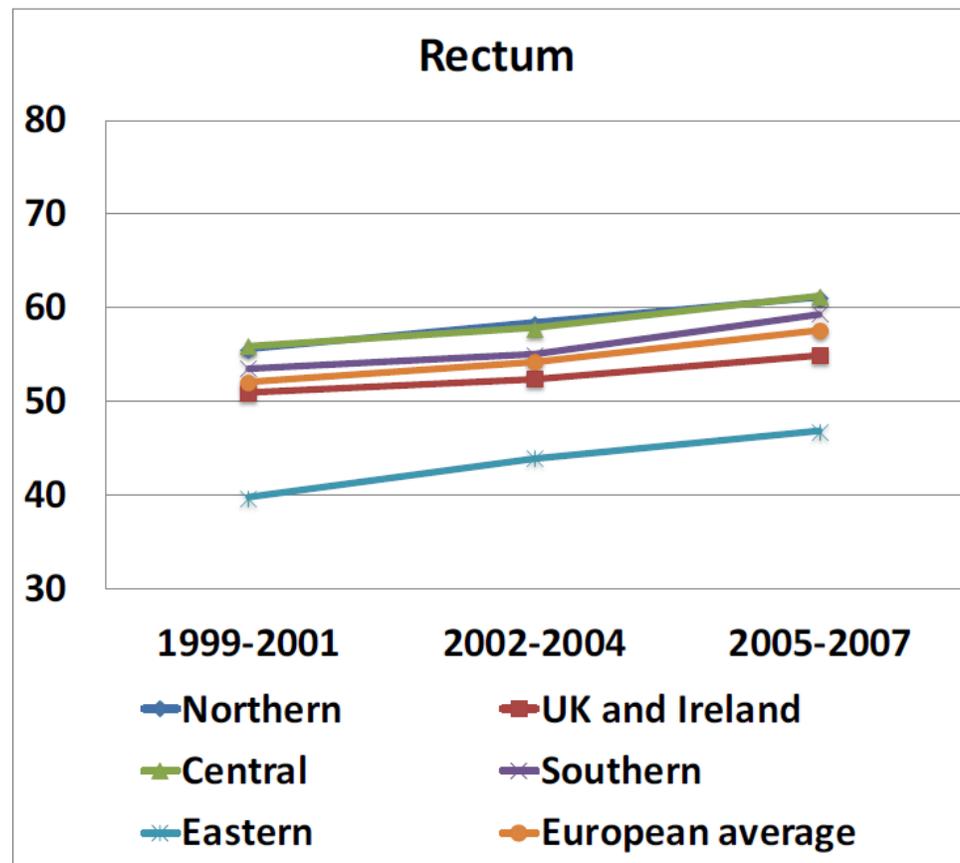
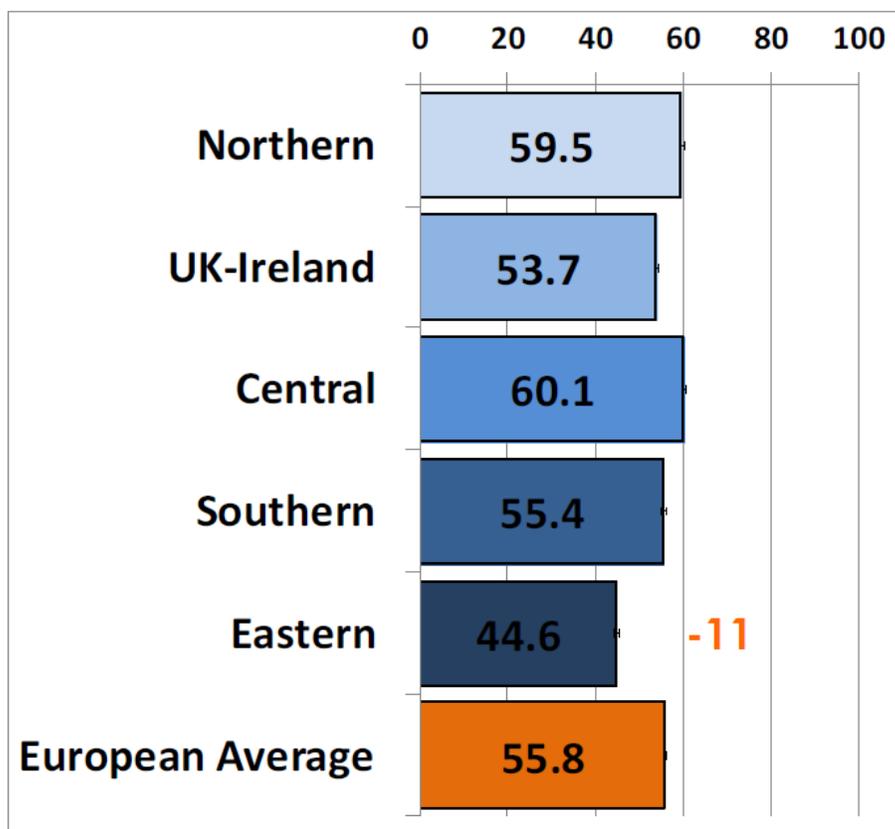
5-y relative survival 2000-07





