Patient Safety

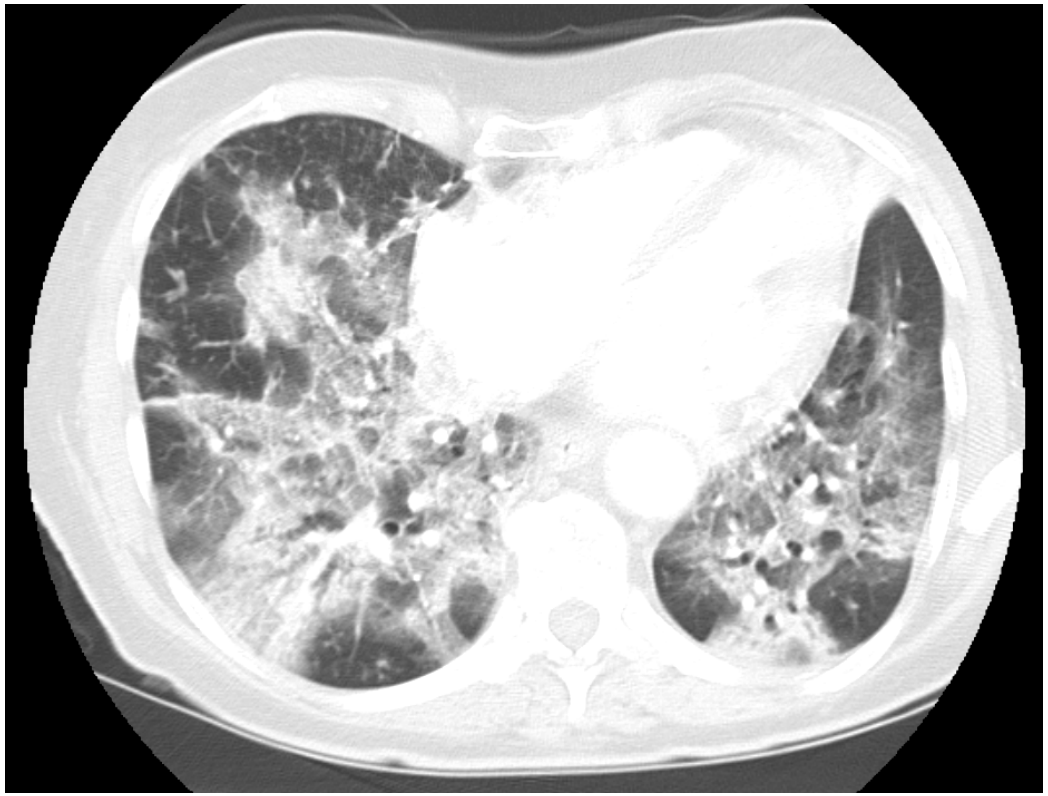
James J. Harding, MD
Assistant Attending
Early Drug Development Service
Gastrointestinal Oncology Service
Department of Medicine
Clinical Research Management and Compliance Course
10/26/2021

Case Presentation: Treatment-Related Death

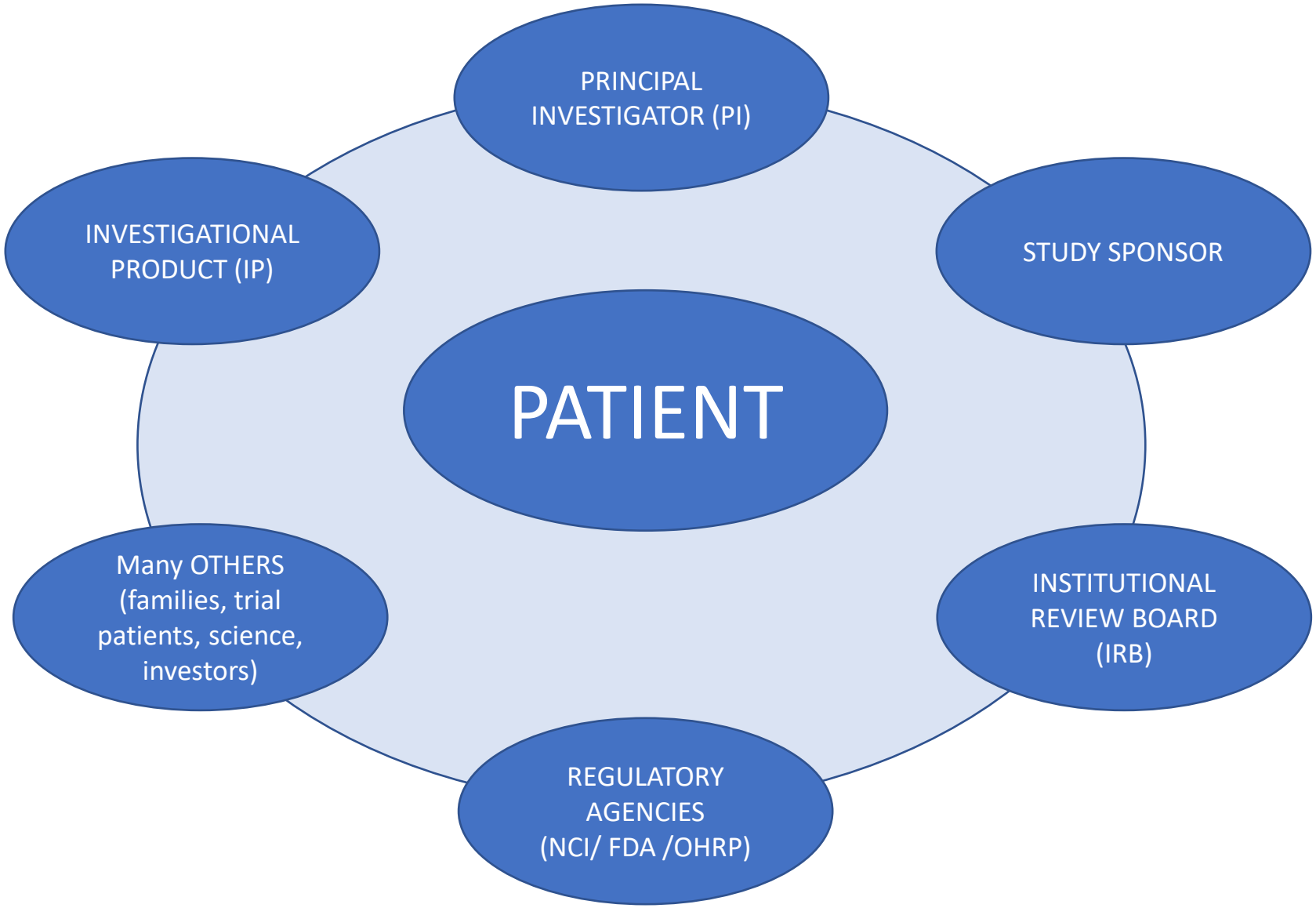
- 80 y/o F
- *MET* altered, PD-L1 +, stage IV NSCLC
- Prior Tx: pembrolizumab; crizotinib
- ECOG PS 0, Intact organ function
- Began MET-targeted Phase 1

Completed 4 cycles of treatment with radiographic response

Progressive SOB/DOE through cycle 4 → acute hypoxemic respiratory failure → intubation → DEATH



Multi-faceted Aspect of Safety on Clinical Trials



The Patient Safety Experience

Patients must…

- be **informed** of risks
- **updated** with changes to risk
- receive in **lay language** written at 8th grade reading level
- have the ability to **review** without coercion
- be **monitored** per protocol for any toxicity

Example of NIVO risk (Page 1 of 4!)

Possible side effects of nivolumab:

Common, some may be serious In 100 people receiving nivolumab, more than 10 and as many as 100 may have:
• Diarrhea • Fatigue • Itching • Rash

Occasional, some may be serious In 100 people receiving nivolumab, between more than 1 and less than 10 may have:
• Abdominal pain • Allergic reaction/ hypersensitivity. Allergic reactions may be mild (such as skin rash or hives) to severe (such as breathing difficulties or shock). • Chills • Constipation • Cough • Decreased appetite • Decreased thyroid gland function (can cause fatigue, weakness, weight gain) • Dizziness • Dry mouth • Dry skin • Fever • Headache • Increased blood sugar • Increased alkaline phosphatase (lab test result associated with liver or bone abnormalities) • Increased ALT and/or AST (lab test results associated with abnormal liver function) • Increased amylase and/or lipase (lab test results associated with pancreatic inflammation) • Increased bilirubin (liver function blood test), which can indicate a problem with or damage to your liver • Increased creatinine (lab test result associated with decreased kidney function) • Increased thyroid gland function (can cause fatigue, tremors, mood swings) • Increased thyroid stimulating hormone (TSH; lab test result associated with abnormal thyroid function)

The PI Safety Experience: Defining, Grading, and Attributing…

"My stomach hurts"

"WORST pain of my life"

"I feel so much better"

"An Elephant is Sitting on my Chest"

Bloating

"It only lasts a few days"

ALOPECIA

GERD

Nausea

Hgb = 7.0

Dry Heaves

"Hi, Dr. Harding, I'm the intern on GI A we admitted Mrs. X last night for periorbital cellulitis."

The PI and study team must take a qualitative experience and quantify it to define toxicity

Harmonization of Adverse Events

The NCI's Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology which can be used for Adverse Event (AE) reporting.

What is an Adverse Event?

- An **adverse event** is any undesirable event that occurs during a clinical trial and it does not necessarily need to be related to the investigational drug/treatment.

- Name of the Event, Grade, Relationship, and start Date

Grade (Severity) of an Adverse Event?

