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PERSONALISED MEDICINE SYMPOSIUM

SIGNALLING PATHWAYS SYMPOSIUM

Targeting the PI3K/AKT/ mTOR pathway in cancer

Sitges, Barcelona **28 February - 1 March 2014**

Toxicity of combinations

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DISCLOSURE

No conflict of interest

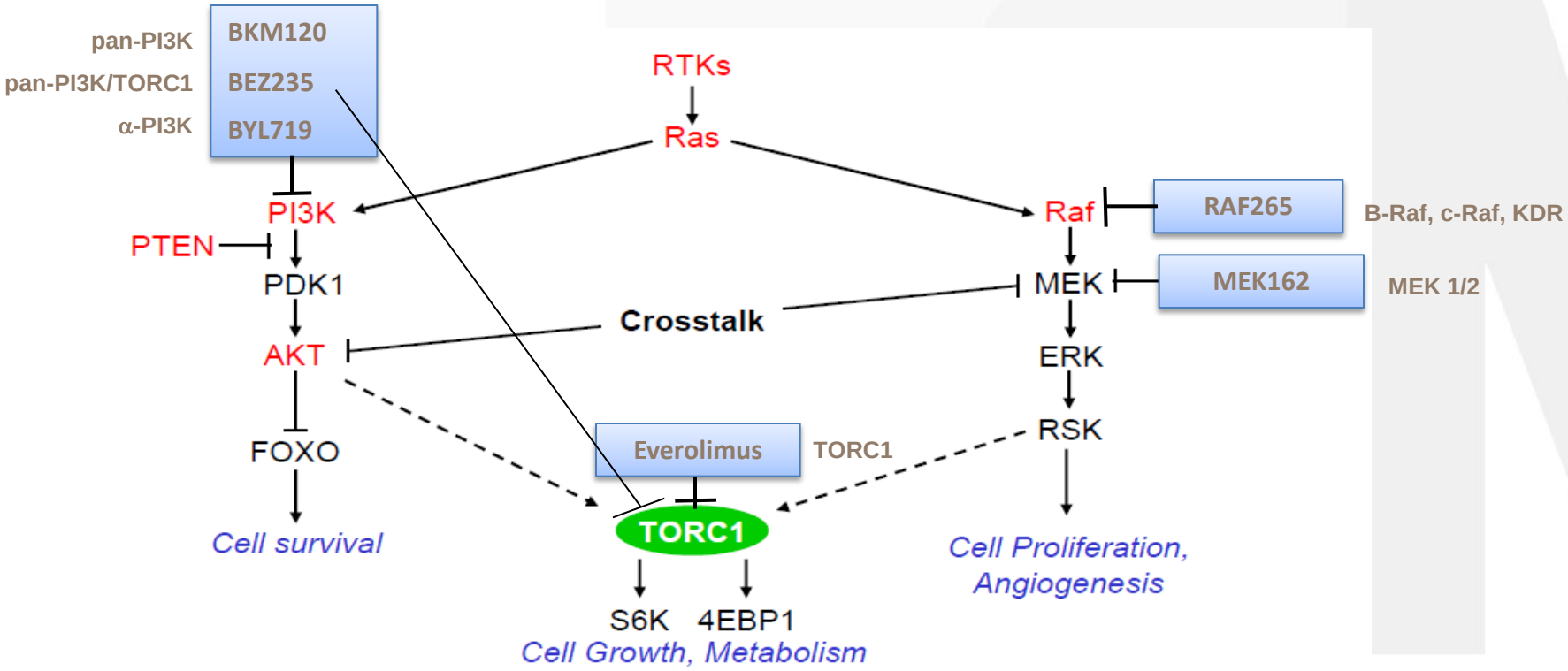
Combinations with PI3K/AKT/mTOR inhibitors

Rationale

- PIK3CA is frequently mutated in human cancers
- Limited single agent activity partially explained by pharmacodynamic / pharmacokinetic factors
- Presence of activating feedback loops, pathway circumvention or simultaneous KRAS mutation

Interaction of the MAPK and PI3K pathways in cancer

- Sharing common upstream activators (e.g. EGFR)
- Common activation by oncogenic Ras
- Cross-talking at various levels (e.g. Akt on MEK)
- Providing compensatory signalling when one or the other is inhibited



frequently mutated in cancers

PI3K inhibitors given in combination with MEK inhibitors

Compound	MoA	T ½ β (h)	Schedule	MTD/RD (mg)	Main toxicities
BKM 120	Oral pan-class I PI3K inhibitor	40	QD cont.	100/100	Rash, hyperglycemia, mood alterations, diarrhea, fatigue
BYL 719	Oral class I α PI3K inhibitor	7.5	QD cont.	400/	Hyperglycemia, nausea, diarrhea, rash, fatigue
PF 0469	Oral pan-class I PI3Ki/mTORi	10-14	QD cont.	8/	Hyperglycemia, rash, fatigue, diarrhea
PF 0521	IV pan-class I PI3Ki/mTORi	40-65	Weekly	154/154	Mucositis, nausea, rash, hyperglycemia
GSK 458	Oral class I α PI3Ki/mTORi	10	QD cont.	2.5/	Diarrhea, fatigue, nausea, hyperglycemia

MEK inhibitors given in combination with Pi3K inhibitors

Compound	MoA	T ½ β (h)	Schedule	MTD/RD (mg)	Main toxicities
MEK 162	Non ATP competitive. selective MEK ½i	7.3	BID cont.	60/45	Skin, GI, eye events, ↑ CPK, mucositis, fatigue
GSK 1120212	Allosteric selective MEK ½i	4 days	QD cont.	3/2	Rash / dermatitis acneiform, diarrhea, peripheral edema, ocular
PD 0325901	Non ATP competitive	ND	BID cont. BID / 3wk on / 1wk off	15/ /<10	Rash, diarrhea, fatigue, nausea, ocular

Phase I studies of PI3K / MEK inhibitors

	KRAS/ BRAF^{mut}	PI3K^{mut}	PI3Ki	MEKi	Starting dose PI3Ki/MEKi (mg)	Main Toxicities	MTD (mg)	RD	Antitumor activity
Glaxo	+	-	GSK 458 QD cont BID cont QD int	GSK112 QD cont	0.5/0.5	Rash, diarrhea, vomiting, fatigue	ND	ND	none
Novartis	+	-	BKM 120 QD cont	GSK112 QD cont	30/0.5	Skin (dermatitis, rash maculo papular)	70/1.5	60/1.5	yes
	+	-	BKM 120 QD cont	MEK 162 cont	50/30		ongoing		
	+	+	BYL 719 QD cont	MEK 162 cont int	200/30		ongoing		
Pfizer	+		PF 0469 QD cont	PD 0325 BID 3wk on / 1wk off	4/8	Rash, diarrhea, fatigue (67% DLT)	4/8	ND	
	+		PF 05212 qwk	PD 0325 BID 3wk on / 1wk off	110/2		ongoing		

Characteristics of patients with low-grade and high-grade serous ovarian cancer

	Low grade	High-grade
Mean overall survival (mo)	99	57
Response rate to platinum or taxane	4%	80%
KRAS or BRAF mutations	30 or 50%	2 or 3%
BRCA mutation	4%	22%

Single-arm, phase 2 study of selumetinib in recurrent low-grade serious carcinoma of the ovary or peritoneum

Characteristics of patients

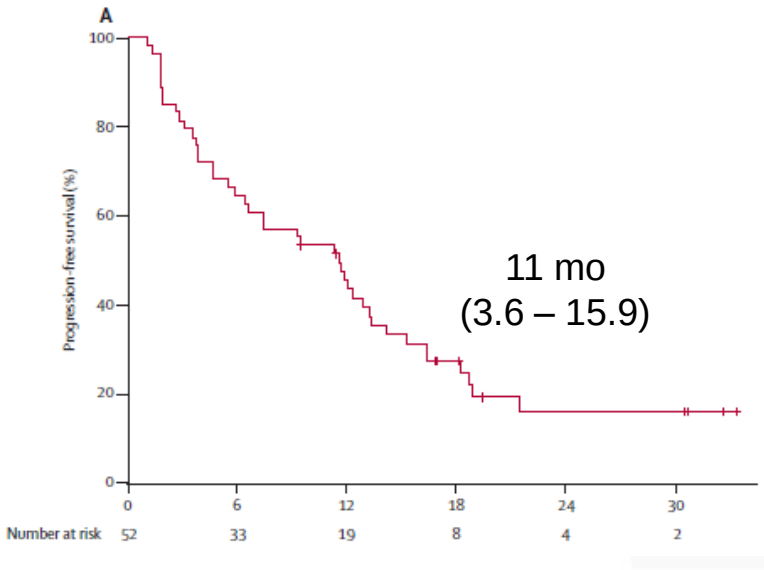
	All pts (n=52)	Mutational analysis subset (n=34)
Site of disease		
Ovary	47 (90%)	30 (88%)
Peritoneum	5 (10%)	4 (12%)
Number of previous regimens		
2	12 (23%)	8 (24%)
≥ 3	30 (58%)	20 (59%)
Previous surgery		
No	3 (6%)	2 (6%)
Yes	49 (94%)	32 (94%)

