Management of treatment related side effects

Michel Ducreux
Villejuif
Disclosure

- Participation to advisory boards:
  - ROCHE
  - MERCK SERONO
  - AMGEN
  - SANOFI
  - BAYER
  - SIRTEX
  - LILLY

- Speaker in symposiums:
  - ROCHE
  - MERCK SERONO
  - SANOFI
  - TERUMO

- Research funding:
  - ROCHE
  - MERCK SERONO
  - PFIZER

- My wife is the Head of the Oncology Business Unit SANDOZ Company
First of all: Talk to the patient (and his family)

- Side effects have to be explained to the patients
- If possible
  - First time by the Medical Oncologist
  - A second time by a specialized nurse
  - General practitioner has to be informed of the choice of the treatment
- Discussion on the toxicity profile can be useful for the choice of the treatment
- Simple explanations needed:
  - Insist on potentially severe side effects: diarrhoea with irinotecan, febrile neutropenia,....
Chemotherapy

- **Specific information:**
  - 5FU: mucositis, diarrhoea,
  - Irinotecan: diarrhoea, alopecia, nausea, vomiting
  - Oxaliplatin: neuropathy, nausea, vomiting

- **General information**
  - Blood samples results before CT administration
  - Prevention of emesis is better
  - Documents have to be given to the patients

- **General and specific information**
  - Sexuality, fertility, pregnancy
  - Driving, drinking alcohol
  - Vaccinations
Chemotherapy, general clinical parameters before...

- Performance status (ECOG 0 – 3)
- Temperature, blood pressure
- Weight, Size = Body surface
- BMI: Look for denutrition
- Central venous access
- Record of all other medications
- Recent CT scan
- **Specificity of targeted therapies**
  - Cetuximab – panitumumab: skin, and feet status
  - Bevacizumab: 28 days at least after surgery
Biological parameters

• **Standard blood count at least before each cycle.**

• **Other blood tests depending on CT:**
  - **Irinotecan:** bilirubin level
  - **Oxaliplatin:** creatinin level

• **Targeted therapies**
  - **Bevacizumab:** dipstick (if 2+ or 3+: 24-hour proteinuria and creatinin clearance)
  - **Cetuximab, panitumumab:** Ras testing, magnesemia, calcemia
Contra-indications

- **5FU**: known DPD homozygous deficit
- **Irinotecan**: Gilbert’s disease (beginning at a low level of dose is recommended)
- **Oxaliplatin**: severe neuropathy (diabetes, alcohol), known allergy
- **Cetuximab, panitumumab**: interstitial pneumopathy
- **Bevacizumab**: recent arterial thrombosis, surgery < 28 days before, unhealed wound, uncontrolled arterial hypertension
Management of toxicity of chemotherapy

- **Neutropenia**
  - Stop the 5FU bolus first
  - Then hematological growth factors or decrease of doses

- **Thrombopenia**
  - Decrease of doses

- **Mucositis**
  - Decrease of doses

- **Diarrhoea**
  - High-dose loperamide

- ............
Treatment of oxaliplatin induced neuropathy by intravenous mangafodipir

A new recent review in the literature

Biological agents in gastrointestinal cancers: adverse effects and their management

Nivedita Arora¹, Arjun Gupta¹, Preet Paul Singh²

© Journal of Gastrointestinal Oncology. All rights reserved. jgo.amcgroups.com J Gastrointest Oncol 2017;8(3):485-498
Infusion of cetuximab, allergic reactions

- **Grade 1:** transient rash and / or fever <38°C
  Reduced rate of 50%, monitor (max length <4 h)
- **Grade 2:** urticaria and / or fever > 38°C:
  Stop and resume to 50% of the initial rate if resolution of the symptoms; Reduced rate and monitor subsequent infusions
- **Grade 3-4:** bronchospasm and / or edema and / or shock
  Definitive exclusion of cetuximab
  Panitumumab has to be used

Premedication with corticosteroids Siena et al, ASCO 2007

=> Reactions 7% vs. 22% (grade 3-4: 1% vs 5%)
Management of skin toxicity of anti-EGFR

Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities

Mario E. Lacouture · Milan J. Anadkat · René-Jean Bensadoun · Jane Bryce · Alexandre Chan · Joel B. Epstein · Beth Eaby-Sandy · Barbara A. Murphy · MASCC Skin Toxicity Study Group
Skin toxicity of anti-EGFR
Chronology

Beech J et al. Future Oncology 2018
Skin toxicity of anti-EGFR Chronology

1. Rash acnéiforme
2. Hyperpigmentation
3. Fissure
4. Paronychie
5. Xerosis
6. Telangectasias
7. Trichomégalie

Time (weeks)
### Acute skin toxicity

#### Table 3 Papulopustular (acneiform) rash recommendations

<table>
<thead>
<tr>
<th>Recommend</th>
<th>Not recommended</th>
<th>Level of evidence</th>
<th>Recommendation grades</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preventive (weeks 1–6 and 8 of EGFRi initiation)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Hydrocortisone 1% cream with moisturizer and sunscreen twice daily</td>
<td>Pimecrolimus 1% cream</td>
<td>II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tazarotene 0.05% cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sunscreen as single agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Minocycline 100 mg daily</td>
<td>Tetracycline 500 mg bid</td>
<td>II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100 mg bid</td>
<td></td>
<td></td>
<td>Doxycycline is preferred in patients with renal impairment. Minocycline is less photosensitizing.</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>Vitamin K1 cream</td>
<td>IV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Topical</td>
<td>Alclometasone 0.05% cream</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluocinonide 0.05% cream bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin 1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Doxycycline 100 mg bid</td>
<td>Acitretin</td>
<td>IV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Minocycline 100 mg daily</td>
<td></td>
<td></td>
<td>Photosensitizing agents</td>
</tr>
<tr>
<td></td>
<td>Isotretinoin at low doses (20–30 mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> EGFRi study
### Xerosis

**Table 8: Xerosis recommendations**

| Preventive | Topical | Bathing techniques using bath oils or mild moisturizing soaps and bathing in tepid water | Regular moisturizing creams | III | B |
| Treatment | Topical (mild/moderate) | Emollient creams that are packaged in a jar/tub that lack fragrances or potential irritants | Alcohol-containing lotions | III | B |
| Topical (severe) | Medium- to high-potency steroid creams (triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone propionate 0.05%; alclometasone 0.05%) | Retinoids or benzoyl peroxide | More greasy creams for use on the limbs, but caution use of greasy creams on the face and chest | Exfoliants may sting or burn when applied to eroded or erythematous skin—apply only on intact skin | III | B |

*EGFRI study*
### Fissure recommendations

<table>
<thead>
<tr>
<th>Recommend</th>
<th>Not recommended</th>
<th>Level of evidence</th>
<th>Recommendation grades</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Wear protective footwear and avoid friction with fingertips, toes, and heals</td>
<td>III</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Thick moisturizers or zinc oxide (13–40%) creams Liquid glues or cyanoacrylate to seal cracks Steroids or steroid tape, hydrocolloid dressings, topical antibiotics Bleach soaks to prevent infection Zinc oxide</td>
<td>III(^a)(^b)</td>
<td>B</td>
<td>Cream application often impractical</td>
</tr>
</tbody>
</table>

\(^a\) EGFRI study

\(^b\) Non-EGFRI cancer treatment study
A problem of severity grading.

