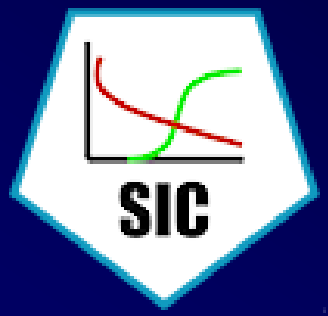
La chemioterapia all'inizio del terzo millennio

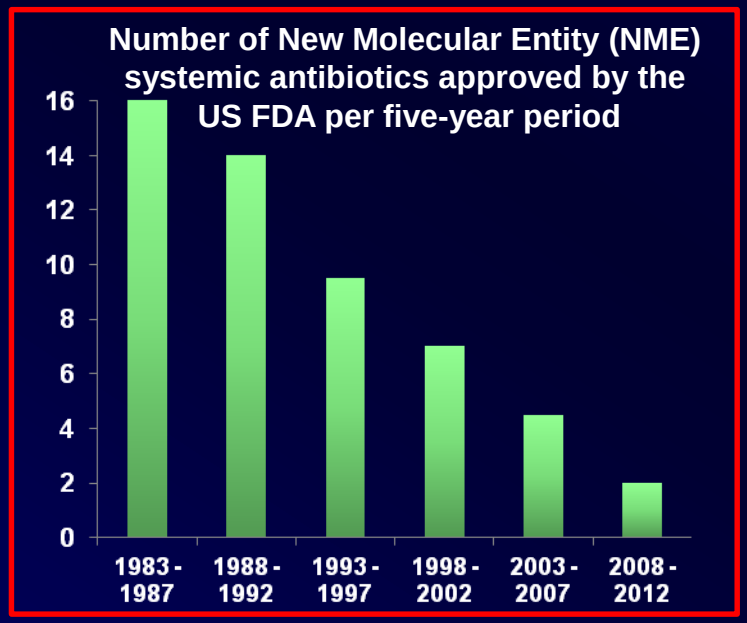
Teresita Mazzei

Presidente
Società Italiana di Chemioterapia

Presidente Ordine Medici-Chirurghi e Odontoiatri di Firenze

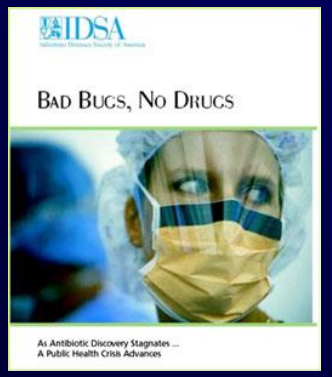


Combating Antimicrobial Resistance: Policy Recommendations to Save Lives IDSA Policy paper



Enterococcus
Staphylococcus
Klebsiella
Acinetobacter
Pseudomonas
ESBL (Enterobacter and E. coli)

CID 2009:48: 1-12
ECDC/EMA 2009



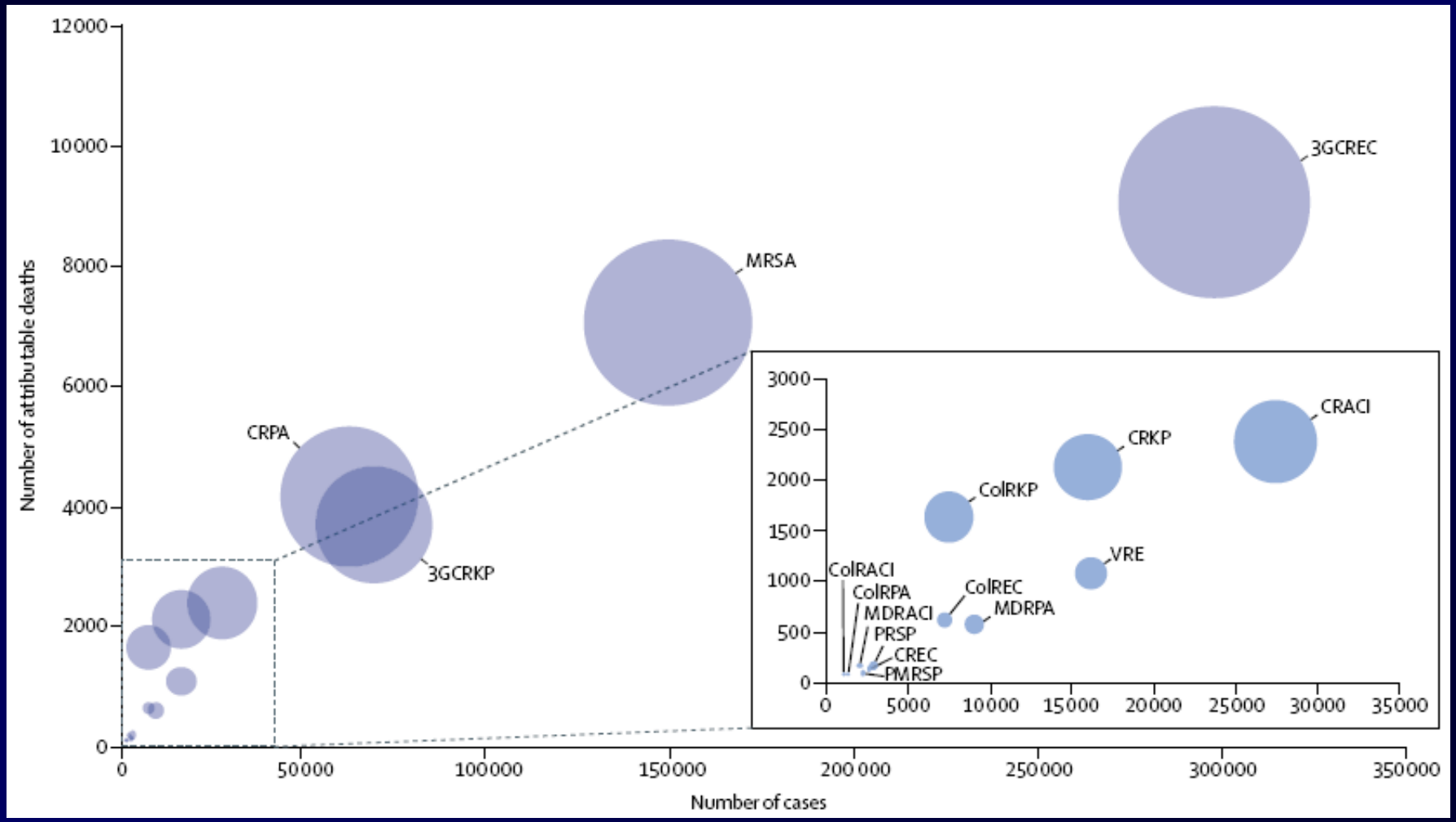
CID 2010:50: 1081-1083

IDSA RECOMMENDS:

- Adoption of economic incentives and support for other collaborative mechanisms to address the market failure of antibiotics
- New regulatory approaches to facilitate antimicrobial development and approval
- Greater coordination of relevant federal agencies' efforts
- Enhancement of antimicrobial resistance surveillance systems
- Strengthening activities to prevent and control antimicrobial resistance
- Significant investments in antimicrobial-focused research
- Greater investment in rapid diagnostics R&D and integration into clinical practice
- Eliminating non-judicious antibiotic use in animals, plants, and marine environments

Clinical Infect Dis 2011: 52 (Suppl 5): S397-S428; CID 2013: 56: 1685-1694

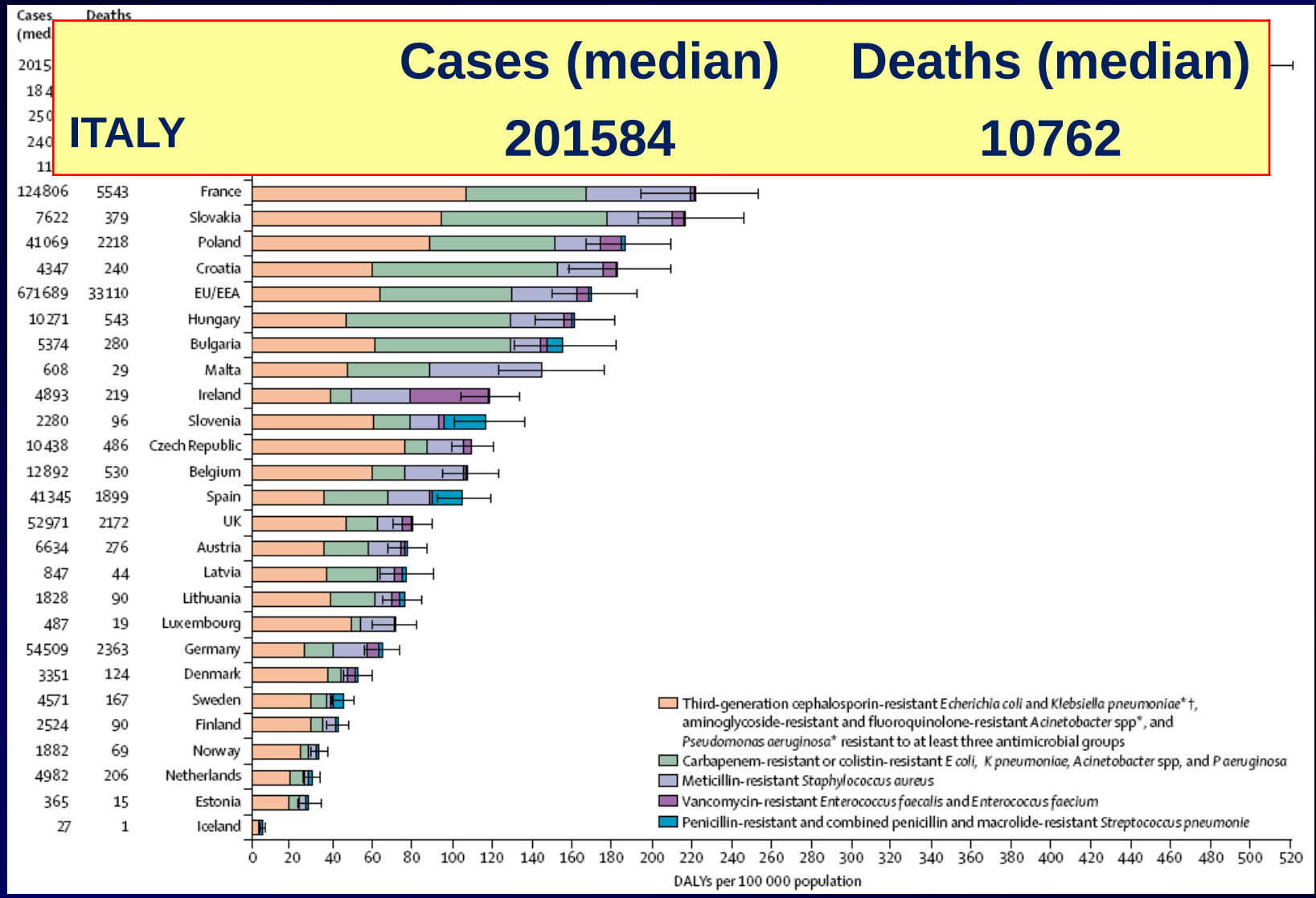
Infections with antibiotic-resistant bacteria, EU and European Economic Area, 2015



Cassini A et al., Lancet Infect Dis, Nov 2018

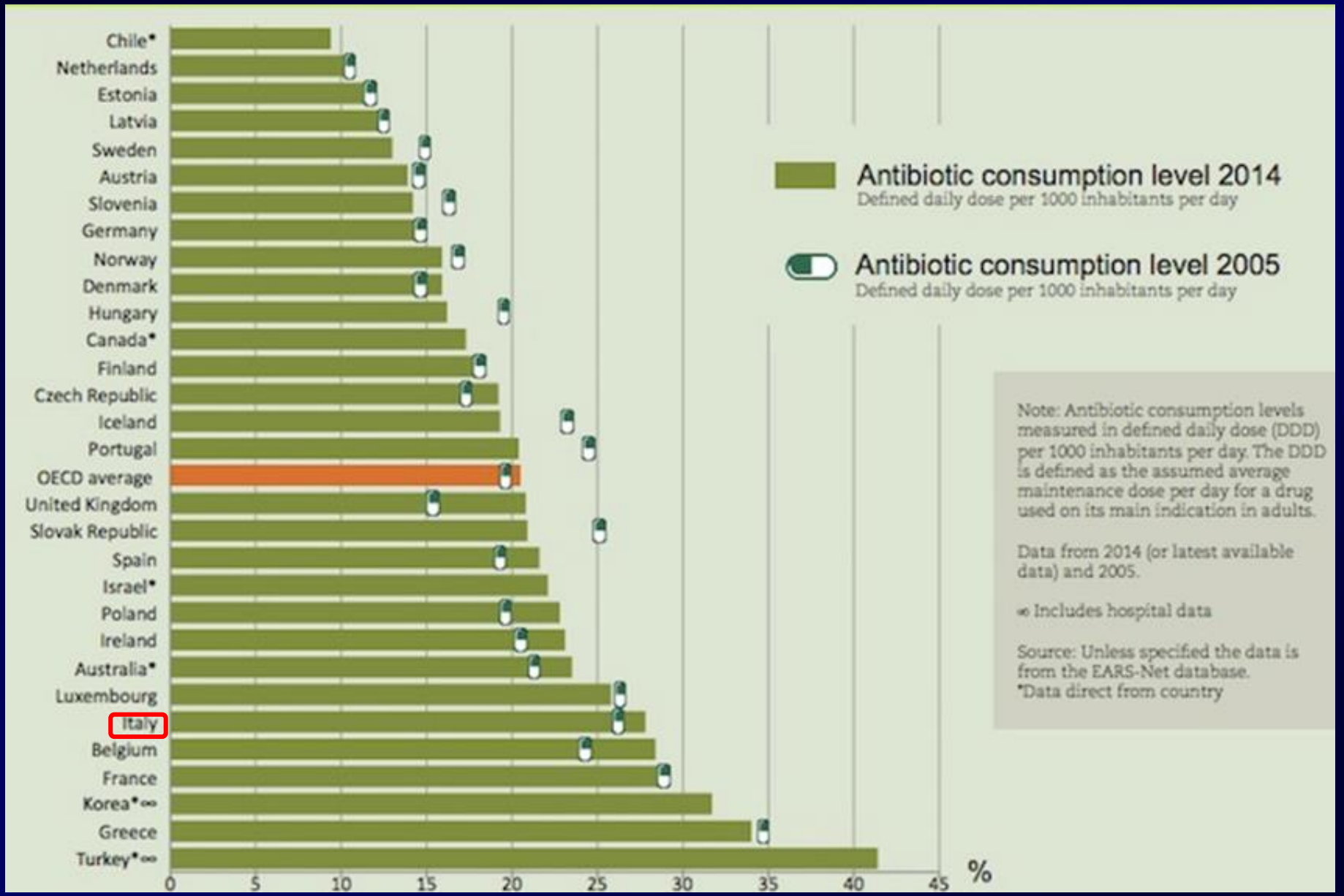
Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015