Farley et al, Lancet Oncol 2013

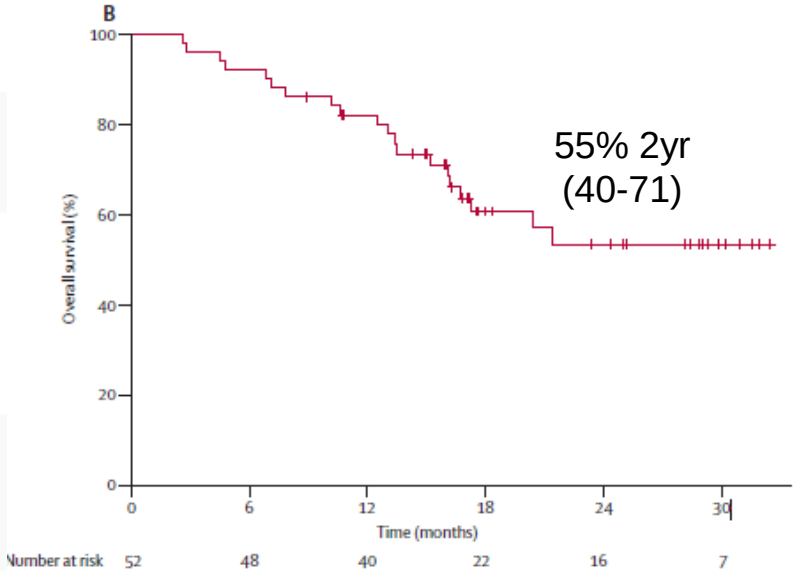
Single-arm, phase 2 study of selumetinib in recurrent low-grade serious carcinoma of the ovary or peritoneum

Antitumour activity in all patients

	Response to treatment (n=52)	Median time to response (mo)	Duration (mo)
Objective response	8 (15%)	4.8	10.5
Stable disease	34 (65%)	-	-



Progression free survival



Overall Survival

Farley et al, Lancet Oncol 2013

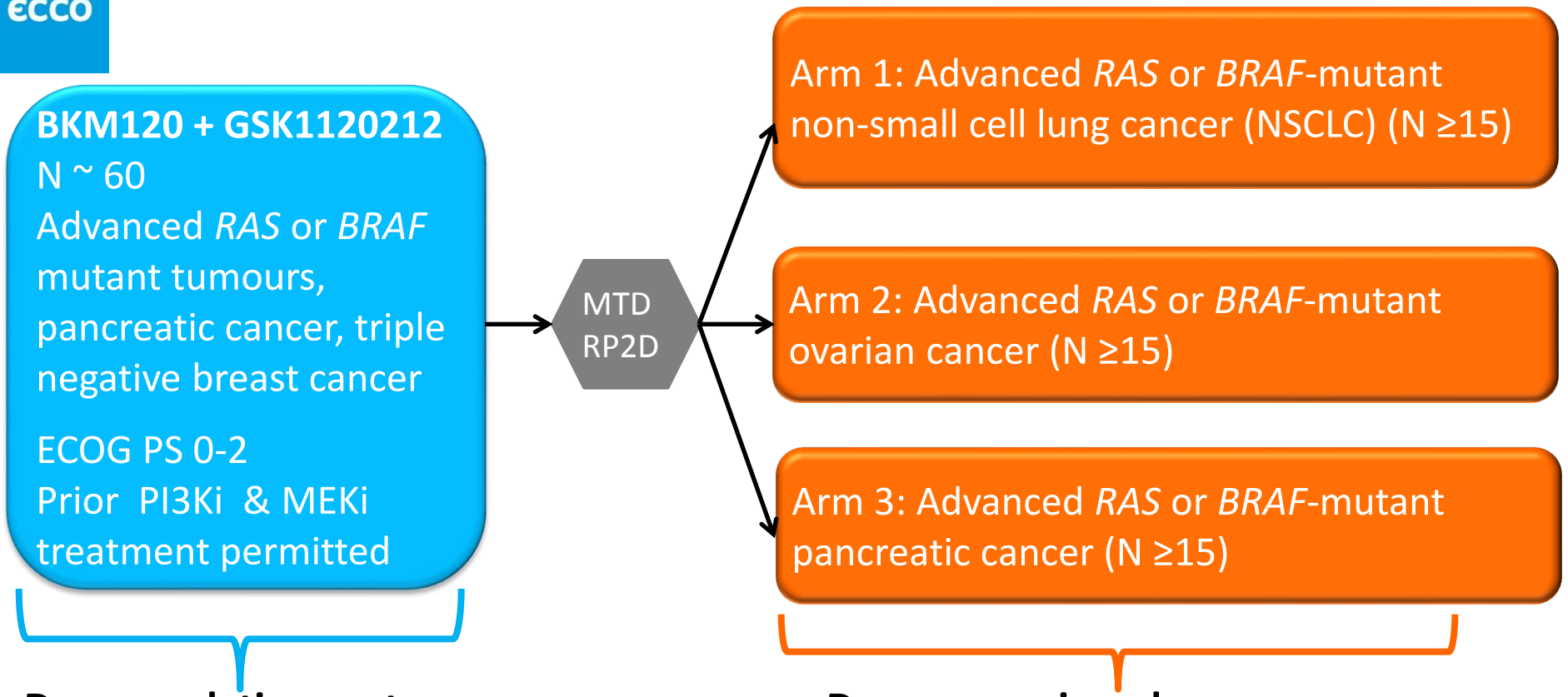
Single-arm, phase 2 study of selumetinib in recurrent low-grade serious carcinoma of the ovary or peritoneum

Antitumour activity by mutations

	Number of patients	Response (%)
BRAF		
No	32	7 (22%)
Yes	2	0
KRAS		
No	20	5 (25%)
Yes	14	2 (14%)
BRAF or KRAS		
No	18	5 (28%)
Yes	16	2 (13%)

Farley et al, Lancet Oncol 2013

Study Design



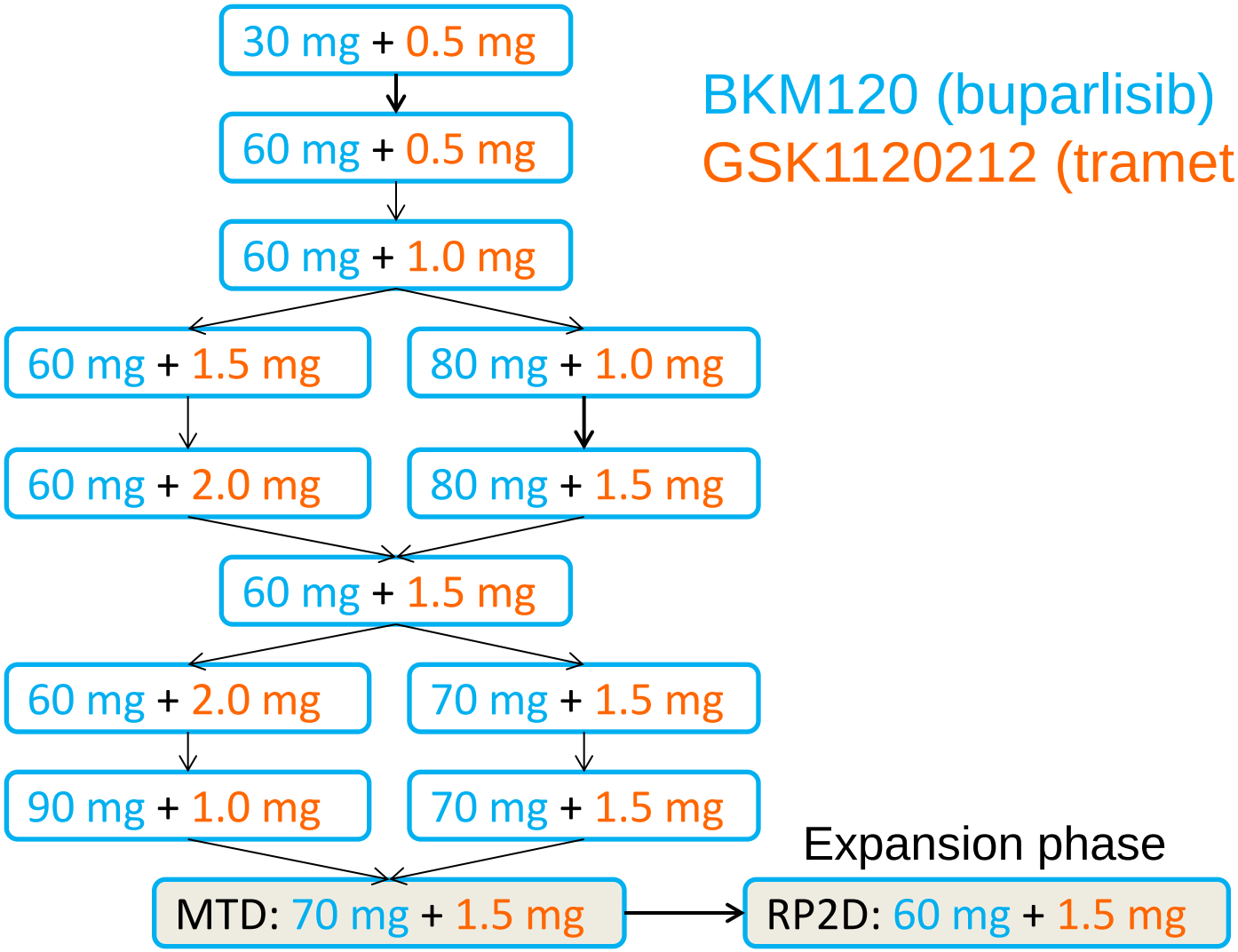
- Primary objective: to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)
- Secondary objectives: safety, tolerability, PK and efficacy

