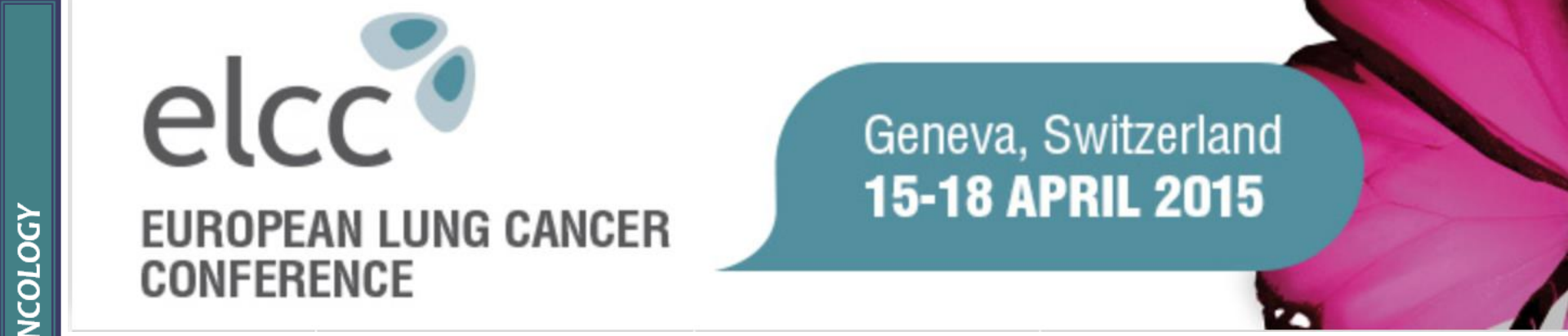

UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

Uncommon (cardiac, hepatic, endocrine) toxicities of targeted agents and their management

Silvia Novello
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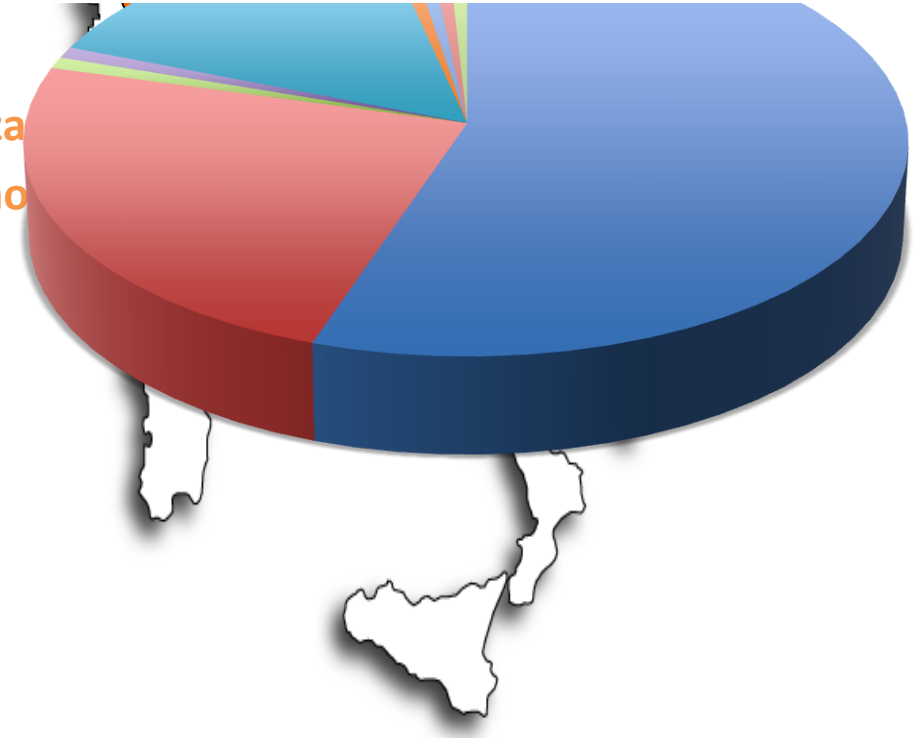
New Toxicities of Targeted Therapies

Italian multicenter survey to evaluate the opinion of patients and their reference clinicians on the "tolerance" to targeted therapies already available for non-small cell lung cancer treatment in daily clinical practice

Transl Lung Cancer Res 2014;3(3):173-180

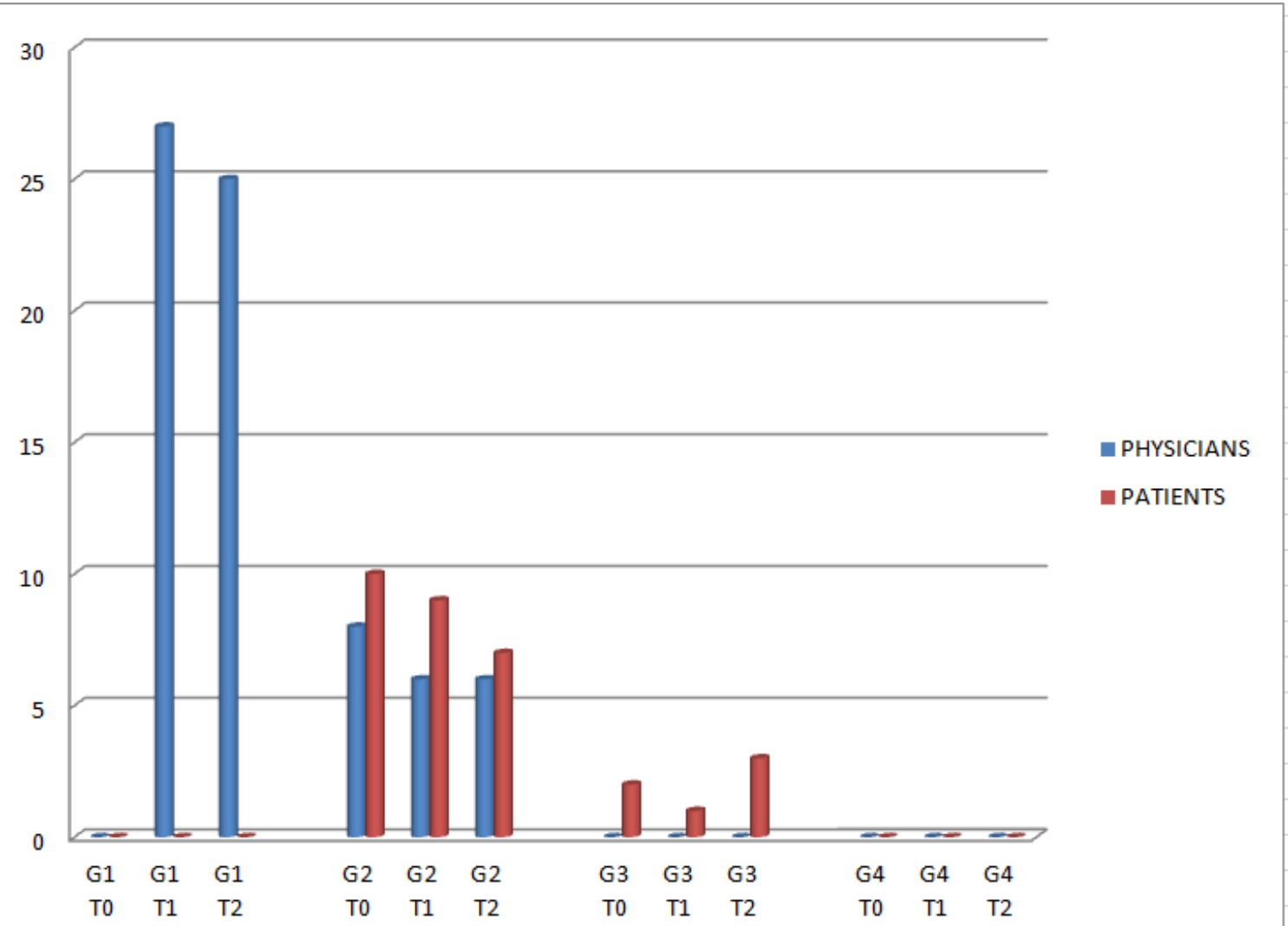
Silvia Novello[1], Enrica Capelletto[1], Diego Cortinovis[2], Marcello Tiseo[3], Domenico Galetta[4], Giuseppe Valmadre[5], Clelia Casartelli[6], Simonetta Grazia Rapetti[1], Antonio Rossi[7]

Casartelli C, Como
Cortinovis DP, Monza
Seebacher C, Bolzano
Bria E, Verona
Binato S, Vicenza
Tiseo M, Parma
Merlo V, Udine
Di Maio M, Napoli
Rossi A, Avellino
Galetta D, Bari



Novello S et al, Transl Lung Cancer Res 2014

During the previous days of therapy, During the preceding cycle of therapy, did you did you experience diarrhea?