<table>
<thead>
<tr>
<th>Contributing factors</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact on patient’s quality of life</td>
<td>Mild: Not limiting day-to-day life activities</td>
</tr>
<tr>
<td>Intervention needed</td>
<td>Mild: Can be self-managed by the patient</td>
</tr>
<tr>
<td>Ability to continue EGFR1 treatment</td>
<td>Mild: No dose modification required</td>
</tr>
</tbody>
</table>

Example appearance: **Skin**
- Mild: Redness and flushing only, with or without itch
- Moderate: Papules, pustules and irritation (acneiform)
- Severe: Crusted, eroded pustular acneiform lesions
  - Example of a severe EGFR1-induced acneiform rash:
To make it simple

Grade 1
Emollients
Hydrocortisone 1% cream

Grade 2
Emollients
Hydrocortisone 1% cream
Oral doxycycline 100 mg

Grade 3
Stop treatment
Dermatologist advice
Oral doxycycline + local antibiotics
Avoid sun, hot water, "fat" emollient
Advisor makeup covering skin lesions
Paronychias
Table 10 Paronychia recommendations

<table>
<thead>
<tr>
<th>Recommend</th>
<th>Not recommended</th>
<th>Level of evidence</th>
<th>Recommendation grades</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td></td>
<td>II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
<td>Recommend final concentration of approximately 0.005% (approximately 1/4–1/8 cup of 6% bleach for 3–5 gal water)</td>
</tr>
<tr>
<td>Avoid irritants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Diluted bleach soaks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcineur inhibitors</td>
<td></td>
<td>II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
<td>Recommend usage of ultrapotent topical steroids as first-line therapy given cost and availability of these agents</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Tetracyclines</td>
<td>IV&lt;sup&gt;b&lt;/sup&gt;/II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>D/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Biotin for brittle nails</td>
<td></td>
<td>III&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reserved for pyogenic granulomata; consensus of experts</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>IV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Silver nitrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical cauterization weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrodesiccation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail avulsion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Non-EGFRI noncancer treatment study
<sup>b</sup> EGFRI study
### Table 2. Proposed grading of severity of EGFR-associated cutaneous toxicity.

<table>
<thead>
<tr>
<th>Contributing factors</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nails</strong></td>
<td></td>
</tr>
<tr>
<td>Nail-fold edema or erythema; disruption of the cuticle</td>
<td>Edema or erythema with discharge or nail-plate separation resulting in discomfort</td>
</tr>
<tr>
<td>Example of mild EGFR-induced paronychia</td>
<td>Example of moderate EGFR-induced paronychia</td>
</tr>
<tr>
<td>Example of severe EGFR-induced paronychia</td>
<td>Example of severe EGFR-induced paronychia</td>
</tr>
</tbody>
</table>

Beech J et al. Future Oncology 2018
Ocular lesions: conjunctivitis, keratitis
Mucosal lesions: mouth, nose, genital
Cycle 1
Preventive treatment and advice for all patients commencing EGFRi treatment (cycle 1)

PRESCRIPTION
For prophylactic use
- Light emollient (lotion) applied daily as required
- Antiseptic-containing soap substitute used daily
For reactive use in case of symptoms (redness, dryness, early acniform spots†)
- Mild topical steroid cream (e.g. 1% hydrocortisone) +/- antifungal TDS for up to 14 days initially
- Oral tetracycline (e.g. lymecycline or doxycycline at licensed dose) OD for up to 14 days or, if tetracyclines are contraindicated, erythromycin or clarithromycin

GENERAL ADVICE
- Use sunblock (SPF 50) when outdoors and avoid strong sun and weather extremes
- Avoid hot baths, showers and saunas
- Avoid alcohol-based and fragranced skin-care products that may exacerbate dry skin
- Apply petroleum jelly to periungal skin to create water-proof layer
- Avoid manicure/pedicures and avoid tight fitting shoes
- For patients with pre-existing eczema: intensify usual skin care routine
- For patients with active rosacea, acne or eczema: refer immediately to the dermatology department

Patients should contact the oncology team or pharmacy team at the onset of symptoms and for additional skin-care advice between clinic appointments.
Skin toxicity assessment and management for patients continuing EGFRi treatment (cycle 2 onwards)

Is skin toxicity evident?
- Xerosis
- Eczema
- Acneiform rash
- Paronychia

If yes:
- Continue to follow prophylactic advice, including the daily use of emollient cream and antiseptic soap substitute
- Treat aggressively and manage as follows depending on grading of severity, with review at every treatment cycle

If no:
- Record skin toxicity assessment in notes and continue to review at every treatment cycle
- Continue preventative treatment and advice as per cycle 1

