JUEVES 4 DE MAYO 2017
11:00h

SIMPOSIO AMGEN

INNOVACIÓN EN EL DESARROLLO DE FÁRMACOS

Moderador: Raúl Ferrando. Jefe Servicio Farmacia Hospital General Universitario Castellón.
Ponente: José Luis Motellón. Director Medico AMGEN.


TODOS
LO llaman
INSOMNIO,
YO LO llamo
CONGRESO SVFH


START


trending
topics
shutterstock

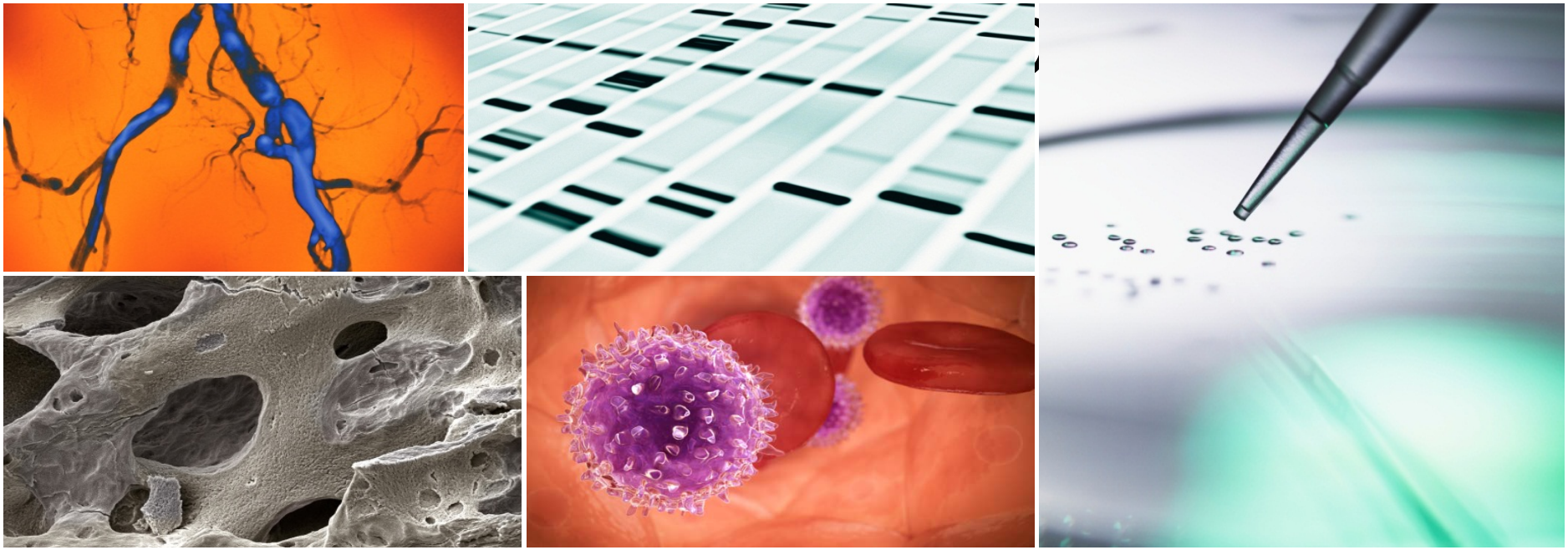
EL VALOR DE LA FARMACIA HOSPITALARIA


innovation
sustainable
social
inclusion
development
work
economics
justice
society
political
systems
different
science
need
power
forms
inclusive
new
3-D
help
MEDICAL

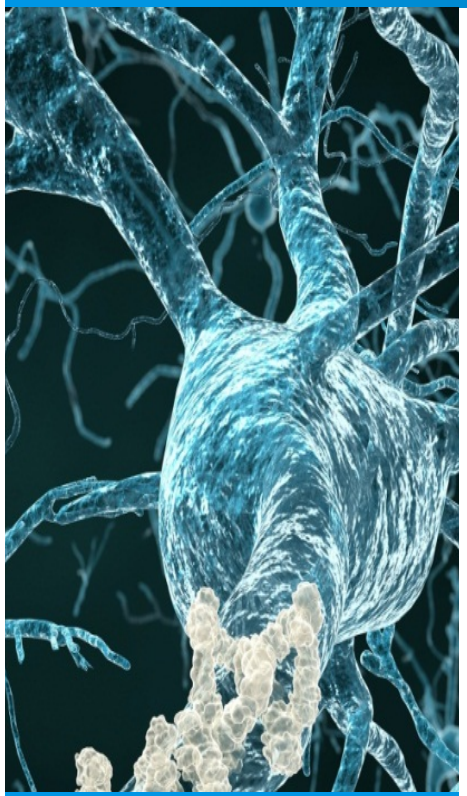

¿Quién?


¿Cómo lo
hacemos?

