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SKIN TOXICITIES

RELATED TO TARGETED THERAPY IN GI AND LIVER ONCOLOGY

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INTRODUCTION

- Welcome to this educational programme on skin toxicities related to targeted therapy in gastrointestinal (GI) and liver oncology
- This programme has been developed by a panel of experts:
  - **Dr Catherine Frenette**, hepatologist from San Diego, USA
  - **Dr Victor Hugo Fonseca de Jesus**, medical oncologist from São Paulo, Brazil
  - **Natasha Pinheiro**, nurse practitioner from New York, USA
  - **Dr Nicole LeBoeuf,** dermatologist from Boston, USA
- Targeted therapies result in more dermatologic adverse events (AEs) than do non-targeted therapies[1]
- Dermatologic AEs may lead to dosing changes and both physical and psychological discomfort or pain[2]. These events have a considerable economic burden and increase the risk of total treatment interruption, potentially leading to cancer exacerbation[2,3]
- Pre-emptively addressing and treating potential skin toxicities may improve patients' quality of life and allow them to remain longer on therapy[2]
- Upon completion of this educational programme you will:
  - understand adverse skin reactions to targeted therapy in GI and liver cancers
  - know how to prevent and manage skin toxicities associated with targeted therapies in GI and liver cancers
  - be able to involve a multidisciplinary team in the prevention, diagnosis, and management of skin toxicities associated with targeted therapy in GI and liver cancers

The magnifying glass symbol appears on a number of slides within this slide set to indicate more detailed information on a particular topic or area.

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AE, adverse event

1. Guztmer R, et al. Dtsch Arztebl Int. 2012;109:133-40. 2. Joshi SS, et al. Cancer. 2010;116:3916-23. 3. Borovicka JH, et al. Arch Dermatol. 2011;147:1403-9.

CONTENTS

INTRODUCING THE **SCIENTIFIC COMMITTEE**

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NATASHA PINHEIRO,

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- Active member of ONS
- **Member of GI NURSES CONNECT**

DR NICOLE LEBOEUF,

Dermatologist, Harvard Medical School, Boston, USA

- Director of the Program in Skin Toxicities for Anticancer Therapy
- Clinical Director of Cutaneous Oncology
- Assistant Professor of Dermatology at Harvard Medical School
- **Honorary collaborator with the CONNECTs groups**

AGA, American Gastroenterology Association; AST, American Society of Transplantation; GI, gastrointestinal; HCC, hepatocellular carcinoma; ONS, Oncology Nursing Society

WHAT WILL **YOU LEARN?**

Understand skin toxicities associated with targeted therapy in GI and liver cancers

Know how to prevent and manage skin toxicities associated with targeted therapies in GI and liver cancers

Be able to **involve a multidisciplinary team** in the prevention, diagnosis, and management of skin toxicities associated with targeted therapy in GI and liver cancers

GI, gastrointestinal

SKIN TOXICITY

ASSOCIATED WITH TARGETED THERAPY

1

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LEARNING OBJECTIVE

UNDERSTAND SKIN TOXICITY ASSOCIATED WITH TARGETED THERAPY IN GI AND LIVER CANCERS

WHAT
WILL YOU LEARN?

- **What skin toxicity may occur during treatment with targeted therapy in GI and liver cancers**

WHY
IS THIS IMPORTANT?

- **By knowing what skin toxicity to expect, you will be able to:**
  - **better educate patients and carers**
  - **diagnose and treat skin reactions at an earlier stage**
  - **maintain an appropriate dose and duration of therapy**

GI, gastrointestinal

ADVERSE EVENTS
ARE MOST COMMONLY GRADED USING THE CTCAE

- **AEs are defined as** any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure
- The Common Terminology Criteria for Adverse Events (CTCAE) are used to grade AEs
  - Version 5.0 was published in November 2017 by the U.S. Department of Health and Human Services

GRADE 1
Mild

- Asymptomatic or mild symptoms
- Clinical or diagnostic observations only
- Intervention not indicated

GRADE 2
Moderate

- Limiting age-appropriate instrumental activities of daily living (ADL)*
- Minimal, local, or non-invasive intervention indicated

GRADE 3
Severe or medically significant, but not immediately life-threatening

- Limiting self-care ADL**
- Disabling
- (Prolongation of) hospitalisation indicated

GRADE 4
Life-threatening consequences

- Urgent intervention indicated

GRADE 5
Death related to AE

*Instrumental ADL are preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL are bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ADL, activities of daily living

National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.)

MESTT CAN BE USED TO GRADE EFGR-INHIBITOR **RELATED SKIN TOXICITY IN THE TRIAL SETTING**

- The Multinational Association for Supportive Care in Cancer (MASCC) EGFR Inhibitor Skin Toxicity Tool (MESTT) is a grading system specific for skin toxicity related to EGFR inhibitors[1,2]
- The complexity of the MESTT makes it unsuitable for routine clinical use,[2] but it is relevant in the trial setting

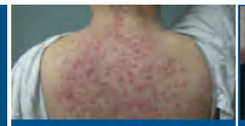
Grading EGFR-inhibitor related acneiform rash with the MESTT[1]

Acneiform rash, description	Grade 1		Grade 2		Grade 3	
	1A	1B	2A	2B	3A	3B
Papulopustular eruption (grade individually for face, scalp, chest, and back)	• < 5 papules or pustules OR • 1 area of erythema or oedema < 1 cm in size	• < 5 papules or pustules OR • 1 area of erythema or oedema < 1 cm in size AND pain or pruritus	• 6–20 papules or pustules OR • 2–5 areas of erythema or oedema < 1 cm in size	• 6–20 papules or pustules OR • 2–5 areas of erythema or oedema < 1 cm in size AND pain, pruritus, or effect on emotions or functioning	• > 20 papules or pustules OR • > 5 areas of erythema or oedema < 1 cm in size	• > 20 papules or pustules OR • > 5 areas of erythema or oedema < 1 cm in size AND pain, pruritus, or effect on emotions or functioning

EGFR, epidermal growth factor receptor; MESTT, MASCC EGFR inhibitor Skin Toxicity Tool

1. Lacouture ME, et al. Support Care Cancer. 2010;18:509-22. 2. Hofheinz R-D, et al. Oncologist. 2016;21:1483-91.

SKIN TOXICITIES **BY DRUG CLASS ANY GRADE**

Drug class	Examples	 Papulopustular rash	 Maculopapular rash	 HFSR	 Dry skin, pruritus, or photosensitivity	 Changes in nails, hair, or mucosa	 Poor wound healing	 Cutaneous malignancies
EGFR inhibitors	cetuximab[1] erlotinib[2] panitumumab[3]	++	+/–	–	++	+	–	–
MKIs	sorafenib[4] sunitinib[5] regorafenib[6] lenvatinib[7] cabozantinib[8] avapritinib[9]	+	+/–	++	+	+	++	–
VEGF(R) inhibitors	bevacizumab[10] aflibercept[11] ramucirumab[12]	–	+/–	–	+	+	++	–
BCR–ABL TKIs	imatinib[13] nilotinib*[14] dasatinib*[15]	+	+/–	–	+	+	–	–
BRAF inhibitors	encorafenib[16]	++	+/–	+	++	+	–	+

This table is based on the listed drugs' Prescribing Information and the clinical experience of the Scientific Committee.

At the time of creation of this educational programme, the PARP inhibitor olaparib was approved for use in pancreatic cancer. As PARP inhibitors are generally not associated with skin toxicity, it was considered out of scope.

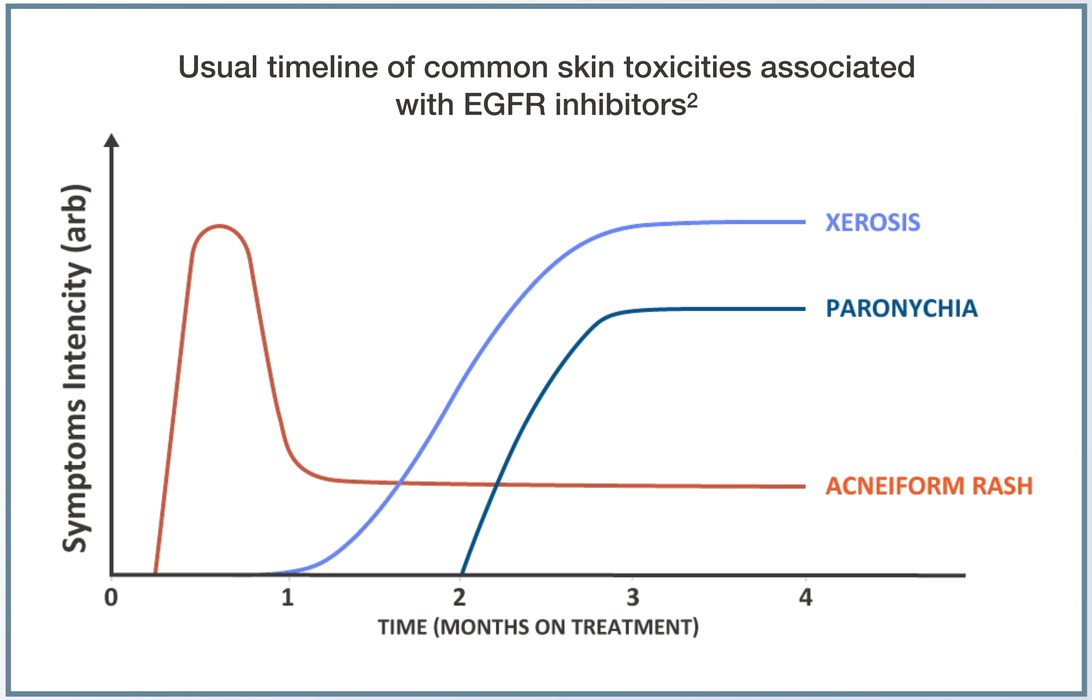
++ very common
+ common
+/– uncommon
– rare

*Not approved for use in GI or liver cancers but sometimes used off label in patients with GIST.

1. Erbitux (cetuximab) Prescribing Information. 2. Tarceva (erlotinib) Prescribing Information. 3. Vectibix (panitumumab) Prescribing Information. 4. Nexavar (sorafenib) Prescribing Information. 5. Sutent (sunitinib) Prescribing Information. 6. Stivarga (regorafenib) Prescribing Information. 7. Lenvima (lenvatinib) Prescribing Information. 8. Cabometyx (cabozantinib) Prescribing Information. 9. Ayvakit (avapritinib) Prescribing Information. 10. Avastin (bevacizumab) Prescribing Information. 11. Zaltrap (aflibercept) Prescribing Information. 12. Cyramza (ramucirumab) Prescribing Information. 13. Gleevec (imatinib) Prescribing Information. 14. Tasigna (nilotinib) Prescribing Information. 15. Sprycel (dasatinib) Prescribing Information.
16. Braftovi (encorafenib) Prescribing Information.

EGFR INHIBITORS ARE MOST OFTEN ASSOCIATED **WITH PAPULOPUSTULAR RASH, DRY SKIN, AND PRURITUS**

- Skin toxicity occurs in about 90% of patients treated with EGFR inhibitors, and 10–20% of patients experience grade 3 or 4 toxicity[1]
- The earliest and most common skin AE is **papulopustular rash**, which develops in 60–80% of patients, usually within the first 2 weeks[2]
- Other common skin toxicities include dry skin, pruritus, and nail and hair abnormalities[1–5]



AE, adverse event; EGFR, epidermal growth factor receptor.

1. Lacouture ME, et al. Clin Colorectal Cancer. 2018;17: 85-96. 2. Beech J, et al. Future Oncol. 2018;14:2531-41. 3. Erbitux (cetuximab) Prescribing Information. 4. Tarceva (erlotinib) Prescribing Information. 5. Vectibix (panitumumab) Prescribing Information.

COMMON SKIN TOXICITIES WITH EGFR INHIBITORS

IN GI AND LIVER CANCERS, AS REPORTED IN THE PRESCRIBING INFORMATION

Skin AEs reported in ≥ 10% of patients in clinical trials: % any grade (% grade ≥ 3)

Category	AE	cetuximab in CRC[1]			erlotinib in pancreatic cancer[2]	panitumumab in CRC[3]	
		cetuximab	cetuximab + FOLFIRI	cetuximab + irinotecan*	erlotinib + gemcitabine	panitumumab	panitumumab + FOLFOX
Skin	Rash	95 (16)	86 (18)	88 (14)	70 (5)	18–57 (1–7)	32–56 (10–17)
	Acne		14 (2)			14 (1)	14 (3)
	Erythema					66 (6)	16 (2)
	Pruritus	47 (2)	14 (0)			58 (3)	23 (< 1)
	Dry skin	57 (0)	22 (0)			10 (0)	21 (2)
	HFS		19 (4)				9 (1)
	Skin fissures		19 (2)			20 (1)	16 (< 1)
Nails	Nail disorder or changes	31 (0)				10 (0)	10 (1)
	Paronychia		20 (4)			25 (2)	21 (3)
Hair	Alopecia						15 (0)
Mucosa	Stomatitis or mucositis	32 (1)	31 (3)		22 (< 1)	7 (< 1)	25-27 (4–5)

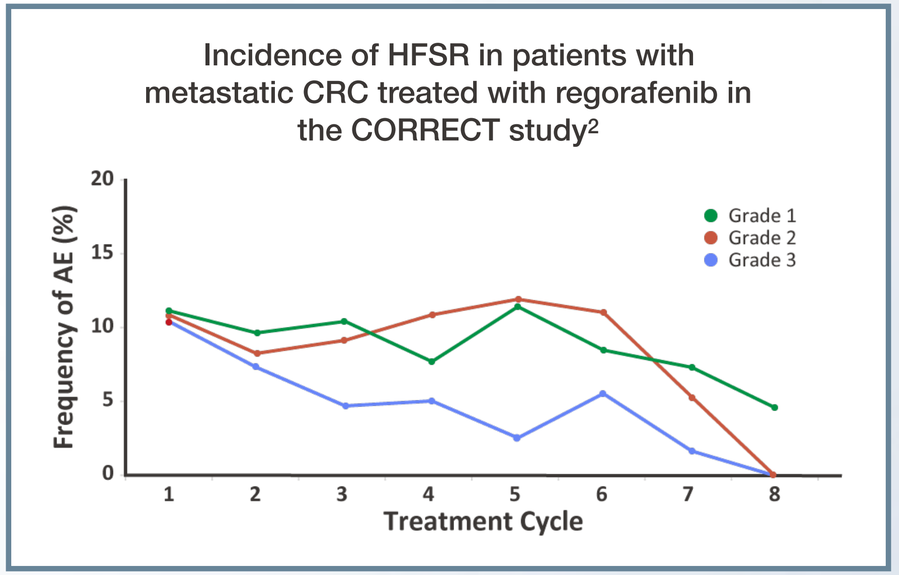
This table is not intended for between-drug comparisons.
*The Prescribing Information reports only the most common AEs.