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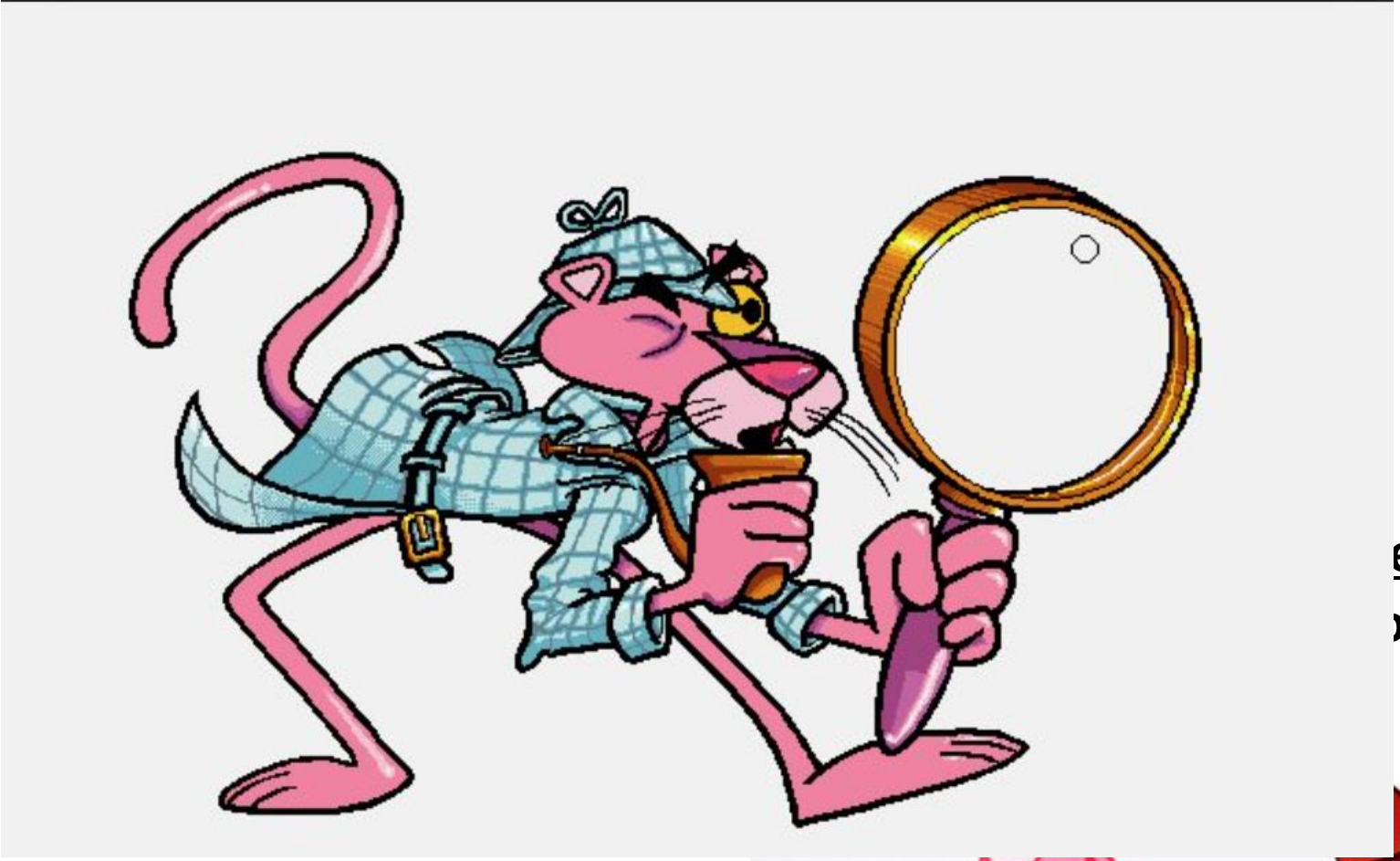
ung Cancer Res 2014



e

ntext

Female patient, AMT, 58 years old

FBS 02.08.12 Diagnosis of adenocarcinoma, stage IV, T1N2M1b
EGFR and KRAS WT, ALK not re-arranged.

First-line treatment started on 17.09.12:
Cisplatin 75 mg/mq + Pemetrexed 500 mg/mq q3wks (4 cycles induction followed by maintenance treatment with Pemetrexed 500 mg/mq, 5 cycles until Apr 2013).

Best response: partial response
Maintained until November 2013

CT scan performed on 5/11/2013 evidenced brain PD (multiple lesions).
She referred occasional but worsening headache.
Whole Brain RT (30 Gy/10 fr) was performed.

She was evaluated for the inclusion in clinical trial with PD1 inhibitor.
She started with the PD1 inhibitor on 27 May 14

From cycle III (08 Jul 2014) the patient reported diarrhea (G1): she continued on treatment with supportive oral fluid intake and loperamide.

From cycle VI (12 Sep 2014) she referred **diarrhea G2**, hyporexia and weight loss.

Lab: hypokaliemia G3

No cardiac symptoms or abdominal pain.

Protocol Procedures

- In subjects with moderate enterocolitis (e.g., Gr 2 diarrhea or Gr 2 abdominal pain), MK-3475 should be withheld and anti-diarrheal treatment should be started, if appropriate. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475 refer to Section 5.2.

Treatment was stopped and supportive therapy with intravenous hydration, intravenous and oral integration of potassium, corticosteroids and was started (together with anti-diarrheals).

The patient had no fever or blood or mucus in stool, in any case infectious etiologies were investigated and ruled out (neg).

Progressive, but slow normalization of hypokaliemia and gastrointestinal toxicity was evidenced.

On 01.12.2014 she started again MK-3475-010 immunotherapy.

She is still on treatment without any evidence of gastrointestinal toxicity.

Diarrhea: literature data

	Frequency	
	All Grades	**Grade 3+**
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	**18-66%**	**<1-34%**
EGFR inhibitors (erlotinib, cetuximab)	**20-66%**	**2-16%**
Afatinib*	**95.2%**	**G3 14.4%**

*LuxLung3

Modified from Grace K. Dy, et al CA CANCER J CLIN 2013

Diarrhea….such a common event

Agent	Main side effects and relative frequency
Cetuximab [4,9,20,21]	Skin rash (90%), other skin toxicities (xerosis 35%, paronychia 15%) Diarrhea (2%) Electrolyte abnormalities (4 – 6%) Allergic reactions (5%)
Panitumumab [3]	Skin rash (57%), other skin toxicities (xerosis 10%, paronychia 25%) Mucosal inflammation (7%) Electrolyte abnormities (39%)
Erlotinib [14,17,19]	Skin rash (70%), other skin toxicity (xerosis 7.7%, paronychia 6%) Diarrhea (48 – 62%) Mucosal inflammation (12%) Interstitial lung disease (< 1%)
Gefitinib [11-13]	Diarrhea (48 – 62%) Skin rash (61%), other skin toxicity (xerosis 30%, paronychia 15%) Interstitial lung disease (1%)
Afatinib [18]	Diarrhea (90%), nausea (23%) and vomiting (20%) Skin rash (73%), xerosis (26%)
Lapatinib [7,8]	Diarrhea (64%), nausea (31%) Skin rash (44%), other skin toxicities (xerosis 13%, paronychia 11%) QT prolongation, decreased LVEF, symptomatic cardiac failure (1.4%)
Sorafenib [6,10]	Diarrhea (43%), nausea (24%) Skin rash (40%), hand-foot reactions (30%) Hypertension (9 – 17%)
Sunitinib [5,15,16]	Diarrhea (40 – 55%), nausea (30 – 54%) Skin rash (38%), mucositis (50%) Hypertension (28%)
Vandetanib [22]	Diarrhea (56%), skin rash (45%), nausea (33%) Hypertension (32%) ECG QT prolongation (14%)

LVEF: Left ventricular ejection fraction.

Lucchini E et al, Expert Opin. Drug Saf. (2014) 13(5)

- The exact pathophysiology of anti-EGFR agent–related diarrhea remains unclear. EGF is involved in the maintenance of mucosal integrity and is also a potent mitogen of the gastric epithelium

- Diarrhea is a dose-limiting toxicity (DLT) for most small molecule EGFR TKIs

- Regardless of etiology, management of diarrhea includes the proactive use of antidiarrheal/antimotility agents such as loperamide or diphenoxylate/atropine at the first sign of diarrhea to avoid life-threatening dehydration, hydration, dietary changes.

- Withhold treatment for CTC grade 3 diarrhea and resume at a lower dose upon improvement to baseline or CTC grade 1.

Widakowich C et al; The Oncologist 2007;
Grace K. Dy, et al CA CANCER J CLIN 2013

PD-1 Inhibitors - Safety

Keynote 001: pembrolizumab

AE, %	N = 262	
	Any Grade	Grade 3-5
Treatment-related with incidence ≥5%		
Fatigue	20	<1
Pruritus	9	0
Arthralgia	8	<1
Decreased appetite	8	0
Diarrhea	7	0
Hypothyroidism	6	0
Pyrexia	6	0
Rash	6	0
Nausea	5	<1
Other of clinical interest ≥1%		
Pneumonitis	4	2
Hyperthyroidism	2	<1

- Other potentially immune-mediated AEs that occurred in <1% of patients were colitis and hyponatremia

Felip E et al, ESMO 2014

CheckMate 063: nivolumab

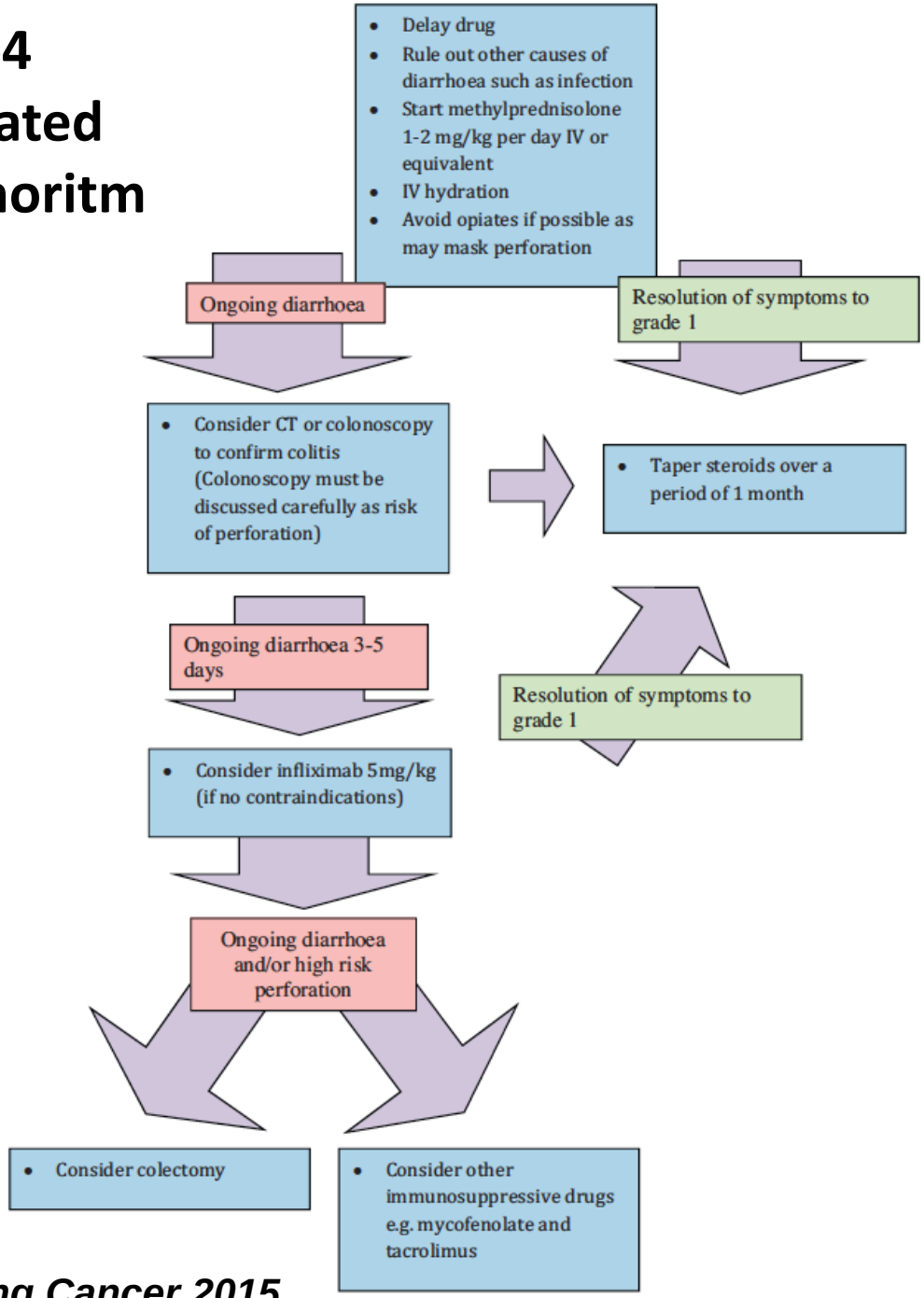
	Any grade	Grade 3–4
Any	87 (74%)	20 (17%)
General disorders		
Fatigue	38 (33%)	5 (4%)*
Asthenia	14 (12%)	0
Gastrointestinal disorders		
Nausea	18 (15%)	0
Diarrhoea	12 (10%)	3 (3%)*
Dry mouth	7 (6%)	0
Vomiting	7 (6%)	0
Constipation	6 (5%)	0
Metabolism and nutrition disorders		
Decreased appetite	22 (19%)	0
Skin and subcutaneous tissue disorders		
Rash	13 (11%)	1 (1%)*
Pruritus	7 (6%)	1 (1%)*
Musculoskeletal disorders		
Myalgia	6 (5%)	1 (1%)*
Respiratory disorders		
Dyspnoea	6 (5%)	0
Pneumonitis	6 (5%)	4 (3%)*
Blood and lymphatic system disorders		
Anaemia	7 (6%)	1 (1%)*