Patient Characteristics

Characteristic	All patients (N = 113)
Median age - years (range)	56 (25–84)
Male / female	49 / 64
Median prior lines of treatment (range)	3 (1–14)
WHO performance status, 0 / 1 / 2	46 / 65 / 2

Tumour Type	Escalation (N = 66)	Expansion (N = 47)
Colorectal	33	-
Melanoma	10	-
Pancreatic	9	15
Ovarian	4	17
TNBC	4	-
NSCLC	2	15
Other	4	-

Dose-escalation Schedule



BKM120 (buparlisib)
GSK1120212 (trametinib)

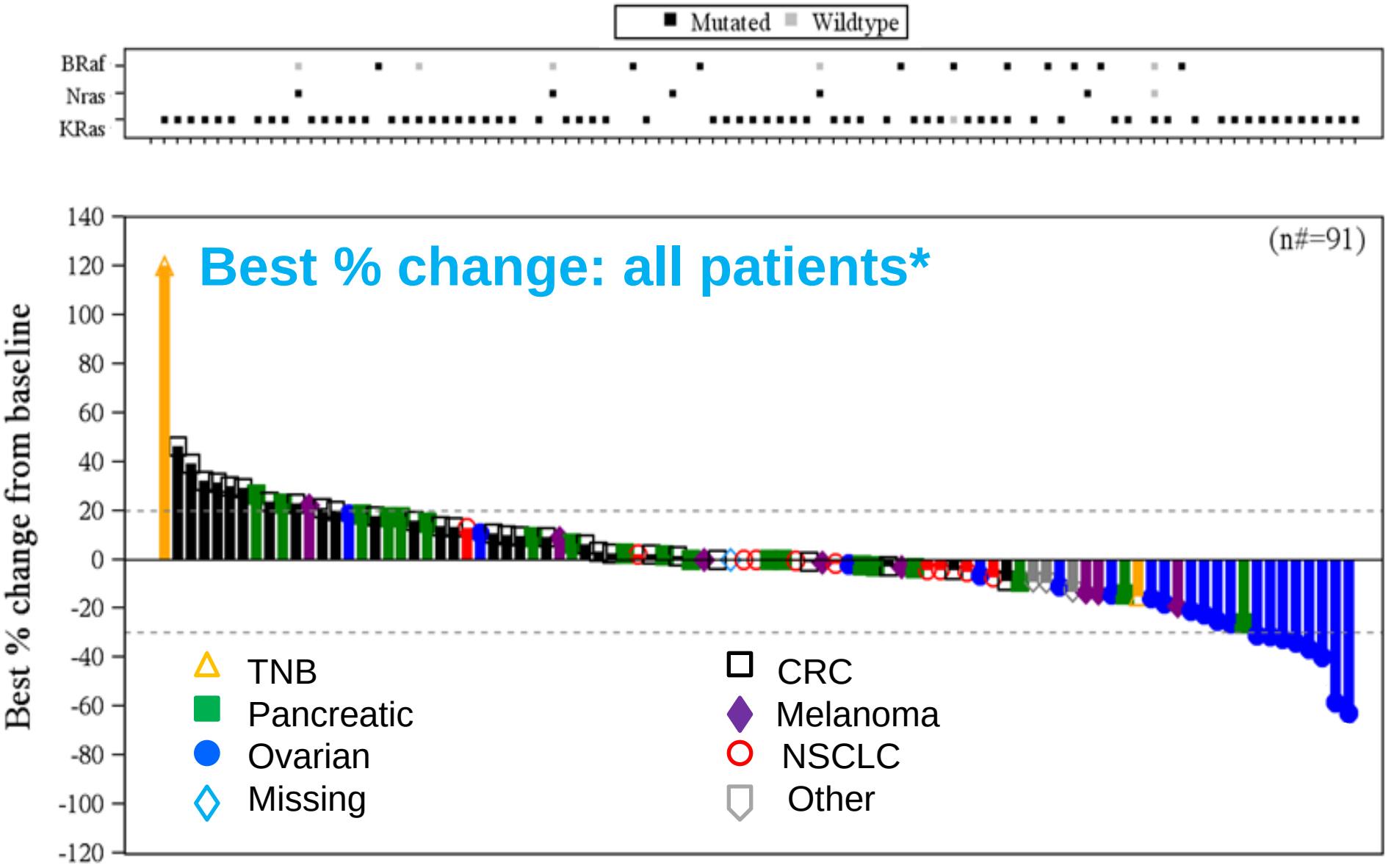
Dose-limiting Toxicities (DLTs)

BKM120	GSK1120212	N	DLT	Nature of DLT *
30 mg	0.5 mg	4	0	–
60 mg	0.5 mg	5	0	–
60 mg	1.0 mg	6	1	G3 stomatitis
60 mg	1.5 mg	11	1	G3 type II diabetes, G3 hyperlipasemia
60 mg	2.0 mg	9	1	G3 stomatitis
70 mg	1.5 mg	16	5	G3 stomatitis, G3 dysphagia, G3 CK elevation, skipped/delayed dose (G2 dysphagia, G2 diarrhea)
80 mg	1.0 mg	4	0	–
80 mg	1.5 mg	6	3	G3 CK elevation, 20% LVEF decrease, G3 nausea, G3 anorexia, G3 decreased oral intake
90 mg	1.0 mg	5	1	Skipped/delayed dose (G2 stomatitis)
All		**66**	**12**	As 15th of February 2013

