Instituto de Investigación
Hospital 12 de Octubre

SPANISH NATIONAL CANCER RESEARCH CENTRE

UNIVERSIDAD COMPLUTENSE MADRID

Lost in traslation

Barriers from research to Clinic

Luis Paz-Ares

Hospital Universitario 12 de Octubre

Disclosures

- **Honoraria (self)**: Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Ipsen, Merck, Merck Sharp & Dohme, Mirati, Novartis, Pfizer, Pharmamar, Roche, Sanofi, Servier, Sysmex, Takeda
- **Speaker Bureau / Expert testimony**: AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Roche
- **Leadership role**: Altum Sequencing
- **Research grant / Funding (self)**: AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme
- **Officer / Board of Directors**: Genómica
- **Spouse / Financial dependant**: AAA, Advanz Pharma, Bayer, HMP, Ipsen, Merck, Merck, Sharp & Dohme, Midatech Pharma, Novartis, Pfizer, PharmaMar, Pierre Fabre, Roche, Sanofi, Servier

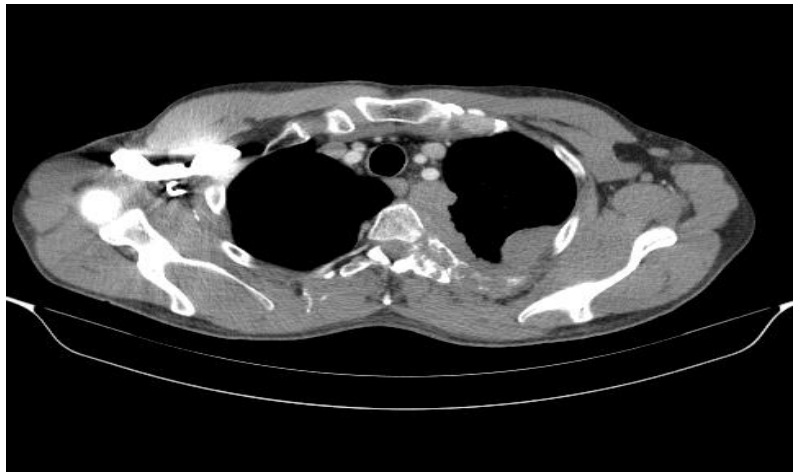
Caso Clínico

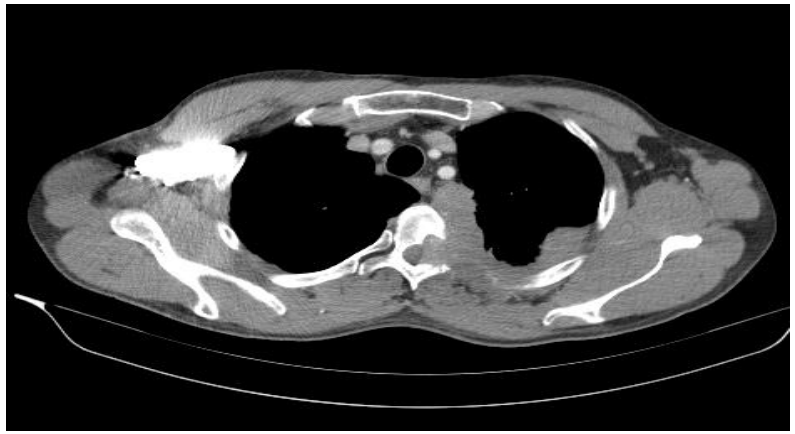
- Varón de 38 años
- AP: fumador (IPA:15)
- Dic 2015:

  - Ca pulmón epidermoide estadio IV (compresión medular)
  - Radioterapia (10 x 300 cGy)
- Enero 2016:

  - Segunda opinión en HU 12 de Octubre: Ensayo clínico ??
  - **CM 227 trial – Ensayo aleatorizado randomized to Ipi + Nivo**

