Vall d'Hebron
Hospital

Infeccions relacionades amb les teràpies biològiques

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Disclosure

- Astellas
- Gilead Sciences
- MSD
- Novartis
- Pfizer

natalizumab

antiTNF

antiCD20: rituximab, obinutuzumab, ofatumumab

gemtuzumab (antiCD33)

alemtuzumab (antiCD52)

daratumumab (antiCD38)

Inotuzumab (antiCD22)

Brentuximab (CD30)

Secukinumab (anti IL-17)

Tocilizumab (antiIL6)

Guselkumab (anti IL12/23)

PI3K inhibitors
(copanlisib, duvelisib, more ...

PARP inh: olaparib, rucaparib

Roxulitinib, tofacitinib (JAK inh)

Immunotherapy: ipilimumab (CTLA-4), tremelimumab (CTLA-4), nivolimumab (PD1/PDL1), Pembrolizumab (PD1), atezolizumab (PDL-1) more.....

TK inhibitors : Imatinib, dasatinib, masitinib, bosutinib, nilotinib, fostamatinib (spleen), ibrutinib (BTK), alisertib (ATK), axatinib, lapatinib, vamdetanib, axitinib, pazopanib, crizotinib, sorafenib, verumafenib

Belimumab (antiBAFF)

Cabozantinib: MET, RET, VEGFR2

mTOR: temsirolimus,everolimus

HER2/neu: trastuzumab, lapatinib

VEGFR: bevacizumab, sorafenib, sunitinib

MAPK inh: dabrafenib, vemurafenib, sorafenib

EGFR: cetuximab, panitumumab, erlotinib, gefitinib

MEK inh: Trametinib, selumetinib , cobimetenib

Selinexor (XPO1 antagonist)

Index

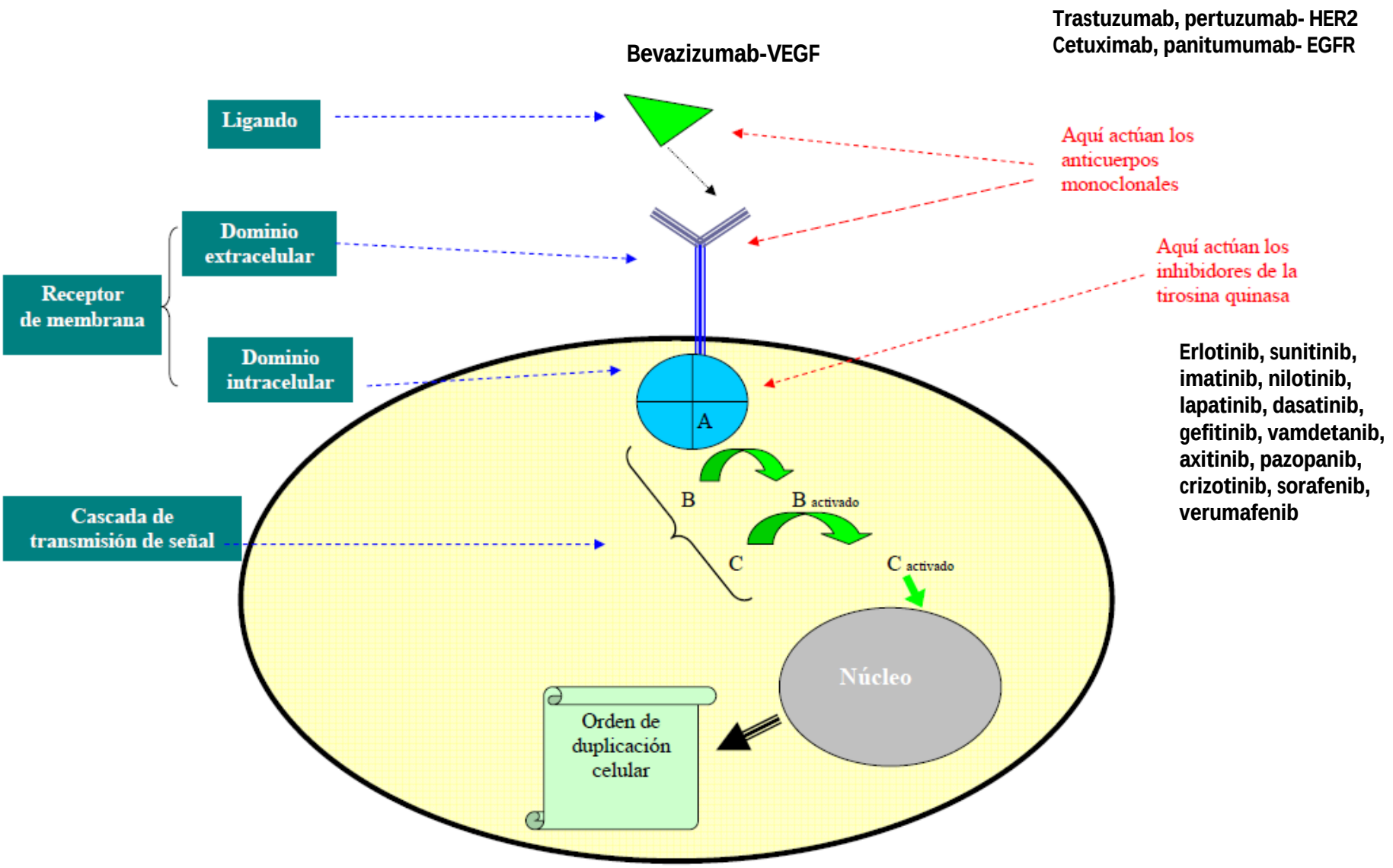
- Antecedents
- Biològics pel tractament de malalties oncològiques
  - Dianes terapèutiques
  - Risc d'infecció
- Prevenció

What are we talking about?

- development of drugs directed at specific **molecular targets** for the treatment of disease.
- **“biological therapies”** : monoclonal antibodies, receptor analogues, and chimeric small molecules designed to bind to or mimic their molecular targets
- Advantages: potency, specificity, theoretically decreased side effects

Problems in determining causality between biological therapy and infection:

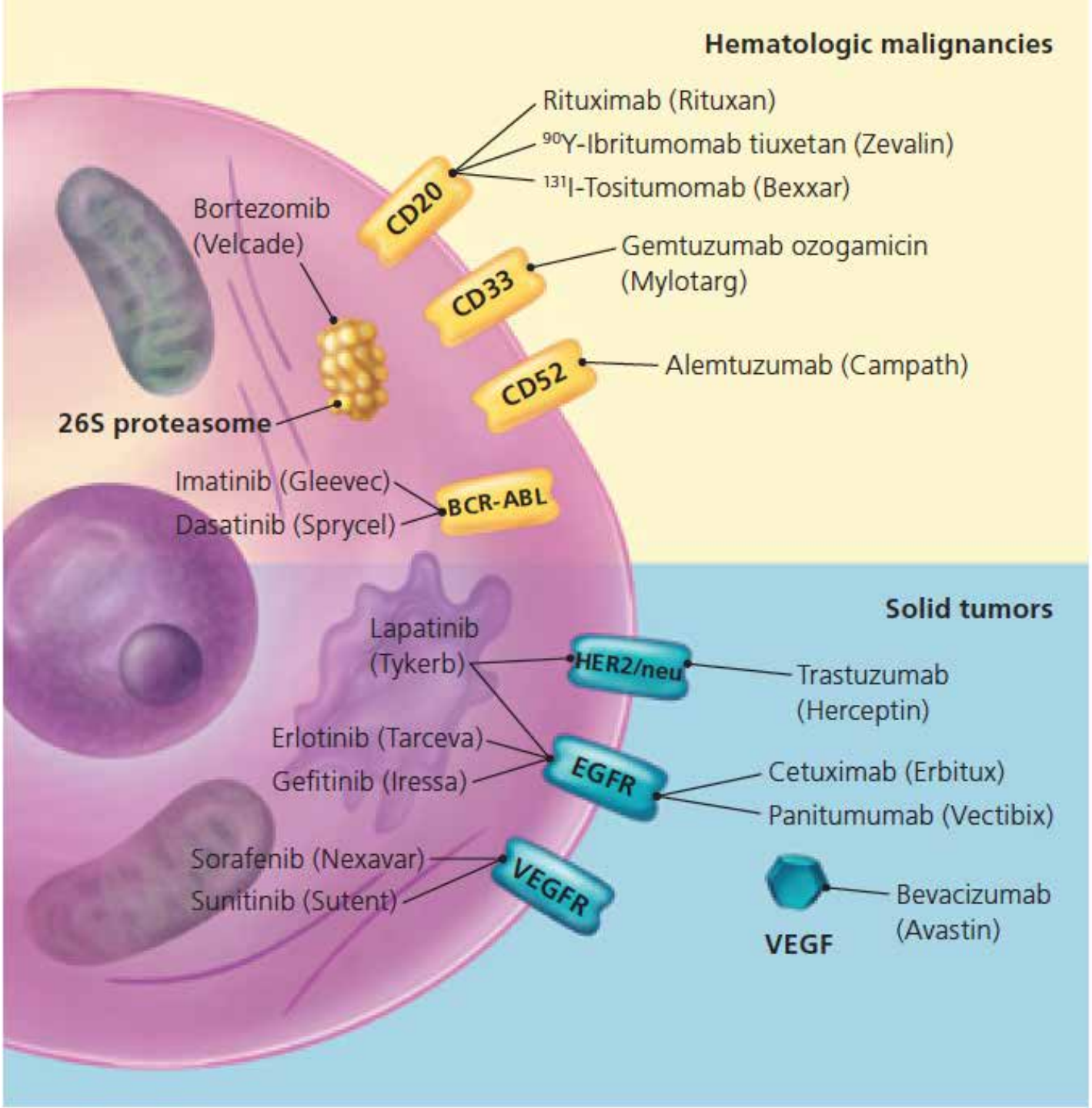
- **Underlying disease causes immunosupression**
- **Small number events difficult establish a true association**
- **Large number of confounders**



LA CÉLULA Y LA TRANSMISIÓN DE LA SEÑAL DE CRECIMIENTO Y DUPLICACIÓN CELULAR

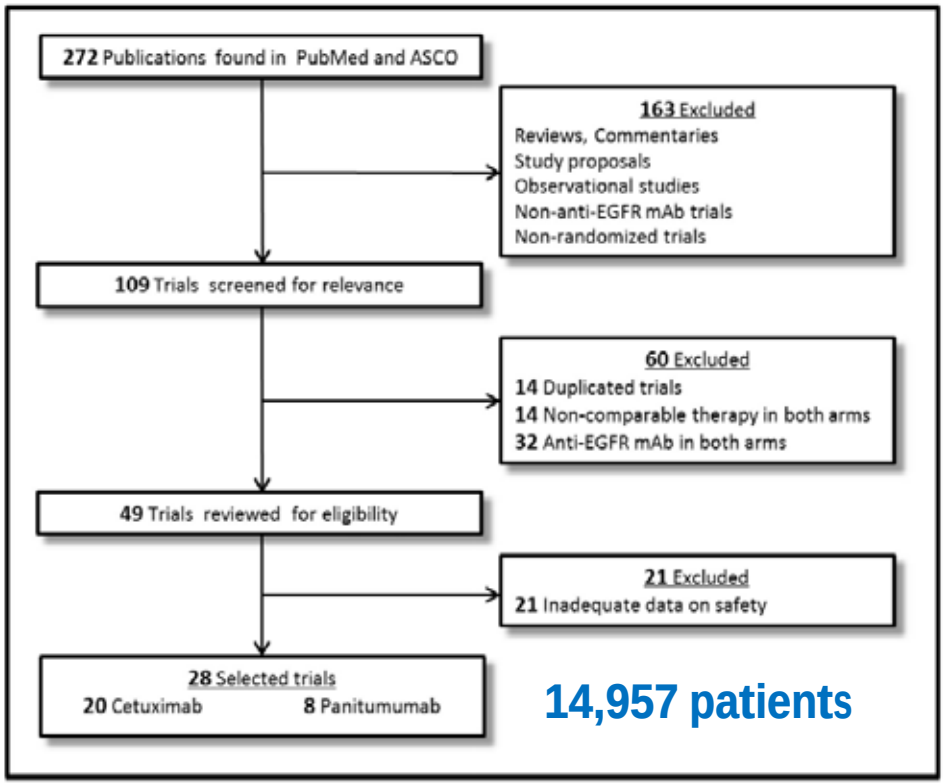
Crecimiento tumoral, invasión, metástasis