AE, adverse event; CRC, colorectal cancer; FOLFIRI, leucovorin calcium (calcium folinate), 5-fluorouracil, and irinotecan; FOLFOX, leucovorin calcium (calcium folinate), 5-fluorouracil, and oxaliplatin; GI, gastrointestinal; HFS, hand–foot syndrome

1. Erbitux (cetuximab) Prescribing Information. 2. Tarceva (erlotinib) Prescribing Information. 3. Vectibix (panitumumab) Prescribing Information.

THE MOST NOTABLE SKIN TOXICITY
WITH MKIs IS HAND–FOOT SKIN REACTION (HFSR)

- Skin toxicities are very common during treatment with MKIs, although the incidence of individual skin toxicities differs depending on the drug and tumour indication[1]
- The most notable skin toxicity with MKIs is **HFSR**[1]



1 cycle: 3 weeks on therapy followed by 1 week off therapy. Treatment continued until there was no more clinical benefit or unacceptable toxicity occurred.

CRC, colorectal cancer; HCC, hepatocellular carcinoma; HFSR, hand–foot skin reaction; MKI, multiple kinase inhibitor.

1. Guztmer R, et al. Dtsch Arztebl Int. 2012;109:133-40. 2. Grothey A, et al. Poster presented at ASCO Annual Meeting I, 2013. J Clin Oncol. 2013;31:15 suppl.3637.

COMMON SKIN TOXICITIES WITH MKIs

IN GI AND LIVER CANCERS, AS REPORTED IN THE PRESCRIBING INFORMATION

Skin AEs reported in ≥ 10% of patients in clinical trials: % any grade (% grade ≥ 3)

Category	AE	sorafenib in HCC[1]	sunitinib in GIST[2]	sunitinib in pancreatic NET[2]	regorafenib in CRC[3]	regorafenib in HCC[3]	regorafenib in GIST[3]	lenvatinib in HCC[4]	cabozantinib in HCC[5]	avapritinib in GIST[6]
Skin	HFSR	21 (8)	14 (4)	23 (6)	45 (17)	51 (12)	67 (22)	27 (3)	46 (17)	
	Rash	19 (1)	14 (1)	18 (0)	26 (6)		30 (7)	14 (0)	21 (2)	23 (2)
	Pruritus	14 (< 1)								
	Dry skin	10 (0)		15 (0)						
	Skin discolouration		30 (0)							
Hair	Alopecia	14 (0)					24 (2)			13
	Hair colour changes			29 (1)						21 (< 1)
Mucosa	Mucositis or stomatitis		29 (1)	48 (6)	33 (4)	13 (1)	40 (2)	11 (< 1)	13–14 (2)	
Wound healing	Impaired wound healing	Not reported in ≥ 10% of patients in clinical trials but identified during post-marketing experience and/or warnings included in Prescribing Information								

This table is not intended for between-drug comparisons.

AE, adverse event; CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HFSR, hand–foot skin reaction; MKI, multiple kinase inhibitor.

1. Nexavar (sorafenib) Prescribing Information. 2. Sutent (sunitinib) Prescribing Information. 3. Stivarga (regorafenib) Prescribing Information. 4. Lenvima (lenvatinib) Prescribing Information. 5. Cabometyx (cabozantinib) Prescribing Information. 6. Ayvakit (avapritinib) Prescribing Information.

VEGF(R) INHIBITORS ARE MOST OFTEN **ASSOCIATED WITH POOR WOUND HEALING**

- Cutaneous side-effects do not dominate the safety profile of VEGF(R) inhibitors[1]
  - VEGF(R) inhibitors are often combined with chemotherapeutic agents, so statements on frequencies of AEs must be viewed with caution because the event may be related to the chemotherapeutic agent, not the VEGF(R) inhibitor
- **Impaired wound healing** is the main skin-related AE seen with VEGF(R) inhibition[1–4]

The Prescribing Information on each VEGF(R) inhibitor contains warnings about impaired wound healing[2–4]

- Discontinue the VEGF(R) inhibitor in patients with wound-healing complications
  - …that require medical intervention (ramucirumab and bevacizumab)
  - …or necrotizing fasciitis (bevacizumab)
- Do not administer the VEGF(R) inhibitor for at least 28 days after surgery, until the wound is fully healed
- Withhold the VEGF(R) inhibitor for 28 days before elective surgery

AE, adverse event; VEGFR, vascular endothelial growth factor receptor.

1. Wozel G, et al. J Dtsch Dermatol Ges. 2010;8:243-9. 2. Avastin (bevacizumab) Prescribing Information. 3. Zaltrap (aflibercept) Prescribing Information. 4. Cyramza (ramucirumab) Prescribing Information.

COMMON SKIN TOXICITIES WITH VEGF(R) INHIBITORS IN GI AND **LIVER CANCERS, AS REPORTED IN THE PRESCRIBING INFORMATION**

Skin AEs reported in clinical trials: % any grade (% grade ≥ 3)

Category	AE	bevacizumab in CRC[1]*	bevacizumab in HCC[2]**	aflibercept in CRC[3]	ramucirumab in gastric cancer[4]		ramucirumab in CRC[4]	ramucirumab in HCC[4]
			bevacizumab + atezolizumab	aflibercept + FOLFIRI	ramucirumab	ramucirumab + paclitaxel	ramucirumab + FOLFIRI	
Skin	Exfoliative dermatitis	> 10						Only AEs occurring in ≥ 10% of patients reported; no skin AEs
	Dry skin	> 10						
	HFS		2	11 (3)†			13 (1)†	
	Skin hyperpigmentation			8 (0)†				
Mucosa	Stomatitis			50 (13)†		20 (1)†	31 (4)†	
Hair	Alopecia		2					
Wound healing	Impaired wound healing	15		0.3 (and evidence from animal studies)	"can occur"			

This table is not intended for between-drug comparisons.

*Only the most common any-grade AEs across indications are reported (no CRC-specific data).
**Bevacizumab + atezolizumab is not yet approved for use in HCC.
† These AEs were most probably related to the chemotherapeutic agent.

AE, adverse event; CRC, colorectal cancer; FOLFIRI, leucovorin calcium (calcium folinate), 5-fluorouracil, and irinotecan; GI, gastrointestinal; HCC, hepatocellular carcinoma; HFS, hand–foot syndrome.

1. Avastin (bevacizumab) Prescribing Information. 2. Cheng A-L, et al. Oral presentation at ESMO Asia 2019. Ann Oncol. 2019;30 suppl 9:ix183-202. 3. Zaltrap (aflibercept) Prescribing Information. 4. Cyramza (ramucirumab) Prescribing Information.

BCR–ABL TKIs ARE ASSOCIATED **WITH RASH AND PIGMENTARY CHANGES**

- **Rash** is a common side-effect of BCR–ABL TKIs[1–3]
  - It is usually mild and self-limiting and responds well to topical treatment[4]
  - However, later-generation BRC–ABL TKIs, such as ponatinib, can cause more significant skin reactions, including pityriasis rubra pilaris-like, hyperkeratotic, folliculocentric, and ichthyosiform rash[5]
- BCR–ABL TKIs are also associated with **pigmentary changes**, including both hypo- and hyperpigmentation of the skin

BCR–ABL, Philadelphia translocation; TKI, tyrosine kinase inhibitor.

1. Gleevec (imatinib) Prescribing Information. 2. Tasigna (nilotinib). Prescribing Information. 3. Sprycel (dasatinib) Prescribing Information. 4. Scott LC, et al. Sarcoma. 2005;9:157-60. 5. Alloo A, et al. Br J Dermatol. 2015;173:574-7.

COMMON SKIN TOXICITIES WITH BCR–ABL TKIs
IN GI CANCERS, AS REPORTED IN THE PRESCRIBING INFORMATION

Skin AEs reported in ≥ 5% of patients in clinical trials: % any grade (% grade ≥ 3)

Category	AE	imatinib in GIST[1]			nilotinib in GIST[2]*	dasatinib in GIST[3]**
		imatinib 400 mg	imatinib 800 mg	imatinib as adjuvant treatment		
Skin	Rash or dermatitis	38 (8)	50 (9)	9–39 (< 1–3)	27 (1)	11–21 (0–2)
	Pruritus	15 (5)	19 (4)	11–13 (< 1)	13 (0)	12 (1)
	Dry skin			7 (< 1)		
	Photosensitivity reaction			7 (0)		
Mucosa	Stomatitis or pharyngitis	9 (5)	10 (4)	5 (< 1)		
Hair	Alopecia	12 (4)	15 (3)	10–11 (0)	10 (0)	

This table is not intended for between-drug comparisons.

*Not FDA approved. Clinical trial data shown.
**Not FDA approved. Insufficient clinical trial data available. Data on other (adult) indications shown, as listed in the Prescribing Information.

AE, adverse event; BCR–ABL, Philadelphia translocation; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor.

1. Gleevec (imatinib) Prescribing Information. 2. Blay J-Y, et al. Lancet Oncol. 2015;16:550-60. 3. Sprycel (dasatinib) Prescribing Information.

BRAF INHIBITORS ARE ASSOCIATED **WITH RASH AND CUTANEOUS MALIGNANCIES**

- The BRAF inhibitor encorafenib was already used in melanoma, but in April 2020 it was approved by the FDA for use in combination with cetuximab in patients with metastatic CRC and a BRAF V600E mutation[1]
- **Rash** is a common side-effect of BRAF inhibitors[1]
- **Cutaneous malignancies** have been reported during the use of BRAF inhibitors[1,2]
  - In the BEACON CRC study, in which patients with CRC received encorafenib + cetuximab, cutaneous squamous cell carcinomas, including keratoacanthoma, occurred in 1.4% and a new primary melanoma occurred in 1.4% of patients[2]

CRC, colorectal cancer; BRAF, v-raf murine sarcoma viral oncogene homolog B1; FDA, U.S. Food and Drug Admninstration.

1. Braftovi (encorafenib) Prescribing Information. 2. Kopetz S, et al. N Engl J Med. 2019;381:1632-1643.

COMMON SKIN TOXICITIES WITH BRAF INHIBITORS
IN GI CANCERS, AS REPORTED IN THE PRESCRIBING INFORMATION

Skin AEs reported in clinical trials: % any grade (% grade ≥ 3)

Category	AE	encorafenib + cetuximab in CRC[1,2]
Skin	Rash or acneiform dermatitis	26–32 (0–1)
	Pruritus	14 (0)
	Dry skin	13 (0)
	Melanocytic naevus	14 (0)
	HFSR*	4 (<1)
Mucosa	Stomatitis*	6 (0)

The rates of skin toxicity with encorafenib in CRC are potentially confounded by the co-administration of cetuximab.

*Not included in Prescribing Information. Clinical trial data shown.

AE, adverse event; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CRC, colorectal cancer; GI, gastrointestinal; HFSR, hand–foot skin reaction.

1. Braftovi (encorafenib) Prescribing Information. 2. Kopetz S, et al. N Engl J Med. 2019;381:1632-1643.

PAPULOPUSTULAR RASH

Symptoms[1–3]	Location[1–3]	Onset	Incidence	Differential diagnosis[3]
• **Itching and burning erythematous follicular papules that may evolve into pustules** ✦ Can be accompanied by telangiectasia, diffuse erythema, and pain	• Usually confined to the **seborrhoeic areas** (face, scalp, neck, retroauricular area, upper trunk) • Sometimes on the lower back, abdomen, buttocks, arms, legs	• Usually occurs early in the treatment course[4] ✦ In a cetuximab study, the median time to onset of rash was **10 days**[5]	• Most common with **EGFR inhibitors**; rash occurs in **60–80%** of patients[4] • Common with **MKIs and BRAF inhibitors** as well; rash occurs in **14–30%** of patients treated for GI/liver cancers[6–12]	• Acne vulgaris ✦ Comedones and nodules ✦ Itch is rare ✦ Scalp involvement is rare • Steroid acne ✦ Monomorphic papules resembling comedinal acne or malassezia folliculitis • Antibiotic-resistant folliculitis • Rosacea or periorificial dermatitis ✦ Itch is rare ✦ Located only on the face