	Cases (median)	Deaths (median)
ITALY	201584	10762

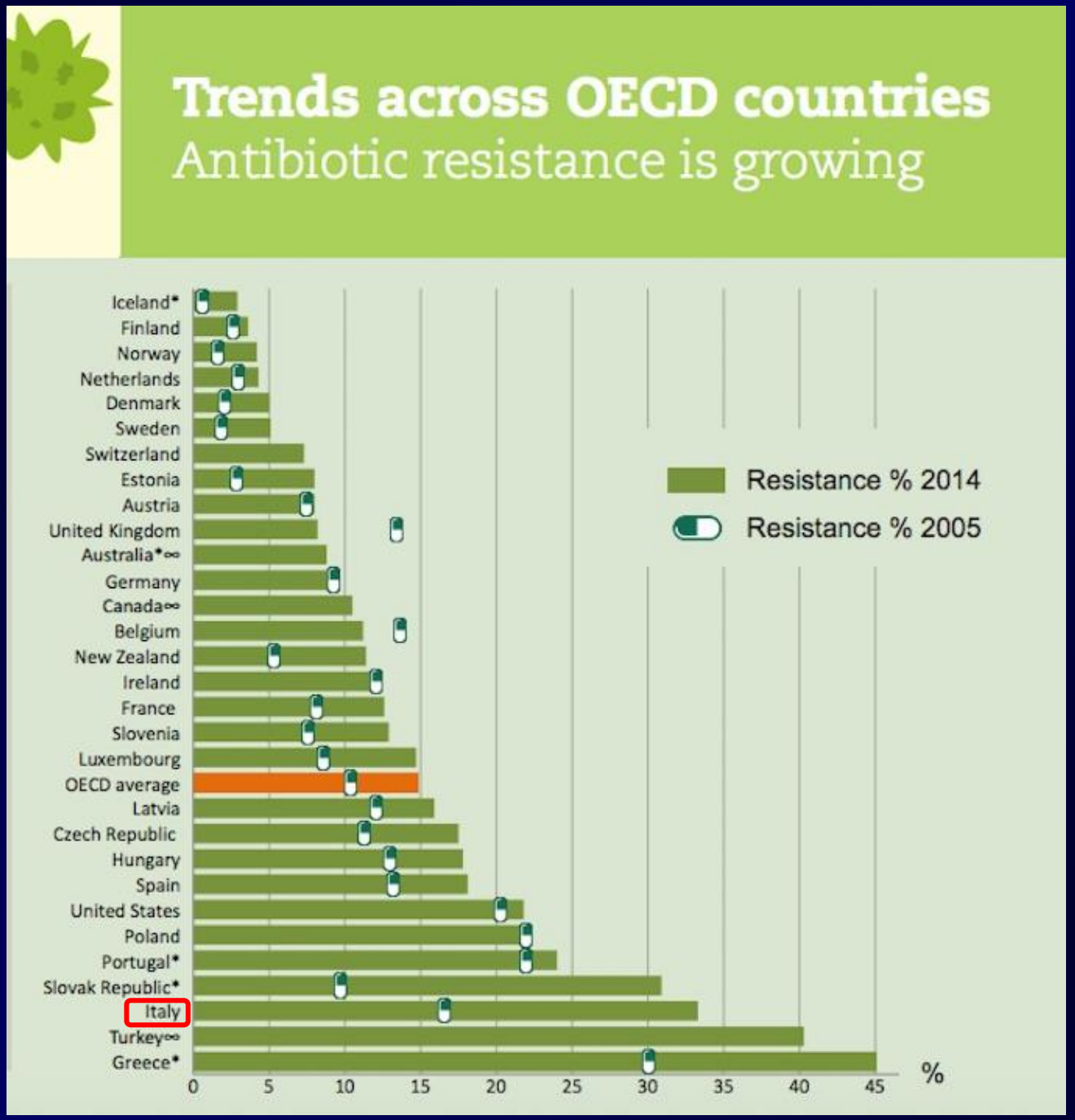


Cassini A et al., Lancet Infect Dis, Nov 2018

Human consumption of antibiotics



Antimicrobial Resistance OECD 2016



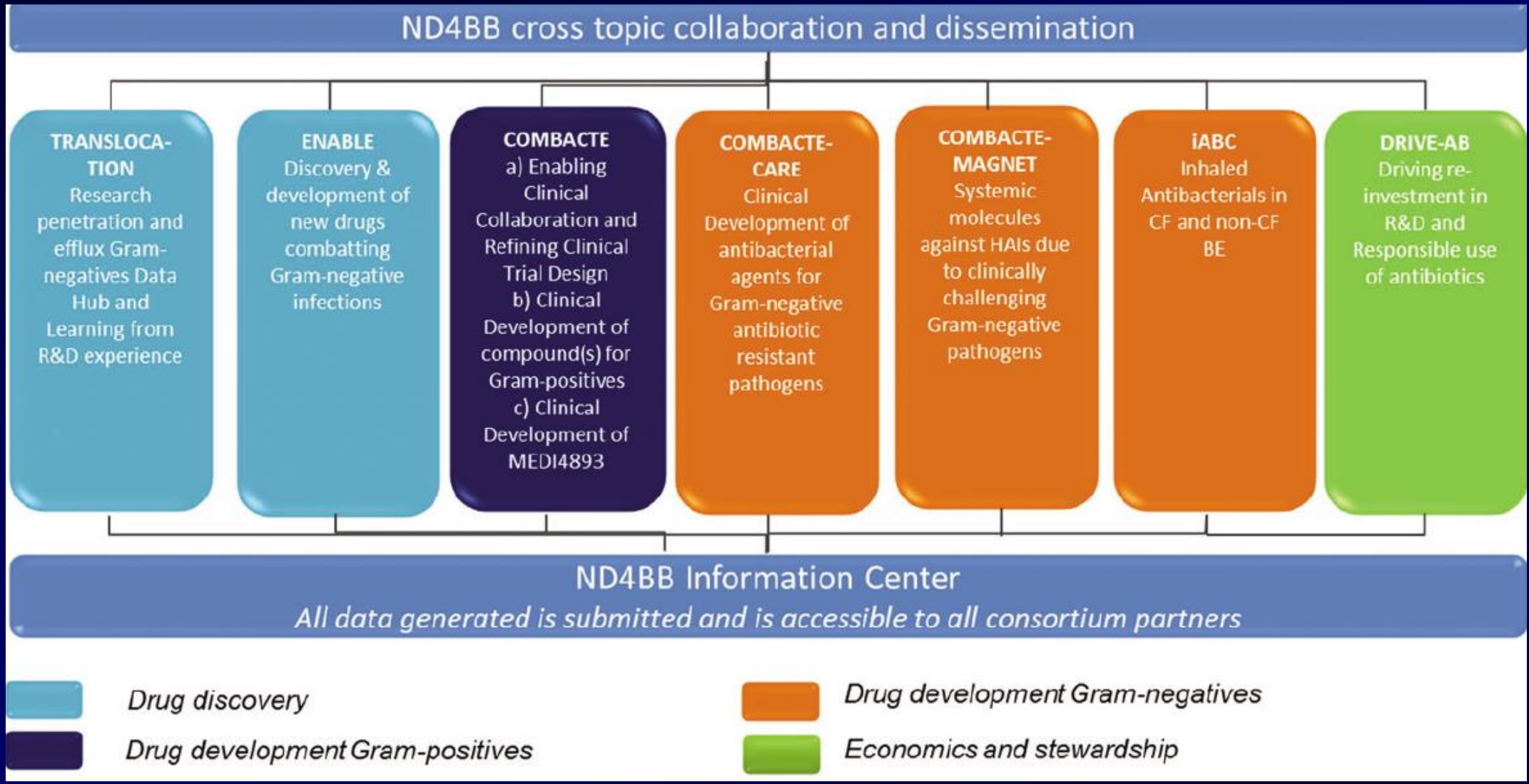
Antimicrobial Resistance OECD 2016

The innovative medicines initiative's new drugs for bad bugs programme: european public–private partnerships for the development of new strategies to tackle antibiotic resistance

Kostyanev T, Bonten MJM, O'Brien S, Steel H, Ross S, François B, Tacconelli E, Winterhalter M, Stavenger RA, Karlén A, Harbarth S, Hackett J, Jafri HS, Vuong C, MacGowan A, Witschi A, Angyalosi G, Elborn JS, deWinter R and Goossens H

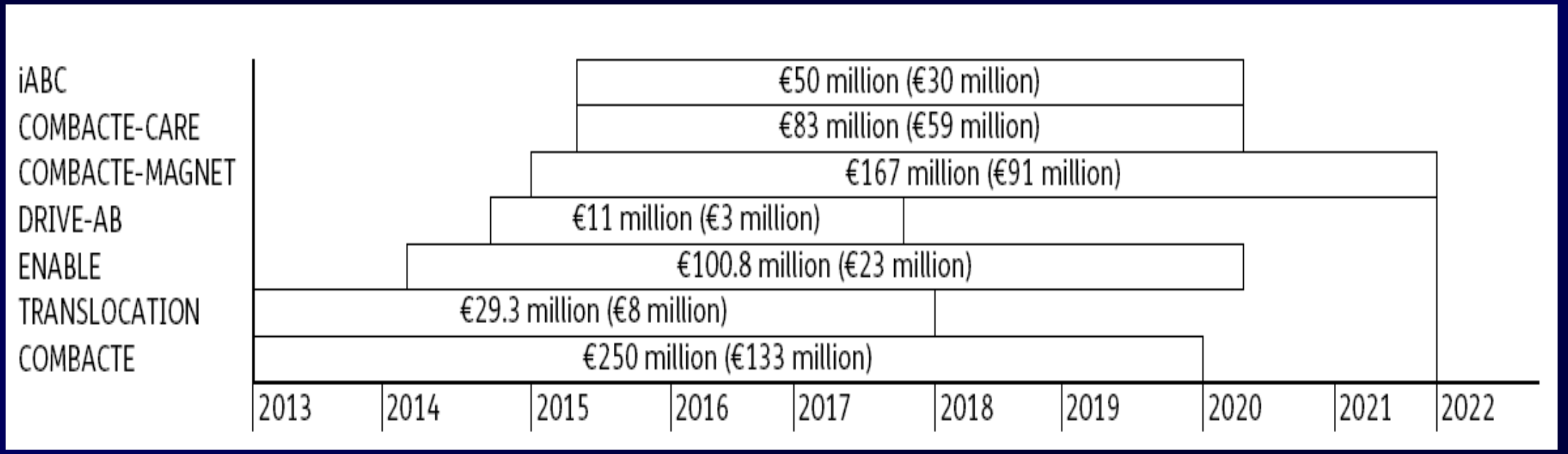
J Antimicrob Chemother 2016; 71: 290–295

New drugs ND for Bad Bugs (ND4BB) initiative



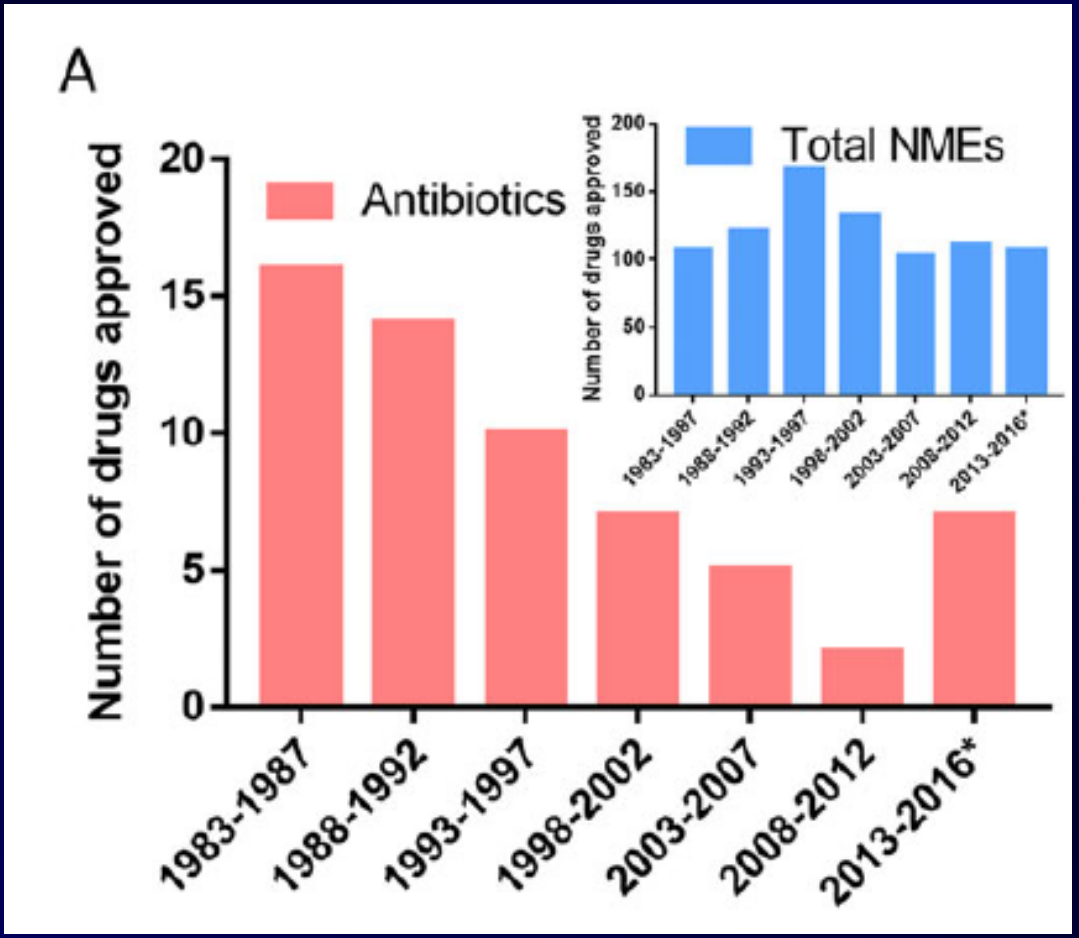
Kostyanev T et al., J Antimicrob Chemother, 2016