Mild
- Continue EGFRi and assess adherence to current supportive treatment. If adherence is poor, advise on correct use; if good, intensify treatment as follows:
  - For acneiform rash: mild topical steroid +/- antifungal TDS until clinical improvement or review; and continue oral tetracycline (e.g. lymecycline or doxycycline) once daily for at least 12 weeks
  - For scalp involvement: betamethasone 0.1% scalp application used daily until clinical improvement

Moderate
- Treat as per mild and intensify treatment as follows:
  - For acneiform rash: increase dose of oral tetracycline to BD for 4 weeks where appropriate
  - For scalp involvement: potent topical steroid lotion twice daily for 2 weeks
  - For xerosis or eczema: consider switching emollient to a more greasy preparation (ointment)
  - For pruritus: anti-histamine, such as hydroxyzine, once daily before bed where pruritus is disruptive to sleep
  - For paronychia: potent topical steroid cream (betamethasone 0.1%) applied under occlusion until clinical improvement or review. If purulent, culture and prescribe oral antibiotic based on sensitivity
Is skin toxicity evident?
- Xerosis
- Eczema
- Acneiform rash
- Paronychia

Yes
- Continue to follow prophylactic advice, including the daily use of emollient cream and antiseptic soap substitute
- Treat aggressively and manage as follows depending on grading of severity, with review at every treatment cycle

No
- Record skin toxicity assessment in notes and continue to review at every treatment cycle
- Continue preventative treatment and advice as per cycle 1

Severe
Defer EGFRi until symptoms have resolved to mild and consider dose reduction according to licence. Treat as per moderate and intensify treatment as follows:
- **For xerosis or eczema**: switch to a more potent topical steroid +/- antifungal and use ointment preparation instead of cream.
  Advise more frequent application of emollient and switch to a more greasy preparation (ointment) if not already done so.
  Prescribe oral steroid (e.g. prednisolone), with or without gastroprotection; titrate down, for example from 20 mg to 5 mg OD over 14 days, and review (monitor blood sugars).
- **For acneiform rash**: switch to a lighter emollient.
  Switch to a moderate intensity topical steroid, e.g. 0.025% betamethasone valerate
  As for severe xerosis or eczema, prescribe oral steroid.
- **For all severe cutaneous reactions, including paronychia**: swab lesions for culture and susceptibility testing and prescribe antibiotic accordingly

Seek advice from dermatology department.
Hypomagnesemia (+/- -calcemia, - kaliemia)

Follow-up of magnesemia and calcemia

- Before
- Every two weeks on treatment
- 8 weeks after the end

Grade 1: N to 12 mg/L  => New control 2 weeks later

Grade 2: from 12 to 9 mg/L
=> IV magnesium sulfate: 4 g infused in 2h each cycle

Grade 3: from 9 to 7 mg/L  Grade 4  (≤ 7 mg/L)
=> IV magnesium sulfate: 8 g infused in 4 hours every 2 days
Bevacizumab specific toxicities

Managing Bevacizumab-Related Toxicities in Patients with Colorectal Cancer

M. Wasif Saif, MD, MBBS

J Support Oncol 2009;7:245–251

• Overestimation => Too early stop of anti-angiogenic agents
• Underestimation => serious complications, stroke, HTA
Bevacizumab specific toxicities

### Major Toxicities of Bevacizumab

<table>
<thead>
<tr>
<th>STUDY</th>
<th>BEVACIZUMAB DOSE</th>
<th>FREQUENCY OF ADVERSE EVENTS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HYPERTENSION (GRADE 3)</td>
</tr>
<tr>
<td>AVF2107g↑5</td>
<td>5 mg/kg every 2 weeks</td>
<td>11</td>
</tr>
<tr>
<td>E3200↑6</td>
<td>10 mg/kg every 2 weeks</td>
<td>5</td>
</tr>
<tr>
<td>BRITE↑7</td>
<td>5 mg/kg every 2 weeks</td>
<td>16↑b</td>
</tr>
<tr>
<td>First BEAT↑8</td>
<td>5 mg/kg every 2 weeks (5-FU regimens) or 7.5 mg/kg every 3 weeks (capecitabine regimens)</td>
<td>1</td>
</tr>
</tbody>
</table>