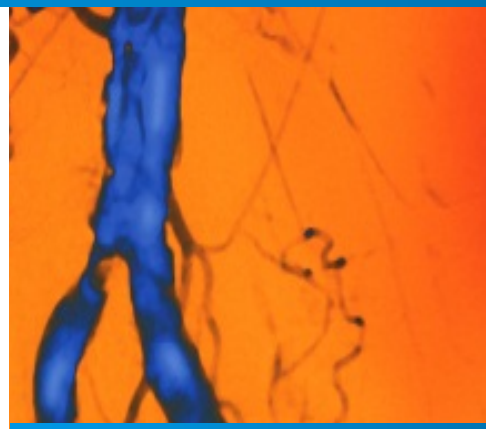

AMGEN®



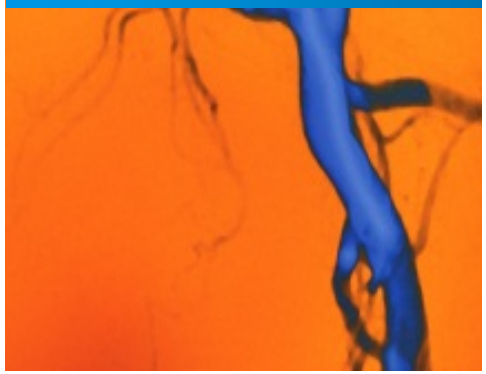
ÁREAS TERAPEUTICAS

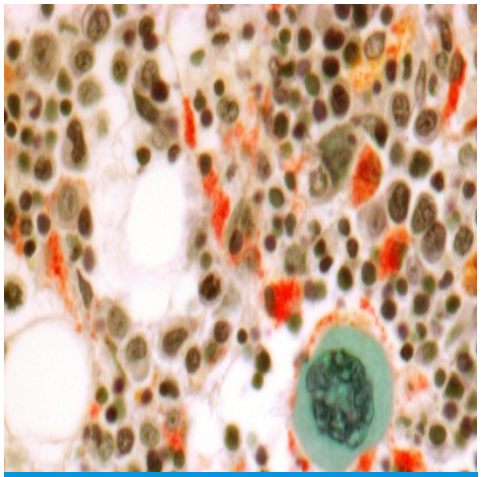


Neurociencias



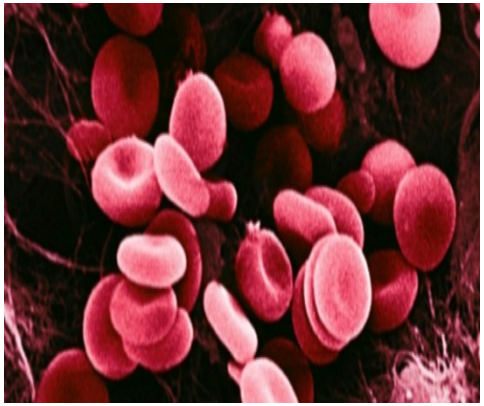
Cardiovascular

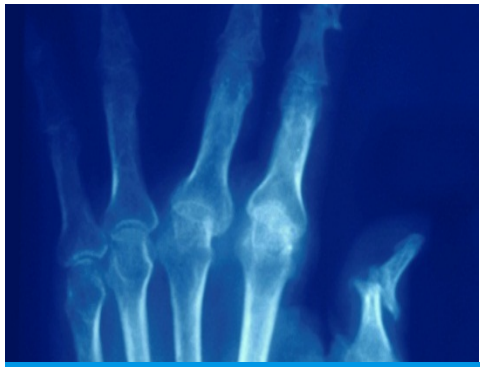




Oncología

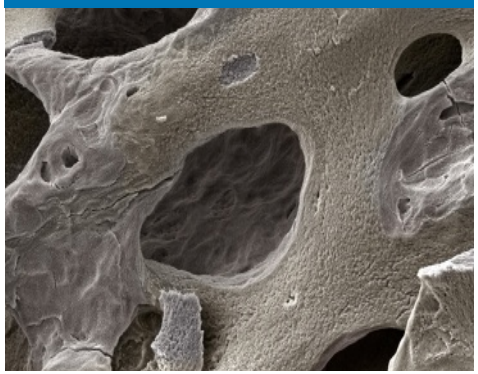
Nefrología





Inflamación

Metabolismo óseo



Pipeline

PHASE ONE

AMG 172 Hematology/ Oncology	AMG 208 Hematology/ Oncology	AMG 211 Hematology/ Oncology
AMG 228 Hematology/ Oncology	AMG 232 Hematology/ Oncology	AMG 282 Inflammation
AMG 301 Neuroscience	AMG 319 Hematology/ Oncology	AMG 330 Hematology/ Oncology
AMG 357 Inflammation	AMG 557 Inflammation	AMG 581 Neuroscience
AMG 595 Hematology/ Oncology	AMG 780 Hematology/ Oncology	AMG 811 Inflammation
AMG 820 Hematology/ Oncology	AMG 876 Metabolic Disorders	AMG 900 Hematology/ Oncology
Oprozomib Hematology/ Oncology		

PHASE TWO

AMG 139 Inflammation	AMG 157 Inflammation	AMG 181 Inflammation
AMG 334 Neuroscience	AMG 337 Hematology/ Oncology	AMG 899 (TA-8995) Cardiovascular
BLINCYTO® (blinatumomab) Hematology/ Oncology	Kyprolis® (carfilzomib) Hematology/ Oncology	Omecamtiv mecarbil Cardiovascular
XGEVA® (denosumab) Hematology/ Oncology		

PHASE THREE

AMG 334 Neuroscience	Aranesp® (darbepoetin alfa) Hematology/ Oncology	BLINCYTO® (blinatumomab) Hematology/ Oncology
Etelcalcetide (AMG 416) Nephrology	IMLYGIC™ (talimogene laherparepvec) Hematology/ Oncology	Kyprolis® (carfilzomib) Hematology/ Oncology
Prolia® (denosumab) Bone Health	Repatha® (evolocumab) Cardiovascular	Romosozumab Bone Health
Trebananib Hematology/ Oncology	Vectibix® (panitumumab) Hematology/ Oncology	XGEVA® (denosumab) Hematology/ Oncology

BIOSIMILARS‡

ABP 501 (biosimilar adalimumab) Inflammation	ABP 710 (biosimilar infliximab) Inflammation	ABP 980 (biosimilar trastuzumab) Hematology/ Oncology	ABP 494 (biosimilar cetuximab) Hematology/ Oncology	ABP 215 (biosimilar bevacizumab) Hematology/ Oncology	ABP 798 (biosimilar rituximab) Hematology/ Oncology & Inflammation

‡Amgen has an additional three biosimilar programs in development which are undisclosed at this time.

This information reflects public disclosures current as of **November 2, 2015**. Amgen's product pipeline will change over time as molecules move through the drug development process, including progressing to market or failing in clinical trials, due to the nature of the development process. This description contains forward-looking statements that involve significant risks and uncertainties, including those discussed in Amgen's most recent Form 10-K and in Amgen's periodic reports on Form 10-Q and Form 8-K, and actual results may vary materially. Amgen is providing this information as of the date above and does not undertake any obligation to update any forward-looking statements contained in this table as a result of new information, future events or otherwise.

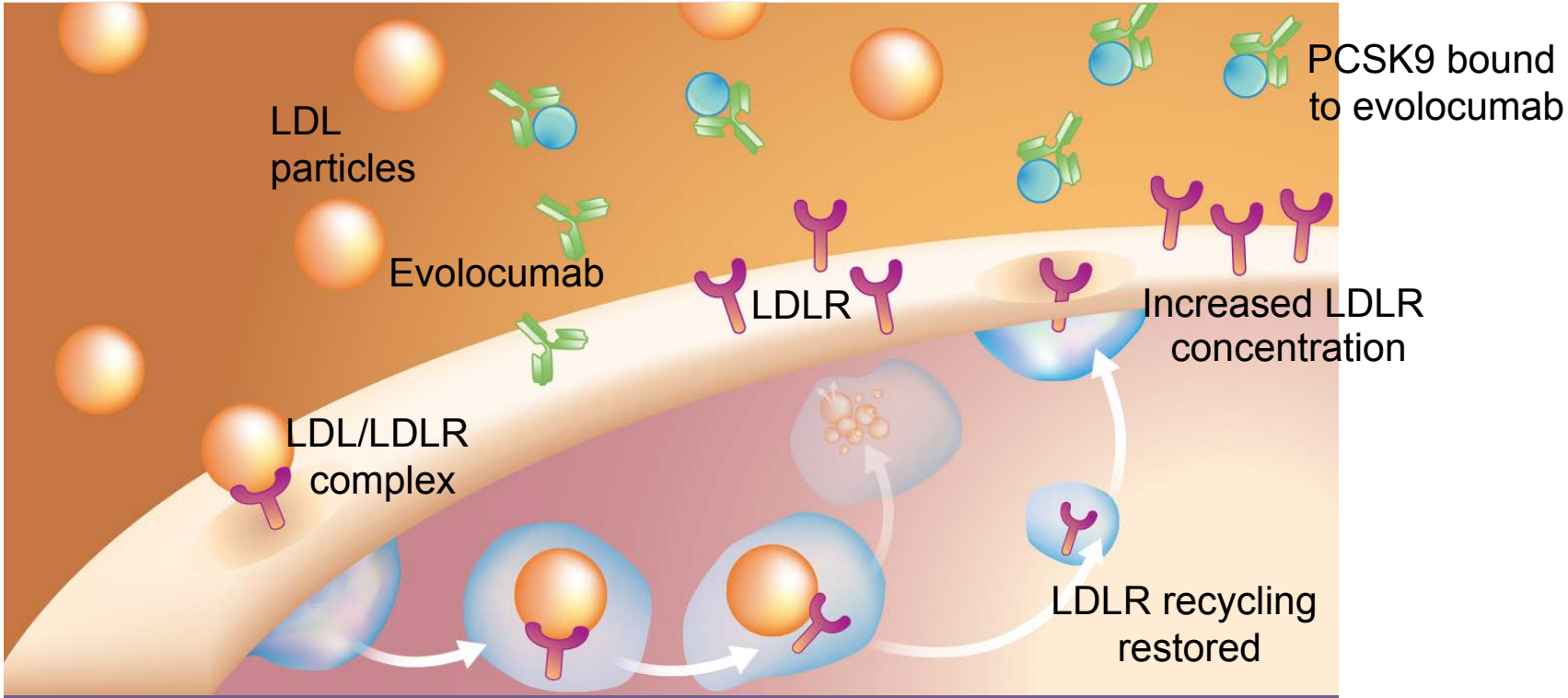

INNOVACIÓN

PCSK9 inhibition with Evolocumab

AMGEN®

Cardiovascular

Evolocumab is a fully human monoclonal antibody that binds PCSK9



Presence of evolocumab = absence of PCSK9, more LDLR, lower plasma LDL-C

"Overdosing" is not generally seen with a blocking antibody such as evolocumab

Chan et al. Proc Nat Acad Sci USA 2009;106:9820–9825.