Timeline and total budget estimation of the seven topics of the ND4BB programme



Kostyanev T et al., J Antimicrob Chemother, 2016

Number of US FDA-approved new antibiotics and total new molecular entities



Zheng W et al., Br J Pharmacol, 2018

Important antibiotic-resistant pathogens according to the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC)

WHO's Critical Priority

Carbapenem- and 3rd generation cephalosporin-resistant Enterobacteriaceae

Carbapenem-resistant *P. aeruginosa*

Carbapenem-resistant *A. baumannii*

CDC's Urgent Threats

Carbapenem-resistant Enterobacteriaceae

Clostridium difficile

Neisseria gonorrhoeae

WHO's High Priority

Clarithromycin-resistant *Helicobacter pylori*

Fluoroquinolone-resistant *Campylobacter* and *Salmonella* spp.

MDR *Neisseria gonorrhoeae*

Others: vancomycin-resistant *E. faecium*, methicillin- and vancomycin-resistant *S. aureus*

CDC's Serious Threats

MDR *Acinetobacter* spp.

ESBL-producing Enterobacteriaceae

MDR *P. aeruginosa*

MDR *Salmonella, Shigella*, and *Campylobacter* spp.
Others: MRSA, *S. pneumoniae, M. tuberculosis*, VRE, fluconazole-resistant *Candida* spp

Avery LM & Nicolau DP, Expert Opin Investig Drugs, 2018

Summary of new β-lactam/β-lactam inhibitors for multidrug-resistant Gram-negative infections

Anti-infective	Company	CRE activity	MDR *P. aeruginosa* activity	MDR *A. baumannii* activity	Key features (+ activity)
Cefepime/zidebactam	Wockhardt	√	√	√	AmpC, ESBL, KPC, OXA, MBL
WCK-5153	Wockhardt	NA	√	√	OXA-23, MBL
Meropenem/nacubactam	Roche	√	√		AmpC, ESBL, KPC, OXA
Cefepime/AAI101	Allecra	√			AmpC, ESBL, KPC, OXA: 2000/500 mg (30-min infusion) q8h
VNRX-5133	VenatoRx	NA	NA	NA	AmpC, ESBL, KPC, OXA, MBL
Aztreonam/avibactam	Pfizer	√			AmpC, ESBL, KPC, OXA, MBL
Ceftaroline/avibactam	Pfizer	√			AmpC, ESBL, KPC
Cefiderocol	Shionogi	√	√	√	AmpC, ESBL, KPC, OXA, MBL; 2 g IV (3-hr infusion) q8h
Imipenem/relebactam	Merck	√	√		AmpC, ESBL, KPC: 500/250 mg IV q6h; 200/100 mg in renal impairment
Recently approved					
Meropenem/vaborbactam	Melinta	√			AmpC, ESBL, KPC; 4 g IV (3-hr infusion) q8h (reduce if eGFR <50)

Avery LM & Nicolau DP, Expert Opin Investig Drugs, 2018

Summary of non β-lactam for multidrug-resistant Gram-negative infections

Anti-infective	Company	CRE activity	MDR *P. aeruginosa* activity	MDR *A. baumannii* activity	Dosage regimens studied
Murepavadin	Polyphor		√		2.5 mg/kg IV (2-hr infusion) q8h
Finafloxacin	MerLion	√		√	800 mg IV or orally once daily
Eravacycline	Tetraphase	√		√	1 mg/kg IV q12h; 1.5 mg/kg IV once daily
Omadacycline	Paratek	√		√	100 mg IV daily, or 200–300 mg orally once daily
Plazomicin	Achaogen	√	√	√	15 mg/kg IV (30-min infusion) daily
Recently approved					
Delafloxacin	Melinta			√	300 mg IV (1-hr infusion) or 450 mg orally q12h Dose reduction recommended if eGFR <30

Avery LM & Nicolau DP, Expert Opin Investig Drugs, 2018

Recently approved antibacterials for MRSA and other Gram-positive pathogens (I)

	Tedizolid	Oritavancin	Dalbavancin
Drug class	Oxazolidinone	Lipoglycopeptide	
Spectrum	Most Gram-positive bacteria, including anaerobes, streptococci, staphylococci and enterococci	Most Gram-positive bacteria, including VRE, small-colony variants of Staphylococcus aureus, mecC-positive MRSA, VRSA (oritavancin) and some VISA/hVISA	
Pharmacokinetics	Bioavailability, 91% Half-life, 12 h Extensive tissue distribution Protein binding, 80%	Half-life, >250 h Extensive tissue distribution Protein binding, 90%	Half-life, 350 h Extensive tissue distribution Protein binding, 95%
Dosage	200 mg daily, i.v. or p.o.	1200 mg i.v., only one dose	1000 mg i.v. Day 1, 500 mg i.v. Day 8
Approved for	ABSSSI	ABSSSI	
Weaknesses	Bacteriostatic Cost	Only i.v. Cost	
Strengths	Oral drug Tissue diffusion No dose adjustment for renal failure Safety profile better than linezolid Active against *cfr*-positive S. aureus	Bactericidal Long half-life Convenient dosing Safety profile Reduce duration of inpatient stay	
Comments	May be useful for CNS and osteoarticular infections	May be useful for osteoarticular, bloodstream and foreign body-related infections	

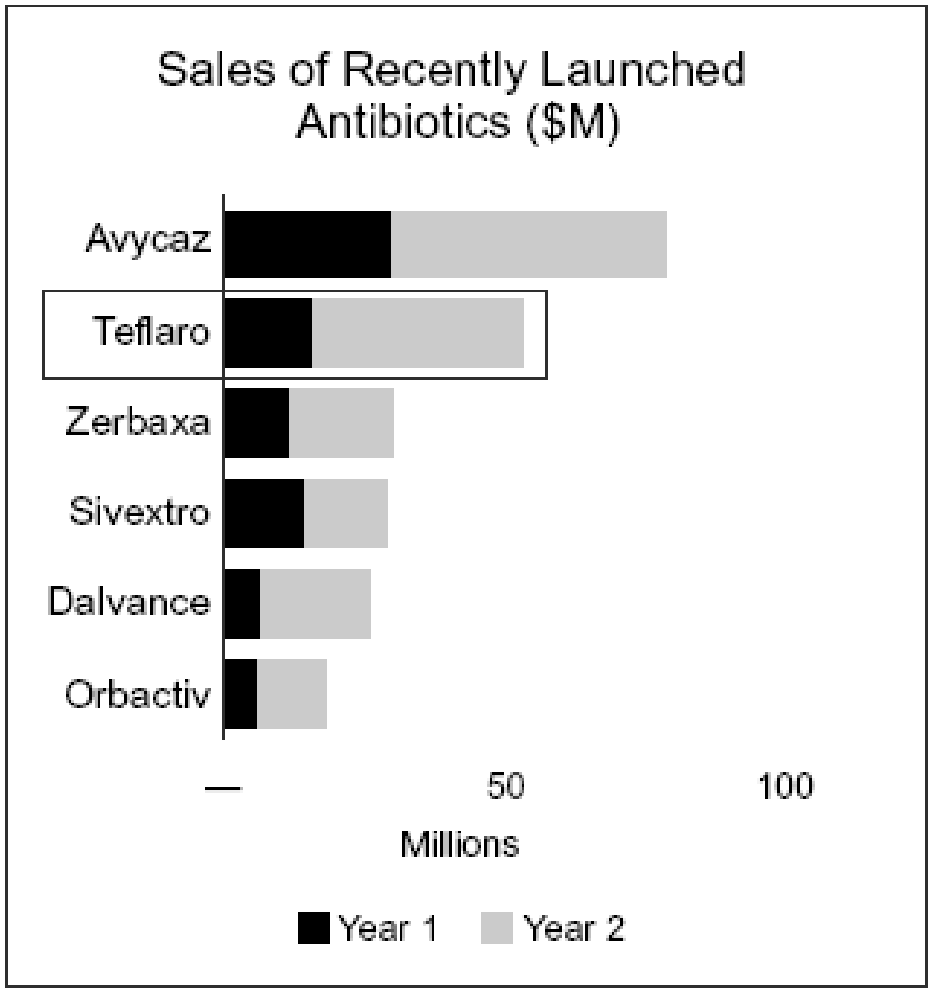
David MZ et al., Int J Antimicrob Agents, 2017

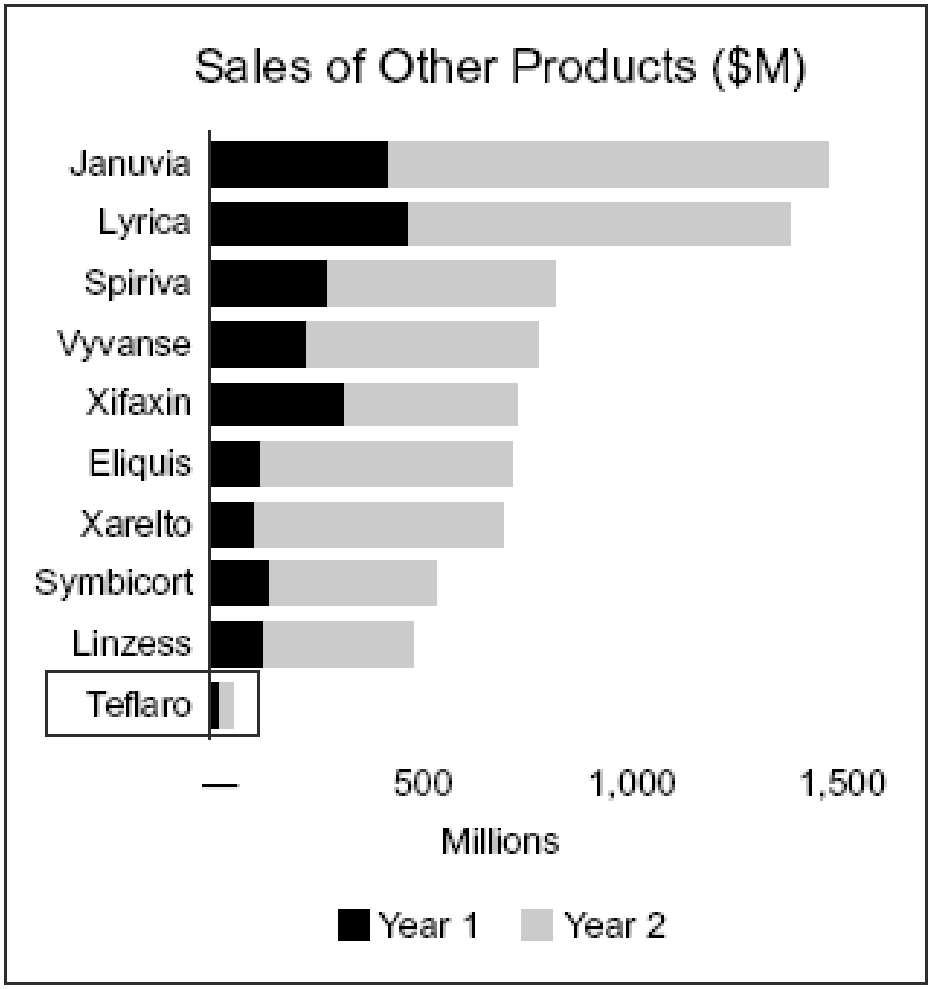
Recently approved antibacterials for MRSA and other Gram-positive pathogens (II)

	Ceftaroline	Ceftobiprole
Drug class	Cephalosporin	
Spectrum	Most Gram-positive bacteria, including methicillinresistant staphylococci, and Enterobacteriaceae (although not those with ESBL or AmpC β-lactamase)	
Pharmacokinetics	Half-life, 2 h Good tissue distribution Protein binding, 20% Time/MIC	Half-life, 3.5 h Good tissue distribution Protein binding, 16% Time/MIC
Dosage	600 mg i.v. twice daily	500 mg i.v. three times daily
Approved for	ABSSSI and CAP	
Weaknesses	Only i.v. Cost	
Strengths	Bactericidal Safety profile Some Gram-negative coverage	
Comments	May be useful for bloodstream infections, including endocarditis. Ceftaroline under development as a combination with avibactam	

