Clinical Pharmacology Program (CPP)

Office of the Clinical Director

W. Douglas Figg

Senior Investigator and Program Chief

Center for Cancer Research, NCI, NIH

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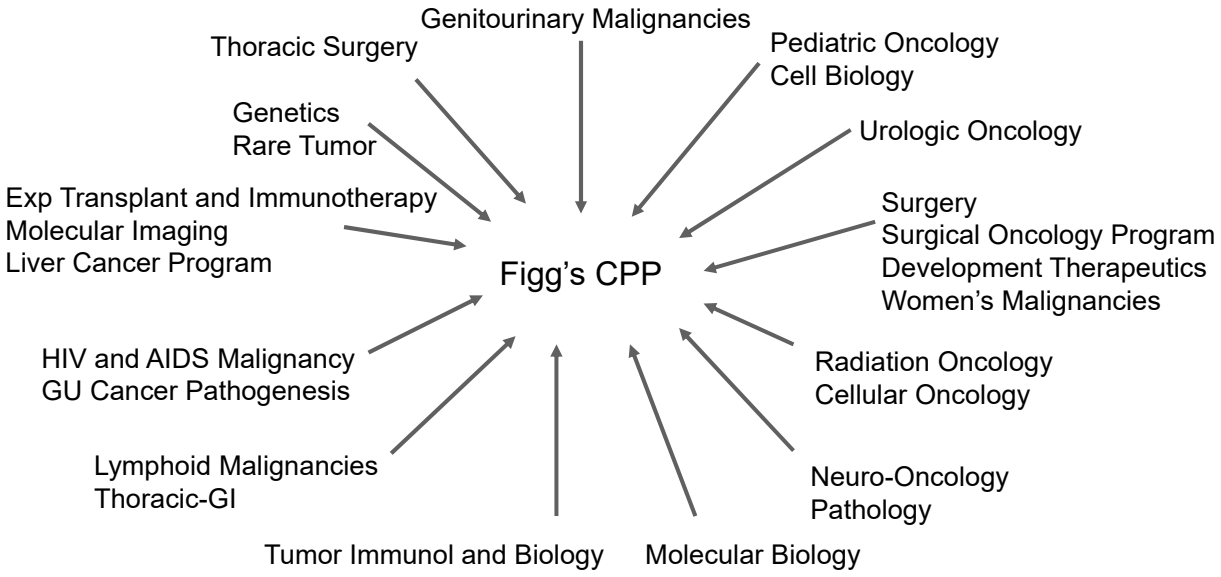
1

Office of the Clinical Director



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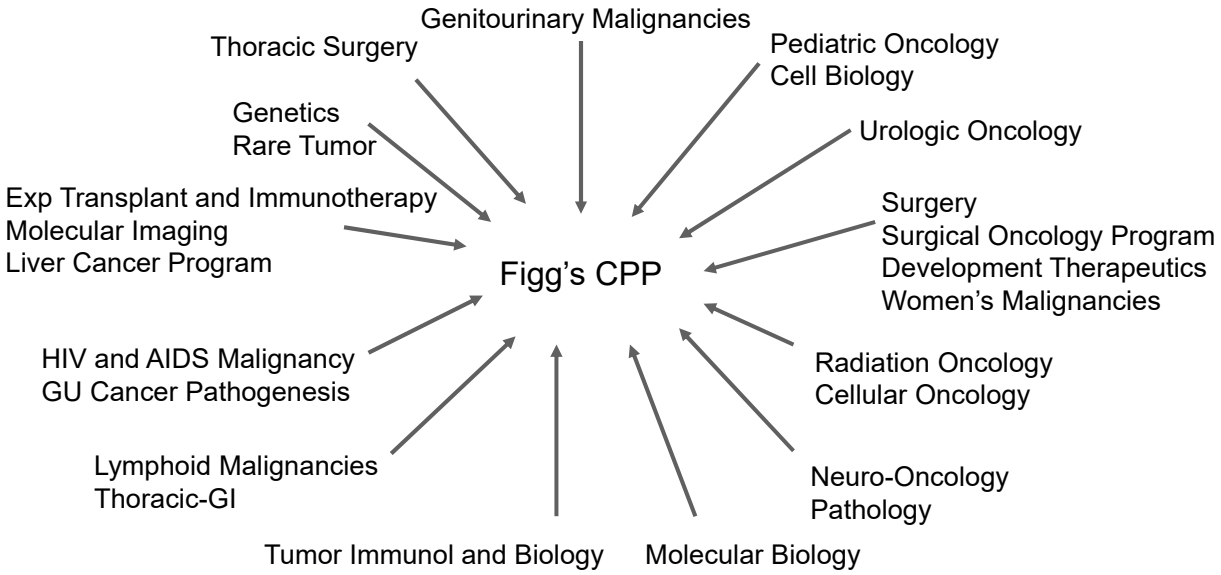
2