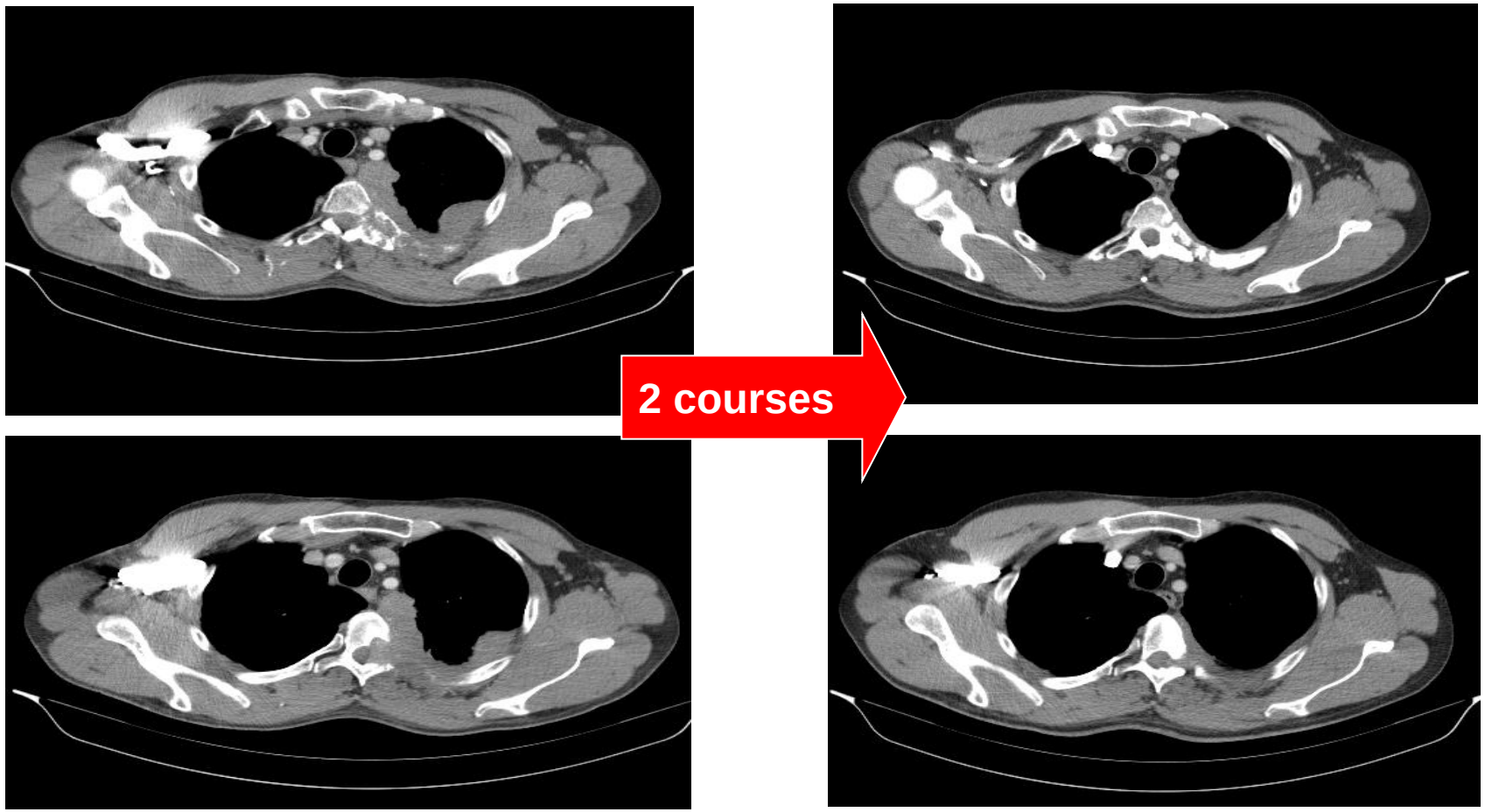
Caso Clínico





Enero 2016

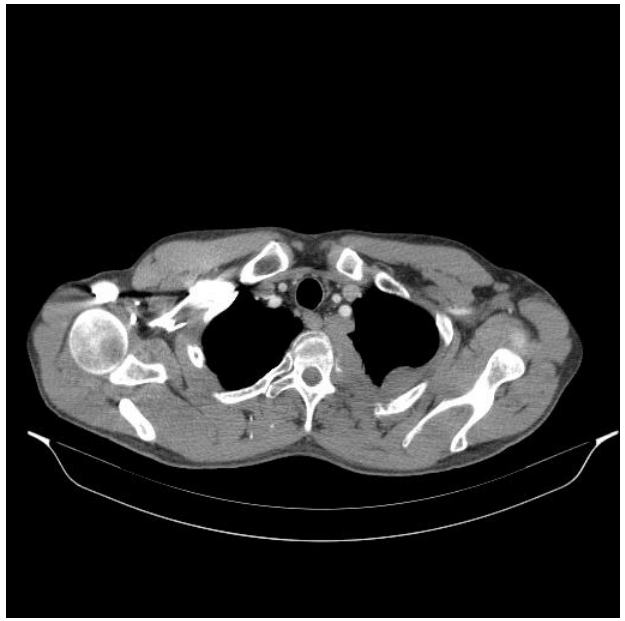
Caso Clínico

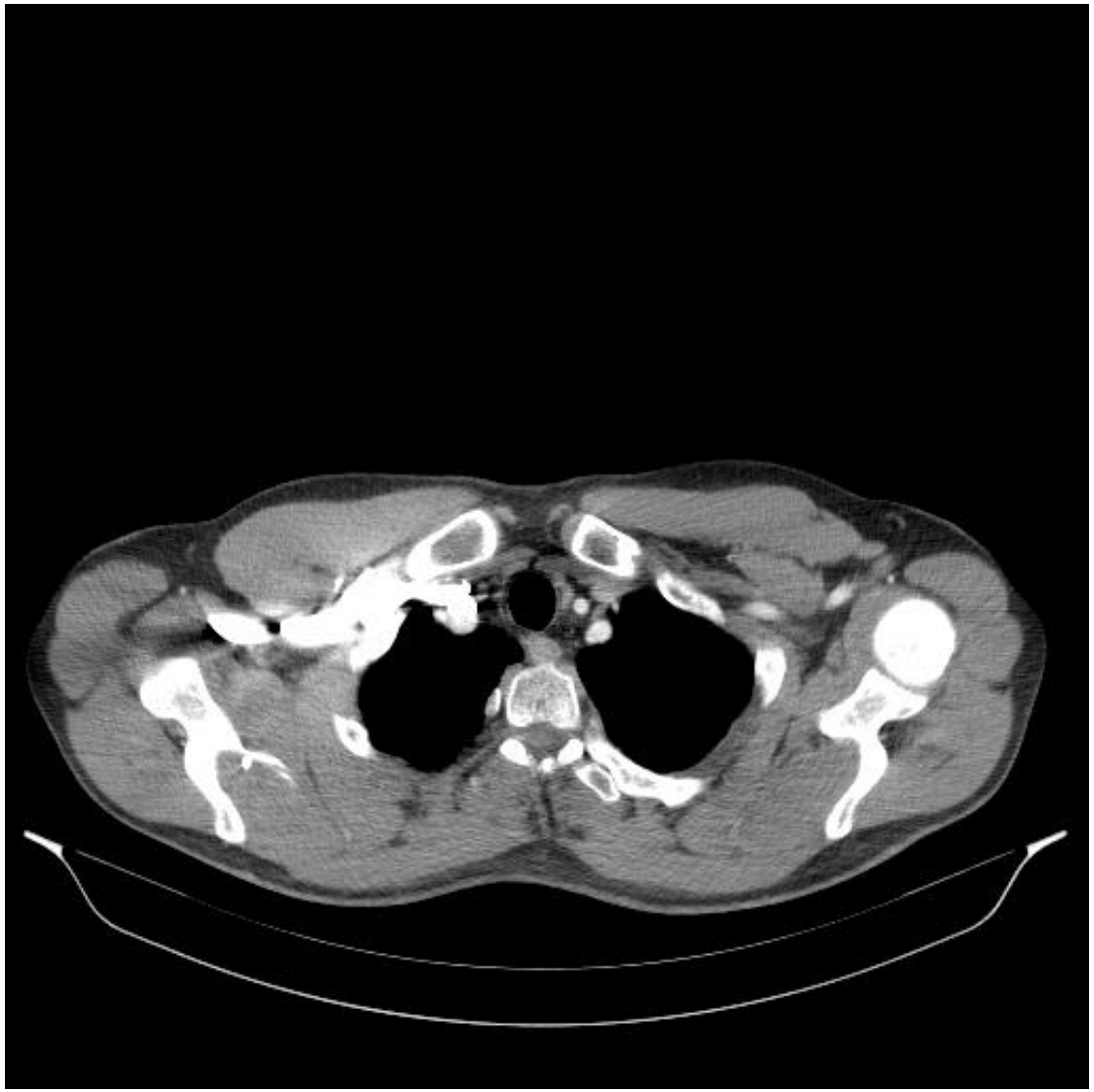


Enero 2016

Marzo 2016

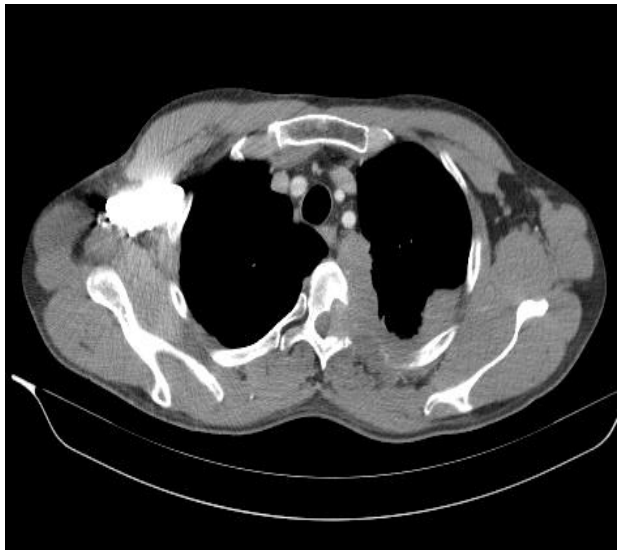
Caso Clínico

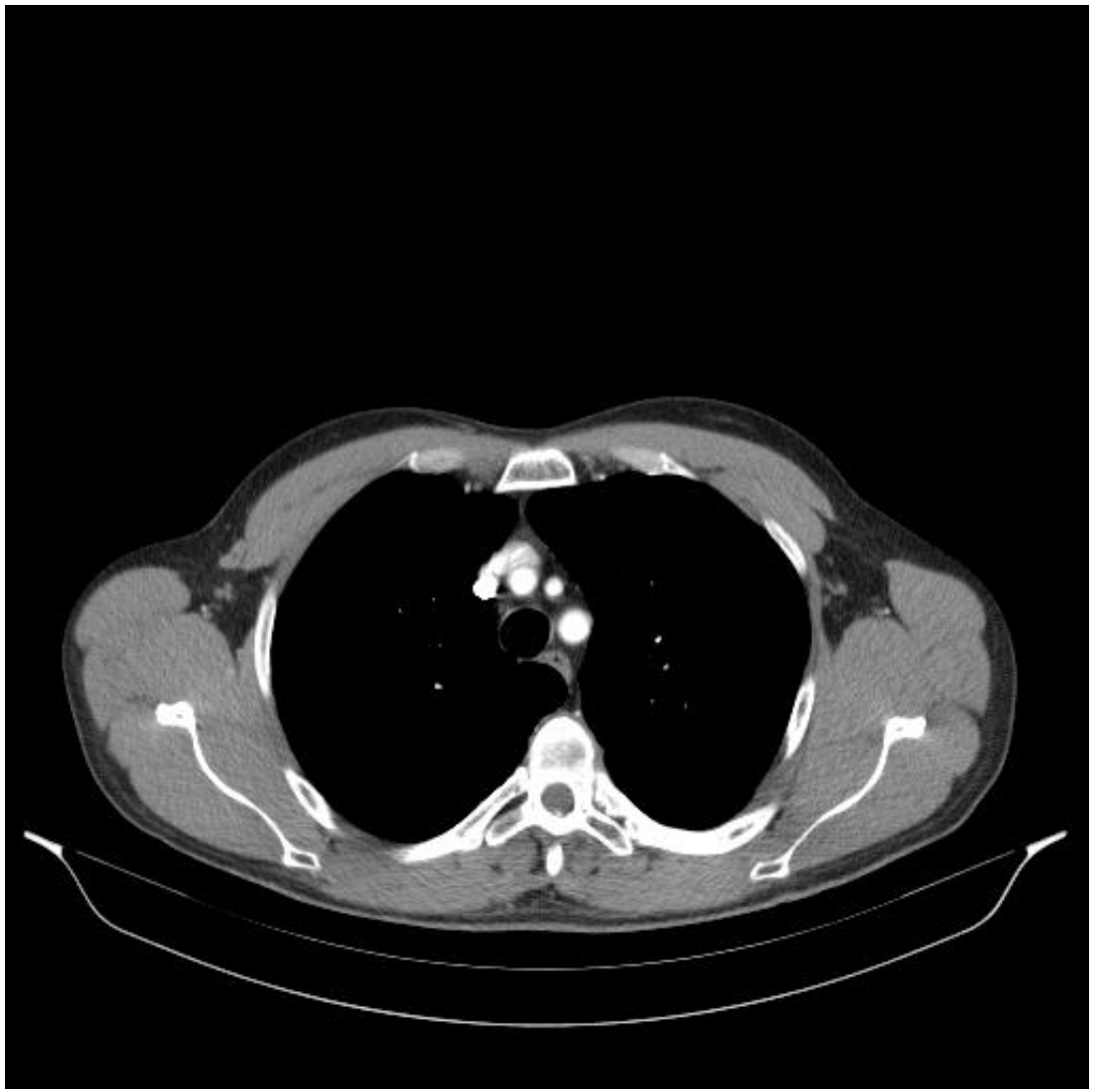




Septiembre 2023

Caso Clínico





Noviembre 2023

Agenda

- The oncologist
- The research budget
- The approval
- The reinbursement

Agenda

- **The oncologist**
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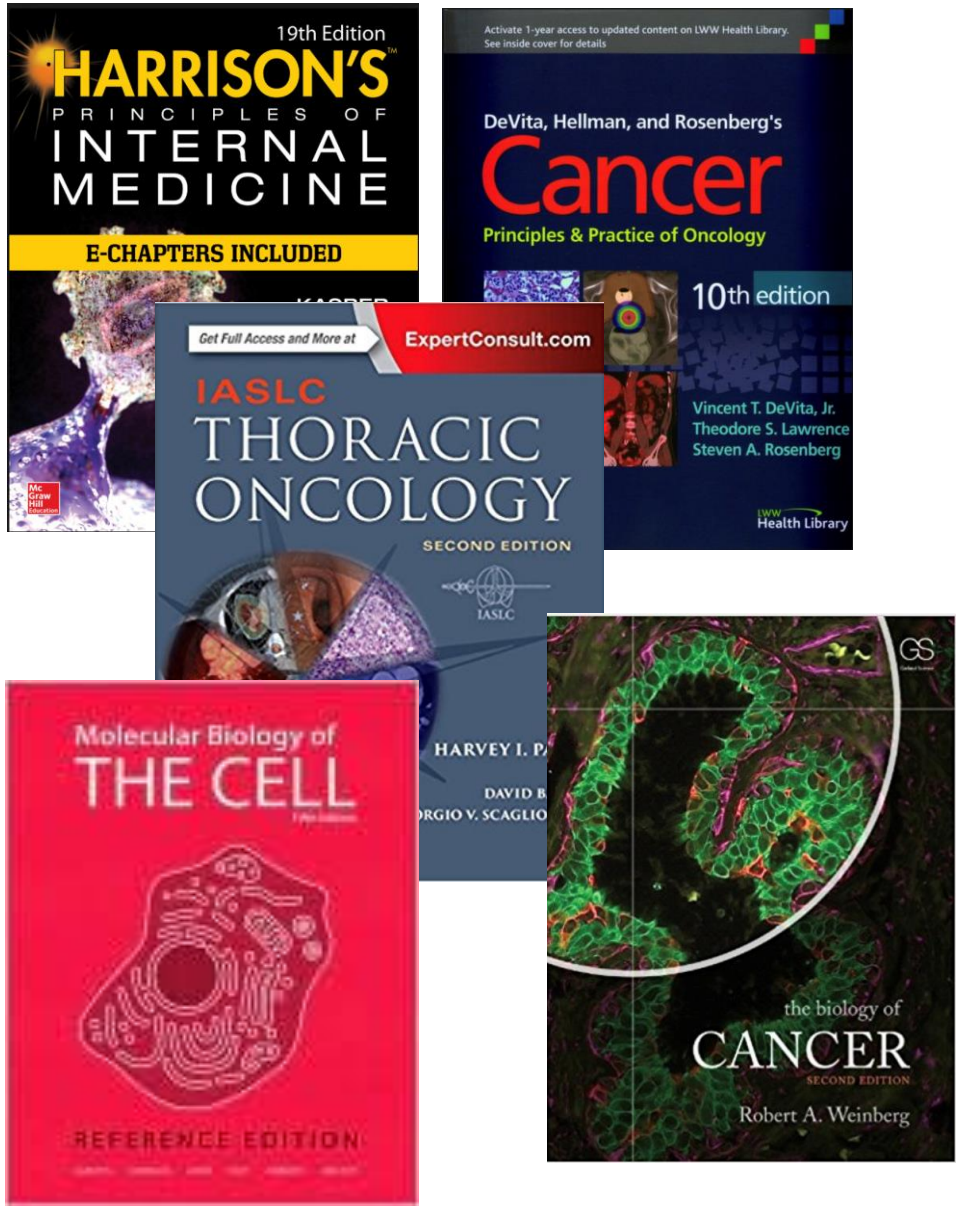
Training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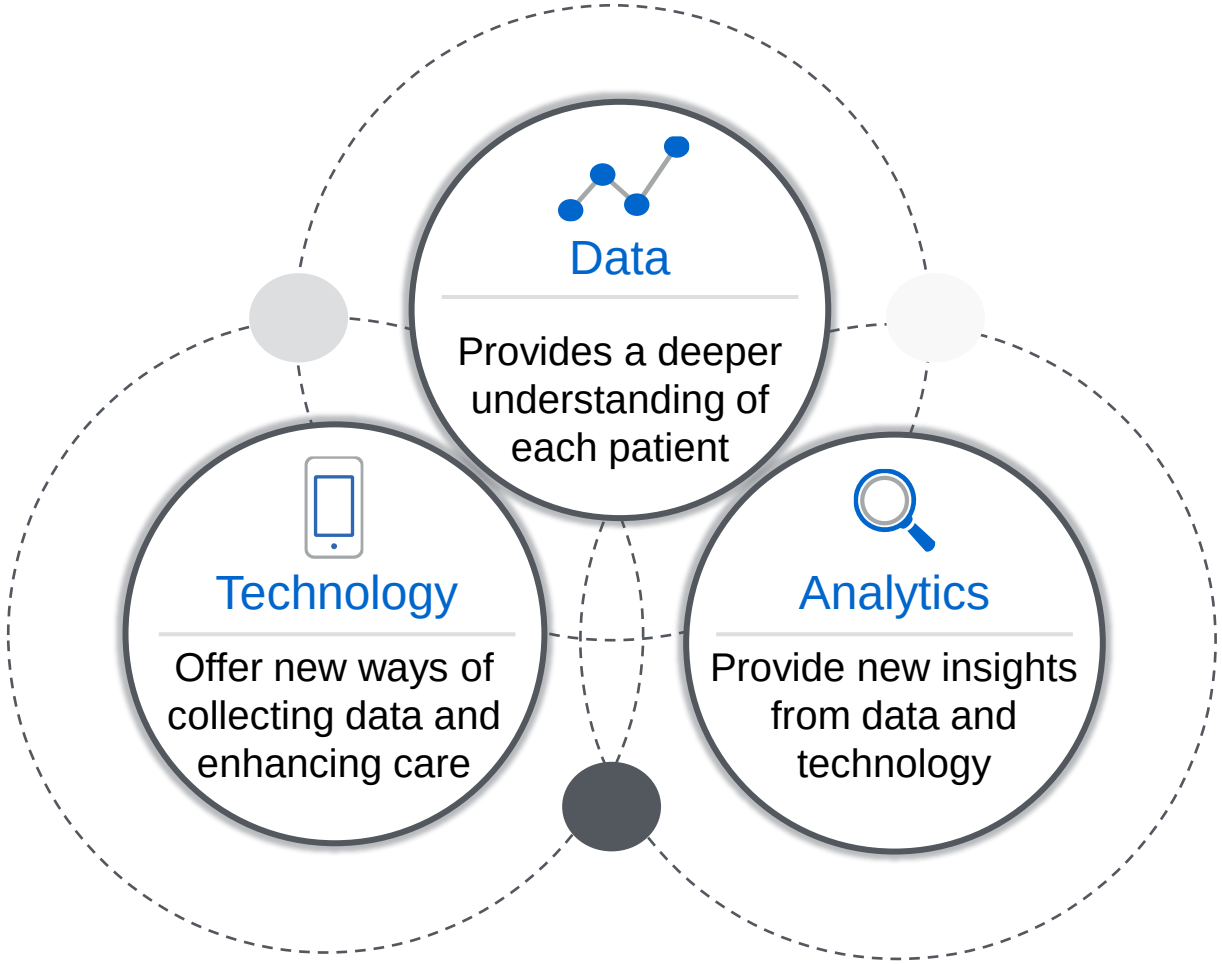
DANA-FARBER
CANCER INSTITUTE
CARE
60
YEARS

Need of Traslational Research experience?