Data are number of events (%). Includes events reported between the first dose and 30 days after the last dose of nivolumab. Grade 3–4 adverse events reported by less than 5% of patients included: hyponatraemia (two [2%]); and polyneuropathy, decreased lymphocyte count, herpes zoster, adrenal insufficiency, vasculitis, hypersensitivity, anaphylactic reaction, and unassigned, each reported by one patient (one [1%]). One patient (1%) died from pneumonia, and one patient (1%) from ischaemic stroke. *All grade 3.

Table 3: **Treatment-related adverse events that occurred in at least 5% of all treated patients**

Rizvi NA et al, Lancet Oncology 2015

Grade 3-4 Immunorelated Diarrhea alghoritm



M. Howell et al, Lung Cancer 2015

Female patient ,F.P. 59 years old

Pleural biopsy (13.09.2011)
NSCLC (adenocarcinoma) stage IV, T4N2M1a
EGFR, ALK, KRAS not evaluable at diagnosis.

First-line treatment (05/10/2011 – 17/01/2012):
Cisplatin 75 mg/mq + Pemetrexed 500 mg/mq 6 cycles

Best response: Stable Disease Maintained until April 2012

At a CT scan performed on 27.04.2012 progressive disease on lung lesions.
A new broncoscopy was performed (18.05.2012): adenocarcinoma EGFR wt, no tissue available for ALK or KRAS evaluation.

Second line treatment (23/05/2012 – 17/09/2012):
Docetaxel 75 mg/mq 6 cycles.
Best response: partial response
Maintained until June 2013

At a CT scan performed on 17.06.2013:
Evidence of progressive disease on lung lesions and a new right axillary adenopathy.

A lymph node biopsy was performed on 16.07.13:
Adenocarcinoma, evidence of ALK re-arrangement

She was evaluated within CLDK378A2203 clinical trial
-**LDK378 750 Mg/die**

I cycle started on 18 September 2013.
From cycle II (16 Oct 2013) the patient reported **diarrhea G1**: as per protocol, she maintained the same dose, adjusting anti-diarrhea treatment.
From cycle V (8 Jan 2014) she referred occasional diarrhea G1; at the clinical chemistry **hypokaliemia G1** was evidenced.

Oral integration of potassium was started and she continued on treatment.

At clinical evaluation on cycles VI and VII no diarrhea was referred and serum potassium value returned within laboratory ranges. The patient continued with oral integration of potassium.

At cycle VIII (3 Apr 2014) **hypokaliemia G3** was evidenced. The patient was completely asymptomatic, she continued on treatment but, for clinical decision, at a lower dose (600 mg/die-no specific recommendations in the protocol). She did not stop oral potassium intake.

From IX to XVI cycle the patient presented occasional hypokaliemia G1, no other symptoms/signs. PS=0. She never stopped oral potassium intake.

Electrolyte Disorders

Authors, year [reference]	Main symptoms	Design	Type of TKI	*n*	Tumor type	Hypokalemia, *n* (%)	
						All grades	Grade 3/4
Miller *et al.*, 2012 [58]	Digestive, muscular, and cardiac disorders	IIb/III	Afatinib	390	NSCLC M+	34 (9%)	11 (2.8%)
Sternberg *et al.*, 2013 [38]		III	Pazopanib	290	Advanced/M+ RCC	28 (10%)	5 (2%)

Kotecki N et al, Curr Opin Oncol 2015

- **Electrolyte disorders during treatment with targeted therapies are quite common**
- **Easily reversible with treatment**
- **Can also cause severe complications and can negatively alter QoL**
- **Most frequently reported: dyskalemia, hypophosphatemia, hypocalcemia, hypomagnesemia, and hyponatremia**
- **Management is mainly symptomatic**

Ceritinib-Safety

AEs G3-4 suspected to be related

Event	Dose						
	50–300 mg/day (N = 10)	400 mg/day (N = 14)	500 mg/day (N = 10)	600 mg/day (N = 10)	700 mg/day (N = 5)	750 mg/day (N = 81)	Total (N = 130)
	number of patients with event (percent)						
Any event	2 (20)	4 (29)	3 (30)	5 (50)	4 (80)	46 (57)	64 (49)
Elevated alanine aminotransferase level	1 (10)	1 (7)	2 (20)	0	4 (80)	19 (23)	27 (21)
Elevated aspartate aminotransferase level	0	1 (7)	0	0	3 (60)	10 (12)	14 (11)
Diarrhea	0	1 (7)	1 (10)	1 (10)	0	6 (7)	9 (7)
Elevated lipase level	0	0	0	1 (10)	0	8 (10)	9 (7)
Nausea	0	0	1 (10)	0	0	6 (7)	7 (5)
Fatigue	0	0	1 (10)	0	0	5 (6)	6 (5)
Vomiting	0	0	0	1 (10)	0	5 (6)	6 (5)
Hypophosphatemia	0	1 (7)	0	1 (10)	0	2 (2)	4 (3)
Elevated amylase level	0	0	0	1 (10)	0	2 (2)	3 (2)
Elevated blood alkaline phosphatase level	0	0	0	0	1 (20)	2 (2)	3 (2)
Hyperglycemia	0	0	0	0	0	3 (4)	3 (2)

Shaw A et al, NEJM 2014

Ceritinib-Safety(Electrolytes)

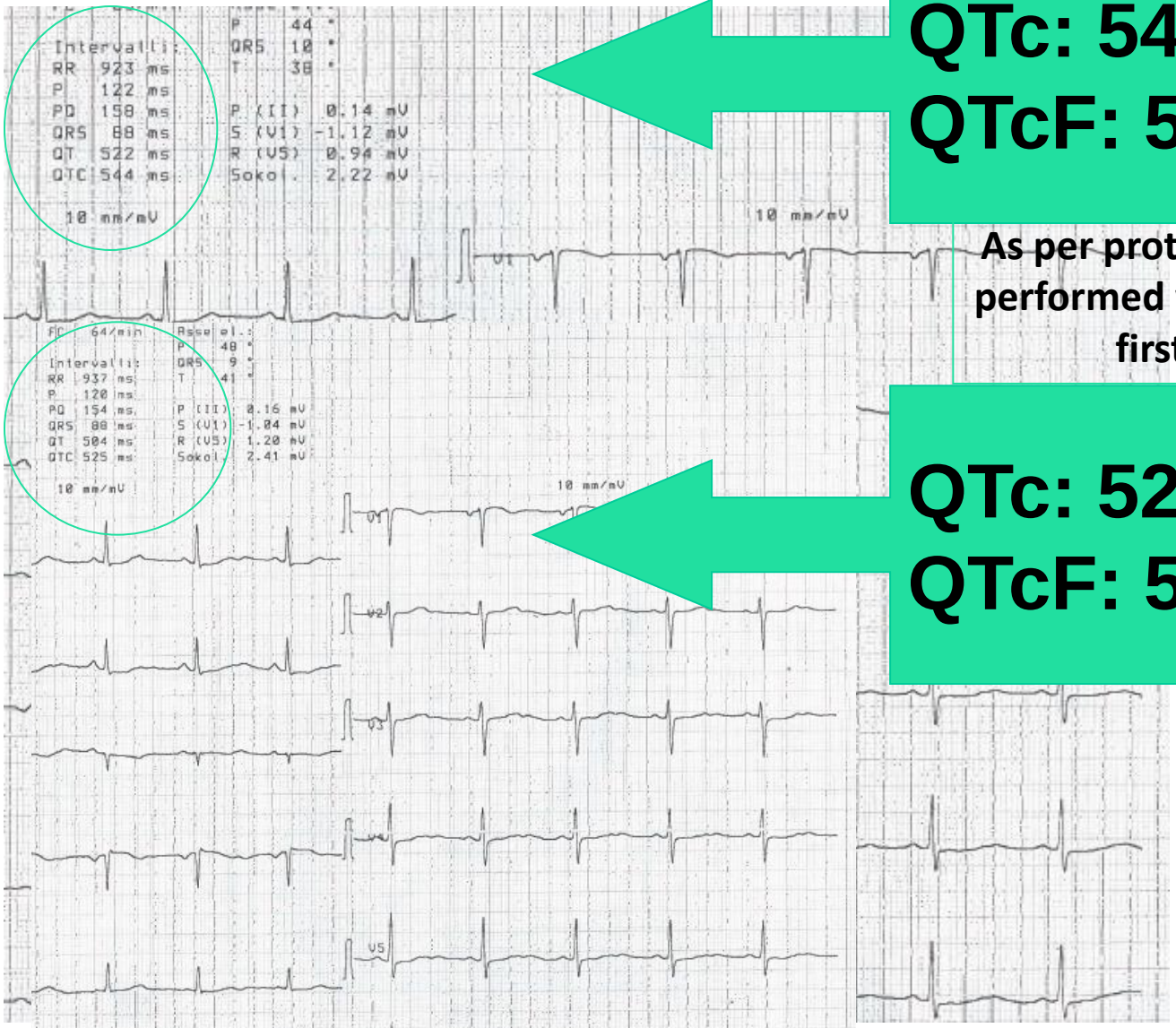
Adverse Events of **Any Grade**, Regardless of Study Drug Relationship, in ≥ 5% of Patients