David MZ et al., Int J Antimicrob Agents, 2017

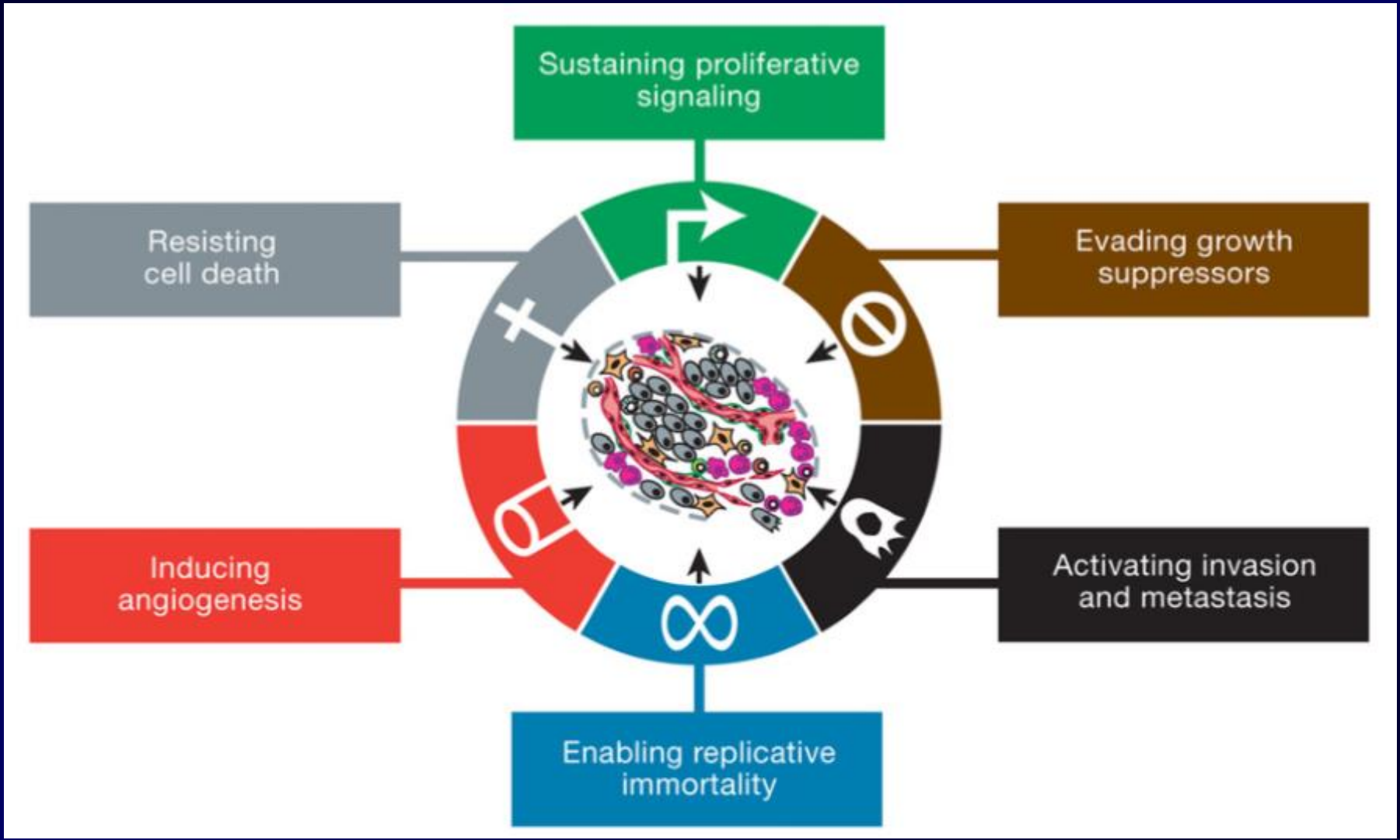
Product launches: new antibiotics vs other brands





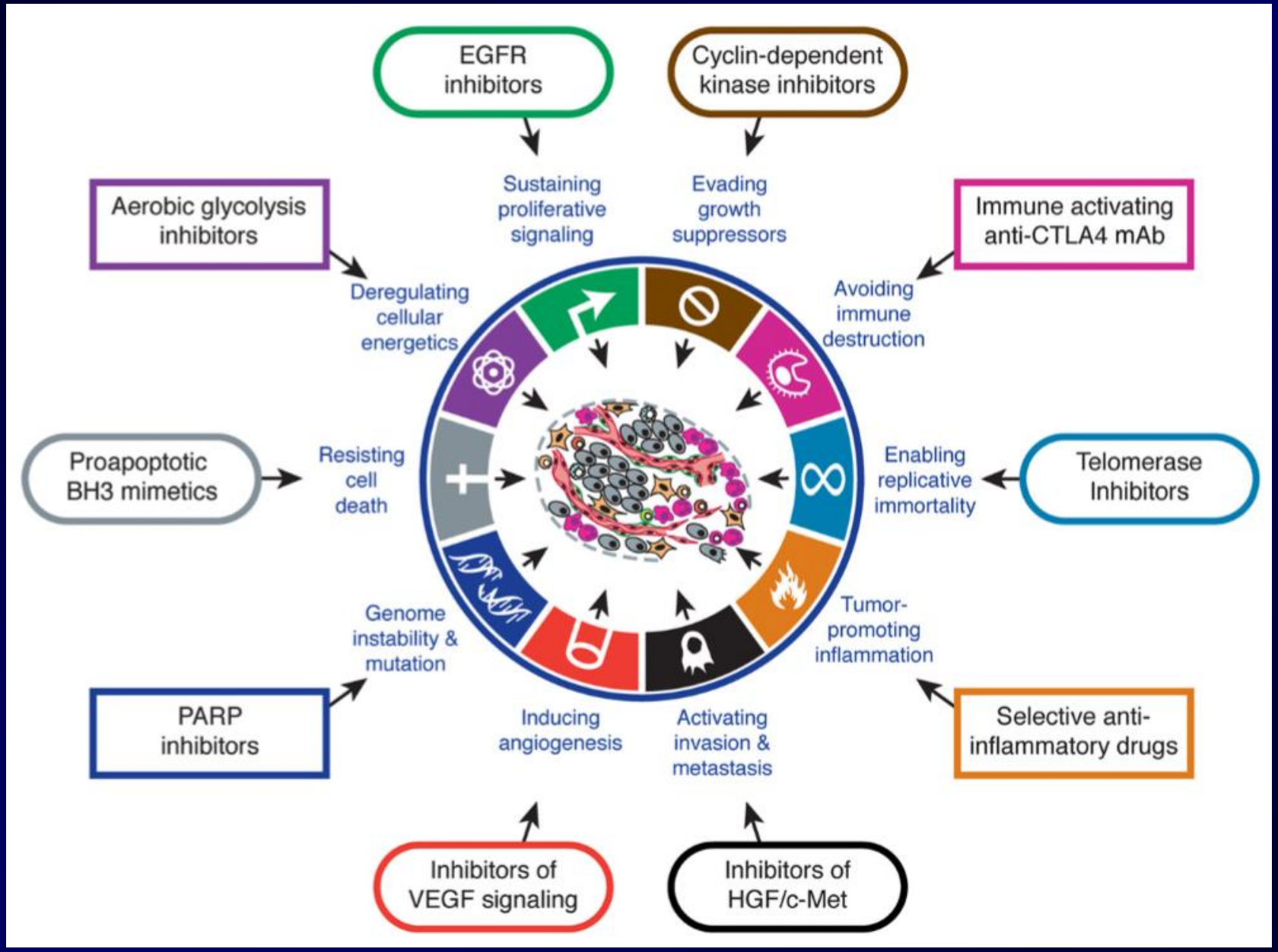
Fernandes P & Martens E, Biochem Pharmacol, 2017

The hallmarks of cancer



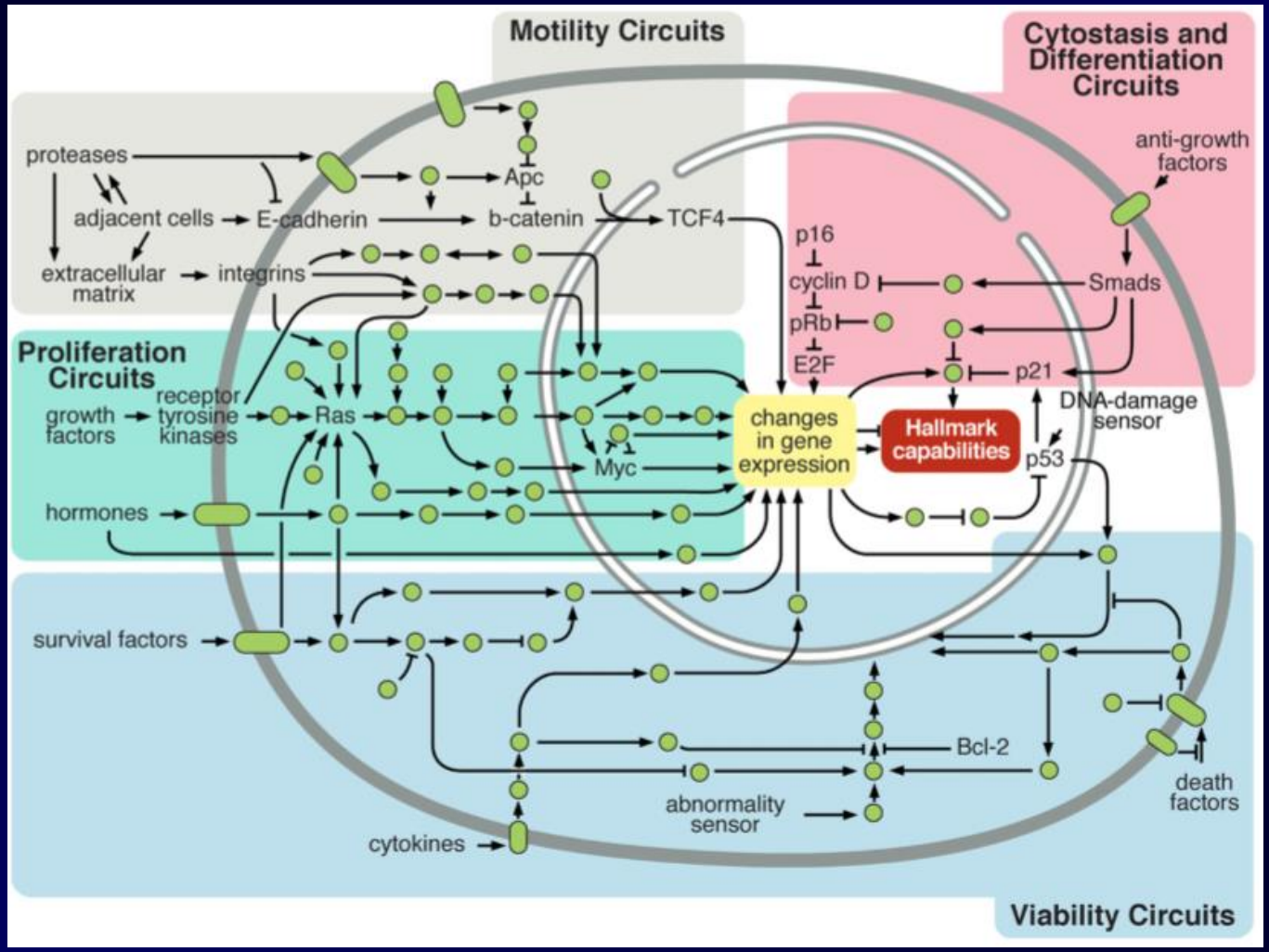
Hanahan D & and Weinberg RA, Cell, 2000 & 2011

Therapeutic targeting of the hallmarks of cancer



Hanahan D & and Weinberg RA, Cell, 2011

Intracellular signaling networks regulate the operations of the cancer cell

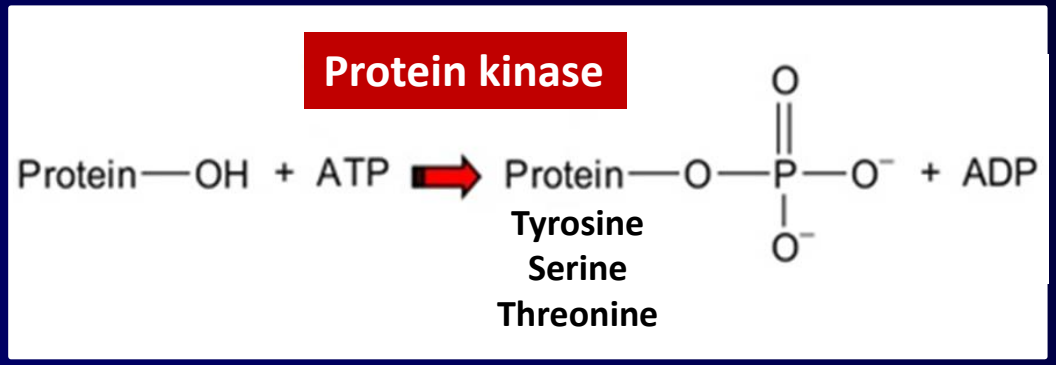


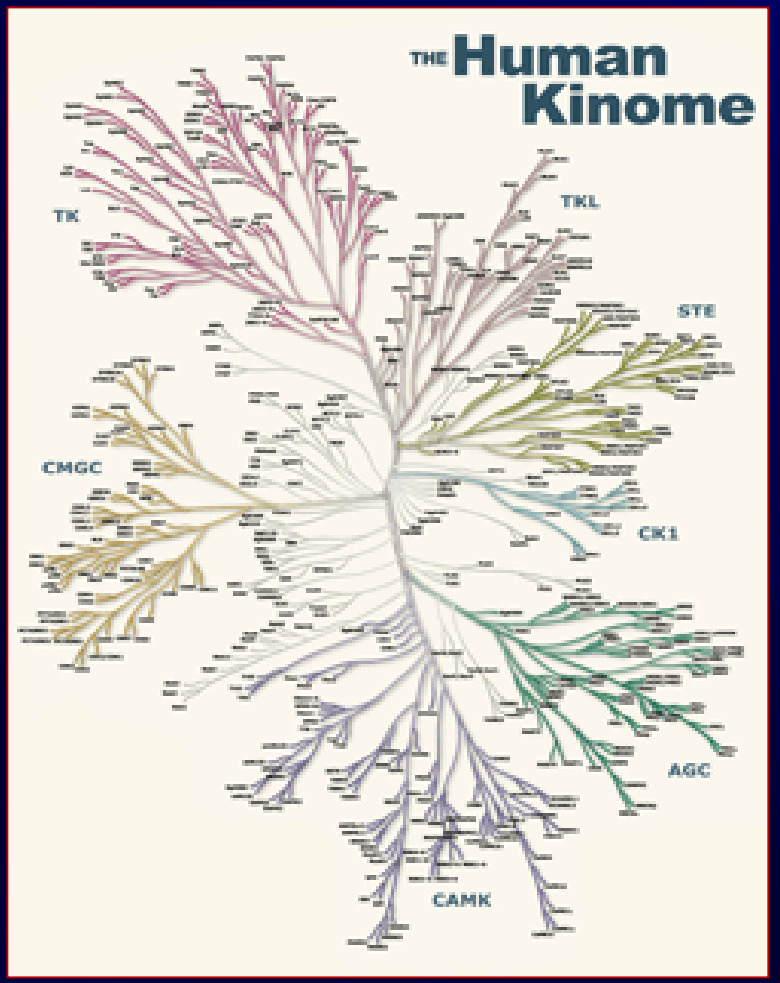
An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumor microenvironment.