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

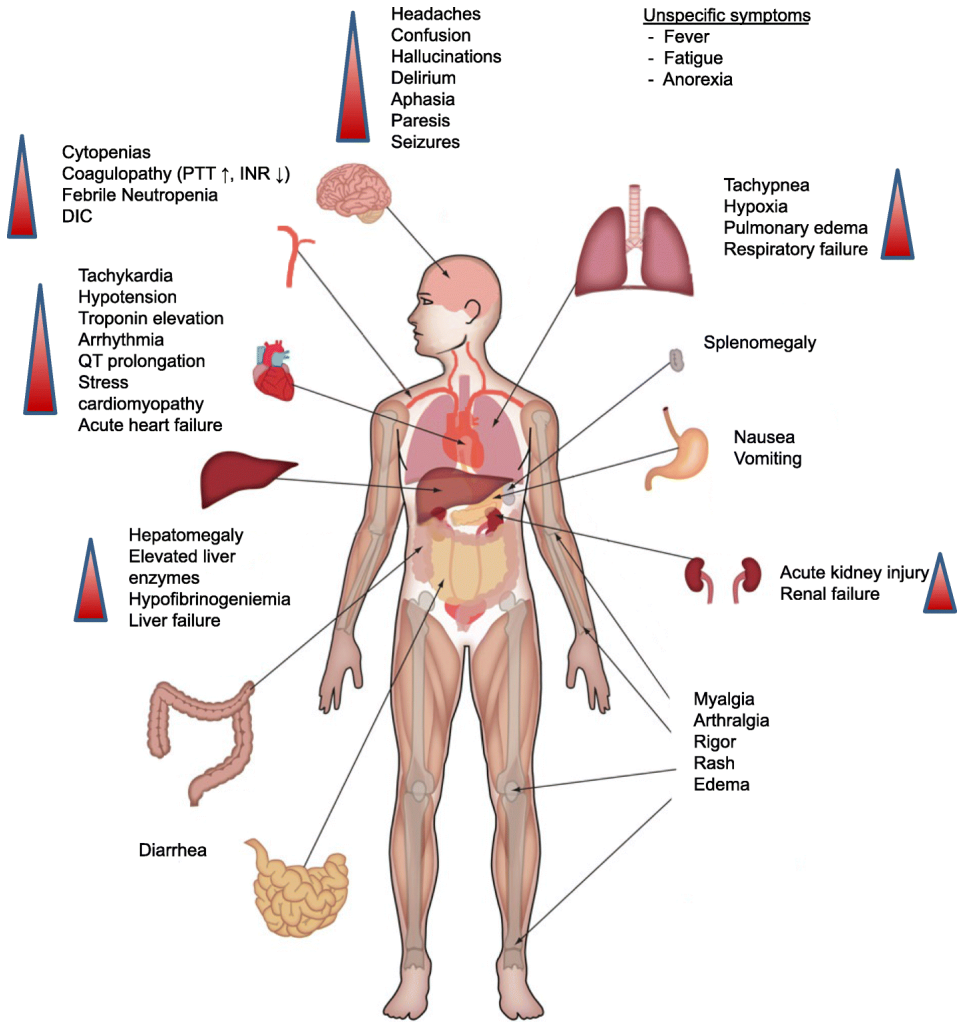
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

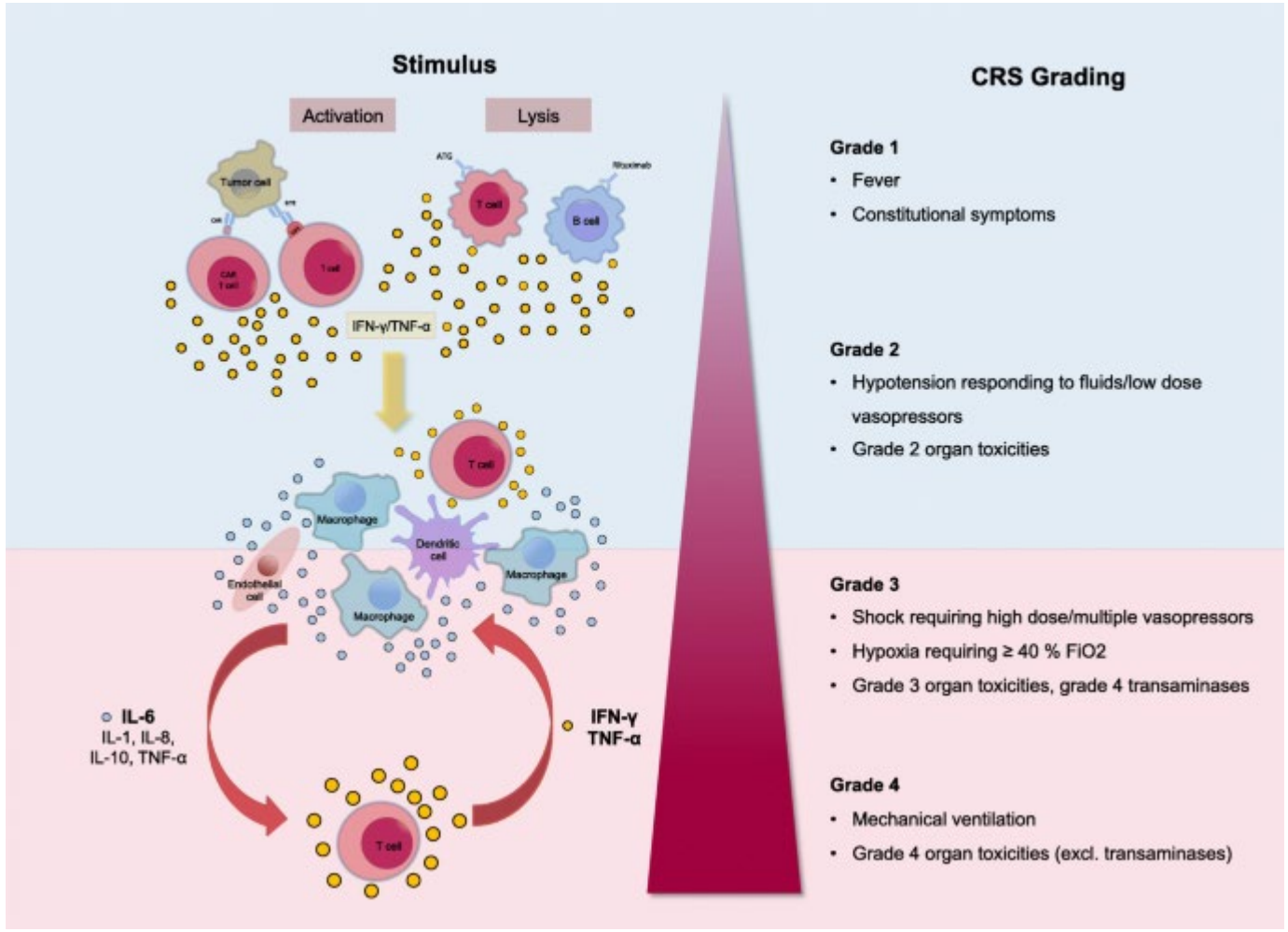
Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Navigational Note: -					

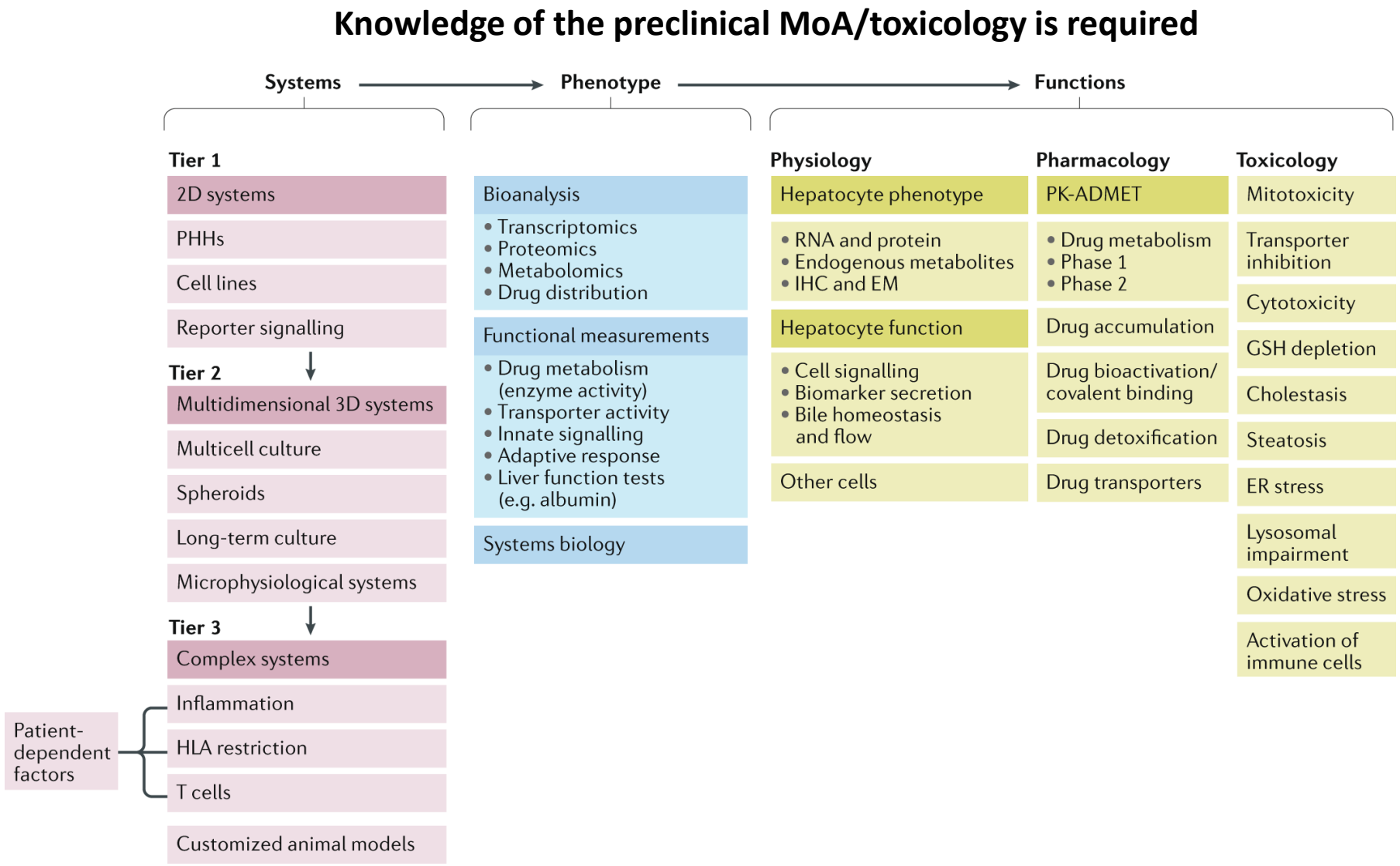
Other grading systems for AEs?





Unique criteria may need to be developed based on the MoA of drug

Is the AE related to the drug or not?



Nature Reviews Drug Development 2020

Consult your Investigator's Brochure (IB)…

Table 1. FDA guidance relevant for IND submission

S1 Carcinogenicity,
S2 Genetic toxicity,
S3 Toxicokinetics,
S4 Duration of Chronic Toxicity Testing,
S5 Reproductive toxicity,
S6 Biotechnology,
S7 Safety Pharmacology,
S9 Nonclinical Studies for Development Anticancer Drugs and Biologics (under review),
M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials.

NOTE: From the FDA Guidance (Drugs) website (23).

Table 2. Elements of an IND

Cover sheet: FDA form 1571
Table of contents
Introductory statements and general investigations: developmental plan for the drug into perspective and plans contingent on the outcome of the studies
Investigator's brochure
Chemistry, manufacturing, and control information
Pharmacology and toxicology information
Protocols (21 CFR 312.23(a) (6)
Previous human experience with the investigational drug: presented in an integrated summary report

NOTE: From the Electronic Code of Federal Regulations (24).

PF-06671008
Investigator's Brochure
October 2015

INVESTIGATOR'S BROCHURE

PF-06671008

October 2015

…and the protocol, your co-PI, the study sponsor! When in doubt err on the side of <u>related</u> until more data are available

What is a Serious Adverse Event (SAE) and what is PI regulatory responsibility ?

