Toxicités oculaires des traitements cytotoxiques anticancéreux et des thérapies ciblées

ACADEMIE NATIONALE DE PHARMACIE

Séance du 16 mai 2018

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Conflit d'intérêt: aucun

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Introduction
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Cytotoxiques systémiques ou « classiques » responsables de toxicités aigues et chroniques variées engageants le pronostic vital:

- myélosuppressives, digestives, hépatiques, pulmonaires, rénales, cardiaques notamment,

Sous déclaration/estimation des toxicités oculaires TO (essais cliniques et études post marketing),

Protocoles plus agressifs/combinaisons d'agents cytotoxiques/allongement espérance de vie:

- augmentation significatives de cas rapportés de troubles oculaires,

Profil de tolérance différent et recul insuffisant pour les thérapies ciblées (TC)

→ Plus de 60 types distincts de TO imputables aux cytotoxiques systémiques et TC (vs 26 NCI CTCAE)

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Introduction
2/2

Il faut dissocier les troubles oculaires liés à:

- l'évolution de la maladie M (sein, poumon, mélanome, digestif, prostate et rein), Sd paranéoplasique,
  - M+: iris, corps ciliaire, rétine, nerf optique et choroïde essentiellement,
- des toxicités indirectes (Sd infectieux « opportunistes »): viraux (VZV, HSV, CMV), fongiques ou bactériens,
- des toxicités directes: absence de spécificité ou inversement similarité de cible entre cellules cancéreuses et microenvironnements locaux (œil),

MAIS imputabilité délicate:

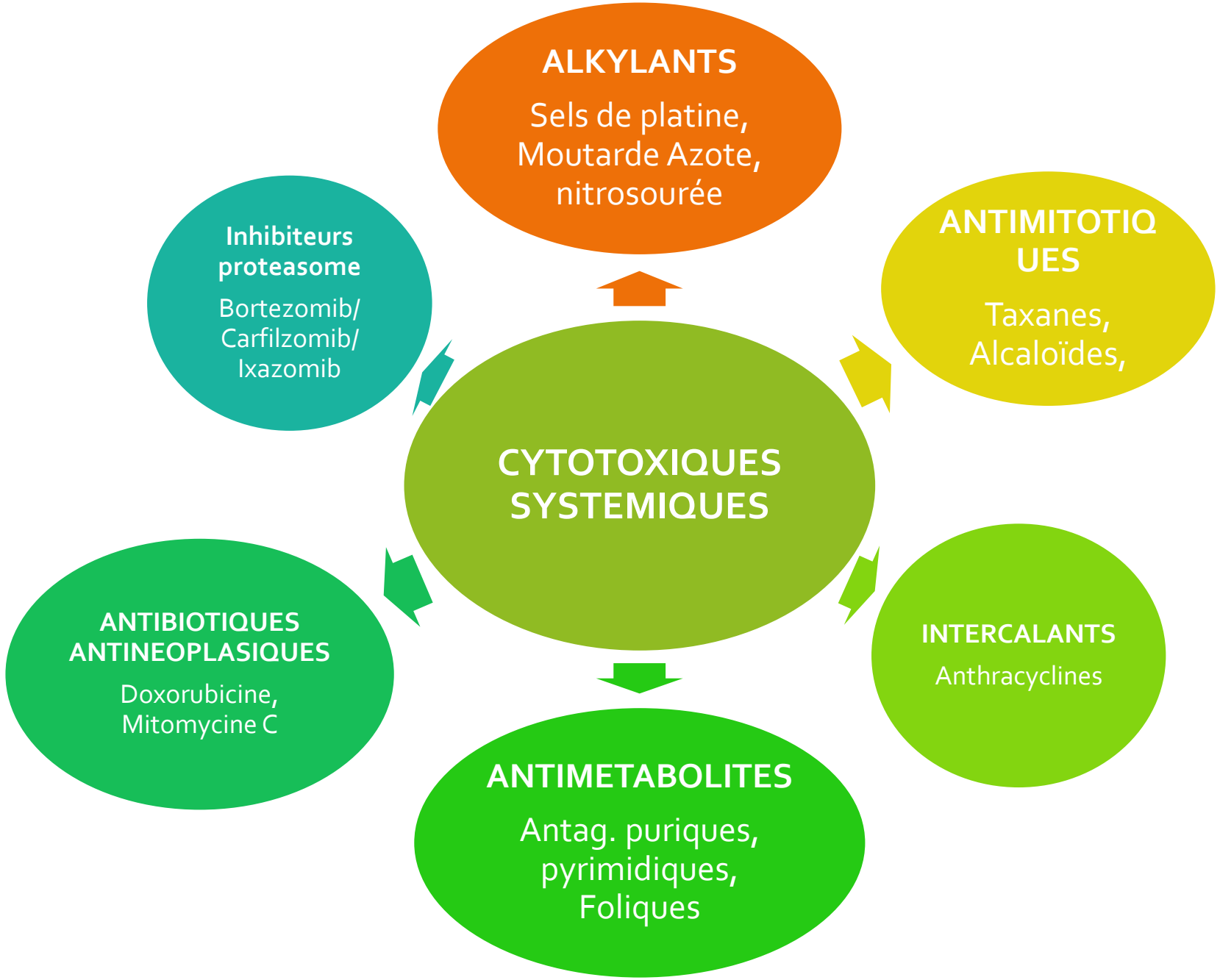
- combinaison thérapeutique,
- en cas d'association à des séquences de radiothérapie,
- en l'absence de bilan ophtalmologique systématique à l'instauration+++++

Cytotoxiques systémiques et T.O.

Quelques chiffres:

- 57 imputables aux cytotoxiques systémiques (Schmid KE *et al*):
  - 46% TO issues de case reports (incidence ≤10%),
  - 38% TO « rares » (incidence de 10-19%),
  - 15% TO peu fréquentes (incidence 20-49%),
  - Seulement 1.4% de TO rapportées comme fréquentes,

Cytotoxiques systémiques et T.O.