Rectal cancer

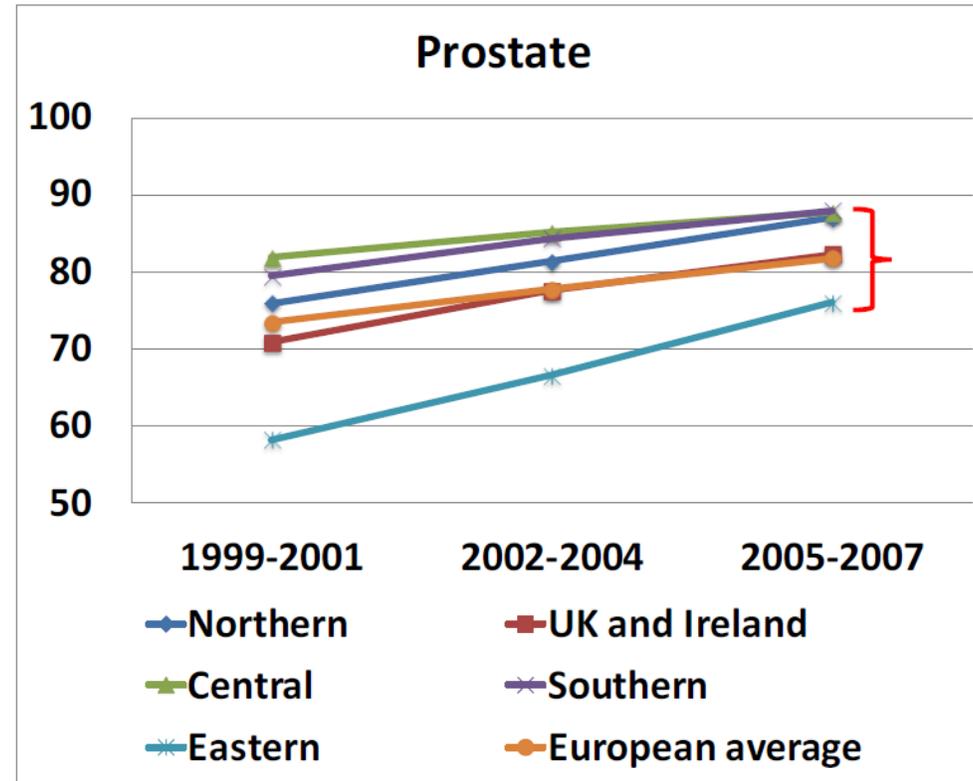
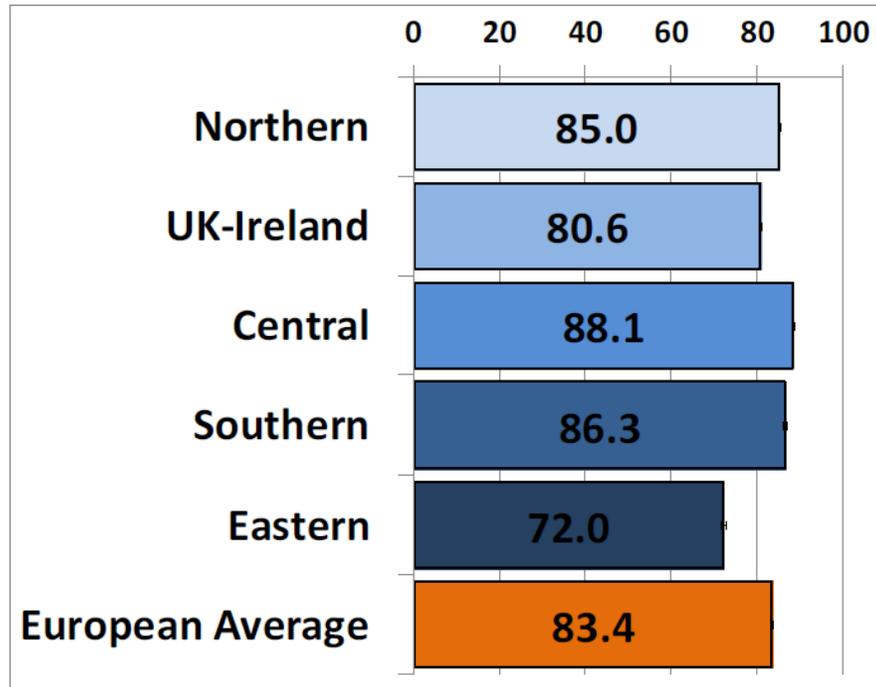
5-y relative survival 2000-07 and time trends 1999-2007