Targeted therapies



Infectious complications in cancer patients treated with anti-EGFR monoclonal antibodies cetuximab and panitumumab: A systematic review and meta-analysis

Tomohiro Funakoshi [a,*], Maya Suzuki [b], Kazuo Tamura [c] Cancer Treatment Reviews 40 (2014) 1221–1229



High grade infection:

RR 1.49(95% CI, 1.33-1.66: p<0.001)

Independent time

Colorectal cancer, NSCLC and SCCHN

Febrile neutropenia:

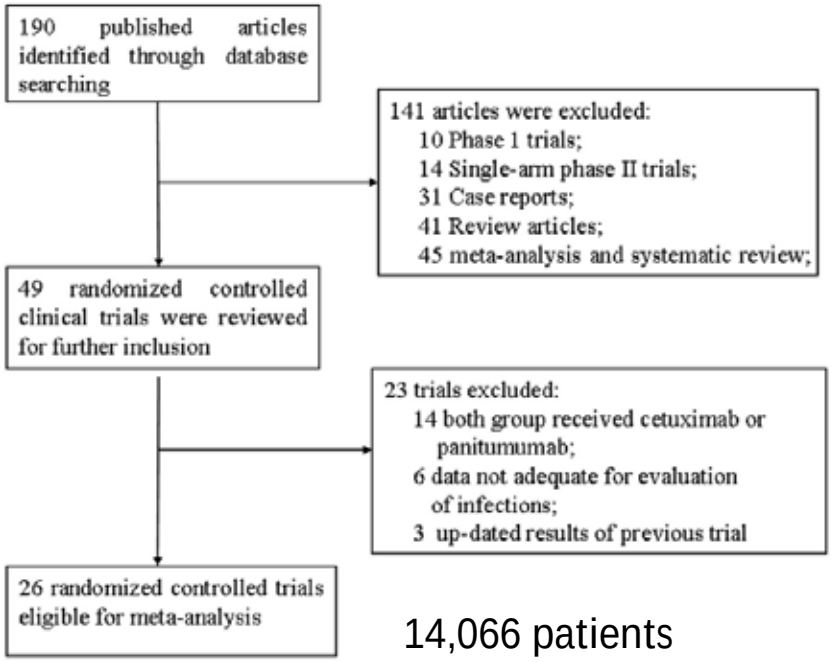
RR 1.27(95% CI, 1.09-1.48: p=0.002)

Longer duration >3.1 months

NSCLC

Incidence and risk of severe infections associated with anti-epidermal growth factor receptor monoclonal antibodies in cancer patients: a systematic review and meta-analysis

Qi *et al. BMC Medicine* 2014, **12**:203



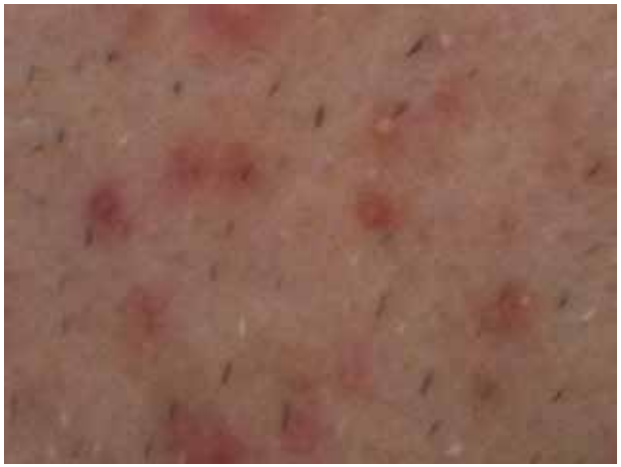
14,066 patients

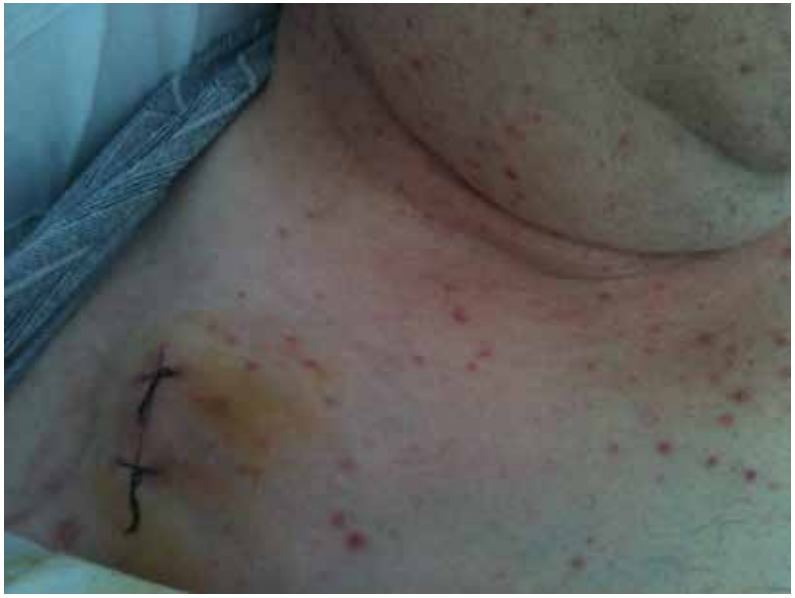
a **severe infection is 1.34-fold higher** in patients treated with anti-EGFR MoAbs, while the use of anti-EGFR MoAbs **does not significantly increase the risk of fatal infections**.

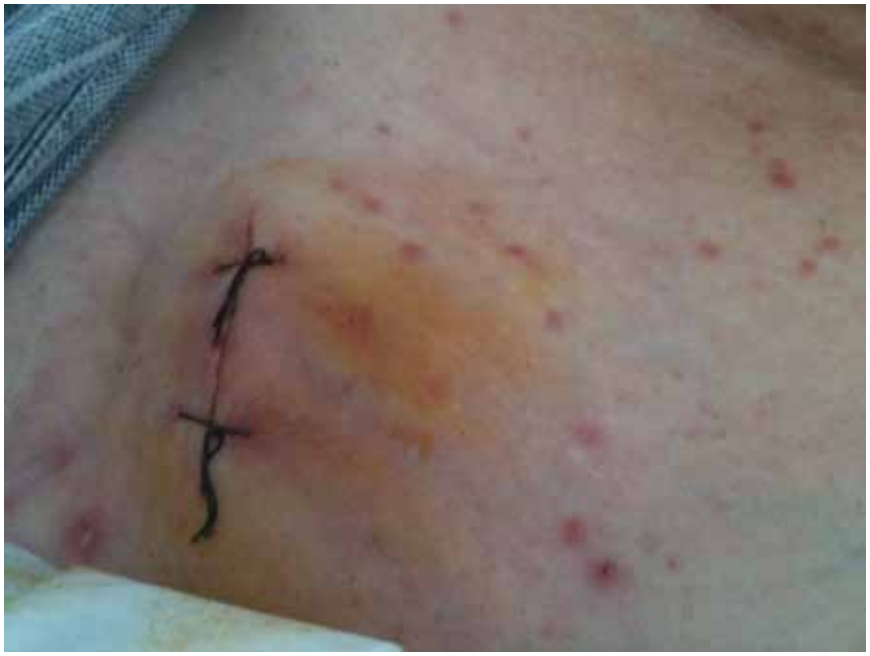
severe infections might possibly occur early in the treatment with anti-EGFR MoAbs.

colorectal cancer, non-small-cell lung cancer, and head and neck cancer.

cisplatin or irinotecan may **increase** the **risk** of severe infections







- 62 years, male
- Colorectal cancer different lines of treatment ICECREAM (cetuximab), 6 doses.
- Pain in PAC area (fever, pain, erythema, edema 48h)

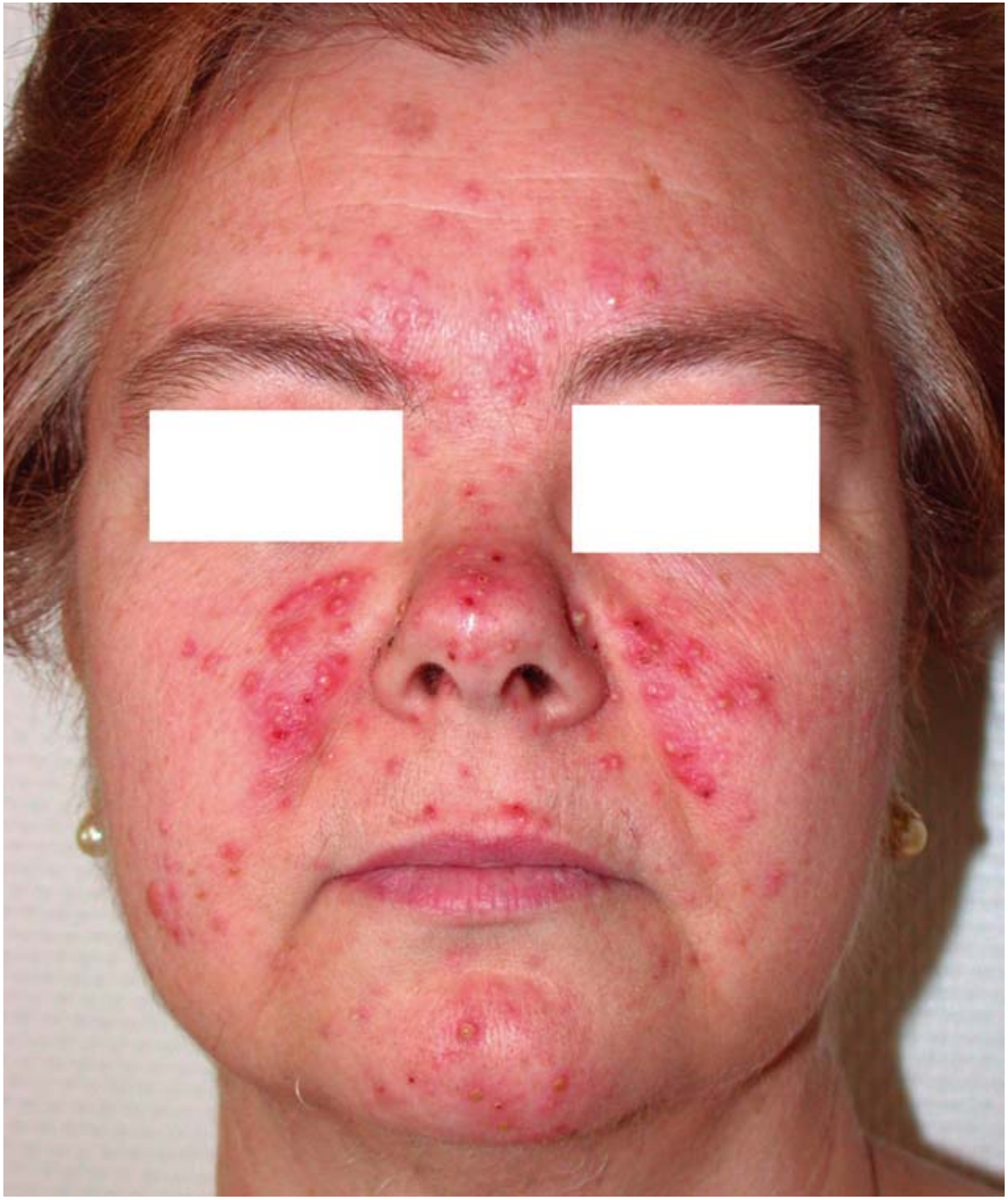
Negative Blood culture
PAC culture *S.aureus*