Adverse Event (Preferred Term)	Dose Level — mg per day									
	50	100	200	300	400	500	600	700	750	Total
	n=2	n=2	n=3	n = 3	n = 14	n = 10	n = 10	n = 5	n = 81	N = 130
	no. of patients (%)									
Patients with any adverse event	2 (100)	2 (100)	3 (100)	3 (100)	14 (100)	10 (100)	10 (100)	5 (100)	81 (100)	**130 (100)**
Hypokalemia	0	0	1 (33)	0	2 (14)	1 (10)	0	1 (20)	14 (17)	**19 (15)**
Hypophosphatemia	0	0	0	0	1 (7)	1 (10)	2 (20)	0	9 (11)	**13 (10)**
Hypomagnesemia	0	0	1 (33)	0	1 (7)	1 (10)	2 (20)	0	6 (7)	**11 (8)**
Hyponatremia	0	0	0	0	1 (7)	1 (10)	2 (20)	0	4 (5)	**8 (6)**

*Patients who experienced more than one occurrence of the same event are only counted once within each category. Patients are categorized according to initial dose received.

Shaw A et al, NEJM 2014

cycle XVII: at ECG evaluation QTC prolongation was evidenced. Asymptomatic.

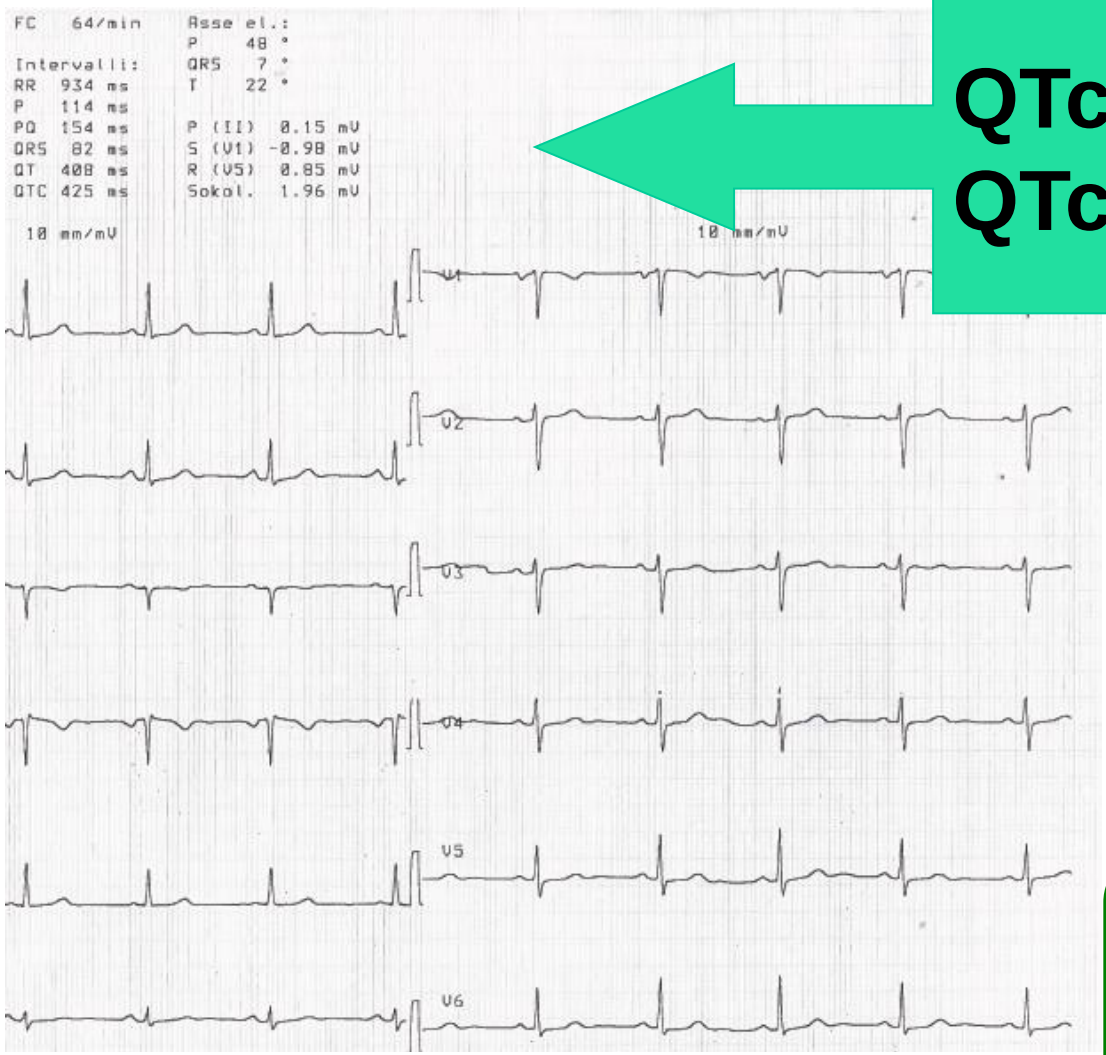


QTc: 544 msec G3
QTcF: 536 msec

As per protocol a repeat ECG was performed within one hour of the first QTcF of ≥501:

QTc: 525 msec G3
QTcF: 515 msec

The patient interrupted LDK378, performed analysis of serum potassium, calcium, phosphorus and magnesium (all within normal lab ranges).
PS=0 no symptoms/signs. She repeated ECG evaluation at least one per day.
At D8, QTcF returned < Grade 1.



QTc: 425 msec
QTcF: 417 msec

She continued on treatment at a lower dose (450 mg).
She maintained PS=0,
No more diarrhea
One week later again hypokaliemia G1 (always supplemented with oral potassium intake).

She is still on treatment. At CT scans she maintained partial response.

QTc Prolongation

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
QT prolongation				
Multikinase angiogenesis inhibitors	NR-14%	<1%-8%	Cabozantinib, Ponatinib << Pazopanib, Sunitinib << Vandetanib (69% had QT prolongation > 450 ms and 7% had QT prolongation > 500 ms)	Use with caution in patients with pre-existing cardiac disease (eg, bradycardia, heart failure, on anti-arrhythmic) or concomitant medications that may prolong QT interval. Baseline and periodic monitoring of ECG as well as maintenance of adequate electrolyte balance are recommended. As these agents can cause diarrhea, associated electrolyte disturbances can elevate risk for toxicity.
ALK/c-met inhibitors	NR	1.3%-3.5%	Crizotinib (3.5% incidence of >60 msec increase in QTc from baseline)	

Grace K. Dy, Alex A. Adjei. CA 2013

Ceritinib-Safety(QTc prolongation)

Adverse Events of **Any Grade**, Regardless of Study Drug Relationship, in ≥ 5% of Patients

Adverse Event (Preferred Term)	Dose Level — mg per day									
	50	100	200	300	400	500	600	700	750	Total
	n=2	n=2	n=3	n = 3	n = 14	n = 10	n = 10	n = 5	n = 81	N = 130
	no. of patients (%)									
Patients with any adverse event	2 (100)	2 (100)	3 (100)	3 (100)	14 (100)	10 (100)	10 (100)	5 (100)	81 (100)	**130 (100)**
QTc prolongation	0	0	0	0	0	0	2 (20)	1 (20)	5 (6)	**8 (6)**

Shaw A et al, NEJM 2014

- Female patient ,F.P. 57 years old

- Bone biopsy (14 Aug 2013)
- Adenocarcinoma stage IV, T4N2M1b
- EGFR mutation (deletion in exon 19)

- First-line treatment with Erlotinib 150 mg/die (September 2013 - September 2014)

- At the time of lung disease progression (19 Sept 2014) a re-biopsy was performed on the lung lesion.
A T790M mutation was identified and the patient was evaluated within a clinical trial with a third generation EGFR