Sels de platine:

- **TO:** Neurotoxicité, tb de la vision, oedeme papillaire, névrite rétrobulbaire uni/bilatérale, variation pigmentation maculaire, cécité corticale (carboplatine),
- **Particularités:**
  - Dose cumulative dépendante: 400-800 mg/m² (Wilding *et al.*),
  - Généralement réversible à l'arrêt du traitement,

Dérivés moutarde à l'azote:

- **TO:** Vision tble, Sd œil sec (50% certaines séries), conjonctivite, Sd Stevens Johnson, cataracte en cas d'association aux corticoïdes et kératite (ttt long court chlorambucil)
- **Particularités:** Généralement réversible à l'arrêt de la perfusion ou du traitement,

Alkyl sulfonate (Busulfan):

- **TO:** Vision trouble, Sd œil sec, Cataracte (12,7%),

Nitroso-urée (Carmustine):

- **TO:** Vision tble, douleur, oedeme cornéen, glaucome, rétinopathie, névrite optique, hémorragie rétinienne (25%),
- **Particularités:**
  - Toxicité retardée (➔14 sem.) : métabolites actifs,
  - Barrière hémato-rétinienne: toxicité neuro-rétinienne,

Antagonistes pyrimidiques:

Cytarabine:

- **TO:** Douleurs, larmoiement, sensation corps étranger, photosensibilité, vision trouble avec conjonctivite bilatérale,
- **Particularités:**
  - Récupération acuité visuelle à 4 sem. après arrêt du traitement,
  - Incidence 40-100% pour les protocoles « haute dose »,

5-fluorouracile (5-FU)/capécitabine:

- **TO:** Vision tble, douleur, photophobie, œil sec, larmoiement (30-50%), conjonctivite (40%), œdème orbital, ectropion (1,9%) et kératite,
- **Particularités:**
  - Inh. mitose cellules épithéliales rétiniennes et fibrocytes (Stern *et al.*): inflammation muqueuse (mucite, conjonctivite, etc.),
  - Dose et schéma d'administration dépendante,
  - 5-FU dans les larmes: tox. de surface oculaire (reflex lacrymal) et sténose canal lacrymal,

Antagonistes puriques:

Fludarabine:

- **TO:** Démyélinisation progressive (inh. synth. ADN): ↓acuité, diplopie,
- **Particularités:** 31% des patients traités par des doses journalières >96mg/m² pdt 5-7 jrs,

Antagoniste folique: Méthotrexate (MTX)

- **TO:** Œdème periorbital, douleur, vision trouble, photosensibilité, conjonctivite, blépharite, diminution production reflexe lacrymale,
- **Particularités:**
  - Jusqu'à 25% des patients traités par des protocoles « Haute dose » de MTX,
  - Excrétion lacrymale du MTX: sténose canal lacrymal et TO superficielles,
  - Neuropathie optique en cas d'administration IT du MTX,
  - TO 2 à 7 jours après initiation,
  - Réversible généralement 10 jours après arrêt du ttt,

Antagoniste folique: Pemetrexed

- **TO:** Œdème paupière inf. et œdème péri-orbital (15%), Conjonctivite (26%),

Taxanes:

- **TO:** Photopsie (20%; débute souvent lors de la perfusion, jusqu'à 3 heures après), neuropathie optique ischémique (NOI), œdème maculaire,
- **Particularités:**
  - Neurotoxicité et dose dépendance (≈platines),
  - TO lors d'administration de doses >250mg/m2,
  - Réversible à l'arrêt du traitement,
  - Docétaxel: Epiphora (21-86%), obstruction conduit naso-lacrymal liée à fibrose stromale (Esmaeli *et al.*),

Vinca-alcaloïdes:

- **TO:** Neurotoxicité, Paralysie nerf crânien (ptosis), neuropathie optique, cécité corticale/nocturne,
- **Particularités:**
  - Dose dépendant/Dose cumulative 17-18 mg,
  - Toxicités retardées: médiane de 10 semaines,
  - TO partiellement réversible: 75% (Albert *et al.*),

Anthracyclines:

Larmoiement et conjonctivite:

- 25% des patients traités par Doxorubicine en association avec le Docétaxel,
- 39% des patients traités par Doxorubicine en association avec 5-FU et Cyclophosphamide,

Non cytotoxique, mais non spécifique d'une anomalie moléculaire: Inhibiteurs proteasome (bortezomib et ~~carfilzomib/ixazomib)~~

- Dysfonctionnement des glandes de meibomius (meibum; épiderme paupière, film lacrymal composé de triglycérides): Sd œil sec,
- Chalazion,

Toxicités oculaires **peu fréquentes** des cytotoxiques systémiques ou « classiques » d'après:

Schmid KE, Kornek GV, Scheithauer W *et al.* Update on ocular complications of systemic cancer chemotherapy. *Surv Ophtalmol.* 2006 ; 51(1) :19-40.

Effet indésirable	Drogue	Voie administration
Shunt artérioveineux (SNC)	Carmustine	Intra artériel
Vision trouble	Busulfan	Intraveineuse
Conjonctivite	5-fluorouracile	Intraveineuse
Opacité cornéenne	5-fluorouracile	Intraveineuse
Paralysie nerf crânien	Alcaloïdes	Intraveineuse
Epiphora	5-fluorouracile	Intraveineuse
Douleur oculaire	5-fluorouracile	Intraveineuse
Démyélinisation focale nerf optique	Carmustine/Cisplatine	Intra artériel
Sensation de corps étranger	Cytarabine 5-fluorouracile	Intraveineuse
Kératite	Cytarabine 5-fluorouracile	Intraveineuse
Sd œil sec	Cyclophosphamide Busulfan	Intraveineuse
Pigment maculaire	Cisplatine	Intraveineuse
Œdème papillaire	Carmustine	Intra artériel
Œdème péri orbital	Méthotrexate 5-fluorouracile	Intraveineuse
Photophobie	5-fluorouracile	Intraveineuse
Ptosis	Alcaloïdes	Intraveineuse
Rétrécissement artériel rétinien	Carmustine	Intra artériel
Hémorragie rétinienne	Carmustine	Intra artériel

Thérapies ciblées et T.O.

Quelques chiffres:

- Thérapies ciblées:
  - RCP: TO 40% pour TC de BPM et 25% pour TC HPM,
  - MAIS selon review de Fu C. *et al*. (données post AMM):
    - Plus fréquent: conjonctivite sévère pour 20% et tbl visuels avec 22% des TC,
    - Imatinib: TO de garde III,
    - Imatinib et Crizotinib: 64 à 70% de TO tous grades,
    - TO entraînant cécité: rare (<1%) pour environ 10% des TC (Erlotinib, Gefitinib, Trametinib, Vemurafenib et Ipilimumab),

Renouf DJ *et al*. JCO 2012 et Schmid KE *et al*. Surv Ophtalmol. 2006

Thérapies ciblées et T.O.