MTD

RP2D

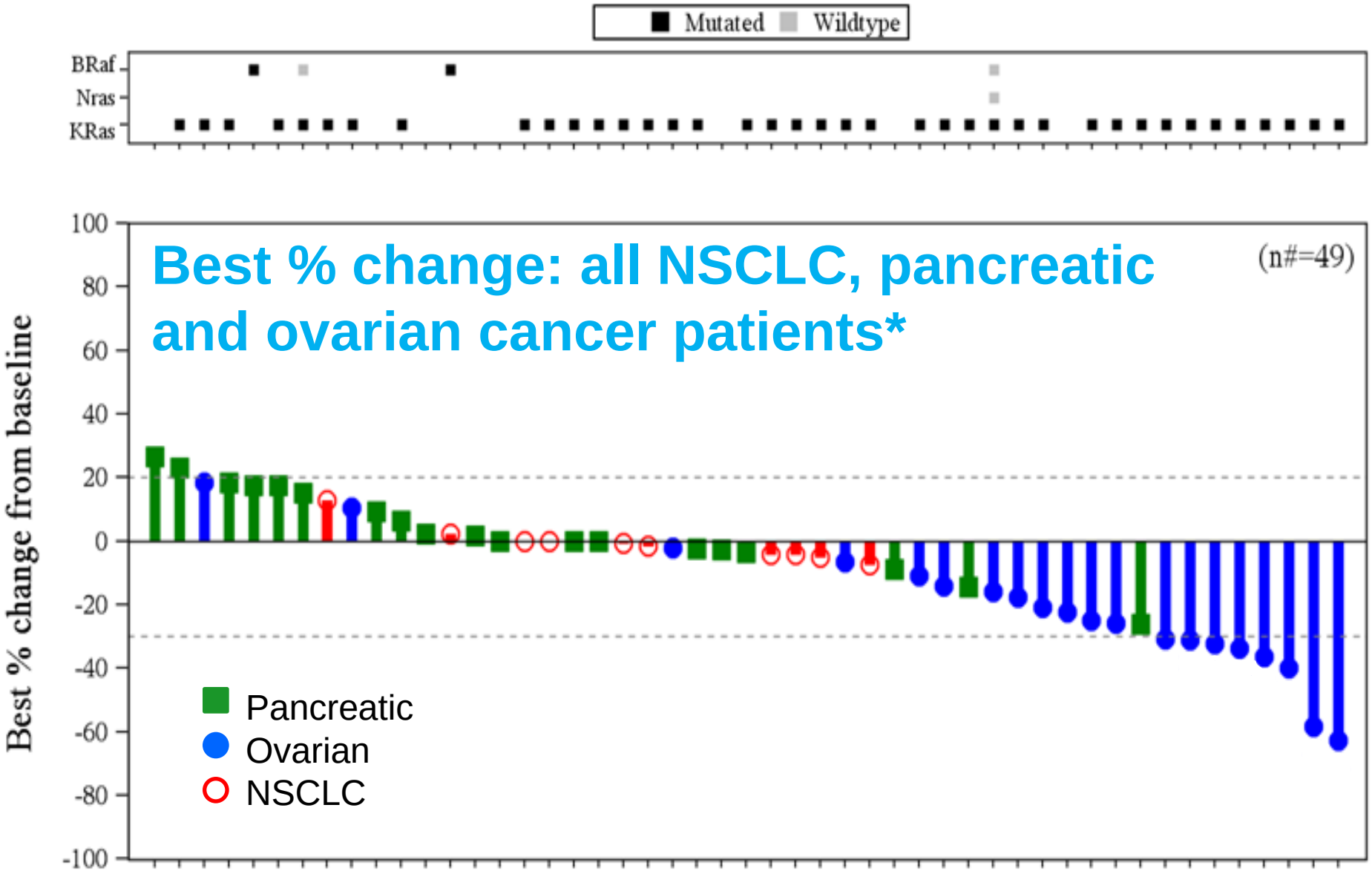
* Patients may have more than one DLT



*as of 15 February 2013

PR = partial response

patients with missing best percentage change from baseline are not included



*as of 15 February 2013

PR = partial response

patients with missing best percentage change from baseline are not included

Overall Response Rate (ORR): ovarian cancer patients

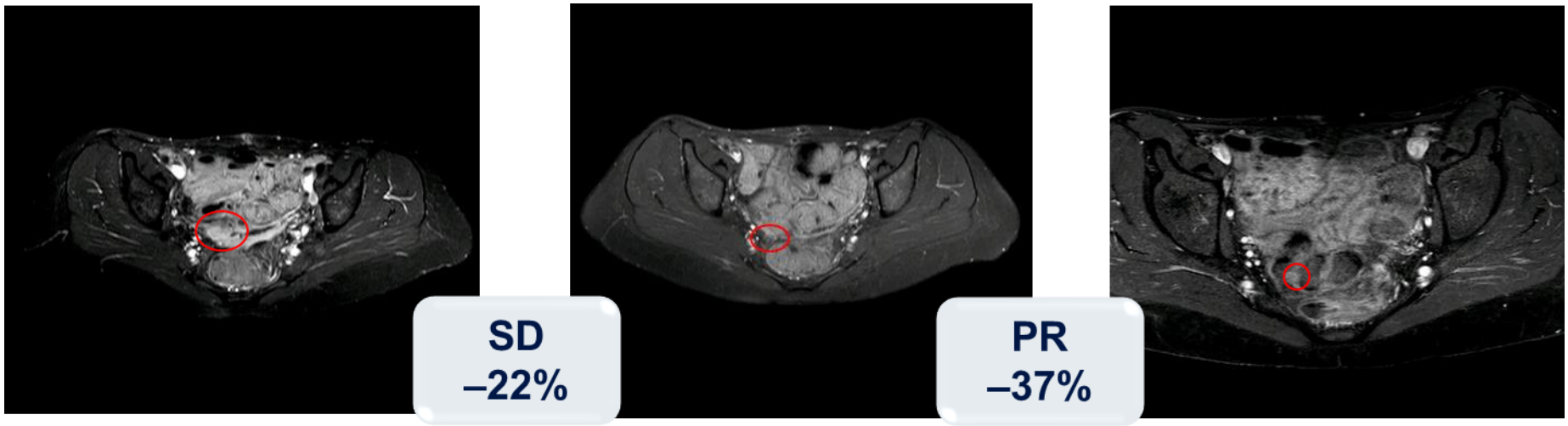
(as of 15 February 2013)	BKM 60mg + GSK 1mg N=1 n (%)	BKM 60mg + GSK 1.5mg N=8 n (%)	BKM 70mg + GSK 1.5mg N=12 n (%)	All patients N=21 n (%)
Overall response rate (CR or PR)	0	4 (50.0)	2 (16.7)	6 (28.6)
90 % Confidence interval*	[0.0; 95.0]	[19.3; 80.7]	[3.0; 43.8]	[13.2; 48.7]
Overall response rate (including unconfirmed CR/PR)	0	4 (50.0)	3 (25.0)	7 (33.3)
90 % Confidence interval*	[0.0; 95.0]	[19.3; 80.7]	[7.2; 52.7]	[16.8; 53.6]

* Estimate (90% CI) for ORR was obtained using exact binomial 90% confidence interval test

Ovarian cancer: patient 0001-0102 - 31 years

Initial diagnosis: Borderline serous ovarian cancer with invasive peritoneal implants

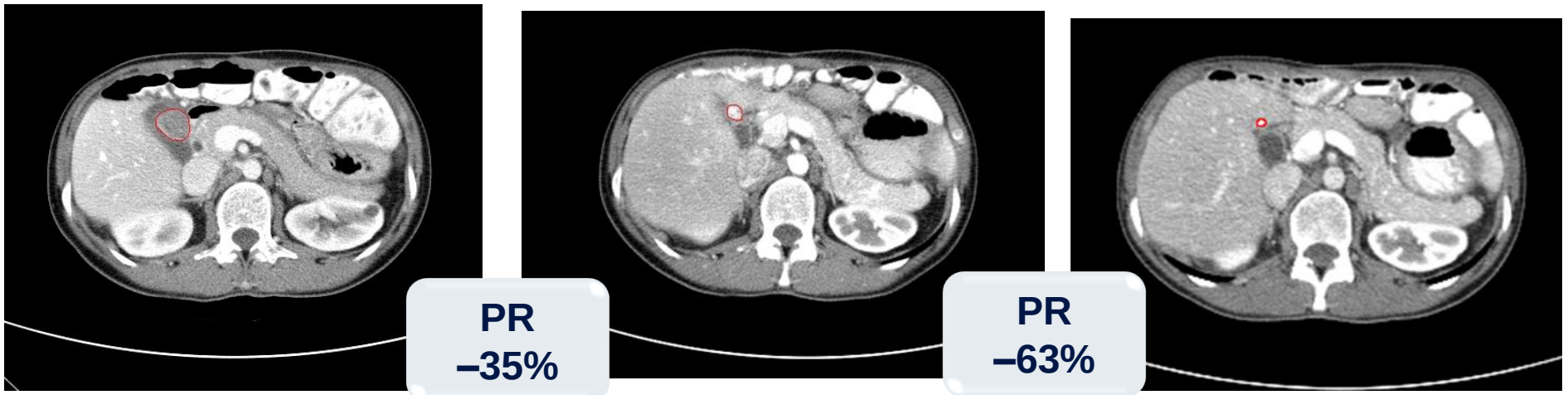
- TAHBSO followed by Platinum based CT (6 cycles)
- Inc. of CA125, lymphadenectomy: nodal metastasis, peritoneal washings
- Invasive low grade G12V *KRAS*-mutant ovarian cancer
- C1 Starting dose BKM 60 mg + GSK 1.0 mg → 60 mg + 0.5 mg*→ 30mg + 0.5 mg**
- Treatment discontinued after 24 cycles for PD



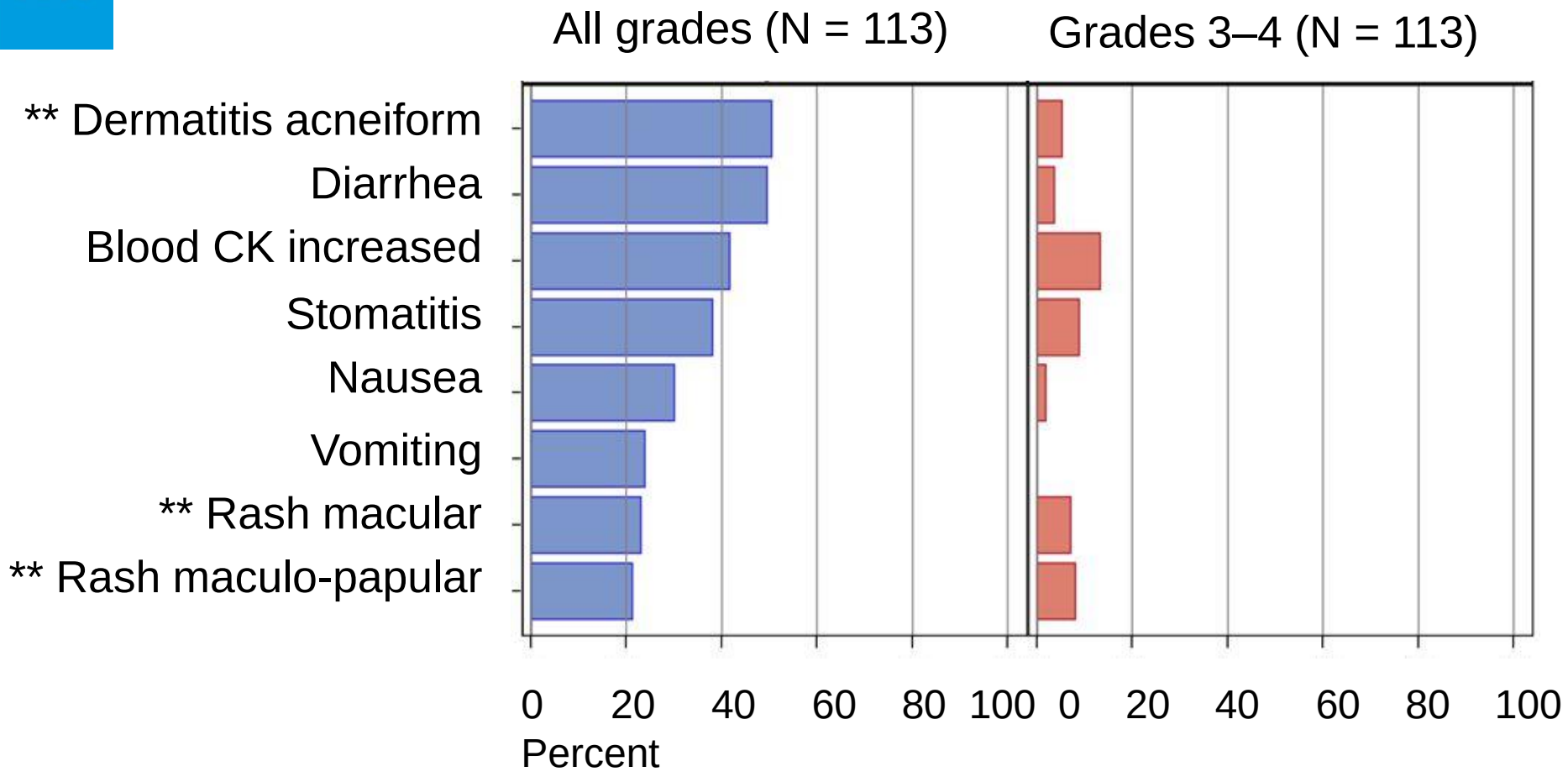
Ovarian cancer: patient 0001-0105 – 35 years