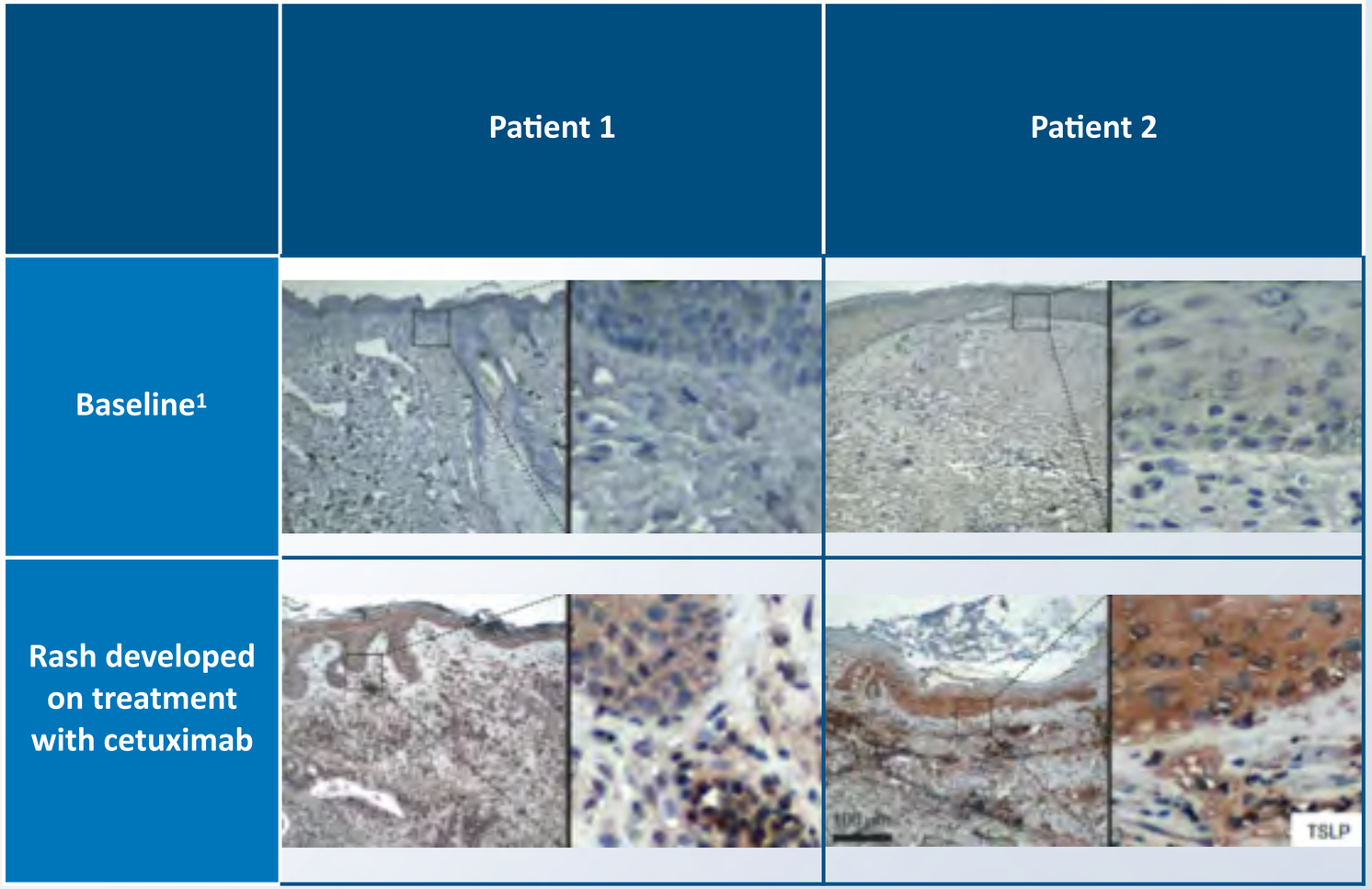
Papulopustular rash is also referred to as acneiform rash, acne-like rash, or folliculitis

BRAF, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; MKI, multiple kinase inhibitor.

1. Widakowich C, et al. Oncologist. 2007;12;1443-55. 2. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 3. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308. 4. Beech J, et al. Future Oncol. 2018;14:2531-41. 5. Jonker DJ, et al. N Engl J Med. 2007;357:2040-8. 6. Nexavar (sorafenib) Prescribing Information. 7. Sutent (sunitinib) Prescribing Information. 8. Stivarga (regorafenib) Prescribing Information. 9. Lenvima (lenvatinib) Prescribing Information. 10. Cabometyx (cabozantinib) Prescribing Information. 11. Ayvakit (avapritinib) Prescribing Information. 12. Braftovi (encorafenib) Prescribing Information.

PAPULOPUSTULAR RASH
PATHOLOGY

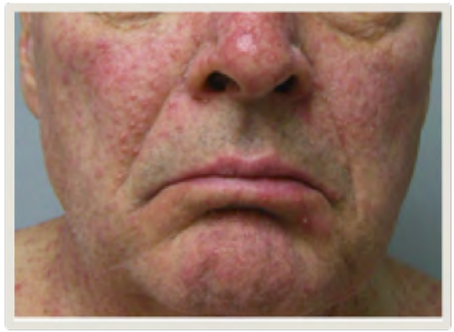
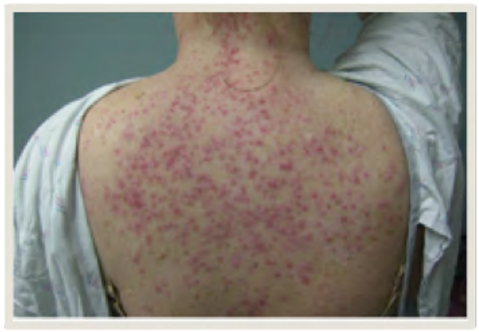
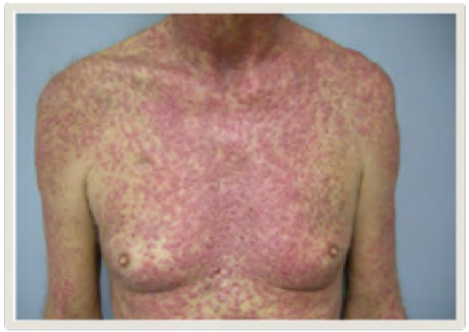
- EGFR/ERK signalling is required during *de novo* hair eruption in hair-follicle stem cells to secure barrier integrity and prevent invasion by the commensal microbiota[1]
- When EGFR/ERK signalling is inhibited, commensal skin microbes can invade the follicular opening of erupting hair and provoke an atopic-like (Th2-dominated) inflammatory skin disease[1]
- Histologically, early infiltration of T lymphocytes is seen, followed by a hyperkeratotic appearance of the follicular infundibula and a florid, neutrophilic suppurative infiltrate[2]



ERK, Extracellular signal-regulated kinase; EGFR, epidermal growth factor receptor; Th, T helper cell.

1. Klufa J, et al. Sci Transl Med. 2019;11:eaax2693. 2. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308.

PAPULOPUSTULAR RASH **GRADING**

Grade 1	Grade 2	Grade 3	Grade 4
• Papules or pustules (or both) covering **< 10% of the body surface area (BSA)** that may or may not be associated with symptoms of pruritus or tenderness	• Papules or pustules (or both) covering **10–30% of BSA** that may or may not be associated with symptoms of pruritus or tenderness • Associated with **psychosocial impact** • **Limiting instrumental ADL*** • Papules or pustules (or both) covering **> 30% of BSA with or without mild symptoms**	• Papules or pustules (or both) covering >**30% of BSA with moderate or severe symptoms** • **Limiting self-care ADL**** • Associated with **local superinfection**, and oral antibiotics are indicated	• **Life-threatening consequences** • Papules or pustules (or both) covering **any % of BSA** and which may or may not be associated with symptoms of pruritus or tenderness and are associated with **extensive superinfection** with intravenous antibiotics indicated
			

* Instrumental ADL are preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL are bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

ADL, activities of daily living; BSA, body surface area

1. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.) Images from Lacouture ME, et al. Clin Colorectal Cancer. 2018;17:85-96.

MACULOPAPULAR RASH

Symptoms[1]	Incidence	Onset	Pathophysiology	Differential diagnosis
• **Flat, red area on the skin that is covered with small confluent bumps** (papules) • Skin tenderness • Mucosal involvement • Systemic involvement • Associated with pruritus • Location ✦ Frequently affects the upper trunk	• Rash, including maculopapular rash, is reported to be a very common skin toxicity with targeted therapies[2–14]	• Usually within **1–4 weeks** from the start of treatment[15]	• Unlike papulopustular rash, which is specific to certain targeted therapies, maculopapular rash is a non-specific **allergic reaction** to treatment	• Reaction to another drug • Viral exanthem • Urticaria • Graft-versus-host disease after transplantation • If severe: SCAR!

Maculopapular rash is also referred to as morbilliform rash, maculopapular eruption, morbilliform exanthema, and maculopapular exanthema

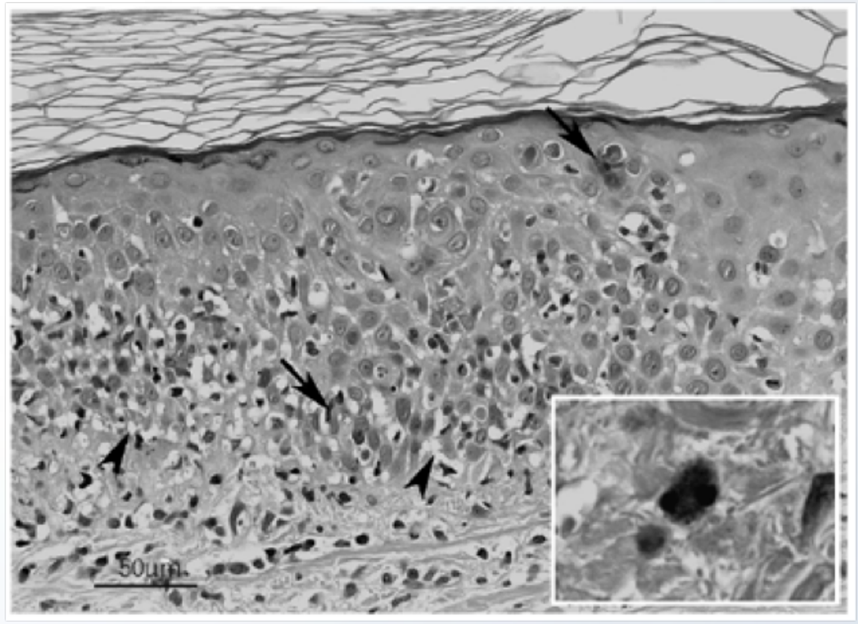
Be aware of potential SCARs, delayed type IV hypersensitivity reactions to drugs[16]
Urgently consult a dermatologist in case of:
- **blisters**
- **skin tenderness**
- **mucous membrane involvement**
- **rapid progression, turning dusky (grey or purple overtones)**
- **skin sloughing**

SCAR, severe cutaneous adverse reaction.

1. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.) 2. Erbitux (cetuximab) Prescribing Information. 3. Tarceva (erlotinib) Prescribing Information. 4. Vectibix (panitumumab) Prescribing Information. 5. Nexavar (sorafenib) Prescribing Information. 6. Sutent (sunitinib) Prescribing Information.
7. Stivarga (regorafenib) Prescribing Information. 8. Lenvima (lenvatinib) Prescribing Information. 9. Cabometyx (cabozantinib) Prescribing Information. 10. Gleevec (imatinib) Prescribing Information.
11. Tasigna (nilotinib). Prescribing Information. 12. Sprycel (dasatinib) Prescribing Information. 13. Ayvakit (avapritinib) Prescribing Information 14. Braftovi (encorafenib) Prescribing Information.
15. Ely JW, Stone MS. Am Fam Physician. 2010;81:726-34. 16. Bellón T. Drug Saf. 2019;42:973-92.

MACULOPAPULAR RASH
PATHOLOGY

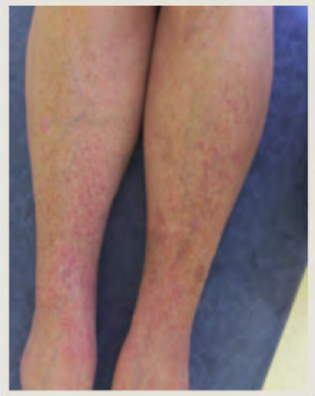
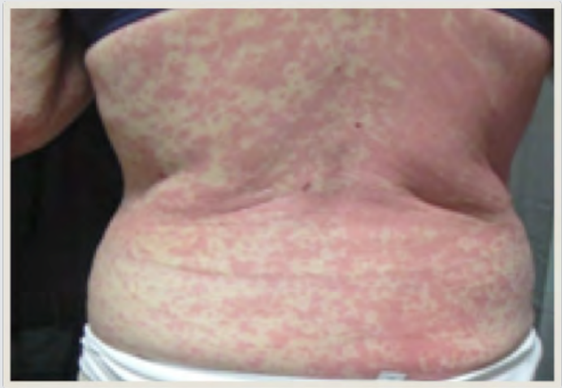
Characterised by orthokeratosis, focal basal spongiosis, mild exocytosis of lymphocytes, Civatte bodies (arrow, dyskeratotic, or apoptotic keratinocytes) in all epidermal layers, hydropic degeneration of basal keratinocytes (arrowhead), and a superficial perivascular infiltrate of lymphocytes with few eosinophils (inset)



Haematoxylin and eosin staining of drug-induced maculopapular rash

1. Brönnimann M, Yawalkar N. Curr Opin Allergy Clin Immunol. 2005;5:317-21.

MACULOPAPULAR RASH
GRADING

Grade 1	Grade 2	Grade 3
• Macules or papules covering **< 10% of BSA** with or without symptoms (e.g. pruritus, burning, tightness)	• Macules or papules covering **10–30% of BSA** with or without symptoms • **Limiting instrumental ADL*** • Rash covering **> 30% of BSA with or without mild symptoms**	• Macules or papules covering **> 30% of BSA with moderate or severe symptoms** • **Limiting self-care ADL****
		

For the grading of SCAR, please refer to CTCAE v5.0.

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** Self-care ADL are bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

ADL, activities of daily living; BSA, body surface area; SCAR, severe cutaneous adverse reaction.

National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.) Images courtesy of Siegfried Segaert, MD, PhD.

HAND–FOOT SKIN REACTION (HFSR) RASH

Symptoms[1–5]	Onset	Incidence	Differential diagnosis[5]
• **Tenderness of the palms of the hands and soles of feet** ✦ Lesions are sharply demarcated, erythematous, oedematous, and very tender • Followed by thickened or hyperkeratotic skin with or without blistering • Inflamed and painful calluses • Location: ✦ Areas of pressure or friction, such as the heels and metatarsal heads ✦	• Days to weeks from the start of treatment[5,6] • In the phase 3 CORRECT study of regorafenib in CRC, the median time to first occurrence was **15 days**[6]	• HFSR was reported in **14–67%** of patients with GI or liver cancers treated with **MKIs**[7–11] ✦ 3–22% of patients have grade ≥ 3 HFSR • HFSR is **dose-dependent** • Avapritinib is rarely associated with HFSR[12]	• **HFSR is distinct from HFS** (also known as palmar-plantar erythrodysaesthesia) which is associated with chemotherapy

HFSR versus HFS[5]	HFSR	HFS
Treatment association	MKIs	Chemotherapy
Onset	Days to weeks	Weeks to months
Distribution	Pressure or friction points	Diffuse involvement of palms or soles (or both)
Presentation	•Dysaesthesia •Erythema •Pain •Epidermal blistering •Calluses	•Dysaesthesia •Erythema •Pain •Oedema •Scaling

CRC, colorectal cancer; HFS, hand–foot syndrome; HFSR, hand–foot skin reaction; MKI, multiple kinase inhibitor

1. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308. 2. Manchen E, et al. J Support Oncol. 2011;9:13-23. 3. Lacouture ME, et al. Oncologist. 2008;13:1001-11. 4. De Wit M, et al. Support Care Cancer. 2014;22:837-46. 5. McLellan B, Kerr H. Dermatol Ther. 2011;24:396-400. 6. Grothey A, et al. J Clin Oncol. 2013;31:suppl 3637. 7. Nexavar (sorafenib) Prescribing Information. 8. Sutent (sunitinib) Prescribing Information. 9. Stivarga (regorafenib) Prescribing Information. 10. Lenvima (lenvatinib) Prescribing Information. 11. Cabometyx (cabozantinib) Prescribing Information. 12. Ayvakit (avapritinib) Prescribing Information.