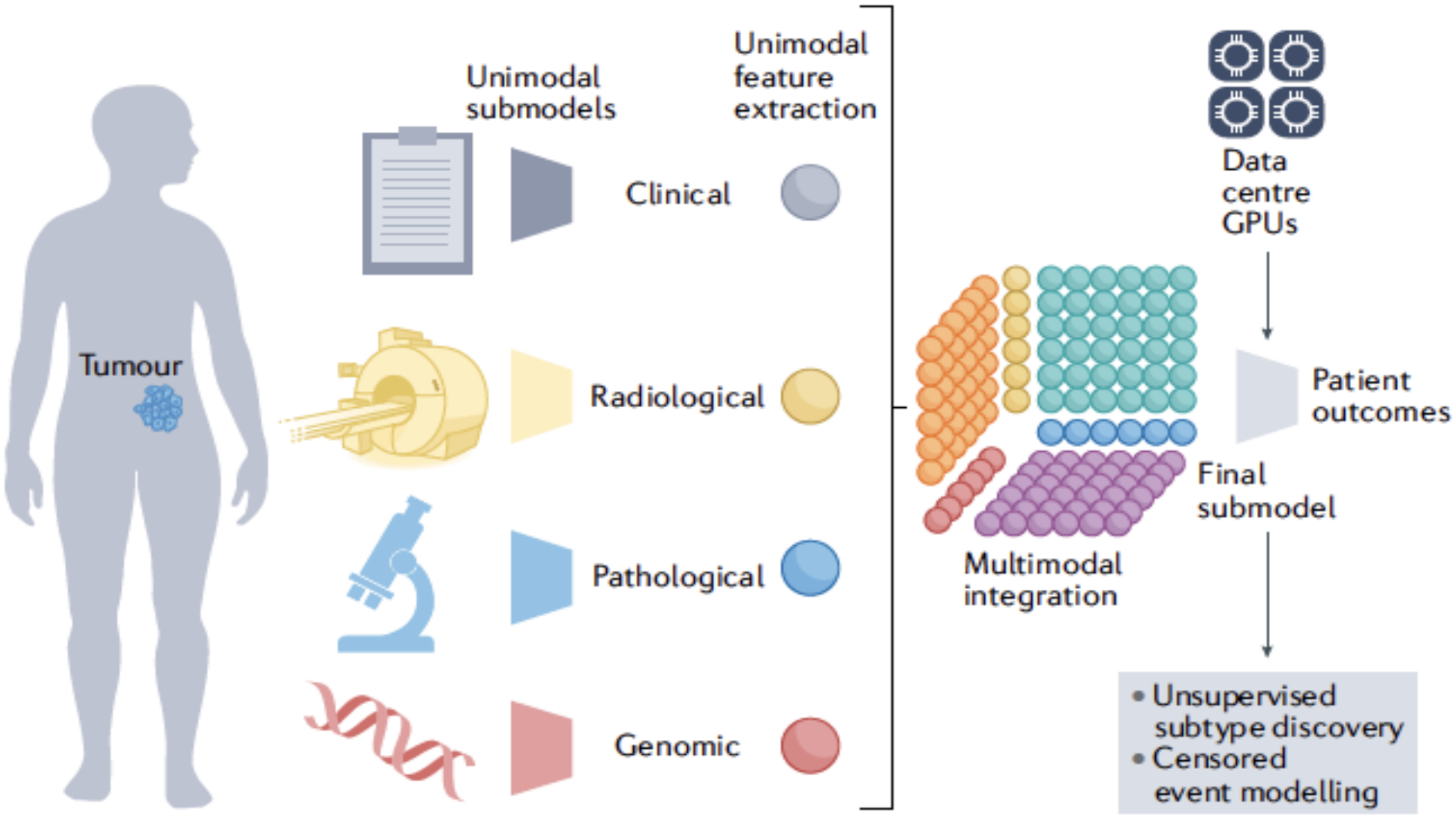
- Broad knowledge
- Lab Experience – center of excellence better!
- Look at your local environment rules (non-written!)
  - Mentor advice
  - Cases of success
- Your career will be longer (but fascinating) !!!

The convergence of science and technology provides an exceptional opportunity to transform healthcare



Data, technology and analytics provide opportunities to address healthcare challenges, accelerate R&D and improve patient outcomes

Data extraction and integration



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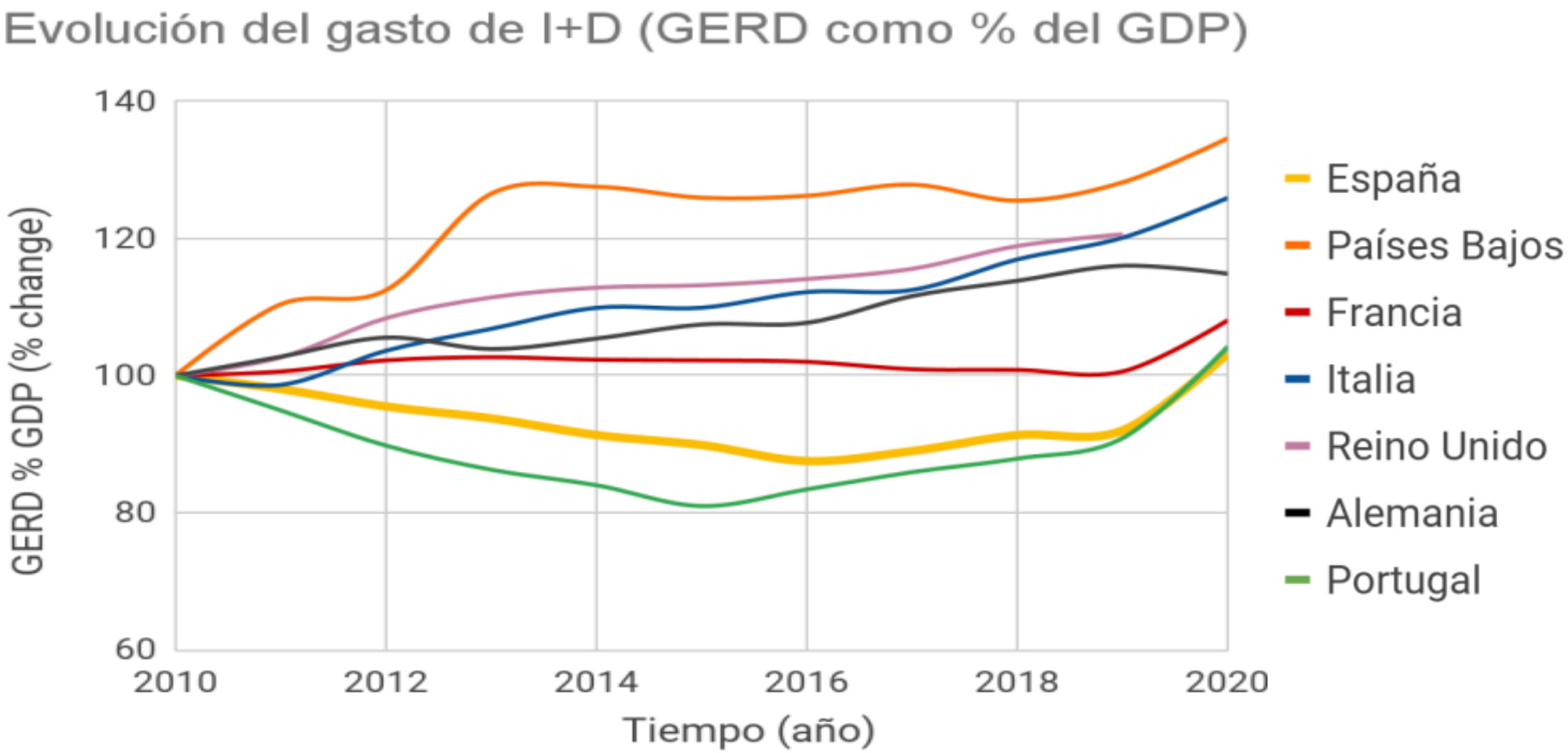
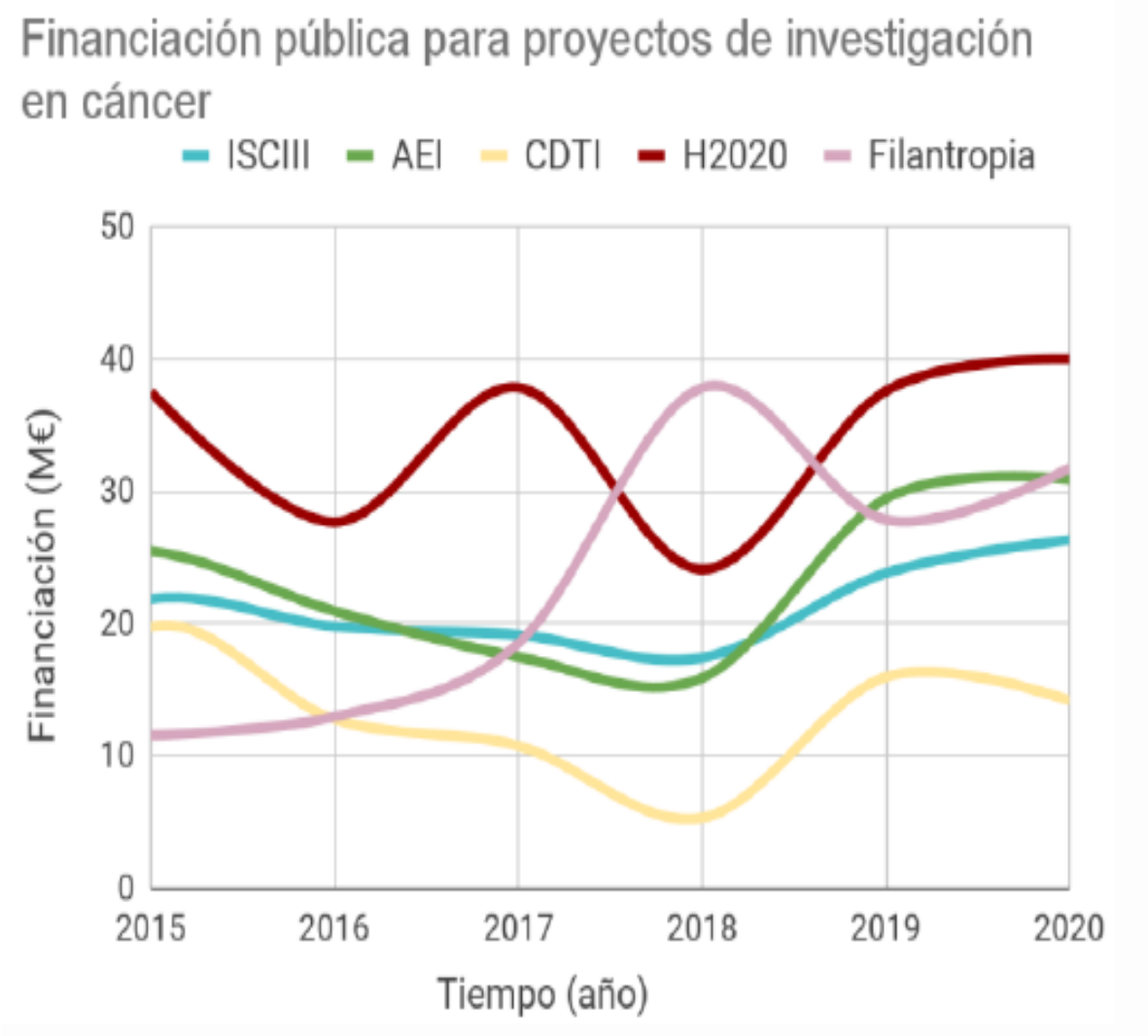
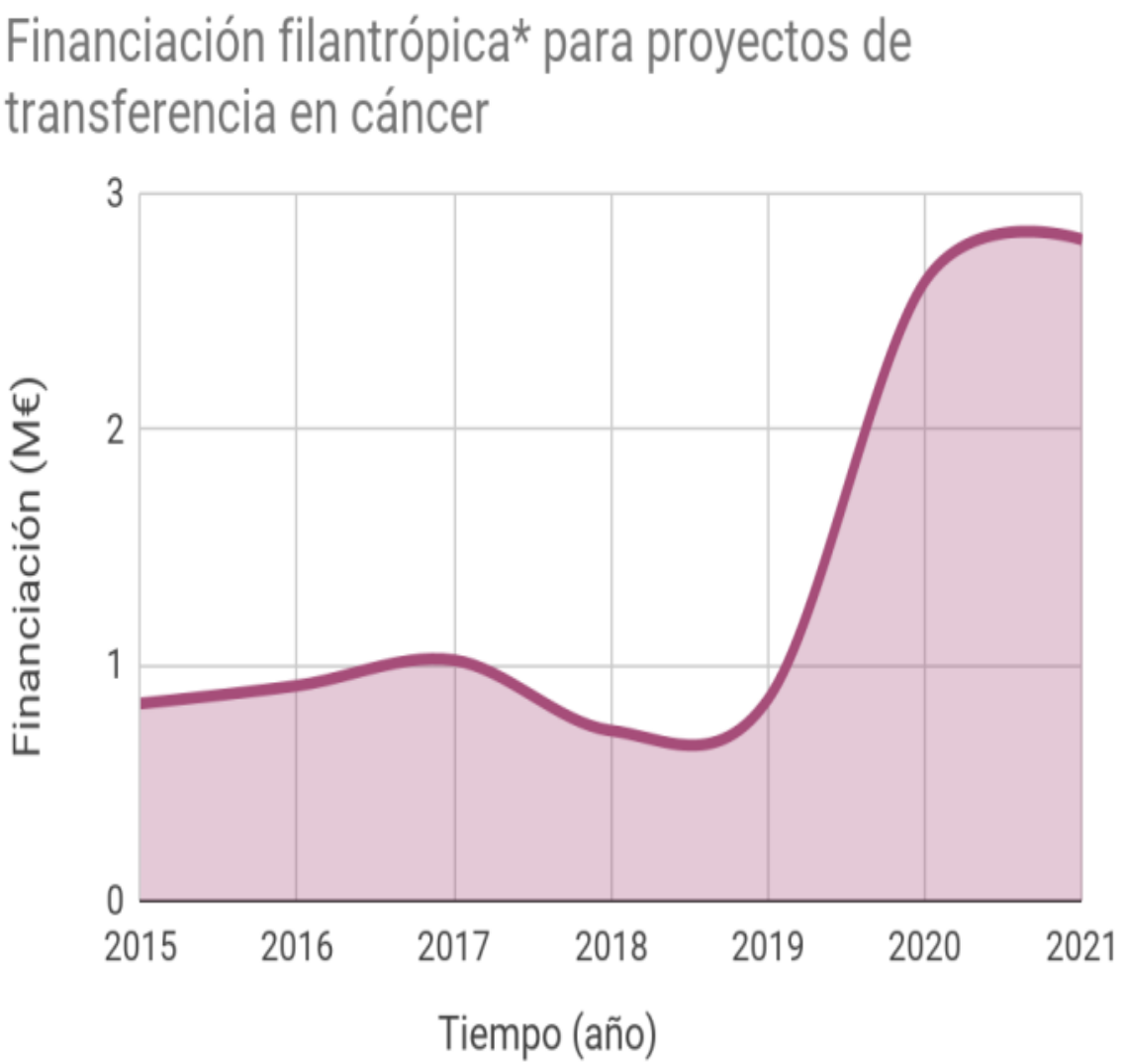
Cancer research investment in Spain