Initial diagnosis: Borderline serous ovarian cancer with non invasive peritoneal implants

- TAHBSO followed by single agent Carboplatin
- Peritoneal recurrence surgically assessed : invasive peritoneal implants low grade G12V *KRAS*-mutant ovarian cancer
- Repeated resections followed by platinum based adjuvant CTs
- C1 Starting dose BKM 60 mg + GSK 1.5 mg → 60 mg + 1.0 mg*
- Off study due to PD after 19 cycles, subcutaneous KRAS mut nodule



Most Common Treatment-related AEs (>20%): All Patients*



* as of 15 February 2013

** ~80% patients experienced skin-related toxicities, such as dermatitis acneiform, rash, and maculopapular rash, irrespective of causality

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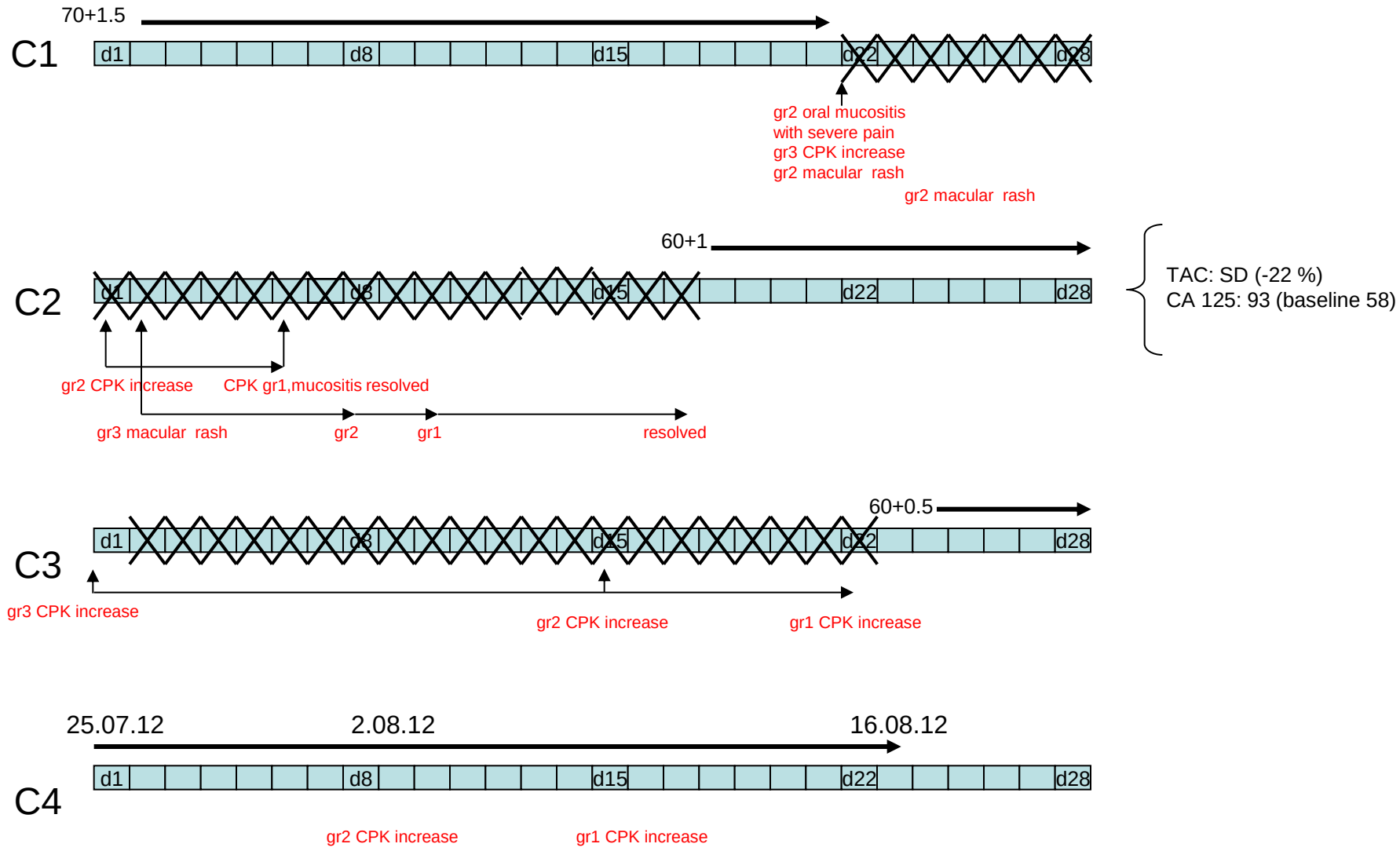
70+1.5
C1
d1
d8
d15
d22
d28
gr2 oral mucositis
with severe pain
gr3 CPK increase
gr2 macular rash
gr2 macular rash
60+1
C2
d1
d8
d15
d22
d28
TAC: SD (-22 %)
CA 125: 93 (baseline 58)
gr2 CPK increase
CPK gr1,mucositis resolved
gr3 macular rash
gr2
gr1
resolved
60+0.5
C3
d1
d8
d15
d22
d28
gr3 CPK increase
gr2 CPK increase
gr1 CPK increase
25.07.12
2.08.12
16.08.12
C4
d1
d8
d15
d22
d28
gr2 CPK increase
gr1 CPK increase