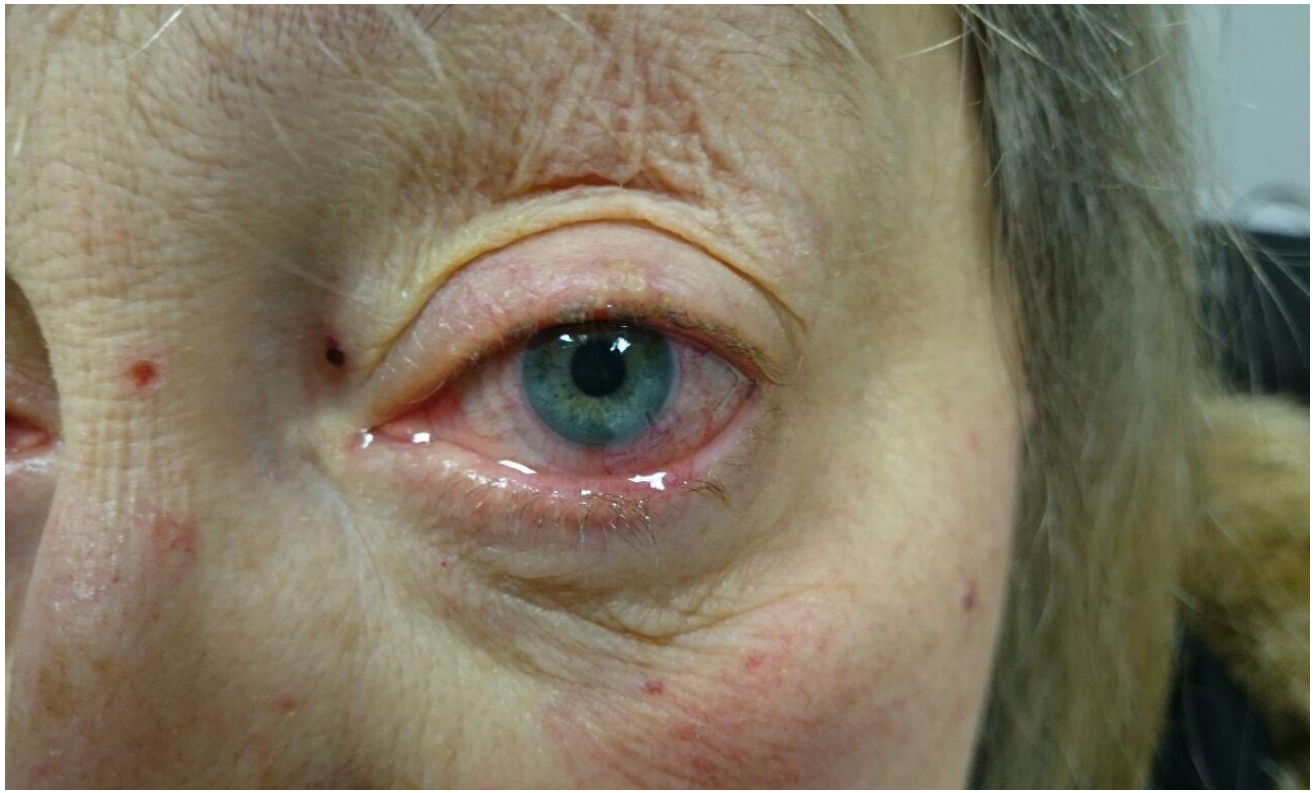
- Start On 02 Oct 2014

Best response: partial response

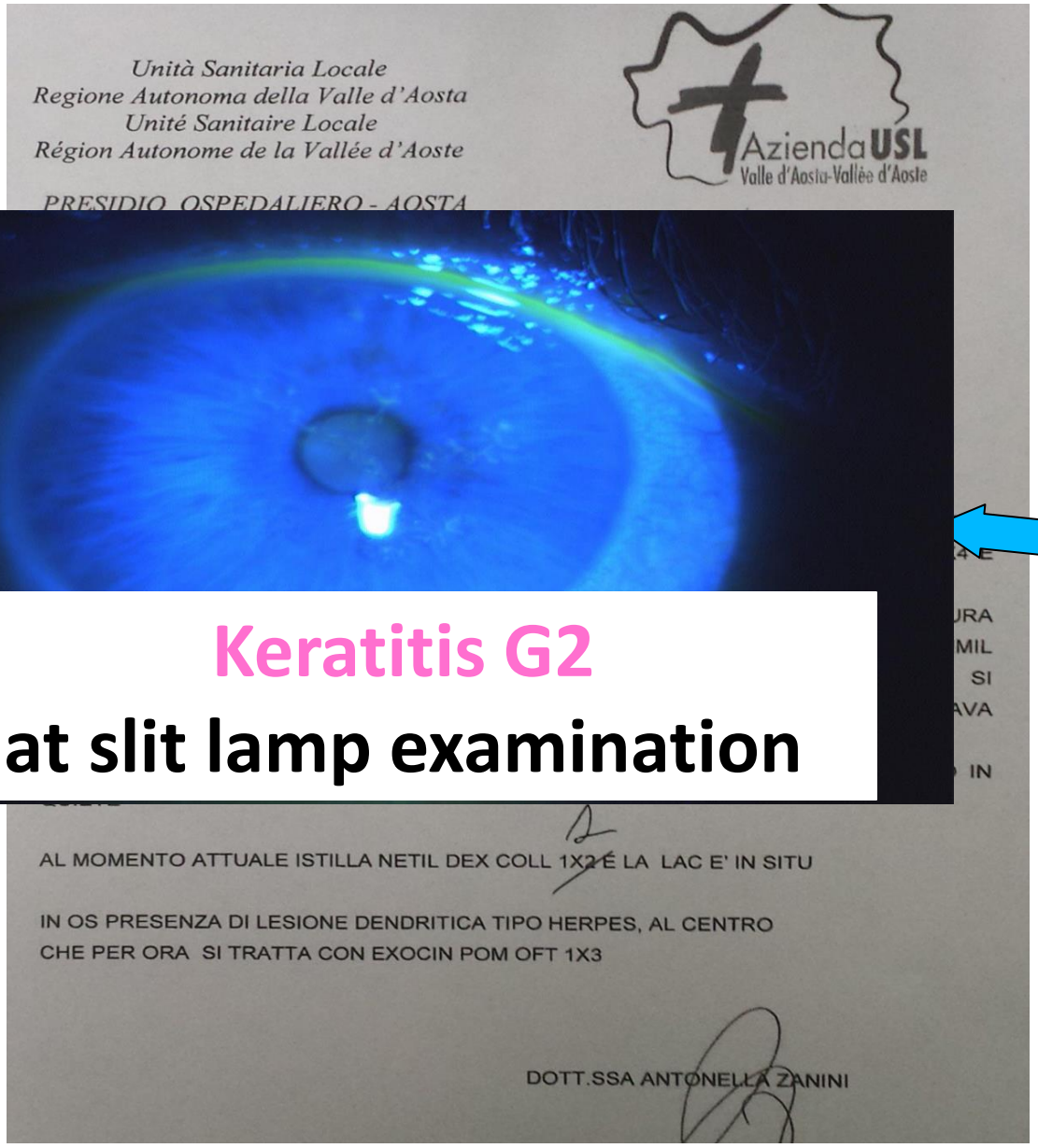
From October 2014 to January 2015 the patient referred:

- Skin toxicity G1

On 31 Jan 2015 the patient reported **left eye** inflammation, pain and itch.



From 31 Jan until 02 Feb 2015 Tobradex® (tobramycin + dexamethasone) was prescribed without benefit. An ophtalmologic assessment was requested and third generation EGFRi was temporarly interrupted.



Keratitis G2

at slit lamp examination

Diagnosis of **keratitis** was done.

Local treatment was prescribed: Netildex® eyewash (netilmicin+ dexamethasone) and contact lens

, where the Investigator considers the AE of concern to be specifically associated with AZD9291, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines

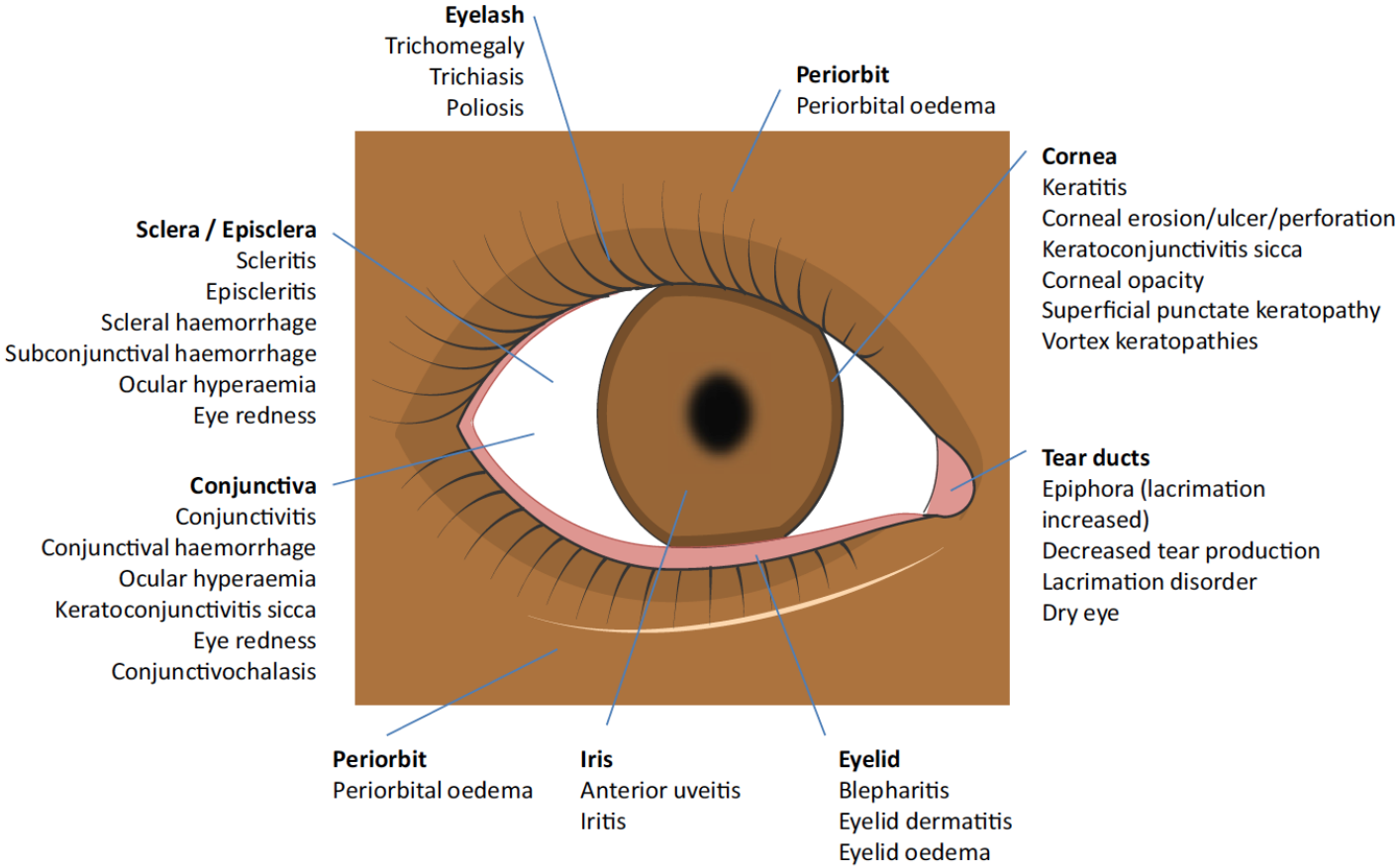
After 18 days of third gen. EGFRi suspension, prosecution of supportive therapy for keratitis and contact lens, ocular toxicity disappeared and the patient resumed the drug at a lower dose.