Hanahan D & and Weinberg RA, Cell, 2011

Protein kinases: major targets for novel agents

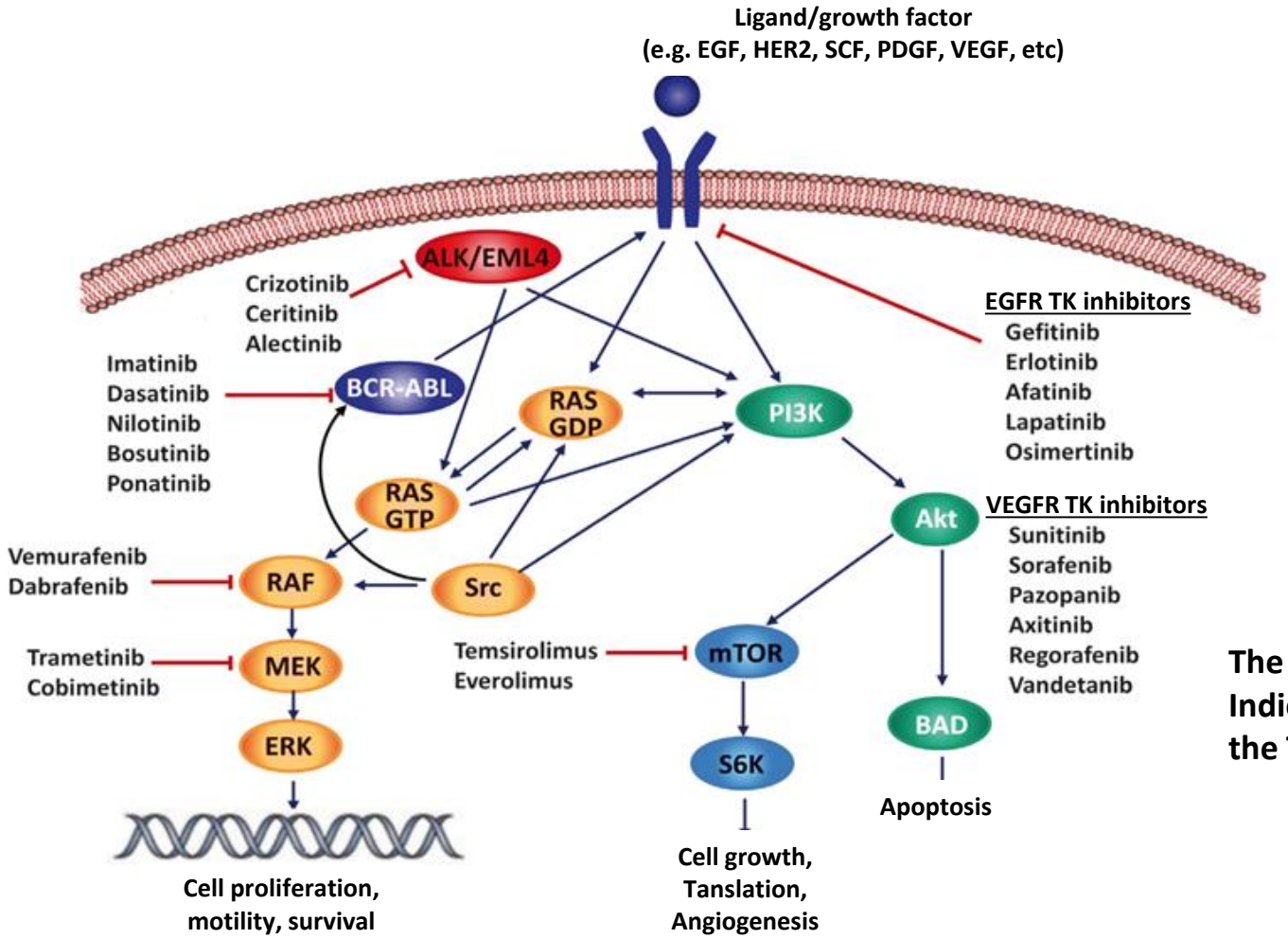
- There are 518 protein kinases in the human genome (90 tyrosine kinases)
- Major role in intracellular signalling
- Deregulation of kinase activity implicated in the growth and survival of many solid tumour types
- Protein kinases catalyze the transfer of the terminal phosphate of ATP (or GTP) to protein substrates





Manning G et al., Science, 2002

Schematic diagram showing mechanisms of action of protein kinase inhibitors



The arrows
Indicate stimulation and
the T lines inhibition

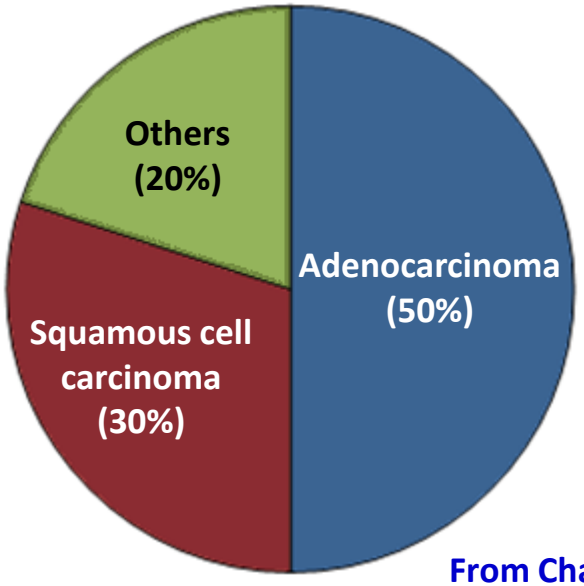
From: Farmacologia - Principi di base e applicazioni terapeutiche (Rossi, Cuomo, Riccardi ed.) Chapter 9, Danesi, Mazzei, Mini, 2016

Evolution of NSCLC taxonomy

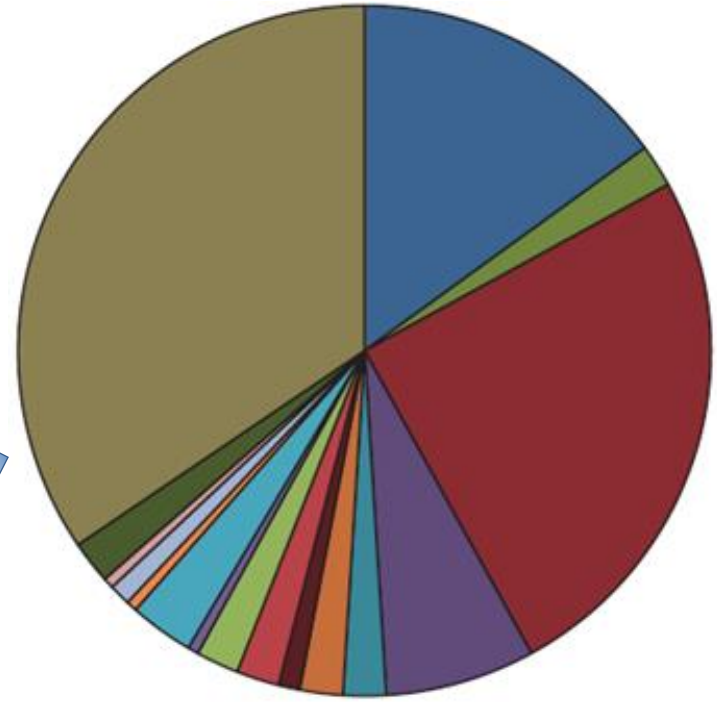
from histological to molecular based

NSCLC
as one disease

Histological based subtyping



Molecular based subtyping

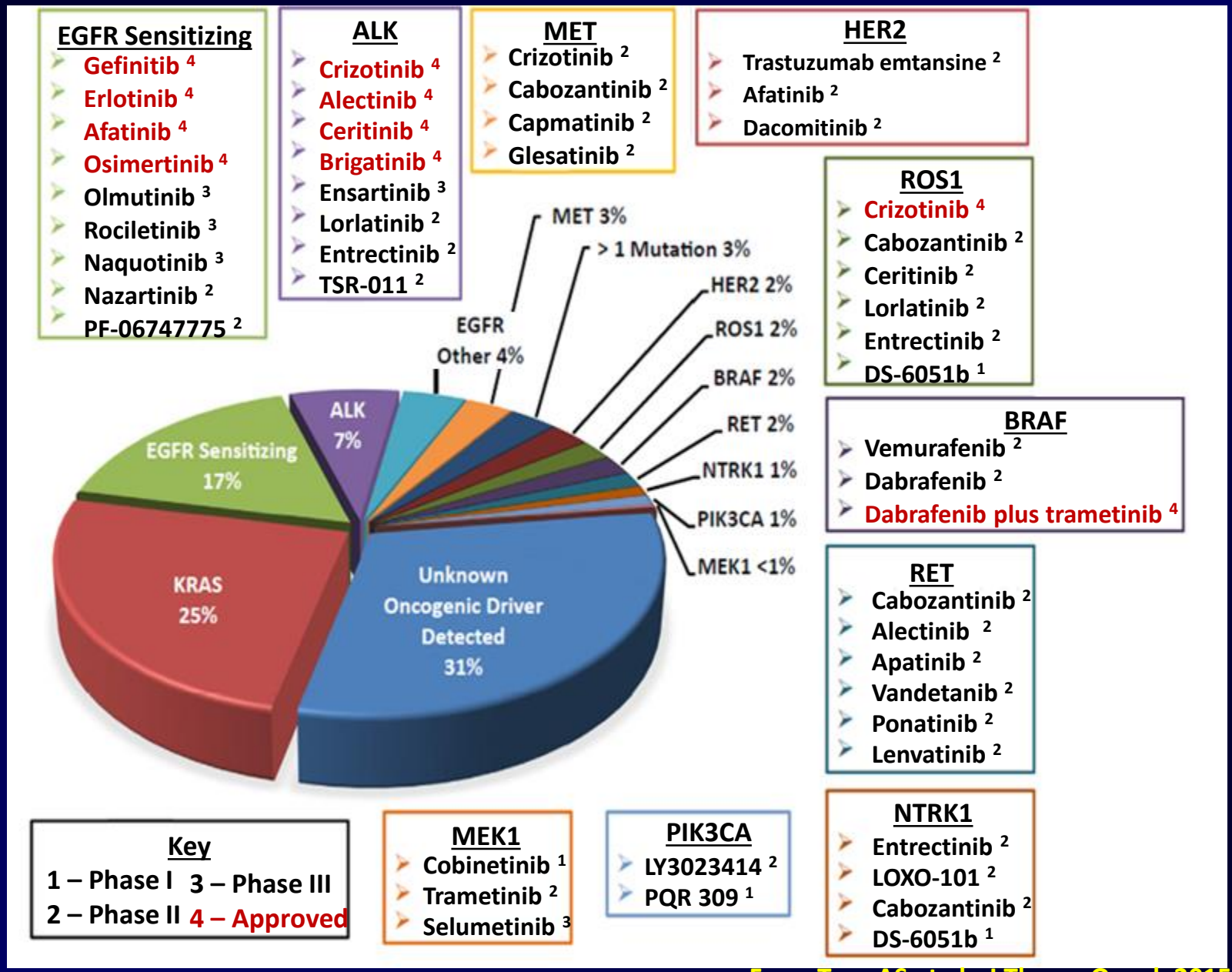


Adenocarcinoma

- EGFR-sensitising (17%)
- EGFR other (4%)
- KRAS (25%)
- ALK (7%)
- HER2 (2%)
- BRAFV600E (2%)
- BRAF other (1%)
- ROS1 (2%)
- RET(2%)
- NTRK1 (0.5%)
- MET (3%)
- MAP2K1 (0.5%)
- PI3KCA (1%)
- NRAS (0.5%)
- >1 mutation (3%)
- Unknown (31%)

From Chan BA et al., Transl Lung Cancer Res, 2015 & Hirsch FR et al., Lancet, 2016 & Lancet, 2017, modified