SAEs are:

- Death (grade 5)
- Life threatening Adverse Event
- An AE that results in inpatient hospitalization or prolongation of hospitalization
- A persistent or significant incapacity or substantial disruption
- A congenital anomaly/birth defect
- **Important Medical Event as per the PI.**
- **Anything that the protocol mandates is an SAE!!**

Several people/groups may need to be notified of an SAE including:

- Principal Investigator (PI)
- MSK IRB
- Data Safety Monitoring Board
- Study Sponsor
- Drug Supplier/funder
- Food and Drug Administration (FDA)
- National Cancer Institute (NCI)

Review the protocol for specifics

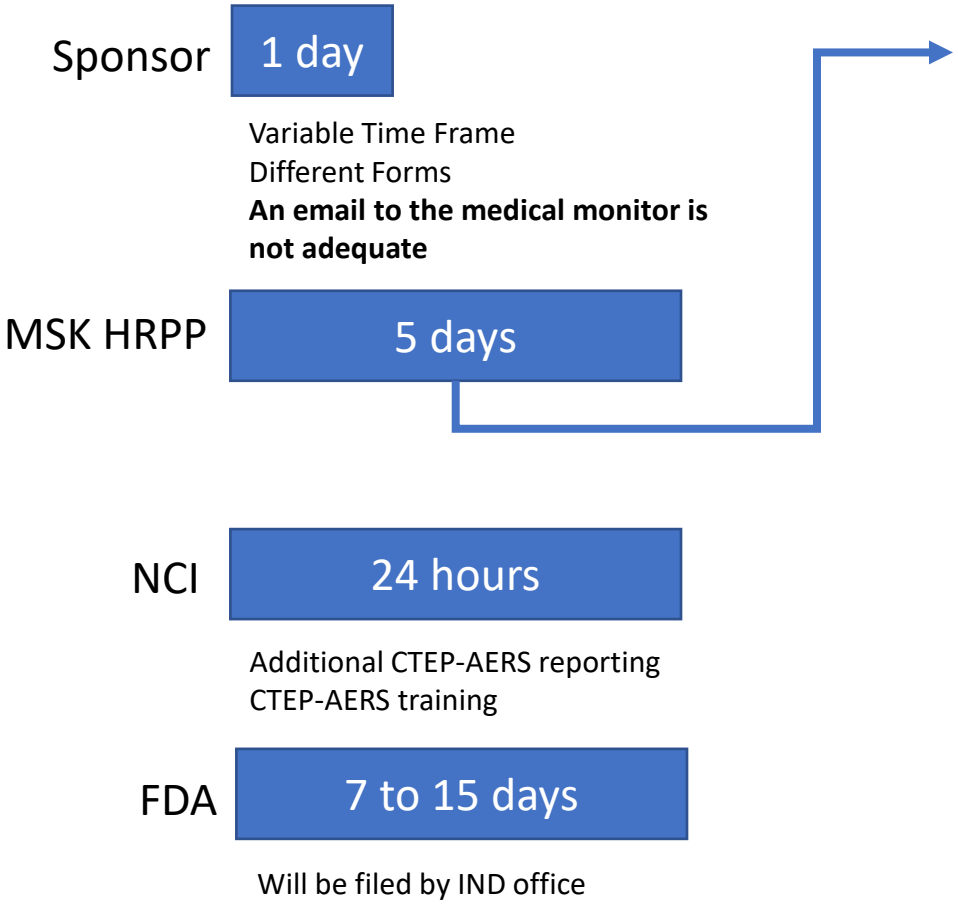
Expected or Unexpected: A regulatory definition

Expected:
Any experience previously reported (in nature, severity, or incidence) in the current Investigator's Brochure or general investigational plan

Unexpected:*
Any experience not previously reported (in nature, severity, or incidence) in the current Investigator's Brochure or general investigational plan

*An **unexpected** AE that is related and serious may require additional reporting to the local IRB or other regulatory

Timeframe for SAE reporting



The following SAEs must be reported to the MSK HRPP within 5 calendar days* of the event:

- For MSK-held IND/IDE protocols: All SAEs
- Unexpected and related (possible, probable, or definite attribution) SAEs
- Grade 5 (fatal) SAEs
- Single Patient Use (SPU) SAEs

*If event occurs outside of MSK, report within 5 calendar days of learning of the event

All other SAEs must be filed in the regulatory binder within 30 calendar days* of the event.

*If event occurs outside of MSK, report within 30 calendar days of learning of the event

What about when the SAEs are occurring at another site?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

- Enrolled 296 patients, 8+ expansion cohorts

The Study Sponsor

- Establishes prospective, encrypted, database for all AEs, regardless of attribution (i.e. Medidata, Rave, CRDB).
- Monitors all aspects of study safety at set intervals
- Reviews all safety reports at set intervals
- Provides safety reports to DSMB at set intervals
- Updates protocol and informed consents
- **Provides correspondences to the study PIs detailing AEs/SAE and plan to modify the protocol for safety**

Example of Sponsor Study Correspondence

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	ROMANIA			[redacted]	64 Years	Male	106.00 kg	25	JUL	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Hypothyroidism [Hypothyroidism]

Case Description: Protocol title (CA209-9LA): A Phase 3, Randomized Study of Nivolumab plus Ipilimumab in Combination with Chemotherapy vs Chemotherapy alone as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC)

PID: CA209-9LA-0031-00629 / BMS-2019-074621 / Romania

Reportable SAE: Hypothyroidism (SUSAR for nivolumab and

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ OTHER

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (Include generic name)
#1) NIVOLUMAB (NIVOLUMAB) SOLUTION FOR INJECTION {Lot # Unknown}
#2) IPILIMUMAB (IPILIMUMAB) SOLUTION FOR INJECTION {Lot # (Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 360 milligram	#1) IV
#2) 106 milligram	#2) IV

17. INDICATION(S) FOR USE
#1) Non-Small Cell Lung Carcinoma (Non-small cell lung cancer)
#2) Non-small cell lung cancer (Non-small cell lung cancer)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 14-AUG-2018 / Unknown	#1) Unknown
#2) 14-AUG-2018 / Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ZOPICLONE (ZOPICLONE) ; 17-OCT-2018 / Ongoing
#2) DIHYDROCODEINE;DIHYDROCODEINE BITARTRATE (DIHYDROCO
#3) EUTHYROX (LEVOTHYROXINE SODIUM) ; 25-APR-2019 / 01-AUG-2019
#4) THEOPHYLLINE (THEOPHYLLINE) ; 24-MAR-2016 / Ongoing
#5) ESOMEPRAZOLE (ESOMEPRAZOLE) ; 01-JAN-2017 / Ongoing
#6) CO-APROVEL (HYDROCHLOROTHIAZIDE, IRBESARTAN) ; 24-MAR-2016 / Ongoing (Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	
Unknown	Historical Condition	Arterial hypertension (Hypertension)

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Bristol-Myers Squibb Company
Eileen Leonard
GPV HW19-1.01 P.O. Box 5400
Princeton, NJ 08543-5400 UNITED STATES
Phone: 6098183513

26. REMARKS
World Wide #: RO-BRISTOL-MYERS SQUIBB
COMPANY-BMS-2019-074621
Patient ID: 00629
Study ID: CA209-9LA(continued)

24b. MFR CONTROL NO.
BMS-2019-074621

25b. NAME AND ADDRESS OF REPORTER
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
01-AUG-2019

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

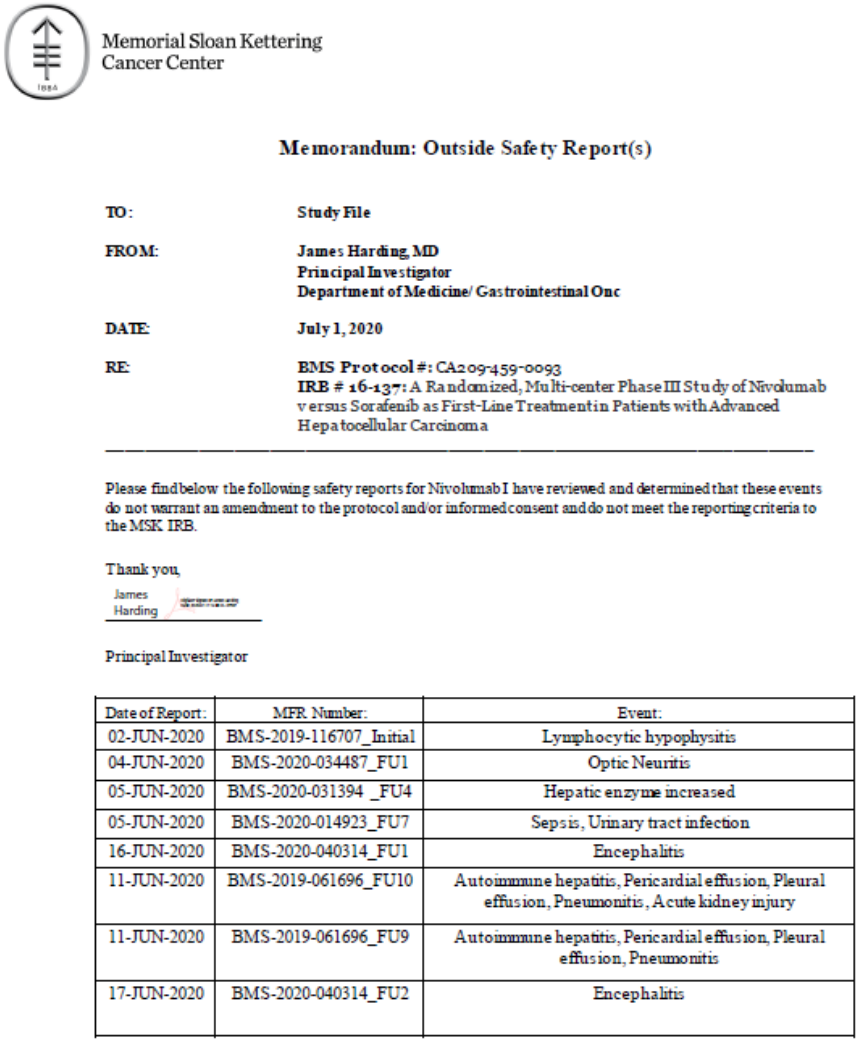
DATE OF THIS REPORT
07-AUG-2019

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP: 1

07-Aug-2019 19:14

Approved v1.0 930142772 1.0

The PI is responsible for notifying the IRB, updating protocol, notify patients, etc.



Memorial Sloan Kettering Cancer Center

Memorandum: Outside Safety Report(s)

TO: **Study File**

FROM: **James Harding, MD**
Principal Investigator
Department of Medicine/ Gastrointestinal Onc

DATE: **July 1, 2020**

RE: **BMS Protocol #:** CA209-459-0093
IRB # 16-137: A Randomized, Multi-center Phase III Study of Nivolumab versus Sorafenib as First-Line Treatment in Patients with Advanced Hepatocellular Carcinoma

---

Please find below the following safety reports for Nivolumab I have reviewed and determined that these events do not warrant an amendment to the protocol and/or informed consent and do not meet the reporting criteria to the MSK IRB.