Incidence and potential severity of ocular adverse events reported in non-pivotal clinical trials.

Molecular targeted agent	Conjunctiva/ episclera/sclera	Anterior ocular segment	Posterior ocular segment	Ocular adnexa	Other
Erlotinib	Severe conjunctivitis (33%)	Severe keratitis (33%)			
Gefitinib	Severe conjunctivitis (NK)	Severe bilateral uveitis (NK)			Ophthalmologic adverse event (20.5%)
Crizotinib					Visual disturbance (41.5%)

NK, Not Known.

Modified from O. Huillard et al. / European Journal of Cancer 50 (2014) 638–64



Poster 449PD, Annals of Oncology, Volume 25, Supplement 4, 2014
Presented by James C.-H. Yang at the 34th Congress of the European Society for Medical Oncology, ESMO 2014

Table 2. Safety overview of adverse events*

Patients with an AE, n (%)	20 mg N=21	40 mg N=58	80 mg N=90	160 mg N=63	240 mg N=21	Total N=253
Any AE	21 (100)	56 (97)	83 (92)	63 (100)	21 (100)	244 (96)
Any AE, drug-related#	14 (67)	38 (66)	71 (79)	59 (94)	21 (100)	203 (80)
Any AE Grade ≥3	6 (29)	21 (36)	26 (29)	24 (38)	5 (24)	82 (32)
Any AE Grade ≥3, drug-related#	2 (10)	2 (3)	10 (11)	16 (25)	3 (14)	33 (13)
AE leading to dose reduction	0	1 (2)	0	10 (16)	6 (29)	17 (7)
AE leading to discontinuation	3 (14)	1 (2)	4 (4)	4 (6)	2 (10)	14 (6)
AE leading to discontinuation, drug-related#	2 (10)	0	1 (1)	3 (5)	1 (5)	7 (3)
Serious AE	4 (19)	13 (22)	20 (22)	16 (25)	3 (14)	56 (22)
Serious AE, drug-related#	3 (14)	1 (2)	4 (4)	6 (10)	1 (5)	15 (6)

*Data are preliminary from an ongoing study and do not include first-line cohorts. #As assessed by the investigator

New EGFR inhibitors – AZD9291 Safety

All Causalities - All Grades

Patients with an AE, n (%)	20 mg N=21	40 mg N=58	80 mg N=90	160 mg N=63	240 mg N=21	Total N=253
AE by preferred term occurring in at least 10% of patients overall						
Diarrhoea	5 (24)	24 (41)	30 (33)	43 (68)	16 (76)	118 (47)
Rash (grouped term)	5 (24)	13 (22)	29 (32)	40 (63)	15 (71)	102 (40)
Nausea	3 (14)	10 (17)	16 (18)	19 (30)	7 (33)	55 (22)
Decreased appetite	7 (33)	11 (19)	14 (16)	16 (25)	6 (29)	54 (21)
Dry skin	2 (10)	9 (16)	10 (11)	25 (40)	5 (24)	51 (20)
Pruritus	2 (10)	11 (19)	15 (17)	12 (19)	7 (33)	47 (19)
Fatigue	4 (19)	15 (26)	9 (10)	11 (17)	5 (24)	44 (17)
Paronychia	2 (10)	5 (9)	11 (12)	18 (29)	6 (29)	42 (17)
Constipation	1 (5)	13 (22)	15 (17)	10 (16)	1 (5)	40 (16)
Cough	3 (14)	9 (16)	12 (13)	13 (21)	0	37 (15)
Stomatitis	1 (5)	5 (9)	9 (10)	13 (21)	3 (14)	31 (12)
Vomiting	3 (14)	4 (7)	9 (10)	7 (11)	6 (29)	29 (11)
Anaemia	0	6 (10)	11 (12)	9 (14)	2 (10)	28 (11)
Dyspnoea	2 (10)	8 (14)	9 (10)	8 (13)	0	27(11)
Upper respiratory tract infection	5 (24)	5 (9)	9 (10)	5 (8)	1 (5)	25 (10)
Headache	0	6 (10)	9 (10)	9 (14)	1 (5)	25 (10)
Select AEs of interest						
Hyperglycaemia	0	1 (2)	3 (3)	2 (3)	0	6 (2)
QT prolongation	0	2 (3)	4 (4)	4 (6)	1 (5)	11 (4)
Pneumonitis-like events*#	0	0	2 (2)	4 (6)	0	6 (2)
Any AE Grade ≥3, drug-related#	**2 (10)**	**2(3)**	**10 (11)**	**16 (25)**	**3 (14)**	**33 (13)**

Male patient, A.S. 61 years old.

Right supraclavicular lymph node FNA (28 May 2012)
Diagnosis of adenocarcinoma, Stage IIIB (T1N3M0)
ALK: not rearranged, EGFR wt.

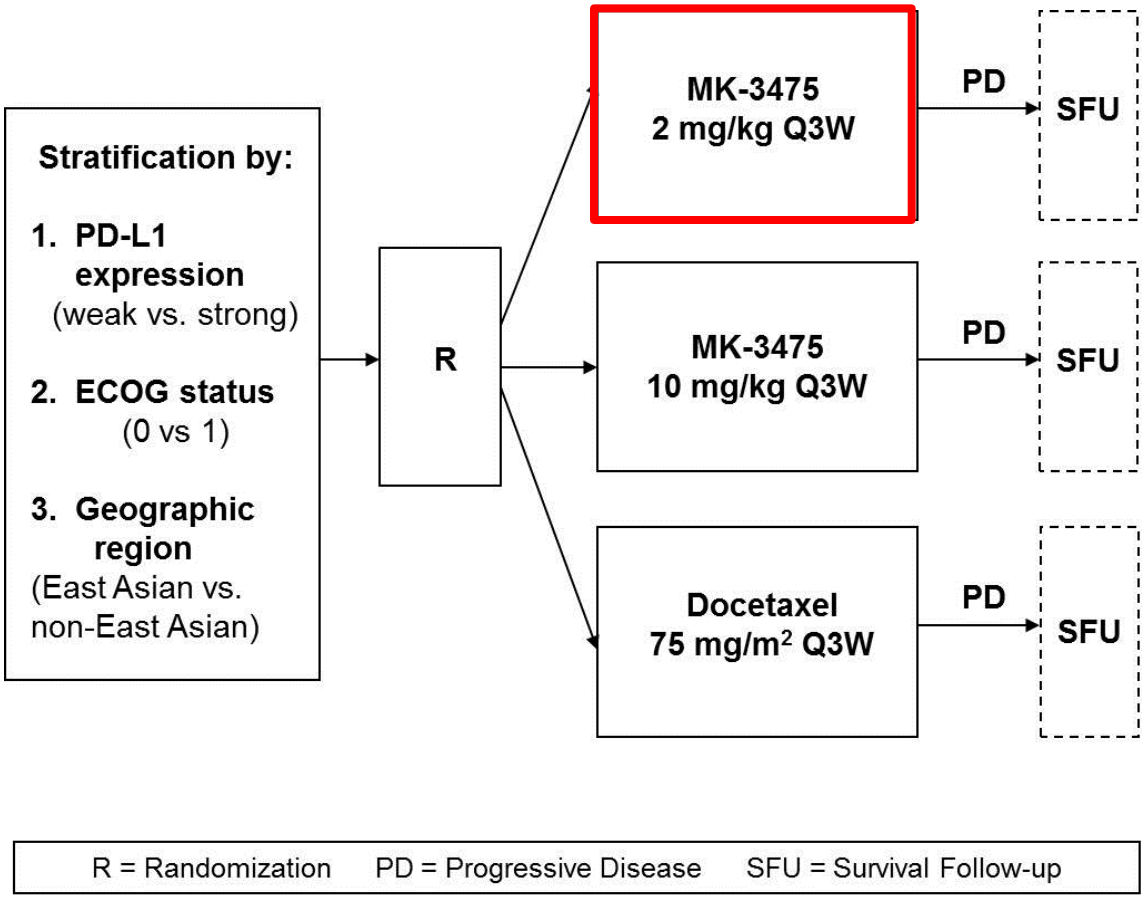
First-line treatment (June 2012 – August 2012):
Cisplatin 75 mg/mq – Pemetrexed 500 mg/mq (3 cycles), shifted to Carboplatin AUC 6 because of GFR reduction.
Sequential thoracic mediastinal radiotherapy: DFT 60Gy/30 fr

Best response: Stable Disease
Maintained until October 2013

After nodal progression (laterocervical lymph nodes), the patient was evaluated within MK-3475-010 clinical trial.

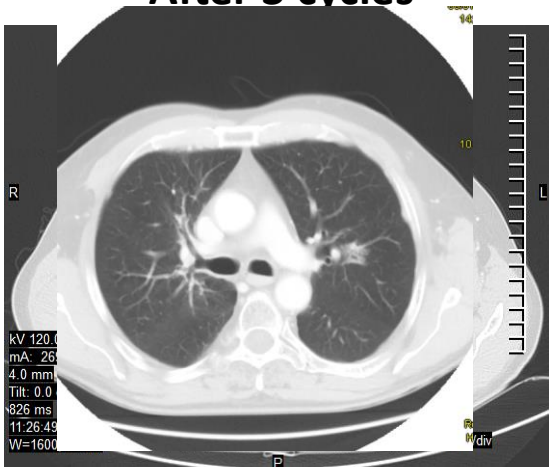
PD-L1 expression on diagnostic tissue was evaluated and described.