5-FU = 5-fluorouracil; NR = not reported; VTE = venous thromboembolic event; ATE = arterial thromboembolic event

↑ Thromboembolism (listed as "any thrombotic event")

b Specified as hypertension requiring medication
# Hypertension

<table>
<thead>
<tr>
<th><strong>GRADE</strong></th>
<th><strong>DESCRIPTION</strong></th>
<th><strong>MANAGEMENT</strong></th>
</tr>
</thead>
</table>
| Grade 1   | • Asymptomatic, transient (< 24 hours) increase in blood pressure by 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously within normal limits; intervention not indicated  
  • Pediatric: asymptomatic, transient (< 24 hours) increase in blood pressure beyond upper limit of normal; intervention not indicated | No action needed |
| Grade 2   | • Recurrent or persistent (≥ 24 hours) or symptomatic increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously within normal limits; monotherapy may be indicated  
  • Pediatric: recurrent or persistent (≥ 24 hours) increase in blood pressure beyond upper limit of normal; monotherapy may be indicated | No action needed |
| Grade 3   | Requiring more than one drug or more intensive therapy than used previously | If not controlled with medication, discontinue bevacizumab |
| Grade 4   | Life-threatening consequences (eg, hypertensive crisis) | Discontinue bevacizumab |

* Grade based on National Cancer Institute–Common Toxicity Criteria, v 3.0
If absence of proteinuria, the 5 main classes of anti-HTA can be used

Angiotensin-converting enzyme inhibitors (IEC), Renin-angiotensin system antagonists (ARA2), beta blockers (B-bloquant), diuretics (diurétique thiazidique), calcium-channel blockers (inhibiteur calcique)

Recommended bitherapies *HAS 2005*

- B-blocker
- Angiotensin receptor blocker
- Angiotensin converting enzyme inhibitor
- Thiazidic diuretics
- Calcium channel blocker
### Bevacizumab-Associated Proteinuria: Guidelines for Dosing and Schedule Modification

<table>
<thead>
<tr>
<th>GRADE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DESCRIPTION</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>≥ 1 g of protein or 0.15–1 g/24 h</td>
<td>No action needed</td>
</tr>
</tbody>
</table>
| Grade 2          | ≥ 2 to ≥ 3 g of protein or > 1–3.5 g/24 h | • Hold bevacizumab until proteinuria improves to ≤ 2 g of protein per 24 hours  
                  |                                                                 | • Discontinue bevacizumab in a patient with > 2 g proteinuria per 24 hours that does not resolve within 3 months after holding bevacizumab  
                  |                                                                 | • Workup for proteinuria, such as renal biopsy, should be considered |
| Grade 3          | ≥ 4 g of protein or > 3.5 g/24 h    | Discontinue bevacizumab                                                    |
| Grade 4          | Nephrotic syndrome                 | Discontinue bevacizumab                                                    |

<sup>a</sup> Grade based on National Cancer Institute–Common Toxicity Criteria, v 3.0
GI perforation

- 1% of the patients
- A little bit more in patients with primary in place (up to 3%)
- Tumoural or non tumoural
- **Best surgical options have to be discussed**
- 20% of death rate after this kind of event…
- No bevacizumab
  - If symptomatic peritoneal carcinomatosis
  - Huge ulcerated lesion
  - Colic stent
Surgery in patients receiving bevacizumab

- Pooled analysis of two studies (1132 patients)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts with major surgery</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + bevacizumab</td>
<td>75</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>CT + placebo</td>
<td>29</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Scappaticci et al. J Surg Oncol 2005

**Emergency**

- First of all you have to inform the surgeon and discuss the risk/benefit ration
- Cautious perioperative hemostasis
- Cautious post-operative follow-up
Wound healing