Developmental phases of available drugs against oncogenic proteins in NSCLC



From Tsao AS et al., J Thorac Oncol, 2015, modified

First line EGFR-TKIs vs platinum based chemotherapy in EGFR-mutated NSCLC

Trial	No. patients	Treatment	Response rate (p)	PFS (months)	HR for PFS (p)	OS (months)	HR for OS (p)
IPASS	261	Gefitinib	71% (<0.001)	9.5	0.48 (<0.001)	21.6	1 (0.99)
		Carboplatin paclitaxel	47%	6.3		21.9	
WJTOG	177	Gefitinib	62% (<0.001)	9.2	0.49 (<0.001)	30.9	1.64 (0.21)
		Cisplatin docetaxel	32%	6.3		NR	
NEJ 002	230	Gefitinib	74% (<0.001)	10.8	0.30 (<0.001)	30.5	NR
		Carboplatin paclitaxel	31%	5.4		23.6	
OPTIMAL	154	Erlotinib	83%(<0.001)	13.1	0.16 (<0.001)	22.6	1.06 (0.68)
		Carboplatin gemcitabine	36%	4.6		28.8	
EURTAC	173	Erlotinib	58% (<0.001)	9.7	0.37 (<0.001)	19.3	1.04 (0.87)
		Platinum doublet	15%	5.2		19.5	
ENSURE	217	Erlotinib	62,7%	11	0.42 (<0.001)	26.3	0.91 (0.607)
		Cisplatin gemcitabine	33,6%	5.6		25.5	
LUX-Lung3	345	Afatinib	69%	11.1	0.58 (<0.001)	28.2	1.12 (0.60)
		Cisplatin pemetrexed	44%	6.9		28.2	
LUX-Lung6	364	Afatinib	74%	11	0.28 (<0.001)	23.1	0.95 (0.76)
		Cisplatin gemcitabine	31%	5.6		23.5	

NR, not reached

From Shea M et al., Ther Adv Respir Dis, 2015, modified

Osimertinib in EGFR T790M-positive lung cancer pts who had PD after first line EGFR-TKI therapy (AURA3 study)

EGFR+ NSCLC

2nd line

R

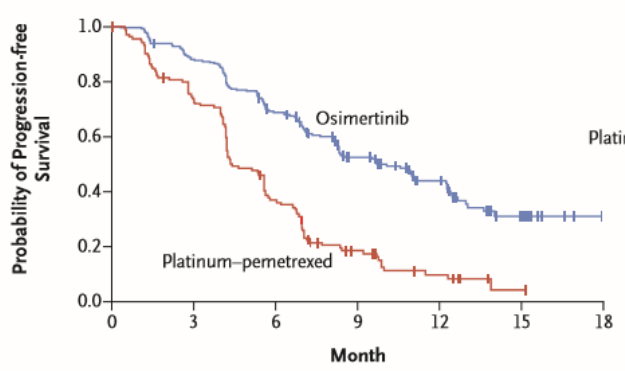
2:1

Osimertinib (n=279)

Platinum-Pemetrexed (n=140)

Primary end point:
PFS by investigator

A. Patients in intention-to-treat population

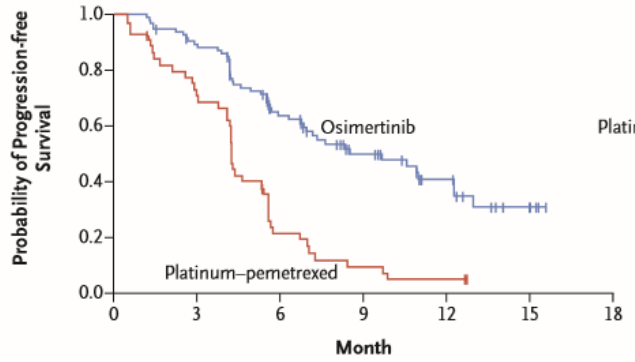


	No. of Patients	Median Progression-free Survival (mo (95% CI))
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

B. Patients with CNS metastases

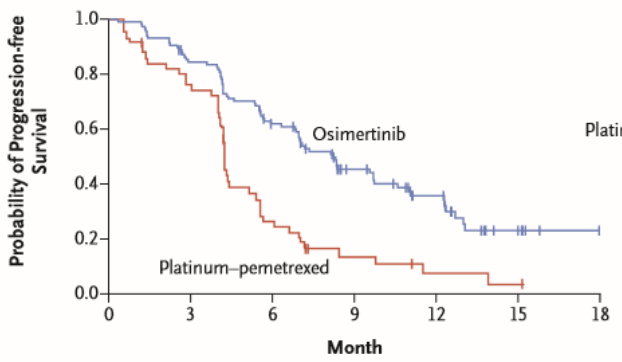


	No. of Patients	Median Progression-free Survival (mo (95% CI))
Osimertinib	93	8.5 (6.8–12.3)
Platinum–pemetrexed	51	4.2 (4.1–5.4)

Hazard ratio for disease progression or death, 0.32 (95% CI, 0.21–0.49)

No. at Risk							
Osimertinib	93	80	46	27	14	4	0
Platinum–pemetrexed	51	32	9	4	2	0	0

C. Patients with EGFR T790M-positive status in both tumor and plasma



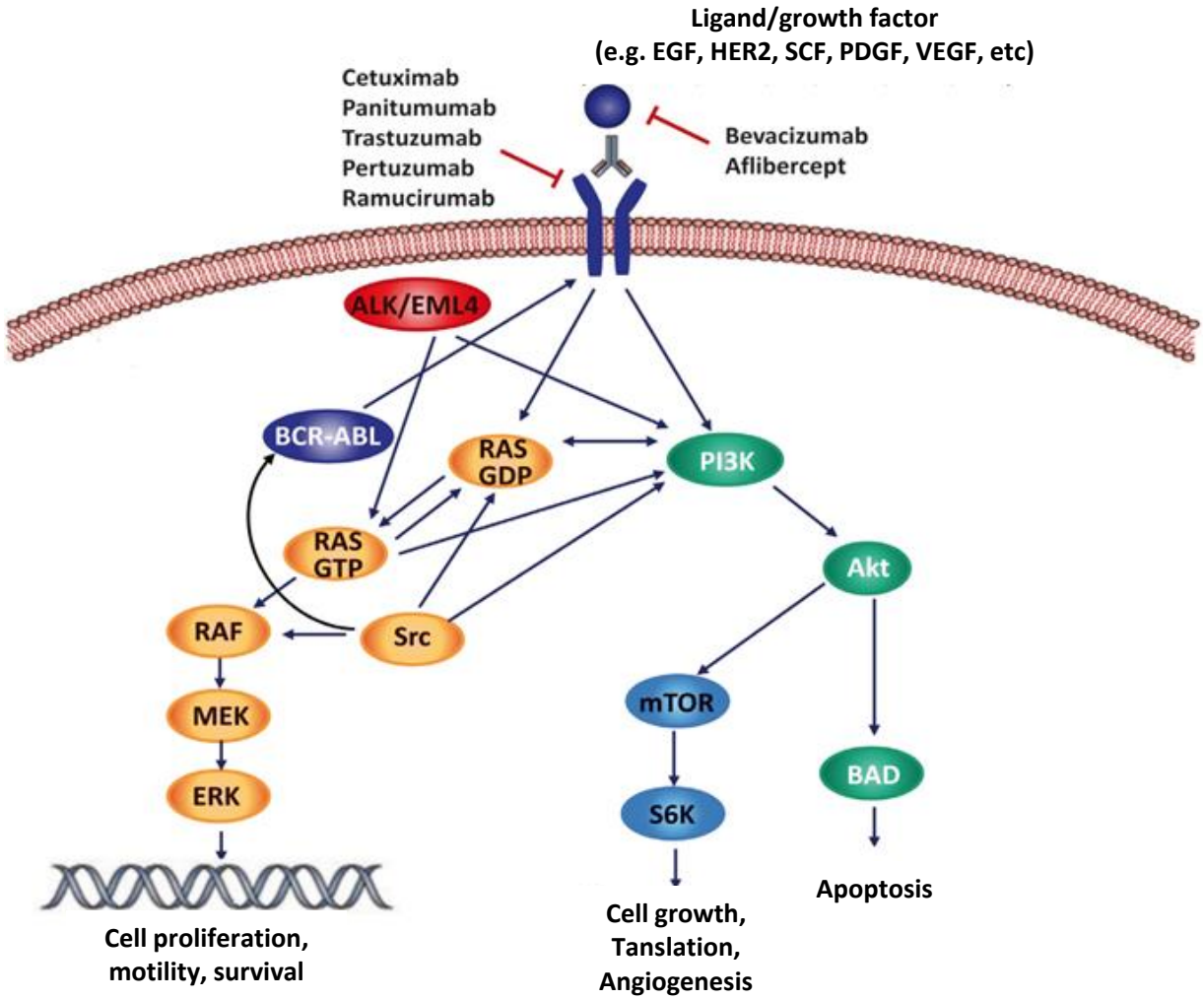
	No. of Patients	Median Progression-free Survival (mo (95% CI))
Osimertinib	116	8.2 (6.8–9.7)
Platinum–pemetrexed	56	4.2 (4.1–5.1)

Hazard ratio for disease progression or death, 0.42 (95% CI, 0.29–0.61)

No. at Risk							
Osimertinib	116	95	63	35	20	5	0
Platinum–pemetrexed	56	39	13	5	2	1	0

Mok TS et al., N Engl J Med, 2016

Schematic diagram showing mechanisms of action of monoclonal antibodies



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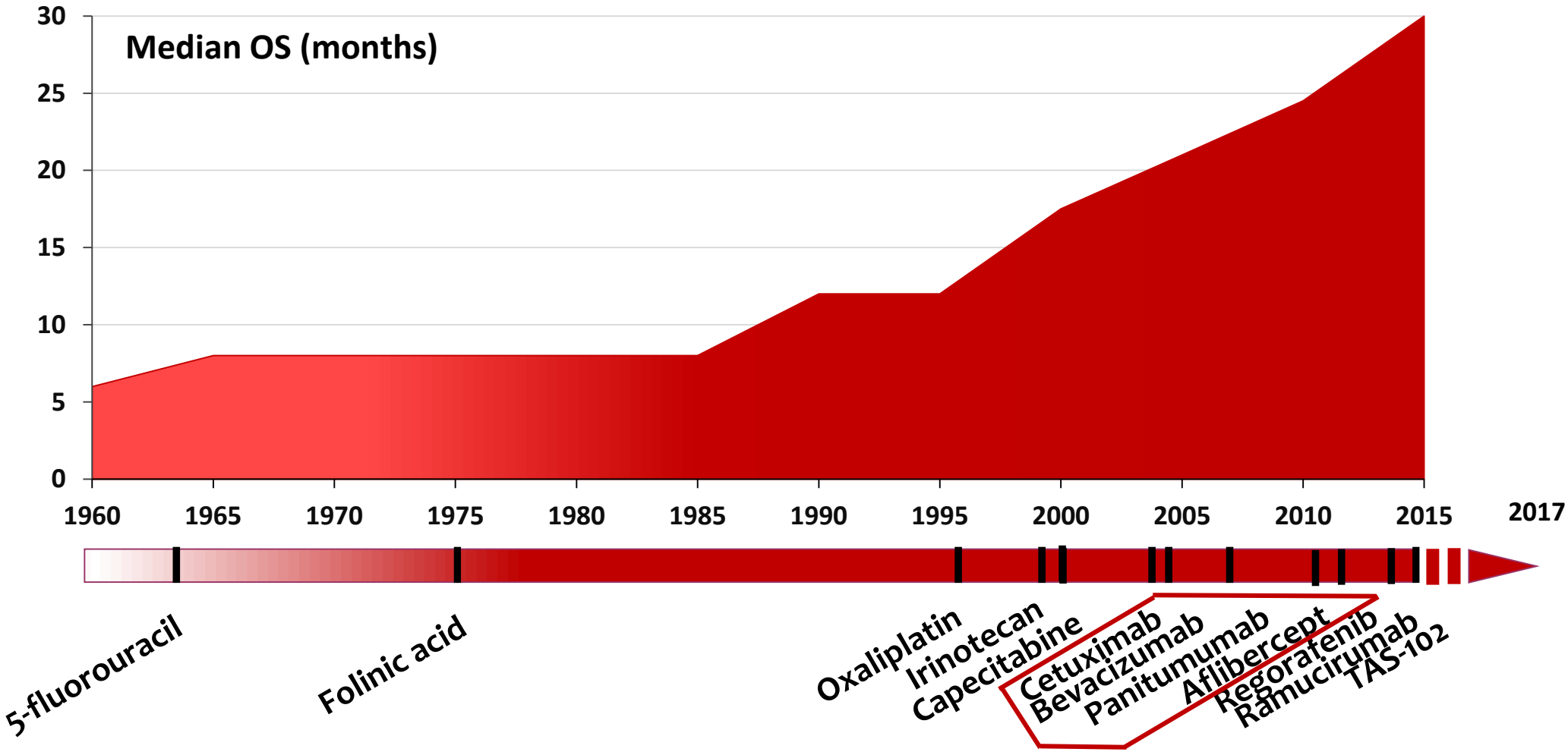
JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L

Treatment of Metastatic Colon Cancer: "The Times They Are A-Changing"