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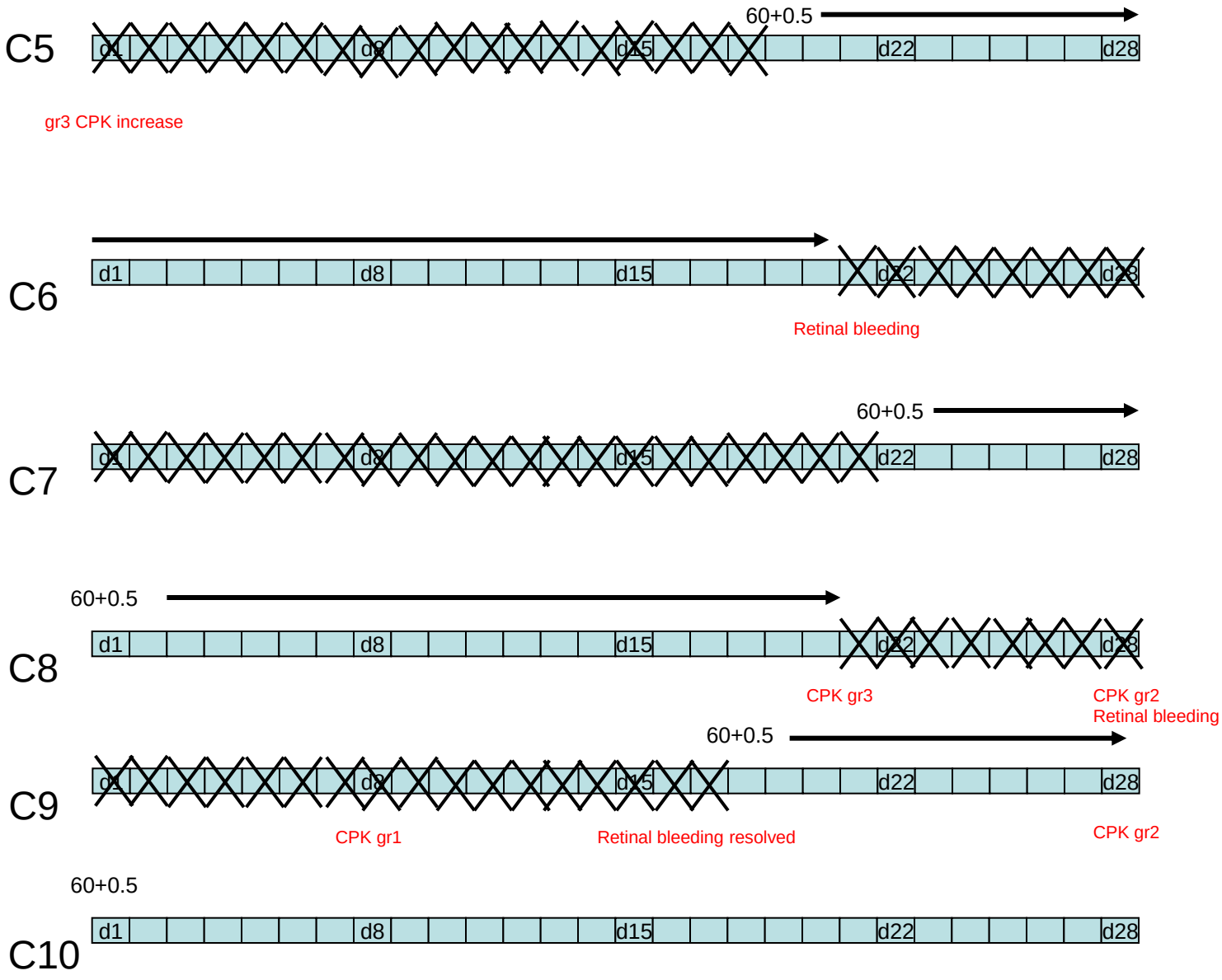
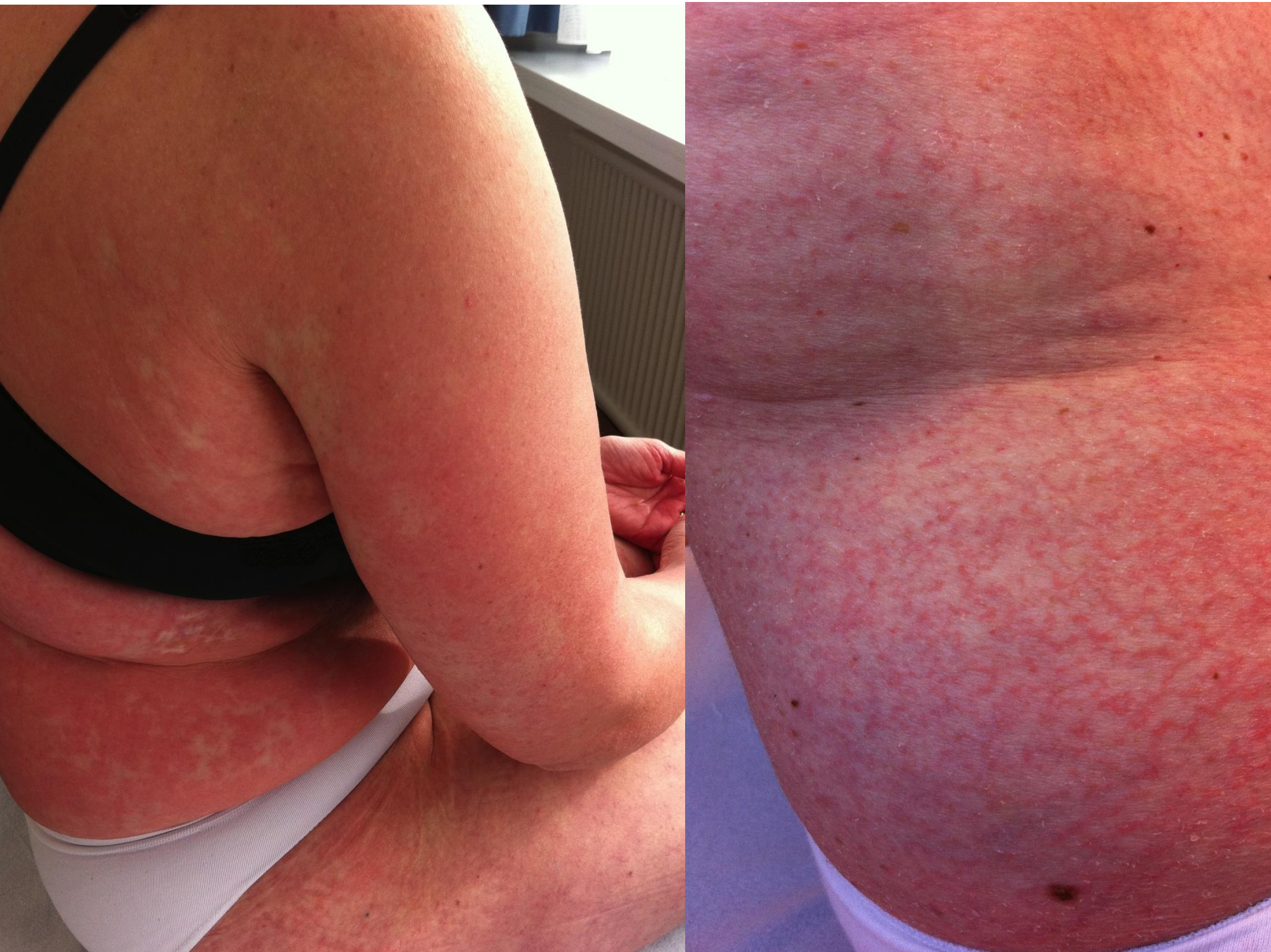