AMGEN®
Cardiovascular

Evolocumab is being clinically evaluated in the PROFICIO trial programme

>35,000 patients

laplace	Combination therapy	Phase 2 (n=631) ✓	Phase 3 (n=2,067) ✓
mendel	Monotherapy	Phase 2 (n=411) ✓	Phase 3 (n=615) ✓
gauss	Statin intolerant	Phase 2 (n=160) ✓	Phase 3 (n=307) ✓; Phase 3 (n=511) ✓
rutherford	HeFH	Phase 2 (n=168) ✓	Phase 3 (n=331) ✓
tesla, taussig	HoFH/Severe FH	Phase 2/3 (n=58) ✓	Phase 2/3 (n=300)
descartes	Long-term safety and efficacy		Phase 3 (n=905) ✓
osler	Open-label extension	Phase 2 (n=1,324)	Phase 3 (n=3,141)
glagov	Atherosclerosis		Phase 3 (n=968) ✓
fourier	Secondary Prevention		Phase 3 (n=27,564) ✓
ebbinghaus	Neurocognition		Phase 3 (n=1,972) ✓

✓ Completed trials ✓ Trials with open-label extension ongoing

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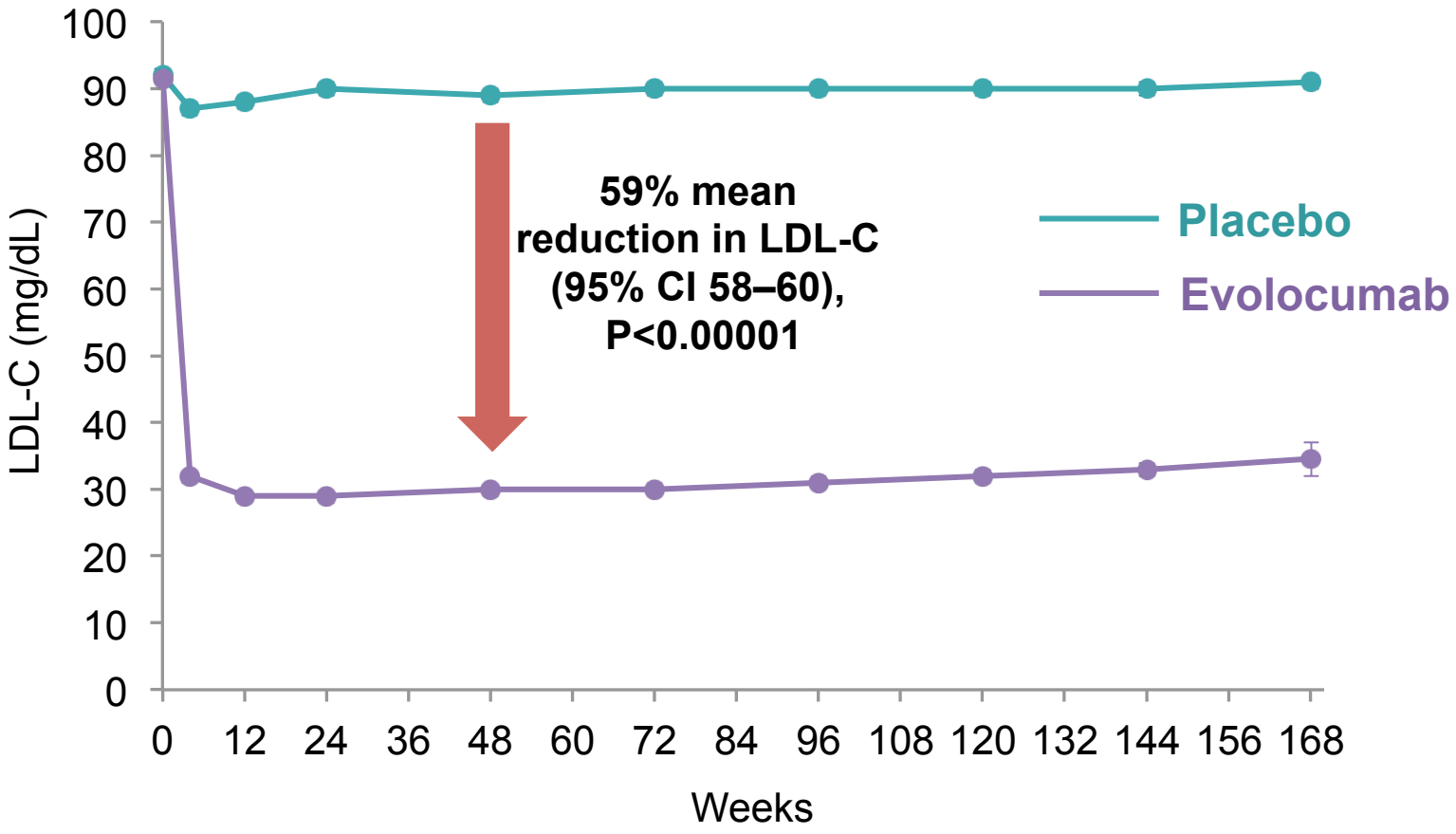
LDL-C reductions are maintained over 3 years

mg/dL

fourier



Absolute reduction in LDL-C for evolocumab vs placebo: 56 mg/dL (95% CI 55–57); 59% mean reduction

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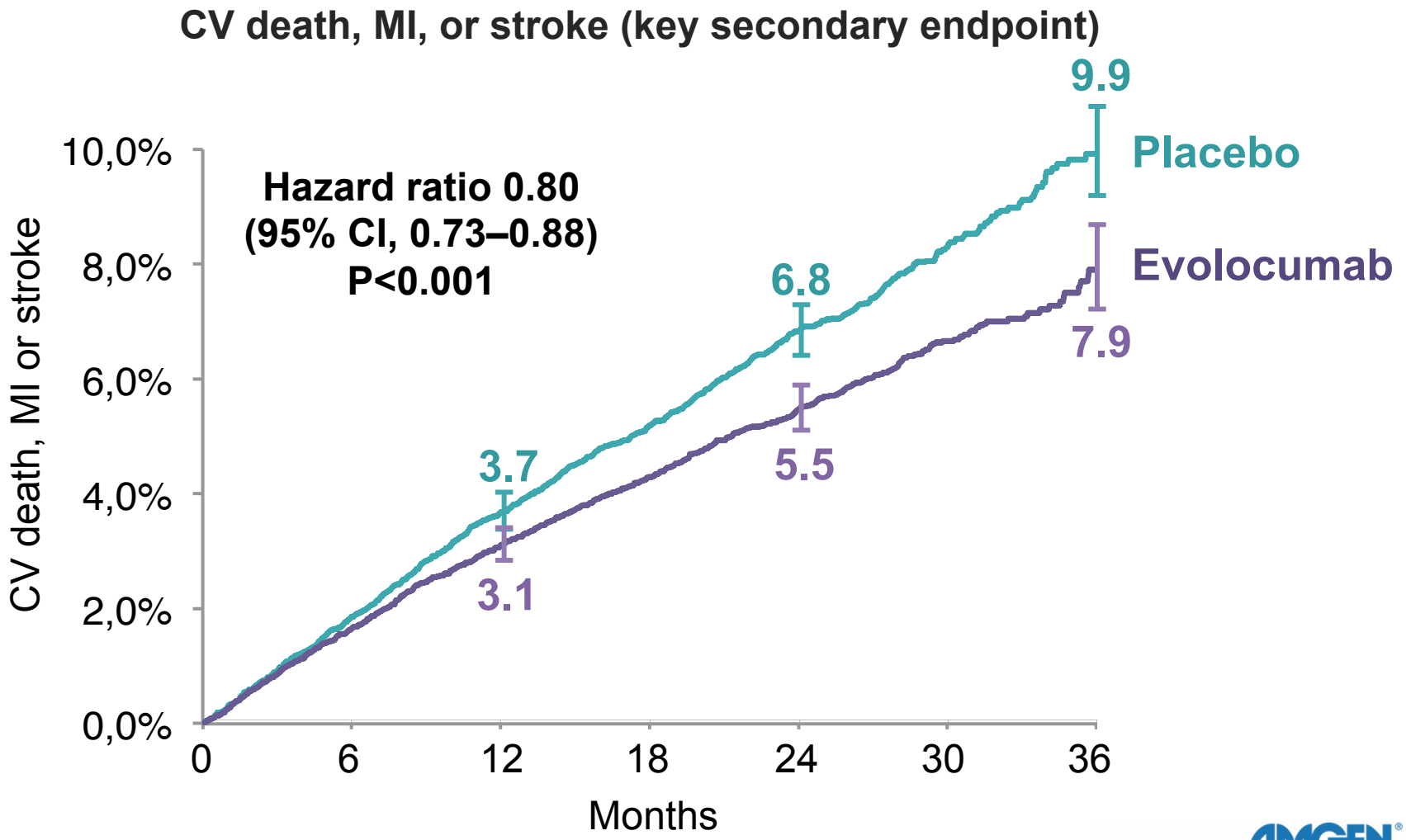
Cardiovascular