The patient was randomized to treatment with MK 3475 2 mg/Kg q3weeks. I cycle started on 23 Jan 2014

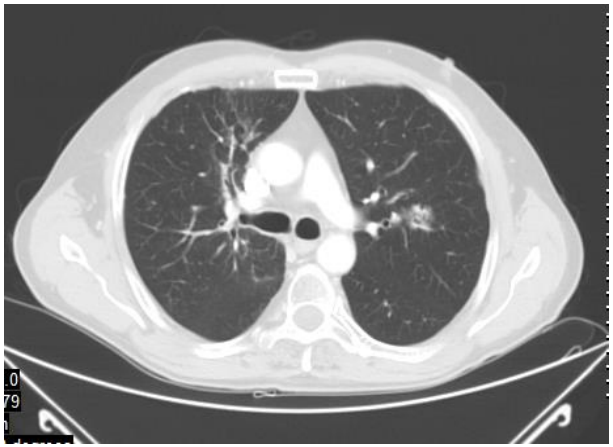


CT scan during treatment

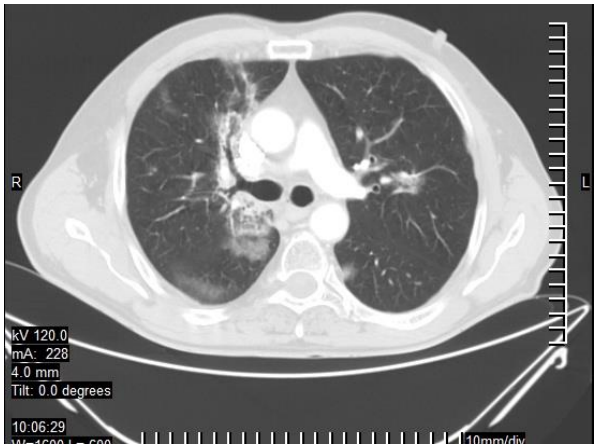
Baseline
After 3 cycles



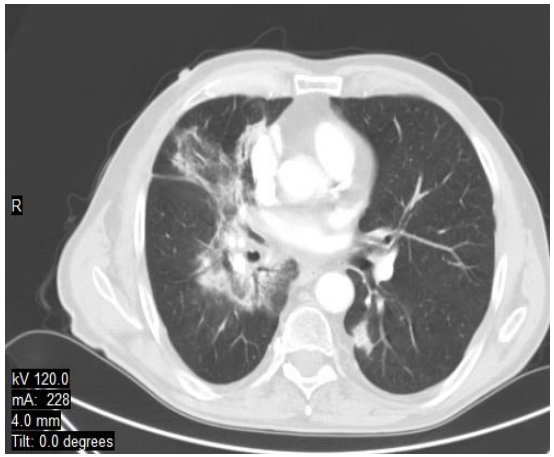
After 6 cycles



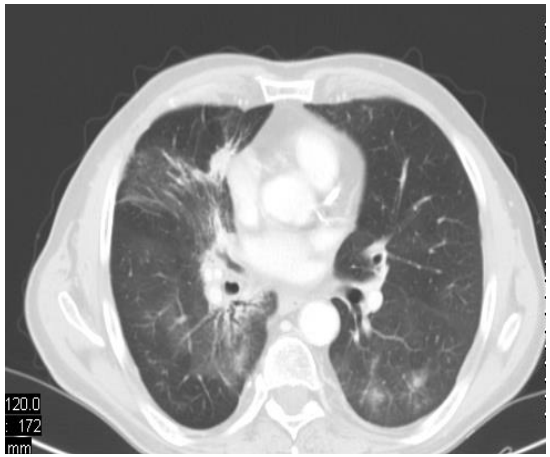
After 9 cycles



… appearance and increase of bilateral ground glass areas



After 12 cycles



After 18 cycles

Pulmonary function testing

Baseline

Spirometria

Espirazione forzata		Ref	CI	Pre Meas	Pre % Ref	P M
FVC	Litri	3.47	1.00	3.39	98	
FEV1	Litri	2.73	0.84	2.64	97	
FEV1/FVC	%	76	12	78		
FEV1/SVC	%	76		76	99	
FEF75%	L/sec	1.30	1.28	0.86	66	
PEF	L/sec	7.51	1.99	9.52	127	
FEF/FIF50				0.71		
FET100%	Sec			3.58		
PEFT	Sec			0.10		

Pletismografia

		Ref	CI	Pre Meas	Pre % Ref	Post Meas
VC	Litri	3.59	0.92	3.49	97	
FRC PL	Litri	3.31	0.99	3.31	100	
RV	Litri	2.30	0.67	2.60	113	
ERV	Litri			0.71		
TLC	Litri	6.02	1.15	6.09	101	
RV/TLC	%	39	9	43		
IC	Litri			2.79		

		Ref	Pre	Pre	Post
Raw	cmH2O/L/sec		1.68		
sGaw	L/s/cmH2O/L		0.125		
Vtg	Litri		4.77		

Diffusione

		Ref	CI	Pre Meas	Pre % Ref
DL Adj	mL/mmHg/min	24.0	6.9	20.2	84
VA	Litri	6.02	1.15	5.24	87
DL/VA Adj	mL/mHg/min/L	3.99		3.86	97

After 17 cycles

Spirometria

Espirazione forzata		Ref	CI	Pre Meas	Pre % Ref	Po Mea
FVC	Litri	3.44	1.00	3.91	114	
FEV1	Litri	2.71	0.84	2.91	108	
FEV1/FVC	%	76	12	74		
FEV1/SVC	%	76		75	98	
FEF75%	L/sec	1.28	1.28	0.82	64	
PEF	L/sec	7.47	1.99	8.30	111	
FEF/FIF50				0.52		
PEFT	Sec			0.11		
FET100%	Sec			5.37		

Pletismografia

		Ref	CI	Pre	Pre	Post
VC	Litri	3.55	0.92	3.91	110	
FRC PL	Litri	3.32	0.99	2.79	84	
RV	Litri	2.33	0.67	1.44	62	
ERV	Litri			1.35		
TLC	Litri	6.02	1.15	5.35	89	
RV/TLC	%	39	9	27		
IC	Litri			2.42		
Raw	cmH2O/L/sec			1.28		
sGaw	L/s/cmH2O/L			0.228		
Vtg	Litri			3.44		

Diffusione

		Ref	CI	Pre Meas	Pre %
DL Adj	mL/mmHg/min	23.8	6.9	14.9	
VA	Litri	6.02	1.15		
DL/VA Adj	mL/mHg/min/L	3.95		3.18	

Decreased Diffusing Capacity (DLCO)
– Asymptomatic patient

From the trial… Instructions for symptomatic patients with pneumonitis

Stop MK - 3475

Evaluation for broncoscopy, cultures and pulmonary functions tests

Recommended treatment for symptomatic pneumonitis:

- Dose interruption of MK-3475 and steroid intervention for Grade 2 with option to return to treatment if the pneumonitis improves to ≤ Grade 1.
- Permanent discontinuation of MK-3475 if Grade 3 or 4 and steroid intervention.

After improvement to Grade ≤1 of the pneumonitis the following rules should apply:

First episode of pneumonitis:

- Improvement occurs in ≤4 weeks and was Grade 2 – dose MK-3475 at usual schedule of Q3W.
- Improvement occurs >4 weeks for Grade 2–recommended to add an additional week in between MK-3475 dosing (e.g., Q3W now becomes Q4W).

Second episode of pneumonitis:

- Permanently discontinue MK-3475 if upon rechallenge patient develops pneumonitis Grade ≥2.

From the trial… Instructions for asymptomatic patients with pneumonitis

Recommendations for asymptomatic pneumonitis:

- Monitor for the development of symptoms or an increased oxygen requirement
- Continue MK-3475 on schedule

Despite radiologic images and pulmonary function testing, the patient remained asymptomatic.

Neither interruption nor dose reduction were performed.

The patient, as per protocol, is still continuing on treatment.

Pulmonary toxicity with checkpoint inhibitors

- Pulmonary irAE can present with dyspnoea, cough, fatigue or respiratory failure
- Grade 1 (asymptomatic radiological changes) may be monitored with no change in immunotherapy treatment.
- Grade 2: immunotherapy therapy should be withheld and oral steroids commenced (1mg/kg/day prednisolone or equivalent)
- Grade 3-4: hospitalisation and review by a respiratory physician, together with high dose intravenous steroids (2–4 mg/kg/day IV methylprednisolone)

M. Howell et al, Lung Cancer 2015

PD-1 Inhibitors - Safety

Keynote 001: pembrolizumab

AE, %	N = 262	
	Any Grade	Grade 3-5
Treatment-related with incidence ≥5%		
Fatigue	20	<1
Pruritus	9	0
Arthralgia	8	<1
Decreased appetite	8	0
Diarrhea	7	0
Hypothyroidism	6	0
Pyrexia	6	0
Rash	6	0
Nausea	5	<1
Other of clinical interest ≥1%		
Pneumonitis	4	2
Hyperthyroidism	2	<1

- Other potentially immune-mediated AEs that occurred in <1% of patients were colitis and hyponatremia

Felip E et al, ESMO 2014

CheckMate 063: nivolumab

	Any grade	Grade 3–4
Any	87 (74%)	20 (17%)
General disorders		
Fatigue	38 (33%)	5 (4%)*
Asthenia	14 (12%)	0
Gastrointestinal disorders		
Nausea	18 (15%)	0
Diarrhoea	12 (10%)	3 (3%)*
Dry mouth	7 (6%)	0
Vomiting	7 (6%)	0
Constipation	6 (5%)	0
Metabolism and nutrition disorders		
Decreased appetite	22 (19%)	0
Skin and subcutaneous tissue disorders		
Rash	13 (11%)	1 (1%)*
Pruritus	7 (6%)	1 (1%)*
Musculoskeletal disorders		
Myalgia	6 (5%)	1 (1%)*
Respiratory disorders		
Dyspnoea	6 (5%)	0
Pneumonitis	6 (5%)	4 (3%)*
Blood and lymphatic system disorders		
Anaemia	7 (6%)	1 (1%)*

Data are number of events (%). Includes events reported between the first dose and 30 days after the last dose of nivolumab. Grade 3–4 adverse events reported by less than 5% of patients included: hyponatraemia (two [2%]); and polyneuropathy, decreased lymphocyte count, herpes zoster, adrenal insufficiency, vasculitis, hypersensitivity, anaphylactic reaction, and unassigned, each reported by one patient (one [1%]). One patient (1%) died from pneumonia, and one patient (1%) from ischaemic stroke. *All grade 3.