Thank you,

James Harding

Principal Investigator

Date of Report:	MFR Number:	Event:
02-JUN-2020	BMS-2019-116707_Initial	Lymphocytic hypophysitis
04-JUN-2020	BMS-2020-034487_FU1	Optic Neuritis
05-JUN-2020	BMS-2020-031394 _FU4	Hepatic enzyme increased
05-JUN-2020	BMS-2020-014923_FU7	Sepsis, Urinary tract infection
16-JUN-2020	BMS-2020-040314_FU1	Encephalitis
11-JUN-2020	BMS-2019-061696_FU10	Autoimmune hepatitis, Pericardial effusion, Pleural effusion, Pneumonitis, Acute kidney injury
11-JUN-2020	BMS-2019-061696_FU9	Autoimmune hepatitis, Pericardial effusion, Pleural effusion, Pneumonitis
17-JUN-2020	BMS-2020-040314_FU2	Encephalitis

Unanticipated Problems

Any incident, experience, or outcome that meets all of the following:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents and (b) the characteristics of the subject population being studied;

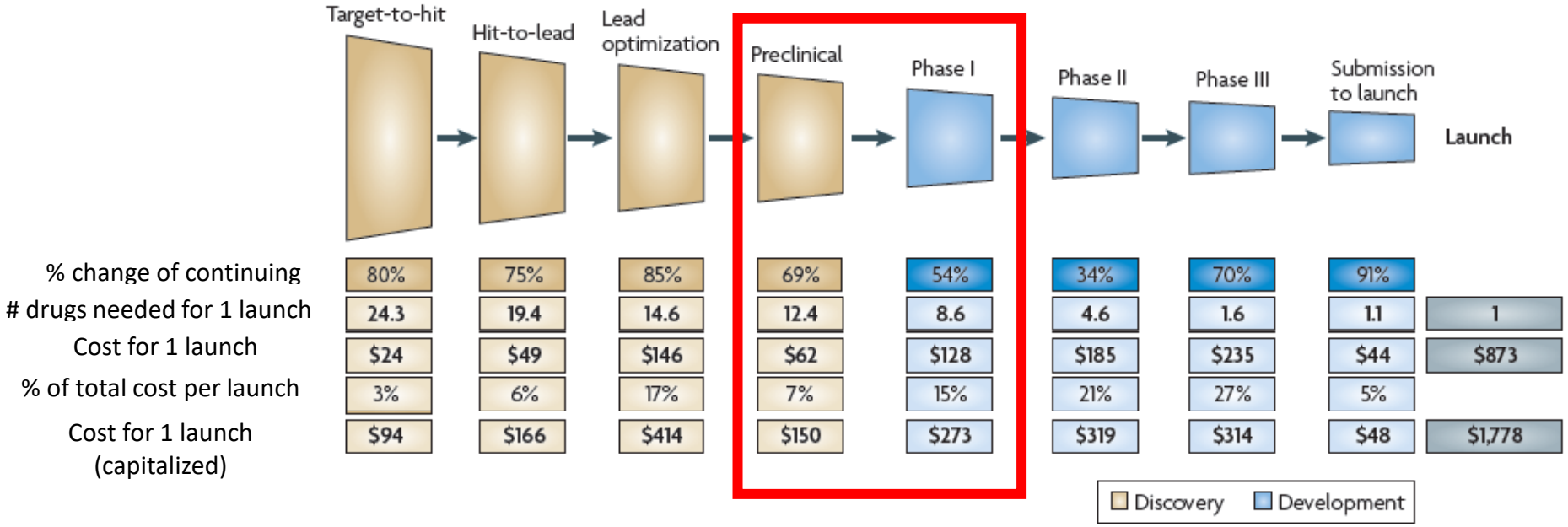
  and

- Related or possibly related to participation in the research (i.e., reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research);
  and

- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized.

IRBPB SOP RR 409:
Unanticipated Problems involving Risk to Participants or Others

Defining Safety: Overview of Drug Development

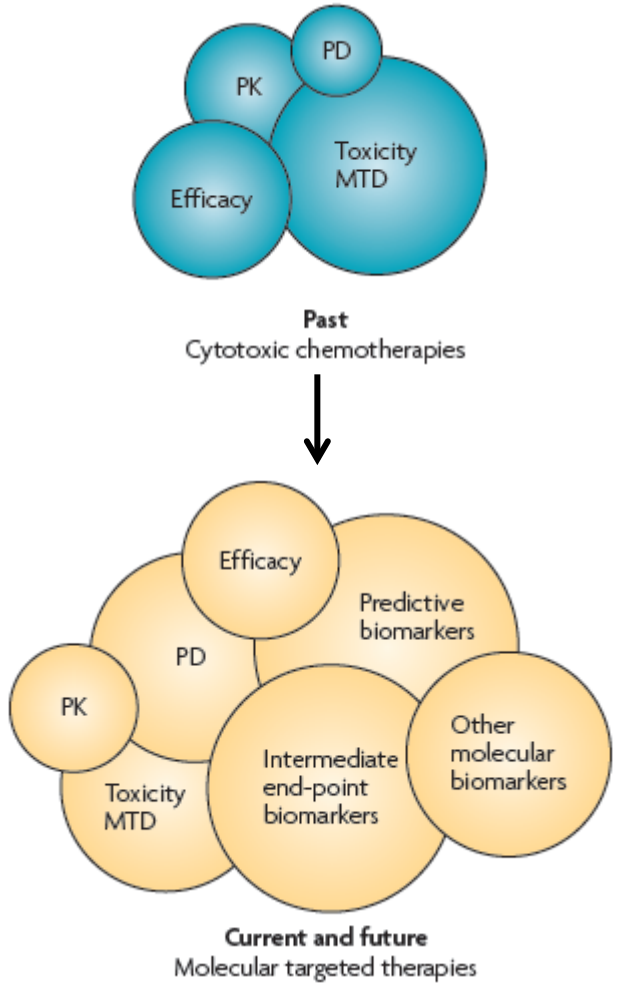


- Only 50% of drugs make it out of Phase I
- Phase I cost per successful drug launch similar to Phase II/III costs

Adapted from Paul et al. MARCH 2010 | VOLUME 9 www.nature.com/reviews/drugdisc

Phase I Objectives

- Primary: To determine the MTD (dose and schedule) of the investigation agent or novel drug combination
- Secondary:
  - PK/PD
  - Response Rate
  - Biomarker analysis
  - Other (food effects, QT effects)

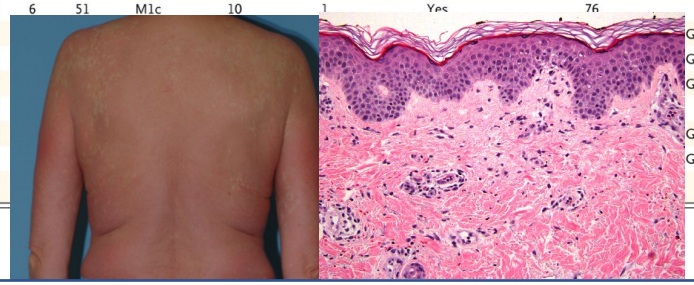


AEs in the Context of Phase 1

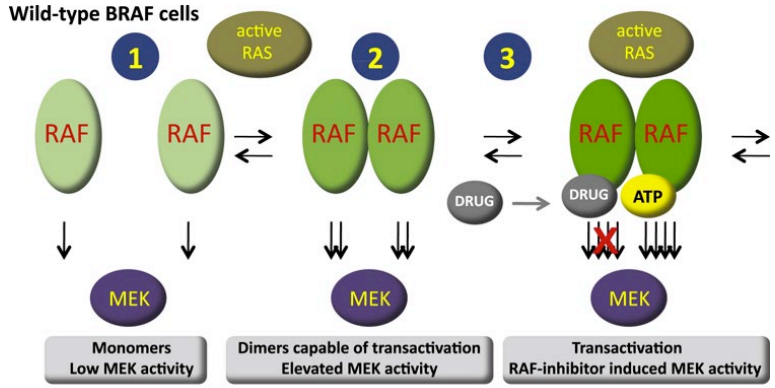
Anti-CTLA-4 + BRAFi Dermatologic AEs

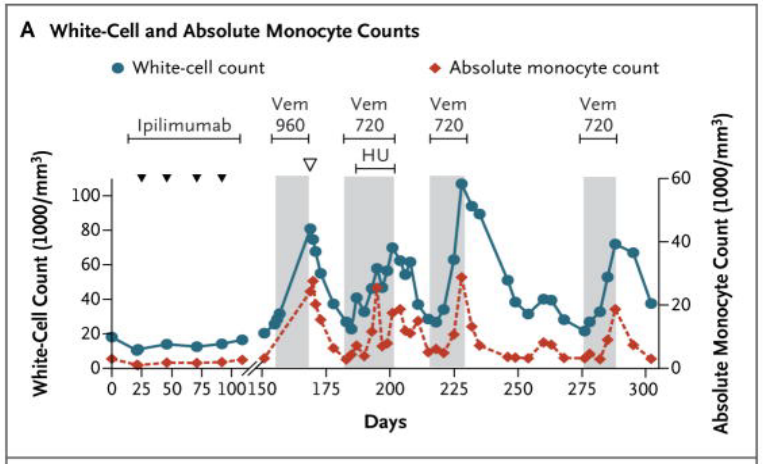
Table 1. Patients with Stage IV Melanoma Harboring a *BRAF V600E* Mutation Treated with Vemurafenib after Receiving Ipilimumab.

Patient No.	Age	Stage of Metastasis	Ipilimumab Dose	No. of Doses of Ipilimumab	Immune-Related Adverse Event with Ipilimumab	No. of Days from Last Dose of Ipilimumab to Start of Vemurafenib	Rash	No. of Days to Onset of Rash
	yr		mg/kg					
1	63	M1c	3	4	Yes	20	Grade 3	6
2	25	M1c	3	4	No	24	Grade 3	8
3	72	M1c	3	6	No	28	Grade 3	8
4	44	M1c	3	1	Yes	36	No	
5	61	M1c	3	4	No	51	Grade 1	Not reported
6	51	M1c	10	1	Yes	76	No	
							Grade 1	2
							Grade 1	15
							Grade 1	13
							No	
							Grade 3	7
							Grade 1	28
							No	