Depuis 2008:

- 30 AMM délivrées pour des TC (sur 42 au total),

Données post AMM contrastées:

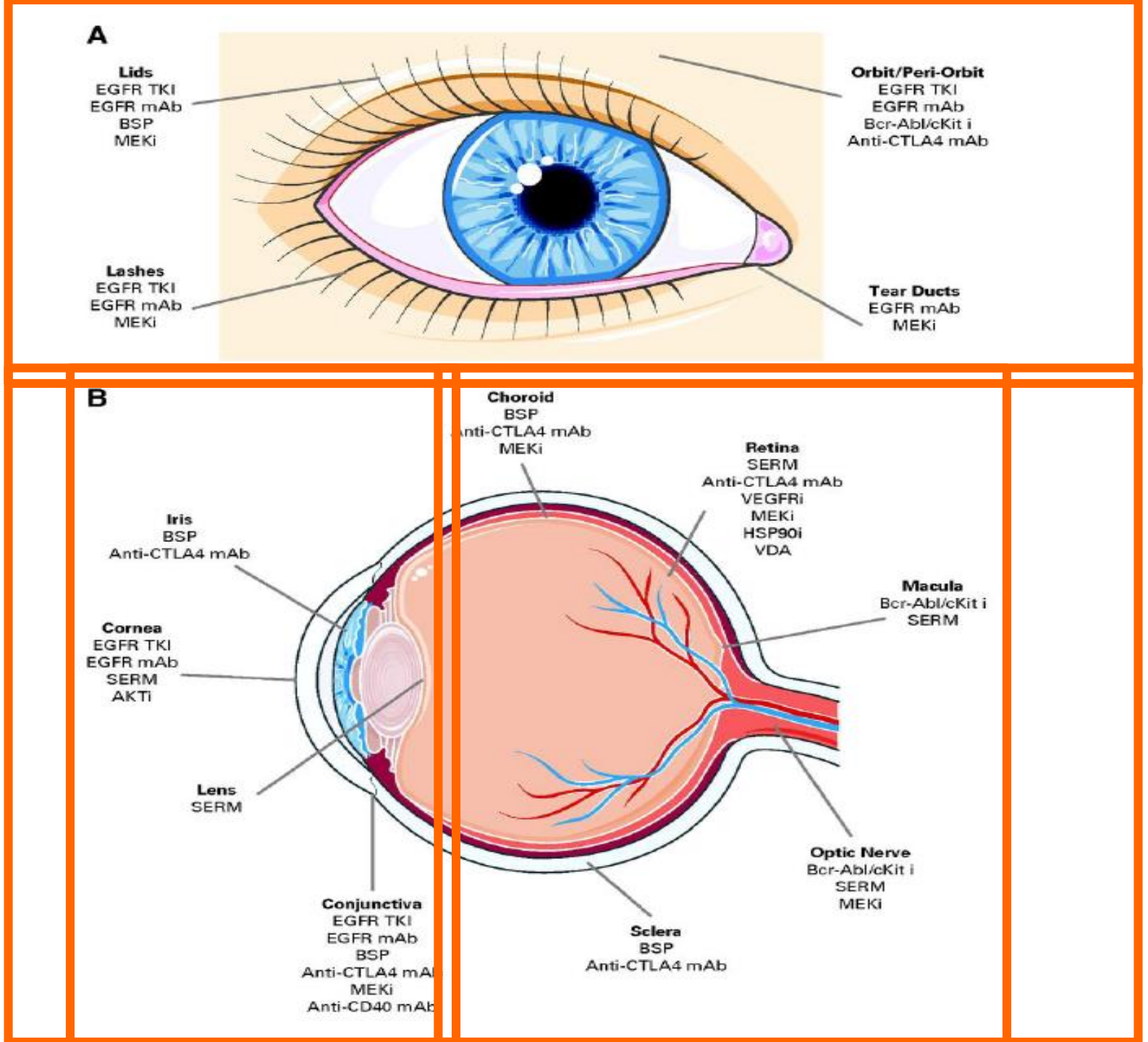
- Profils de tolérance maîtrisé pour les cytotoxiques « classiques »,
- Recul insuffisant avec les TC,
- Nature et fréquence différentes/cytotoxiques « classiques »,

Particularités du profil de tolérance des TC de bas (ITK) et haut PM (Acm):

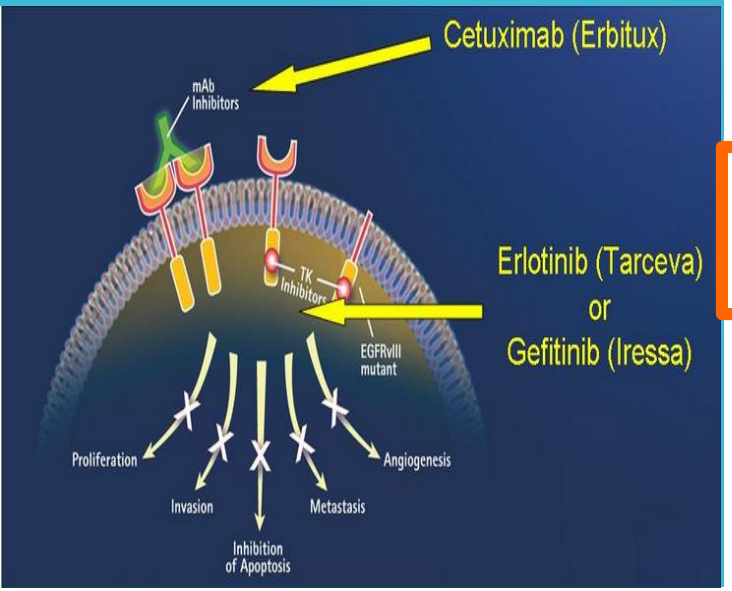
- Discordances données *pré*- et *post*-AMM,
- TO => Ei commun à une grande majorité de TC de bas PM,
- TC et microenvironnement oculaire: nombreux facteurs de croissances, Rc cellulaires et voies de signalisation communes,

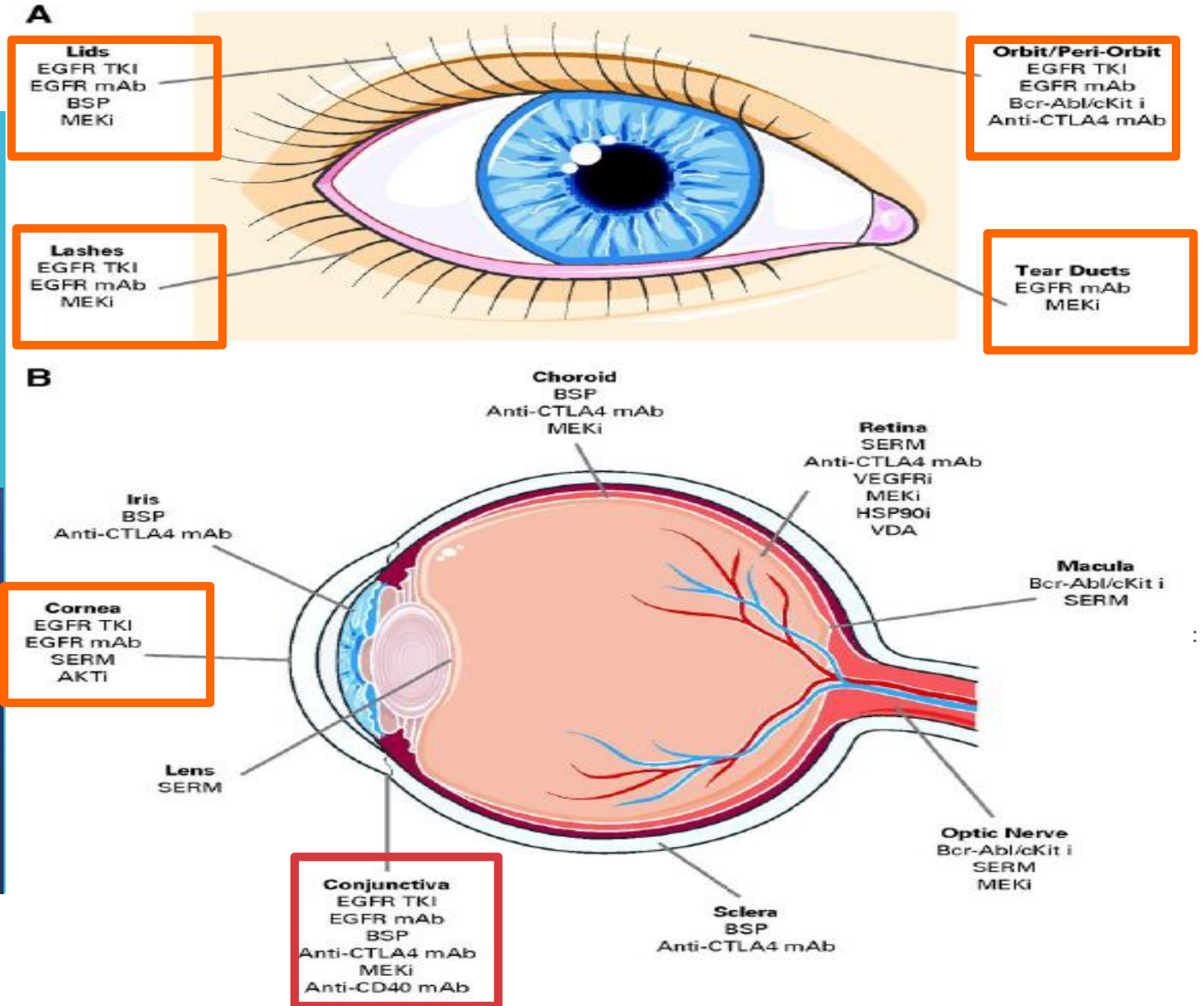
Microenvironnement oculaire et TC

Renouf DJ *et al*. JCO 2012 et Schmid KE *et al*. Surv Ophtalmol. 2006

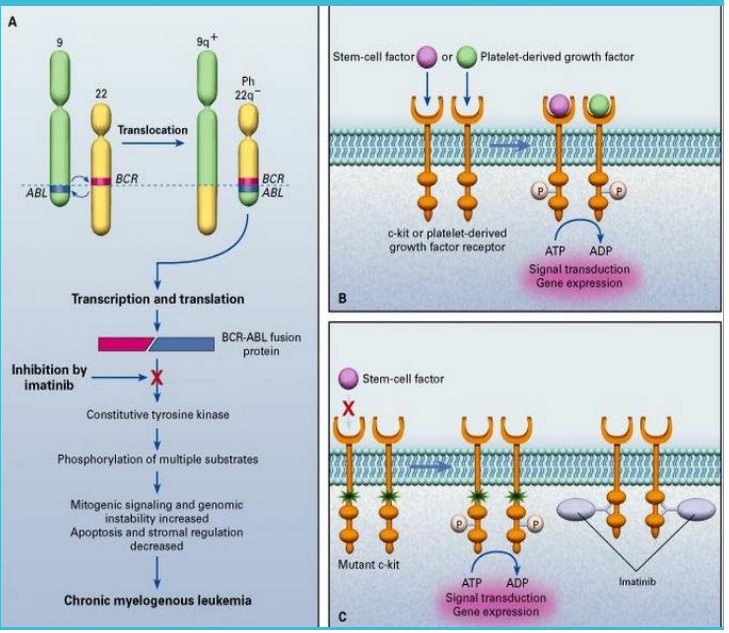


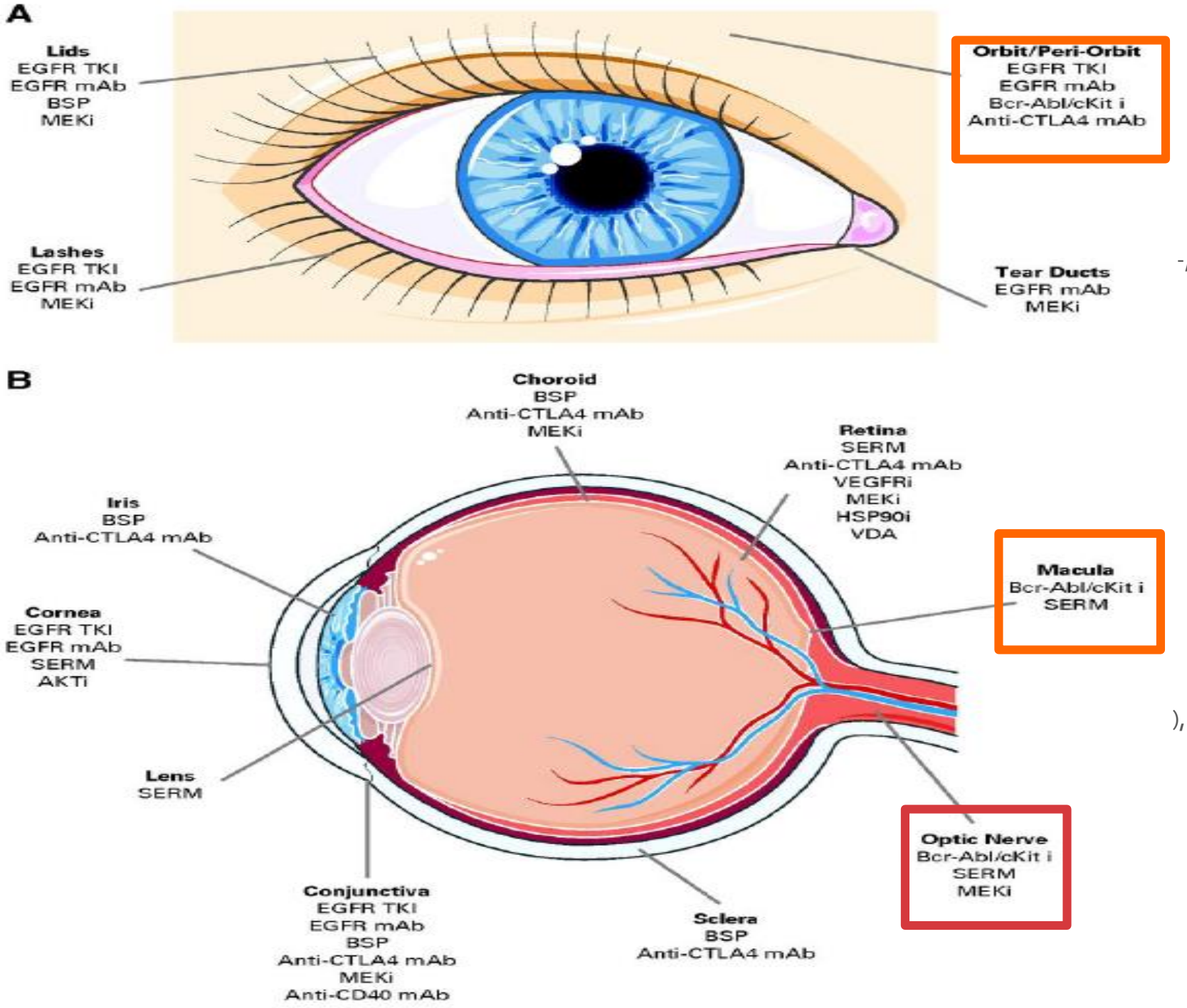
TC ciblant EGFR



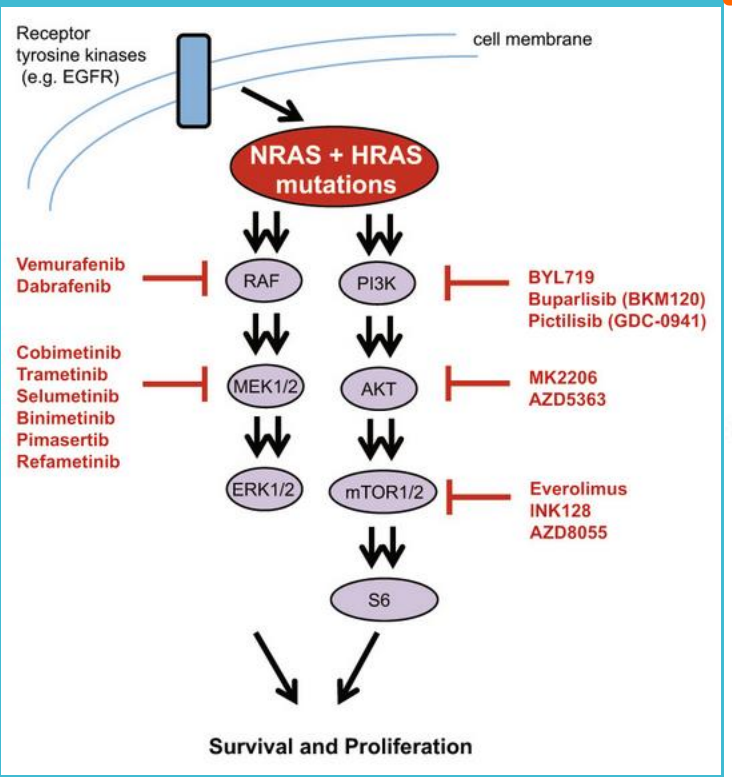


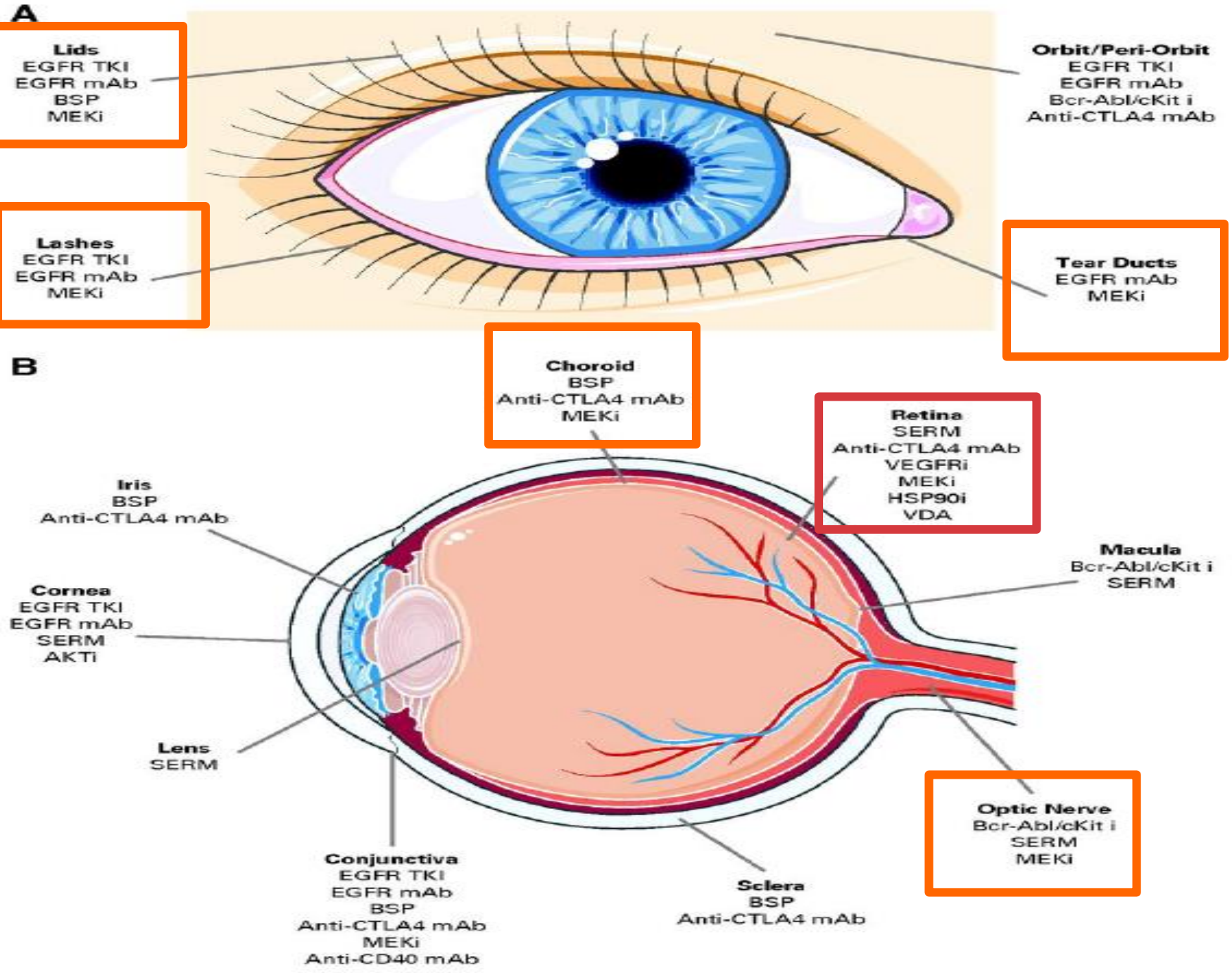
Inhibiteurs Bcr-Abl et c-Kit



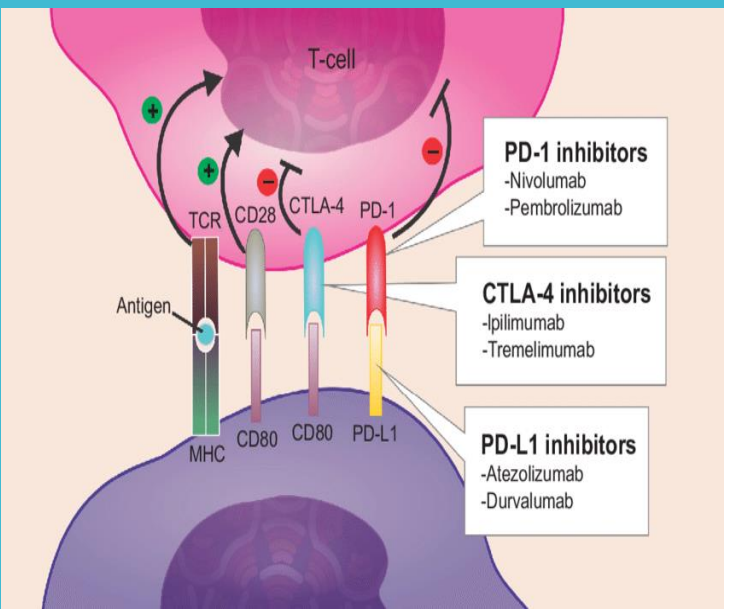


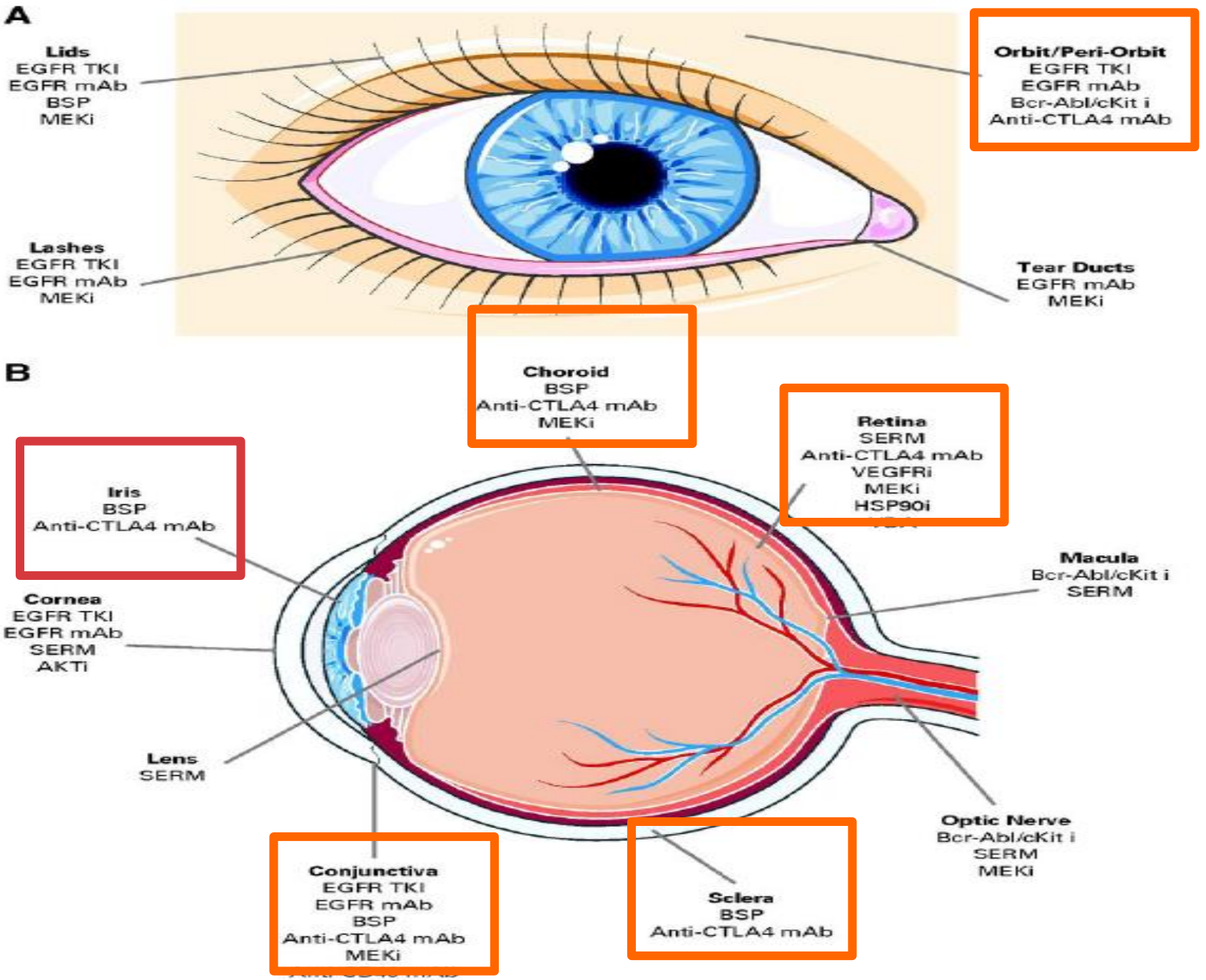
MAP kinase ou MEK inhibiteurs (MEKi)

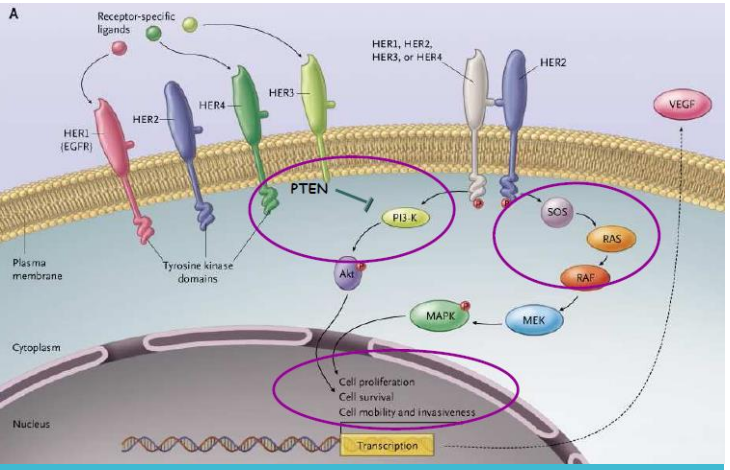




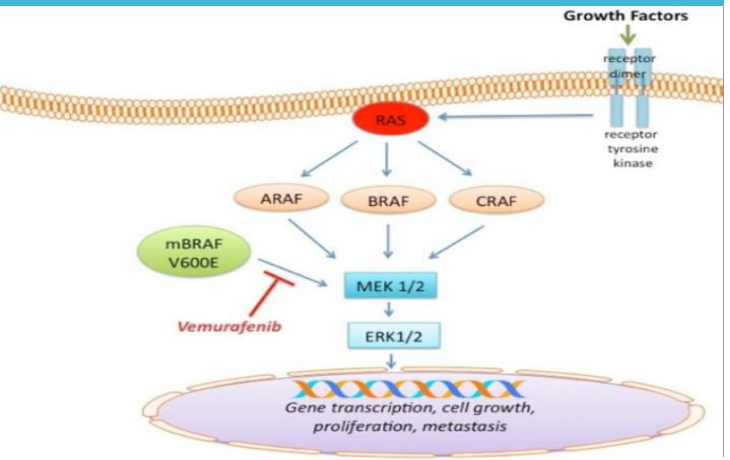
Immune check point inhibitors Ac anti-CTLA4







Inhibiteurs HER2 et BRAF



Inhibiteurs HER2 (Trastuzumab et Trastuzumab/emtansine ou T-DM1):

- Cornée et segment antérieur (31%):
  - Sd œil sec et larmoiement,
  - Vision trouble modérée,
  - Conjonctivite (Trastuzumab),
- Segment postérieur (rétine): Trastuzumab +++
  - Œdème et ischémie maculaire,
  - Décollement rétinien,

Inhibiteurs BRAF (Vemurafenib et Dabrafenib):

- Segment antérieur (2-3%): Sd œil sec, conjonctivite,
- Uvéite (4%),
- Carcinome cellules squameuses (paupières),

RECOMMANDATIONS DE PRISES EN CHARGE

Recommandations « générales »:

- Bilan ophtalmologique initial avant instauration du traitement,
- Balance bénéfice/risque du traitement anticancéreux:
  - Grade I: poursuite du traitement avec PEC des TO,
  - Grade II/III: poursuite ou arrêt temporaire jusqu'au grade I,
  - Grade IV: arrêt définitif du traitement (selon contexte et localisation),

Recommandation spécifiques selon le type de TO et localisation:

- Cornée et segment antérieur,
- Segment postérieur: rétine, nerf optique,
- Uvéite et inflammation oculaire,
- Orbite et péri-orbite,

Cornée et segment antérieur

Sd œil sec

- Larmes artificielles,
- Cas sévères: Vit. A, corticoïdes et ciclosporine (0.05%) en collyre,
- Bouchon lacrymal pour les écoulements réflexes altérants QoL,
- Lifitegrast (USA): antagoniste de l'Ag associé à la fonction lymphocytaire (LFA-1),

Blépharite et dysfonctionnement des glandes de meibomius

- Application eau chaude et compresses chaudes,
- Association antibiotiques/corticoïdes en pommade ophtalmique,
- Tétracyclines (doxycycline) *per os* selon évolution,

Conjonctivite

- Eliminer cause infectieuse et allergique,
- Traitement de courte durée par corticoïdes locaux,
- Larmes artificielles,

EGFR inh. | HER2 inh | BRAF inh. | ITK Bcr-abl et c-kit | Alkylants | 5FU | Anthracyclines

Uvéite et épisclérite

Uvéite

- Corticoïdes collyres et *per os* (uvéite post.+++),
- Collyre mydriatique cycloplégique (mydriase + paralysie transitoire des muscles ciliaires),
- Corticoïdes intraoculaires (injection/implant),

Episclérite

- Lubrifiants oculaires sans conservateurs,
- AINS *per os* ou Glucocorticoïdes (dexamethasone) topiques,

EGFR inh. BRAF inh. Anti-CTLA4 Cytarabine

Orbite et péri-orbite

Trichomégalie

- Lubrifiant oculaire sans conservateur,
- Epilation mécaniques,
- Electrolyse, épilation par radiofréquence, cryothérapie et résection chirurgicale