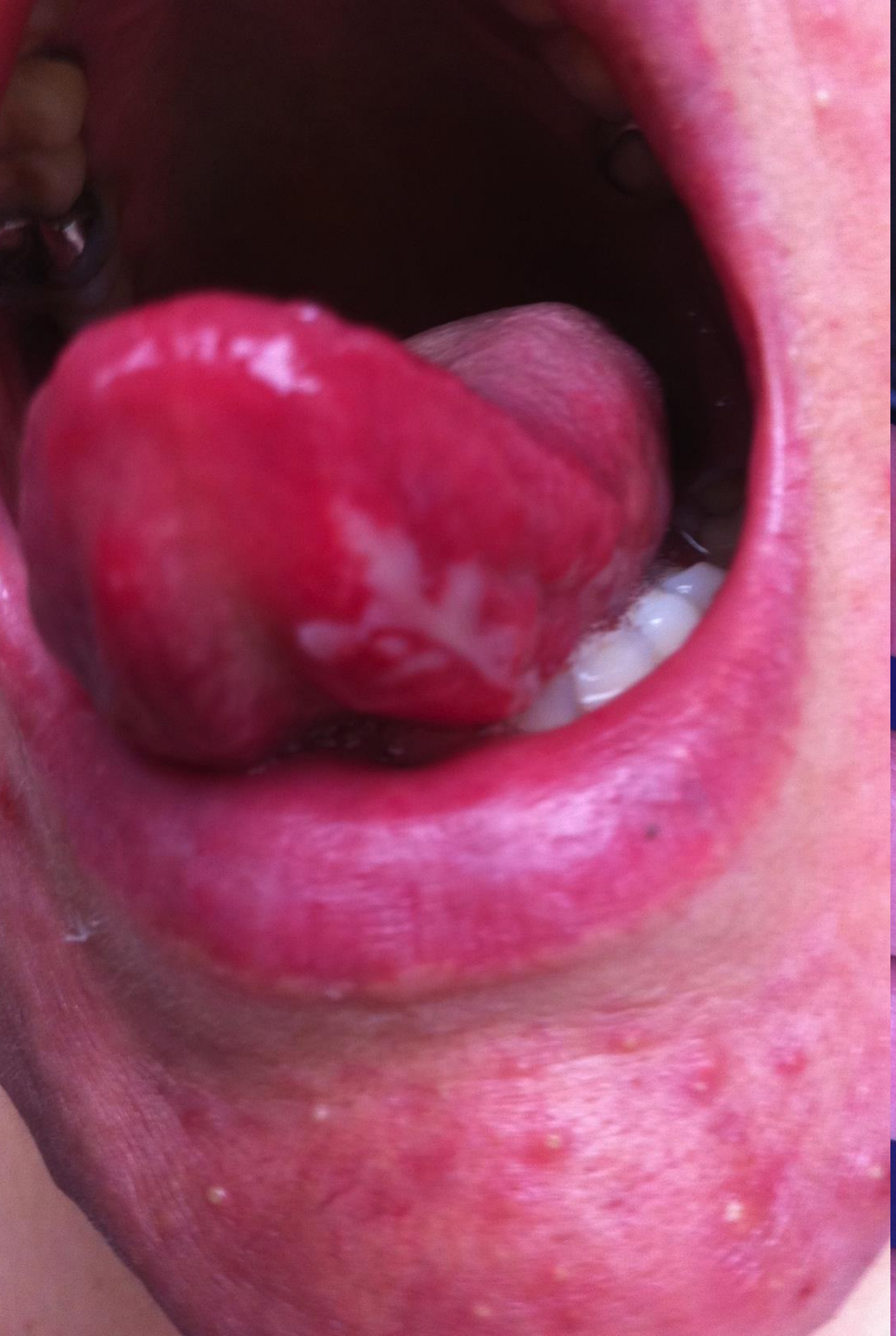
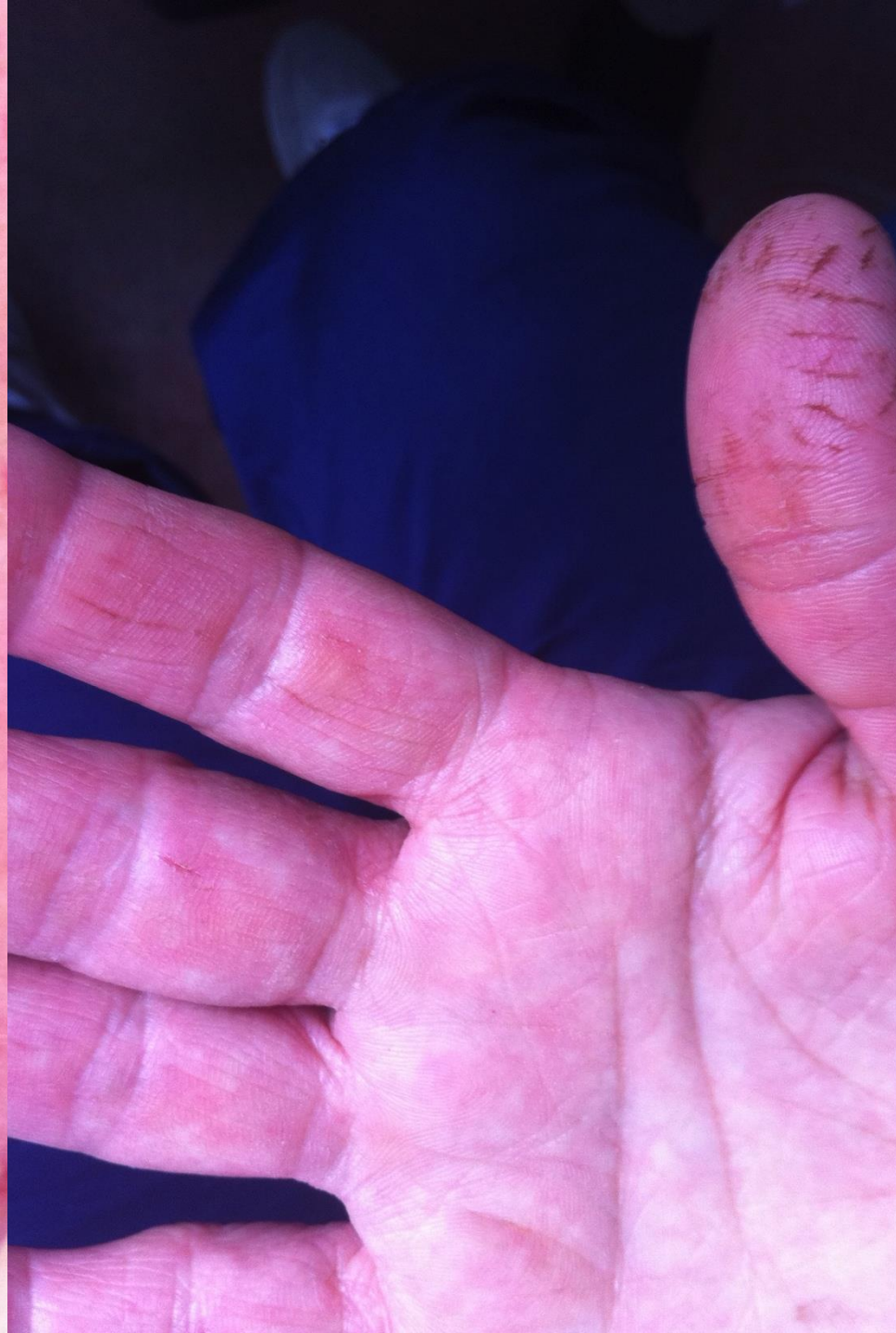
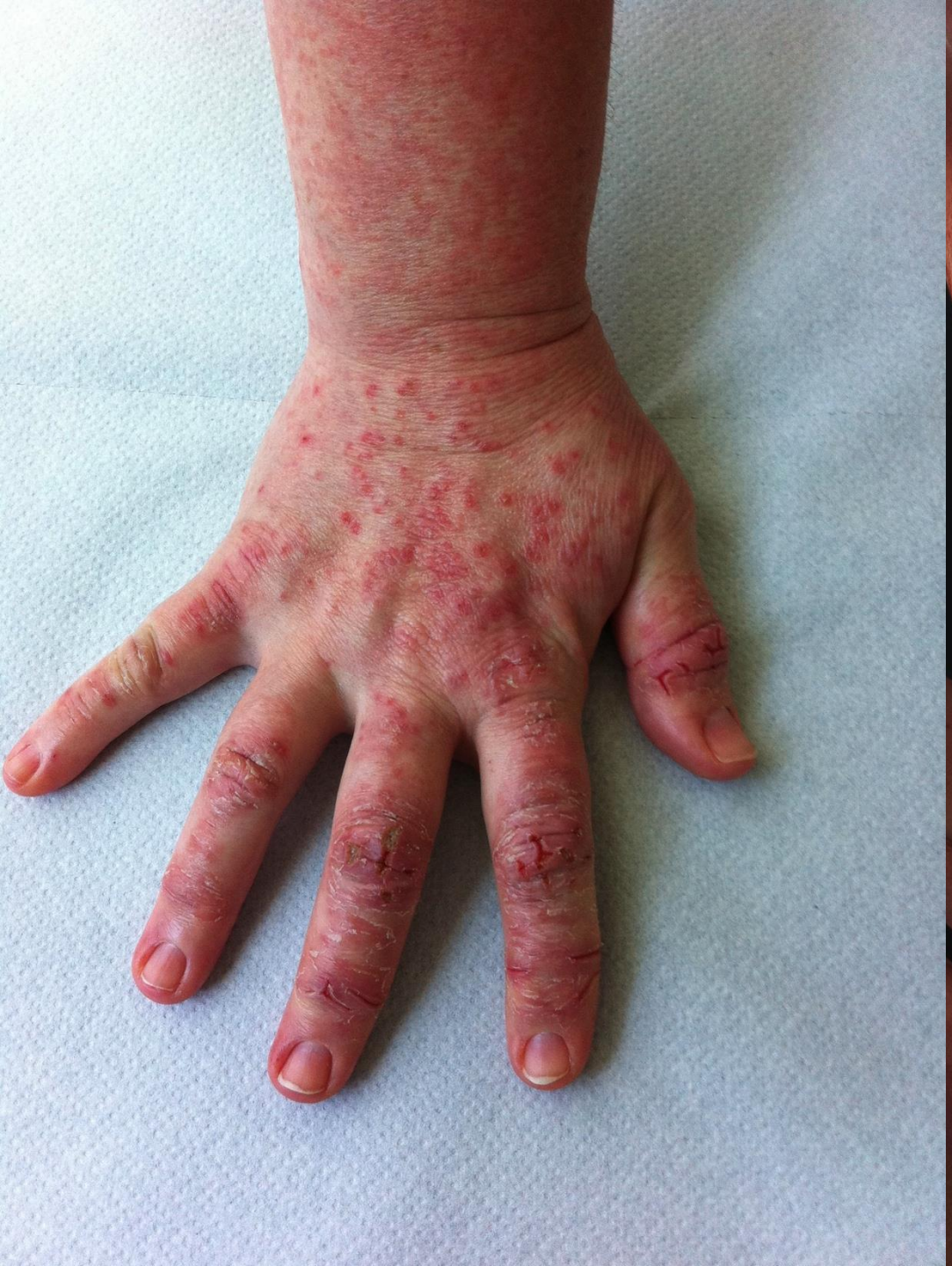
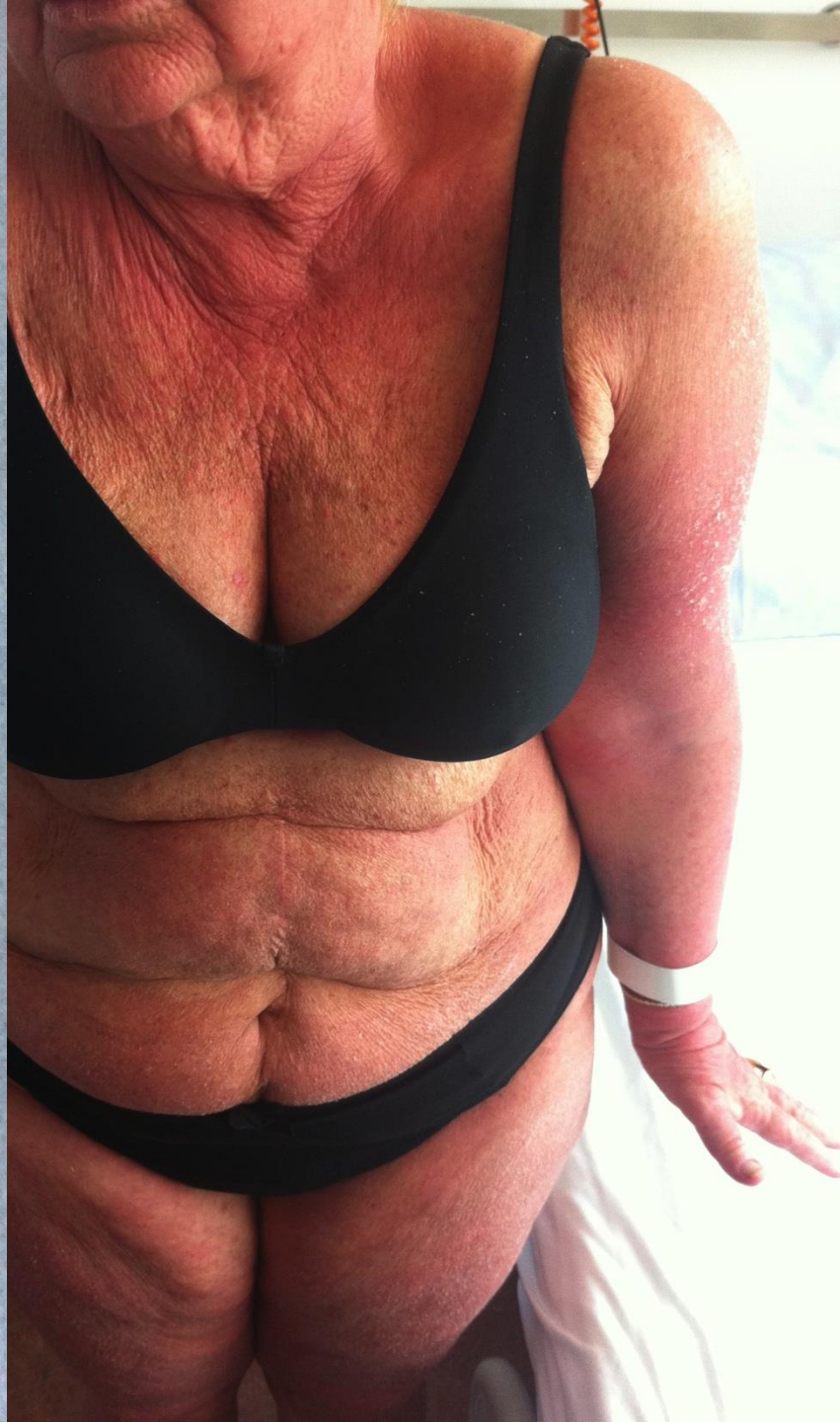