Prostatic cancer

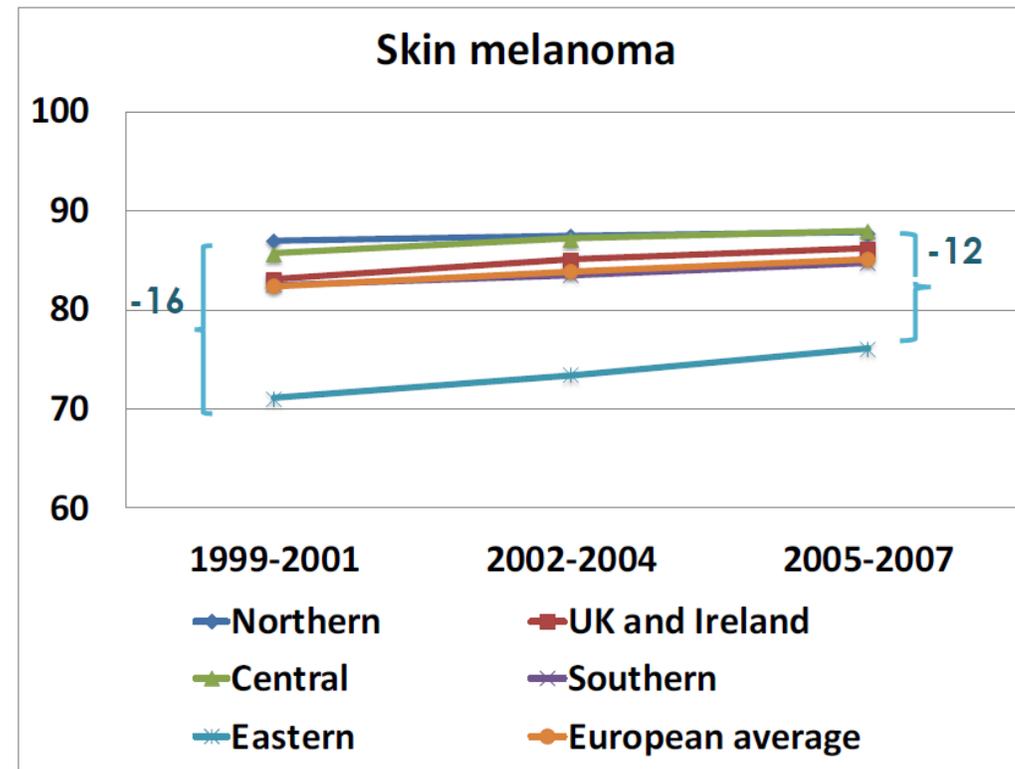
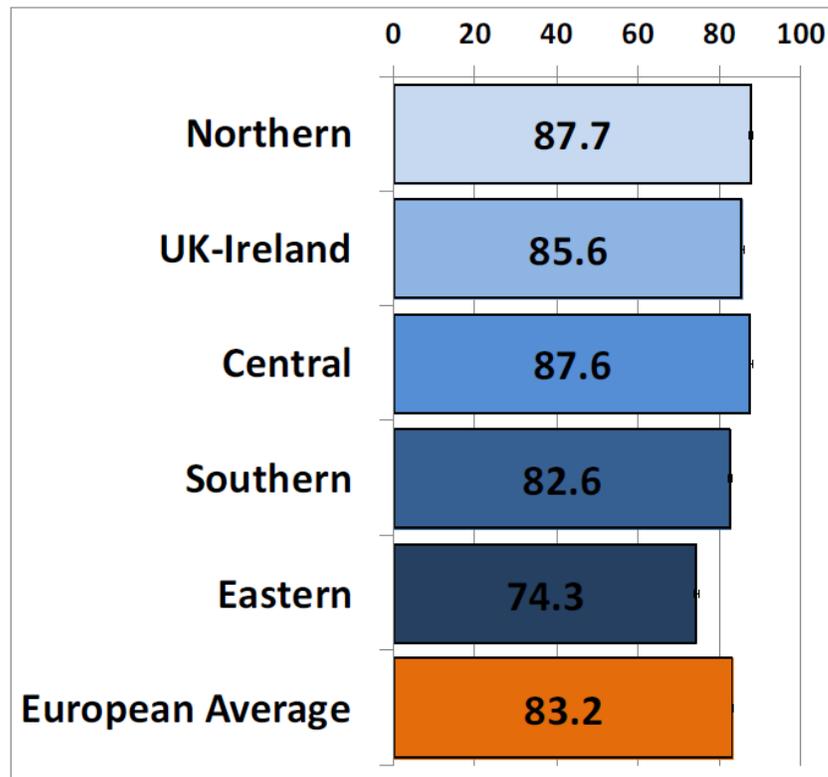
5-y relative survival 2000-07 and time trends 1999-2007