- Bevacizumab has to be stopped 5 to 6 weeks before surgery
  - 6 weeks for huge surgery such as HIPEC
- Resume administration 4 weeks after surgery
## Wound healing

### Bevacizumab-Associated Wound Healing Complications (Noninfectious): Guidelines for Dosing and Schedule Modification

<table>
<thead>
<tr>
<th>GRADE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DESCRIPTION</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Incisional separation of ≤ 25% of wound, no deeper than superficial fascia</td>
<td>No action needed</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Incisional separation &gt; 25% of wound with local care; asymptomatic hernia</td>
<td>No action needed</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated</td>
<td>Discontinue bevacizumab</td>
</tr>
</tbody>
</table>

<sup>a</sup> Grade based on National Cancer Institute–Common Toxicity Criteria, v 3.0
# Bevacizumab-associated thromboembolism

<table>
<thead>
<tr>
<th>GRADE&lt;sup&gt;a&lt;/sup&gt; (venous)</th>
<th>DESCRIPTION</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Not applicable</td>
<td>–</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (eg, anticoagulation, lysis, filter, invasive procedure) not indicated</td>
<td>No action needed</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (eg, anticoagulation, lysis, filter, invasive procedure) indicated</td>
<td>Withhold bevacizumab&lt;br&gt; If the planned duration of therapeutic-dose anticoagulant therapy&lt;sup&gt;b&lt;/sup&gt; is ≤ 2 weeks, bevacizumab should be withheld until the period of therapeutic-dose anticoagulant therapy is over.&lt;br&gt; If the planned duration of therapeutic-dose anticoagulant therapy&lt;sup&gt;b&lt;/sup&gt; is &gt; 2 weeks, bevacizumab should be withheld for 2 weeks and then may be resumed during the period of therapeutic-dose anticoagulant therapy as soon as all of the following criteria are met:&lt;br&gt; • The patient must be on a stable dose of anticoagulant medication and, if on warfarin, have an INR within the target range (usually between 2 and 3) before restarting study drug treatment&lt;br&gt; • The patient has no history of grade 3/4 hemorrhagic events before restarting bevacizumab&lt;br&gt; • The patient has no evidence of tumor invading or abutting major blood vessels on any previous CT scan</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Embolic event, including pulmonary embolism or life-threatening thrombus</td>
<td>Same as for grade 3</td>
</tr>
<tr>
<td>Incidentally discovered pulmonary embolus, first occurrence</td>
<td>Same as for grade 3</td>
<td></td>
</tr>
<tr>
<td>Symptomatic grade 4 venous thromboembolic event, first occurrence</td>
<td>Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td>Any grade of arterial thromboembolic event</td>
<td>Discontinue bevacizumab</td>
<td></td>
</tr>
</tbody>
</table>

INR = international normalized ratio

<sup>a</sup> Grade based on National Cancer Institute–Common Toxicity Criteria, v 3.0

<sup>b</sup> Defined as a dose titrated to maintain an INR of ≥ 1.5 for warfarin or its equivalent for other anticoagulant medications
Bevacizumab-Associated Hemorrhage: Guidelines for Dosing and Schedule Modification

<table>
<thead>
<tr>
<th>GRADE*</th>
<th>DESCRIPTION</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild, intervention (other than iron supplements) not indicated</td>
<td>No action needed</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Symptomatic and medical intervention or minor cauterization indicated</td>
<td>No action needed</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (ie, hemostasis of bleeding site)</td>
<td>Discontinue bevacizumab</td>
</tr>
</tbody>
</table>

* Grade based on National Cancer Institute–Common Toxicity Criteria, v 3.0
Reversible posterior leukoencephalopathy syndrome

- < 0.1 % of the treated patients
- Signs and symptoms:
  - Headache
  - Seizure
  - Lethargy
  - Confusion
  - Blindness
  - Hypertension
- Diagnosis is made by MRI
- Treatment
  - Discontinuation of bevacizumab
  - Treatment of hypertension
Tolerance of bevacizumab and age?
Pooled analysis of phase II and III trials