Sabatine et al. N Eng J Med 2017; doi: 10.1056/NEJMoa1615664.

Evolocumab significantly reduces the risk of MACE events compared with placebo

fourier



Sabatine et al. N Eng J Med 2017; doi: 10.1056/NEJMoa1615664.

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Indicaciones financiadas con cargo al Sistema Nacional de Salud

- Pacientes con enfermedad cardiovascular establecida (cardiopatía isquémica, enfermedad cerebrovascular isquémica y enfermedad arterial periférica) no controlados con la dosis máxima tolerada de estatinas (C-LDL superior a 100 mg/dl);
- Pacientes con Hipercolesterolemia familiar **homocigota** (HFHo) no controlados con la dosis máxima tolerada de estatinas (C-LDL superior a 100 mg/dl).*
- Pacientes con Hipercolesterolemia familiar heterocigota (HFHe) no controlados con la dosis máxima tolerada de estatinas (C-LDL superior a 100 mg/dl).
- Cualquiera de los pacientes de los grupos anteriores, que sean intolerantes a las estatinas o en los que las estatinas están contraindicadas y cuyo nivel de C-LDL sea superior a 100 mg/dl.

*En pacientes a partir de 12 años.

Informe de Posicionamiento Terapéutico de evolocumab (Repatha®) en hipercolesterolemia. AEMPS. Fecha: 3 de marzo de 2016

AMGEN®
Cardiovascular

▼Kyprolis® (Carfilzomib)

Carfilzomib (Kyprolis®), en la Unión Europea, en combinación con lenalidomida y dexametasona o con dexametasona sola está indicado para el tratamiento de **pacientes adultos con mieloma múltiple** que han recibido como mínimo un tratamiento previo.

Actualmente en España, la indicación de Kyprolis® en combinación solo con dexametasona está pendiente de la resolución administrativa sobre su **precio y condiciones de financiación** por parte de la Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia.

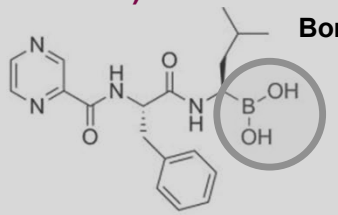
▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

AMGEN®

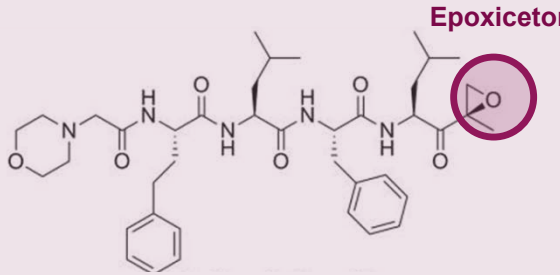
Carfilzomib es un inhibidor del proteosoma selectivo e irreversible, con actividad en células resistentes a bortezomib

Carfilzomib muestra una **mayor selectividad *in vitro*** y **una menor actividad inespecífica** que bortezomib[1]

Bortezomib: IP de 1.ª generación (reversible)[2]



Carfilzomib: IP de 2.ª generación (irreversible y selectivo)[2]



- Se une a un sitio distinto del proteosoma que bortezomib[2]
- La inhibición del proteosoma es más sostenida que con bortezomib[3,5]
- Actividad significativa en líneas celulares refractarias a bortezomib (*in vitro*)[1]

CARFILZOMIB ES UN INHIBIDOR DEL PROTEOSOMA **POTENTE Y ALTAMENTE SELECTIVO,** QUE LO HACE UN TRATAMIENTO **EFICAZ Y TOLERABLE** PARA LOS PACIENTES CON MM[1]

Mayor potencia[5]

KRd mejora **significativamente la supervivencia libre de progresión** en los pacientes con MM en recaída.[6]

KRd logra **unas tasas de respuesta global y completa más elevadas** y **una mayor duración de la respuesta** vs. Rd.[6]

Perfil beneficio-riesgo favorable[6]

El perfil de **seguridad manejable** de KRd permite a los pacientes mantener la dosis planificada con mínimas interrupciones del tratamiento.

KRd se asocia con una **mejora de la calidad de vida relacionada con la salud.**

KRd: Carfilzomib, lenalidomida y dexametasona; MM: mieloma múltiple; IP: inhibidor del proteosoma.

1) Sugumar et al. Pharmacogenomics and Personalized Medicine 2015:8 23–33. 2) McBride et al. Am J Health-Syst Pharm. 2015;72:353-60. 3) Jain et al. Core Evidence 2011:6 43–57. 4) Miller et al. Curr Pharm Des. 2013;19:4140–4151. 5) Dou et al. Curr Cancer Drug Targets. 2014;14(6):517–536. 6) Stewart et al. N Engl J Med 2015;372:142-52.

Randomised, open-label, multicentre, phase 3 trial

Relapsed MM
1–3 prior treatments

Stratification for randomisation: β_2-macroglobulin, prior bortezomib and prior lenalidomide

R

KRd (n=396)
Carfilzomib 27 mg/m^2 i.v. (10 min)
Days 1, 2*, 8, 9, 15, 16 for Cycles 1–12, then Days 1, 2, 15, 16 for Cycles 13–18, then discontinued*
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

