ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

www.immunoscienceacademy.be

Workshop B3

Managing immune related adverse events: focus on endocrine system and skin

Convention room 2, Floor 1

Sandrine Aspeslagh
UZ Brussel

Véronique del Marmol
Erasme Hospital

Mercury number : ONCBE1908737-08
Date of preparation: December 2019

Disclaimer

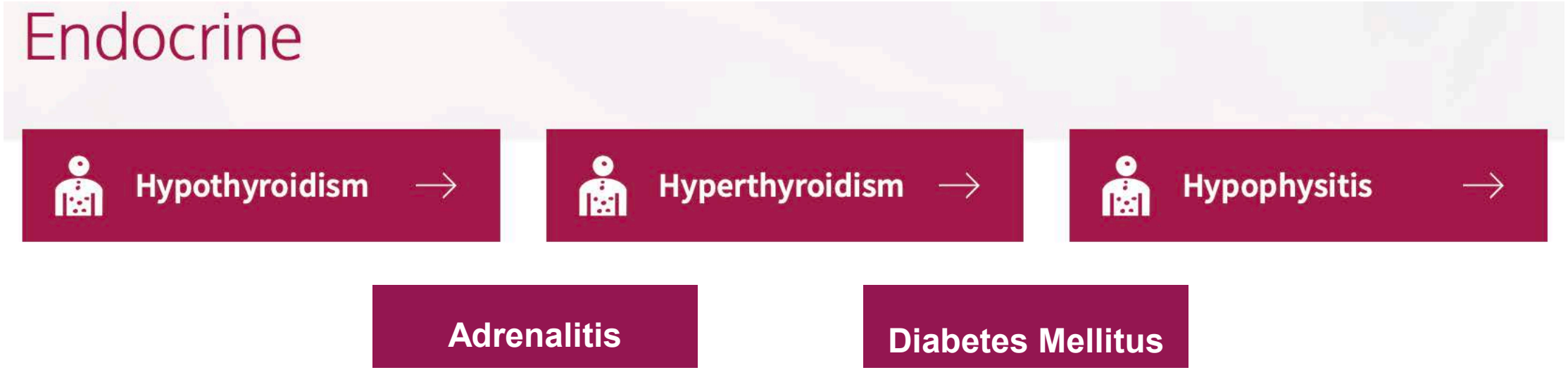
- The case studies within are the speaker's own, BMS has not had any medical input into these

ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Endocrine immune related adverse events