Nancy E. Kemeny, *Memorial Sloan-Kettering Cancer Center, New York, NY*



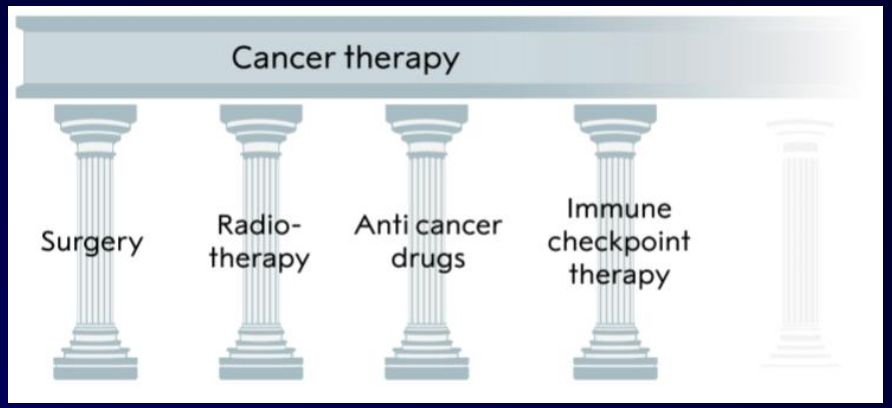
Milestones in cancer chemotherapy

2018

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

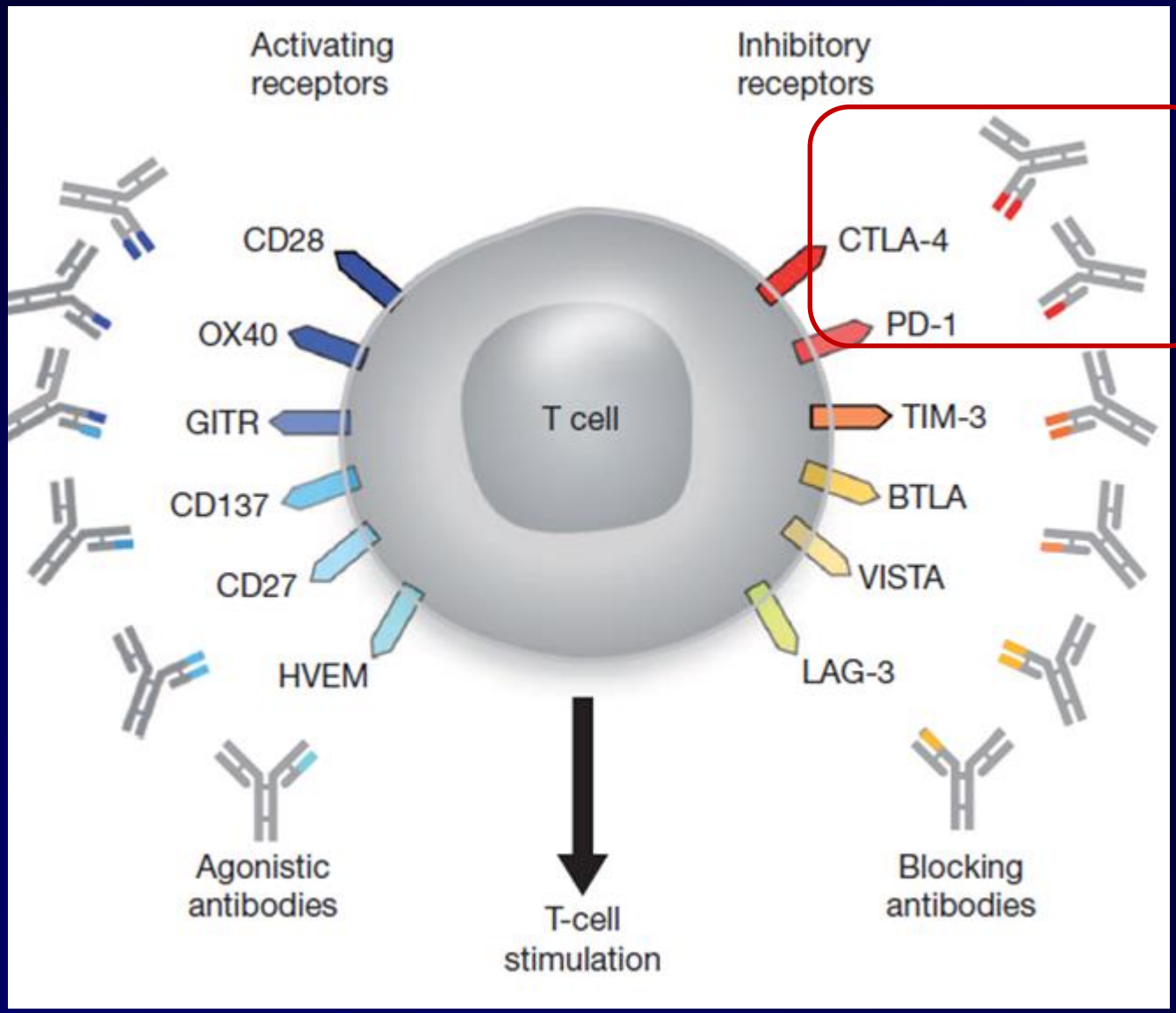
The Nobel Assembly at Karolinska Institutet
has today decided to award
the 2018 Nobel Prize in Physiology or
Medicine jointly to
James P. Allison and Tasuku Honjo

for their discovery of cancer therapy by inhibition of negative immune regulation



C. I. Edvard Smith, Rikard Holmdahl, Olle Kämpe & Klas Kärre, September 30, 2018. www.nobelprize.org

T cells as targets for immunoregulatory antibody therapy

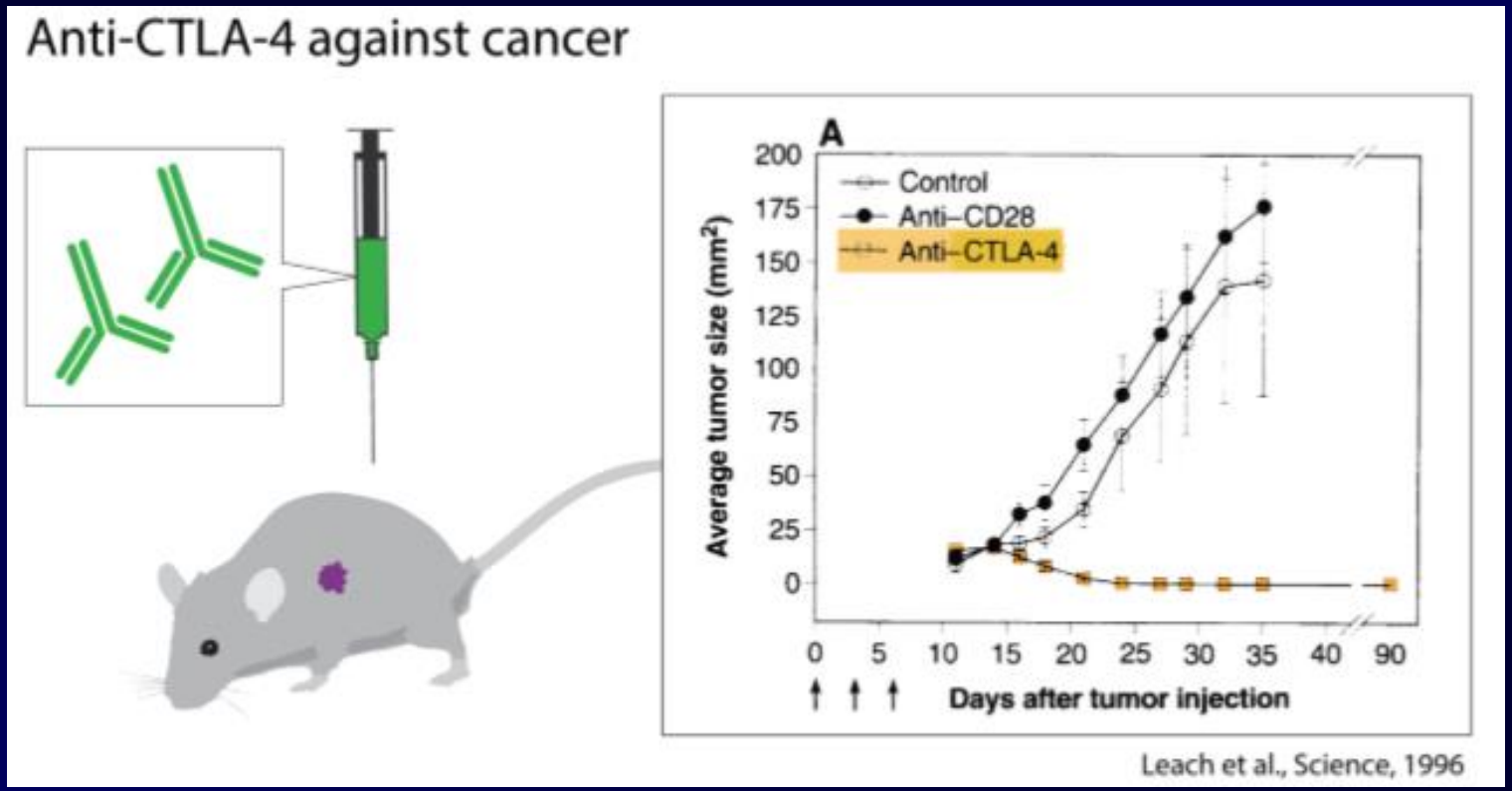


Target	Drug
CTLA-4	Ipilimumab
PD-1	Nivolumab Pembrolizumab
PD-L1	Atezolizumab Durvalumab Avelumab

Science, 2013

Mellman I et al., Nature, 2011

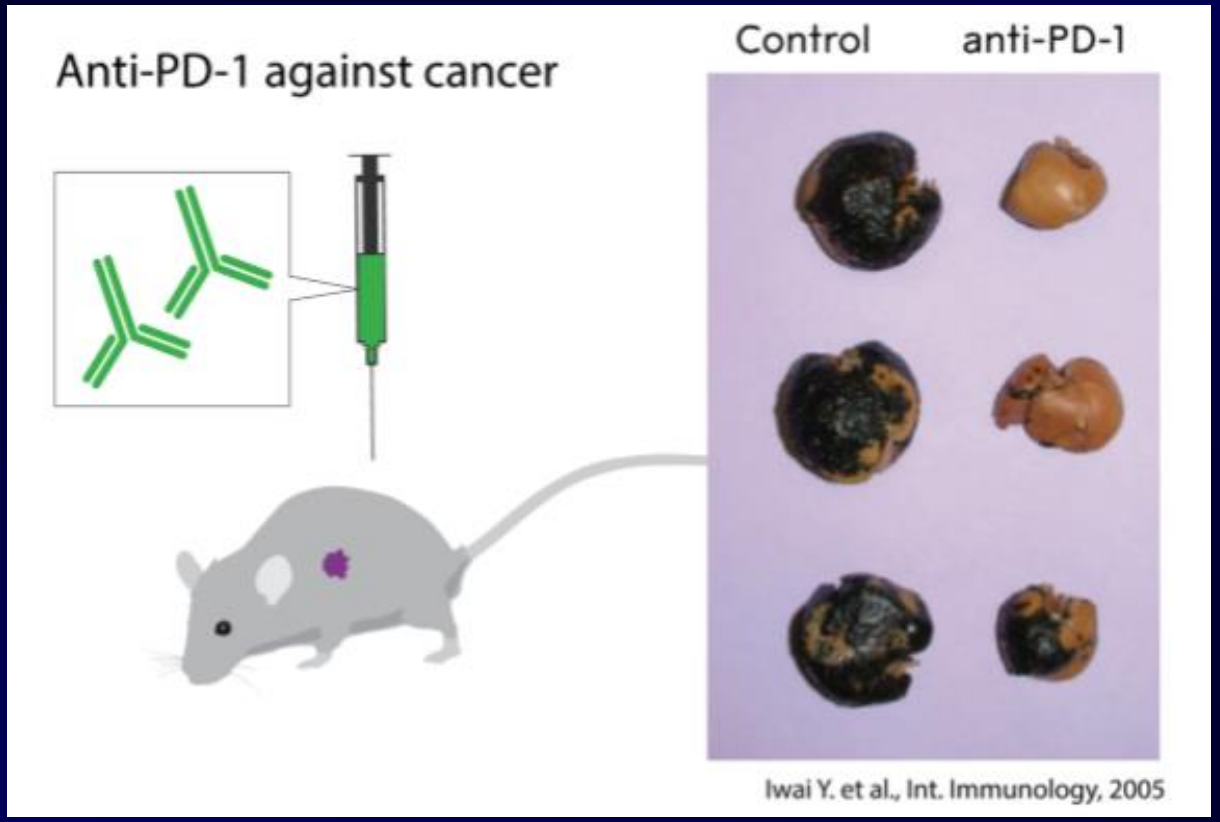
Identification of CTLA-4 as a negative regulator
Inhibition of tumor growth by antibodies against CTLA-4 in animals



The discovery of James P. Allison and coworkers, utilizing the role of CTLA-4 as an inhibitor of activation and developing antibodies to release the brake.
The graph shows the effect of anti-CTLA-4 treatment in tumor-bearing mice compared to controls.