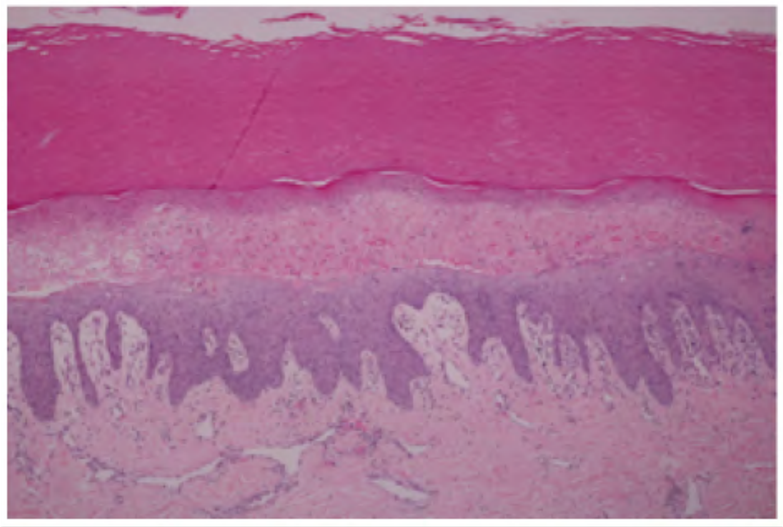
HFSR
PATHOLOGY

Pathological features of HFSR include:[1]

- epidermal keratinocyte apoptosis, dyskeratosis, and vacuolar degeneration with intraepidermal blister formation, followed by
- massive acanthosis, papillomatosis, and parakeratotic hyperkeratosis

The **pathophysiology of HFSR** with targeted therapy has been extensively studied for sorafenib and sunitinib

- These drugs target RAF (sorafenib only), c-KIT, fms-related tyrosine kinase receptor 3 (Flt3), VEGFR, and PDGFR kinases to inhibit tumour-related angiogenesis and tumour growth[2]
- HFSR might occur with these agents because keratinocytes in the epidermis synthesise PDGF-α and PDGF-β, which bind to PDGFRs on dermal fibroblasts, capillaries, and eccrine glands[2,3]
- Dermal eccrine glands also express c-KIT and PDGFR, both of which are targets of sorafenib[2,3]
- Co-inhibition of VEGFR and PDGFR could therefore potentially reduce the ability of vessels to repair themselves in high-pressure areas of the hands and feet, thus causing HFSR in areas such as the palms and soles, which may be repeatedly exposed to subclinical trauma[3]

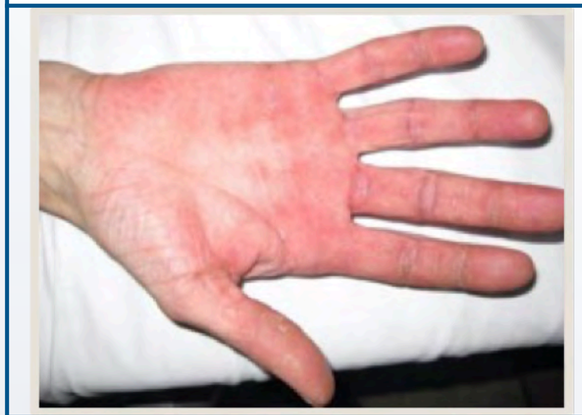
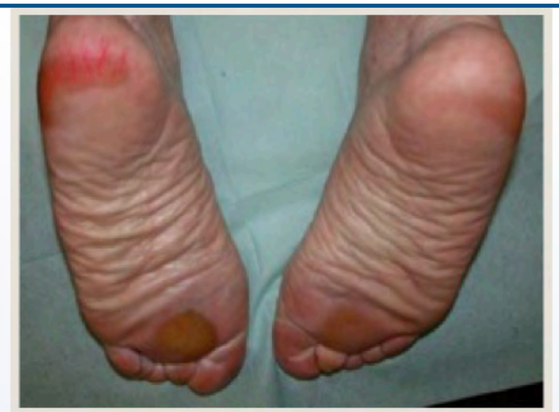
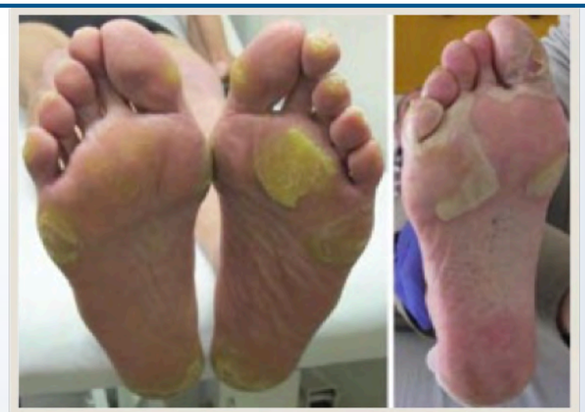


Haematoxylin and eosin staining of a HFSR.[4] Well-defined linear band of necrotic keratinocytes, giving rise to subcorneal blister with epidermal acanthosis and parakeratosis. Mild perivascular lymphocytic cell infiltrate and telangiectasia in the upper dermis.

HFSR, hand–foot skin reaction; PDGF(R), platelet-derived growth factor (receptor); VEGFR, vascular endothelial growth factor receptor.

1. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308. 2. Lacouture ME, et al. Oncologist. 2008;13:1001-11. 3. Gomez P, Lacouture ME. Oncologist. 2011;16:1508-19. 4. Chanprapaph K, et al. Am J Clin Dermatol. 2016;17:387-402.

HFSR
GRADING

Grade 1	Grade 2	Grade 3
• **Minimal skin changes** or dermatitis (e.g. erythema, oedema, or hyperkeratosis) **without pain**	• **Skin changes** (e.g. peeling, blisters, bleeding, fissures, oedema, or hyperkeratosis) **with pain** • **Limiting instrumental ADL***	• **Severe skin changes** (e.g. peeling, blisters, bleeding, fissures, oedema, or hyperkeratosis) **with pain** • **Limiting self-care ADL****
		

Note that the pain can be out of proportion to the clinical picture. Therefore, HFSR should be graded primarily on the basis of symptoms and secondarily according to the clinical picture.

CTCAE v5.0 has no specific grading for HFSR. The grading used for HFS can also be used for HFSR.[1]

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ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; HFS, hand–foot syndrome; HFSR, hand–foot skin reaction.

1. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.) Images from McLellan B, et al. Ann Oncol. 2015:26:2017-26.

HFSR AS A PREDICTOR OF RESPONSE

Some studies have indicated that HFSR is positively correlated with response to MKIs

Sorafenib in HCC[1]	Regorafenib in HCC[2]	Regorafenib in CRC[3]	Lenvatinib in HCC[4]	Sunitinib in GIST[5]
A meta-analysis of 12 cohort studies with 1,017 patients suggested that HFSR is associated with a longer overall survival (OS) and time to progression (TTP) in patients with HCC treated with sorafenib	A retrospective analysis of the RESORCE trial, in which patients with HCC received 2nd-line regorafenib or placebo after sorafenib, showed that HFSR during treatment with regorafenib was associated with longer OS	A post-hoc analysis of the CORRECT trial, in which patients with previously treated metastatic CRC received regorafenib or placebo, suggested that patients who had HFSR had a greater treatment benefit from regorafenib	A retrospective study including 152 patients with HCC from Japan treated with lenvatinib showed that any grade HFSR was associated with longer TTP	A retrospective study including 416 patients with GIST suggested that HFSR is associated with improved ORR, PFS, and OS
• Pooled HR for OS: 0.45 (95% CI 0.36–0.55) • Pooled HR for TTP: 0.41 (95% CI 0.28–0.60)	Median OS in patients with vs without HFSR: • 14.1 months (95% CI 11.7–16.5) vs 6.6 months (95% CI 5.0–8.5) • HR: 0.52 (95% CI 0.40–0.67)	Efficacy in patients with vs without HFSR: • PFS: 3.4 vs 1.8 months (HR 0.54, 95% CI 0.45–0.66) • OS: 9.5 vs 4.7 months (HR 0.41, 95% CI 0.41–0.53)	TTP in patients with vs without HFSR: • Not reached vs 8.9 months (P = 0.007)	Efficacy in patients with vs without HFSR: • ORR: 22.2% vs 10.7% • PFS: 11.0 vs 5.5 months • OS: 35.7 vs 16.6 months • All P < 0.01

HCC, hepatocellular carcinoma; HR, hazard ratio; FSR, hand–foot skin reaction; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression

1. Wang P, et al. Expert Rev Gastroenterol Hepatol. 2018;12:1-8. 2. Bruix J, et al. J Clin Oncol. 2018;36 suppl 4:412. 3. Grothey A, et al. J Clin Oncol. 2017:35 suppl:3551 . 4. Hiraoka A, et al. Cancer Med. 2019;8:3719-28. 5. Puzanov I, et al. J Clin Oncol. 2011;29 suppl 15:e21113

ADDITIONAL SKIN TOXICITIES DRY SKIN

Symptoms[1-3]	Incidence[4-16]	Differential diagnosis
• Flaky, dull, scaly, and itchy skin • Onset 1–3 months after treatment initiation • Often persistent, lasting several months	• EGFR inhibitors: up to 57% • MKIs: up to 15% • BRAF inhibitor: 13% • VEGF(R) inhibitors: up to >10% • BCR–ABL TKIs: up to 7%	• Atopic dermatitis • Ichthyosis vulgaris • Nutritional deficiency • Paraneoplastic • Note: dry skin can be exacerbated by cirrhosis!

Dry skin is also referred to as xerosis (cutis)

GRADING[17]

Grade 1	Grade 2	Grade 3
Covering **< 10% of BSA** Not associated with erythema or pruritus	Covering **10–30% of BSA** Associated with **erythema or pruritus** **Limiting instrumental ADL***	Covering **> 30% of BSA** Associated with pruritus **Limiting self-care ADL****

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ADL, activities of daily living; BCR–ABL, Philadelphia translocation; BRAF, v-raf murine sarcoma viral oncogene homolog B1 ; BSA, body surface area; EGFR, epidermal growth factor receptor; MKI, multiple kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

1. Belum VR, et al. Curr Oncol Rep. 2013;15:249-59. 2. Robert C, et al. Semin Oncol. 2012;39:227-40. 3. Lacouture ME, et al. Clin Colorectal Cancer. 2018:17:85-96. 4. Erbitux (cetuximab) Prescribing Information. 5. Tarceva (erlotinib) Prescribing Information. 6. Vectibix (panitumumab) Prescribing Information. 7. Nexavar (sorafenib) Prescribing Information. 8. Sutent (sunitinib) Prescribing Information.
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14. Cyramza (ramucirumab) Prescribing Information. 15. Gleevec (imatinib) Prescribing Information. 16. Braftovi (encorafenib) Prescribing Information. 17. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.)

ADDITIONAL SKIN TOXICITIES PRURITUS

Symptoms[1-3]	Incidence[4-16]	Differential diagnosis
• Can exist alone or be related to dry skin or rash • Onset 2–3 weeks after treatment initiation	• EGFR inhibitors: up to 58% • BCR–ABL TKIs: up to 19% • MKIs: up to 14% • BRAF inhibitor: 14%	• Related to cholestasis (note: not always accompanied by laboratory changes!) • Renal failure • Thyroid disease • Paraneoplastic • Other infectious skin condition

GRADING[17]

Grade 1	Grade 2	Grade 3
Mild or localised topical intervention indicated	**Widespread and intermittent** **Skin changes** due to scratching **Oral intervention** indicated **Limiting instrumental ADL***	**Widespread and constant** **Systemic** corticosteroid or immunosuppressive **therapy** indicated **Limiting self-care ADL** or sleep**

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9. Stivarga (regorafenib) Prescribing Information. 10. Lenvima (lenvatinib) Prescribing Information. 11. Cabometyx (cabozantinib) Prescribing Information. 12. Avastin (bevacizumab) Prescribing Information. 13. Zaltrap (aflibercept) Prescribing Information.
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ADDITIONAL SKIN TOXICITIES PHOTOSENSITIVITY

Symptoms[1-3]	Incidence[4-16]	Differential diagnosis
• Skin reaction due to increased sensitivity of the skin to light • Onset < 24 hours after sun exposure	• BCR–ABL TKIs: up to 7%	• Related to other medication • Lupus

GRADING[17]

Grade 1	Grade 2	Grade 3	Grade 4
Painless erythema covering **< 10% of BSA**	**Tender** erythema covering **10–30% of BSA**	Erythema covering **> 30% of BSA** Erythema with **blistering** **Oral corticosteroid therapy** indicated **Pain control** indicated	**Life-threatening consequences** Urgent intervention indicated

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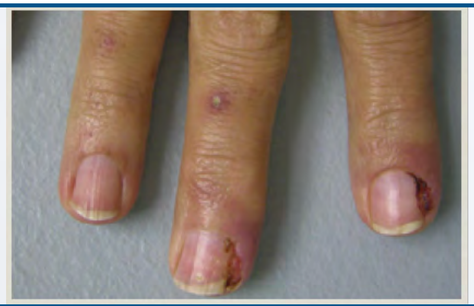
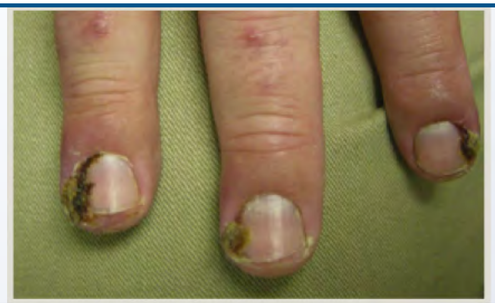
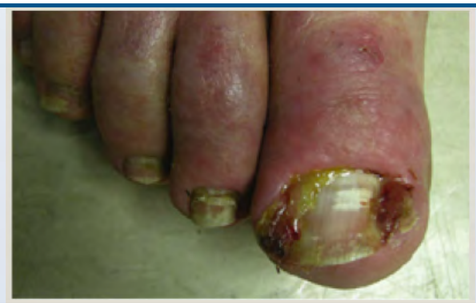
14. Cyramza (ramucirumab) Prescribing Information. 15. Gleevec (imatinib) Prescribing Information. 16. Braftovi (encorafenib) Prescribing Information. 17. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.)