Overview endocrine toxicities



The BSMO immunomanager website will be updated by February 2020

https://www.bsmo.be/immunomanager/irae/

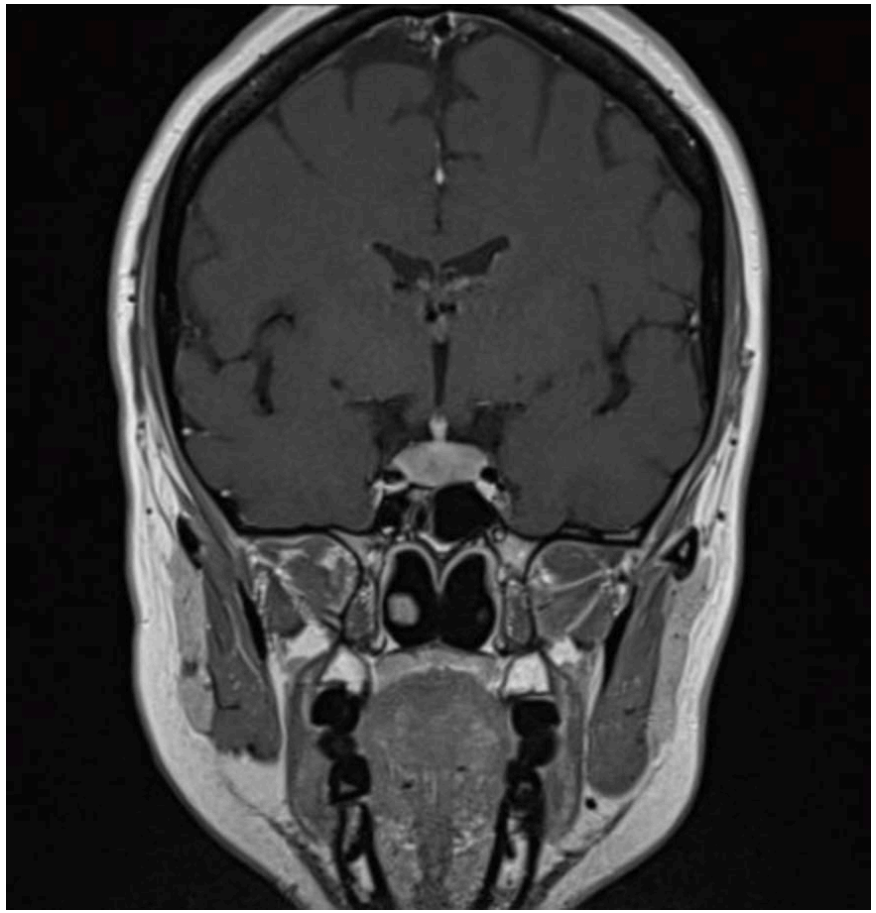
Case 1

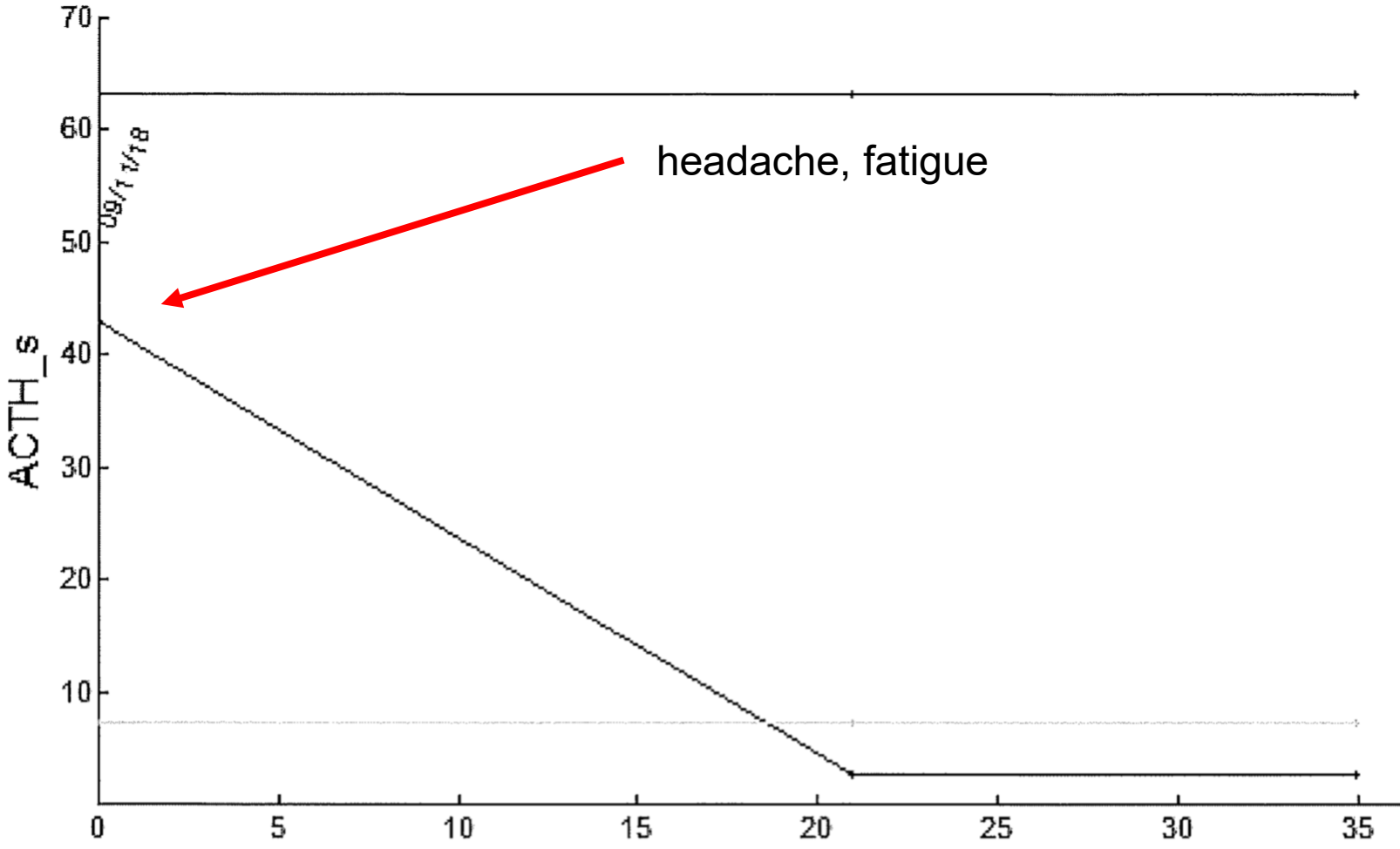
- 44y, woman, hypothyroidism
- Jan 2016: Melanoma right leg: T2N1M0: excision + lymphadenectomy right inguinal region
- Feb 2017: relaps right inguinal region: excision
- Nov 2017: new relaps right inguinal region: excision + start anti-PD1
- Aug 2017: PET scan shows relaps: 3 aorto lumbal lnn
- Sept 2017: start ipilimumab + RT