C. I. Edvard Smith, Rikard Holmdahl, Olle Kämpe & Klas Kärre, September 30, 2018. www.nobelprize.org

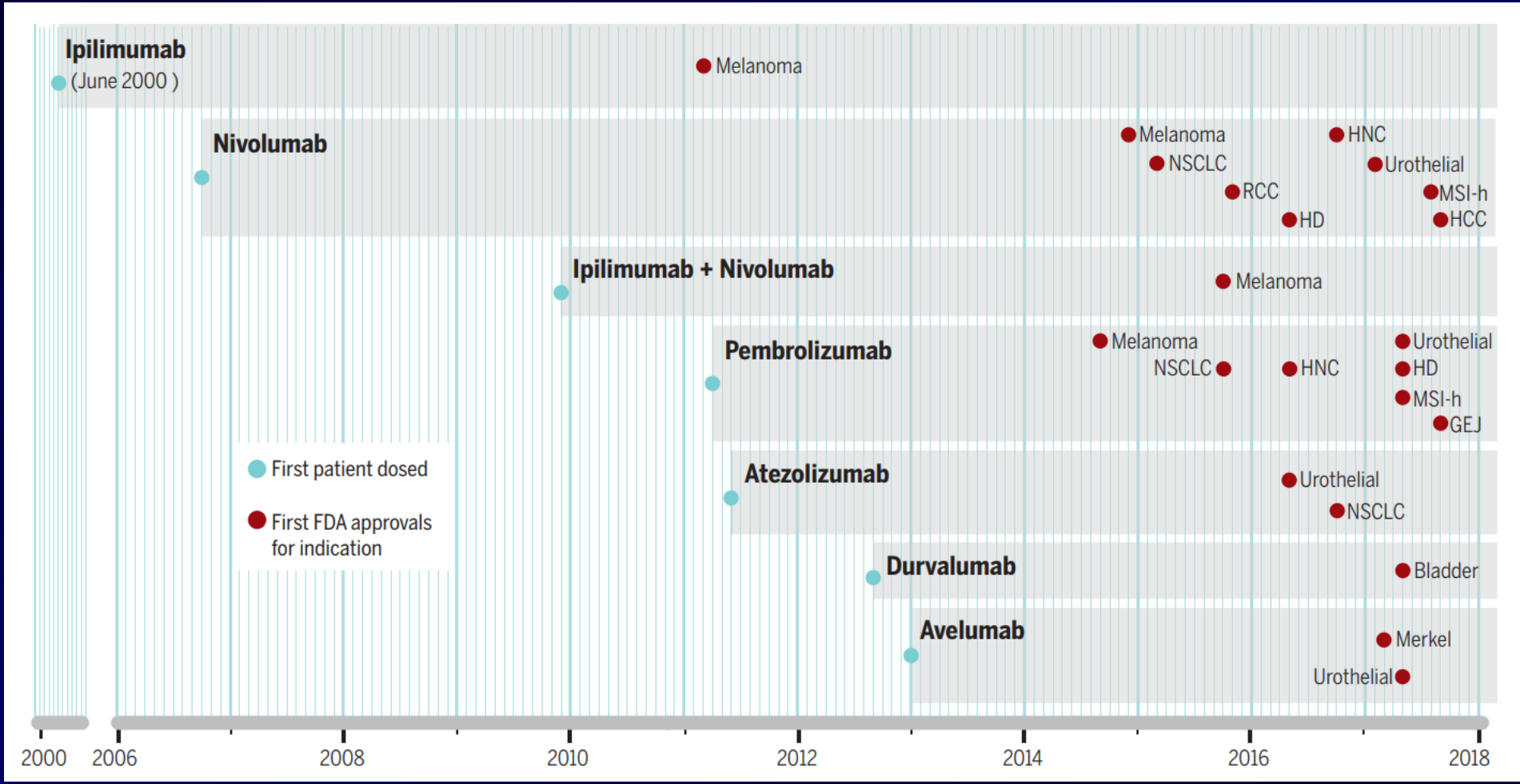
Discovery of the PD-1 receptor and its role in immune responses
PD-1 blockade as a treatment of cancer



The discovery by Tasuku Honjo and coworkers, the identification of the PD-1 surface protein, recognizing its role as an inhibitor of activation and developing antibodies to release the brake.
The graph shows the effect of anti-PD1 treatment in mice with metastasizing melanoma compared to untreated controls.

C. I. Edvard Smith, Rikard Holmdahl, Olle Kämpe & Klas Kärre, September 30, 2018. www.nobelprize.org

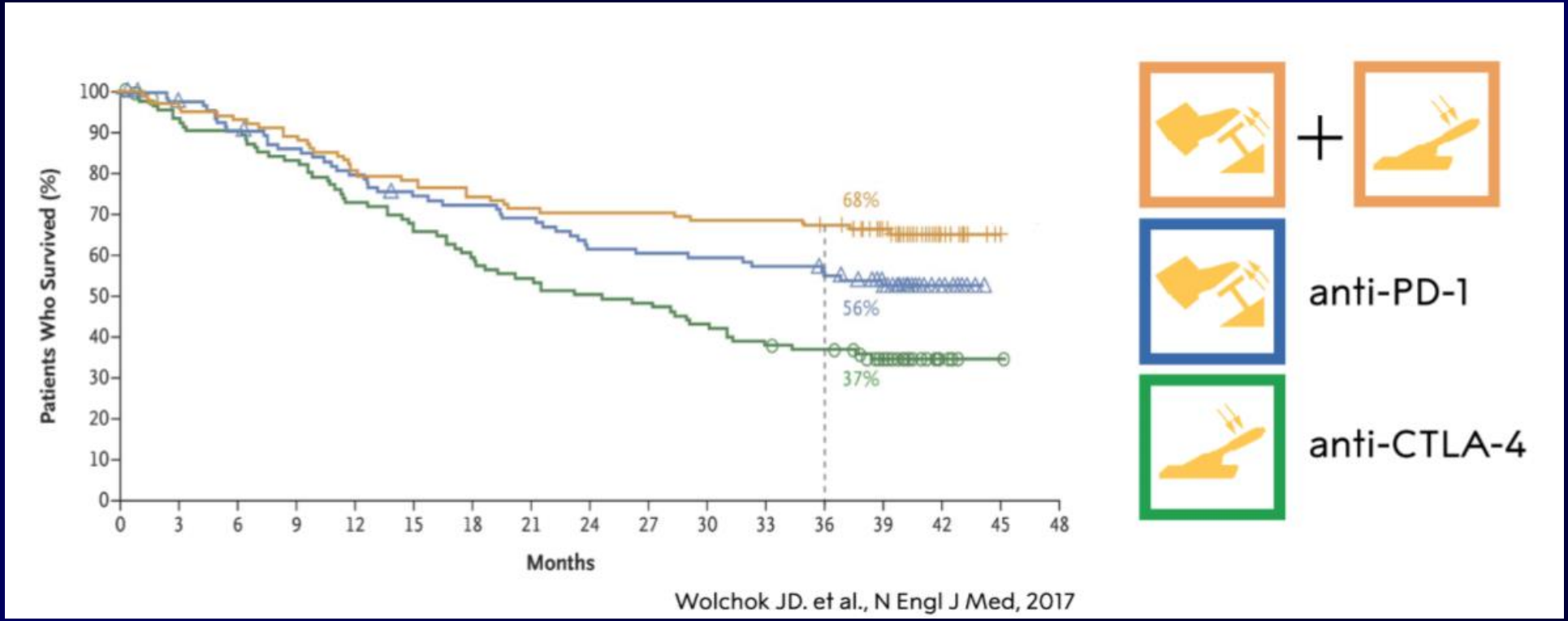
Timing of clinical development of anti–CTLA-4, anti–PD-1, and anti–PD-L1 antibodies, from first administration to humans to FDA approval



Thus far, there has been drug regulatory approval for six antibodies that block immune checkpoints and a combination of two immune checkpoint-blocking antibodies. The gray shading represents the period of clinical development for each of these antibodies, from the dosing of the first patient until regulatory approval (red circles) in different indications. HNC, head and neck cancer; RCC, renal cell carcinoma; MSI-h, high microsatellite instability; HD, CREDITS (GRAPHIC) V. ALTOUNIAN/ Hodgkin's disease; HCC, hepatocellular carcinoma; GEJ, gastroesophageal junction.

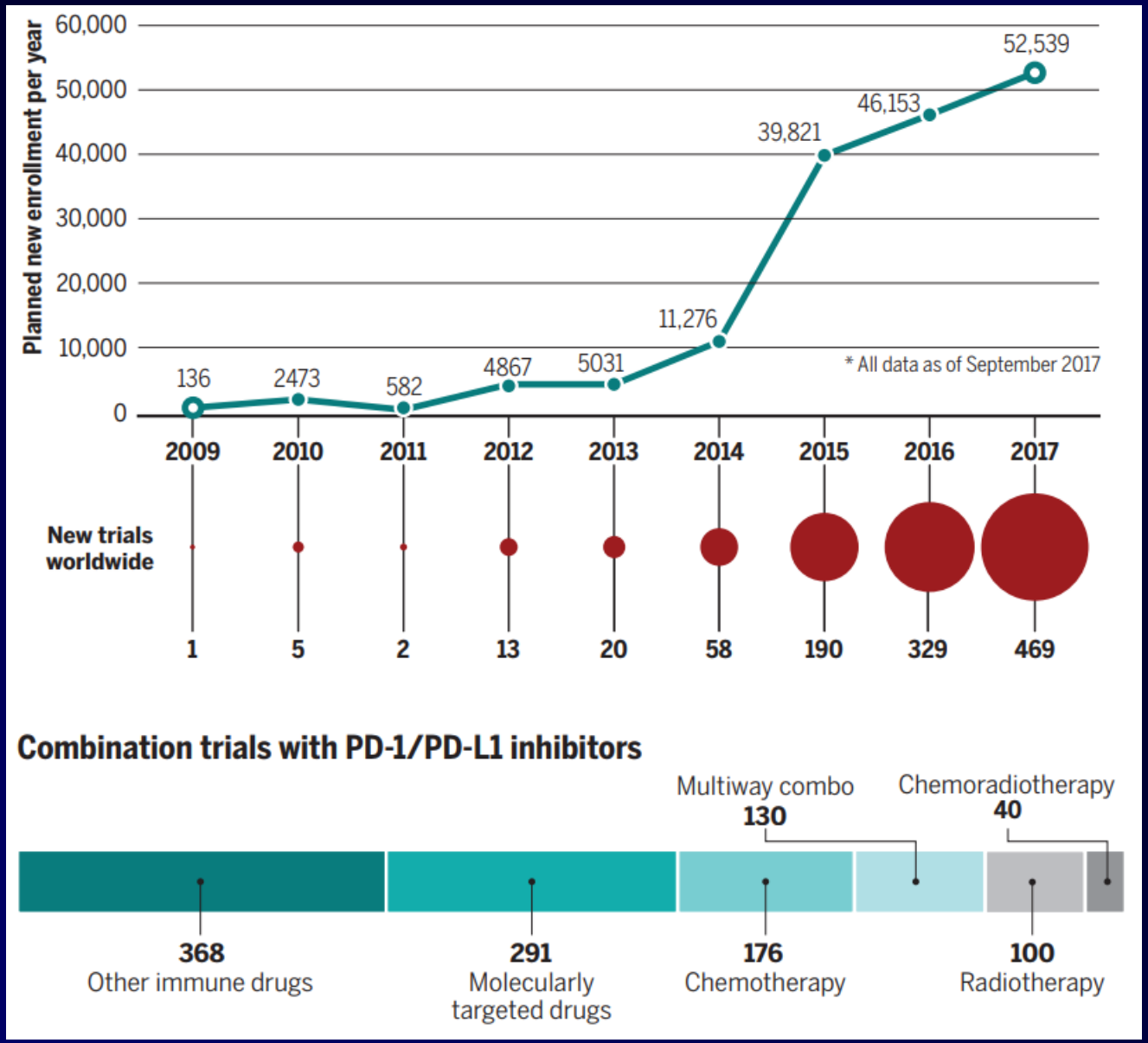
Ribas A & Wolchok JD. Science, 2018

Combination therapy



The effect of anti-CTLA-4, anti-PD-1 and combination therapy in a subgroup of patients with melanoma (adopted from Wolchock et al., 2017).

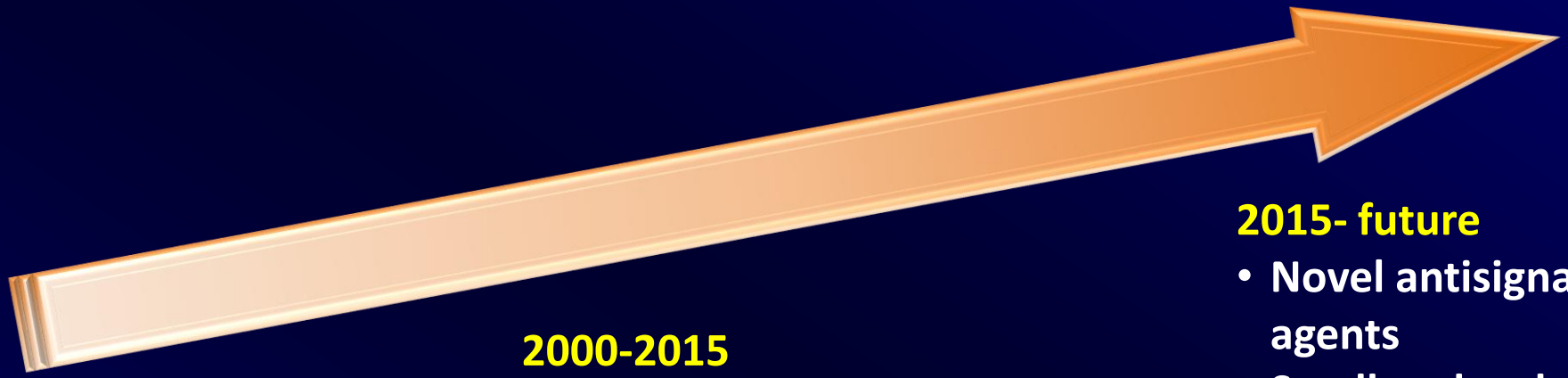
Trial explosion



More than 1000 clinical trials are combining other cancer treatments with immunotherapy drugs, called checkpoint inhibitors, that target the proteins PD-1 or PD-L1 (bottom bars). The number of subjects needed for those trials has skyrocketed (below), and some trials may not find enough patients.

Kaiser J. Science, 2018

The future of cancer chemotherapy



1992-2000

- Cytotoxic & hormonal agents are mainstays

2000-2015

- Cytotoxic and hormonals remain
- Emergence of targeted antisignaling compounds
- Increasing use of biologics
- Novel combination of cytotoxics along with other modalities
- Tailored, individualized chemotherapies

2015- future

- Novel antisignaling agents
- Small molecules and biologics possibly replace cytotoxics
- Immunotherapy revolution (MoAb, CAR-T, cancer vaccine)
- Cancer is viewed as a chronic disease