Informe Comprometidos con el Cáncer ASEICA-AECC-La Caixa 2021

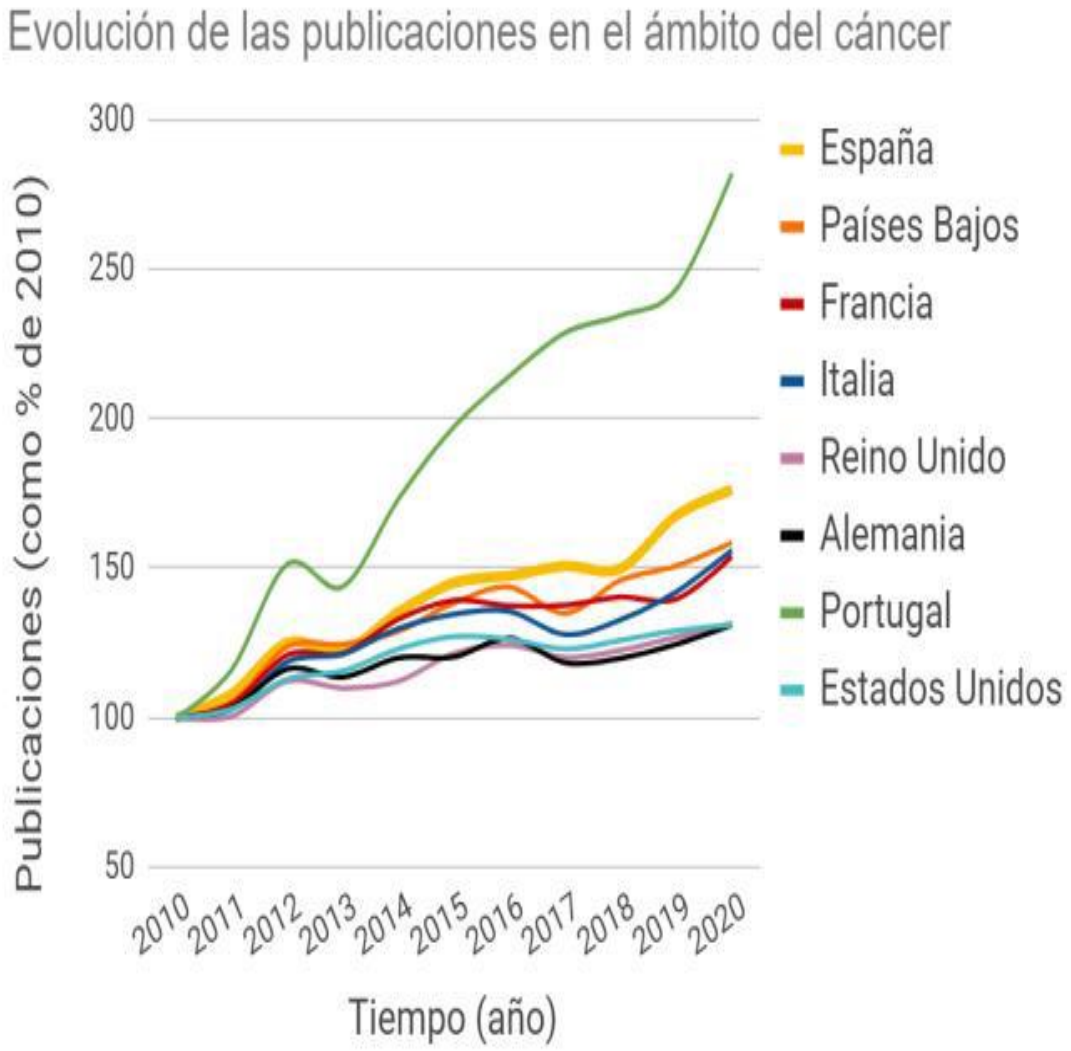
Cancer research investment in Spain

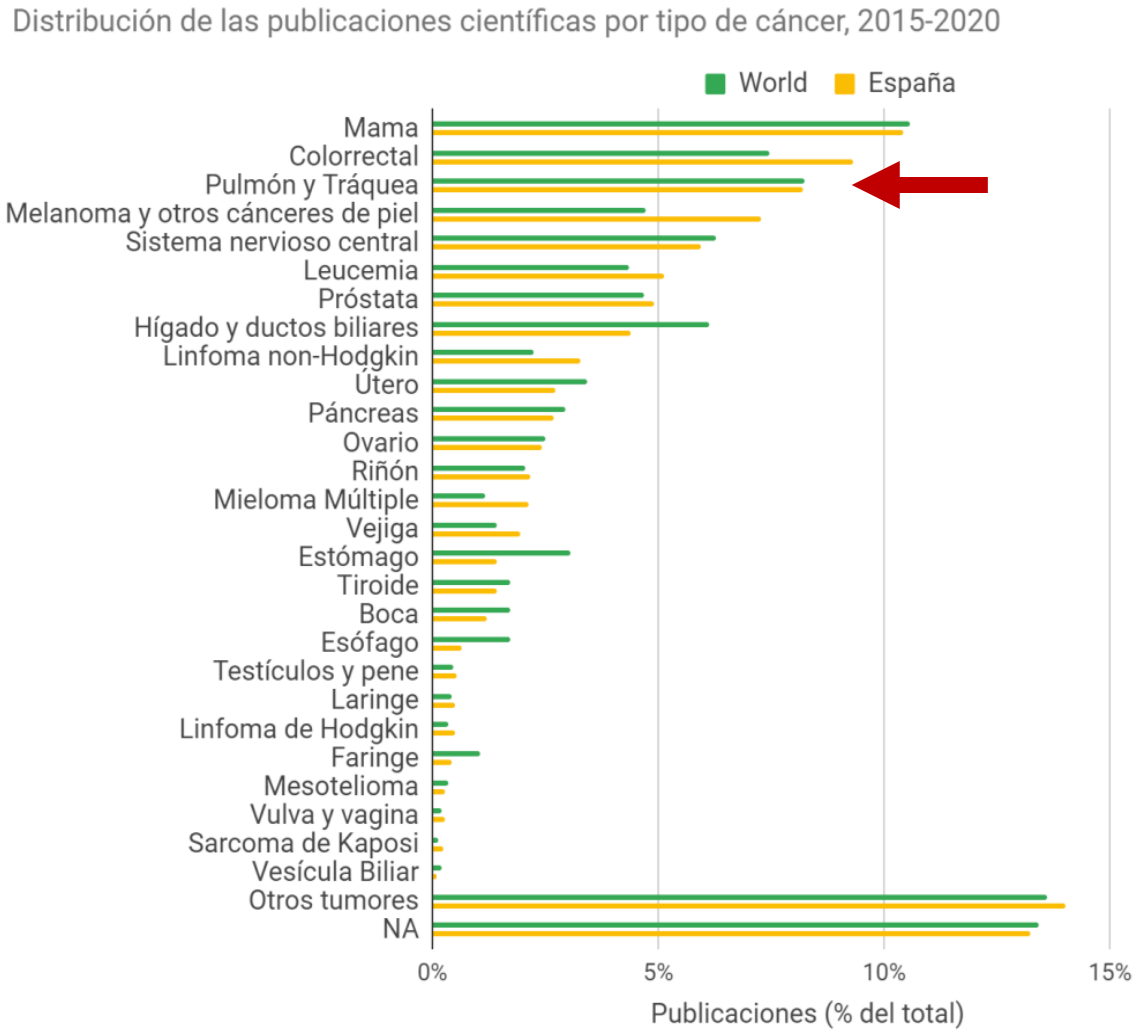




Informe Comprometidos con el Cáncer ASEICA-AECC-La Caixa 2021

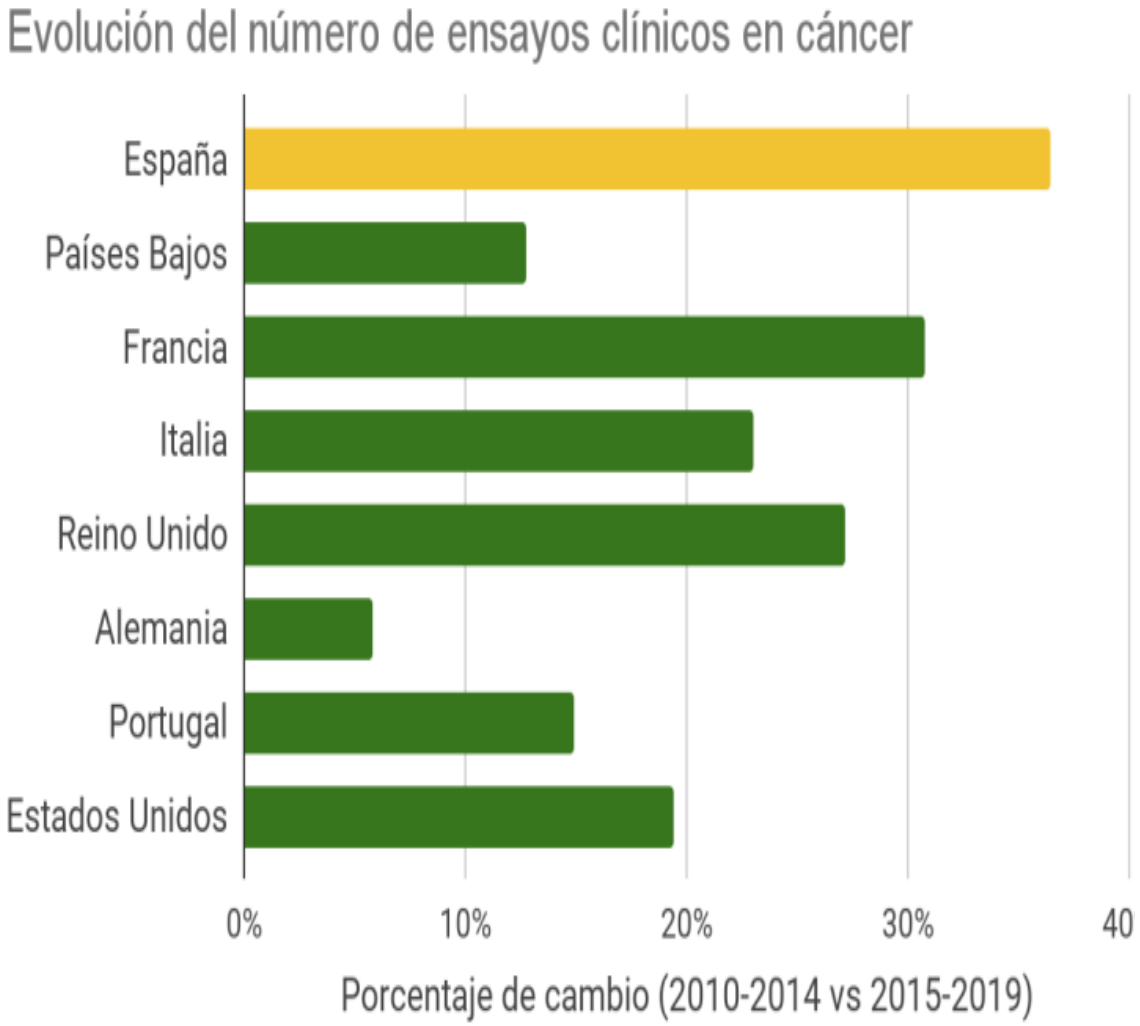
Publications





Informe Comprometidos con el Cáncer ASEICA-AECC-La Caixa 2021

Clinical Trials volumen