Case 1

- 9 Nov 2018: fatigue, headache, TSH low, T4 is nl
- Differential diagnostics:
  - Sinusitis
  - Cerebral metastasis
  - Immune related hypophysitis
- Ionogram: normal; cortisol and ACTH normal
- → NSAID for headache and pause ipilimumab
- 16 nov 2018: MRI head: hypophysitis (ante-hypophysis 12mm)
- 30 nov 2018: low cortisol (33 nmol/L), low ACTH (<0,3ng/L)

Brain MRI



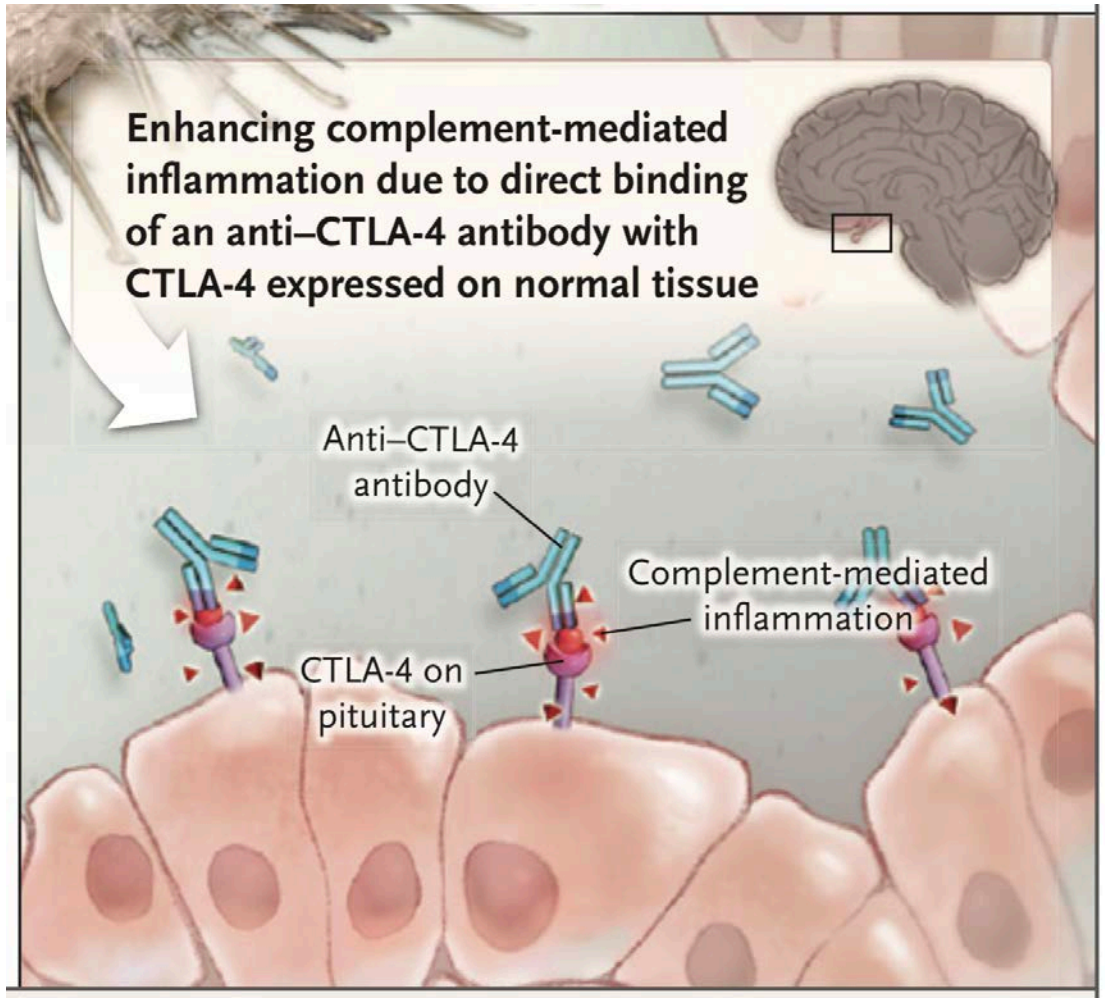


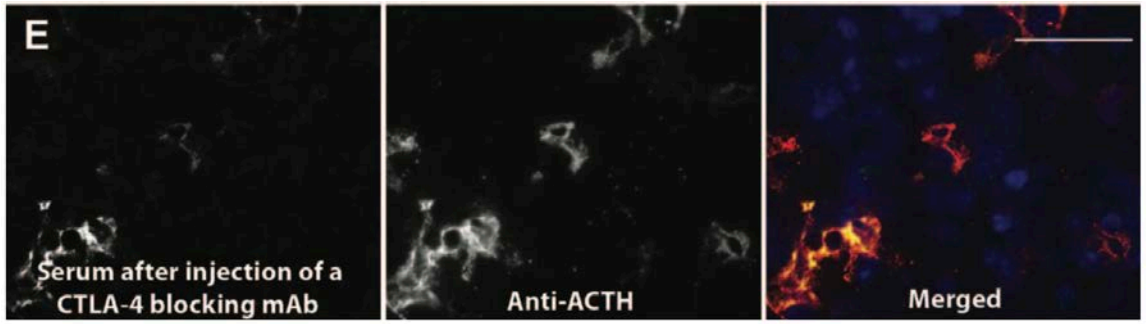
Date	Heure	H	Résultat	Unité	V. réf	Accès
14/12/18	1301	L	<3.0	ng/L	7.2-63.3	49200600
30/11/18	1250	L	<3.0	ng/L	7.2-63.3	49206033
09/11/18	1418		42.9	ng/L	7.2-63.3	49213715

Case 1

- Diagnosis hypophysitis:
  - Start hydrocortisone 20mg-10mg-10mg
  - Symptomatic: add NSAID and delay ipilimumab untill resolution of symptoms
  - Education: 3x daily hydrocortisone dosis in case of stress