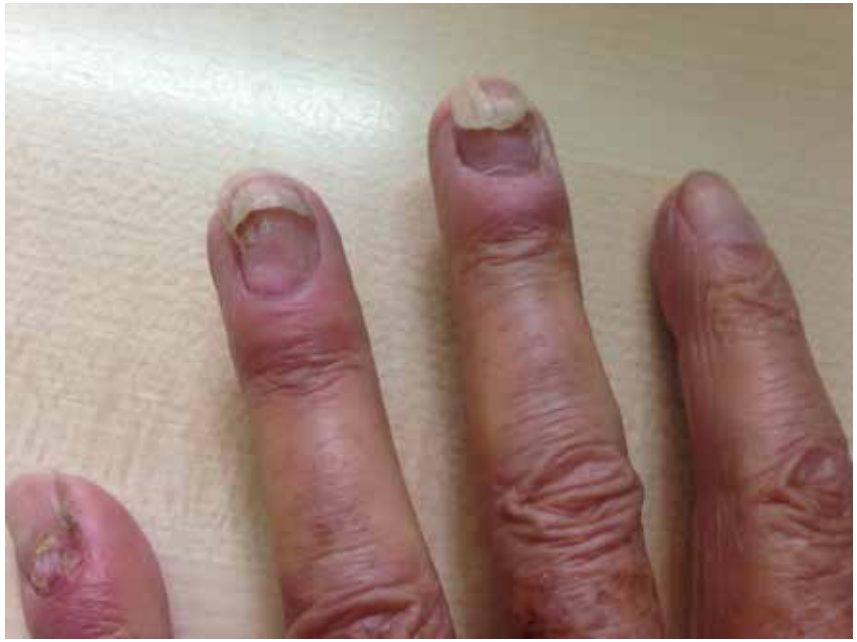
Increased rates of local complication of central venous catheters in the targeted anticancer therapy era: a 2-year retrospective analysis

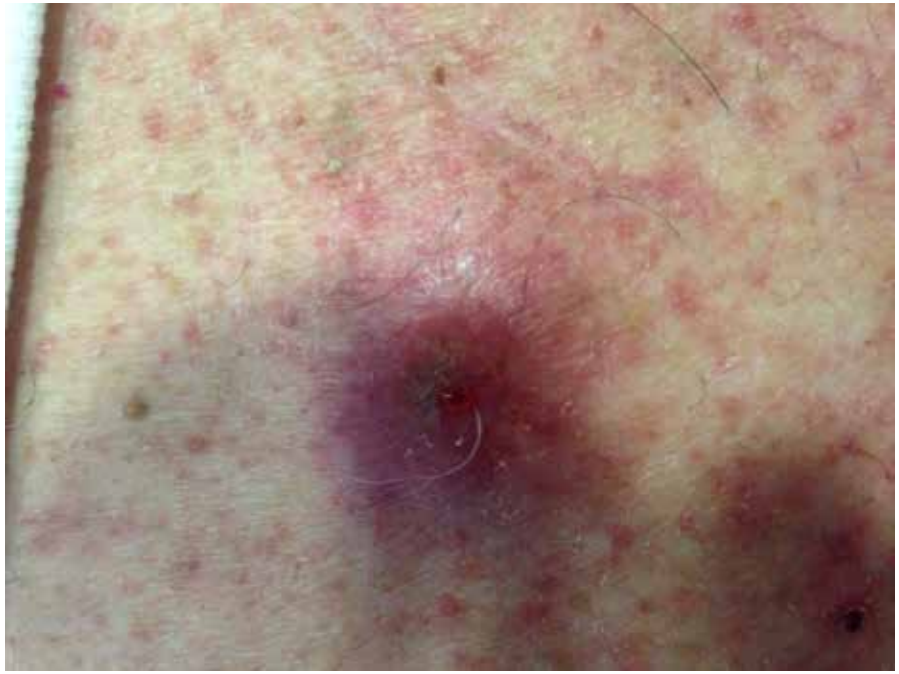
R. Berardi Support Care Cancer 2014

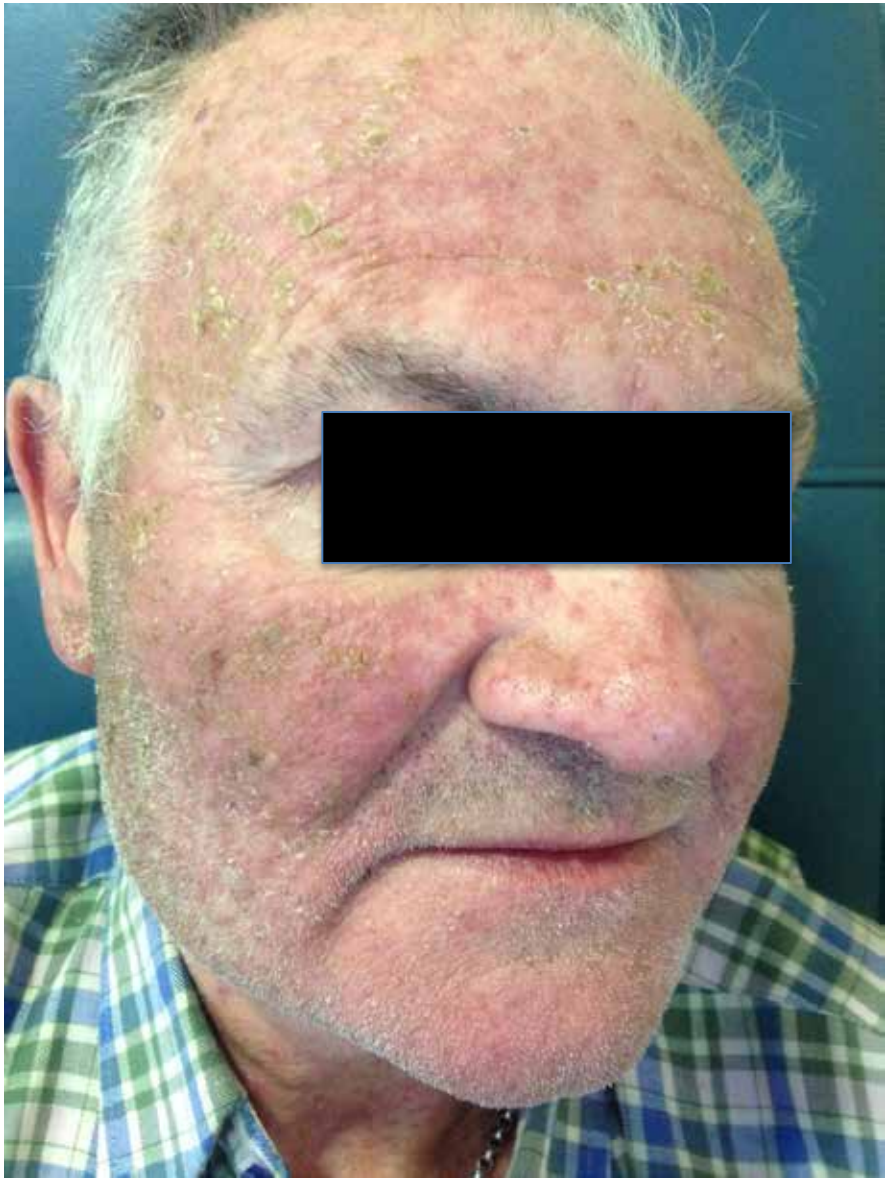
Results Catheter-related complications occurred in 30 out of the 459 analyzed cancer patients (7 %). Local complications occurred in 12 (40 %) and 18 (60 %) patients receiving standard chemotherapy and biological drugs, respectively. Eighteen (72 %) out of 25 patients developing biological complications (BC) were receiving biological drugs. Infusion of a biological drug through a central venous catheter has been shown to increase the risk of central venous catheter complications (p=0.02). No difference between the incidence of complication between anti-angiogenic and anti-epidermal growth factor receptor (EGFR) agents was observed in our study despite the statistically significant early development of port-a-cath complication in the anti-EGFR group. Treatment with a biological drug and the stage of disease, in univariate analysis, had independent effect on the duration for development of catheter-related complications.

Conclusions Molecularly targeted therapy may influence the occurrence of BCs, i.e., infection and dehiscence. Onset of BCs occurred earlier in patients receiving biological drugs (more frequently with bevacizumab than with anti-EGFR therapy) than those undergoing traditional chemotherapy. Further studies are needed to ascertain the findings of our study and to elucidate the reason for the higher incidence of catheter-related complications.



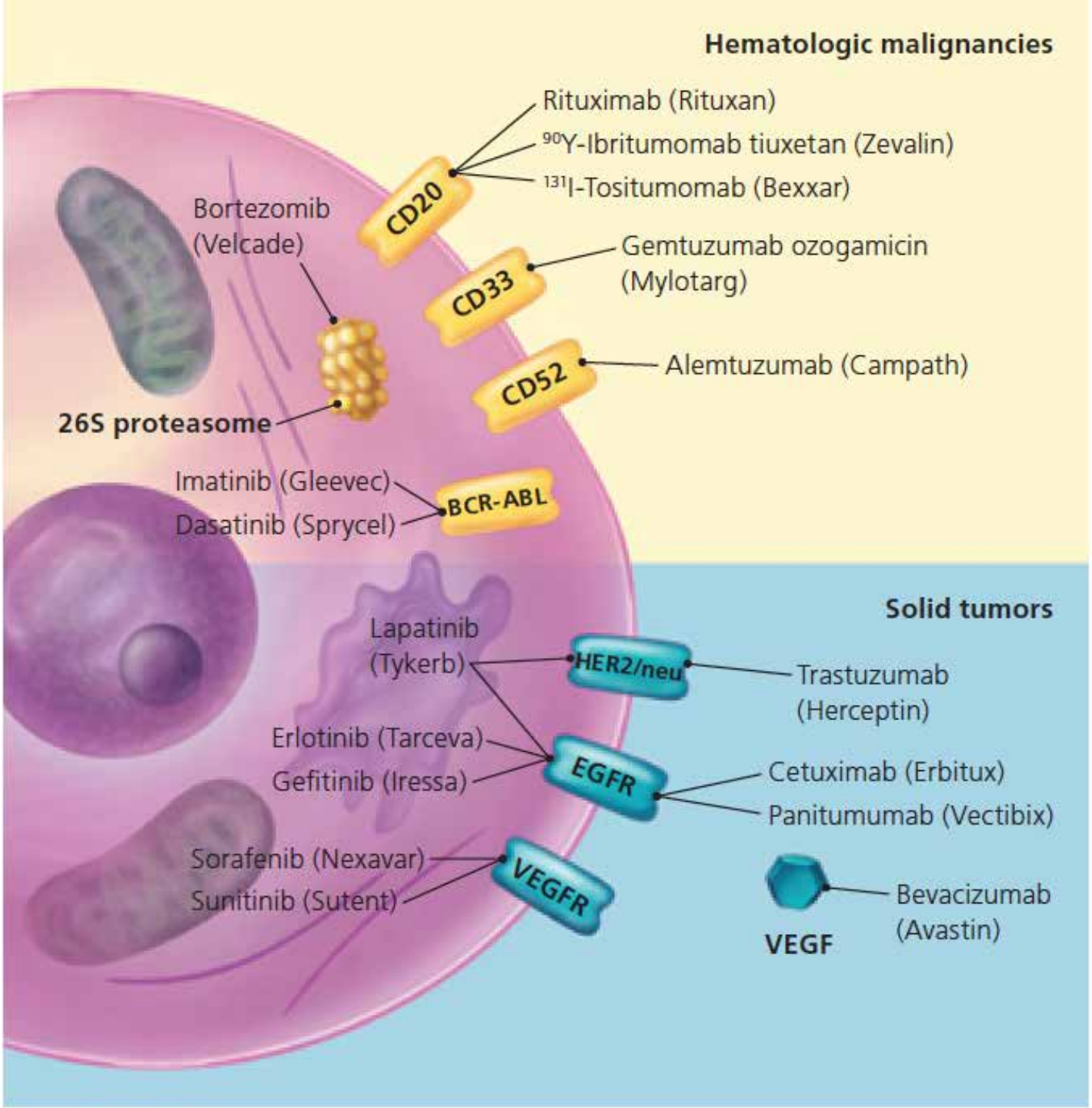






Blood culture + *S.aureus*

Targeted therapies



Infection risk in breast cancer patients treated with trastuzumab: a systematic review and meta-analysis Breast Cancer Res Treat (2015) 149:321–330