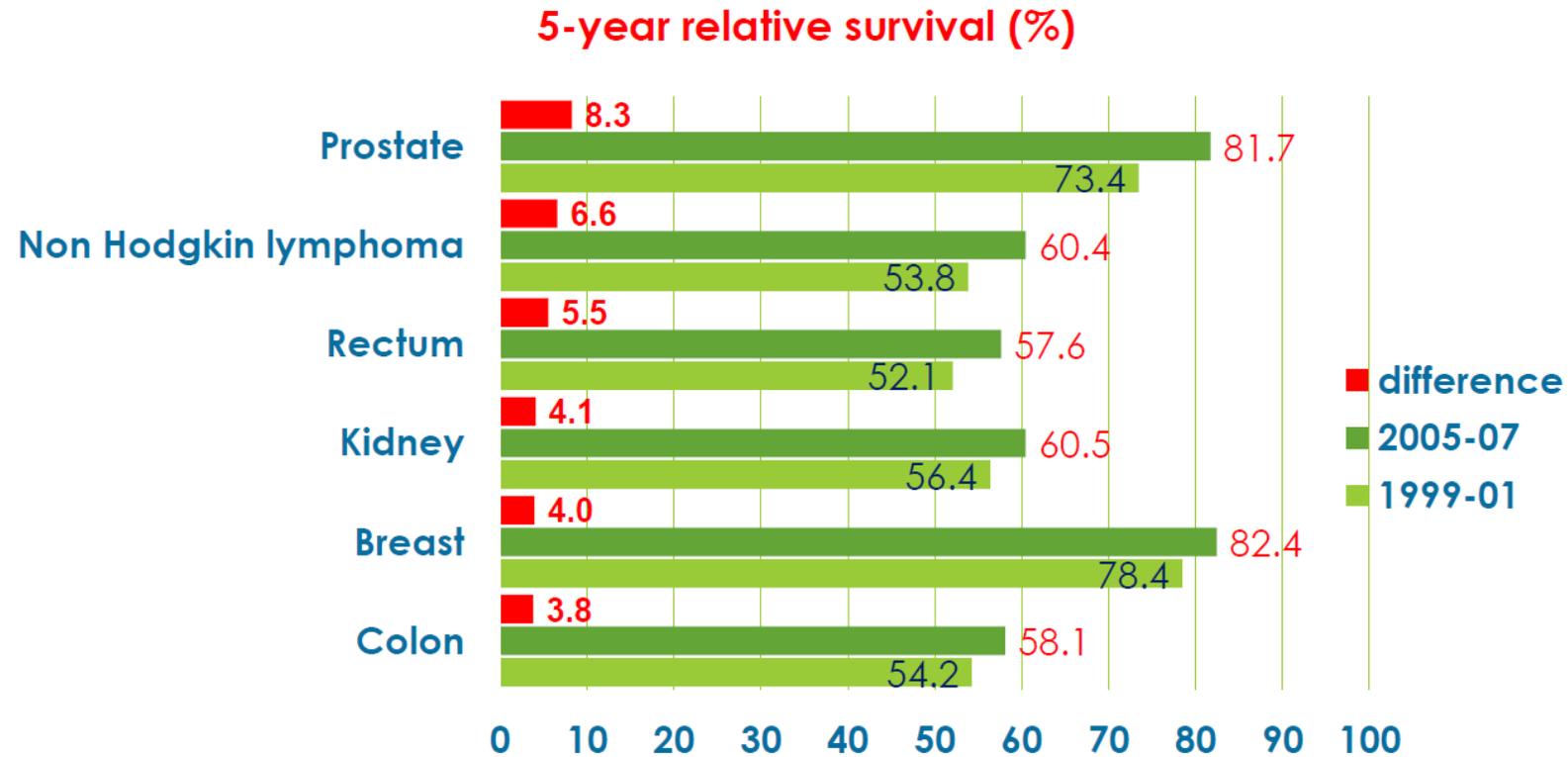
Skin melanoma

5-y relative survival 2000-07 and time trends 1999-07





Survival time trends in Europe 1999-2007



Sales prices for new oncological drugs in European countries

(€/pro unit according to Vogler et al, Lancet Oncol 2015)

Wirkstoff	CH	D	DK	E	F	GR	P	S	UK
Bendamustin-HCl	293,42	274,91	277,94	n.v.	273,81	273,81	n.v.	393,07	283,28
Bortezomib	1365,10	1357,30	1001,60	1120,10	1043,90	855,63	1143,00	1215,80	894,91
Cabazitaxel	n.v.	4395,00	4237,50	4100,00	n.v.	n.v.	n.v.	4978,50	3796,20
Imatinib	24,39	23,92	17,97	19,74	17,47	15,45	17,98	21,64	16,87
Lenalidomid	278,87	266,00	239,75	250,78	165,16	195,59	n.v.	240,05	184,88
Ofatumumab	n.v.	252,08	207,61	n.v.	n.v.	188,61	n.v.	247,74	n.v.
Plerixafor	n.v.	5650,00	5692,50	5482,30	5650,00	4918,50	n.v.	7703,50	5015,10
Vemurafenib	40,59	41,25	36,23	n.v.	37,09	n.v.	n.v.	39,38	32,20
Zoledronsäure	138,47	282,75	253,89	256,37	215,68	128,34	258,00	305,89	204,45

CH = Schweiz; D = Deutschland; DK = Dänemark; E = Spanien; F = Frankreich; GR = Griechenland; P = Portugal; S = Schweden;
UK = Großbritannien; n.v. = nicht verfügbar

What`s about oncology drugs without a confirmed benefit for OS?

Disease-free survival as a surrogate

- In acute leukemias, DFS and EFS are accepted surrogates for OS as the achievement of CR is for DFS.

Progression-free survival as a surrogate

- Analyses and statistical models to assess the concordance between PFS and OS show that predominantly when median OS after progression is short (ie, <12 months), PFS seems to be a even reasonable alternative endpoint to OS.
- **BUT**
 - Subsequent treatments probably dilute initial benefit.
 - Early censoring, discontinuing or patients`lost in the clinical trial.
 - Prolonged exposure to targeted therapies might lead to the evolution of tumours with a different phenotype, thus, off setting any initial advantage from the treatment shown initially as PFS.
 - The effect of immunotherapies (e.g. check-point inhibitors) is a late effect, which might occur after initial tumor progression or have an effect on subsequent therapies
 - ...

What`s about **symptom control** as an additional endpoint?

The actual situation

- Increasing approvals of new anti-cancer drugs
- Therapy is more and more individualizes based not only on histologically but on genetically defined subgroups
- New anti-cancer drugs are mostly „high“ pricing drugs
- Combinations of new anti-cancer drugs rise up to extremely high costs
- Financial strain for the health economy of different European countries
- Disparancies in drug availability for patients in Europe

Disparities in cancer drug availability across Europe and their consequences for cancer care and prognosis – reasons, solutions and perspectives

- Different public health care systems within EU member states and their effects on inequalities in cancer outcome
- Different evaluation criteria of HTA agencies and time schedules – how to overcome
- What can the public health bear in regard to different Economic situations
- Different pricings for cancer drugs in EU member states – its implications
- Different models for early drug availability in different countries by pharma
- Reference pricing and consequences for pharma