Table 3: **Treatment-related adverse events that occurred in at least 5% of all treated patients**

Rizvi NA et al, Lancet Oncology 2015

M. G.P. Male 60 yrs old

Clinical History:

Mild Hypertension under pharmacologial treatment

Former smoker (30 pack/years)

Oncological History:

05.12.2009: Right Median Lobectomy → Histology: Squamous NSCLC, pT1N0M0, Stage at diagnosis IA

July 2012: Thoracic/local disease progression

From 30.07 to 17.10.2012: I line chemotherapy (Cisplatin/Gemcitabine, 4 cycles). Best response PR

From 03.11 to 20.12.2012: Mediastinal radiotherapy (TD 59 Gy, 33 administrations)

From 11.10 to 12.12.2013: II line chemotherapy (Cisplatin/Gemcitabine, 3 cycles). Best response CR

From 25.05 to 07.07.2014: III line chemotherapy (Cisplatin/Gemcitabine, 3 cycles). Best response PD

From 28.08 to 31.10.2014: IV line chemotherapy (Docetaxel, 4 cycles). Best response PD

November 2014
Systemic disease progression (mediastinal and supraclavicular lymph-nodes, lung, bone)

Patient's request of evaluation of the possibility to be enrolled in a experimental clinical trial

15.01.2015: FNA of a jugular lymph-node
Citology: Squamous NSCLC with FGFR1 amplification

January 2015

Patient enrolled in the protocol E-3810-II-02, a single arm, phase II study to assess the efficacy of the dual VEGFR-FGFR TKI LUCITANIB, given orally as a single agent to patients with FGFR1-driven lung cancer.

Starting dose: 15 mg once day

Plasma TSH and thyroid hormones levels (fT3, fT4) should be measured, as per protocol, at screening and subsequent biochemisty evaluations to exclude the presence of Hypothyroidism.

18.02.2015. Cycle 1, Day 1 (start of Lucitanib treatment)

TSH 5,002 mIU/L (high: above 5 mIU/L)
AbTg 1,18 UI/mL (normal), AbTPO 0,18 UI/mL (normal)
fT3 3,600 pg/mL, fT4 0,860 ng/dL (normal)

Echographic evaluation of thyroid: thyroid of lower size than normal limits, dishomogeneous structure, without nodular lesions.

Because of the minimal increase of TSH level, the patient started treatment with Levothyroxine 25 mcg/day.

03.03.2015. Cycle 1, Day 14

Occurrence of G3 Hypertension

TSH 33,432 mIU/L (high)
fT3 2,460 pg/mL, fT4 0,780 ng/dL (normal)

=

Asymptomatic
G1 Hypothyroidism

Because of the need to stop treatment with Lucitanib for hypertension and the absolutely absence of endocrine symptoms, the patient continued treatment with Levothyroxine 25 mcg/day.

Modify of pharmacological treatment for Hypertension with progressive normalization of blood pressure.

18.03.2015. Cycle 2, Day 1

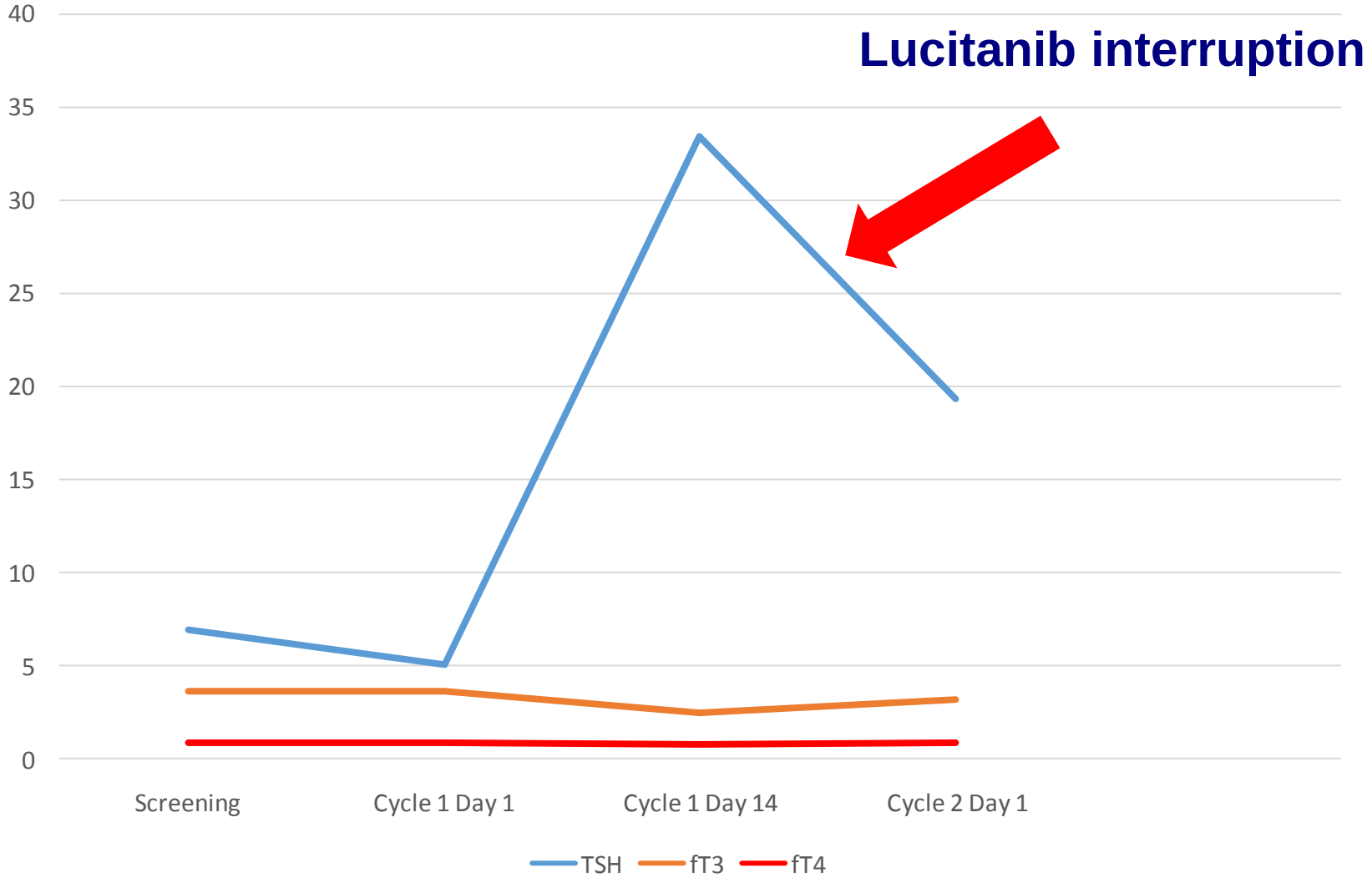
No Hypertension.
Patient started again treatment with Lucitanib at a lower dose (12,5 mg once day)

TSH 19,308 mIU/L (high)
fT3 3,130 pg/mL, fT4 0,890 ng/dL (normal)

= **Asymptomatic**
G1 Hypothyroidism

Because of the need to continue treatment with Lucitanib, despite the absolutely absence of endocrine symptoms, the patient started treatment with Levothyroxine 50 mcg/day.

Thyroid hormones levels



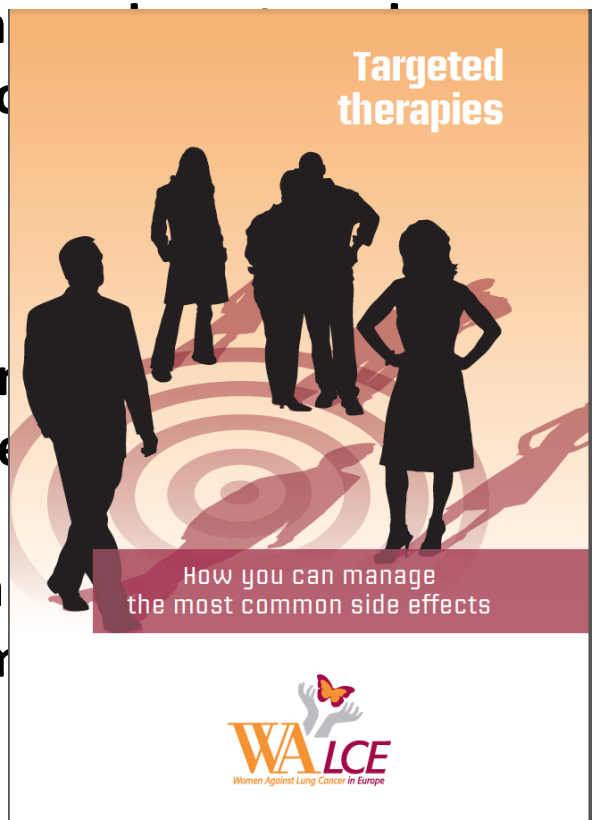
Incidence of endocrine disorders under targeted therapies

Authors, year [reference]	Study design	Type of targeted therapy	No. of patients	Tumor type	Hypothyroidism, *n* (%)	
					All grade	Grade 3/4
Desai *et al.*, 2006 [1]	Observational prospective	Sunitinib	42	GIST	22 (52%)	–
Mannavola *et al.*, 2007 [2]	Observational prospective	Sunitinib	24	GIST	17 (70%)	–
Wolter *et al.*, 2008 [3]	Observational prospective	Sunitinib	59	RCC/GIST	36 (61%)	–
Clement *et al.*, 2008 [4]	Observational prospective	Sorafenib	38	RCC	7 (18.4%)	–
Schmidinger *et al.*, 2011 [5]	Observational prospective	Sunitinib or sorafenib	87	RCC	30 (34%)	–
Wells *et al.*, 2012 [6]	III	Vandetanib	231	MTC	(49.3%)	
Motzer *et al.*, 2013 [7]	III	Axitinib	359	Advanced or M+ RCC	72 (20%)	1 (<1%)
Motzer *et al.*, 2013 [8]	III	Pazopanib	554	Advanced or M+ RCC	67 (12%)	0 (0%)
Motzer *et al.*, 2013 [8]	III	Sunitinib	548	Advanced or M+ RCC	133 (11%)	2 (<1%)

Kotecki N et al, Curr Opin Oncol 2015

Conclusion

- The introduction of targeted drugs in the lung cancer treatment also introduce a different toxicity profile
- It is important to consider co-morbidity when selecting patients for targeted agents
- Multidisciplinary team in thoracic oncology is n
  requested in: diagnostic and therapeutic decisi
  toxicities management
- Considering the average treatment period with
  new toxicity criteria including not only the inter
  duration, should be introduced into the manage
- Patients should be attentively educated, with a
  preventive measures and management recomm

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