10,0094 patients from 13 trials were included

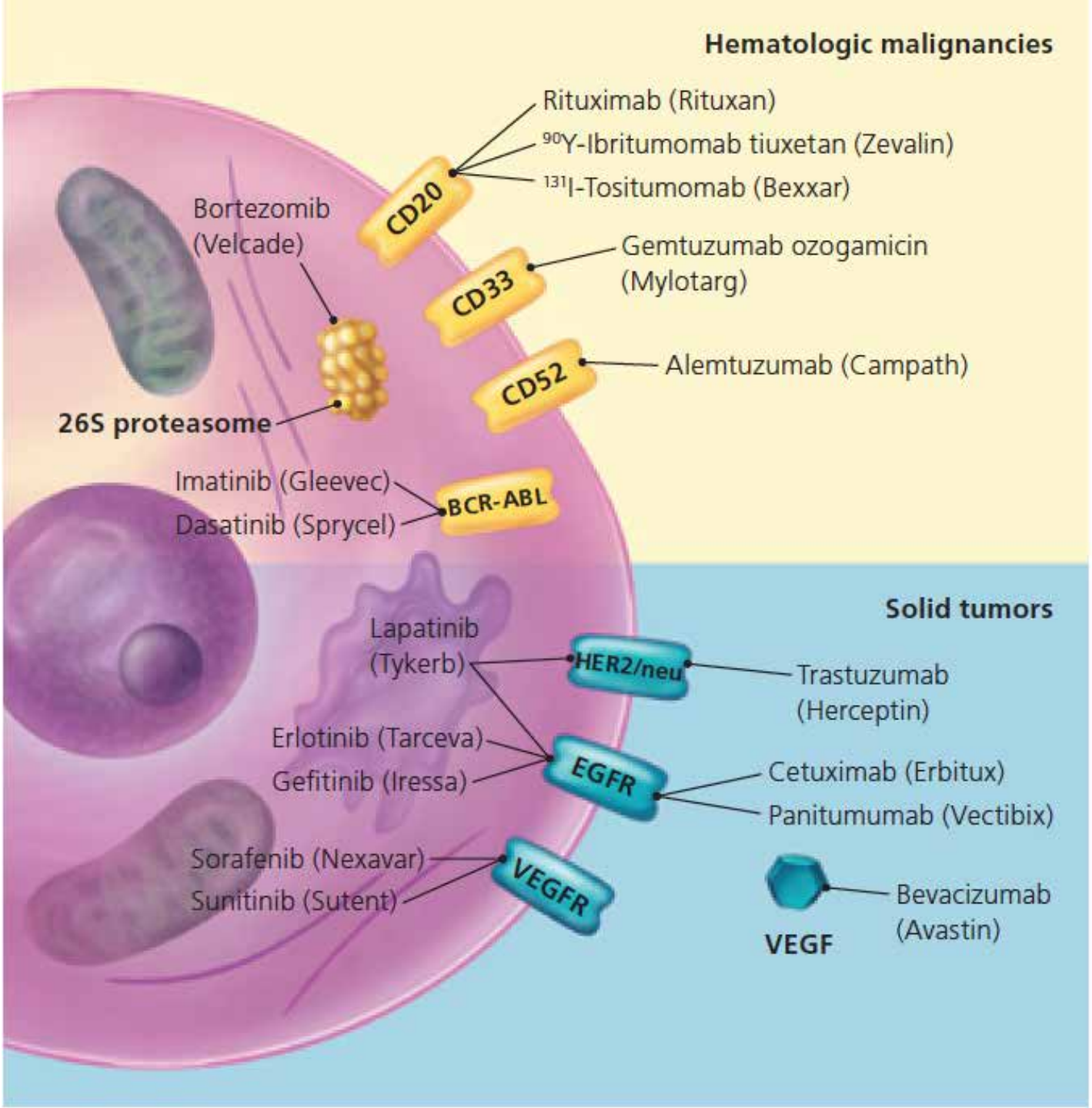
Increased risk of high-grade infection: RR 1.21(95% CI, 1.07-1.37: p=0.002)
Increased risk of febrile neutropenia: RR 1.28(95% CI, 1.08-1.52: p=0.004)

Incidence of high-grade infection due to trastuzumab 8.5% (95% CI, 4.5-15.4%)
Incidence of febrile neutropenia 12% (95% CI 8.1-17.4%)

Risk factors associated with infections could not be established

Higher incidence in the combination therapy

Targeted therapies

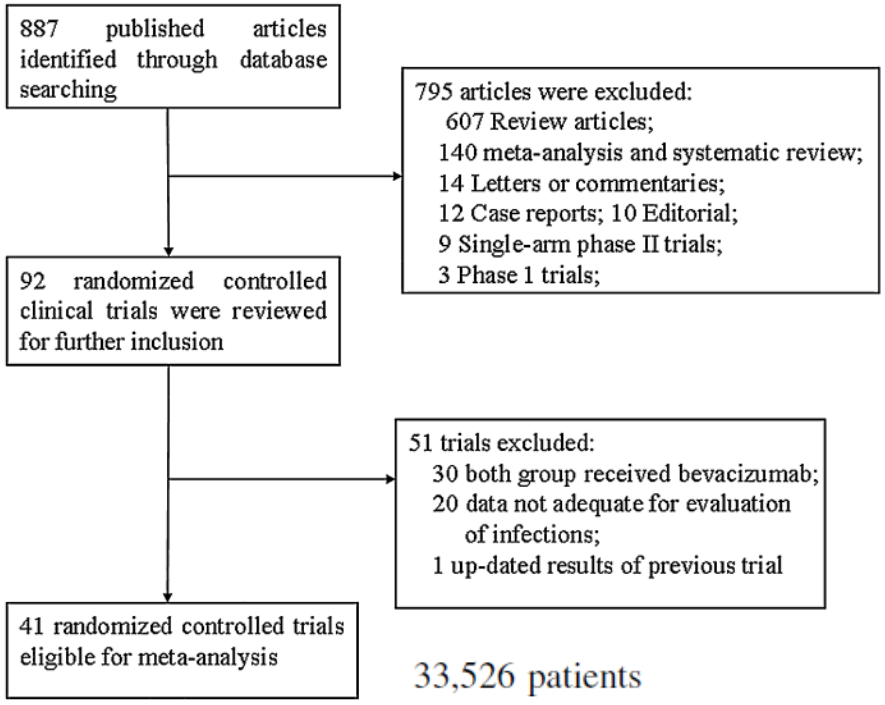


Anti-VEGF

monoclonal anti-VEGF antibody **bevacizumab**	VEGF Trap **aflibercept**	small-molecule tyrosine kinase inhibitors: **sorafenib, sunitinib, vandetanib, pazopanib, axitinib, and regorafenib,**

Bevacizumab increases the risk of infections in cancer patients: A systematic review and pooled analysis of 41 randomized controlled trials

Wei-Xiang Qi Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx



1.45 fold higher risk of infection

1.59 fold increase in the risk of high-grade infection

Fatal infections 0.9%

Cumulative exposure (not stst. sign)

Increased risk: colorectal cancer, NSCLC, breast cancer and gastric cancer, used with taxanes, capecitabine, gemcitabine and oxaliplatin

Patients with active or recently active infections excluded from clinical trials, incidence of infections could be widely underreported

Unusual forms of subacute invasive pulmonary aspergillosis in patients with solid tumors

Journal of Infection (2014) 69, 387–395

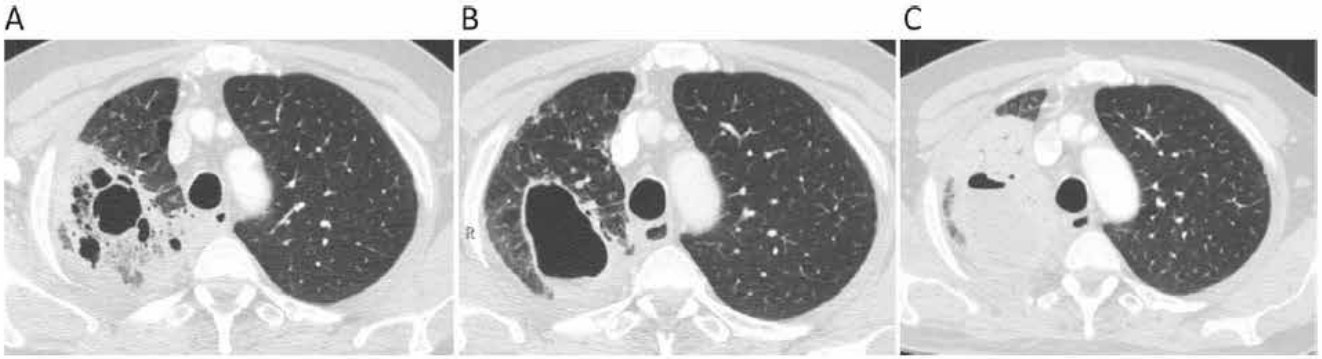


Figure 1 A–C. Patient 14. A) Chest CT scan shows a mass with multiple cavities at the cancer diagnosis. (August 2010). B) Progressive cavitary infiltrate at *Aspergillus* spp. detection (September 2010). C) Progressive consolidation with abscess formation after *Aspergillus* spp. detection (October 2010).

Necrotizing fasciitis caused by *Haemophilus influenzae* type b in a patient with rectal cancer treated with combined bevacizumab and chemotherapy: a case report

Ugai *et al. BMC Infectious Diseases* 2014, **14**:198

Invasive Fungal Infection and Nasal Septum Perforation With Bevacizumab-Based Therapy in Advanced Colon Cancer

Nuria Ruiz, Carlos Fernandez-Martos, Ignacio Romero, Angel Pla, Joaquin Maiquez, Ana Calatrava, and Vicente Guillem
Instituto Valenciano de Oncologia, Valencia, Spain

Incidence and risk of severe infections associated with aflibercept in cancer patients: a systematic review and meta-analysis

Xi Zhang

Study	Phrase	Underlying malignancy	Treatment arms	Control arms	Patients included for analysis	Sever infections	Reported infectious event	CTC version
Chen et al 2014 [17]	II	NSCLC	Aflibercept 6 mg/kg plus pemetrexed and cisplatin	—	42	4	Pneumonia, sepsis	3.0
Allen et al 2014 [7]	II	SCLC	Aflibercept 6 mg/kg plus topotecan	Topotecan	180	4	Infection	3.0
Tannock et al 2013 [6]	III	Prostate cancer	Aflibercept 6 mg/kg plus Docetaxel	Placebo plus Docetaxel	12		Infection	3.0
Rougier et al 2013 [8]	III	Pancreatic cancer	Aflibercept 4 mg/kg plus gemcitabin	P			Fatal infection	3.0
Ramlau et al 2012 [18]	III	NSCLC	Aflib			36	Febrile neutropenia	3.0
Van Cutsem et al 2012 [13]	III	C		FOLFIRI	1216	75	Infections and infestations	3.0
Coleman et al 2012 [21]	II	En c	mg/kg	—	44	2	Infection	3.0
Gotlieb et al 2012 [22]	II	Ov cancer	Aflibercept 4 mg/kg	Placebo	55	4	Pneumonia, sepsis	3.0
Leighl et al 2010 [19]	II	Lung cancer	Aflibercept 4 mg/kg	—	96	1	Urinary tract infection	3.0
Twardowski et al 2010 [20]	II	Urothelial Cancer	Aflibercept 4 mg/kg	—	22	0	Infection	3.0

Neutropenia

4310

7.3 % (95 %CI, 4.3-12.0%), with a mortality of 2.2% (95%CI, 1.5-3.1%).