Anti-CTLA4 and hypophysitis





ACTH secreting pituary cells express CTLA4

Postow et al, 2017 NEJM, Iwama et al, 2014. Science Translational Medicine

Case 2

- 70y, men
- Jan 2014: Melanoma skull: T2N0M0: excision
- July 2018: relaps left cervical region: excision
- Sept 2018: start anti-PD1 adjuvant setting
- Jan 2018: fatigue, speech difficulties due to dry mouth
  - Biopsy of salivary glands: lymphocytic sialoadenitis

Nl range Cortisol morning 166-507nmol/L; nl range ACTH 7,2-63,3 ng/L

Case 2

- April 2018: persistance fatigue
  - Blood test doesn’t show abnormalities, TSH is normal
- Mai 2018: hospitalized due to extreme fatigue
  - Blood test:
    - low morning cortisol (26 nmol/L) and ACTH (5,8 ng/L):
    - ionogram: Na and K within nl range
    - TSH, T4: within nl range
    - → substitution with hydrocortisone
  - Cerebral MRI scan: no signs of hypophysitis

Nl range Cortisol morning 166-507nmol/L; nl range ACTH 7,2-63,3 ng/L

Anti-PD(L)1 and hypophysitis

- Silent, often slowly evolving disease
- Rarely complicated with headache
- Exclude for any unwell patient
- Psychological impact of hypophysitis can be major (research Dr A. Rogiers, Hopital Brugmann)
- Heterogenous presentation, MRI might be negative
- Cave fatigue when corticoids for other irAE are tapered

Lupi I et al, 2019, Endocrinology, diabetes and metabolism; Martins Machado C et al, 2019, BMJ case reports, Faje et al 2019, European *Journal of Endocrinology*

Not always corticoids required for irAE

- **Endocrine toxicity:**
  - only replace hormones
- **Hepatitis:**
  - not indicated unless signs of liver dysfunction (eg jaundice, PT drop)
- **Colitis:**
  - early switch TNFablocker if corticoid resistant
  - Future: fecal transplantation?
- **Lipase increase:**
  - no treatment if no clinical signs of pancreatitis

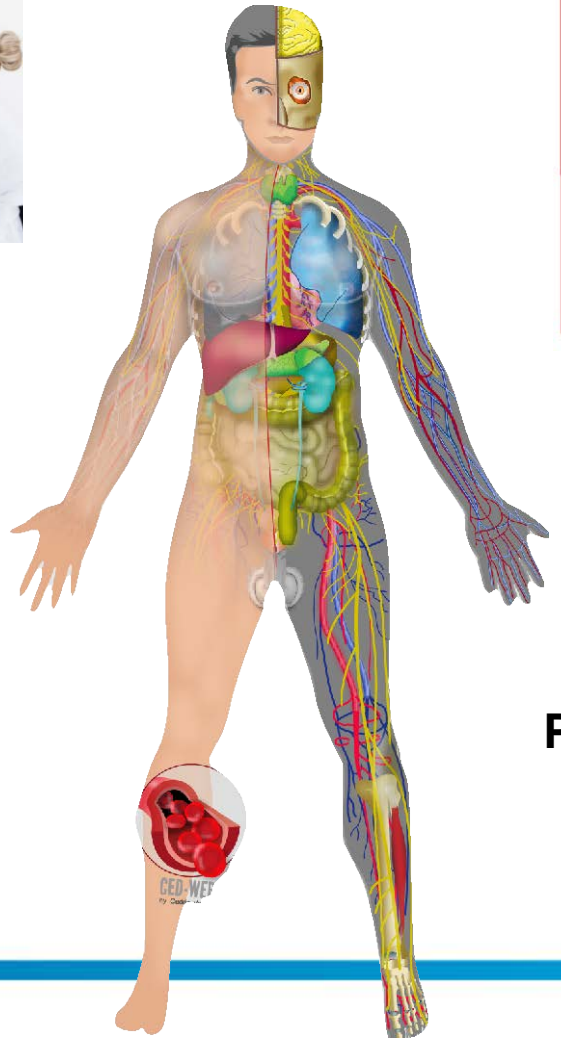
De Martin et al J hepatology 2018 + comment Gauci M et al 2018; Wang Y et al 2018, NatMed, Michot JM et al, 2017, EJC