Diagram showing the percentage of patients with events such as bleeding, hypertension, proteinuria, ATE, VTE, WHC, fistulae/abscess, GI perforation, and CHF, categorized by age groups (<65 years, ≥65 years, ≥70 years) and treatment (Bevacizumab vs Control).
→ Unexpected side effects
Unexpected side effects

- Splenic infarction
- Perforation of the nasal septum
- Eso-tracheal or bronchial fistula
- Mandibular osteonecrosis
Regorafenib

• **Oral drug**
  – But…..
  – Can be toxic at 160 mg/day

• **If you start the treatment at this level of dose**
  – You have to see the patient after 2 weeks of treatment

• **Main toxicities**
  – Asthenia, fatigue
  – Hand-foot syndrome
  – Diarrhoea
  – Rash

• **Treatment**
  – Stop if severe and decrease the dose to 120 mg or even 80 mg…

• **Sequential increase of dose (Redos):** better tolerance
Aflibercept

- Half-life: 7.13 days
- **Anti-angiogenic agent: no specificity:**
  - GI perforation
  - HTA
  - ...
- But:
  - Aflibercept is able to increase the toxicity of chemotherapy
    - **Diarrhoea:** up to 23% grade 3-4 in the VELOUR study
    - Febrile neutropenia…
Aflibercept: increase of the risk of infectious disease

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% CI)</th>
<th>Ev/Trt</th>
<th>Ev/Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al. [7]</td>
<td>0.243 (0.025, 2.365)</td>
<td>0/93</td>
<td>2/87</td>
</tr>
<tr>
<td>Tannock et al. [6]</td>
<td>3.170 (1.281, 7.845)</td>
<td>15/611</td>
<td>4/598</td>
</tr>
<tr>
<td>Rougier et al. [8]</td>
<td>1.004 (0.201, 5.010)</td>
<td>3/270</td>
<td>3/271</td>
</tr>
<tr>
<td>Ramlau et al. [18]</td>
<td>4.222 (0.955, 18.669)</td>
<td>6/452</td>
<td>1/453</td>
</tr>
<tr>
<td>Gotlieb et al. 22</td>
<td>1.661 (0.164, 16.837)</td>
<td>2/30</td>
<td>1/25</td>
</tr>
</tbody>
</table>

**Overall (I^2=33%, P=0.204)**  
2.163 (1.140, 4.105)  26/1456  11/1434

**Figure 5**  
Odds risk of aflibercept-associated fatal infections vs. control from randomized controlled trials of patients with cancer

Ramucirumab

- Half-life: 14 days
- **Anti-angiogenic agent: no specificity:**
  - GI perforation
  - HTA
  - ...
- But:
  - Very moderate increase in chemotherapy related side effects
  - Maybe more active when it is more toxic…
- Pts with any grade of neutropenia: OS = 16.1 months RAM vs 12.6 months Placebo
- Pts without neutropenia: OS = 10.7 months in each arm
TAS 102

- Neutropenia: main side effect...
## Frequency of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>TAS-102 (N=533)</th>
<th>Placebo (N=265)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Gr.</td>
<td>Gr. ≥3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>20 (4)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>43 (8)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>12 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac ischemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Per NCI CTCAE version 4.03.

<sup>a</sup> Events included acute myocardial infarction, angina pectoris, and myocardial ischemia

- One treatment-related death resulting from septic shock was reported

In the future: toxicity of immunotherapy,

Table 3 Major adverse effects associated with immune checkpoint inhibitor therapy and their management