Risk subset	Aflibercept (Ev/Sub)	Bevacizumab* (Ev/Sub)	Relative risk (95% CI)	P value
All-grade infections	675/1878	525/5950	4.07(3.68-4.51)	<0.001
High-grade infections	239/2001	793/17808	2.68(2.34-3.08)	<0.001

Increased risk of severe infections in cancer patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a meta-analysis

OncoTargets and Therapy 2015:8 2361–2374

EA: Mucocutáneos, alt. hepática, perforación GI, toxicidad cardíaca, **infecciones**

Table 1 Relative risk of severe infectious events according to tumor types, VEGFR-TKIs, and phases of trials

Groups	Studies, n	Severe infectious events, n/total, n		RR (95% CI)	*P*-value	Numbers needed to harm	*P*-value for group difference
		VEGFR-TKIs	Control				
Tumor types							
NSCLC	10	362/4,891	210/4,597	1.65 (1.39–1.96)	<0.001	35	0.85
CRC	3	43/1,389	19/995	1.99 (1.19–3.33)	0.009	84	
Thyroid cancer	3	6/510	1/381	3.57 (0.78–16.33)	0.10	109	
HCC	2	2/293	4/302	0.52 (0.10–2.65)	0.44	155	
Others	9	71/1,854	40/1,492	1.73 (1.17–2.56)	0.006	87	
VEGFR-TKIs							
Vandetanib	7	111/2,387	69/1,936	1.25 (0.92–1.70)	0.16	92	0.48
Sorafenib	7	87/1,467	43/1,497	2.11 (1.48–3.00)	<0.001	33	
Sunitinib	5	52/1,732	23/1,435	2.18 (1.35–3.53)	0.001	72	
Cediranib	2	14/653	8/511	1.56 (0.66–3.65)	0.31	174	
Regorafenib	2	9/637	2/319	1.99 (0.57–7.02)	0.28	128	
Others	4	211/2,061	129/2,069	1.62 (1.32–2.00)	<0.001	25	
Phases of trials							
Phase II	4	22/680	15/424	1.21 (0.60–2.44)	0.60	336	0.29
Phase III	23	462/8,257	259/7,343	1.71 (1.47–1.99)	<0.001	48	
Overall	27	484/8,937	274/7,767	1.69 (1.45–1.96)	<0.001	53	NA

Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; RR, relative risk; CI, confidence interval; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; NA, not available.

16.488 pacientes de 27 EC (fases II y III)

Más riesgo colorectal y NSCLC

Table 3 Severe and fatal infectious events with VEGFR-TKIs by specific types

	Infectious events, n/total, n		RR (95% CI)	*P*-value
	VEGFR-TKIs	Control		
Severe infections				
Unspecified	57/1,125	28/834	1.53 (0.98–2.39)	0.062
Febrile neutropenia	298/4,025	195/4,049	1.57 (1.30–1.88)	<0.001
Pneumonia	102/6,273	48/5,172	1.79 (1.29–2.49)	<0.001
Fever	10/844	0/528	5.35 (1.47–19.51)	0.011
Sepsis	17/2,097	3/1,533	3.68 (1.51–8.99)	0.004
Fatal infections				
Pneumonia	36/4,685	24/3,871	1.34 (0.80–2.25)	0.26
Sepsis	16/1,866	3/1,434	3.66 (1.47–9.13)	0.005
Overall	52/4,923	27/4,111	1.78 (1.13–2.81)	0.013

Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; RR, relative risk; CI, confidence interval.

Riesgo global : 1.69 veces

Aumento riesgo infecciones fatales aunque riesgo de infección bajo

Monitorización

sorafenib y sunitinib

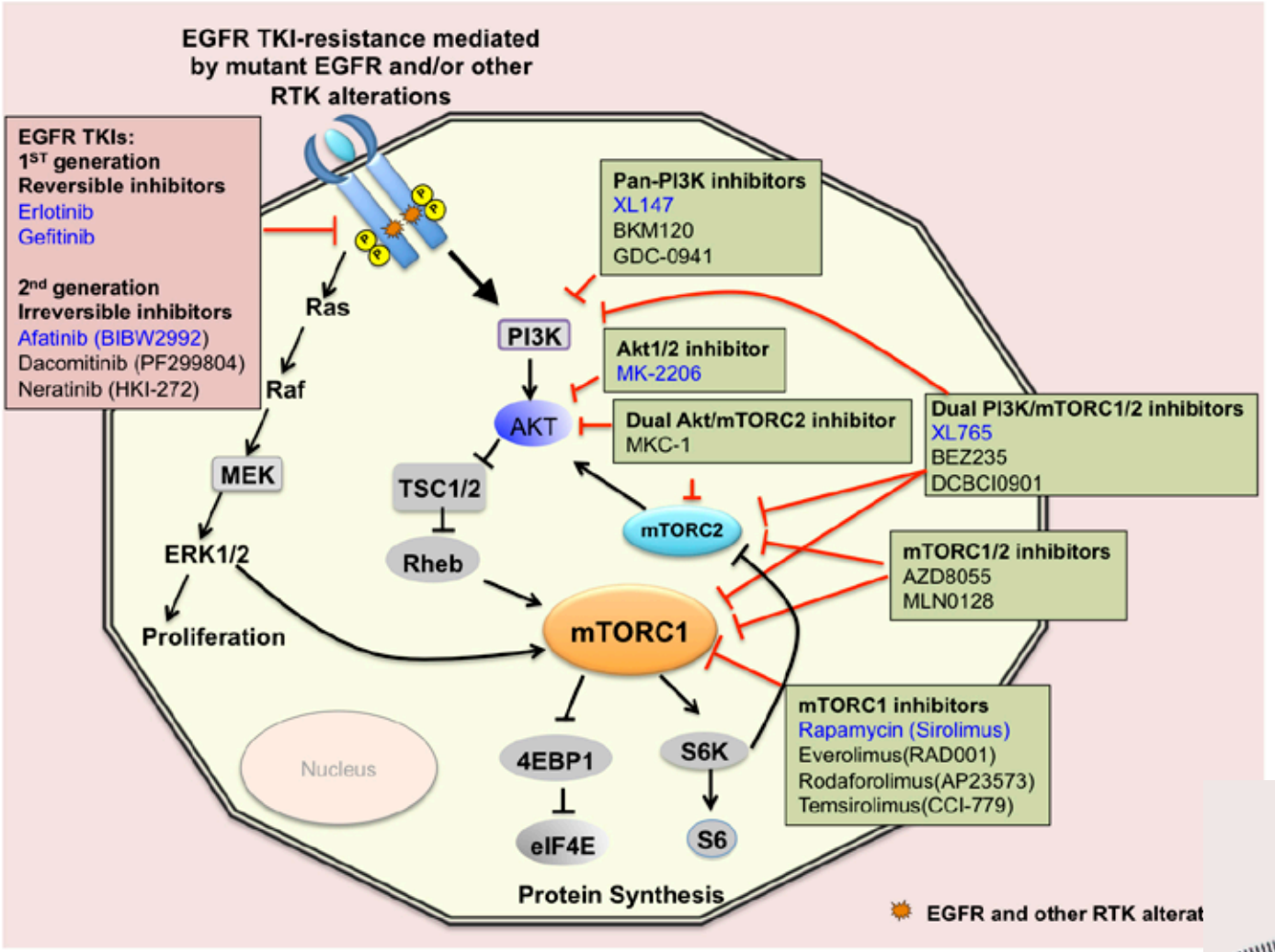
Intervención inmediata

Manejo eficaz

Biological Therapies and their risk of infection

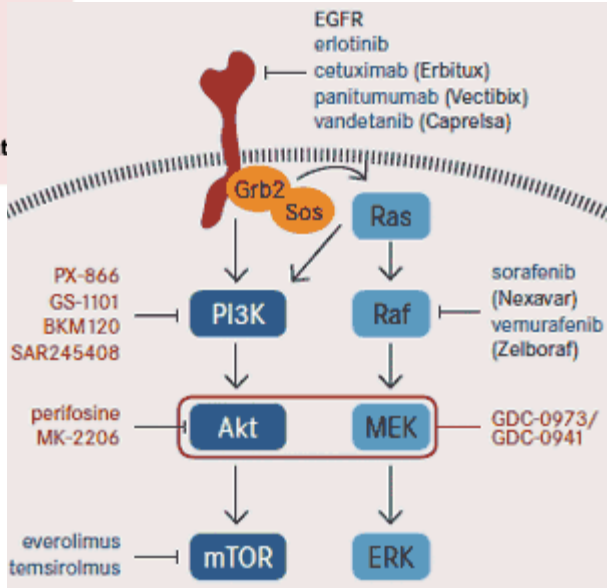
To summarize:

Drug name	*Serious infections*	*Strategy*
Cetuximab	Bacterial (S.aureus, MRSA), fungal Sepsis, febrile neutropenia	Close monitoring
Panitumumab	Similar to cetuximab	Close monitoring
Trastuzumab	Mild bacterial infections (UTI, respiratory) Febrile neutropenia more frequent in combination therapy	Close monitoring --
Bevacizumab	Bacterial and fungal infections Neutropenic fever, sepsis, pneumonitis More frequent in combination	Close monitoring
aflibercept	Bacterial infections Febrile neutropenia	Close monitoring



Different Pathways

Multi-kinase inhibitors



The phosphatidylinositol 3-kinase (PI3K)-AKT-mTOR pathway is a critical signaling pathway which is frequently altered in human cancer

Crecimiento tumoral, invasión, metástasis

Higher risk of infections with PI3K-AKT-mTOR pathway inhibitors in patients with advanced solid tumors on Phase I clinical trials

Saeed Rafii Clin Cancer Res. 2015 Feb 3.

	Cases			Controls		
	Target	No. of trials	No. of patients	Target	No. of trials	No. of patients
Single agent	PI3K	4	80	VEGF	2	22
	mTORC	4	141	EGFR	1	22
	AKT	3	104	MEK	1	12
	Dual PI3K/mTORC inhibitors	1	41	c-MET	1	12
	Total	12	366	HDAC	2	11
Combination with chemotherapy		3	24	HSP90	1	11
Combination with MEK inhibitors		2	42	Integrin	1	5
				Rock	1	4
				IGF-1 R	1	1
Total		17	432	Total	10	100

Table 2. Phase I clinical trials in cases and controls

Phase I clinical trials in the case group comprised of 12 phase I trial of single agent PI3K-AKT-mTOR inhibitors, 3 trials of combination of PI3K-AKT-mTOR inhibitors and chemotherapy and 2 trials of combination of PI3K-AKT-mTOR inhibitors and MEKi.

PI3K-AKT- mTor mechanisms of infection not fully understood

Regulates production of cytokines in innate immune cells

		Cases	Controls
Study subjects (single agent therapy)		366	100
Age, Year Median (Range)		56.7 (22-81)	54.3 (17-88)
Gender	Male	179	53
	Female	187	47
BMI, Kg/m^2 Median (Range)		25.9 (16.9-43)	26.8 (18.3- 38)
Tumor type (All cases, single agents and combinations)	Lung & Mesothelioma	49 (13%)	11 (11%)
	Breast	34 (9.3%)	11 (11%)
	Colorectal	95 (26%)	16 (16%)
	Gynecological	61 (16.6%)	6 (6%)
	RCC	18 (5%)	3 (3%)
	Prostate	22 (6.8%)	10 (10%)
	Others	87 (23.7%)	43 (43%)
No of prior lines of chemotherapy	0-2	183 (50%)	52 (52%)
	3-5	148 (40.5%)	36 (36%)
	>6	20 (5.5%)	4 (4%)
	Unknown	15 (4%)	8 (8%)
Performance Status	0	88 (24%)	26 (26%)
	1	276 (75%)	72 (72%)
	2	2 (0.5%)	2 (2%)
RM Score*	0	68 (18.5%)	22 (22%)
	1	129 (35%)	30 (30%)
	2	106 (29%)	32 (32%)
	3	52 (14.5%)	16 (16%)
	Unknown	11 (3%)	-
Time on trial (days)		84	109

Table 1. Baseline characteristics in cases and controls

Baseline characteristics such as age at the time of recruitment, primary tumor type, prior lines of chemotherapy, performance status were balanced between cases and controls.