C5
60+0.5
d1
d8
d15
d22
d28
gr3 CPK increase
C6
d1
d8
d15
d22
d28
Retinal bleeding
C7
60+0.5
d1
d8
d15
d22
d28
C8
60+0.5
d1
d8
d15
d22
d28
CPK gr3
CPK gr2
Retinal bleeding
C9
60+0.5
d1
d8
d15
d22
d28
CPK gr1
Retinal bleeding resolved
CPK gr2
C10
60+0.5
d1
d8
d15
d22
d28

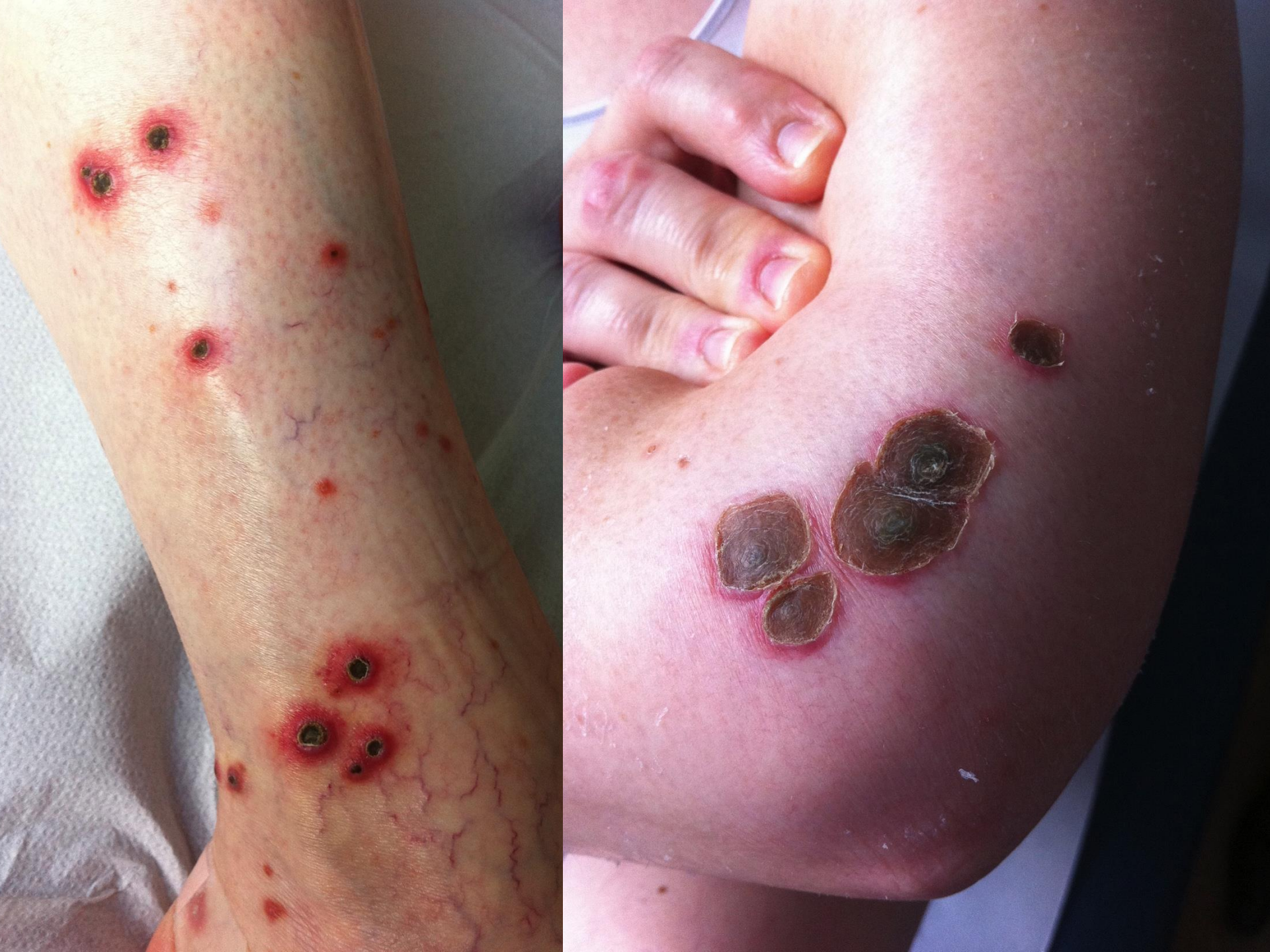












Guidelines for the management of skin toxicity

Maculopapular rash (PI3Ki induced)

Grade	Study drugs	Treatment
Mild (CTAEG1)	Continue	Topical with steroids or antibiotics
Moderate (CTAEG2)	Continue	As for G1 + PO steroids ± PO antibiotics
Severe (CTAEG3)	Discontinue until G≤1 then dose ↓	As for G2

Guidelines for the management of skin toxicity

Acneiform rash (MEKi induced)

Grade	Study drugs	Treatment
Mild (CTAEG1)	Continue	Topical with steroids
Moderate (CTAEG2)	Continue	As for G1 + PO antibiotics
Severe (CTAEG3)	Discontinue until G≤1 then dose ↓	As for G2

Guidelines for the management of skin toxicity

Pruritus

Grade	Study drugs	Treatment
Mild (CTAEG1)	Continue	Topical with antihistamines and steroids
Moderate (CTAEG2)	Continue	As for G1 antihistamines or GABA antagonists
Severe (CTAEG3)	Discontinue until G≤1 then dose ↓	As for G2 + PO Doxepin

Phase IB of buparlisib (BKM120) in combination with trametinib (GSK1120212) in patients with selected advanced solid tumors

Conclusions

- Buparlisib and trametinib can be used in combination with manageable toxicity. Main toxicities: skin, GI, CK elevation and stomatitis

- The MTD was 70mg buparlisib + 1.5mg trametinib, the RP2D 60mg buparlisib + 1.5mg trametinib

- Skin toxicities accounted for treatment interruptions and dose reductions, most frequently observed after cycle 1 and only partially controlled in spite of common specific management guidelines

- Promising clinical efficacy has been observed in BRAF/RAS mutated ovarian cancer patients