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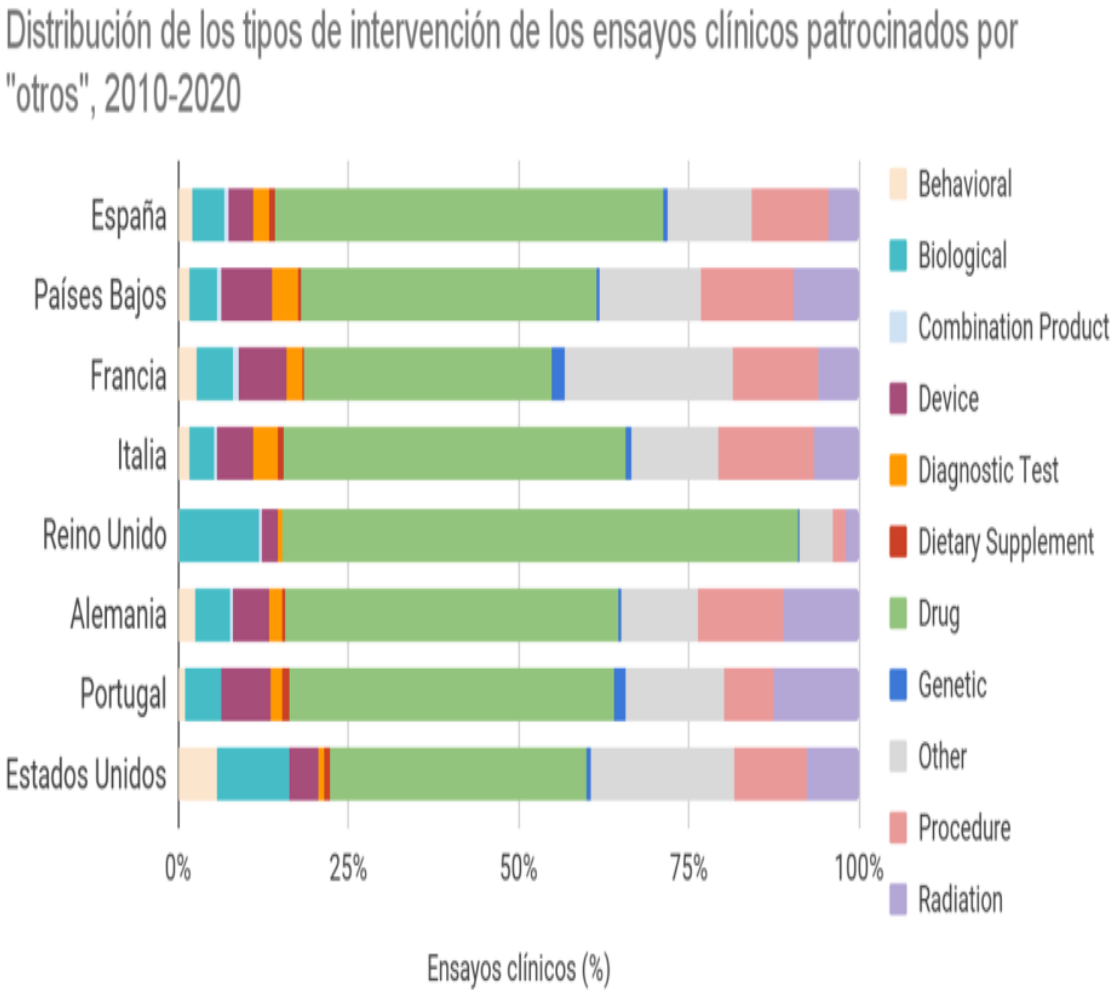
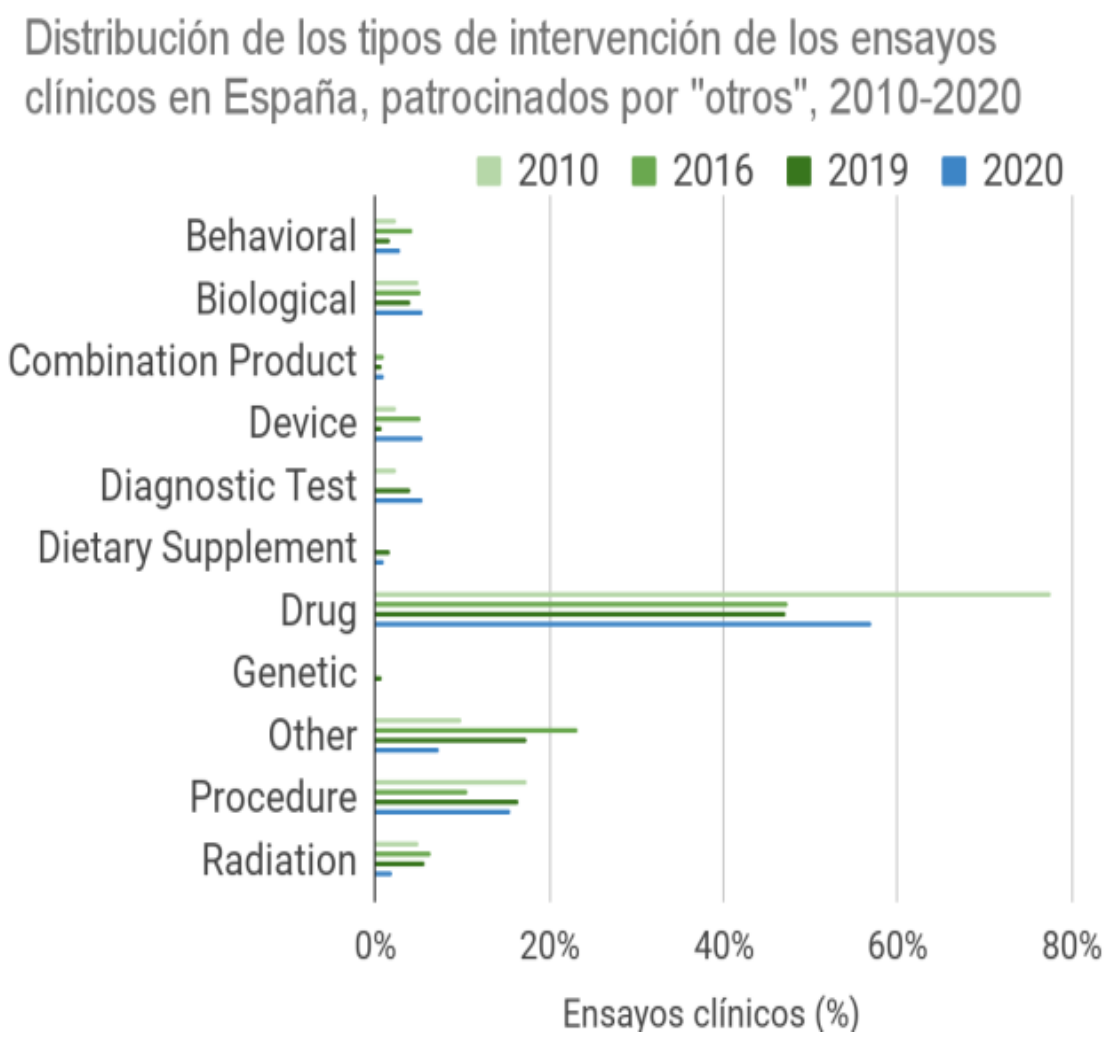
Clinical trials - Intervention

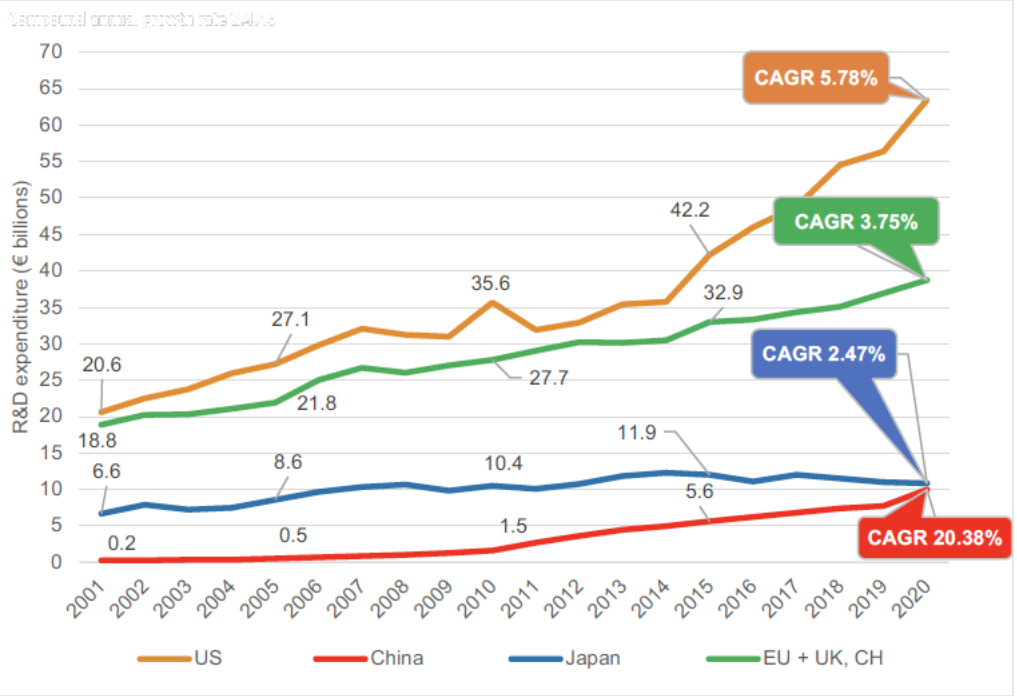




Informe Comprometidos con el Cáncer ASEICA-AECC-La Caixa 2021

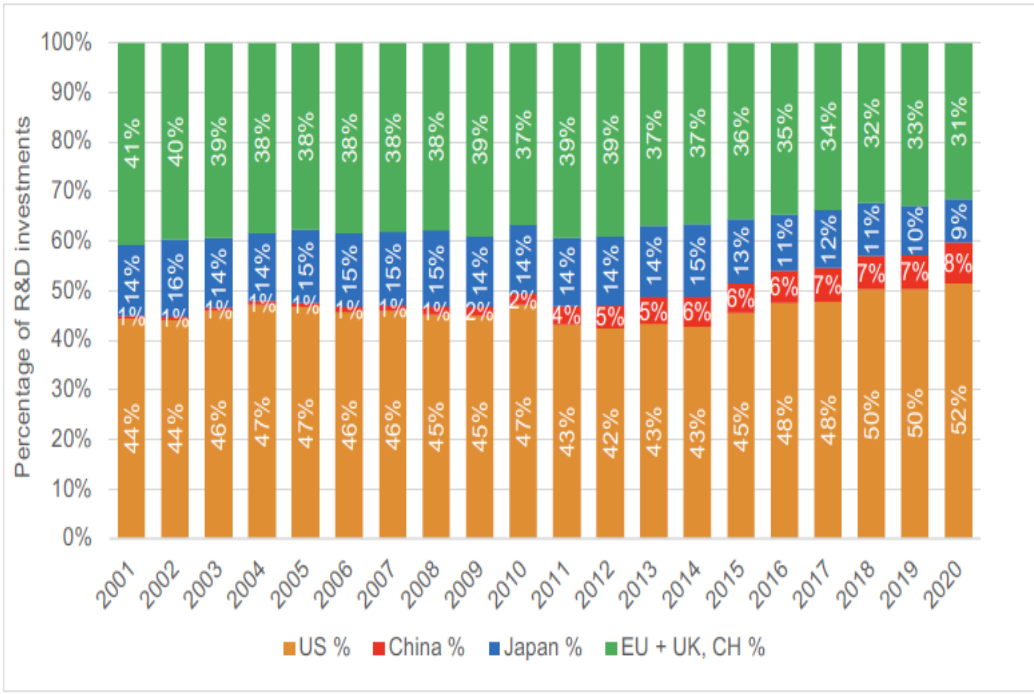
Market and R&D Growth

Figure 1: Pharmaceutical companies' R&D expenditure is growing in all major markets, but fastest in the US and China