* RM score (reference): Albumin + N° metastatic sites + LDH

	All grade infection				Grade 3/4 infection			
	With infection	Without infection	OR (95% CI)	p	With infection	Without infection	OR (95% CI)	p
Controls	8 (8%)	92 (92%)	-	-	3 (3%)	97 (97%)	-	-
Single agent PAMi	99 (27%)	267(73%)	**4.26*** (1.9- 9.1)	**0.0001**	38 (10%)	328 (90%)	**3.74*** (1.1-12.4)	**0.02**
PAMi + Chemotherapy	16 (62%)	9 (38%)	**4.79**** (2.0- 11.2)	**0.0001**	6 (25%)	18 (75%)	**2.87**** (1.0-7.6)	**0.03**
PAMi + MEKi	26 (62%)	16 (38%)	**4.38**** (2.2-8.5)	**<0.0001**	3 (7%)	39 (93%)	0.66** (0.1-2.2)	**0.5**

Table 3. Incidence and risk of infection between cases and controls and between single agent PI3K-AKT-mTOR and combination therapies.

	All grade infection				Grade 3/4 infection			
	No	Yes	OR (95% CI)	p	No	Yes	OR (95% CI)	p
Controls	92 (92%)	8 (8%)	-	-	98 (98%)	2 (2%)	-	-
mTORCi	105 (74.5%)	36 (25.5%)	**3.9** (1.7-8.9)	**0.001**	128 (90.7%)	13 (9.3%)	**4.9** (1.0-22.5)	**0.03**
PI3Ki	62 (79.5%)	16 (20.5%)	**2.9** (1.1-7.3)	**0.019**	70 (89.7%)	8 (10.3%)	**5.6** (1.1-27.1)	**0.03**
Multi kinase PI3K/mTORC inhibitors	15 (36.6%)	26 (63.4%)	**19.9** (7.6-52.1)	**<0.0001**	30 (73.2%)	11(26.8%)	**17.9** (3.7-85.6)	**0.0003**
AKTi	85 (80.2%)	21 (19.8%)	**2.8** (1.1-6.7)	**0.018**	100 (94.4%)	6 (5.6%)	**2.9** (0.5-14.9)	0.19

Table 4. Incidence and risk of infection between different inhibitors of PI3K-AKT-mTOR pathway

To sum up

Higher risk of all grade / high-grade infections, and higher if **combined** with chemotherapy or in dual combinations (sinergistic effect????)

138/140 (98.5%) had **bacterial infections** (urinary, respiratory), 2 HZV .

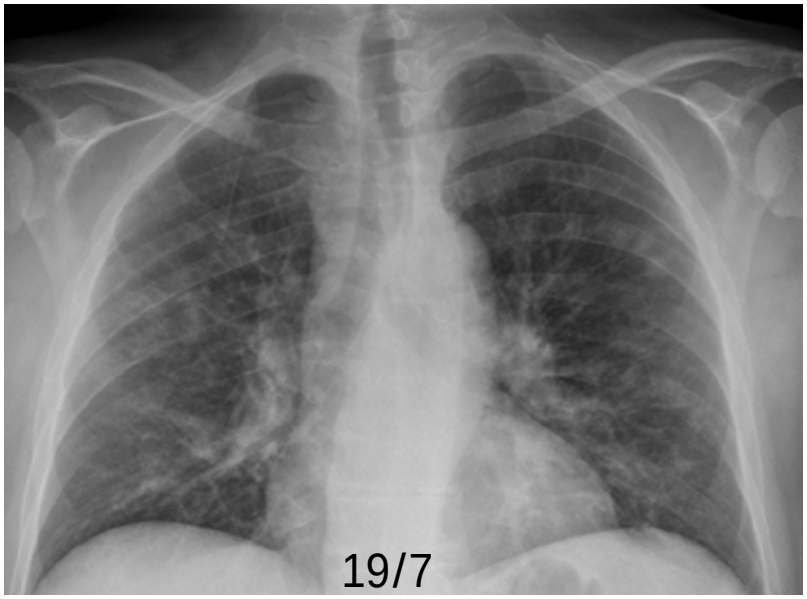
72% had one episode of infection and 28% $\geq$ 2 episodes

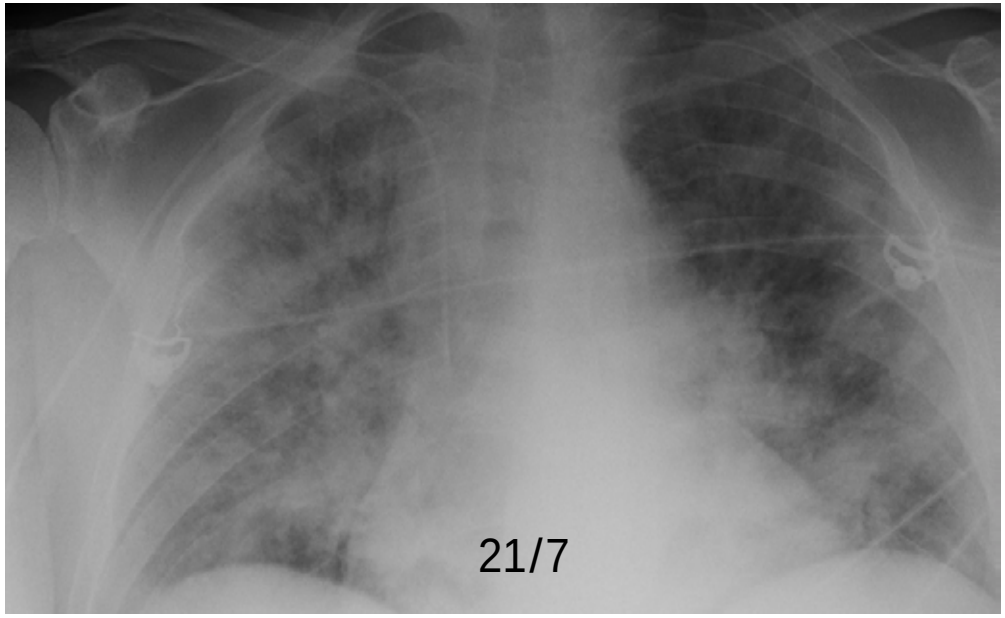
9(6.4%) neutropenic and 43 **(30%) lymphopenic** (1.2 x 10^9/l ; range: 0.2-3.1 x 10^9/l).

The **number of cycles** of treatment was confirmed as a predictor of the risk of infection in the multivariate logistic mixed model (OR: 1.109, 95% CI: 1.02-1.19, p=0.008).

Results from this study **will need to be validated** in future phase II and phase III studies

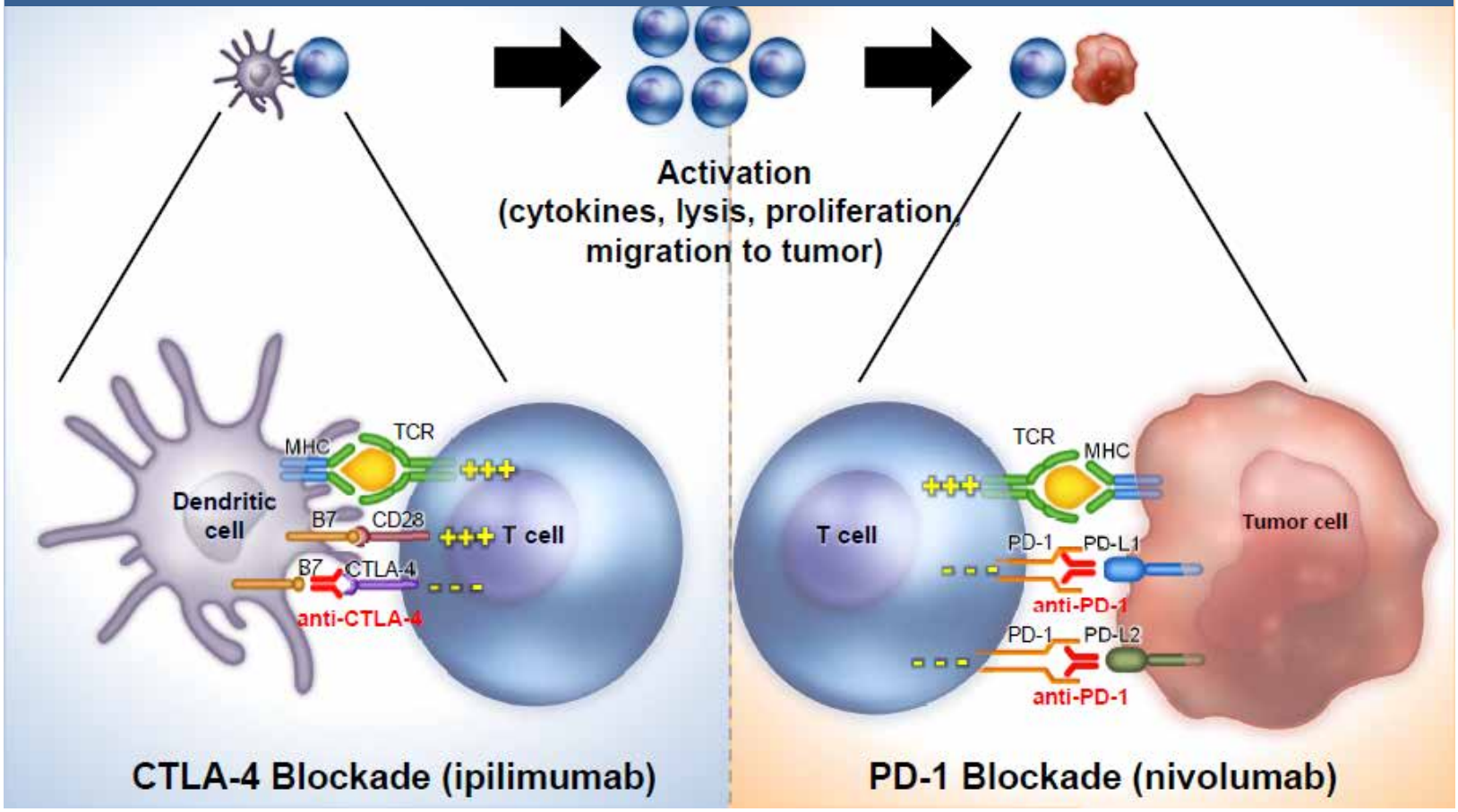
57a. **LLC** inicio tto 2014 (R-FC)
Recaída 10/14 ensayo clínico inh **PI3K (duvelisib): 11 ciclos- PANCITOPENIA**
7/15 Hospital Alcañiz **bacteriemia E.coli** : alta levofloxacino
10d. Ingreso en HUVH. **Sinusitis**.
Tos, dísnea, fiebre...





BAL/BAS: Calcoflúor : + hongos filamentosos
GM >10
Cultivo: + *Aspergillus flavus*