Rd (n=396)
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

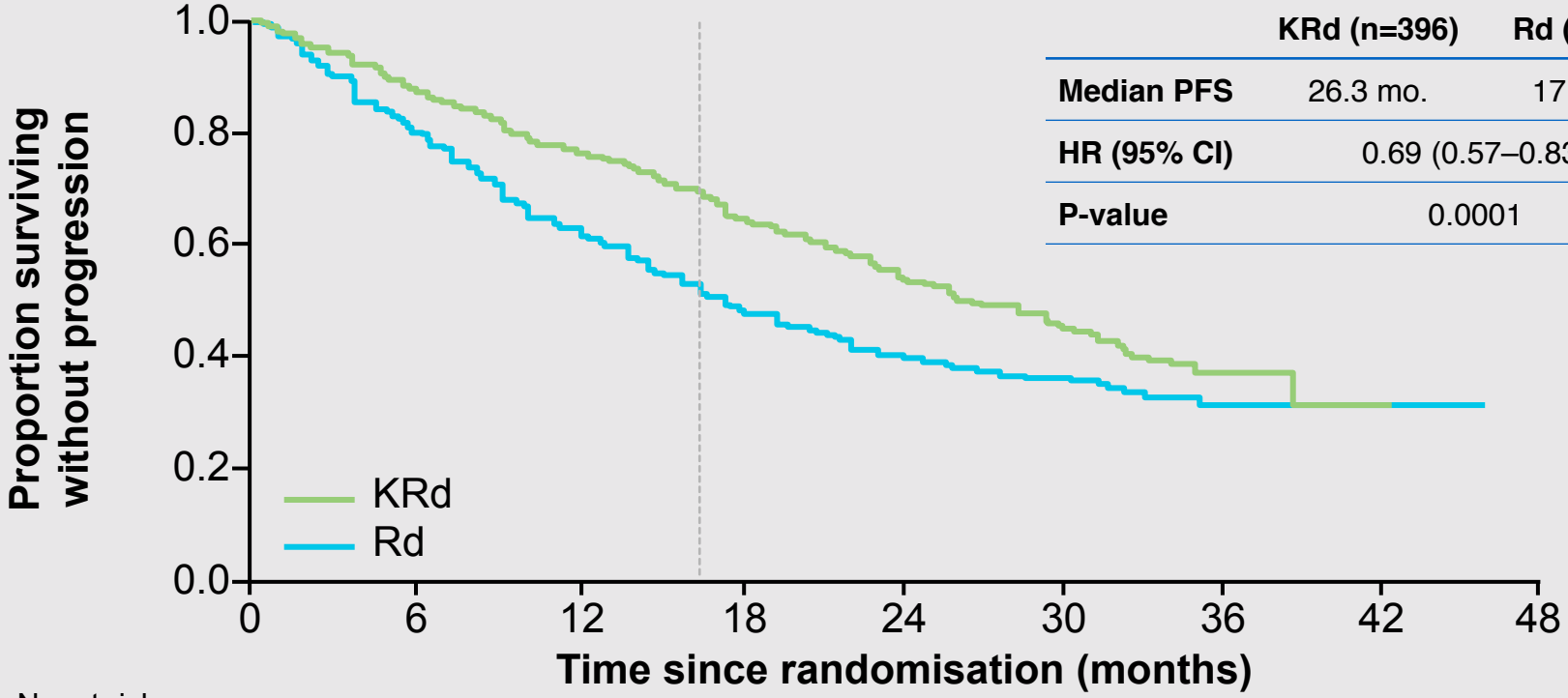
28-day cycles

*20 mg/m^2 on Days 1, 2, Cycle 1 only.

- **Primary endpoint:** PFS in the ITT population
- **Secondary endpoints:** OS, ORR, DOR, HRQoL, safety

DOR, duration of response; HRQoL, health-related quality of life; i.v., intravenous; KRd, carfilzomib with lenalidomide and weekly dexamethasone; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; Rd, lenalidomide and weekly dexamethasone.
Stewart AK, et al. N Engl J Med 2015;372:142–52.

Progression-free survival with KRd vs Rd



	KRd (n=396)	Rd (n=396)
Median PFS	26.3 mo.	17.6 mo.
HR (95% CI)	0.69 (0.57–0.83)	
P-value	0.0001	

No. at risk:

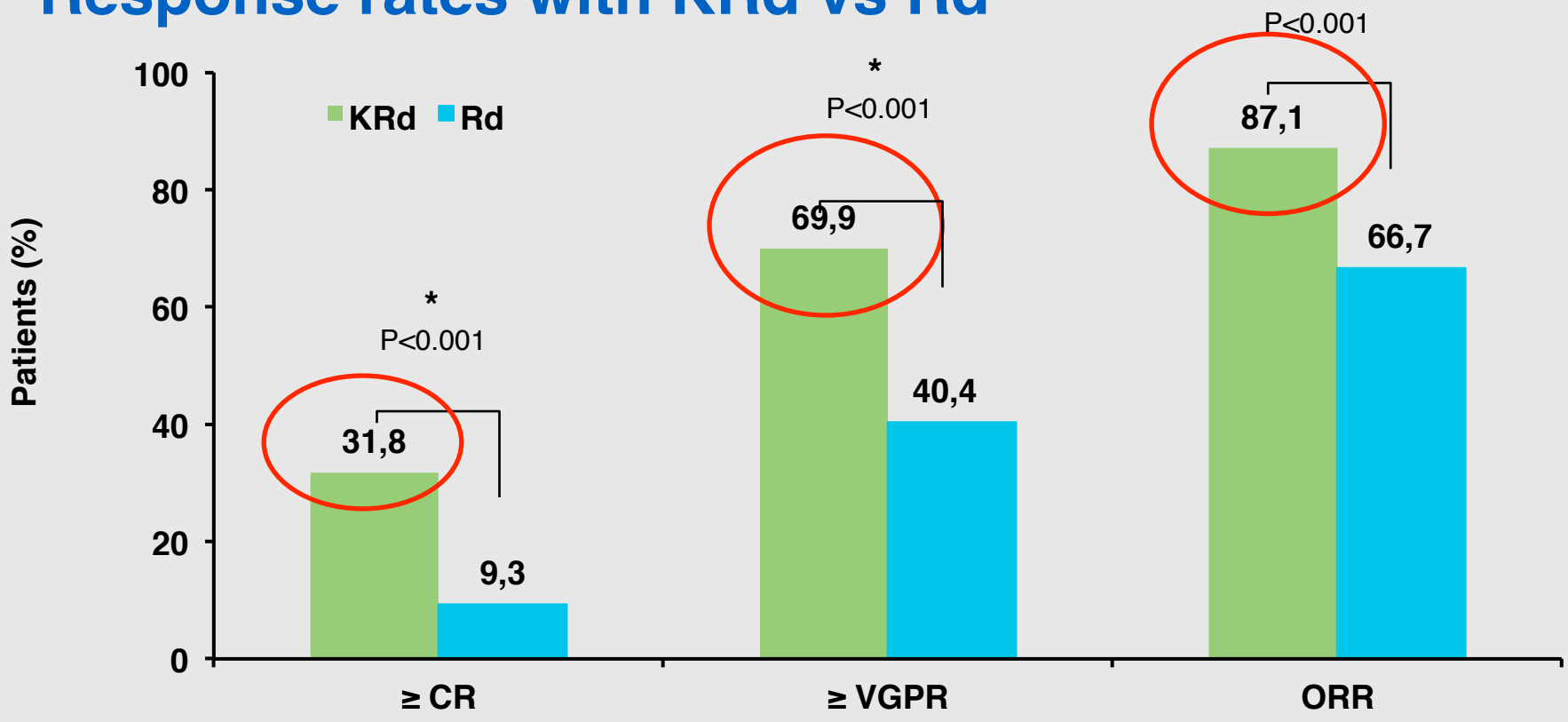
KRd	396	332	279	222	179	112	24	1
Rd	396	287	206	151	117	72	18	1

Carfilzomib was discontinued after cycle 18, which corresponds to 16.5 months since randomisation.

Significant increase in median PFS compared with Rd treatment

CI, confidence interval; HR, hazard ratio; KRd, carfilzomib with lenalidomide and weekly dexamethasone; PFS, progression-free survival; Rd, lenalidomide and weekly dexamethasone.
Stewart AK, et al. N Engl J Med 2015;372:142–52.

Response rates with KRd vs Rd



ORR was used as secondary endpoint; * Data on CR and VGPR are descriptive.

Significantly more patients achieved ≥ CR with KRd compared with Rd

CR, complete response; KRd, carfilzomib with lenalidomide and weekly dexamethasone; ORR, overall response rate; Rd, lenalidomide and weekly dexamethasone; VGPR, very good partial response.
Stewart AK, et al. N Engl J Med 2015;372:142–52.