Take home messages

- Hypophysitis: beware in patients with unexplained fatigue
- Endocrine toxicities don’t require suspension of immunotherapy, neither corticoid therapy

Future perspectives: how to handle irAE

Translational Research



Clinical Care Path/Register for dysimmunity patients

ENSEIGNEMENTS IMMUNO-ONCOLOGIE

Prospective analysis of autoimmune serology

Immune-related AEs: dermatologic

Incidence/onset[1,2,7,8]

- ~40% of patients treated with anti-PD-1
- Combined treatment increases both the incidence and severity of irAEs
- Early onset (3-4 weeks after treatment initiation)
- Can persist after treatment withdrawal (up to 1 y)

Common Manifestations[1–3]

- Maculopapular rash and/or pruritus (trunk or extremities) ~13-21%
- Vitiligo ~8%*
- Dry mouth

* Linked to better tumour responses and outcomes in advanced stage melanoma

Rare manifestations[1,2,4,5]

- Lichenoid dermatitis or psoriasiform
- Bullous reactions (Bullous pemphigoid)
- Dermatitis herpetiformis
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

AE, adverse event; irAE, immune related adverse event; PD-1, programmed cell death receptor 1.

1. Sibaud. Am J Clin Dermatol 2018. doi.org/10.1007/s40257-017-0336-3; 2. Martins et al. Nature Reviews Clin Oncol. 2019 10.1038/s41571-019-0218-0; 3.Perret et al. Int J Dermatol 2017;56:527–33; 4. Mochel et al. J Cutan Pathol 2016;43:787–91; 5. Tetzlaff et al. Am J Dermatopathol 2017 39:121–9. 6. Sibaud. Am J Clin Dermatol 2017. doi: 10.1007/s40257-017-0336-3; 7; Hwang et al. Act Dermo-Sifiliograficas 2017 10.1016/j.ad.2016.05.019; Hodi et al. Lancet Oncol 2018 doi.org/10.1016/S1470-2045(18)30700-9

Immune-related AEs: dermatologic

Grade 1

- Macules/papules covering <10% BSA; with or without symptoms (e.g. pruritus, burning, tightness)

Grade 2

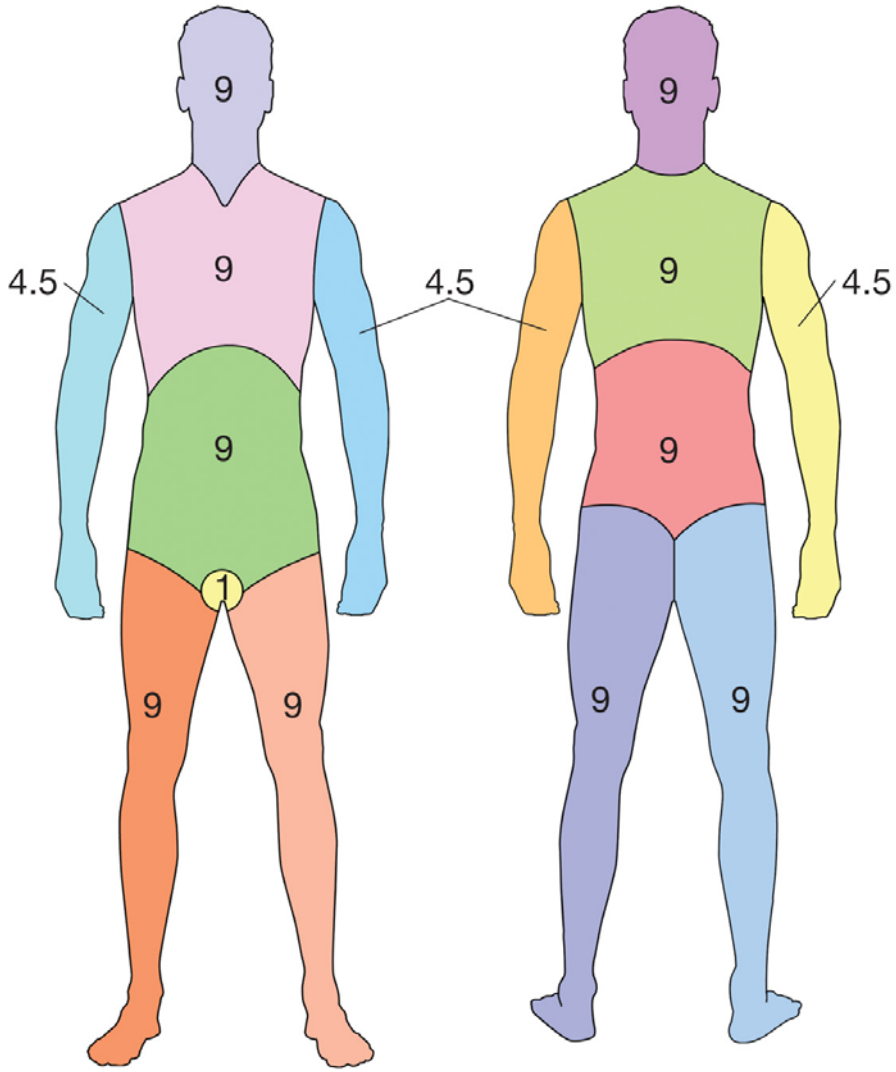
- Macules/papules covering 10%-30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting instrumental activities of daily living, grade 1 persistence