ADDITIONAL SKIN TOXICITIES PARONYCHIA[1,2]

Symptoms[1,2]	Incidence[8-20]	Differential diagnosis
• Inflammation in the nail fold; can be very painful • Secondary superinfection with *S. aureus* may occur • Onset > 2 months from treatment initiation	• EGFR inhibitors: up to 25%	• Ingrown toenail • Bacterial infection • Candida • Pyogenic granuloma

GRADING[21]

Grade 1	Grade 2	Grade 3
• Nail fold oedema or erythema • Disruption of the cuticle	• Nail fold oedema or erythema with **pain** • Associated with **discharge or nail plate separation** • Local or oral intervention indicated • **Limiting instrumental ADL***	• **Operative intervention or intravenous antibiotics indicated** • **Limiting self-care ADL****
		

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1. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 2. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308. 3. McLellan B, Kerr H. Dermatol Ther. 2011;24:396-400. 4. Etienne G, et al. N Engl J Med. 2002;347:446.
5. De Wit M, et al. Support Care Cancer. 2014;22:837-46. 6. Boers-Doets CB, et al. Future Oncol. 2013;9:1883-92. 7. Boers-Doets CB, et al. Oncologist. 2012;17:135-44. 8. Erbitux (cetuximab) Prescribing Information. 9. Tarceva (erlotinib) Prescribing Information. 10. Vectibix (panitumumab) Prescribing Information. 11. Nexavar (sorafenib) Prescribing Information. 12. Sutent (sunitinib) Prescribing Information. 13. Stivarga (regorafenib) Prescribing Information. 14. Lenvima (lenvatinib) Prescribing Information. 15. Cabometyx (cabozantinib) Prescribing Information. 16. Avastin (bevacizumab) Prescribing Information. 17. Zaltrap (aflibercept) Prescribing Information.
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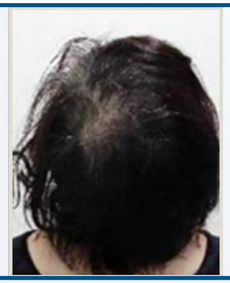
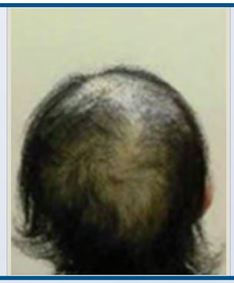
ADDITIONAL SKIN TOXICITIES ALOPECIA[1,3,4]

Symptoms[1,3,4]	Incidence[8-20]	Differential diagnosis
• Alopecia (hair loss) is the main hair-related AE with targeted therapy • Onset 2–3 months from treatment initiation • Other hair changes include hair-colour changes, trichomegaly, and hypertrichosis	• MKIs: up to 24% • BCR–ABL TKIs: up to 15%	Systemic causes include: • thyroid disease • hypogonadism • PCOS • nutritional deficiencies (vitamins, iron)

GRADING[21]

Grade 1	Grade 2
Hair loss of < 50% of normal for that individual • Not obvious from a distance, only on close inspection • Does not require a wig or hair piece to camouflage	**Hair loss of ≥ 50% normal** for that individual • Readily apparent to others • A wig or hair piece is necessary to completely camouflage the hair loss • Associated with psychosocial impact
	

* Instrumental ADL are preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL are bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

AE, adverse event; BCR–ABL, Philadelphia translocation; MKI, multiple kinase inhibitor.

1. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 2. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308. 3. McLellan B, Kerr H. Dermatol Ther. 2011;24:396-400. 4. Etienne G, et al. N Engl J Med. 2002;347:446. 5. De Wit M, et al. Support Care Cancer. 2014;22:837-46. 6. Boers-Doets CB, et al. Future Oncol. 2013;9:1883-92. 7. Boers-Doets CB, et al. Oncologist. 2012;17:135-44. 8. Erbitux (cetuximab) Prescribing Information. 9. Tarceva (erlotinib) Prescribing Information. 10. Vectibix (panitumumab) Prescribing Information. 11. Nexavar (sorafenib) Prescribing Information. 12. Sutent (sunitinib) Prescribing Information. 13. Stivarga (regorafenib) Prescribing Information. 14. Lenvima (lenvatinib) Prescribing Information. 15. Cabometyx (cabozantinib) Prescribing Information. 16. Avastin (bevacizumab) Prescribing Information. 17. Zaltrap (aflibercept) Prescribing Information. 18. Cyramza (ramucirumab) Prescribing Information. 19. Gleevec (imatinib) Prescribing Information. 20. Ayvakit (avapritinib) Prescribing Information. 21 National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.) Images from Kinoshita T, et al. Front Oncol. 2019;9:733.

ADDITIONAL SKIN TOXICITIES STOMATITIS[5–7]

Symptoms[5-7]	Incidence[8-20]	Differential diagnosis
• Inflammation of the oral mucosa, encompassing mucositis, dry mouth, dysgeusia, dysphagia, and oral dysaesthesia • Onset 5–14 days after the start of a treatment cycle	• MKIs: up to 48% • EGFR inhibitors: up to 32% • BCR–ABL TKIs: up to 10%	• Nutritional deficiencies (zinc) • Pill oesophagitis • Aphthous ulcers • Candida • Herpes • Xerostomia related to underlying liver disease

GRADING[21]

The CTCAE v5.0 has no specific grading for stomatitis; follow the general grading for this AE.[1] The grading of stomatitis reflects the impact of the AE on the patient's life. Specific symptoms can be graded separately.

Grade 1	Grade 2	Grade 3	Grade 4
Mild symptoms of dry mouth, oral pain, etc. • without significant dietary alteration • not interfering with oral intake	**Moderate** symptoms of dry mouth, oral pain, dysgeusia, etc. • leading to **change in diet**, **eating or swallowing** • **interfering with oral intake** • **limiting instrumental ADL***	Severe symptoms of dry mouth, oral pain, dysphagia, etc. • calling for **tube feeding, total parenteral nutrition, or hospitalisation** • **limiting self-care ADL****	• Dysphagia with **life-threatening consequences** • Urgent intervention indicated

* Instrumental ADL are preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL are bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

AE, adverse event; ADL, activities of daily living; BCR–ABL, Philadelphia translocation; BRAF, v-raf murine sarcoma viral oncogene homolog B1 ; EGFR, epidermal growth factor receptor; MKI, multiple kinase inhibitor.

1. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 2. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308. 3. McLellan B, Kerr H. Dermatol Ther. 2011;24:396-400. 4. Etienne G, et al. N Engl J Med. 2002;347:446. 5. De Wit M, et al. Support Care Cancer. 2014;22:837-46. 6. Boers-Doets CB, et al. Future Oncol. 2013;9:1883-92. 7. Boers-Doets CB, et al. Oncologist. 2012;17:135-44. 8. Erbitux (cetuximab) Prescribing Information. 9. Tarceva (erlotinib) Prescribing Information. 10. Vectibix (panitumumab) Prescribing Information. 11. Nexavar (sorafenib) Prescribing Information. 12. Sutent (sunitinib) Prescribing Information. 13. Stivarga (regorafenib) Prescribing Information. 14. Lenvima (lenvatinib) Prescribing Information. 15. Cabometyx (cabozantinib) Prescribing Information. 16. Avastin (bevacizumab) Prescribing Information. 17. Zaltrap (aflibercept) Prescribing Information. 18. Cyramza (ramucirumab) Prescribing Information. 19. Gleevec (imatinib) Prescribing Information. 20. Ayvakit (avapritinib) Prescribing Information. 21 National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.)

POOR WOUND HEALING

Symptoms[1]	Incidence[2-9]
• **Wound dehiscence** • **Ecchymosis** • **Surgical site bleeding** • **Wound infection**	• **VEGF(R) inhibitors: up to 15%** • **MKIs: poor wound healing has been reported (rates unknown)**

GRADING[10]

Grade 1	Grade 2	Grade 3	Grade 4
• Wound complication for which **topical intervention** is indicated • **Incisional separation** for which intervention is not indicated	• Wound complication or incisional separation for which **local care** is indicated	• Wound complication or fascial disruption without evisceration for which **operative intervention** is indicated	• Wound complication with **life-threatening consequences** • **Symptomatic hernia** with evidence of strangulation • **Fascial disruption with evisceration** • **Major surgery** indicated (e.g. grafting, amputation)

MKI, multiple kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

1. Gordon CR, et al. Ann Plast Surg. 2009;62:707-9. 2. Avastin (bevacizumab) Prescribing Information. 3. Zaltrap (aflibercept) Prescribing Information. 4. Cyramza (ramucirumab) Prescribing Information. 5. Nexavar (sorafenib) Prescribing Information. 6. Sutent (sunitinib) Prescribing Information. 7. Stivarga (regorafenib) Prescribing Information.
8. Lenvima (lenvatinib) Prescribing Information. 9. Cabometyx (cabozantinib) Prescribing Information. 10. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.)

CUTANEOUS MALIGNANCIES

Types[1]	Incidence[1]
• **Cutaneous squamous cell carcinoma** • **Keratoacanthoma**	• **BRAF inhibitors in CRC: 1-2%**

GRADING A TREATMENT-RELATED SECONDARY MALIGNANCY[2]

Note that CTCAE v5.0 includes Grades 3-5 for the category of treatment-related secondary malignancies, but also includes a category of "other neoplasms, benign, malignant and unspecified", which does allow for Grades 1 and 2.

Grade 1	Grade 2	Grade 3	Grade 4
• Asymptomatic or mild symptoms • Clinical or diagnostic observations only • **Intervention not indicated**	• Moderate • **Minimal, local or noninvasive intervention indicated** • Limiting age-appropriate instrumental ADL*	• **Non-life-threatening** secondary malignancy	• **Acute life-threatening** secondary malignancy

* Instrumental ADL are preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

BRAF, v-raf murine sarcoma viral oncogene homolog B1 ; CTCAE, Common Terminology Criteria for Adverse Events

1. Braftovi (encorafenib) Prescribing Information. 2. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v5.0. 27 November 2017. (Accessed 31 January 2020.)

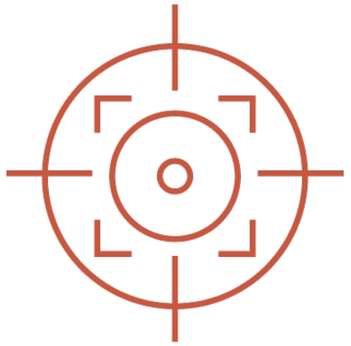
SUMMARY

CUTANEOUS AES ARE **COMMON** WITH TARGETED THERAPY IN PATIENTS WITH **GI OR LIVER CANCERS** AND INCLUDE:

- papulopustular rash
- maculopapular rash
- HFSR
- dry skin, pruritus, and photosensitivity
- changes in nails, hair, or mucosa
- poor wound healing
- cutaneous malignancies

EACH DRUG CLASS **HAS A SPECIFIC SKIN-TOXICITY PROFILE**

- e.g. HFSRs are most often related to MKIs, and cutaneous malignancies are specific to BRAF inhibitors



AE, adverse event; BRAF, v-raf murine sarcoma viral oncogene homolog B1 ; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HFSR, hand–foot skin reaction; MKI, multiple kinase inhibitor.

SKIN TOXICITY

PREVENTION AND MANAGEMENT

2

theconnects®

LEARNING OBJECTIVE

KNOW HOW TO PREVENT AND MANAGE SKIN TOXICITIES ASSOCIATED WITH TARGETED THERAPY IN GI AND LIVER CANCERS

WHAT
WILL YOU LEARN?

- **The things you as a healthcare professional should know about the prevention and management of skin toxicities, including dose modification and alternative dosing schedules**
- **What patients can do to prevent and manage skin toxicities**

WHY
IS THIS IMPORTANT?

- **Pre-emptively addressing and treating potential skin toxicities may improve patients' quality of life and allow them to remain on therapy longer**

GI, gastrointestinal

PREVENTATIVE RATHER THAN REACTIVE THERAPEUTIC **STRATEGIES ARE MORE EFFICIENT TO CONTROL AEs**

In all patients treated with targeted therapies, prophylactic measures include:

- using broad-spectrum (UVA/UVB) sunscreen (SPF 30+)
- avoiding sun exposure
- using skin moisturisers
- nail care
- oral care

A full-body skin examination is recommended before treatment is started

Effective patient education is key to preventing and treating skin toxicities

Management of low-grade toxicity is similar to these prophylactic measures

Management of high-grade toxicity depends on the type of toxicity and the grade

AE, adverse event; SPF, sun protection factor; UVA, ultraviolet A; UVB, ultraviolet B;

1. Lacouture ME, et al. J Clin Oncol. 2010;28:1351-7. 2. Beech J, et al. Future Oncol. 2018;14:2531-41. 3. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308. 4. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95.

PREVENTION AND MANAGEMENT OF **SKIN TOXICITIES INVOLVES A MULTIMODAL STRATEGY**

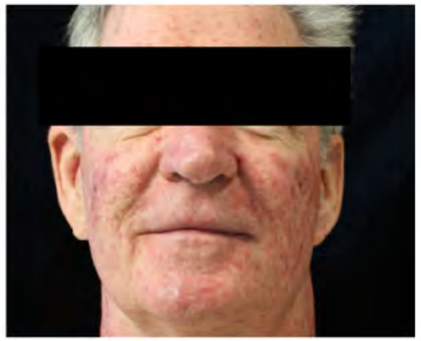
EFFECTIVE MANAGEMENT OF SKIN TOXICITIES INVOLVES A MULTIMODAL STRATEGY THAT INCLUDES:

1. **patient education**
2. **prophylactic and supportive care**
3. **dose modification (including flexible dosing)**

WHEN PRE-EMPTIVE MEASURES ARE INSUFFICIENT TO AVOID AES, EARLY TREATMENT IS CRUCIAL FOR AE MANAGEMENT

- **Encourage patients to contact their healthcare provider straight away upon first appearance of symptoms**

AE, adverse event



Papulopustular rash

PREVENTION AND MANAGEMENT OF **PAPULOPUSTULAR RASH**

Prevention	Grade 1	Grade 2	Grade 3	Grade 4
• **Minimise skin dryness** ✦ Bathe and shower in lukewarm water ✦ Use fragrance-free, mild soap for sensitive skin ✦ Use bland emollient (ointment or cream) • **Avoid UV radiation** ✦ Use broad-spectrum (UVA/UVB) sunscreen (SPF 30+) Wear sun-protective clothing (hats, long sleeves) • **Topical corticosteroids** • **Consider oral antibiotics** • **Consider establishing a connection with a dermatologist**	• **Topical corticosteroids** • **Topical antibiotic for pustules or superinfection** • **Consider oral tetracycline antibiotics**	• **Consider increasing potency of topical corticosteroids** • **Add an oral tetracycline antibiotic** • **Culture the lesion in case of lack of response or suspected superinfection** • **CONSULT A DERMATOLOGIST when the AE does not respond to intervention**	• **CONSULT A DERMATOLOGIST** • **As for grade 2** • **Consider increasing potency of topical corticosteroids** • **Culture lesions** • **Short course of oral corticosteroids when the AE does not respond to intervention**	• **Intravenous antibiotics and corticosteroids** • **Hospitalisation**

Consult a dermatologist if:

- **any skin AE necessitates changes to the cancer treatment**
- **a grade 2 skin AE does not respond to intervention**
- **any grade 3 skin AE occurs**
- **you are uncomfortable treating the skin AE yourself**

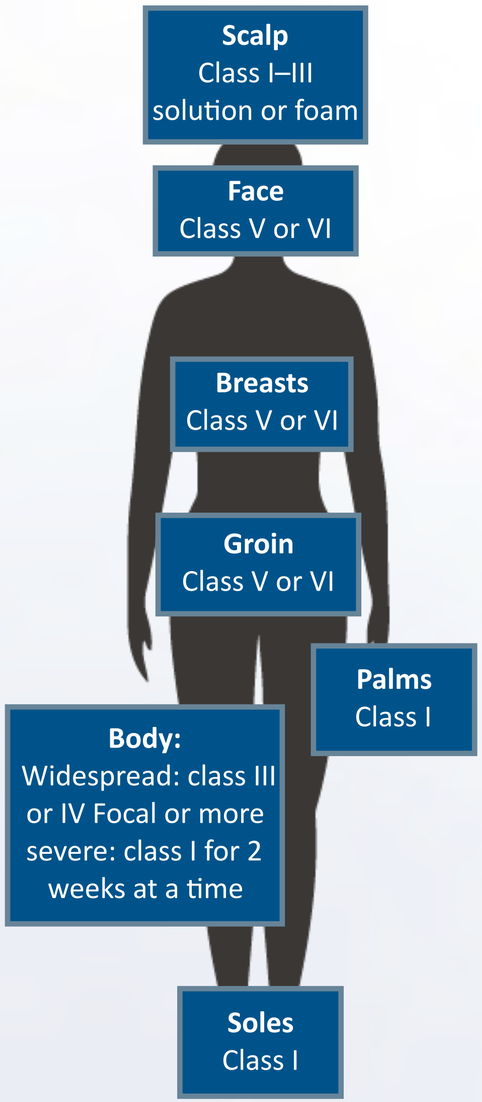
AE, adverse event; SPF, sun protection factor; UVA, ultraviolet A; UVB, ultraviolet B

These recommendations are based on review of the literature and expert experience.

1. Beech J, et al. Future Oncol. 2018;14:2531-41. 2. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 3. Segaert S, et al. Eur J Cancer. 2009;45 suppl 1:295-308.

Image courtesy of Dr Nicole LeBoeuf

WHEN USING CORTICOSTEROIDS FOR SKIN TOXICITY,
CONSIDER POTENCY AND VEHICLE



- **The potency of topical steroid to be used depends on the body part affected**
  - Corticosteroids are better absorbed in regions of thin epidermis than in regions of thicker epidermis
  - High-potency steroids are used for the palms and soles
  - Medium- to high-potency steroids are useful for regions of thinner epidermis or occlusion, such as the eyelid and groin
  - Low-to-medium strength preparations are used for large surface areas, to reduce the risk of systemic absorption

- **It is important to consider the vehicle most suitable for the affected body part**
  - Ointments provide the best penetration of the steroid, but because they are thick and greasy they are not always well tolerated
  - Foams and liquid solutions are available for body parts with dense hair, such as the scalp

These recommendations are based on review of the literature and expert experience.

1. Ference JD, Last AR. Am Fam Physician. 2009;79:135-40.

WHO CLASSIFICATION OF **TOPICAL CORTICOSTEROIDS**

Potency	Class	Topical corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	Amcinonide	Ointment, 0.1%
		Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.025%
		Fluocinonide	Cream, ointment, or gel, 0.05%
		Halcinonide	Cream, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

WHO, World Health Organization

Ference JD, Last AR. Am Fam Physician. 2009;79:135-40.
Bolognia JL, et al. Glucocorticosteroids. Dermatology. 3rd ed. 2012. Ch 125, 2075-88.


Maculopapular rash

MANAGEMENT OF **MACULOPAPULAR RASH**[1,2]

Grade 1	Grade 2	Grade 3	SCAR
• Topical steroids • Oral antihistamine (in case of itch)	• As for grade 1 • Consider increasing potency of topical corticosteroid • CONSULT DERMATOLOGIST when the AE does not respond to intervention	• CONSULT A DERMATOLOGIST • As for grade 2 • Consider prednisone 1 mg/kg/day or equivalent	• CONSULT A DERMATOLOGIST • Admission or emergency evaluation depending on clinical features

Be aware of potential SCARs, delayed type IV hypersensitivity reactions to drugs[3].

Urgently consult a dermatologist in case of:

- blisters
- skin tenderness
- mucous membrane involvement
- rapid progression, turning dusky (grey or purple overtones)
- skin sloughing

Consult a dermatologist if a SCAR is suspected

- a skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

AE, adverse event; SCAR, severe cutaneous adverse reaction

These recommendations are based on review of the literature and expert experience.

1. Tang N, Ratner D. Dermatol Surg. 2016;42 suppl 1:S40-8. 2. De Wit M, et al. Support Care Cancer. 2014;22:837-46. 3. Bellón T. Drug Saf. 2019;42:973-92.

HFSR

PREVENTION AND MANAGEMENT OF **HFSR**

Prevention	Grade 1	Grade 2	Grade 3
• **Consider establishing a connection with the dermatologist** ✦ Skin exam and activity assessment when possible ✦ Treat pre-existing conditions (fungal disease [athlete's foot], dermatitis, callosities) • **Minimise skin dryness** ✦ Bathe and shower in lukewarm water ✦ Use fragrance-free, mild soap for sensitive skin ✦ Use bland emollient (ointment or cream) • **Urea cream** • **Avoid repetitive tasks or vigorous exercise** ✦ Vaseline with gloves for hand-oriented tasks (e.g. gardening) ✦ Lubricate feet in anticipation of activity ✦ Well-fitting shoes and socks (avoid cotton socks during significant activity; consider athletic shoes and socks)	• **Urea 20–40% cream on calluses or hyperkeratotic areas** • **Super-potent topical steroids ointment**	• **As for grade 1** • **Consider dose interruption/ reduction** • **Pain management (topical or systemic as needed)*** • **Topical antibiotics or wound care (or both) for blisters and erosions** • **CONSULT DERMATOLOGIST when the AE does not respond to intervention**	• **CONSULT A DERMATOLOGIST** • **As for grade 2** • **Interrupt targeted therapy** • **Consider dose reduction on reinstitution** • **Potential need for oral analgesic***

*NSAIDs are contraindicated in patients with liver cirrhosis, due to risk of bleeding and renal failure.

Practical tips

- Avoiding heat and friction is key to preventing HFSR
- Use of pumice, pedicures etc. is NOT recommended after starting therapy
- NSAIDs are **contraindicated** in patients with liver cirrhosis, due to risk of bleeding and renal failure

Consult a dermatologist if:

- the skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

AE, adverse event; HFSR, hand–foot skin reaction; NSAID, non-steroidal anti-inflammatory drug

These recommendations are based on review of the literature and expert experience.1. Grothey A et al. Oncologist. 2014;19:669-80. 2. Lacouture ME, et al. Oncologist. 2008;13:1001-11. 3. McLellan B, et al. Ann Oncol. 2015;26:2017-26. Image courtesy of Dr Nicole LeBoeuf

Pruritus

PREVENTION AND MANAGEMENT
PRURITUS

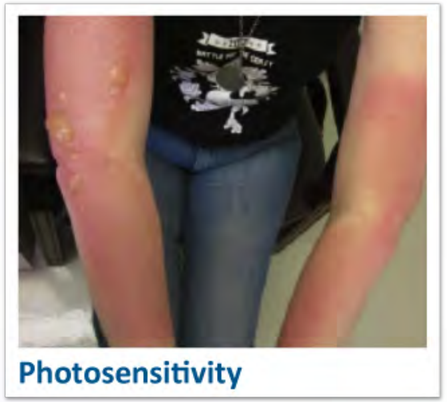
Prevention	Grade 1	Grade 2	Grade 3
• **Minimise skin dryness** ✦ Bathe and shower in lukewarm water ✦ Use fragrance-free, mild soap for sensitive skin ✦ Use bland emollient (ointment or cream) • **Consider establishing a connection with a dermatologist**	• **Topical therapy (menthol, pramoxine, doxepin, etc.)** • **Consider topical corticosteroid** • **Consider oral antihistamine (sedating at bedtime and non-sedating during the day)**	• **Maximise oral antihistamine dose (sedating at bedtime and non-sedating during the day)** • **Consider topical corticosteroid** • **Evaluate for reversible causes of itch (iron deficiency, thyroid dysfunction, etc.)** • **CONSULT DERMATOLOGIST when the AE does not respond to intervention**	• **CONSULT A DERMATOLOGIST** • **Consider oral corticosteroid (short term)** • **Consider oral gabapentin or pregabalin** • **Consider non-steroid agents (e.g. sertraline, mirtazapine, doxepin, aprepitant)**

Consult a dermatologist if:
- the skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

AE, adverse event

These recommendations are based on review of the literature and expert experience.

1. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 2. Potthoff K, et al. Ann Oncol. 2011;22:524-35.



Photosensitivity

PREVENTION AND MANAGEMENT OF **PHOTOSENSITIVITY**

Prevention	Grade 1	Grade 2	Grade 3
• **Avoid UV radiation** ✦ Use broad-spectrum (UVA and UVB) sunscreen (SPF 30+) and lip balm, under all weather conditions; reapply every 2 hours when outdoors ✦ Avoid midday sun (10 am–2 pm) ✦ Wear sun-protective clothing (hats, long sleeves) ✦ Wear sunglasses	• **Cooling gels or compresses** • **Analgesia if required** • **Consider topical steroid**	• **Topical corticosteroid** • **Antihistamines in case of itch** • **CONSULT DERMATOLOGIST when the AE does not respond to intervention**	• **CONSULT DERMATOLOGIST** • **As for grade 2** • **Oral corticosteroid** • **Oral analgesic (NSAIDs* or narcotics)** • **Wound care, ointment-based emollient** • **Add antibiotic ointment if there are signs of a secondary infection (mupirocin ointment)**

*NSAIDs are contraindicated in patients with liver cirrhosis, due to risk of bleeding and renal failure.

Practical tips

- Make patients aware that UVA penetrates window glass
- NSAIDs are **contraindicated** in patients with liver cirrhosis, due to risk of bleeding and renal failure

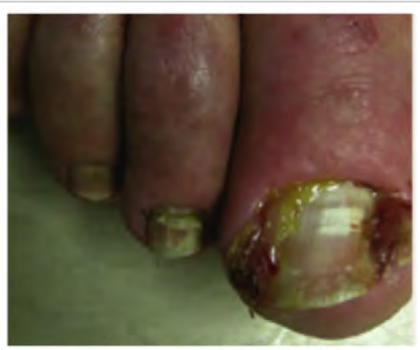
Consult a dermatologist if:

- the skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

AE, adverse event; NSAID, non-steroidal anti-inflammatory drug; SPF, sun protection factor; UVA, ultraviolet A; UVB, ultraviolet B

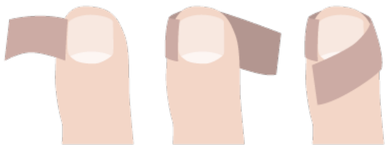
These recommendations are based on review of the literature and expert experience.

1. Beech J, et al. Future Oncol. 2018;14:2531-41. 2. Sinha R, et al. Br J Dermatol. 2012;167:987-94. Image courtesy of Dr Nicole LeBoeuf



Paronychia

PREVENTION AND MANAGEMENT OF **PARONYCHIA**

Prevention	Grade 1	Grade 2	Grade 3
• Wear shoes with a wide toe box • Avoid sharp angles on nails when trimming • Consider establishing a connection with a dermatologist	• Consider dilute vinegar soaks or povidone-iodine-based ointments • High-potency topical corticosteroid • Tape to pull lateral nail fold away • Culture if there is pus 	• As for grade 1 • Oral antibiotics (tetracyclines first line, otherwise based on culture • Consider topical or oral analgesic (or both)* • CONSULT DERMATOLOGIST when the AE does not respond to intervention or is complicated by granulation tissue in need of therapy	• CONSULT DERMATOLOGIST • Continue systemic antibiotics • Consider nail avulsion

Consult a dermatologist if:

- the skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- grade 2 paronychia is complicated by granulation tissue in need of therapy
- any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

* NSAIDs are contraindicated in patients with liver cirrhosis, due to risk of bleeding and renal failure.

AE, adverse event; NSAID, non-steroidal anti-inflammatory drug

These recommendations are based on review of the literature and expert experience.

1. Beech J, et al. Future Oncol. 2018;14:2531-41. 2. Haneke E. Dermatol Res Pract. 2012;2012:783924. 3. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 4. Potthoff K, et al. Ann Oncol. 2011;22:524-35. 5. Sollena P, et al. Drugs Context. 2019; 8:212613.

Image from Lacouture ME, et al. Clin Colorectal Cancer. 2018:17:85-96.