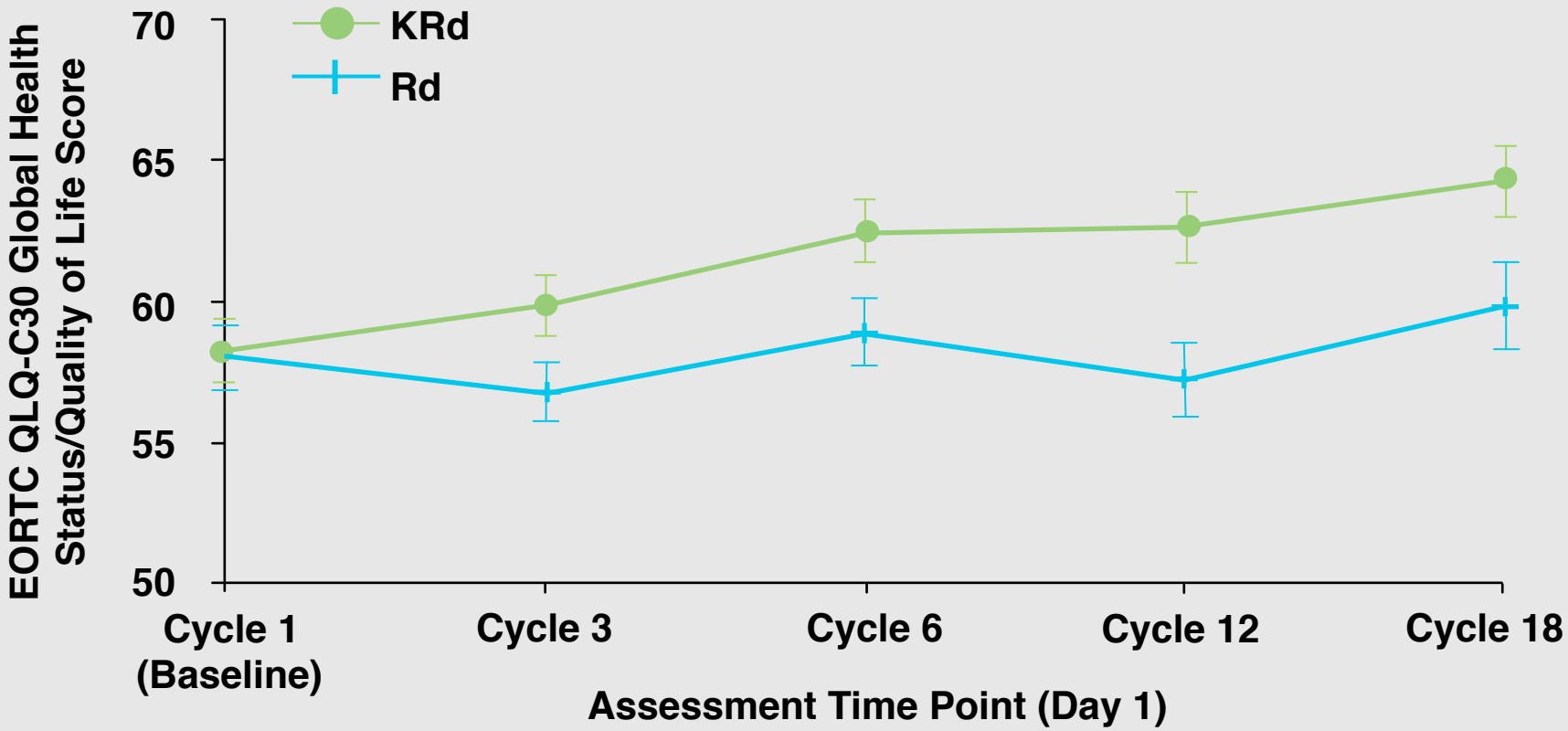
Most frequent adverse events
Safety population (N=781)

AEs occurring in ≥25% of patients in either arm

Adverse event, %	KRd (n=392)		Rd (n=389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Haematologic AEs				
Anaemia	42.6	17.9	39.8	17.2
Neutropenia	37.8	29.6	33.7	26.5
Thrombocytopenia	29.1	16.6	22.6	12.3
Non-haematologic AEs				
Diarrhoea	42.3	3.8	33.7	4.1
Fatigue	32.9	7.7	30.6	6.4
Cough	28.8	0.3	17.2	0
Pyrexia	28.6	1.8	20.8	0.5
Upper respiratory tract infection	28.6	1.8	19.3	1.0
Hypokalaemia	27.6	9.4	13.4	4.9
Muscle spasms	26.5	1.0	21.1	0.8

KRd, carfilzomib with lenalidomide and weekly dexamethasone; Rd, lenalidomide and weekly dexamethasone.
Stewart AK, et al. N Engl J Med 2015;372:142–52.

Health-related quality of life



KRd improved HRQoL (Global Health Status) compared with Rd over 18 cycles of treatment

EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire;
HRQoL, health-related quality of life; KRd, carfilzomib with lenalidomide and weekly dexamethasone; Rd, lenalidomide and weekly dexamethasone.
Stewart AK, et al. N Engl J Med 2015;372:142–52.

Panitumumab (anti-EFGR) en el tratamiento del cáncer colorectal metastásico (CCRm)

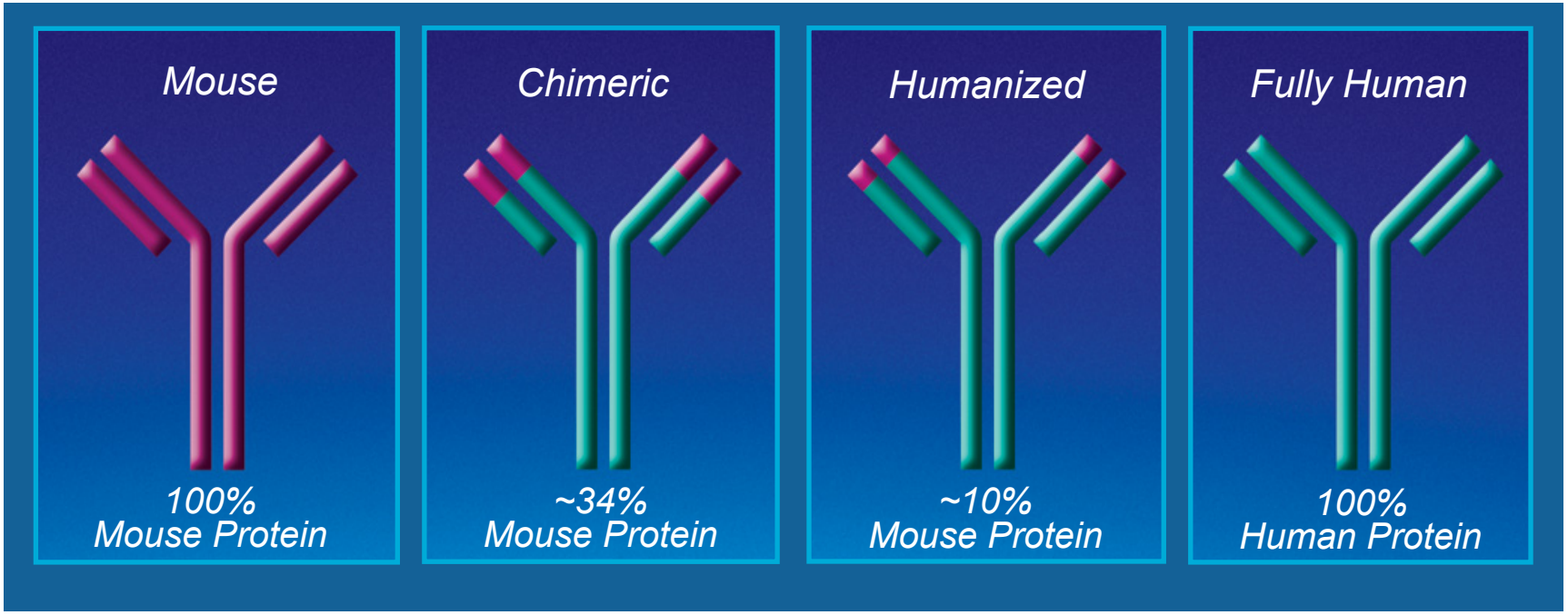
Partial revision of articles.