Grade 3

- Macules/papules covering >30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting self-care activities of daily living

Grade 4-5 = Life-threatening reactions

- Blisters and exfoliative rash, fever, mucosal ulcerations, facial oedema, Nikolsky sign, etc.



AE, adverse event; BSA, body surface area; ADL, activities of daily living.

1. Sibaud. Am J Clin Dermatol 2018. doi.org/10.1007/s40257-017-0336-3; 2. Collins. Current Problems in Cancer 2017. 10.1016/j.currproblcancer.2016.12.001; 3. Martins et al. Nature Reviews Clin Oncol. 2019 10.1038/s41571-019-0218-0

Grade 1

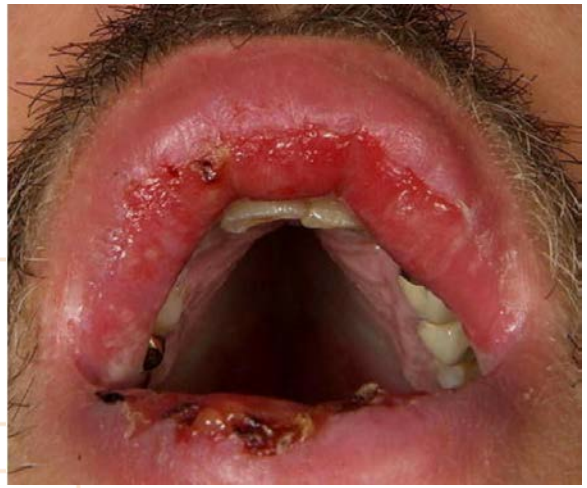
- Macules/papules covering <10% BSA; with or without symptoms (e.g. pruritus, burning, tightness)