*CAGR (compound annual growth rate) is the average rate of growth between two given years

Figure 2: The US and China represent a growing share of biopharmaceutical R&D investments made in major markets



Source: Various[25]

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Time to approval: EMA bv FDA

Drug	First Indication	Gain PFS, OS, TTP (Median, Months)	ESMO-MCBS *	Date of EMA Submission	Date of EMA Approval	Accelerated Assessment (EMA)	Total Time EMA (in Days)	Date of FDA Submission	Date of FDA Approval	Priority Review (FDA)	Total Time FDA (in Days	Time between EMA and FDA Approval (in Days)
Abiraterone	Prostate cancer	3.9 months OS	4	17 December 2010	5 September 2011	16 December 2010	262	20 December 2010	28 April 2011	Yes	129	130
Cabazitaxel	Prostate cancer	2.4 months TTP	2	20 April 2010	17 March 2011	n.a.	331	31 March 2010	17 June 2010	Yes	78	273
Dabrafenib	Melanoma	2.4 months PFS	4	24 July 2012	26 August 2013	n.a.	398	30 July 2012	29 May 2013	No	303	89
Ipilimumab	Melanoma	3.7 months OS	4	05 May 2010	12 July 2011	n.a.	433	10 June 2010	15 March 2011	No	278	119
Nivolumab	Melanoma	4.0 months PFS	4	02 September 2014	19 June 2015	24 July 2014	290	30 July 2014	22 December 2014	No	145	179
Vemurafenib	Melanoma	3.7 months PFS	4	04 May 2011	17 February 2012	14 April 2011	289	28 April 2011	17 August 2011	Yes	111	184
Pertuzumab	Breast cancer	6.1 months PFS	4	01 December 2011	4 March 2013	n.a.	459	06 December 2011	08 June 2012	No	185	269
Enzalutamide	Prostate cancer	4.8 months OS	4	26 June 2012	21 June 2013	n.a.	360	22 May 2012	31 August 2012	Yes	101	294
Pembrolizumab	Melanoma	1.3 months PFS	3	04 June 2014	17 July 2015	n.a.	408	27 February 2014	03 September 2014	No	188	317
Ramucirumab	Gastric cancer	2.2 months OS	2	23 August 2013	19 December 2014	n.a.	483	23 August 2013	21 April 2014	No	241	242
Palbociclib	Breast cancer	10.3 months PFS	3	30 July 2015	9 November 2016	n.a.	468	30 June 2014	03 February 2015	Yes	218	645
Ribociclib	Breast cancer	PFS not reached	3	05 September 2016	22 August 2017	n.a.	351	29 August 2016	13 March 2017	Yes	196	162
Average time (in days)							378				181	242
Average time accelerated assessment/priority review (in days)							280				139	n.a.
Average time in case no accelerated assessment/no priority review (in days)							410				223	n.a.

* Ref. [22] PFS: progression-free survival; OS: overall survival; TTP: time to progression, ESMO-MCBS: European Society Medical Oncology-Magnitude of Clinical Benefit Scale; EMA: European Medicines Agency; FDA: USA Food and Drug Association; n.a.: not applicable.

CA Uyl-deGroot et al.Cancers 2020

LIBRETTO 431 Trial:
Selpercatinib v CT in RET driven stage IV NSCLC

Key Eligibility Criteria
- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:
- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

R 2:1[3]

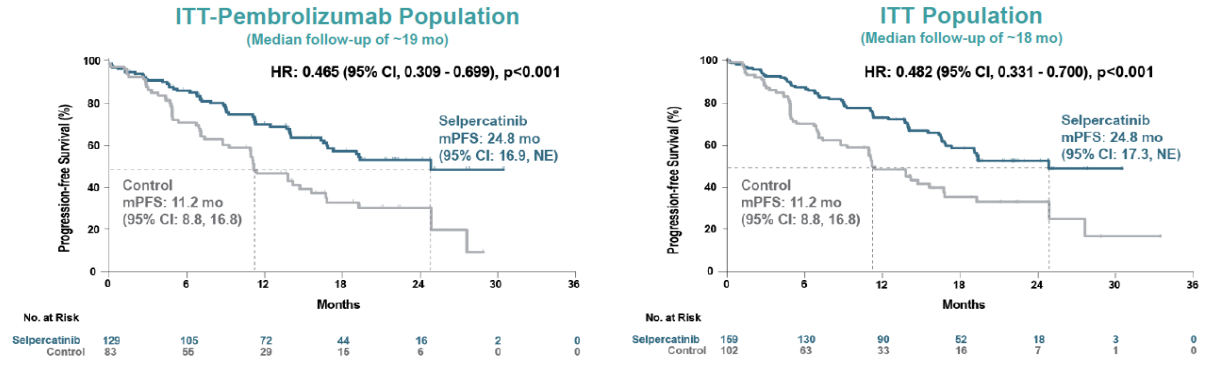
Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover → **Selpercatinib** (Upon BICR confirmed PD)

Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population

Progression-free survival (PFS) assessed by BICR



Objective Responses

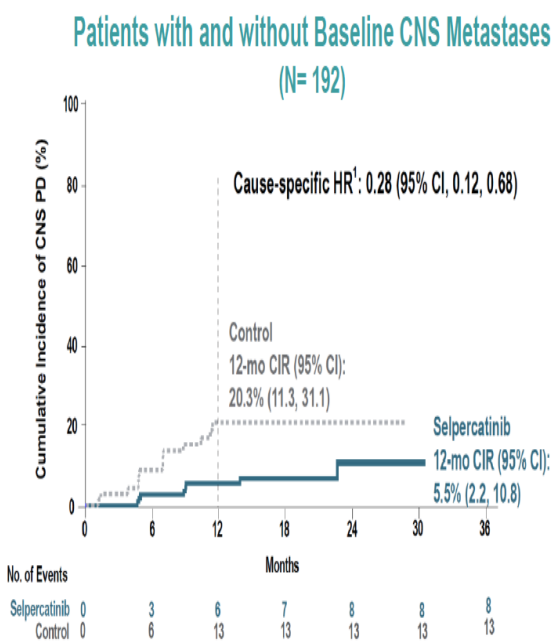
Systemic Outcomes

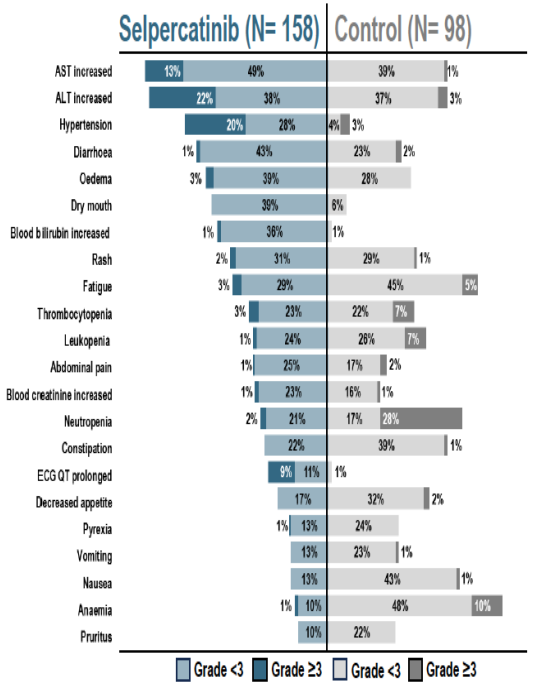
	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

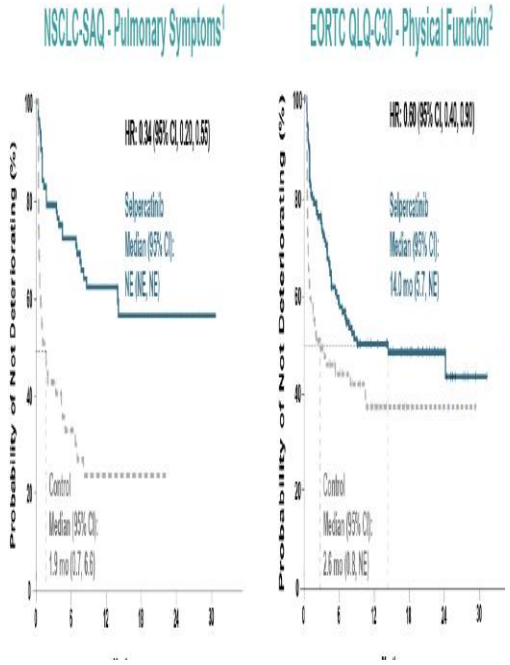
Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)