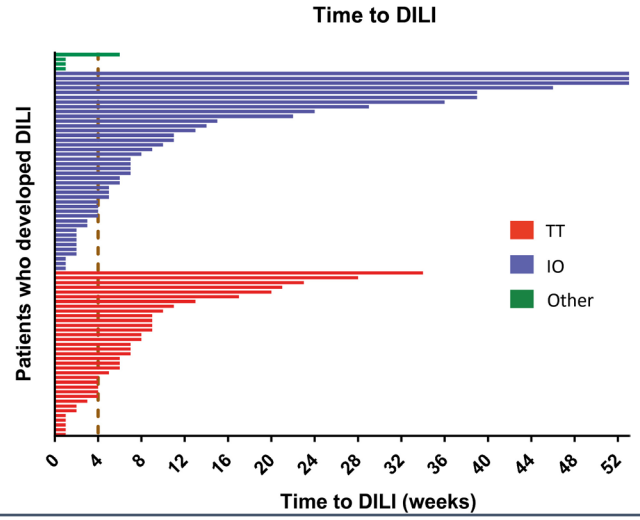


RAFi leads to proliferation of RAS mutant cells

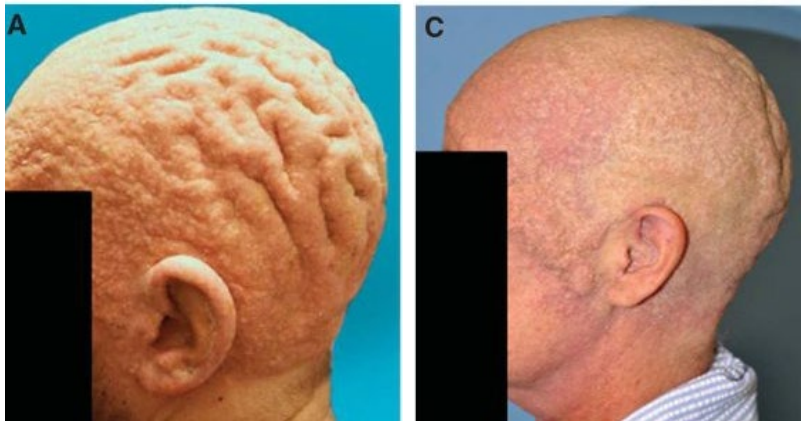




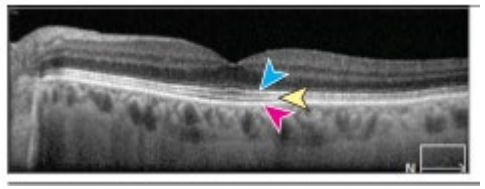
Drug Induced Liver Injury on Modern Phase 1 Studies



Radiosensitization with RAFi + RT



FGFR associated retinopathy



Harding et al. NEJM 2012; Callahan et al. NEJM 2012; Harding et al. JCO 2014 ; Abdel Wahab et al. Cancer Discovery 2014; Mondaca…Harding. Cancer 2020; Francis, Harding JAMA Ophthalmology 2021

Dose Escalation Objectives

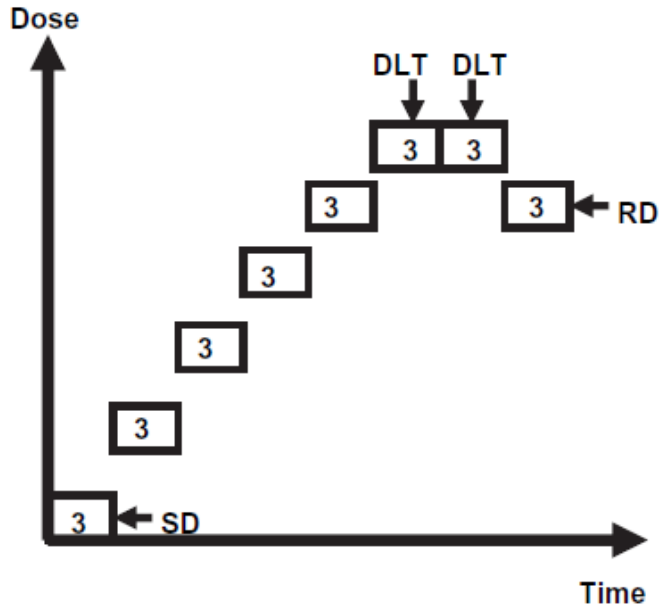
- Competing objectives - treat fewest # pts at:
  - Ineffective doses (<< MTD)
  - Toxic doses (> MTD)
- Other considerations (“efficiency”):
  - Overall number of patients
  - Overall speed of escalation
  - Accuracy of MTD estimation

Dose Escalation Methods

- Rule-Based Designs
  - Does not make assumptions about dose-toxicity curve
  - Traditional “3+3”
  - Accelerated Titration (AT)
  - Pharmacologically Guided
- Model-Based Designs
  - Modified Continual Reassessment Method (mCRM)

“3+3” Design

- 3 pts enrolled in each dose:
  - 0/3 DLTs -> escalate dose
  - 1/3 DLTs -> expand to 6 pts:
    - 1/6 DLTs -> escalate dose
    - 2/6 DLTs -> MTD reached
    - ≥3/6 DLTs -> de-escalate dose
  - ≥2/3 DLTs -> de-escalate dose



- Dose escalation follows modified Fibonacci sequence (100%, 67%, 50%, 40%, and 35%…)
- Intermediate dose levels sometimes added

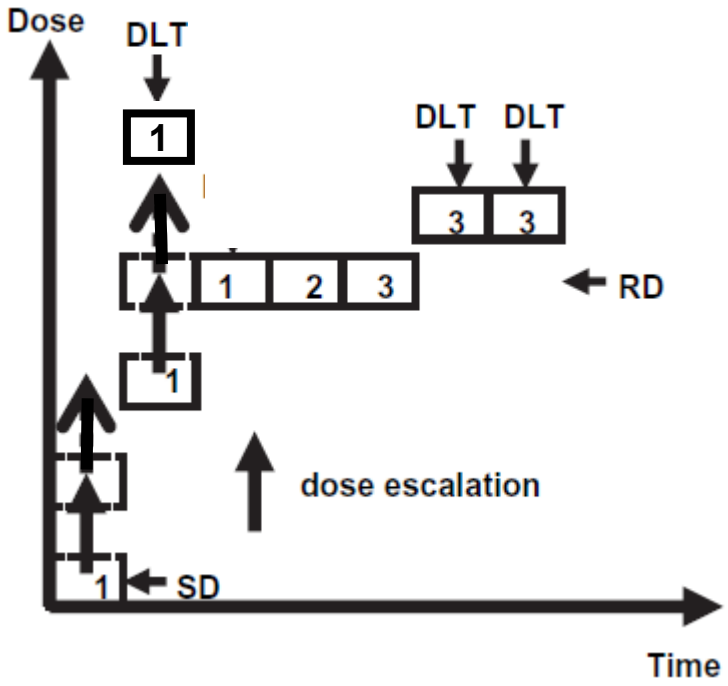
JNCI Vol. 101, Issue 10, May 20, 2009

3+3 Design

- Advantages:
  - Safe
  - Easy to implement (and understand)
  - Multiple patients at each dose level (aids PK)
- Disadvantages:
  - Large number of dose levels (≥6) & patients
  - Few patients treated at MTD
  - Small number of DLTs define MTD (error-prone)

Accelerated Titration (AT) Design

- Single patient cohorts
- Larger dose escalations
- Sometimes allows for intrapatient dose escalation
- Often reverts to “3+3” once a DLT is observed



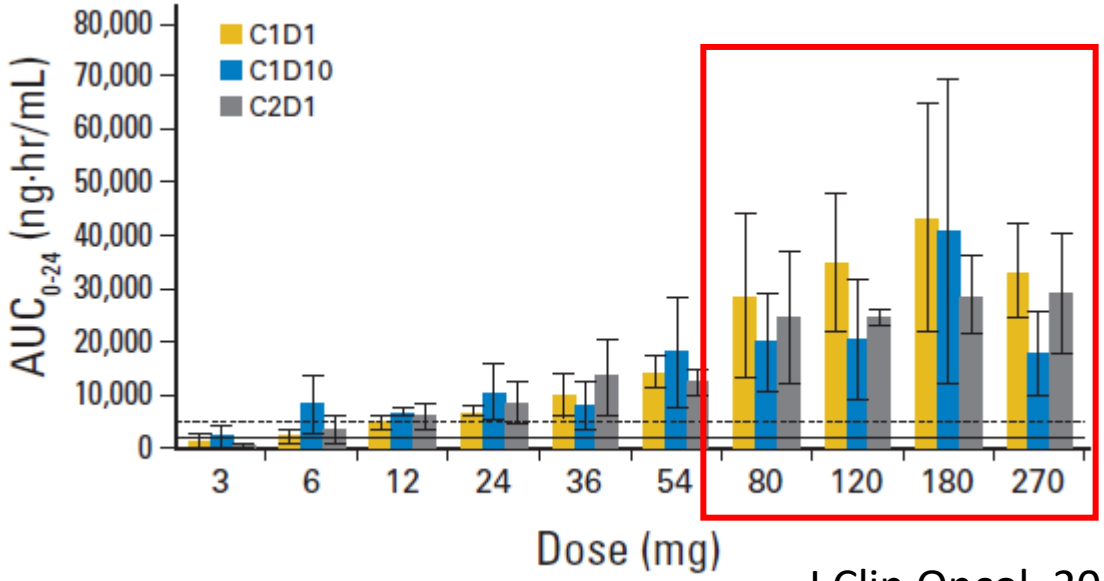
JNCI Vol. 101, Issue 10, May 20, 2009

Accelerated Titration (AT) Design

- Advantages:
  - More rapid dose escalation
  - Exposes greater % of pts to higher doses
- Disadvantages:
  - Intrapatient dose escalation may be complicated by cumulative toxicity
  - Relies on a small number of DLTs to define MTD (error prone)

Pharmacologically Guided

- Provides insight into dose and schedule
- Not widely used in clinical practice:
  - Logistic difficulties
  - Inter-patient PK variability
- Without real-time PK, you miss this:



Auto-induction of metabolism

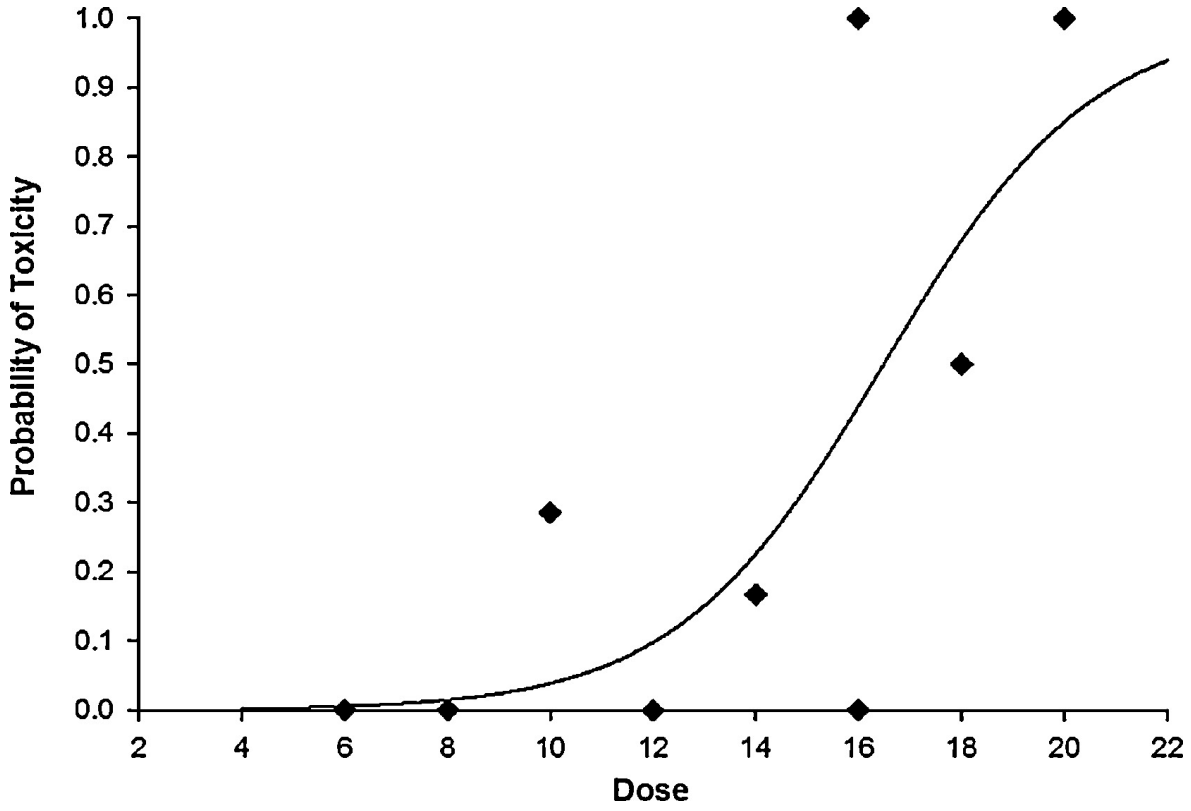
J Clin Oncol. 2012 Jul 1;30(19):2348-53

Continual Reassessment Method (CRM)

- Models dose-toxicity relationship (Bayesian model)
- Predicts probability of a DLT at each dose level
- Dose-toxicity relationship remodeled based on observed DLTs
- “Desired” DLT rate set (typically MTD = 25%)
- Modified CRM (mCRM):
  - Start at lowest dose
  - Escalate only one dose level at a time
  - Prevent escalation if last patient had DLT
  - (3 patient per dose level)

CRM Dose-Toxicity Curve

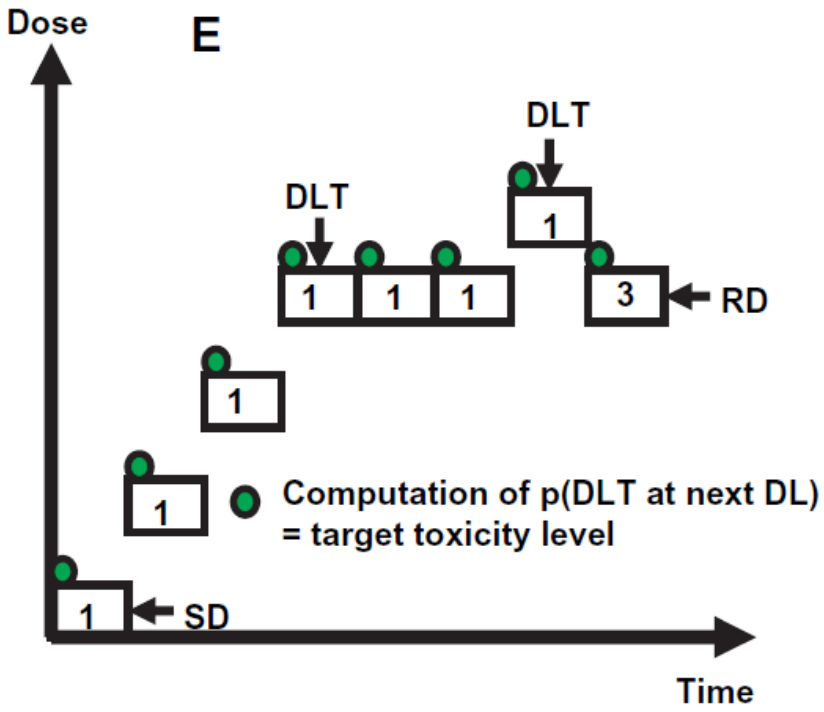
- Phase I of bryostatin-1 and GM-CSF in poor risk AML:



Leukemia Research, Vol 35, Issue 1, Jan 2011, Pages 87-94

mCRM

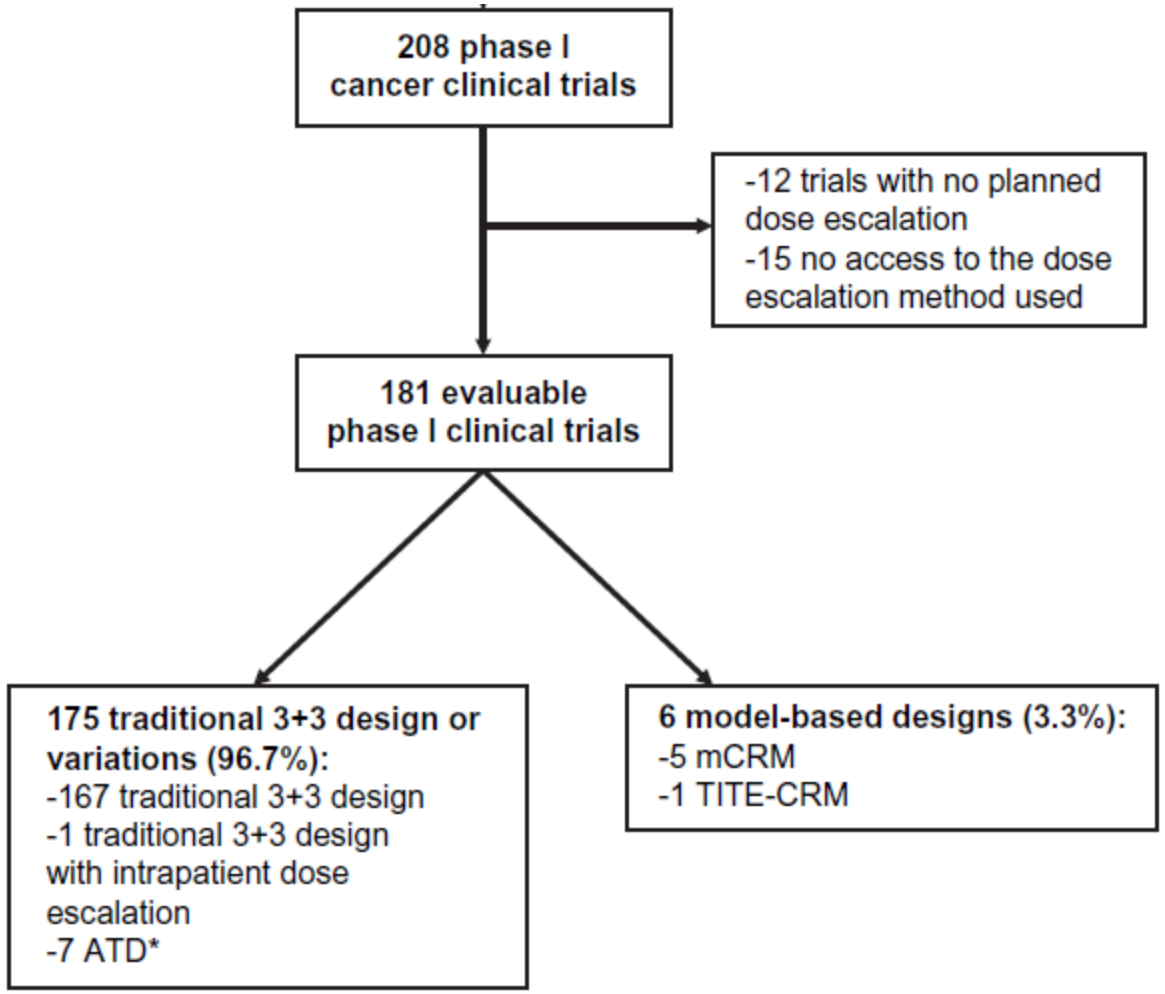
- Advantages:
  - More rapid dose escalation
  - Fewer patients required
  - Uses all DLTs to model MTD
  - More robust to errors in DLT classification
- Disadvantages:
  - Requires starting dose/tox assumptions
  - Difficult to implement (real-time stats support, software)
  - Can result in counter-intuitive recommendations



JNCI Vol. 101, Issue 10, May 20, 2009

Adoption of AT/CRM Designs

- Not widely used
- Novartis has adopted for all Phase I/IB's
- More to come?



JNCI Vol. 101, Issue 10, May 20, 2009

DLTs on Phase I Studies

Toxicity	Overall		Cytotoxic		Combination		Molecular	
	No. of Patients	Rate per 1,000 Patients (%)	No. of Patients	Rate per 1,000 Patients (%)	No. of Patients	Rate per 1,000 Patients (%)	No. of Patients	Rate per 1,000 Patients (%)
Total	728	234.5	117	203.5	313	264.4	298	221.6
Constitutional (total)	155	49.9	26	45.2	57	48.1	60	53.5
Fatigue	108	34.8	22	38.3	38	32.1	48	35.7
Other	53	17.1	5	8.7	21	17.7	27	20.1
Cardiovascular (total)	93	30.0	10	17.4	23	19.4	60	44.6
Hypertension	37	11.9	1	1.7	0	0.0	36	26.8
Other	57	18.4	9	15.7	23	19.4	25	18.6
GI (total)	187	60.2	19	33.0	91	76.9	77	57.2
Anorexia	26	8.4	2	3.5	8	6.8	16	11.9
Diarrhea	78	25.1	7	12.2	48	40.5	23	17.1
Nausea/vomiting	93	30.0	12	20.9	35	29.6	46	34.2
Other	32	10.3	2	3.5	14	11.8	16	11.9
Respiratory	20	6.4	3	5.2	7	5.9	10	7.4
Renal	10	3.2	0	0.0	1	0.8	9	6.7
Metabolic (total)	149	48.0	18	31.3	62	52.4	69	51.3
Liver abnormalities	51	16.4	5	8.7	17	14.4	29	21.6
Amylase/lipase elevation	9	2.9	0	0.0	0	0.0	9	6.7
Hyperglycemia	45	14.5	3	5.2	26	22.0	16	11.9
Other	51	16.4	10	17.4	23	19.4	18	13.4
Dermatologic	44	14.2	0	0.0	9	7.6	35	26.0
Neurologic	17	5.5	1	1.7	8	6.8	8	5.9
Hematologic (total)	233	75.1	60	104.3	127	107.3	46	34.2
Neutropenia	226	72.8	60	104.3	122	103.0	44	32.7
Anemia	2	0.6	0	0.0	1	0.8	1	0.7
Thrombocytopenia	8	2.6	2	3.5	4	3.4	2	1.5
Other (total)	66	21.3	15	26.1	27	22.8	24	17.8
Thrombosis/hemorrhage	26	8.4	3	5.2	13	11.0	10	7.4
Death	13	4.2	4	7.0	5	4.2	4	3.0
Infec				.9	11	9.3	9	6.7
Misc				.7	3	2.5	2	1.5

15-25% overall DLT rate

Hyman et al, JCO 2017

Selecting Phase I Patients

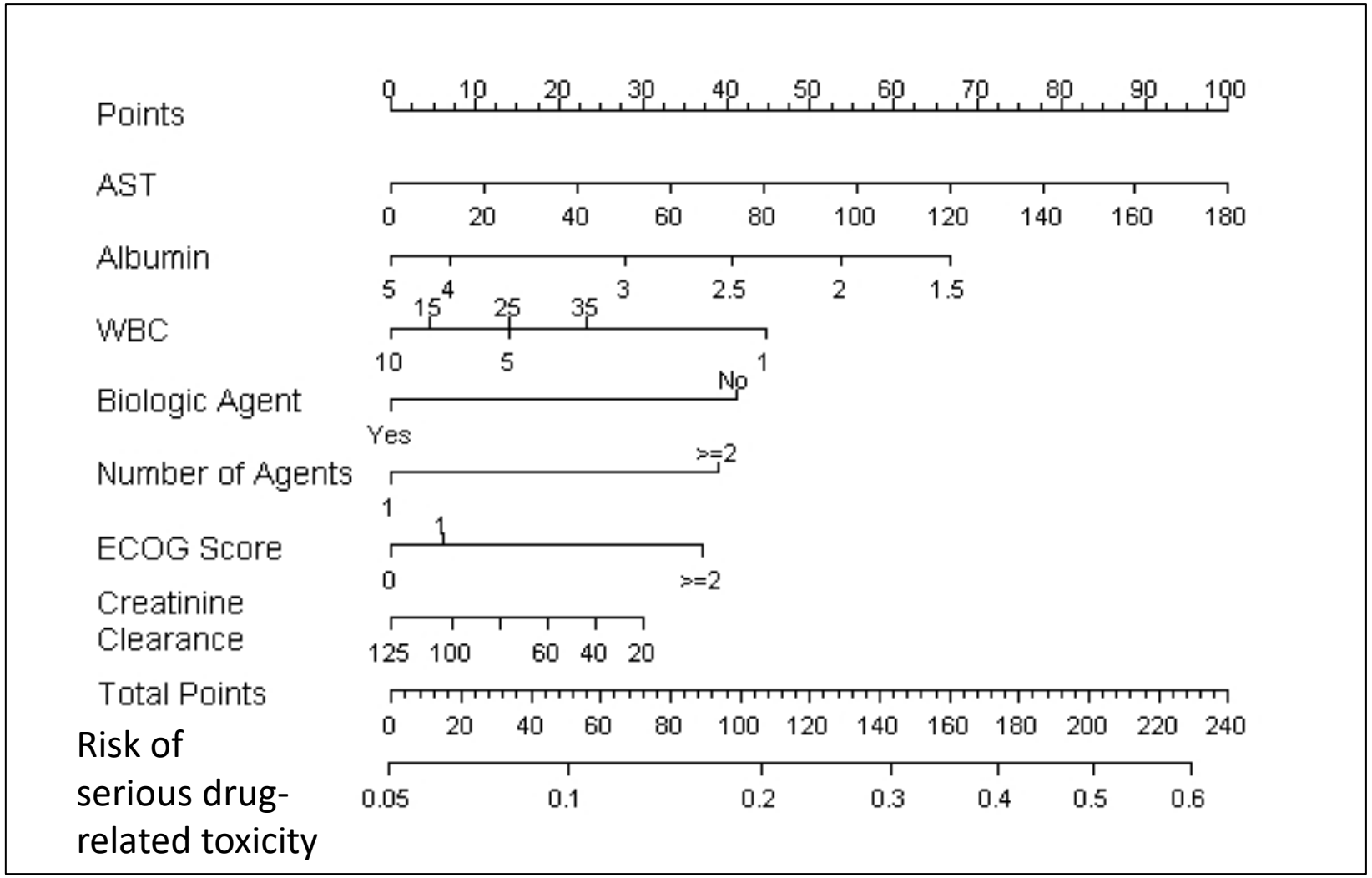
- Typical Criteria:
  - Heme: ANC > 1500, Hg 8-10, platelets > 100-150
  - Renal: Creatinine > 1.5 ULN or > 60 ml/min
  - Hepatic: AST <ULN-3xULN & T.B. <ULN-1.5xULN
  - ECOG 0-2
  - 4 week “washout”
  - Additional based on preclinical or class tox

- Outcome:*
  - Exclude 30% potential patients
  - 16.5% die within 90-days, 15% discontinue within 21-days

Can we do better?

*Olmos D, J Clin Oncol. 2012 Mar 20;30(9):996-1004.

DLT Prediction Nomogram



C-index = 0.61 (CTEP/derivation set), 0.64 (MSKCC/validation set) Hyman et al, JCO (in press)

Memorial Sloan-Kettering Cancer Center

mskcc.org
PREDICTION TOOLS

Prediction Tools ▸ Serious Drug-Related Toxicity in Phase I Clinical Trials: Prediction Tool

Serious Drug-Related Toxicity in Phase I Clinical Trials: Prediction Tool

TEXT SIZE

This tool is intended to identify patients at risk for early (cycle 1) SDRT so that patients and clinicians can assess the baseline risk of SDRT before a decision is made about participation in a phase I trial. It was developed using information from more than 3,100 patients enrolled in 127 phase 1 trials. Refer to the publication cited below for more details, including the definition of SDRT.

Enter Your Information

Clear Calculate ▸

ECOG Performance Status
Select ECOG performance status.
Select ECOG Performance St:

White Blood Cell (WBC) count
Enter white blood cell (WBC) count.
(2.1 to 38.2 billion cells/L)

Creatinine clearance
Enter creatinine clearance.
For patients with creatinine clearance greater than 125, enter 125.
(13 to 125 mL/min)

Albumin level
Enter albumin level.
(1.8 to 5 g/dL)

Aspartate aminotransferase (AST) level
Enter aspartate aminotransferase (AST) level.
(7 to 176 units/L)

Number of drugs being tested in the trial
Select number of drugs being tested.
Select number of drugs

Are any of the drugs being tested biological drugs?
YES NO

Clear Calculate ▸

Your Results

Learn more about your results below.

Probability of Cycle 1 Serious Drug-Related Toxicity in Phase I Clinical Trials

Print These Results

Make an Appointment

Call us to schedule an appointment or contact us online

Contact Us ▸

Hyman et al, JCO (in press)

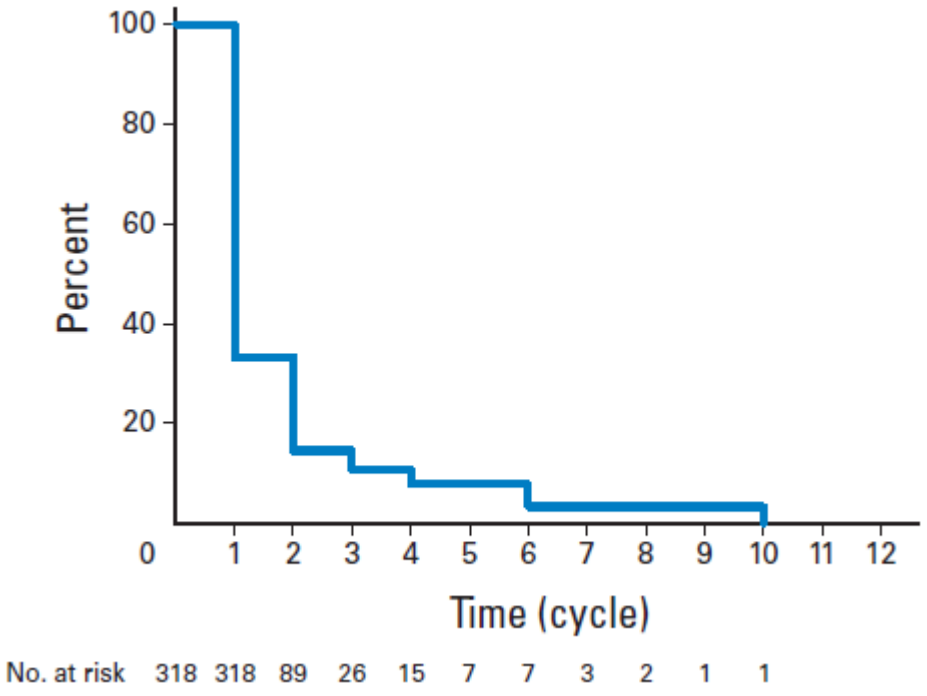
Are we finding the right dose?

- MTD in first-in-human Phase I 175mg daily
- FDA approved for metastatic medullary thyroid cancer (MTC) at 140mg daily
- Phase III RCT trial in MTC (cabo vs placebo):
  - 330 patients
  - Dose reduction: **79%** vs 9%
  - Median dose delays: **1** vs 0
  - Tox leading to rx discontinuation: 16% vs 8%