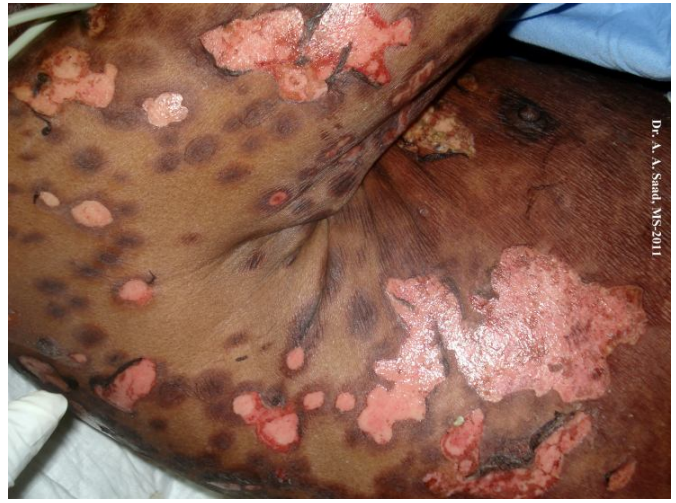
Grade 2

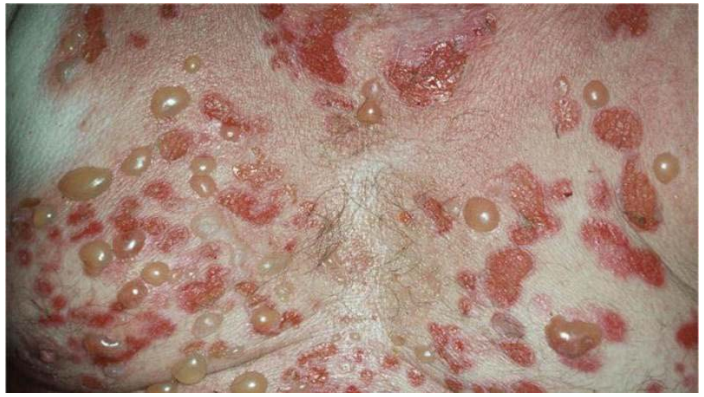
- Macules/papules covering 10%-30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting instrumental ADL, grade 1 persistence

Grade 3

- Macules/papules covering >30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting self-care ADL







Grade 4-5 = Life-threatening reactions

- Blisters and exfoliative rash, fever, mucosal ulcerations, facial oedema, Nikolsky sign, etc.

AE, adverse event; BSA, body surface area; ADL, activities of daily living.

1. Sibaud. Am J Clin Dermatol 2018. doi.org/10.1007/s40257-017-0336-3; 2. Collins. Current Problems in Cancer 2017. 10.1016/j.currproblcancer.2016.12.001; 3. Martins et al. Nature Reviews Clin Oncol. 2019 10.1038/s41571-019-0218-0

Take home message:

1st	**Evaluate severity:** BSA and limitation of the ADL
2nd	**Therapeutic plan:** symptomatic treatment + rediscuss immunotherapy according to grade
3rd	Always **re-evaluate severity/grade:** dynamic algorithm
4th	Delay immunotherapy if needed – **Tackle quality of life**

Sibaud. Am J Clin Dermatol 2018. doi.org/10.1007/s40257-017-0336-3; 2. Martins et al. Nature Reviews Clin Oncol. 2019 10.1038/s41571-019-0218-0

Disclaimer

While Bristol-Myers Squibb uses reasonable efforts to include accurate and up-to-date information in this material, Bristol-Myers Squibb makes no warranties or representations as to its accuracy. Bristol-Myers Squibb assumes no liability or responsibility for any errors or omissions in the content of the material. Neither Bristol-Myers Squibb nor any other party involved in creating, producing or delivering the material is liable for any direct, incidental, consequential, indirect or punitive damages arising out of your access to, or use of, the material.

You should assume that everything you see or read on this presentation is copyrighted, unless otherwise noted, and may not be used without mentioning the source. Bristol-Myers Squibb neither warrants nor represents that your use of materials displayed on the Site will not infringe rights of third parties not owned by or affiliated with Bristol-Myers Squibb.

Nothing on these presentations should be construed as the giving of advice or the making of a recommendation and it should not be relied on as the basis for any decision or action. BMS, nor other parties involved, accepts no liability for the accuracy or completeness or use of, nor any liability to update, the information contained on this Presentation. These materials are provided "AS IS" WITHOUT WARRANTY OF ANY KIND, EITHER EXPRESSED OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT.