2° Convegno interregionale AME

- Emilia Romagna
- Friuli Venezia Giulia
- Lombardia
- Trentino Alto Adige
- Veneto

ASSOCIAZIONE MEDICI ENDOCRINOLOGI
www.associazionemediciendocrinologi.it
Per la qualità clinica in Endocrinologia

AGGIORNAMENTO IN ENDOCRINOLOGIA ONCOLOGICA: NON SOLO TIROIDE

BOLOGNA 10 MAGGIO 2014

TARGET THERAPY: COME GESTIRE GLI EFFETTI COLLATERALI

CHIARA MARTINI
*Clinica Medica 3^*
Azienda Ospedaliera-Università di Padova

- **AE** "ANY UNFAVORABLE AND UNINTEDED SIGN (INCLUDING AN ABNORMAL LABORATORY FINDING), 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"

Common Toxicity Criteria

Table 3. The Evolution of the NCI Common Adverse Effects Grading System

System	*No. of Criteria*	*No. of Organs*	*Modality*	*Phase*
CTC (1983)	18	13	Chemo	Acute
CTC v2.0 (1998)	260	22	All*	Acute
CTCAE v3.0 (2003)	370	All	All	Acute and late

*Limited pediatric and surgical criteria.

Common Terminology Criteria for Advers Events → CTCAE v 4.0
2009

Grading dermatologic adverse events of cancer treatments: The Common Terminology Criteria for Adverse Events Version 4.0

J Am Acad Dermatol Volume 67, Number 5 2012 Chen A.P. et al

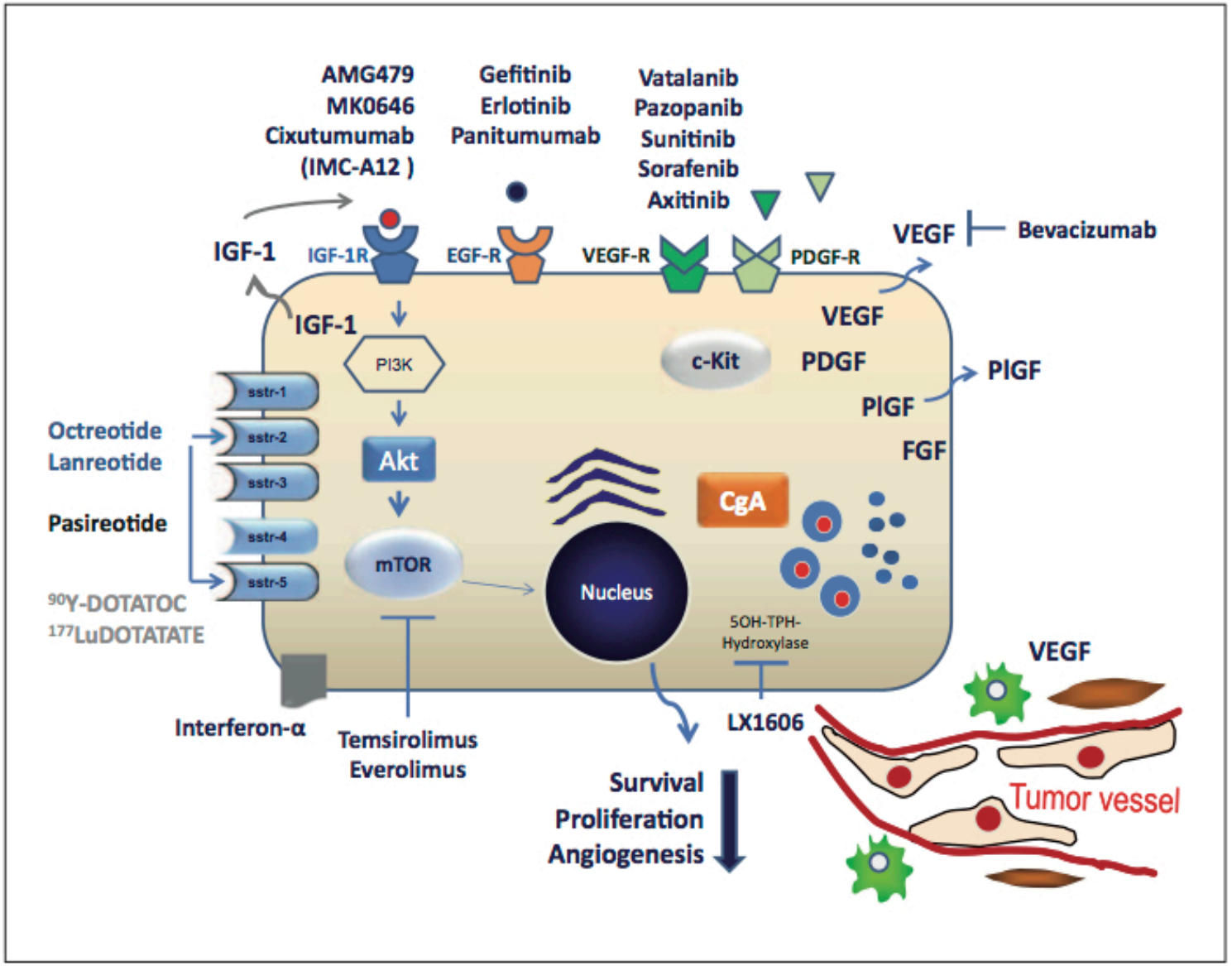
General characteristics of Common Terminology Criteria for Adverse Events grading

Grade	General characteristics
1-Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2-Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
3-Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
4-Life threatening	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

OGNI AE È DEFINITO DA UNA SCALA DI GRADAZIONE, COSTITUTA DA 5 "SCALINI", CHE MISURA LA SEVERITÀ DELLA PRESENTAZIONE CLINICA

MOLECULAR TARGET THERAPY

Interviene sulle vie di segnale regolanti la crescita e altre funzioni cellulari e che sono attivate o iperespresse nelle NEN



SSA
….dal 1988……

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

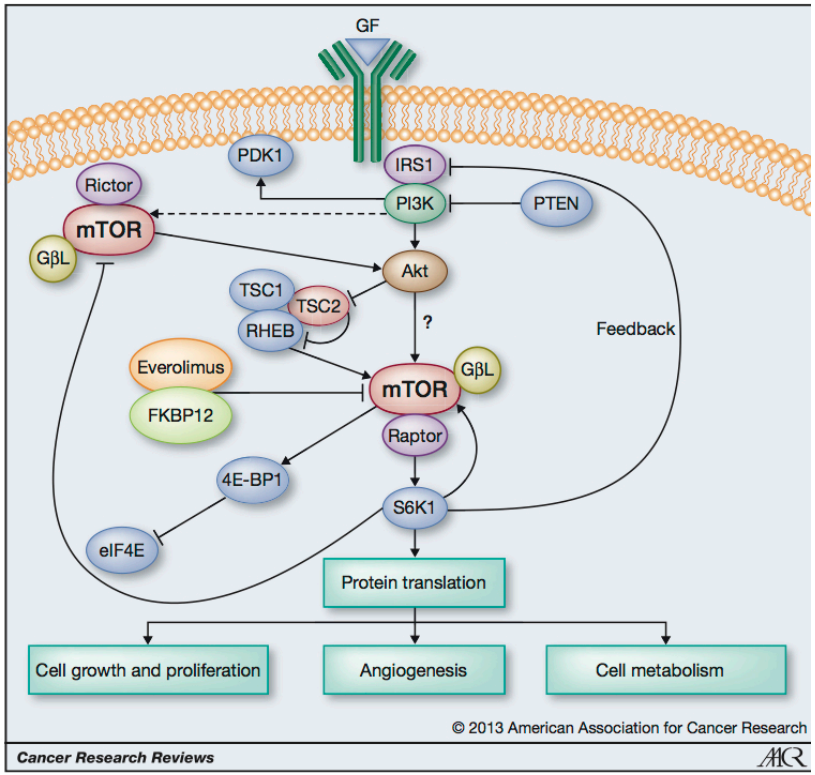
Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

N Engl J Med 2011;364:501-13.

Table 3. Common Adverse Events in the Safety Population.*

Event	Sunitinib (N=83)		
	All Grades	Grade 1 or 2	Grade 3 or 4
Diarrhea	49 (59)	45 (54)	4 (5)
Nausea	37 (45)	36 (43)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)
Vomiting	28 (34)	28 (34)	0
Fatigue	27 (32)	23 (28)	4 (5)
Hair-color changes	24 (29)	23 (28)	1 (1)
Neutropenia	24 (29)	14 (17)	10 (12)
Abdominal pain	23 (28)	19 (23)	4 (5)
Hypertension	22 (26)	14 (17)	8 (10)
Palmar–plantar erythrodysesthesia	19 (23)	14 (17)	5 (6)
Anorexia	18 (22)	16 (19)	2 (2)
Stomatitis	18 (22)	15 (18)	3 (4)
Dysgeusia	17 (20)	17 (20)	0
Epistaxis	17 (20)	16 (19)	1 (1)
Headache	15 (18)	15 (18)	0
Insomnia	15 (18)	15 (18)	0
Rash	15 (18)	15 (18)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)
Mucosal inflammation	13 (16)	12 (14)	1 (1)
Weight loss	13 (16)	12 (14)	1 (1)
Constipation	12 (14)	12 (14)	0
Back pain	10 (12)	10 (12)	0

mTOR: SERINA-TREONINA KINASI CHE RAPPRESENTA UN NODO CENTRALE DEL NETWORK DI VIE DI TRASMISSIONE DEI SEGNALI CHE CONTROLLANO IL METABOLISMO, LA CRESCITA, LA SOPRAVVIVENZA E LA PROLIFERAZIONE CELLULARE, OLTRE CHE IL PROCESSO DI ANGIOGENESI E LA FUNZIONE IMMUNITARIA.



EVEROLIMUS (INIBITORE mTOR)

POSTMENOPAUSAL WOMEN WITH HR$^+$, HER2$^-$ ADVANCED BREAST CANCER, in combination with exemestane, recurring or progressing during/after a non-steroidal aromatase inhibitor treatmet

PROGRESSIVE NEUROENDOCRINE TUMORS OF PANCREATIC ORIGIN (pNET) that is unresectable, or metastatic, well or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease

ADVANCED RENAL CELL CARCINOMA (RCC) on or after treatment with VEGF targeted therapy

Adverse event management in patients with advanced cancer receiving oral everolimus: focus on breast cancer

M. Aapro[1*], F. Andre[2,3], K. Blackwell[4], E. Calvo[5], M. Jahanzeb[6], K. Papazisis[7], C. Porta[8], K. Pritchard[9] & A. Ravaud[10] *Annals of Oncology* 25: 763–773, 2014

Table 1. Incidence of key class-effect toxicities from phase III studies of everolimus in advanced solid tumors

	Metastatic renal cell carcinoma [8]		Neuroendocrine tumors of pancreatic origin [6]		Advanced breast cancer [15]	
	Everolimus + best supportive care ($n = 274$), %		Everolimus ($n = 204$), %		Everolimus + exemestane ($n = 482$), %	
	All Grades	Grade 3/grade 4	All grades	Grade 3/4[a]	All grades	Grade 3/grade 4
Stomatitis	44	4/<1	64	7	59	8/0
Rash	29	1/0	49	<1	39	1/0
Noninfectious pneumonitis	14	4/0	17	2	16	3/0
Hyperglycemia	57[b]	15/<1[b]	13	5	14[c]	5/<1
Infections[d]	37	7/3	23	2	50[e]	4/1[e]

RECORD-1 RADIANT-3 BOLERO-2

[a]Breakdown by grade 3 and 4 not reported.
[b]Based on laboratory values.
[c]Based on investigator-reported adverse events.
[d]Incidence based on system organ class (SOC); includes all infections.
[e]Data from Afinitor prescribing information [2].

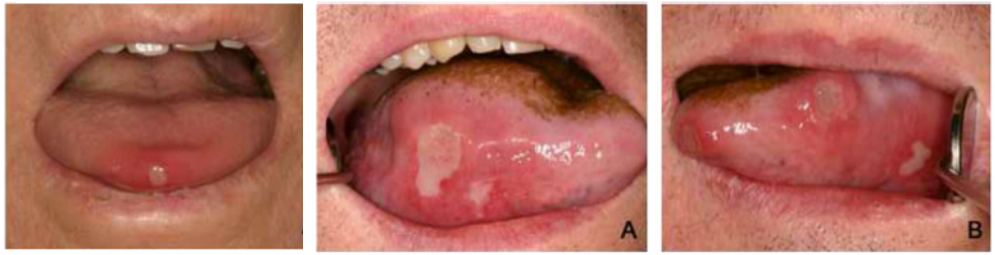
STOMATITE (mTOR Inhibitor-Associated Stomatitis, mIAS)

- AE precoce (mediamente 1 settimana) e più frequente
- Ulcere dolorose simil-aftose, ben delimitate, ovalari, superficiali, con una pseudomembrana bianco-grigiastra, circondate da alone eritematoso, generalmente < a 1 cm, a carico della mucosa non cheratinizzata (versante interno delle labbra, margine e superficie inferiore della lingua, palato molle)

Clinical presentation and management of mTOR inhibitor-associated stomatitis

Marcio Augusto de Oliveira [a], Fabiana Martins e Martins [a], Qian Wang [b], Stephen Sonis [c,d], George Demetri [e], Suzanne George [e], James Butrynski [e], Nathaniel S. Treister [c,d,*]

Oral Oncology 47 (2011) 998–1003



- Verosimile reazione infiammatoria T-cell mediata
- Dolore, disfagia, disgeusia → impossibilità ad alimentarsi

PROFILASSI

BUONA IGIENE ORALE: spazzolino morbido, dentifricio non aggressivo, filo interdentale, sciacqui frequenti (salina, sodio bicarbonato, colluttori senza alcool)

DIETA: evitare cibi acidi, speziati, duri o croccanti, assumere cibi tiepidi

DIAGNOSI PRECOCE → per ridurre il numero e la gravità delle ulcere

Table 5 – Clinical management strategy: stomatitis.

Grade	Description	Treatment	Dose modification
1	• Minimal (normal diet)	• Non-alcoholic mouth wash or 0.9% salt water	• No change
2	• Symptomatic, but can eat and swallow modified diet	• Topical analgesic mouth treatments • Topical corticosteroids • Antiviral therapy if herpetic infection confirmed • Antifungal therapy (topical preferred) may be administered on a case-by-case basis • Avoid agents containing hydrogen peroxide, iodine and thyme derivatives	• Maintain dose if tolerable • Hold dose if intolerable until recovery to grade ⩽1, then restart at same dose
3	• Symptomatic and unable to adequately aliment or hydrate orally	• Same as for Grade 2	• Hold dose until recovery to grade ⩽1, then restart at reduced dose
4	• Symptoms associated with life-threatening consequences	• Same as for Grade 2	• Discontinue treatment

Clobetasol gel 0.05%

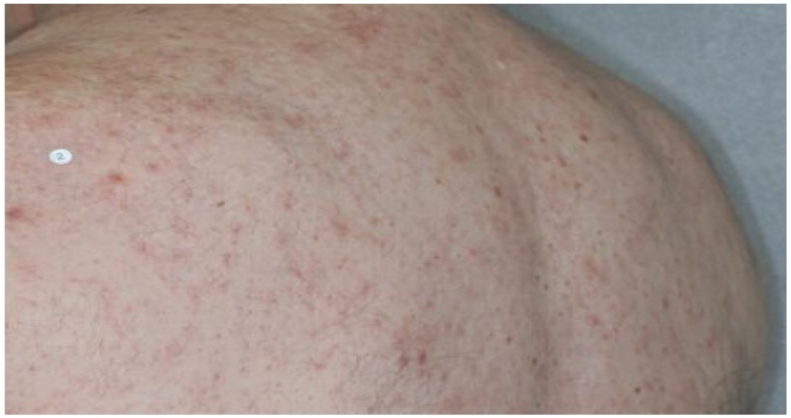
Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma

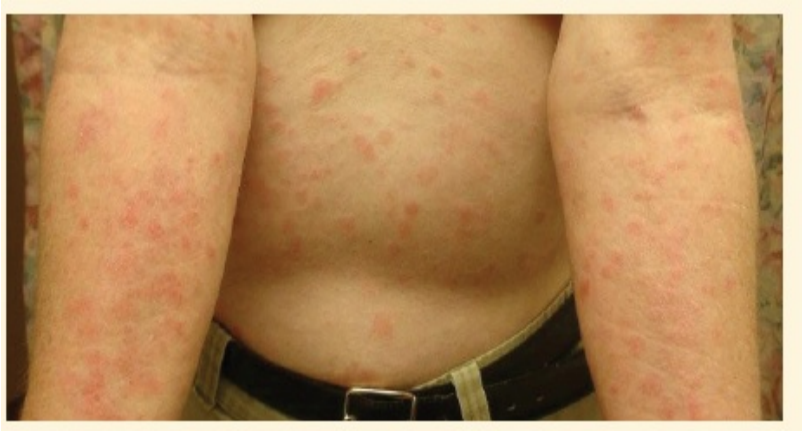
Camillo Porta [a,], Susanne Osanto [b], Alain Ravaud [c], Miguel-Angel Climent [d], Ulka Vaishampayan [e], Dorothy A. White [f], Patricia Creel [g], Brenda Dickow [e], Patricia Fischer [f], Suzanne Sweeney Gornell [f], Federica Meloni [a], Robert J. Motzer [f]*

EUROPEAN JOURNAL OF CANCER 47 (2011) 1287–1298

RASH CUTANEO

- ✓ AE precoce, nel corso del primo mese di trattamento, frequentemente di grado 1-2, raramente di grado 3 o 4
- ✓ Lesioni eritemato-maculo-papulari o papulo-pustolose, spesso pruriginose ma anche eczematose. Più tardivamente comedoni





- ✓ Possibili alterazioni ungueali e modificazioni del colorito cutaneo
- ✓ Tronco, cuoio capelluto, volto, collo, ed estremità (zone inusuali per manifestazioni acneiche)

MISURE GENERALI

- EVITARE L'ECCESSIVA ESPOSIZIONE AL SOLE E UTILZZARE CREME SOLARI CON FILTRI AD ALTA PROTEZIONE (almeno 15)
- IDRATARE LA CUTE CON CREME EMOLLIENTI PRIVE DI ALCOOL
- FARE BREVI DOCCE TIEPIDE UTILIZZANDO SAPONE IDRATANTE NON PROFUMATO
- FARE BAGNI IN ACQUA TIEPIDA CON 1 O 2 TAZZE DI BICARBONATO DI SODIO (o Aveeno®)

Everolimus: side effect profile and management of toxicities in breast cancer

Elisavet Paplomata · Amelia Zelnak Ruth O'Regan

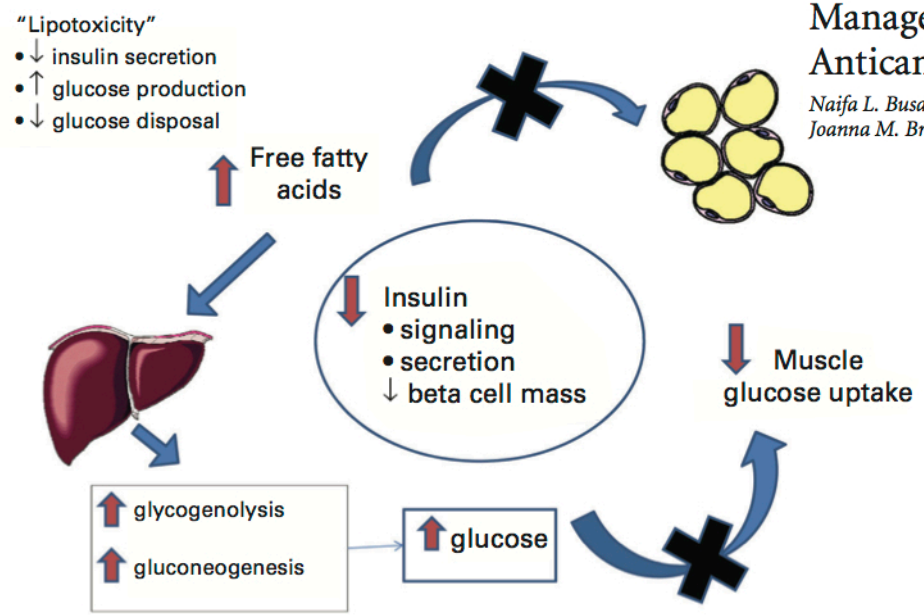
Breast Cancer Res Treat (2013) 140:453–462

Rash (management depends on the type of rash)	*Grade 1* rash covering <10 % BSA, with or without symptoms (pruritus, tenderness)	If tolerable, no dose adjustment Can use topical steroids, retinoids, antibiotics or antihistamines for symptom control (see text)
	Grade 2 rash covering 10–30 % BSA, with or without symptoms; limiting daily activities	If intolerable, interrupt temporarily, re-initiate at same dose. If recurs at grade 2, resume with dose reduction
	Grade 3 rash covering >30 % BSA, with or without symptoms, limiting self care, or with mild superinfection treated with oral antibiotics	Interrupt treatment until grade ≤1, restart with dose reduction; consider discontinuation if grade 3 toxicity recurs Oral antibiotics for infection
	Grade 4 for papulopustular/acneiform rash: covering any % BSA but with superinfection treated with IV antibiotics, life threatening	Discontinue everolimus IV antibiotics for infection

Doxiciclina o Minociclina per 2-4 settimane

COMPLICANZE METABOLICHE
IPERGLICEMIA

- Meccanismo fisiopatologico complesso (riduzione della funzione β-cellulare, insulino-resistenza con riduzione dell'uptake periferico del glucosio e aumento della neoglucogenesi)



Management of Metabolic Effects Associated With Anticancer Agents Targeting the PI3K-Akt-mTOR Pathway

Naifa L. Busaidy, Azeez Farooki, Afshin Dowlati, John P. Perentesis, Janet E. Dancey, Laurence A. Doyle, Joanna M. Brell, and Lillian L. Siu

J Clin Oncol 30:2919-2928. © 2012

- AE che può verificarsi sia in diabetici noti che in pazienti precedentemente euglicemici. Nei primi deve essere ottenuto un soddisfacente controllo glicemico prima di iniziare il trattamento.

COMPLICANZE METABOLICHE
IPERGLICEMIA

- Valutare la glicemia a digiuno ed eventualmente l'HbA1c prima di iniziare il trattamento.
- Educare il paziente al riconoscimento dei segni e sintomi legati ad uno scompenso glicemico.
- Monitorare della glicemia a digiuno dopo l'inizio del trattamento

QUALE L'OBIETTIVO TERAPEUTICO PER UN PAZIENTE ONCOLOGICO CON MALATTIA METASTATICA:

- Riduzione della morbilità e mortalità a lungo termine associate alle alterazioni metaboliche?
- Riduzione della morbilità a breve termine legata all'iperglicemia (infezioni, ipercoagulabilità, diuresi osmotica, stato catabolico) e mantenimento di una buona qualità di vita?

ATTENZIONE ALLE IPOGLICEMIE

COMPLICANZE METABOLICHE
DISLIPDEMIA (CT- LDL e trigliceridi)

- NEI PAZIENTI DISLIPDEMICI OTTENERE UN ADEGUATO CONTROLLO PRIMA DI INIZIARE IL TRATTAMENTO.
- VALUTARE ASSETTO LIPIDICO E INDICI DI FUNZIONALITA' EPATICA PRIMA DI INIZIARE IL TRATTAMENTO
- MONITORAGGIO PERIODICO ASSETTO LIPIDICO
- AGIRE SULLO STILE DI VITA (quando indicata riduzione del PC, incremento dell' attività fisica)
- OBIETTIVO TERAPEUTICO PRIMARIO:
  LDL-c (in relazione alle classi di rischio CV)
  secondariamente trigliceridi (ATTENZIONE: TG > 500 mg/dl)
- LE STATINE POSSONO ESSERE CONSIDERATE FARMACI SICURI NON INTERFERENDO CON LA CLEARANCE DI EVEROLIMUS MA MONITORARE TRANSAMINASI E CPK

COMPLICANZE METABOLICHE
IPERGLICEMIA-DISLIPIDEMIA

Table 6 – Clinical management strategy: metabolic abnormalities.

Grade	Description	Treatment	Dose modification
1 150-300	• HG: >ULN – 160 mg/dL • HCE: >ULN – 300 mg/dL • HT: >ULN – 2.5 × ULN	• None	• No change
2 300-500	• HG: >160–250 mg/dL • HCE: >300–400 mg/dL • HT: >2.5–5.0 × ULN	• Treat hyperglycaemia according to the ADA and EASD consensus approach[25] • Treat hyperlipidemia according to standard guidelines[26–28] • Triglycerides ⩾500 mg/dL present risk of pancreatitis; treat urgently with fibrates	• Maintain dose if tolerable • Hold dose if intolerable until recovery to grade ⩽1, then restart at same dose[a]
3 500-1000	• HG: >250–500 mg/dL • HCE: >400–500 mg/dL • HT: >5.0–10 × ULN	• Same as for Grade 2	• Hold dose until recovery to grade ⩽1, then restart at reduced dose or discontinue per clinical judgement
4 >1000	• HG: >500 mg/dL • HCE: >500 mg/dL • HT: >10 × ULN	• Same as for Grade 2	• Discontinue treatment

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; HCE, hypercholesterolaemia; HG, hyperglycaemia; HT, hypertriglyceridemia.

Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma

Camillo Porta [a,], Susanne Osanto [b], Alain Ravaud [c], Miguel-Angel Climent [d], Ulka Vaishampayan [e], Dorothy A. White [f], Patricia Creel [g], Brenda Dickow [e], Patricia Fischer [f], Suzanne Sweeney Gornell [f], Federica Meloni [a], Robert J. Motzer [f]*

EUROPEAN JOURNAL OF CANCER 47 (2011) 1287–1298

IPOFASFATEMIA meccanismo non noto
Se importante: debolezza muscolare, astenia generalizzata.
Supplementazione con la dieta

TOSSICITA' POLMONARE
polmonite non infettiva NIP

INFILTRATI INFIAMMATORI NON INFETTIVI E NON NEOPLASTICI
Processo immunomediato (T-cell mediated)

INCIDENZA?

Incidence and risk of pulmonary toxicity in patients treated with mTOR inhibitors for malignancy. A meta-analysis of published trials

ROBERTO IACOVELLI, ANTONELLA PALAZZO, SILVIA MEZI, FEDERICA MORANO, GIUSEPPE NASO & ENRICO CORTESI

Acta Oncologica, 2012; 51: 873–879

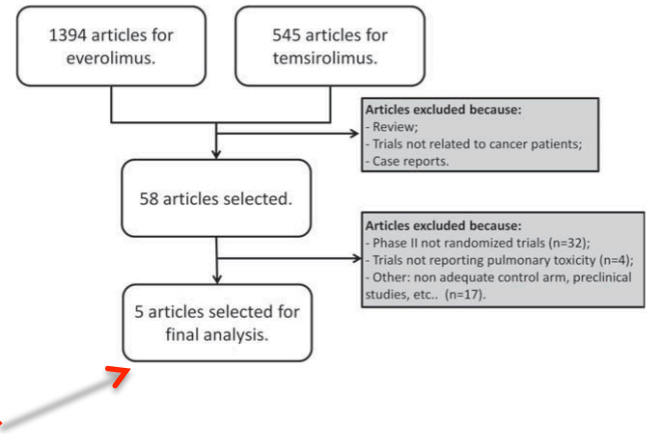


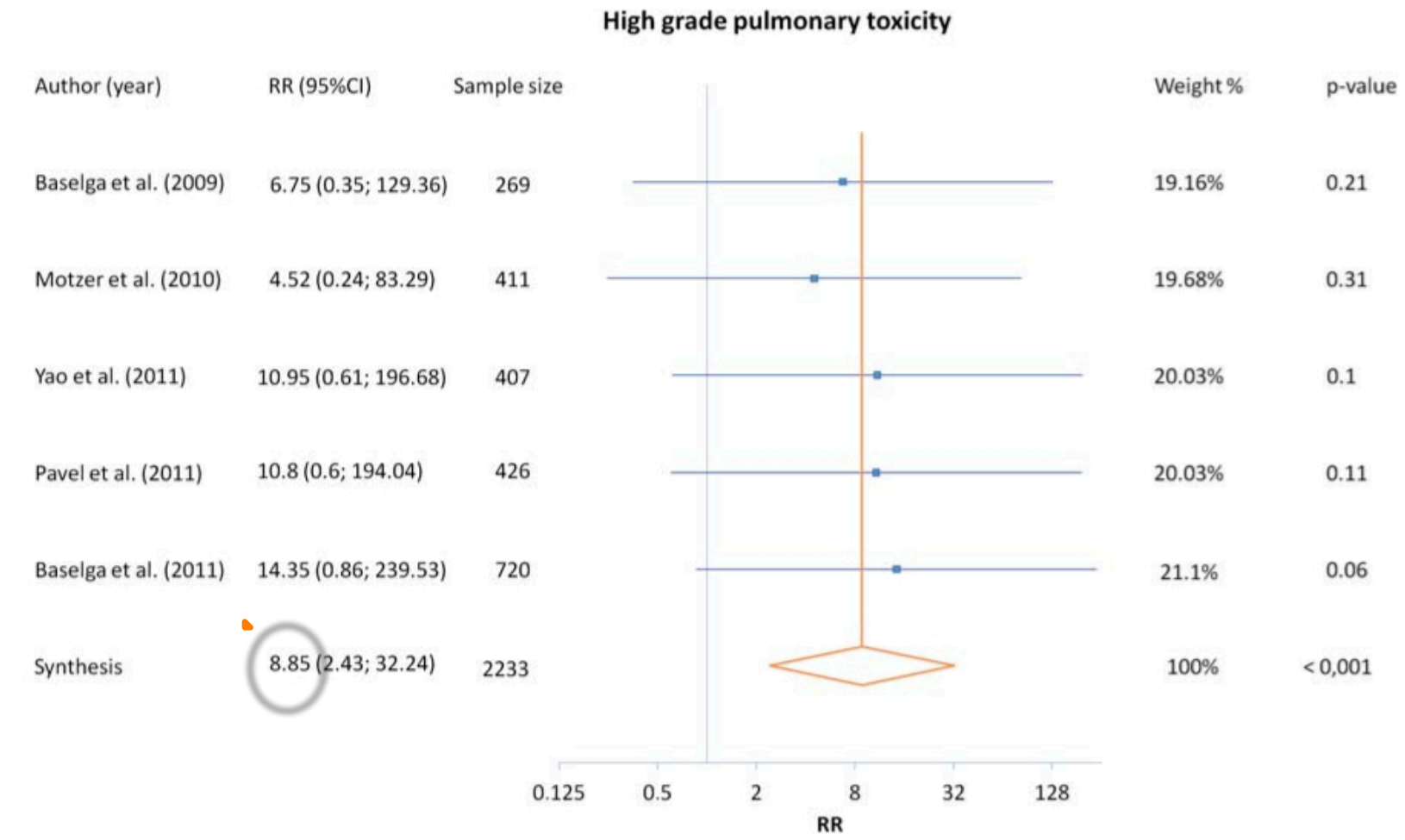
Table II. Results of overall incidence of all- and high-grade of pulmonary toxicity from all included trials.

					Pulmonary toxicity					
					All grades			High grades		
First author	Year	Drug	Type of cancer	Evaluable patients	No of events	Incidence (%)	95% CI	No of events	Incidence (%)	95% CI
Baselga et al.	2009	eve	BC	137	4	3.3	0–6.6	3	2.5	0–5.5
Motzer et al.	2010	eve	RCC	275	14	5.3	2.4–8.1	4	1.6	0–3.3
Yao et al.	2011	eve	NET	204	35	17.3	11.9–22.7	5	2.7	0.2–5.1
Pavel et al.	2011	eve	NET	215	25	11.8	7.3–16.3	5	2.5	0.2–4.9
Baselga et al.	2011	eve	BC	482	58	12.1	9.1–15.1	14	3.0	1.4–4.6
Combined				1313	136	10.4	8.7–12.1	31	2.4	1.5–3.2

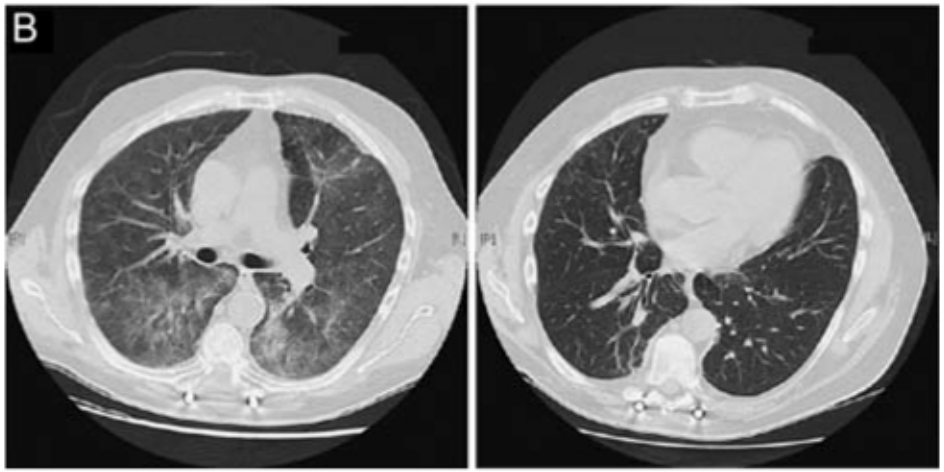
Incidence and risk of pulmonary toxicity in patients treated with mTOR inhibitors for malignancy. A meta-analysis of published trials

ROBERTO IACOVELLI, ANTONELLA PALAZZO, SILVIA MEZI, FEDERICA MORANO, GIUSEPPE NASO & ENRICO CORTESI

Acta Oncologica, 2012; 51: 873–879



- Compare in genere entro i primi sei mesi dall'inizio del trattamento
- Le manifestazioni radiologiche in genere precedono quelle cliniche



CLINICA

Silente
Tosse non produttiva
Dispnea
Sintomi sistemici:
- Spossatezza (fatigue)
- Febbre

IMAGING RADIOLOGICO (HRCT)

OPACITA' A VETRO SMERIGLIATO (non maschera le strutture sottostanti)
ISPESSIMENTO DEI SETTI INTRA E INTERLOBULARI
CONSOLIDAMENTO PARENCHIMALE MULTIFOCALE
distribuzione prevalente ai lobi inferiori, bilateralmente ma in maniera asimmetrica

DIAGNOSI DIFFERENZIALE

Linfangite carcinomatosa: ispessimento irregolare dei setti, presenza di multipli noduli, versamento pleurico
Infezioni (virali, Pneumocystis carinii, Legionella etc) → escreatocolutura, BAL, procalcitonina (se febbre)
Sottostante malattia interstiziale (imaging di base + PFR)

Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma

Camillo Porta [a,*], Susanne Osanto [b], Alain Ravaud [c], Miguel-Angel Climent [d], Ulka Vaishampayan [e], Dorothy A. White [f], Patricia Creel [g], Brenda Dickow [e], Patricia Fischer [f], Suzanne Sweeney Gornell [f], Federica Meloni [a], Robert J. Motzer [f]

EUROPEAN JOURNAL OF CANCER 47 (2011) 1287–1298

Table 3 – Clinical management strategy: non-infectious pneumonitis.

Grade	Description	Treatment	Dose modification
1	Asymptomatic, radiographic findings only	• No intervention • Continue everolimus	• No change in dose
2 **2a** modesta tosse **2b** tosse severa, dispnea e ipossia da sforzo	Symptomatic, not interfering with activities of daily living	Depending on severity of symptoms: • Consider everolimus dose interruption/ reduction • Consult pulmonologist • Consider diagnostics to exclude infectious causes • Consider corticosteroids	• Restart at reduced dose when grade ⩽1 and consider re-escalation • If no recovery to grade ⩽1, discontinue everolimus
3	Symptomatic, interfering with activities of daily living, supplemental oxygen required	• Interrupt everolimus • Consult pulmonologist • Diagnostics to exclude infectious causes • Corticosteroids if infectious cause excluded Prednisone 1 mg/kg/die • For impending respiratory distress: concomitant treatment with antibiotics and corticosteroids is recommended	• Hold treatment until recovery to grade 1; may restart within 2 weeks at a reduced dose (by 1 level) if evidence of clinical benefit
4	Life-threatening; ventilatory support indicated	• Interrupt everolimus • Consult pulmonologist • Diagnostics to exclude infectious causes • Corticosteroids if infectious cause excluded Prednisone 1 mg/kg/die • For impending respiratory distress, concomitant treatment with antibiotics and corticosteroids is recommended	• Discontinue permanently

Incidence and management of mTOR inhibitor-associated pneumonitis in patients with metastatic renal cell carcinoma

L. Albiges[1*], F. Chamming's[2], B. Duclos[3], M. Stern[4], R. J. Motzer[5], A. Ravaud[6] & P. Camus[7]

Annals of Oncology 23: 1943–1953, 2012

INIZIO TRATTAMENTO

- Verificare la disponibilità di Rx torace e HRCT recenti
- PFR se preesistente patologia polmonare
- Se DILD porre attenzione e mantenere stretto follow up

No sintomi
Imaging suggestivo

Tosse e dispnea

Valutazione clinica, controllo Rx torace e HRCT
DD

GRADO 1
No sintomi

GRADO 2a
Tosse lieve/ moderata

GRADO 2b
Tosse severa dispnea

GRADO 3
Interf ADL
O2 terapia

GRADO 4
Potenzial fatale

Educare il paziente a maggior attenzione
Intensificazione dei controlli clinici

Ricovero ospedaliero
Interruzione trattamento

(Opzionale)
Clinico: 2 sett
Rx: 4 sett

No riduzione dose
No trattamento

Clinico:1-2 sett
Rx: 4 sett

Sintomo stabile
No riduzione dose
Peggioramento
Riduz dose (opzionale)

Clinico:1 sett
Rx:2 sett

Riduzione dose
se non miglioramento
Steroidi

PFR
Broncoscopia e BAL (raccomand)

Steroidi (escludere infez)
Antibiotici (se infez interc)
segnalazione

FOLLOW UP

Clinico 4 sett
HRCT 8 sett

Clinico 4 sett
HRCT 6-8 sett

sino alla risoluzione
Clinico ogni 2-3 settimane-HRCT ogni 4 sett
Riconsiderare aumento/ripresa EVE

SOSPENSIONE DEFINITIVA

INFEZIONI

- Use caution in patients with a history of prior infections (hepatitis, fungal, other opportunistic infections)
- Consider evaluating the risk of infection on the basis of CD4+ cell absolute count (<200/μL) or percentage (<12%)
- A basal evaluation of the antibody immune status is potentially useful (e.g. antibody status for Toxoplasma, CMV, HSV, EBV)
- Investigate possible latent tuberculosis infection (especially in endemic countries or in migrants from these countries) through:
  - Patient medical history
  - Mantoux reaction
  - QuantiFERON®-TB Gold test (in case of a positive or doubtful Mantoux test, or – if negative – in case of concomitant immunosuppression (e.g. CD4+ cells <200/μL)
- Depending on the epidemiological setting, consider persistent bowel parasites (e.g. latent tropical strongyloides)
- Patients with fungal infections are not recommended for everolimus therapy, though medical judgment should be exercised
  - Patients should have complete resolution of fungal infection before initiation of everolimus
- Recommend preventive therapy for hepatitis B infection to avoid reactivation (in both HBsAg-positive and HBcAb-positive patients)

Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma

Camillo Porta [a,], Susanne Osanto [b], Alain Ravaud [c], Miguel-Angel Climent [d], Ulka Vaishampayan [e], Dorothy A. White [f], Patricia Creel [g], Brenda Dickow [e], Patricia Fischer [f], Suzanne Sweeney Gornell [f], Federica Meloni [a], Robert J. Motzer [f]*

EUROPEAN JOURNAL OF CANCER 47 (2011) 1287–1298

Table 4 – Clinical management strategy: infections.

Grade	Description	Treatment	Dose modifications
1	• None	• Provide adequate treatment of infection • Appropriate antibiotic use • Culture and be aware of the risk of atypical infections • Consider prophylaxis with entecavir or tenofovir in hepatitis B surface antigen-positive patients	• No change in dose
2	• Localised infection, with local intervention indicated	• Same as for Grade 1	• Maintain dose if tolerated • Hold dose if intolerable until recovery to grade ⩽1, then restart at same dose • If AE recurs at grade 2 level, hold dose until recovery to grade ⩽1, then restart at reduced dose • If dose held >21 d, discontinue treatment
3	• IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or surgery indicated	• Same as for Grade 1	• Hold dose until recovery to grade ⩽1, then restart at reduced dose • If dose held >21 d, discontinue treatment
4	• Life-threatening consequences such as septic shock, hypotension, acidosis or necrosis	• Same as for Grade 1	• Discontinue everolimus

TOSSICITA' MIDOLLARE

Monitorare la crasi ematica prima di iniziare il trattamento e durante lo stesso

- Anemia (91%)
- Leucopenia/neutropenia (26%/11%)
  - N < 1000/mm^3 (grado 3)
    sospendere sino a grado 1 e poi riprendere alla stessa posologia
  - N <500/mm^3 (grado 4)
    sospendere sino a grado 1 e poi riprendere a posologia ridotta

- Trombocitopenia (20%)
  - PLTS <75000/mm^3 (grado 2)
    sospendere sino a grado 1 e poi riprendere alla stessa posologia
  - PLTS <50000/mm^3 (grado 3)
    sospendere sino a grado 1 e poi riprendere a posologia ridotta
  - PLTS <25000/mm^3 (grado 2)
    sospendere sino a grado 1 e poi riprendere a posologia ridotta

DIARREA AE frequente

Modificazioni dietetiche (evitare alcool e cibi contenenti lattosio; fare pasti piccoli e frequenti), adeguata idratazione.
Loperamide come trattamento farmacologico.

Everolimus: side effect profile and management of toxicities in breast cancer

Elisavet Paplomata · Amelia Zelnak
Ruth O'Regan

Breast Cancer Res Treat (2013) 140:453–462

- EVEROLIMUS È SUBSTRATO PER IL CITOCROMO p450 ISOENZIMA 3A4 (CYP3A4) E SUBSTRATO E MODERATO INIBITORE DELLA GLICOPROTEINA PgP. L'ASSORBIMENTO E L'ELIMNAZIONE DEL FARMACO POSSONO PERTANTO ESSERE INFLUENZATE DA TUTTI QUEI FARMACI CHE INTERFERISCONO CON CYP3A4 e/o PgP

- EMIVITA È AUMENTATA IN CASO DI INSUFFICIENZA EPATICA
  Child-Pugh score A: 7.5 mg/die
  Child-Pugh score B: 5 mg/die
  Child-Pugh score C: valutare rischio/beneficio e in caso 2.5 mg/die

Table 1 Drug interactions: agents that can affect blood levels of everolimus

Interaction	Drug	Recommendations
Strong CYP3A4 inhibitors	Ketoconazole Itraconazole Clarithromycin Atazanavir Nefazodone Saquinavir Telithromycin Ritonavir Indinavir Nelfinavir Voriconazole	Combination should be avoided
Moderate CYP3A4 and/or PgP (P-glycoprotein) inhibitors	Aprepitant Erythromycin Fluconazole Verapamil Diltiazem Amprenavir Fosamprenavir	Caution and close monitoring required. Starting dose is 2.5 mg/day. If well tolerated, the dose can be increased to 5 mg/day
Strong CYP3A4 inducers	Phenytoin Carbamazepine Rifampin Rifabutin Rifapentine Phenobarbital	Combination should generally be avoided. If the benefit outweighs the risk, the starting dose of 10 mg daily can be gradually increased to a maximum of 20 mg daily in 5 mg increments
Inhibitors of cytochrome P450 and PgP activity	Grapefruit Grapefruit juice	Combination should be avoided
Unpredictable decrease on everolimus exposure	St. John's Wort (Hypericum perforatum)	Use should be avoided
No significant interactions	Atorvastatin Pravastatin Simvastatin	Combination appears to be safe, always weigh risk and benefit

GRAZIE

CONCLUSIONI

- EVEROLIMUS E' UN FARMACO GENERALMENTE BEN TOLLERATO E MOLTI DEGLI AEs RAPPRESENTANO DEGLI EFFETTI DI QUESTA CLASSE DI COMPOSTI

- LA LORO CONOSCENZA DA PARTE DEL CLINICO, L'EDUCAZIONE DEL PAZIENTE AL PRECOCE RICONOSCIMENTO DEI SINTOMI DI PRESENTAZIONE, IL COSTANTE MONITORAGGIO DEL PAZIENTE E LA MESSA IN OPERA DEI PROTOCOLLI DI TRATTAMENTO STANDARDIZZATI, RAPPRESENTANO DEI PRESUPPOSTI INDISPENSABILI PER L'UTILIZZO DI QUESTO FARMACO E IL CONTROLLO DELLA SEVERITA' E DELLA DURATA DEGLI AEs AD ESSO CORRELATI.

- LA NIP, SEPPUR NON FREQUENTE, RAPPRESENTA UNO DEGLI AEs, INSIEME ALLE INFEZIONI, POTENZIALMENTE FATALE