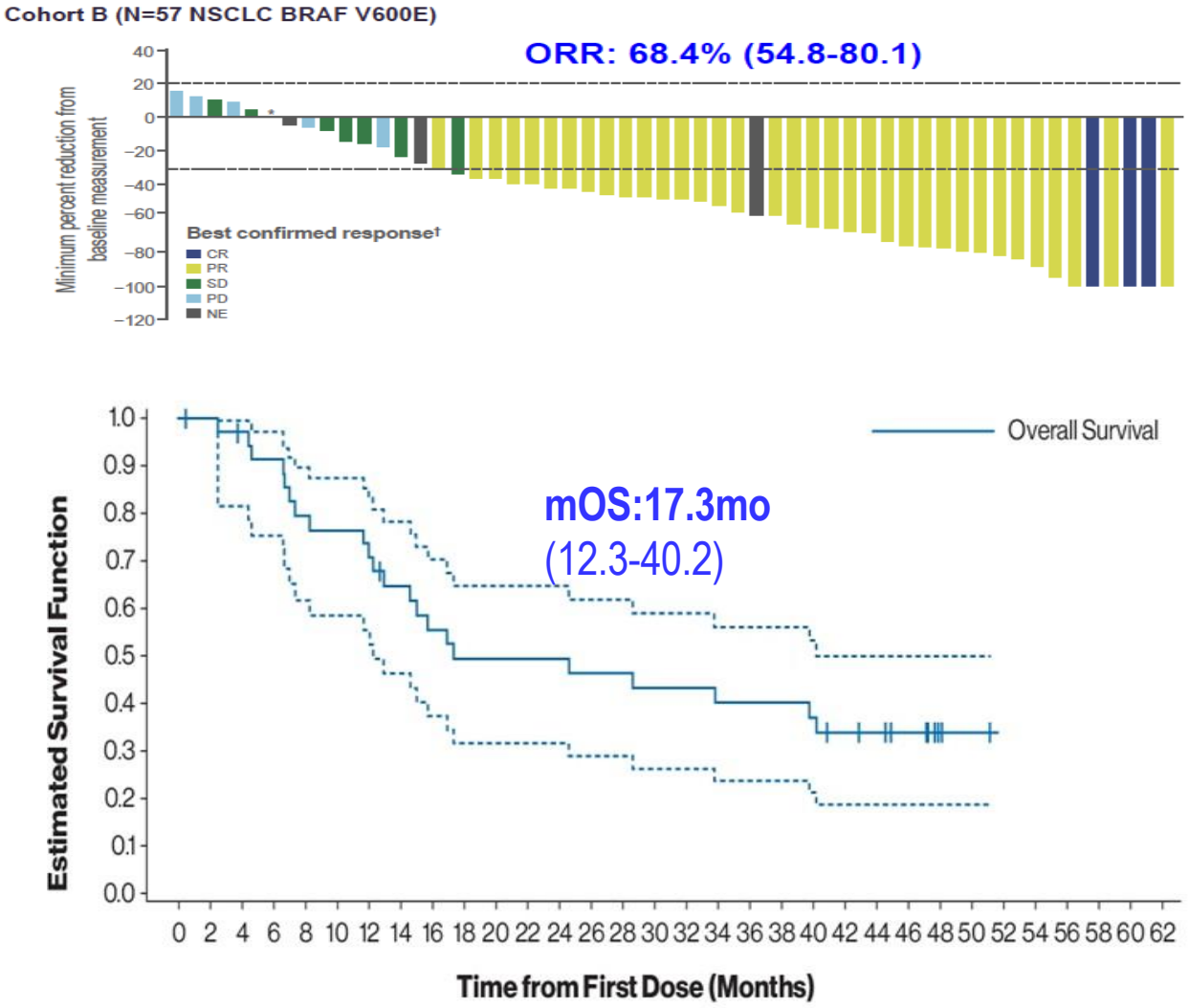




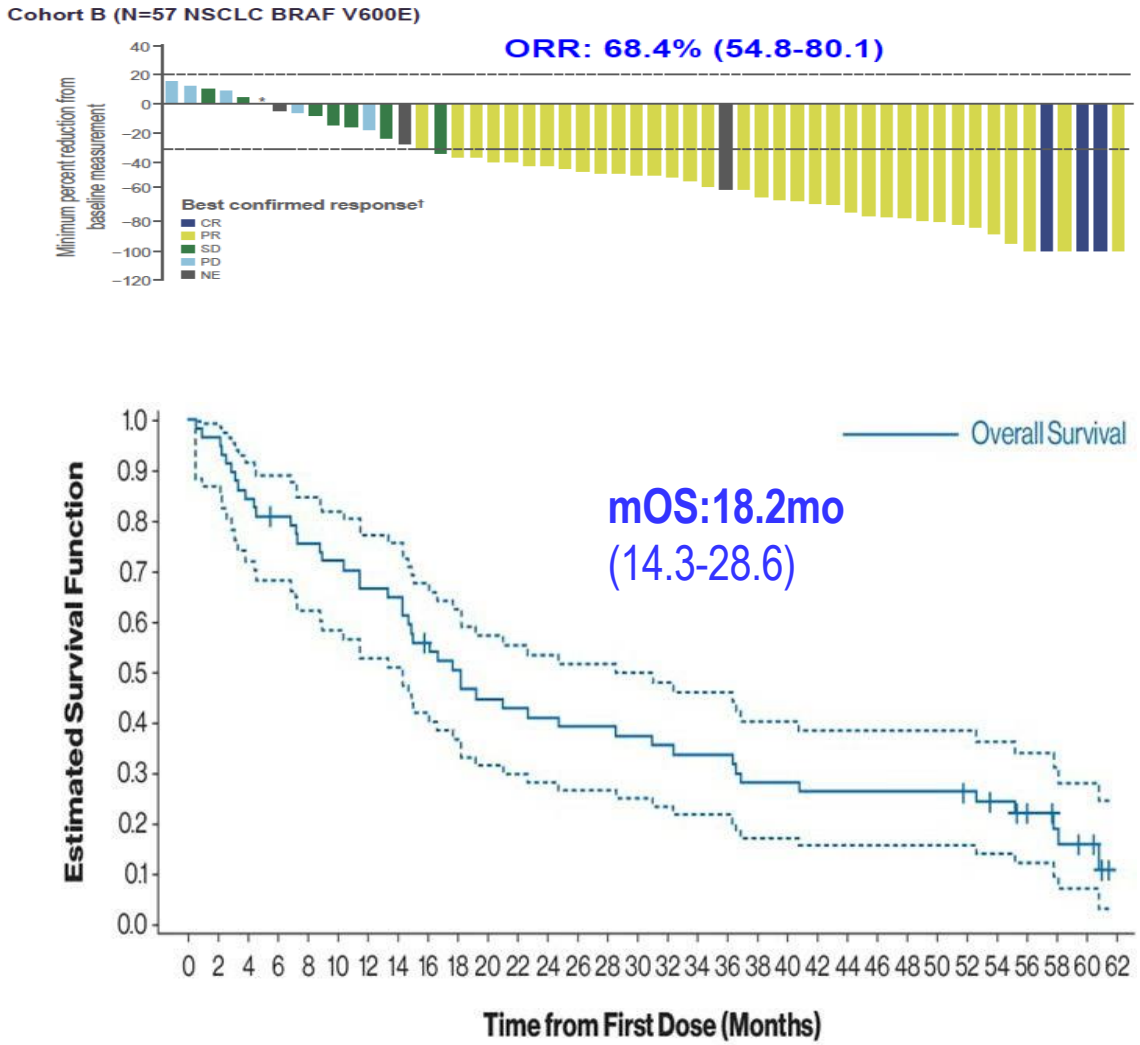
Loong et al. 2023

Do we need a RCT of Dafrabenib+Trametinib in BRAF m+ NSCLC?

Naive patients (Cohort C)



Pretreated patients (Cohort B)



D.Plancard et al, JTO 2021

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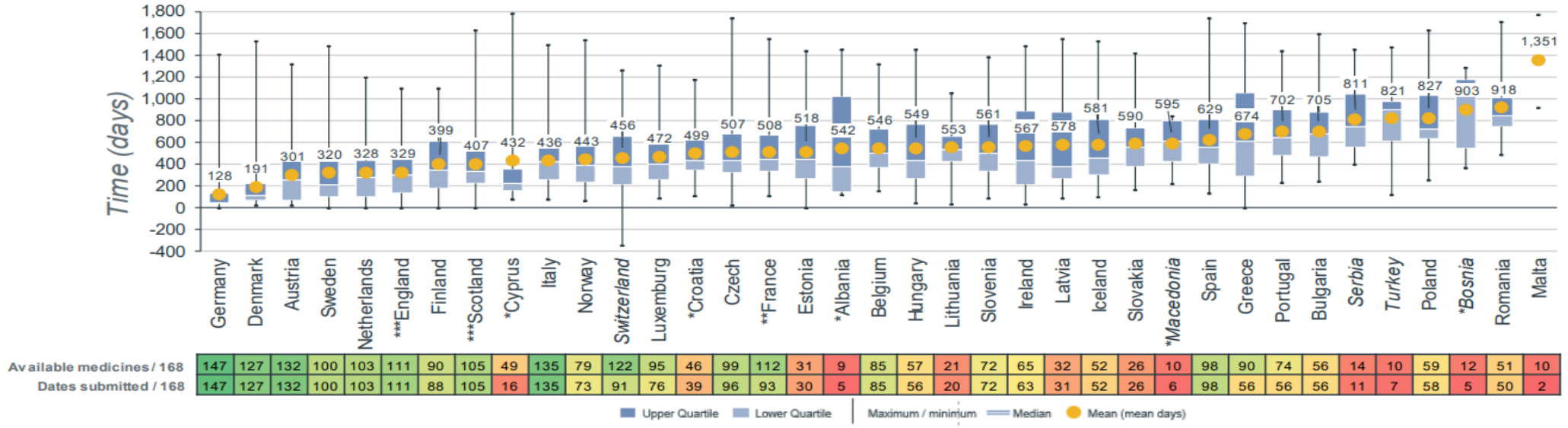
Time from Approval to Availability

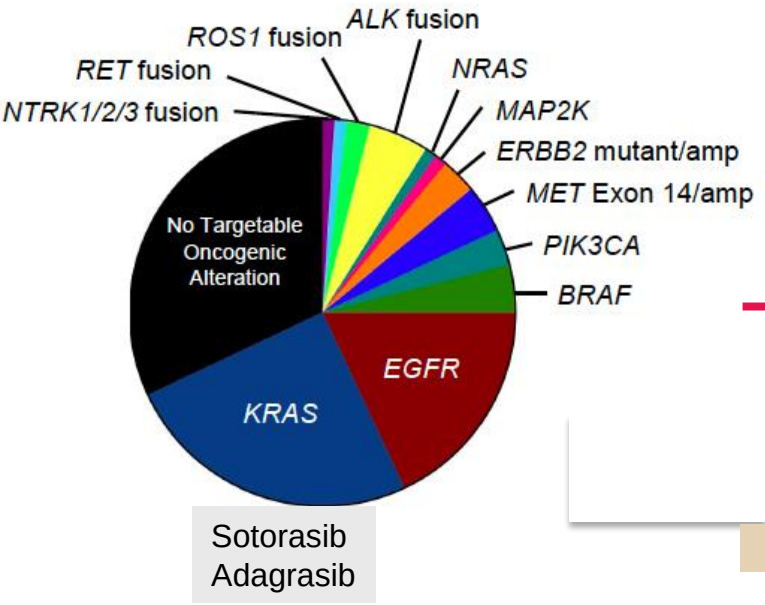
The average time until availability in Spain is 629 days since the European Commission authorizes the marketing of these therapies.

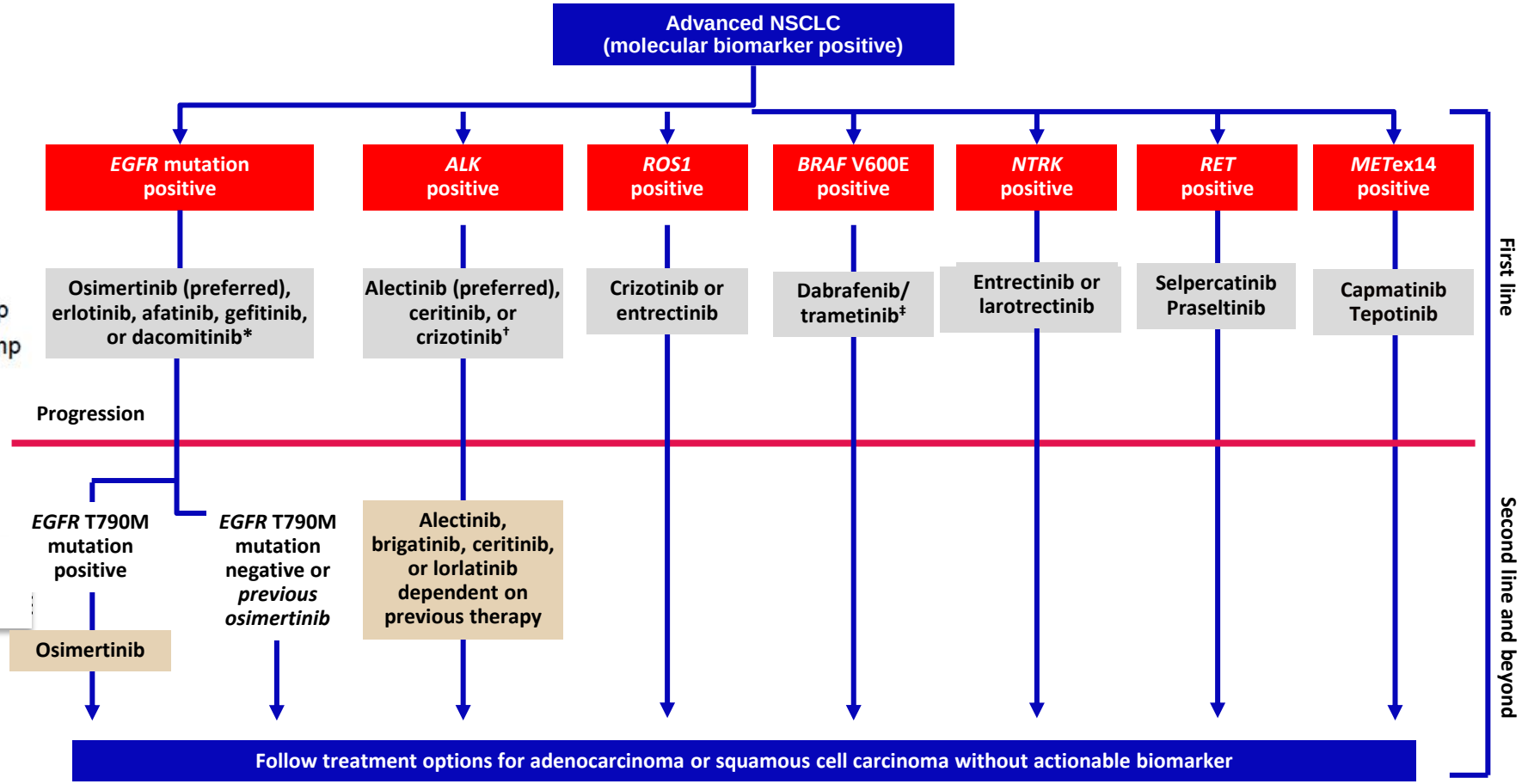
Time from central approval to availability (2018-2021)

The **time from central approval to availability** is the days between marketing authorisation and the date of availability to patients in European countries (for most this is the point at which products gain access to the reimbursement list†). The marketing authorisation date is the date of central EU authorisation throughout.



Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC

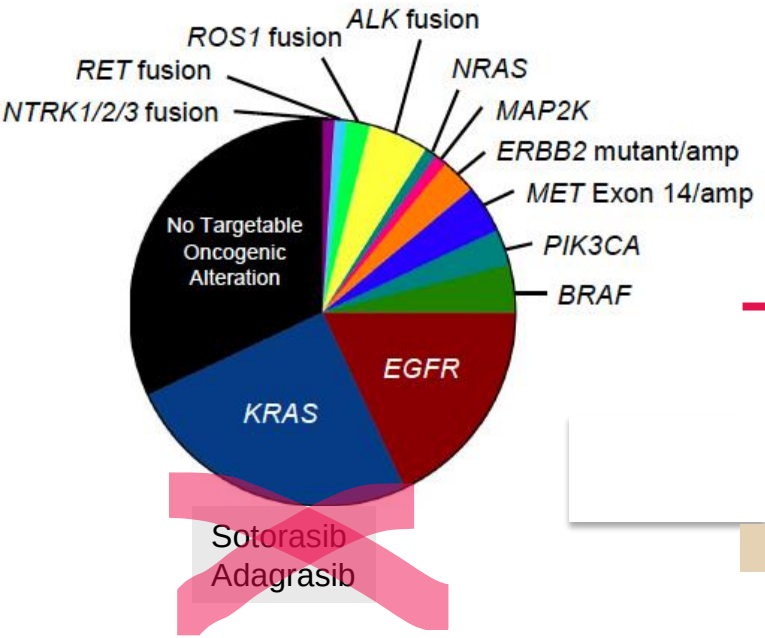


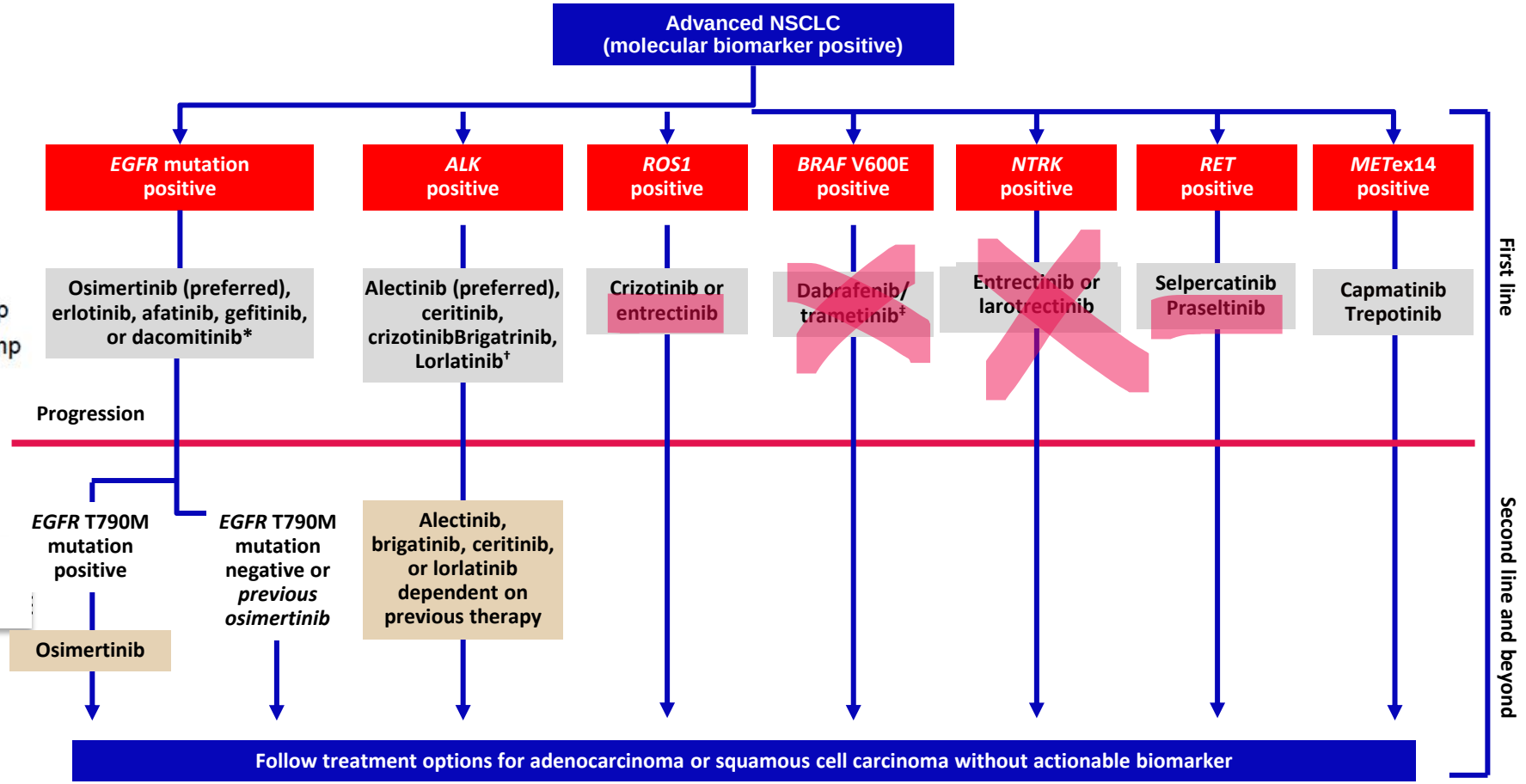


*Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q.
†Brigatinib under priority review by the FDA for first-line *ALK* positive NSCLC. ‡Or as second-line after CT.

Afatinib PI. Alectinib PI. Capmatinib PI. Ceritinib PI. Crizotinib PI. Dabrafenib PI. Dacomitinib PI. Entrectinib PI. Erlotinib PI. Gefitinib PI. Larotrectinib PI. Osimertinib PI. Selpercatinib PI. Trametinib PI.

Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC in SPAIN





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Informed patients

Patient-Centred Care

Is shared decision making a reality in the care pathway?

A story

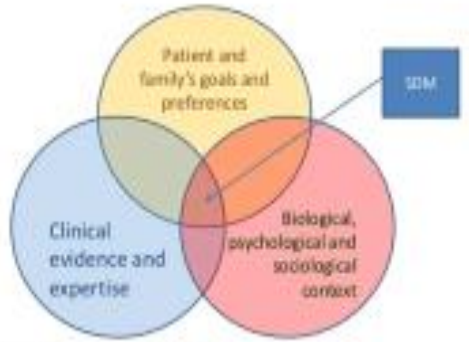
Shared Decision Making Defined

A Shared Decision Making (SDM) process results in medical decisions that are:

- *Shared by doctors and patients*
- *Informed by the best evidence available about alternative treatments*
- *Weighted according to the specific **needs, preferences and values of the patient***

(Légaré et al., 2006)

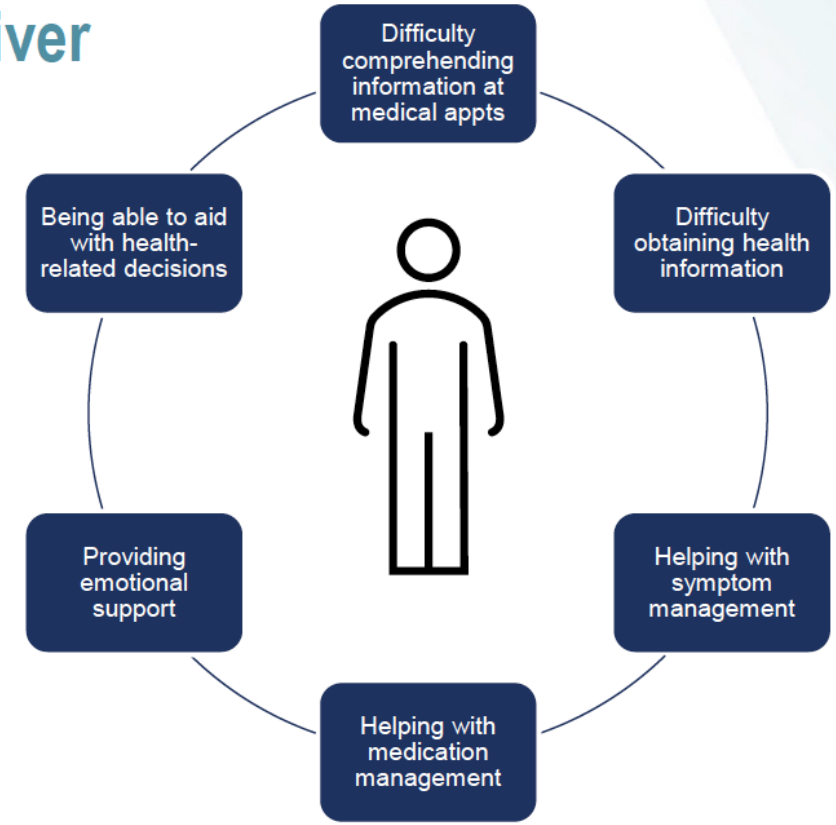
Decision-making process



http://www.cincinnatichildrens.org/

Health literacy

Cancer Caregiver

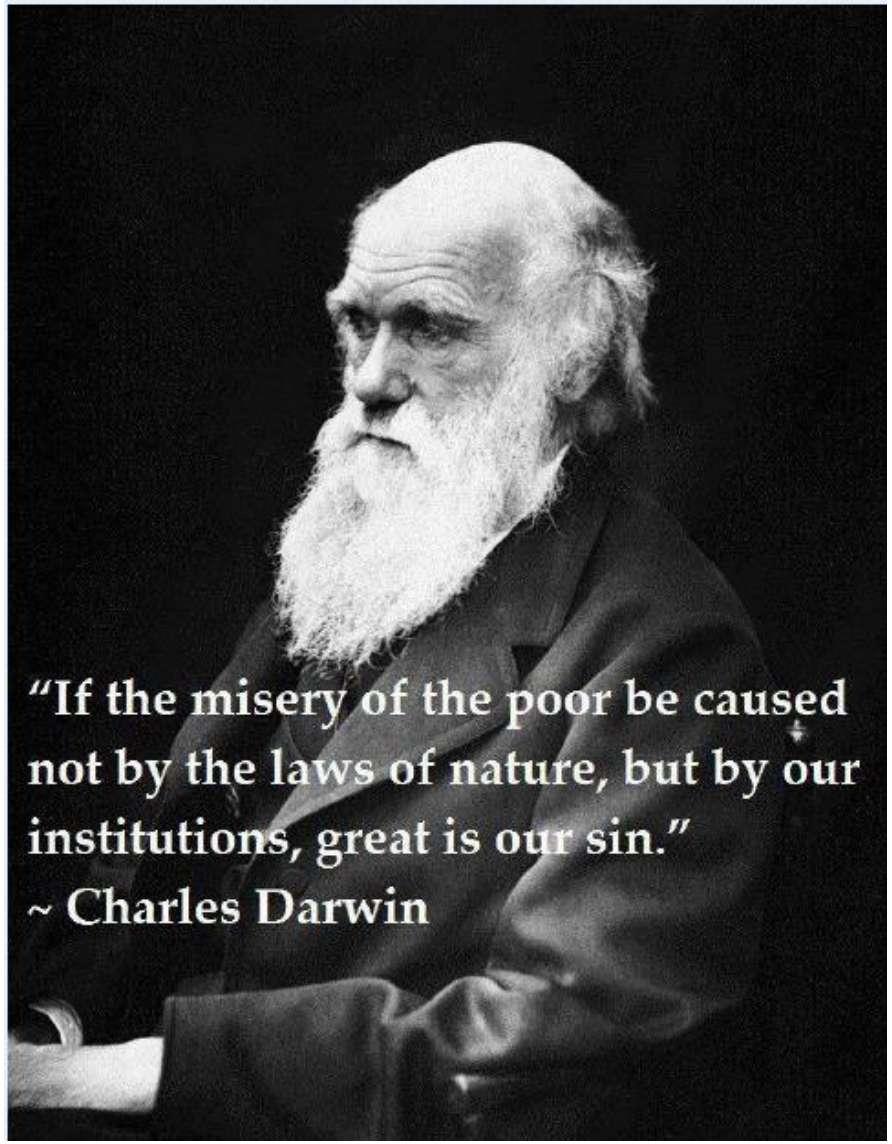


Equity

Of all inequalities, injustice in health is the most shocking and inhumane

Equity?

Martin Luther King



Gracias

lpazaresr@seom.org