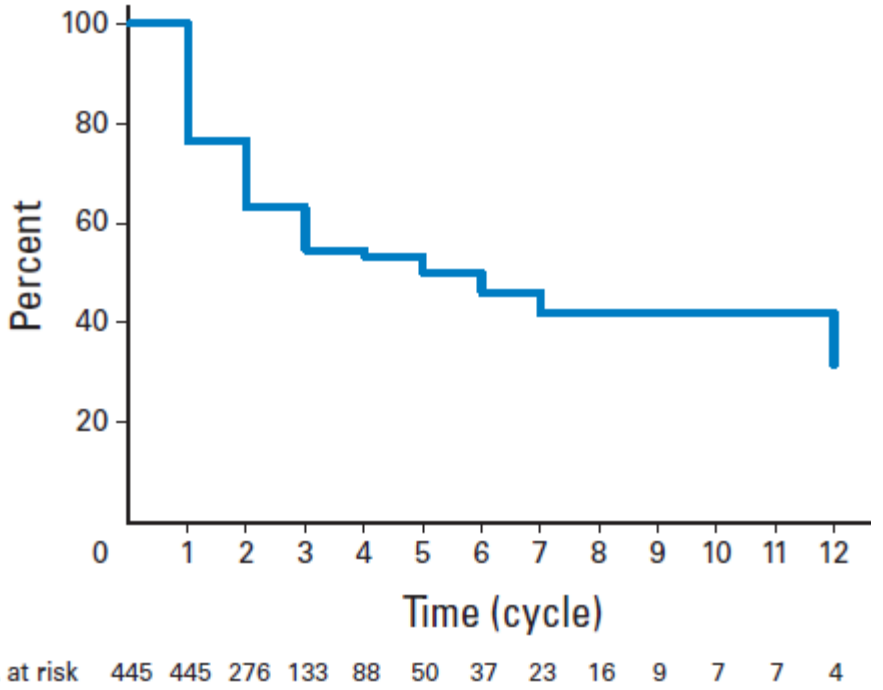
Chronic Toxicity

- MTD does not use Cycle 2+ toxicity
- Targeted agents administered chronically

Time to Worst Grade Toxicity



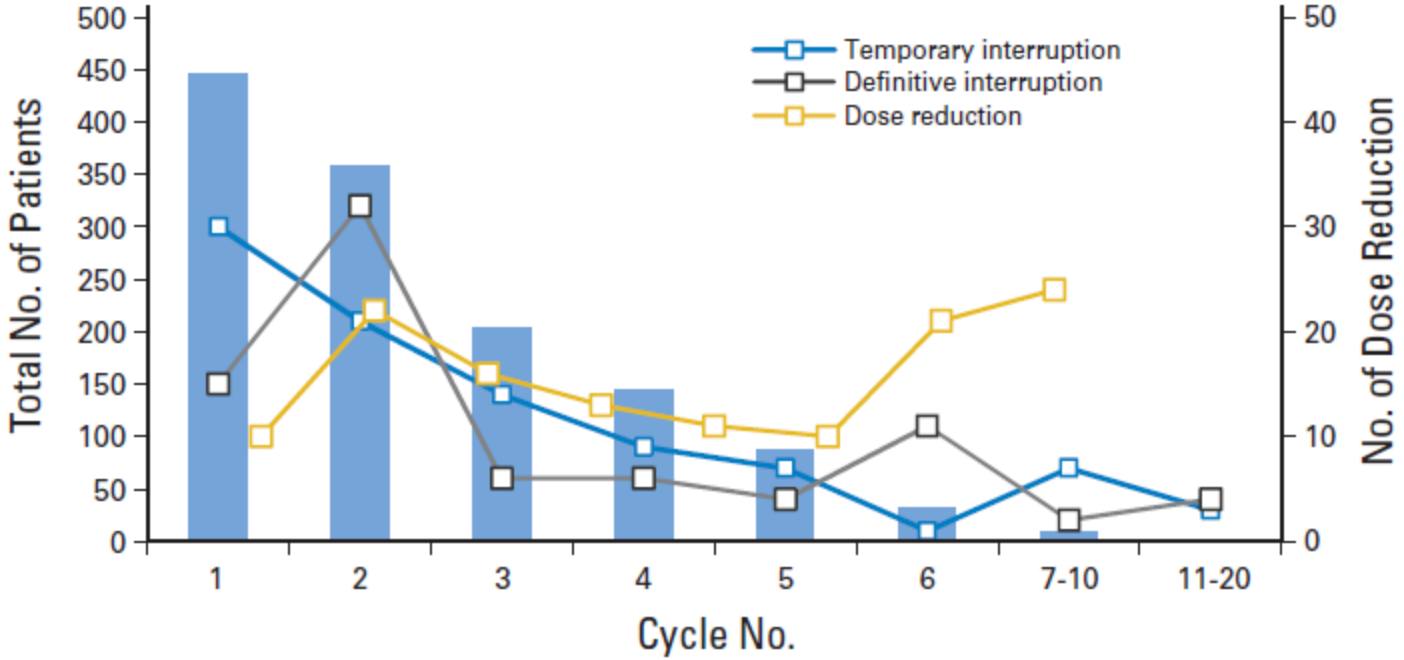
Time to 1st Grade 3/4 Toxicity



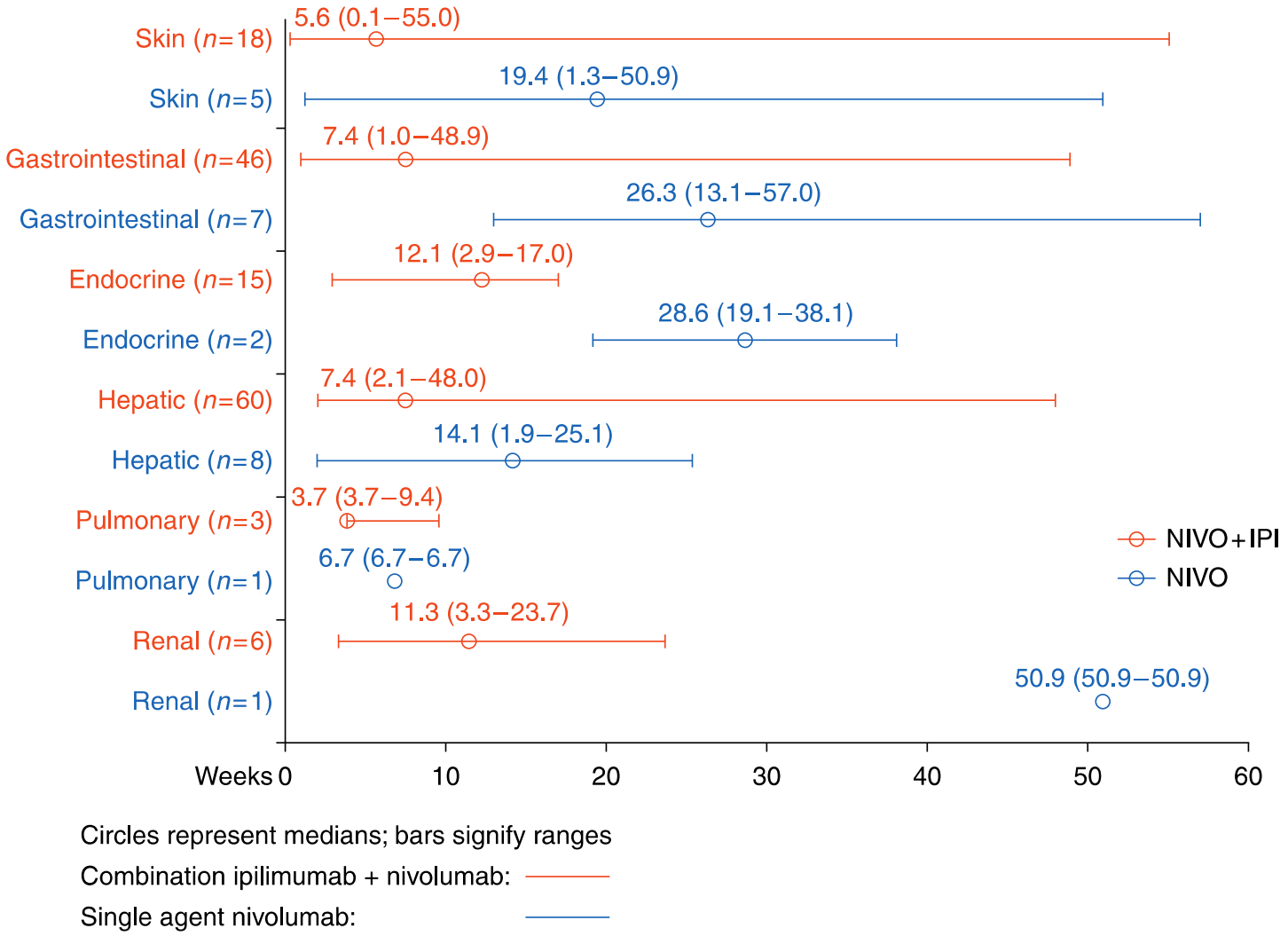
Postel-Vinay, JCO Vol 29, Num 13, may 1 2011

Chronic Toxicity

- Treatment interruption / dose-reductions continue after cycle 1:

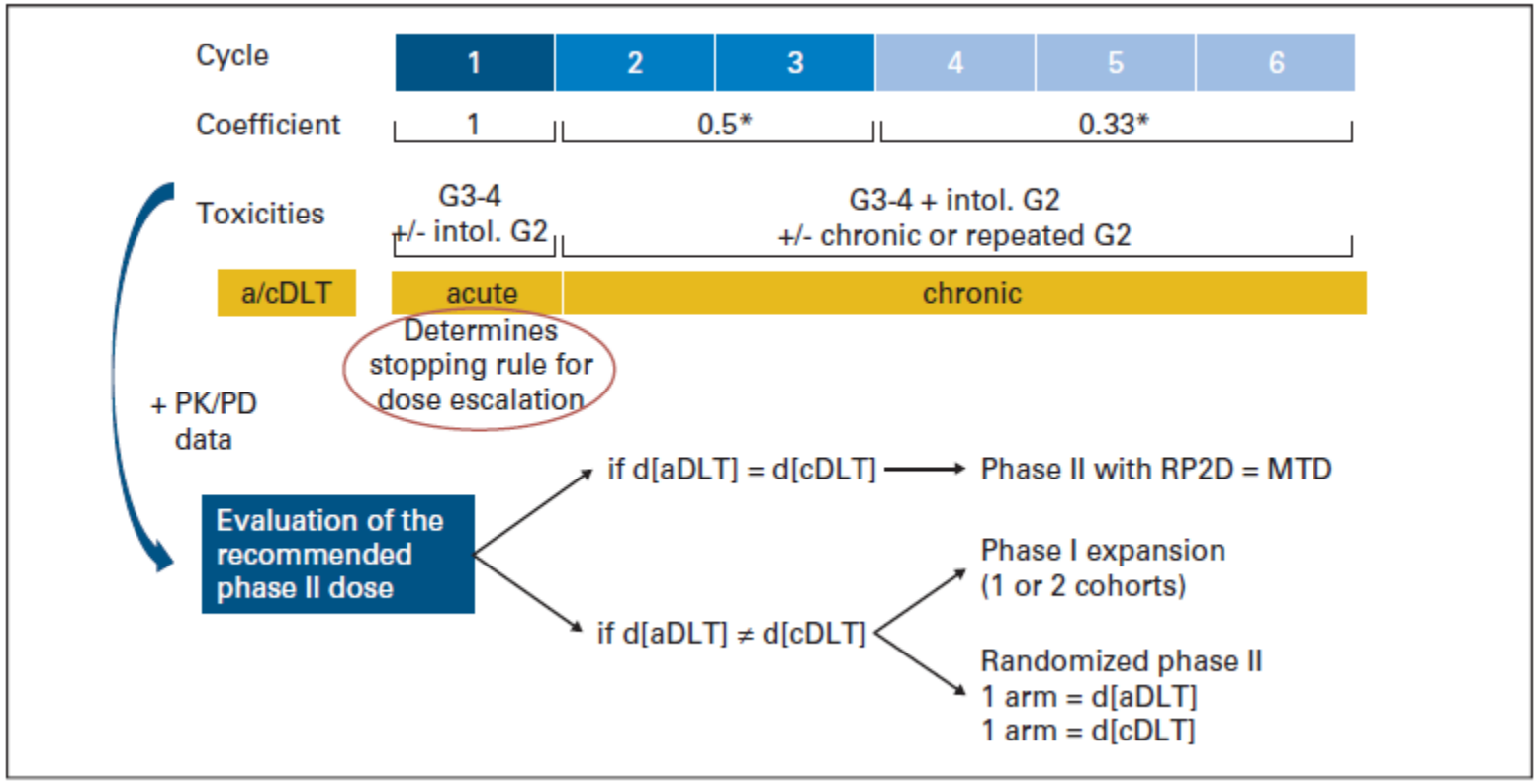


Postel-Vinay, JCO Vol 29, Num 13, may 1 2011



• **Haanen et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017**

Is there a better way?



Concept: Define both Acute MTD and Chronic MTD for each chronically dosed agent

Postel-Vinay, JCO Vol 29, Num 13, may 1 2011

Conclusions

- ‘Safety’ has multiple components in drug development
- The patient is primary focus! BUT as PI you will interface with multiple entities whereby safety becomes **a regulatory and protocol definition**
- Always Consult the protocol and Sponsor
- Phase 1 help to define saftey.