Chalazion

- Hygiène ++++,
- Compresses chaudes
- Pommade ophtalmiques ATB + corticoïdes,
- Tétracyclines per os,
- Drainage par incision,

Epiphora et obstruction canal naso-lacrymal

- Prévention obstruction complète: mise en place sonde en silicone,
- Chirurgie obstruction complète,

EGFR inh. | Anti-CTLA4 | BRAF inh. | ITK Bcr-abl et c-kit | Docétaxel | 5FU, Pemetrexed | Bortezomib

Rétine

Occlusion Veine Rétinienne (OVR)

- Baisse acuité irréversible si >90 minutes,
- Aucun traitement spécifique,
- Arrêt chimiothérapie en cause,

Œdème maculaire, décollement rétinien

- Arrêt chimiothérapie en cause,
- Absence traitement spécifique,

EGFR inh. | Anti-CTLA4 | BRAF inh. | Platines | Cytarabine | Fludarabine | Taxanes

Recommandations spécifiques ASCO 2018 pour ICPi

Brahmer J., Lacchetti C., Schneider B. *et al.*. *Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. JCO 2018.*

10.1 Uveitis/iritis

Definition: Inflammation of the middle layer of the eye

Diagnostic work-up: as per above

Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Medical intervention required, anterior uveitis	Hold ICPi temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity Re-treat after return to G1 or less
G3: Posterior or panuveitis	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion

Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment[121,122]

10.2 Episcleritis

Definition: Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection

Diagnostic work-up: As per 10.0

Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Vision 20/40 or better	Hold ICPi therapy temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 2/40	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents

Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment[121,122]

10.3 Blepharitis

Definition: Inflammation of the eyelid that affects the eyelashes or tear production

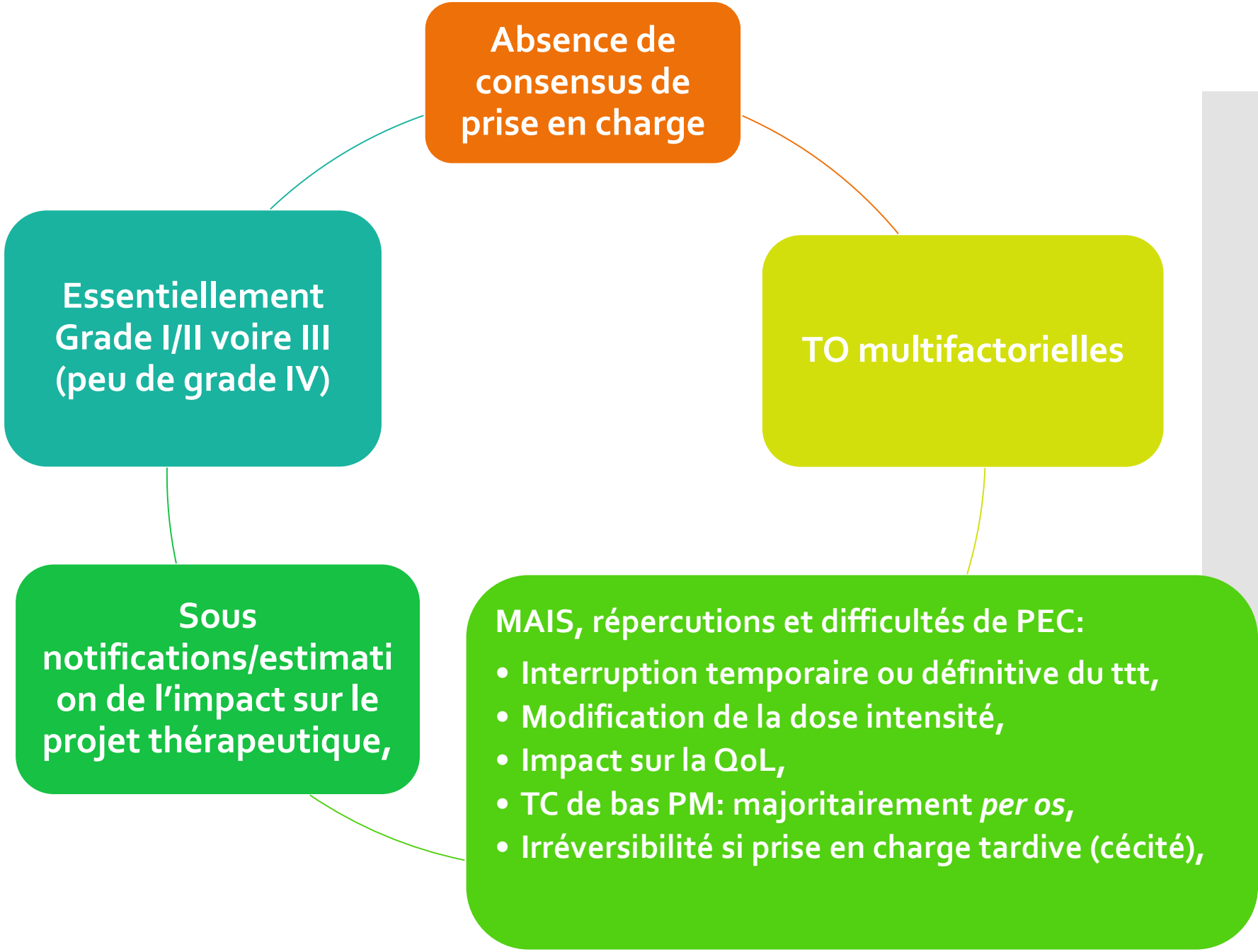
Diagnostic work-up: As per 10.0

Grading	Management
No formal grading system	Warm compresses and lubrication drops Continue therapy unless persistent and serious

All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

Abbreviations: ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous, TNF, tumor necrosis factor.

CONCLUSION


Absence de consensus de prise en charge
TO multifactorielles
MAIS, répercutions et difficultés de PEC:
• Interruption temporaire ou définitive du ttt,
• Modification de la dose intensité,
• Impact sur la QoL,
• TC de bas PM: majoritairement *per os*,
• Irréversibilité si prise en charge tardive (cécité),
Sous notifications/estimation de l'impact sur le projet thérapeutique,
Essentiellement Grade I/II voire III (peu de grade IV)

Merci pour votre attention

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