Therapeutic Indication (EU)

- Panitumumab is indicated for the treatment of adult patients with **wild-type *RAS*** metastatic colorectal cancer (mCRC):
  - In **first-line** in combination with FOLFOX or FOLFIRI
  - In **second-line** in combination with FOLFIRI for patients who have received **first-line** fluoropyrimidine-based chemotherapy (excluding irinotecan)
  - As monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
- The combination of panitumumab with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown
- The recommended dose of panitumumab is 6 mg/kg of bodyweight given once every two weeks

Vectibix® Summary of Product Characteristics.

The Development of Human Monoclonal Antibodies



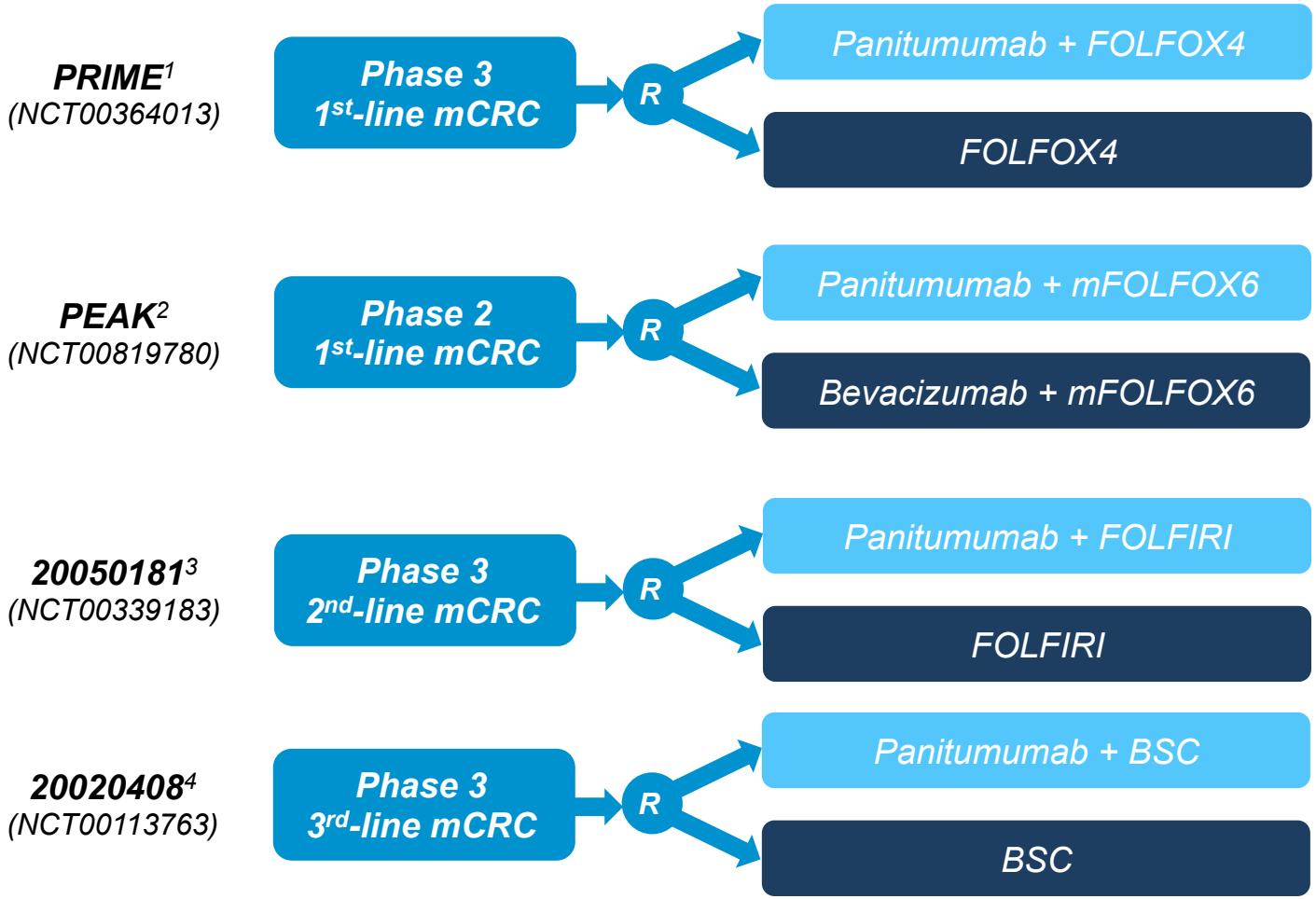
cetuximab
rituximab

bevacizumab

panitumumab

Yang XD, et al. Crit Rev Oncol Hematol. 2001;38:17-23.

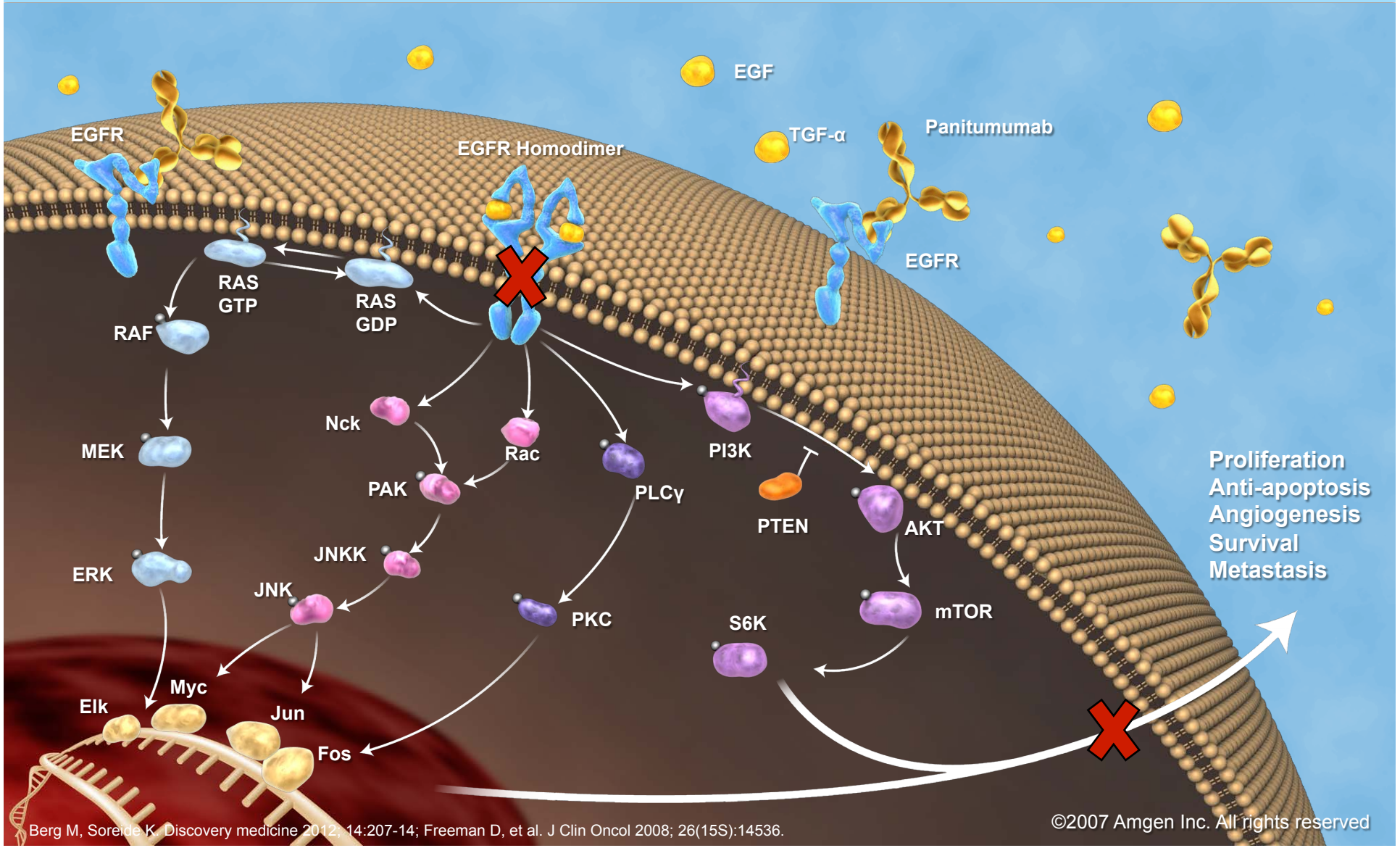
Panitumumab clinical development program in mCRC