Alopecia

PREVENTION AND MANAGEMENT OF **ALOPECIA**

Prevention	Grade 1	Grade 2

• Minoxidil twice daily
• Gentle hair care
  ✦ Avoid excessive processing (combing, blow-drying, colouring, etc.)
• UV protection (hats, sunscreen in areas of sparse hair)
• Consider establishing a connection with a dermatologist
	• Scalp inflammation:
	  ✦ Class 1 topical steroid
	  ✦ Anti-dandruff shampoo
	• Signs of secondary infection: topical or oral antibiotics
		• As for grade 1
		• CONSULT DERMATOLOGIST when the AE does not respond to intervention

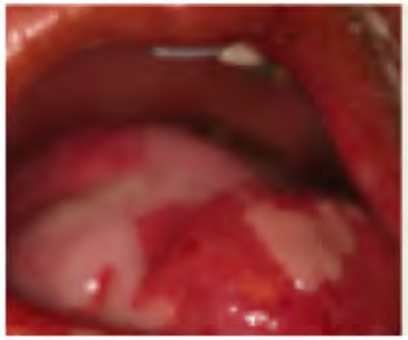
Practical tip:
- Treating inflammation early limits irreversible scarring alopecia

Consult a dermatologist if:
- the skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- you are uncomfortable treating the skin AE yourself

AE, adverse event

These recommendations are based on review of the literature and expert experience.

1. Lacouture ME, et al. Support Care Cancer. 2011;19:1079-95. 2. Rossi A, et al. J Cosmet Dermatol. 2017;16:537-41.
Image from Kinoshita T, et al. Front Oncol. 2019;9:733.



Stomatitis

PREVENTION AND MANAGEMENT OF **STOMATITIS**

Practical tip:
- NSAIDs are contraindicated in patients with liver cirrhosis, due to risk of bleeding and renal failure

Consult a dermatologist if:
- the skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

Prevention	Grade 1	Grade 2	Grade 3	Grade 4
• Practice good oral hygiene using of a soft toothbrush or swab after each meal and before going to sleep • Avoid foods that cause symptoms • Consider alcohol-free dexamethasone oral solution 0.5 mg/5 mL 4 times daily (swish for 2 minutes and spit)[1]* • Consider establishing a connection with a dermatologist	• Mouthwash (saline- or chlorhexidine-based) • Topical steroids (swish and spit or topical application)	• Increase the frequency of mouthwash • Dietary modification (e.g. avoid hot, spicy, or acidic food and drinks) • Use antiseptic and analgesic mouthwashes for symptomatic relief • Consider topical or systemic anti-inflammatory and analgesic drugs** • CONSULT DERMATOLOGIST when the AE does not respond to intervention	• CONSULT DERMATOLOGIST • As grade 2 • Consider non-oral nutrition	• Requires tube feeding, analgesic**, systemic antibiotic or antifungal treatment, or hospitalisation

*Based on the SWISH-study protocol, a phase 2 study investigating the efficacy of dexamethasone mouthwash for everolimus-related stomatitis prevention in hormone receptor-positive metastatic breast cancer.[1]

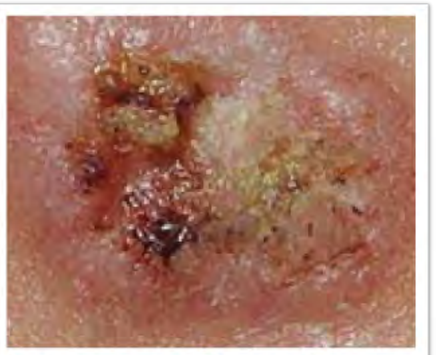
** NSAIDs are contraindicated in patients with liver cirrhosis, due to risk of bleeding and renal failure.

AE, adverse event; NSAID, non-steroidal anti-inflammatory drug

These recommendations are based on review of the literature and expert experience.

1. Rugo HS, et al. Lancet Oncol. 2017;18:654-62. 2. De Wit M, et al. Support Care Cancer. 2014;22:837-46. 3. Krishnamoorthy SK, et al. Therap Adv Gastroenterol. 2015;8:285-97.

Image from Lacouture ME, et al. Support Care Cancer 2011;19:1079-95


Cutaneous malignancies

PREVENTION AND MANAGEMENT OF **CUTANEOUS MALIGNANCIES**

Prevention	Management
• **Avoid UV radiation** ✦ Use broad-spectrum (UVA or UVB) sunscreen (SPF 30+) and lip balm under all weather conditions; reapply every 2 hours when outdoors ✦ Avoid midday sun (10 am–2 pm) ✦ Wear sun-protective clothing (hats, long sleeves) • **Consider establishing a connection with a dermatologist** ✦ Perform dermatologic evaluations before starting, every 2 months during treatment, and for up to 6 months after discontinuation[1] • **Advise patients to contact their healthcare provider immediately for change in or development of new skin lesions**[1]	• **CONSULT DERMATOLOGIST** • **Manage suspicious skin lesions with excision and dermatopathologic evaluation**[1]

Consult a dermatologist if:
- the skin AE necessitates changes to the cancer treatment
- Any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

AE, adverse event; SPF, sun protection factor; UVA, ultraviolet A; UVB, ultraviolet B

1. Braftovi (encorafenib) Prescribing Information.

Image from Aslam AM, Patel AN. BMJ. 2016;352:i1513.

DOSE REDUCTIONS AND DRUG HOLIDAYS
EGFR INHIBITORS IN GI AND LIVER CANCERS

Management of skin toxicities may involve dose adjustments as defined in each drug's Prescribing Information.

EGFR inhibitor	Dose modification for skin toxicity			Discontinuation for skin toxicity
cetuximab[1]	1st occurrence, grade 3 or 4 •Delay infusion 1–2 weeks •Upon improvement continue at 250 mg/m^2	2nd occurrence, grade 3 or 4 •Delay infusion 1–2 weeks •Upon improvement continue at 200 mg/m^2	3rd occurrence, grade 3 or 4 •Delay infusion 1–2 weeks •Upon improvement continue at 150 mg/m^2	•No improvement of a grade 3 or 4 AE upon delaying infusion for 1–2 weeks •4th occurrence of a grade 3 or 4 AE
erlotinib[2]	Severe rash not responsive to medical management •Withhold drug until rash is resolved to baseline level or grade ≤ 1 •Reduce dose by 50 mg when restarting therapy			Severe bullous, blistering, or exfoliating skin conditions
panitumumab[3]	1st occurrence, grade 3 •Withhold 1 or 2 doses •Upon improvement to grade < 3 resume at original dose	2nd occurrence, grade 3 •Withhold 1 or 2 doses •Upon improvement to grade < 3 resume at 80% of original dose	3rd occurrence, grade 3 •Withhold 1 or 2 doses •Upon improvement to grade < 3 resume at 60% of original dose	•4th occurrence of a grade 3 AE •Grade 3 AE that does not improve after withholding 1 or 2 doses •Grade 4 AE

AE, adverse event, EGFR, epidermal growth factor receptor; GI, gastrointestinal.

1. Erbitux (cetuximab) Prescribing Information. 2. Tarceva (erlotinib) Prescribing Information. 3. Vectibix (panitumumab) Prescribing Information.

DOSE REDUCTIONS AND DRUG HOLIDAYS
MKIS IN GI AND/OR LIVER CANCERS

MKI	Dose modification for skin toxicity			Discontinuation for skin toxicity
sorafenib[1]	Grade 2, 1st occurrence and no improvement in ≤ 7 days of topical treatment, or 2nd or 3rd occurrence: interrupt until grade is ≤ 1 and resume at a dose reduced by 1 level		Grade 3, 1st or 2nd occurrence: interrupt until grade is ≤ 1 and resume at a dose reduced by 1 level	• 4th occurrence of a grade 2 AE • 3rd occurrence of a grade 3 AE
	After improvement to grade ≤ 1 and ≥ 28 days of treatment at a reduced dose, the dose may be increased 1 level			
sunitinib[2]	Interrupt or modify dose by 12.5 mg increments or decrements according to individual safety and tolerability			
regorafenib[3]	Interrupt treatment for • a grade 2 HFSR that is recurrent or does • not improve in < 7 days, despite dose reduction ≥ 7 days for a grade 3 HFSR any grade 3 or 4 AE	Reduce dose to 120 mg • upon 1st occurrence of a grade 2 HFSR • after recovery of a grade 3 or 4 AE	Reduce dose to 80 mg • upon recurrence of a grade 2 HFSR at the 120 mg dose • after recovery of a grade 3 or 4 AE at the 120 mg dose	• Failure to tolerate 80 mg dose • Grade 4 AE; resume only if the potential benefit outweighs the risks
lenvatinib[4]	No specific recommendations for skin toxicity. The recommendations for 'other adverse reactions', including diarrhoea, hypocalcaemia and haemorrhagic events are:			
	Persistent or intolerable grade 2 or 3 AE • Withhold until improvement to grade ≤ 1 • Resume at reduced dose			Grade 4 AE
cabozantinib[5]	Withhold for • an intolerable grade 2 AE • a grade 3 or 4 AE	Upon resolution or improvement to baseline level or grade 1, reduce the daily dose by 20 mg. Patients who were on a 20 mg/day dose remain on that dose.		Failure to tolerate 20 mg dose
avapritinib[6]	Withhold for a grade 3 or 4 AE until improvement to grade ≤ 2 Resume at the same dose or a reduced dose, as clinically appropriate			

AE, adverse event; GI, gastrointestinal; HFSR, hand–foot skin reaction; MKI, multiple kinase inhibitor

1. Nexavar (sorafenib) Prescribing Information. 2. Sutent (sunitinib) Prescribing Information. 3. Stivarga (regorafenib) Prescribing Information. 4. Lenvima (lenvatinib) Prescribing Information. 5. Cabometyx (cabozantinib) Prescribing Information. 6. Ayvakit (avapritinib) Prescribing Information.

DOSE REDUCTIONS AND DRUG HOLIDAYS
VEGF(R) INHIBITORS IN GI AND LIVER CANCERS

The Prescribing Information on each VEGF(R) inhibitor contains warnings about impaired wound healing[1–3]

- **Discontinue the VEGF(R) inhibitor in patients with wound-healing complications**
  …that require medical intervention (ramucirumab and bevacizumab)
  …or necrotizing fasciitis (bevacizumab)

- **Do not administer the VEGF(R) inhibitor** for ≥ 28 days after surgery, until the wound is fully healed

- **Withhold the VEGF(R) inhibitor** for ≥ 28 days before elective surgery

GI, gastrointestinal; VEGFR, vascular endothelial growth factor receptor

1. Avastin (bevacizumab) Prescribing Information. 2. Zaltrap (aflibercept) Prescribing Information. 3. Cyramza (ramucirumab) Prescribing Information.

DOSE REDUCTIONS AND DRUG HOLIDAYS
BCR–ABL TKIs IN GI AND LIVER CANCERS

BCR–ABL TKI	Dose modification for skin toxicity
imatinib[1]	**Severe AE** • Withhold until the event has resolved • When the AE is resolved, treatment can be resumed as appropriate depending on the initial severity of the event
nilotinib[2]*	**Moderate or severe AE** • Withhold until the event has resolved • Consider resuming at a reduced dose • If clinically appropriate, consider re-escalation to the original dose
dasatinib[3]*	**Severe AE** • Withhold until the event has resolved or improved • Resume as appropriate at a reduced dose, depending on the severity and recurrence of the event

*Not FDA approved for use in GI or liver cancers. Dose modification advice for other indications is shown (as stated in the Prescribing Information).

AE, adverse event, BCR–ABL, Philadelphia translocation; FDA, U.S. Food and Drug Admninstration; GI, gastrointestinal; TKI, tyrosine kinase inhibitor

1. Gleevec (imatinib) Prescribing Information. 2. Tasigna (nilotinib) Prescribing Information. 3. Sprycel (dasatinib) Prescribing Information.

DOSE REDUCTIONS AND DRUG HOLIDAYS
BRAF INHIBITORS IN GI AND LIVER CANCERS

BRAF inhibitor	Dose modification for skin toxicity			Discontinuation for skin toxicity
encorafenib (combined with cetuximab)[1]	Dermatologic AE (not HFSR) • Grade 2 that does not improve in < 2 weeks ✦ Withhold until grade is ≤ 1 ✦ Resume at same dose • Grade 3: withhold until grade is ≤ 1 ✦ 1st occurrence: resume at same dose ✦ Recurrent: reduce dose	Recurrent grade 2 or 1st occurrence of grade 3 HFSR • Withhold for ≤ 4 weeks • Resume at reduced dose if improvement to grade ≤ 1 or baseline level Consider this approach or discontinuation for a 1st occurrence of grade 4 HFSR	Dose modification • 1st reduction: 225 mg/day • 2nd reduction: 150 mg/day	If cetuximab is discontinued, discontinue encorafenib Permanently discontinue: • if patient is unable to tolerate 150 mg/day • for grade 4 AEs other than HFSR • for recurrent grade 4 HFSR • if no improvement of grade 2 or 3 HFSR after withholding treatment for ≤ 4 weeks Consider discontinuing • upon 1st occurrence of grade 4 HFSR • for recurrent grade 3 HFSR
	Note: dose modification is not recommended for new primary cutaneous malignancies			

AE, adverse event; BRAF, v-raf murine sarcoma viral oncogene homolog B1; GI, gastrointestinal, HFSR, hand–foot skin reaction

1. Braftovi (encorafenib) Prescribing Information.

DOSING
FLEXIBLE DOSING

Regorafenib	Sunitinib
ReDOS[1] • Randomised, open-label, phase 2 trial in 123 patients with refractory metastatic CRC, comparing: ✦ standard dose (160 mg/day; 3 weeks on, 1 week off) vs ✦ dose escalation (80 mg/day in week 1, 120 mg/day in week 2, and 160 mg/day in week 3 if no significant drug-related AEs occurred) **Results** • More patients started cycle 3 in the dose-escalation group than in the standard-dose group (43% vs 26%; P = 0.043) • **Dose escalation did not appear to jeopardise efficacy** • **The most common AEs were the same in each group** • The dose-escalation strategy appeared to reduce the severity of some common AEs, including HFSR	**RESTORE**[3] • Randomised, open-label, phase 2 trial in 74 treatment-naïve patients with clear-cell metastatic RCC, comparing: ✦ standard 4/2 schedule (4 weeks on, 2 weeks off) vs ✦ 2/1 schedule (2 weeks on, 1 week off) **Results** • The 2/1 schedule was associated with **less toxicity and a higher failure-free survival rate** at 6 months than was the 4/2 schedule, without compromising efficacy (ORR and TTP) • Neutropenia and fatigue in particular were less common with the 2/1 schedule
REARRANGE[2] • Randomised phase 2 trial in 299 patients with metastatic CRC, comparing: ✦ standard dose (160 mg/day; 3 weeks on, 1 week off) vs ✦ reduced dose (120 mg/day; 3 weeks on, 1 week off) vs ✦ intermittent dosing (160 mg/day; 1 week on, 1 week off) **Results** • There was no difference in survival outcomes • The **primary endpoint of improving global tolerability in the reduced-dose and intermittent-dosing groups was not met** • Flexible dosing resulted in numerical improvement in relevant AEs, including fatigue, HFSR, and hypertension	

Flexible dosing strategies have been studied with regorafenib in CRC and with sunitinib in RCC[1–3]

- The NCCN guidelines recommend a dose-escalation strategy when using regorafenib for CRC[4]
- In clinical practice, the data on sunitinib in RCC are extrapolated to GI cancers

AE, adverse event; CRC, colorectal cancer; HFSR, hand–foot skin reaction; ORR, overall response rate; TTP, time to progression

1. Bekaii-Saab TS, et al. Lancet Oncol. 2019;20:1070-82. 2. Argilés G, et al. Ann Oncol. 2019;30 suppl 4:iv135(O-026). 3. Lee JL, et al. Ann Oncol. 2015;26:2300-5. 4. NCCN Guidelines. Colon Cancer. Version 2.2020 (3 March 2020).