Mechanism of action of Ipilimumab and Nivolumab



tremelimumab **Pembrolizumab, atezolizumab**

iAE:rash, diarrea, alt. hepática, neumonitis, alt. tiroideas

Opportunistic infections in patients treated with immunotherapy for cancer

Kyi *et al. Journal for ImmunoTherapy of Cancer* 2014, **2**:19

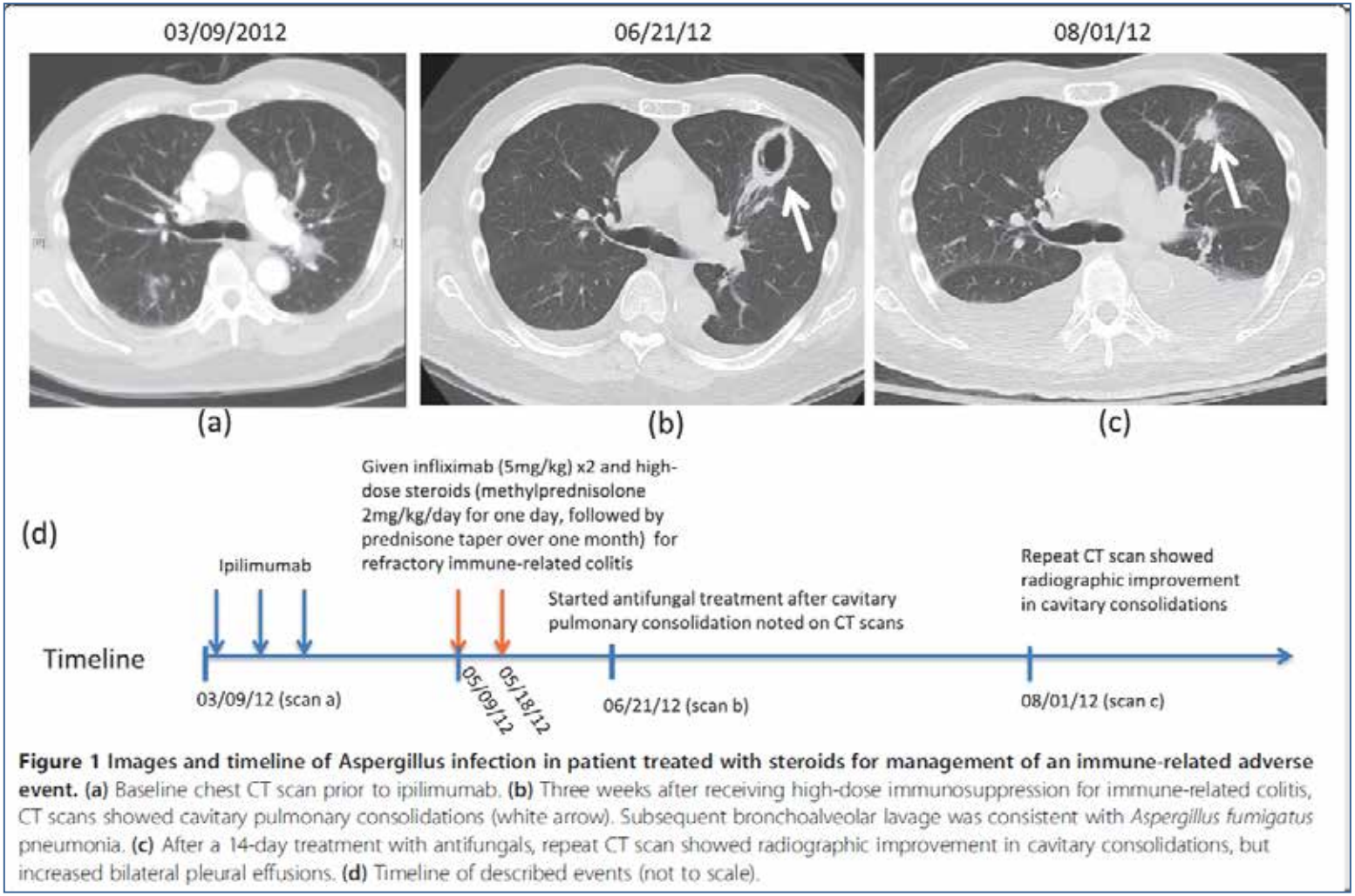


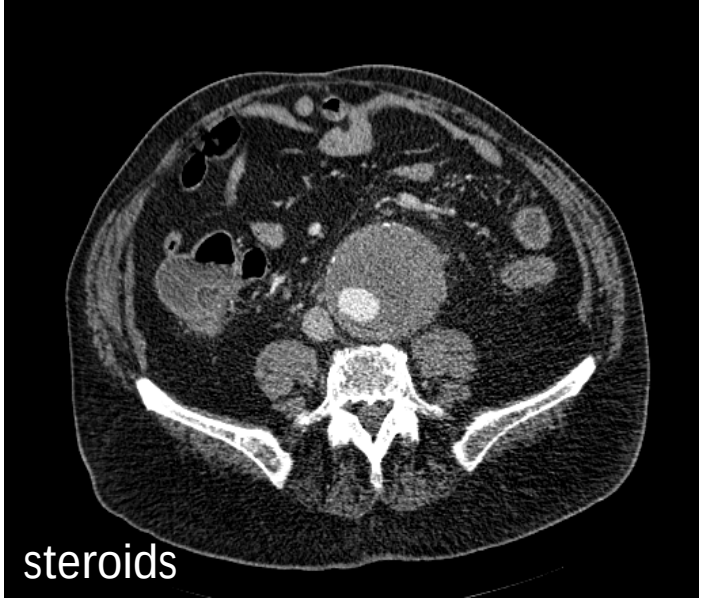
Figure 1 Images and timeline of Aspergillus infection in patient treated with steroids for management of an immune-related adverse event. (a) Baseline chest CT scan prior to ipilimumab. **(b)** Three weeks after receiving high-dose immunosuppression for immune-related colitis, CT scans showed cavitary pulmonary consolidations (white arrow). Subsequent bronchoalveolar lavage was consistent with *Aspergillus fumigatus* pneumonia. **(c)** After a 14-day treatment with antifungals, repeat CT scan showed radiographic improvement in cavitary consolidations, but increased bilateral pleural effusions. **(d)** Timeline of described events (not to scale).

Fournier's gangrene, CMV viremia

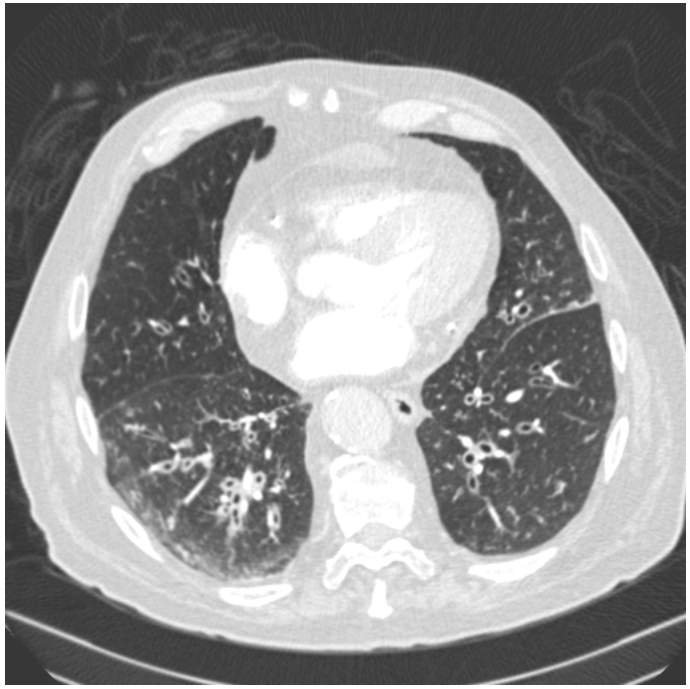
76 y male SCLC S IV
CBDP-VP 16 +/- ipilimumab (4 doses)

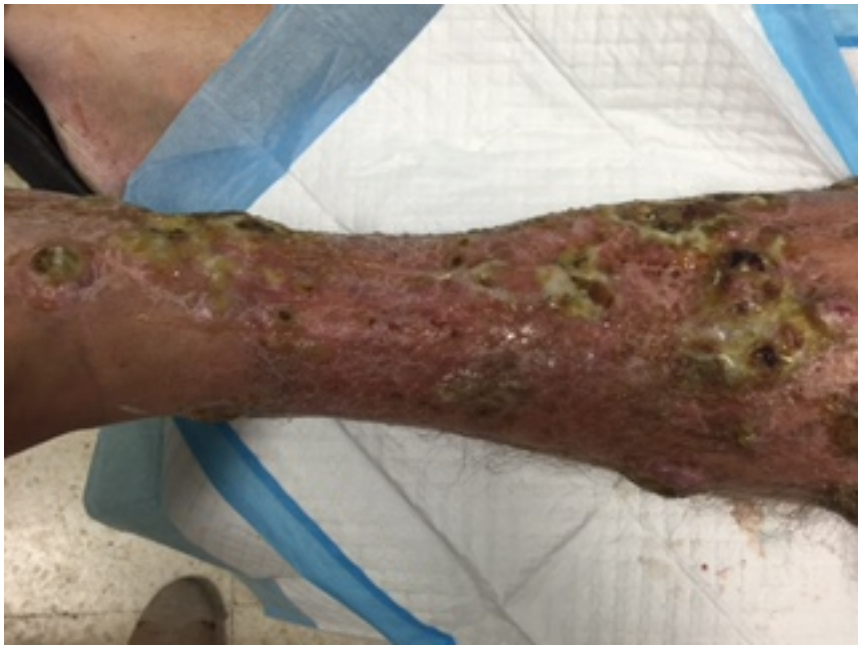
Bloody diarrhea
Hypotension, tachycardia, hypoK+

Copro negative
CD toxine negative
No lymphopenia



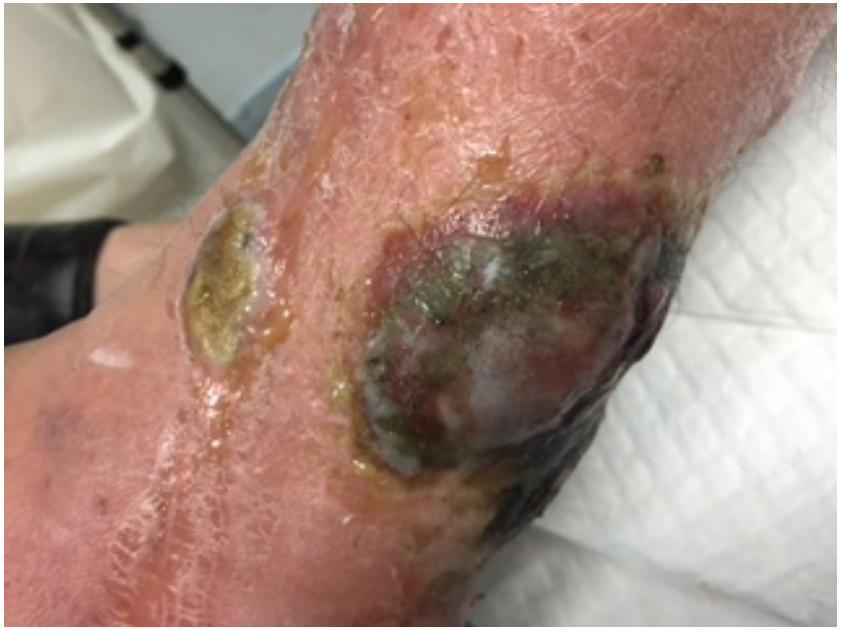
Bloody diarrhea persisted (>1 month)
Colonoscopy:
- ulcers in all colon
- PCR/immunochemistry positive CMV
- CMV PCR 6500 copies
- Ganciclovir/valganciclovir