1. Douillard JY, et al. N Engl J Med 2013;369:1023–34;
2. Schwartzberg LS, et al. J Clin Oncol 2014;32:2240–7;
3. Peeters M, et al. Clin Cancer Res 2015;21:5469–79.
4. Van Cutsem E, et al. J Clin Oncol 2007;25:1658−64

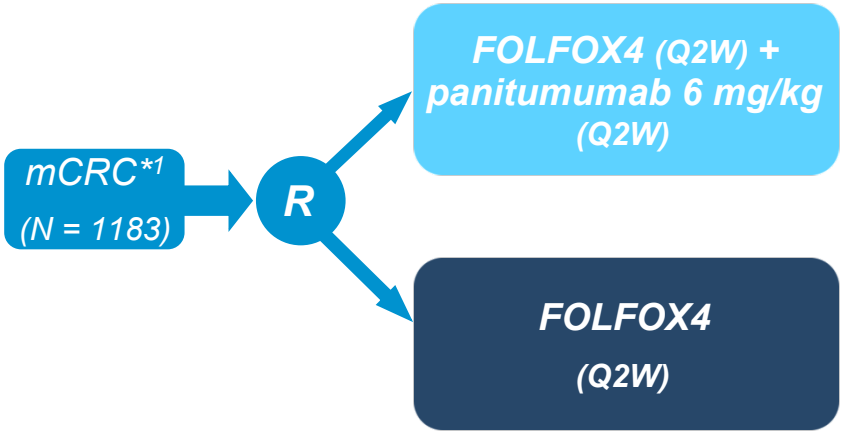
BSC (best supportive care)

Panitumumab inhibits EGFR dimerisation and subsequent downstream signalling



Berg M, Soreide K. Discovery medicine 2012; 14:207-14; Freeman D, et al. J Clin Oncol 2008; 26(15S):14536.

PRIME study overview
FOLFOX4 ± panitumumab in 1st-line treatment of mCRC



- *Primary endpoint: PFS[1]*
- *Prospective−retrospective extended RAS analysis[2]*
  - *RAS ascertainment rate: 90%*

WT *RAS*	Panitumumab + FOLFOX4 (n = 259)	FOLFOX4 (n = 253)
Median PFS, mo†[2]	10.1	7.9
HR (95% CI) P-value	0.72 (0.58–0.90) P = 0.004	
Median OS, mo†[2]	26.0	20.2
HR (95% CI) P-value	0.78 (0.62–0.99) P = 0.04	
ORR, n (%)†‡[3] (95% CI)	149 (59) (52–65)	114 (46) (40–53)
Adjusted OR P-value	1.63 P = 0.009	
AE, %[2] Grade 3/4 Grade 5	(n = 256) 84.8 5.5	(n = 250) 70.0 6.4

1. Douillard JY, et al. J Clin Oncol 2010;28:4697−705;
2. Douillard JY, et al. N Engl J Med 2013;369:1023−34;
3. Vectibix® EPAR Assessment Report. 2013; EMA/CHMP/367675/2013.

*Design amended to focus on prospective hypothesis testing in the WT *KRAS* (codons 12 and 13) stratum; †Primary analysis; ‡By central radiological assessment. WT *RAS* = WT *KRAS* and *NRAS* exons 2, 3, 4 (includes 7 patients harbouring *KRAS*/*NRAS* codon 59 mutations).

Summary: Panitumumab in mCRC (1)

- *RAS* mutations are predictive of panitumumab treatment effect in mCRC[1−3]
  - The benefit−risk profile of 1st-line panitumumab was improved by excluding patients with MT *RAS* tumours[1,2]

FIRST LINE:

- **PRIME study:** significantly improved OS and PFS with 1st-line panitumumab + FOLFOX4 vs FOLFOX4 in WT *RAS* mCRC[1]
  - OS: 26 vs. 20.2 months; HR = 0.78 (P = 0.04) [1]
- **PEAK study:** Prolonged OS with 1st-line panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6[3]
  - OS: 36.9 vs. 28.9 months; HR = 0.76 (P = 0.15) [3]
- **PLANET study**: Panitumumab combined with either FOLFOX4 or FOLFIRI as 1st-line treatment for patients with WT *RAS* mCRC and LLD[4]
  - OS: 39 and 45.8 months; Wilcoxon P-value = 0.634[4]

1. Douillard JY, et al. N Engl J Med 2013;369:1023−34; 2. Schwartzberg LS, et al. J Clin Oncol 2014;32:2240−7; 3. Rivera F, et al. Eur J Cancer 2015;51(Suppl 3):S1–S810:abstract 2014 (and poster); 4. Abad A, et al. Ann Oncol 2014;25(Suppl 4):iv189 (poster 551P).

WT *RAS* = WT *KRAS* and *NRAS* exons 2/3/4.
†Final analysis

Summary: Panitumumab in mCRC (2)

SECOND & THIRD LINES:

- **181 study:** Significantly improved PFS and longer OS with 2nd-line panitumumab + FOLFIRI vs FOLFIRI in WT *RAS* mCRC[1]
  - PFS: HR = 0.70 (P = 0.007); OS: HR = 0.81 (P = 0.08) [1]
- **408 study:** Significantly improved PFS with 3rd-line panitumumab + BSC vs BSC in WT *RAS* mCRC[2]
  - PFS: HR = 0.36 (P < 0.001)
    - In the original WT *KRAS* exon 2 population, HR = 0.45 (P < 0.001)[3]

SAFETY:

The safety profile of panitumumab is well established[4]

ADMINISTRATION BENEFITS:

- **Lower number of infusional** reactions compared to cetuximab[4,5]
- No need of premedication or charge dose[4]
- **Synchronization with Chemotherapy**: Panitumumab is the only EGFR inhibitor approved for administration every **two weeks[4,6]**

1. Peeters M, et al. J Clin Oncol 2014;32(Suppl 5):abstract 3568 (and poster); 2. Peeters M, et al. Ann Oncol 2013;24(Suppl 4):abstract PD-0008 (and poster); 3. Amado RG, et al. J Clin Oncol 2008;26:1626−34; 4. Vectibix SmPC; 5. PriceTJ, et al. Lancet Oncol. 2014 May;15(6): 569–79; 6. Erbitux SmPC

JUEVES 4 DE MAYO 2017
11:00h

SIMPOSIO AMGEN

INNOVACIÓN EN EL DESARROLLO DE FÁRMACOS

Moderador: Raúl Ferrando. Jefe Servicio Farmacia Hospital General Universitario Castellón.
Ponente: José Luis Motellón. Director Medico AMGEN.