WHAT PATIENTS **CAN DO**

Use the link found next to this slide set to download your own version of the leaflet, designed to help patients prevent and manage skin toxicities related to their targeted therapy.

Fight CRC also provide additional helpful **patient resources:**

https://fightcolorectalcancer.org/resources/skin-toxicity-resources/

	TO DO	TO AVOID
	Contact your healthcare provider straight away when you have a skin reaction	
	Use fragrance-free, mild soap for sensitive skin Bathe and shower in lukewarm water Use a bland emollient (ointment or cream)	Avoid hot showers
	Use broad-spectrum sunscreen (SPF 30+) and lip balm, under all weather conditions Wear sun-protective clothing (hats, long sleeves)	Avoid midday sun (10 am–2 pm)
	Lubricate your hands and feet before any activity Use gloves for hand-oriented tasks (e.g. gardening) Wear well-fitting shoes and socks	Avoid heat and friction on hands and feet Avoid repetitive tasks and vigorous exercise
	Wear shoes with a wide toe box	Avoid sharp angles on nails when trimming
	Use gentle hair care Wear a hat and use sunscreen on areas of sparse hair	Avoid excessive processing (e.g. colouring, straightening, blow-drying)
	Keep good oral hygiene	
	Use medication as prescribed Use prophylactic medication even if you have no symptoms	

CRC, colorectal cancer.

SUMMARY

EFFECTIVE MANAGEMENT OF SKIN TOXICITIES INVOLVES A **MULTIMODAL STRATEGY** THAT INCLUDES:

- patient education
- prophylactic and supportive care
- dose modification (including flexible dosing)

MANAGEMENT

- Management of low-grade toxicity is similar to prophylactic measures
- Management of high-grade toxicity depends on the type of toxicity and the grade

FOR ALL PATIENTS TREATED WITH TARGETED THERAPIES, PROPHYLACTIC MEASURES INCLUDE:

- using broad-spectrum sunscreen
- avoiding sun exposure
- using skin moisturisers
- nail and oral care

CONSULT A DERMATOLOGIST IF:

- the skin AE necessitates changes to the cancer treatment
- a grade 2 skin AE does not respond to intervention
- any grade 3 skin AE occurs
- you are uncomfortable treating the skin AE yourself

AE, adverse event.

SKIN TOXICITY

MULTIDISCIPLINARY APPROACH TO PREVENTION AND MANAGEMENT

3

theconnects®

LEARNING OBJECTIVE

BE ABLE TO INVOLVE A MULTIDISCIPLINARY TEAM IN THE PREVENTION, DIAGNOSIS, AND MANAGEMENT OF SKIN TOXICITIES ASSOCIATED WITH TARGETED THERAPY IN GI AND LIVER CANCERS

WHAT
WILL YOU LEARN?

- **In this case-based section you will learn about the role of a multidisciplinary team in the prevention, diagnosis, and management of skin toxicities**

WHY
IS THIS IMPORTANT?

- **When each member of the multidisciplinary team participates in prevention, diagnosis, and management, skin toxicities can be more effectively prevented and managed and diagnosed earlier**

HCC PATIENT CASE – PART 1
MR GRAHAM

PATIENT

- 63-year old Mr Graham is diagnosed with HCC
- After progressing on locoregional therapy, he received sorafenib for 9 months at full dose, with one dose modification for HFSR
- Mr Graham has now progressed on sorafenib and is about to start regorafenib

CLINICAL CHALLENGE

- How can we prevent the occurrence of HFSR during 2nd-line treatment with regorafenib?

MULTIDISCIPLINARY TEAM DECISION

- Consult a dermatologist before starting regorafenib
- Discuss with the patient whether to start regorafenib at a full dose or at a reduced dose
- Educate on prevention, including gentle skin care, minimizing skin dryness and avoiding heat and friction
- Prescribe urea cream for pre-emptive use and a topical corticosteroid for use with the first signs of HFSR

HCC, hepatocellular carcinoma; HFSR, hand–foot skin reaction.

HCC PATIENT CASE – PART 2
MR GRAHAM

PATIENT

- After 6 months of treatment with regorafenib, Mr Graham develops severe HFSR

CLINICAL CHALLENGE

- Why did the patient develop HFSR now?
- Should regorafenib be stopped or should the dose be changed?

MULTIDISCIPLINARY TEAM DECISION

- Reinforce education on preventative measures, as the symptoms started after increased physical activity
- Reduce the dose of regorafenib and escalate to highest tolerated dose when the HFSR resolves to grade < 1
- Consult a dermatologist for further treatment and guidance

HFSR, hand–foot skin reaction.

GI CANCER PATIENT CASE – PART 1
MS WILLIAMS

PATIENT

- 55-year old Ms Williams is diagnosed with RAS wild type, microsatellite stable, left-sided mCRC with a heavy disease burden, including bi-lobar liver metastases, lung metastases and lymphadenopathy
- She is about to start FOLFOX + cetuximab

CLINICAL CHALLENGE

- Ms Williams works in sales and does not want people to know she has cancer. Therefore, she is very worried about the possibility of getting a treatment-related rash
- What can we do to help prevent papulopustular rash?

MULTIDISCIPLINARY TEAM DECISION

- Educate the patient on minimizing skin dryness and avoiding UV radiation
- Start topical corticosteroids
- As the patient is so worried, the team decides prophylactic oral antibiotics are indicated as well

FOLFOX, leucovorin calcium (calcium folinate), 5-fluorouracil, and oxaliplatin; GI, gastrointestinal; mCRC, metastatic colorectal cancer, UV, ultraviolet.

GI CANCER PATIENT CASE – PART 2
MS WILLIAMS

PATIENT

- 6 months later, Ms Williams is responding to treatment very well and is feeling good. She has even been on holiday to the Bahama's
- Despite being compliant with using her prophylactic topical corticosteroids and oral doxycycline, she has developed a grade 1/2 papulopustular rash on her face

CLINICAL CHALLENGE

- Why did the patient develop rash now?
- How should the rash be treated?

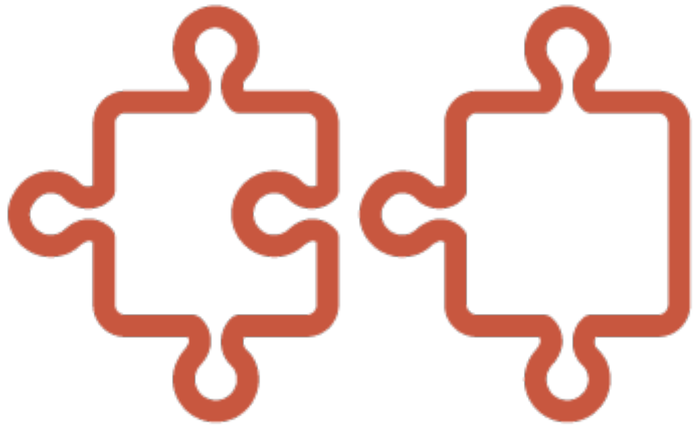
MULTIDISCIPLINARY TEAM DECISION

- Sun exposure can trigger a flare of papulopustular rash, so insufficient sun protection on holiday might have triggered it. Doxycycline-related photosensitivity might also have contributed
- She may have developed resistance to the antibiotic
- The team decides to keep the cancer treatment unchanged and refer Ms Williams to the dermatologist for treatment of the rash

GI, gastrointestinal.

SUMMARY

WHEN EACH MEMBER OF THE **MULTIDISCIPLINARY TEAM** PARTICIPATES IN PREVENTION, DIAGNOSIS, AND MANAGEMENT, SKIN TOXICITIES CAN BE MORE **EFFECTIVELY PREVENTED AND MANAGED AND DIAGNOSED EARLIER**



SUMMARY

AND CLOSE

BEFORE YOU GO…

- Thank you for participating in this educational programme on skin toxicities related to targeted therapy in GI and liver oncology
- You now understand more about:
  - the skin toxicity associated with targeted therapy in GI and liver cancers
  - preventing and managing skin toxicities associated with targeted therapies in GI and liver cancers
  - involving a multidisciplinary team in the prevention, diagnosis, and management of skin toxicities associated with targeted therapy in GI and liver cancers
- We hope you have found this educational programme useful for your daily practice
- Throughout the slide set, there are links to additional information and resources
  - If you wish, you can revisit either resource at any time and dig deeper into a specific topic
  - On **ESMO OncologyPRO** you will find more information about **MKI-related skin toxicities**

ESMO, European Society for Medical Oncology; GI, gastrointestinal; MKI, multiple kinase inhibitor

THANK YOU

- Please visit the **accredited e-learning at COR2ED Checkpoint** to further explore:
  - the skin toxicity associated with targeted therapy in GI and liver cancers
  - the prevention and management of skin toxicities associated with targeted therapies in GI and liver cancers
  - involvement of a multidisciplinary team in the prevention, diagnosis, and management of skin toxicities associated with targeted therapy in GI and liver cancers
- You can complete an assessment at the end of the e-learning and apply for your CME credit or MOC point.

CME, continuing medical education; GI, gastrointestinal; MOC, Maintenance of Certification

ADDITIONAL

RESOURCES AND INFORMATION

WHAT PATIENTS **CAN DO**

- Fight Colorectal Cancer offers a variety of resources dedicated to educating patients and caregivers on skin toxicities such as Hand Foot Skin Reaction, Hand Foot Syndrome, and EGFR rash. All resources are reviewed by members of Fight CRC's distinguished medical advisory board. Find access to these resources at **https://fightcolorectalcancer.org/resources/skin-toxicity-resources/**
  - **Skin Toxicity Mini Magazine**: offered in print or online
  - Patient testimonies: watch videos of patients detailing their experiences with side effects of the skin
  - Expert videos: watch videos of experts in the field discussing skin toxicities in lay terminology

ESMO, European Society for Medical Oncology; GI, gastrointestinal; MKI, multiple kinase inhibitor

ABBREVIATIONS

- **ABIM**, American Board of Internal Medicine
- **ACCME**, Accreditation Council for Continuing Medical Education
- **ADL**, activities of daily living
- **AE**, adverse event
- **AGA**, American Gastroenterology Association
- **AMA**, American Medical Association
- **ASCO**, American Society of Clinical Oncology
- **AST,** American Society of Transplantation
- **BCR–ABL**, Philadelphia translocation
- **BRAF**, v-raf murine sarcoma viral oncogene homolog B1
- **BSA**, body surface area
- **CME**, continuing medical education
- **CRC**, colorectal cancer
- **CTCAE**, Common Terminology Criteria for Adverse Events
- **EACCME**, European Accreditation Council for Continuing Medical Education
- **EGFR**, epidermal growth factor receptor
- **ERK**, Extracellular signal-regulated kinase
- **ESMO,** European Society for Medical Oncology
- **FDA**, U.S. Food and Drug Admninstration
- **Flt3**, fms-related tyrosine kinase receptor 3
- **FOLFIRI**, leucovorin calcium (calcium folinate), 5-fluorouracil, and irinotecan
- **FOLFOX**, leucovorin calcium (calcium folinate), 5-fluorouracil, and oxaliplatin
- **GI**, gastrointestinal
- **GIST**, gastrointestinal stromal tumor
- **HCC**, hepatocellular carcinoma
- **HFS,** hand–foot syndrome
- **HFSR**, hand–foot skin reaction
- **HR**, hazard ratio
- **MASCC**, Multinational Association for Supportive Care in Cancer
- **mCRC**, metastatic colorectal cancer
- **MESTT**, MASCC EGFR inhibitor Skin Toxicity Tool
- **MKI**, multiple kinase inhibitor
- **MOC**, Maintenance of Certification
- **NA**, not applicable
- **NCCN**, U.S. National Comprehensive Cancer Network
- **NSAID**, non-steroidal anti-inflammatory drug
- **ONS**, Oncology Nursing Society
- **ORR**, overall response rate
- **OS**, overall survival
- **PARP**, poly ADP ribose polymerase
- **PCOS**, polycystic ovary syndrome
- **PDGF(R)**, platelet-derived growth factor (receptor)
- **PFS**, progression-free survival
- **PRA**, Physician's Recognition Award
- **RCC**, renal cell carcinoma
- **SCAR**, severe cutaneous adverse reaction
- **SPF,** sun protection factor
- **Th**, T helper cell
- **TKI,** tyrosine kinase inhibitor
- **TTP,** time to progression
- **UEMS,** Union of European Medical Specialists
- **UVA,** ultraviolet A
- **UVB,** ultraviolet B
- **VEGFR,** vascular endothelial growth factor receptor
- **WHO,** World Health Organization

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Dr. Catherine Frenette, *Scripps Clinic Center for Organ and Cell Transplantation, San Diego, USA*

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GI, gastrointestinal; HCC, hepatocellular carcinoma