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Incidence and agents</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological toxicities</td>
<td>34% of patients who received nivolumab, 39% of patients who received pembrolizumab (98), 47–69% of patients with ipilimumab (99)</td>
<td>Maculopapular rash, papulopustular rash, Sweet syndrome, follicular dermatitis, urticarial dermatitis, vitiligo, bullous pemphigoid, lichenous dermatitis (100)</td>
<td>Dermatological evaluation necessary for patients with atypical rash, lack of improvement with intervention, grade 3–4 lesions, or oral mucosal involvement. Serum testing for liver and kidney function, tryptase and IgE levels. Grade 1—continue immunotherapy, topical corticosteroids, oral antihistaminics for pruritus. Grade 2—oral prednisone 1 mg/kg/d, oral antihistaminics. If improves to ≤ grade 1, resume immunotherapy. After symptoms improve, taper steroids over ≥1 month. Discontinue immunotherapy if rash does not improve after 12 weeks from last dose. Grade 3–4—hold immunotherapy, oral prednisone 1 mg/kg/d, oral antihistaminics. If improves to ≤ grade 1, taper steroids over ≥1 month. If worsens, additional immunotherapy may be required (infliximab, mycophenolate mofetil, cyclophosphamide) (98)</td>
</tr>
<tr>
<td>Endocrine toxicities</td>
<td>Any grade endocrine toxicity in about 5–10% (101)</td>
<td>Hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency</td>
<td>Hypothyroidism requires thyroid hormone replacement. Early thyroiditis may present with symptoms of hyperthyroidism which can be symptomatically managed with β-blockers. Most endocrinopathies can be successfully treated with hormone replacement, hence discontinuation of therapy is not usually required (101)</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>Incidence is ≤10% (102). Higher rates of grade 3–4 events have been reported when anti-PD-1 was combined with anti-CTLA-4 mAbs, or when ipilimumab was combined with dacarbazine (99)</td>
<td>Usually asymptomatic elevations in AST and ALT levels. Radiologically can appear as hepatomegaly, periporal edema, periporal lymphadenopathy (103)</td>
<td>Patients should have standard liver function tests, exclusion of viral and drug induced hepatitis and exclusion of malignancy. Grade 1—continue immunotherapy if asymptomatic, monitor LFTs routinely. Grade 2—hold immunotherapy, oral prednisone 1 mg/kg/d, monitor LFT daily. If improves and LFT improves to ≤ grade 1, resume immunotherapy. After improvement, taper steroids over ≥1 month with weekly LFTs. Grade 3–4—discontinue immunotherapy, intravenous methylprednisolone, monitor LFTs daily. If no improvement, consider additional immunosuppression. Do not use infliximab as it can cause hepatotoxicity (98,99)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Incidence is ≤10% with anti-PD1/PD-L1 therapy (98). Development of sarcoidosis has also been reported with ipilimumab (104-106)</td>
<td>Acute interstitial pneumonia or acute respiratory distress type pattern on radiology</td>
<td>Investigations include high resolution CT scan, microbial assessment, bronchoscopy and pulmonary consultation as necessary. Grade 1—continue immunotherapy with monitoring for symptoms every 3 days. Repeat CT at every cycle. Grade 2—hold immunotherapy. Daily monitoring. Oral prednisone 1 mg/kg/d. If improves to ≤ grade 1 within 3 days of supportive care, resume immunotherapy. Taper steroids over ≥1 month after improvement. Grade 3–4—discontinue immunotherapy, hospitalization, intravenous methylprednisolone, prophylactic antibiotics, consider additional immunosuppression. If improves to ≤ grade 1, taper steroids over ≥6 weeks (98)</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>Diarrhea occurs in up to 44% of patients treated with ipilimumab, with an incidence of grade 3–4 diarrhea of 18% (99). With anti-PD-1 antibodies, incidence of all grade diarrhea is 6–16% and that of high grade diarrhea is 2.2% (102)</td>
<td>–</td>
<td>Rule out other causes like infection by stool studies. Endoscopy to confirm or exclude colitis may be needed in persistent diarrhea or ≥ grade 2. Grade 1—continue immunotherapy, symptomatic management, loperamide, electrolyte replacement. Grade 2—interrupt immunotherapy, symptomatic and supportive management, consider methylprednisolone and prophylactic antibiotics. Grade 3–4—discontinue immunotherapy, high dose corticosteroids. Prophylactic antibiotics. Additional immunosuppression may be required. If improvement seen, taper corticosteroids over &gt;4 weeks (98,99)</td>
</tr>
</tbody>
</table>