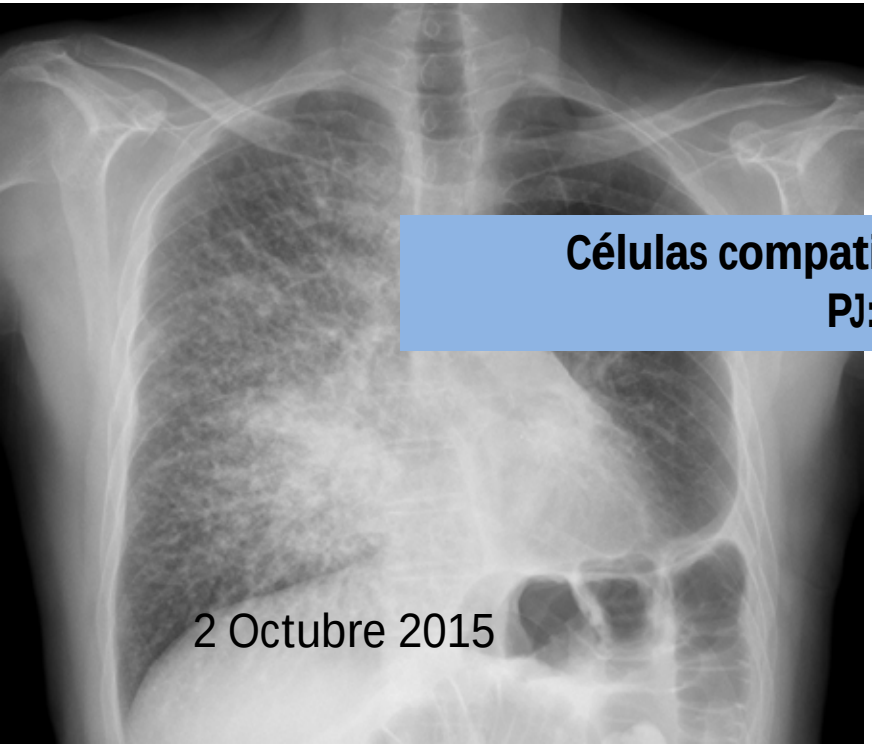


39 años
Melanoma
Ipilimumab+Nivolumab

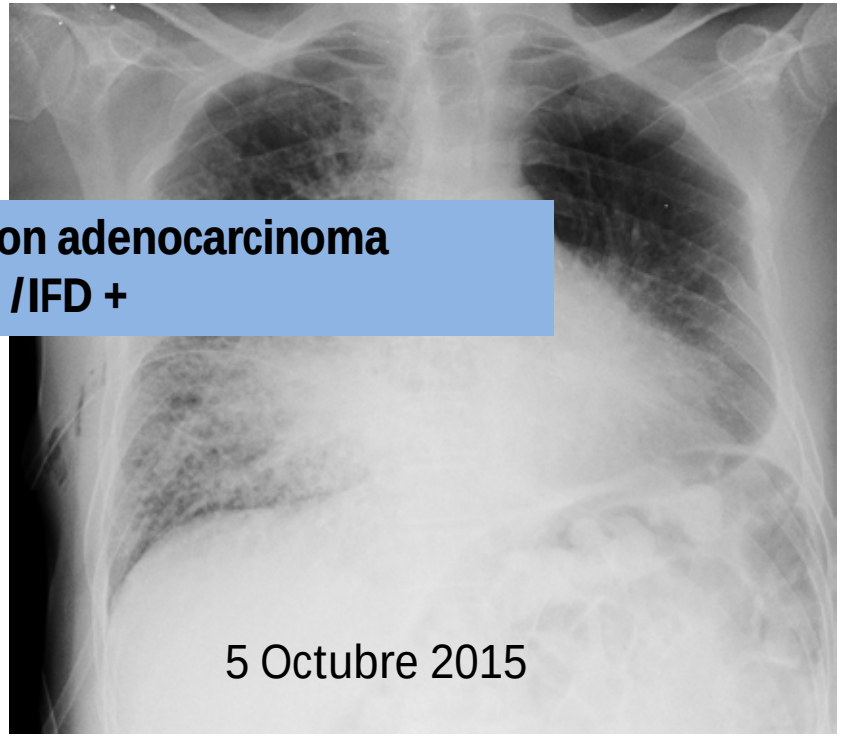
Enterobacter cloacae
E.coli
S.aureus
S.agalactiae

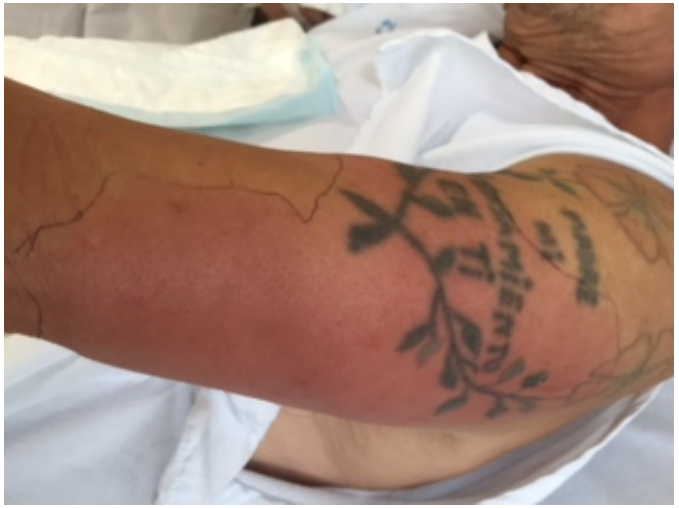


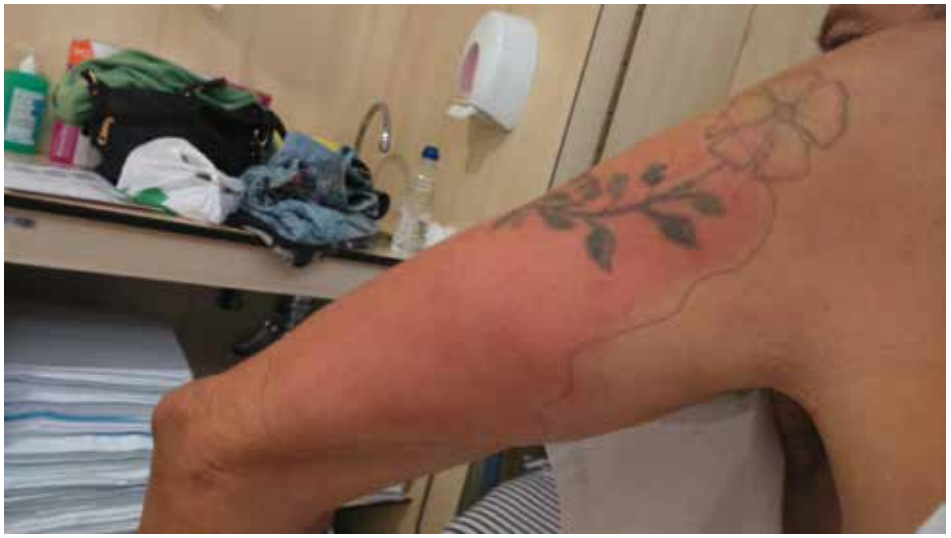
52a. Portugal antecedentes **hipotiroidismo**
12/2013 NSCLC (Adenocarcinoma)- 1/14 Lobectomia LII+linfadenectomia mediastínica
QT (cisplatino/vinorelbina) +RT mediastínica- Fin Junio 2014
11/2014 recidiva adenopática mediastínica
2ª opinión HUVH.
EC Fase 3 CA209-026 abierto aleatorizado de **Nivolumab** (3/2015) cada 2 semanas
Enf actual:
Empeoramiento hipotiroidismo en control Endocrino
06/15 **disnea progresiva**. La relaciona con nivolumab. **No fiebre**. **Tos seca**.
Tandas azitromicina/levo/ esteroides
Progresión adenopática. Analíticamente **linfopenia**



Células compatibles con adenocarcinoma
PJ: PCR+ /IFD +







Manejo de la infección y la neutropenia febril en el paciente con cáncer sólido☆

José María Aguado[a,*], Juan Jesús Cruz[b], Juan Antonio Virizuela[c], Manuela Aguilar[d], Alberto Carmona[e], Javier Cassinello[f], Carlota Gudiol[g], Paula Jiménez Fonseca[h], Manuel Lizasoain[a], Francesc Marco[i], Isabel Ruiz[j], Maribel Ruiz[k], Miguel Salavert[l], David Vicente[m] y Jordi Carratalà[g]

Enferm Infecc Microbiol Clin. 2015;**xxx(xx)**:xxx.e1–xxx.e10

General preventive measures

- Vaccination
- Screening for latent infections
  - TB (active and latent-LTBI)
  - HBV/HCV
  - Imported diseases
  - Viral infections: HSV, VZV, CMV, HIV
- *Papilomavirus* infection
- *P.jiroveci* infection (follow up)

Cotrimoxazol:

- PJP
- *Listeria*
- *Legionella*
- *Salmonella*
- *Toxoplasma*
- *Isosopora*
- *Nocardia*
- other: enterobacteries, *Haemophilus, Moraxella, Stenotrophomonas, Staphylococcus…*

Table 1. Main Characteristics of Studies That Provide Evidence of Additional Protection Against Infection in Patients Taking Trimethoprim-Sulfamethoxazole Prophylaxis for *Pneumocystis jirovecii* Pneumonia

First Author [Reference]	Study Type	No. of Enrolled Patients	Patient Type	Infection Protection
Anglaret [31]	Randomized controlled trial	545 (271T, 270C)	HIV	Bacterial pneumonia, isosporosis, and malaria
Wilcox [32]	Randomized controlled trial	771 (386T, 385C)	HIV-1	Enteritis (isosporiasis and nontyphoid *Salmonella* spp), septicemia
Fox [33]	Prospective randomized double-blind study	132 (66T, 66C)	Kidney recipients	Bacterial infections
Green [34]	Meta-analysis of randomized trials	1156	Cancer pts, bone marrow and SOT recipients, corticosteroid- receiving pts and other immunosuppressive condition other than HIV	Bacterial infections
Hirschtick [35]	Multicenter prospective observational study	1297 (1130 HIV, 167 non-HIV)	General population	Bacterial pneumonia
Dworkin [4]	Retrospective study	19 061 (13 518T, 9282C)	HIV <200 CD4	*Haemophilus* spp, *Salmonella* spp, Toxoplasmosis, and *Staphylococcus aureus* infections
Fernandez-Sabe [5]	Multicenter matched case-control study	66 (22 cases, 44C)	SOT recipients	Toxoplasmosis
Fernandez-Sabe [6]	Multicenter matched case-control study	90 (30 cases, 60C)	SOT recipients	Listeriosis
Edge [36]	Case-control and prospective study	171 (57 cases, 114C)	HIV	Community-acquired bacteremia

Abbreviations: C, patients not treated with trimethoprim-sulfamethoxazole (control or placebo patients); HIV, human immunodeficiency virus; HIV-1, HIV type 1; pts, patients; SOT, solid organ transplant; T, patients treated with trimethoprim-sulfamethoxazole prophylaxis.

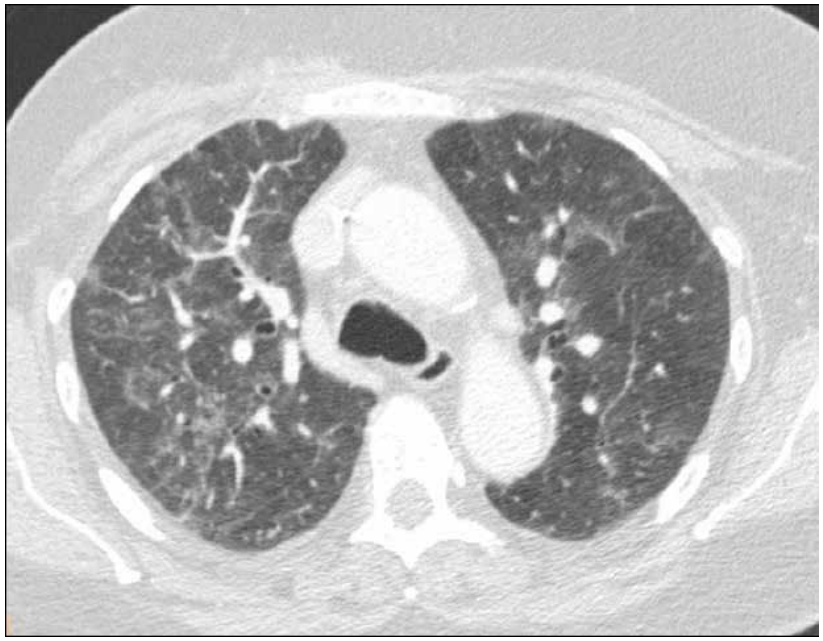
Immune Checkpoint Blockade in Cancer Therapy

Michael A. Postow, Margaret K. Callahan, and Jedd D. Wolchok

Prolonged immunosuppression, often required to treat irAEs, unfortunately carries the risk of predisposing patients to opportunistic infections. In one case report, a patient treated with ipilimumab who required corticosteroids and infliximab for colitis ultimately developed *Aspergillus* pneumonia.[67] Given this risk, in patients receiving prolonged immunosuppression to treat an irAE, such as prednisone $\geq$ 20 mg per day for at least 4 weeks, we recommend considering prophylaxis against infectious organisms such as *Pneumocystis jirovecii* following the guidelines established by the National Comprehensive Cancer Network.[68]

Sometimes …

- 65 y breast cancer
- docetaxel +bevacizumab
- 3w TC: PR
- 1w fever+dispnea+dry cough
- pO_2 66, 600 lymphocytes



Conclusions

Increment exponencial en el nombre de **teràpies biològiques** pel tractament de malalties **immunològiques i oncològiques**

El **risc d'infecció** que presenten els pacients amb càncer **pot augmentar** per **algunes teràpies dirigides** (gran nombre de factors confusors)

Notificar les infeccions, estudis prospectius poden ajudar a definir la incidència

Conclusions

Estar atent. Els efectes adversos semblen infeccions. Les infeccions afecten a neutropènics i no neutropènics.

Prevenció i **diagnòstic precoç** pot ser la clau