CCR Collaborators



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3

Clinical Pharmacology Program: Prioritizing

- Oversight Committee (Clinical)
  - NCI Clinical Director (Dr. Dahut)
  - Medical Oncology Service Chief (Dr. Gulley)
  - Pediatric Oncology Service Chief (Dr. Widemann)
  - Surgical Oncology Service Chief (Dr. Zeiger)
  - Radiation Oncology Service Chief (Dr. Camphausen)

  - The Drug Development Collaborative committee (chaired by Dr. Steeg) prioritizes preclinical PK projects

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4

Clinical Pharmacology Program: Prioritizing

- We prioritize PK/PG projects in the following order:
  1) Clinical
     a. Data Impacts Clinical Decisions
     b. Retrospective Analysis
  2) Preclinical/in vitro

- Even with the high demand for CPP collaborations, we support all CCR project requiring pharmacology assistance that are scientifically sound

- Only engage in extramural collaboration if we have the assay validated and/or if the project is of extremely high impact

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5

Clinical Pharmacology Program: Prioritizing

- The CPP is not a core (no fee-for-service)
  - it assesses the merit of the hypothesis, the prior literature, the potential scientific impact, centrally funded at the CCR level

- The CPP goes beyond bioanalytical method development and characterization of the PK
  - also assesses protein binding, determines pharmacogenetic impact on elimination, characterizes the renal elimination, builds PK and exposure-response models (pharmacometrics), assesses target occupancy, identifies pharmacodynamic changes, and evaluates other pharmacology endpoints.

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6

Clinical Pharmacology Program: Organizational Structure

- Pharmacokinetics and Pharmacometric Section - Dr. Cody Peer
  - Bioanalytical Unit - Dr. Tyler Yin
  - Preclinical Pharmacology Unit – vice-Strope
- Pharmacogenetics Section - Dr. Tristan Sissung
- Clinical Section - Dr. Keith Schmidt
- Biospecimen Processing Core – CDR Paula Carter, RN

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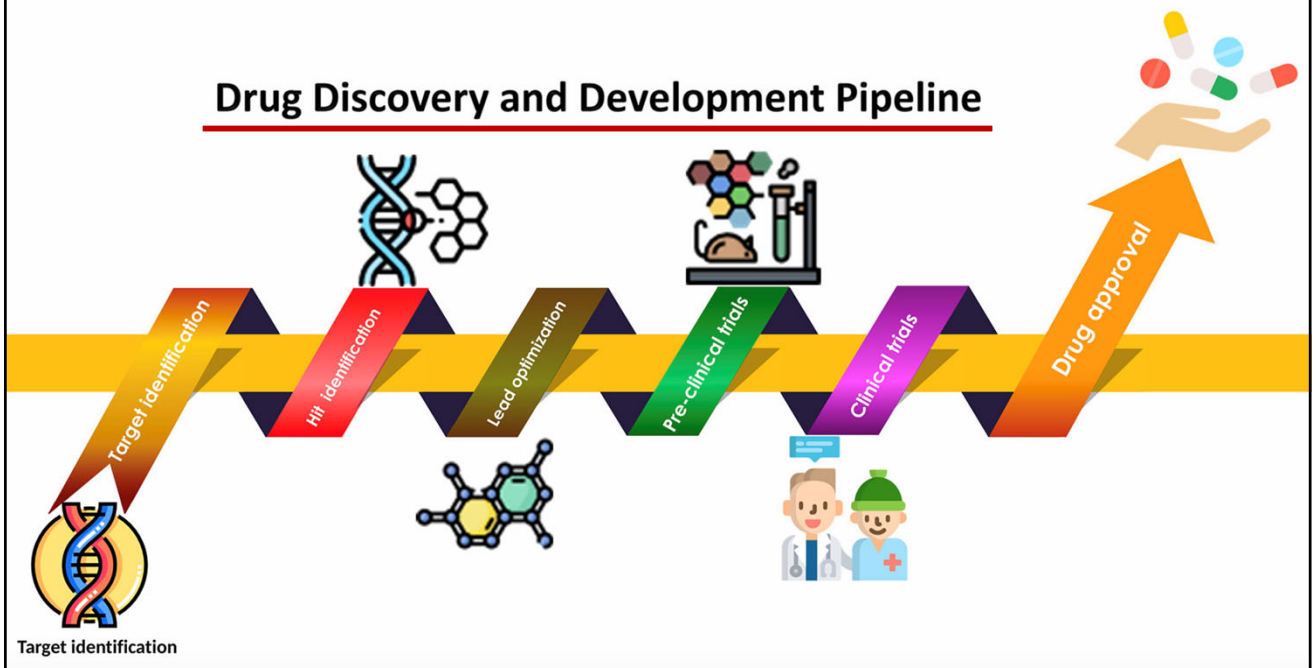
7

Drug Discovery and Development Pipeline



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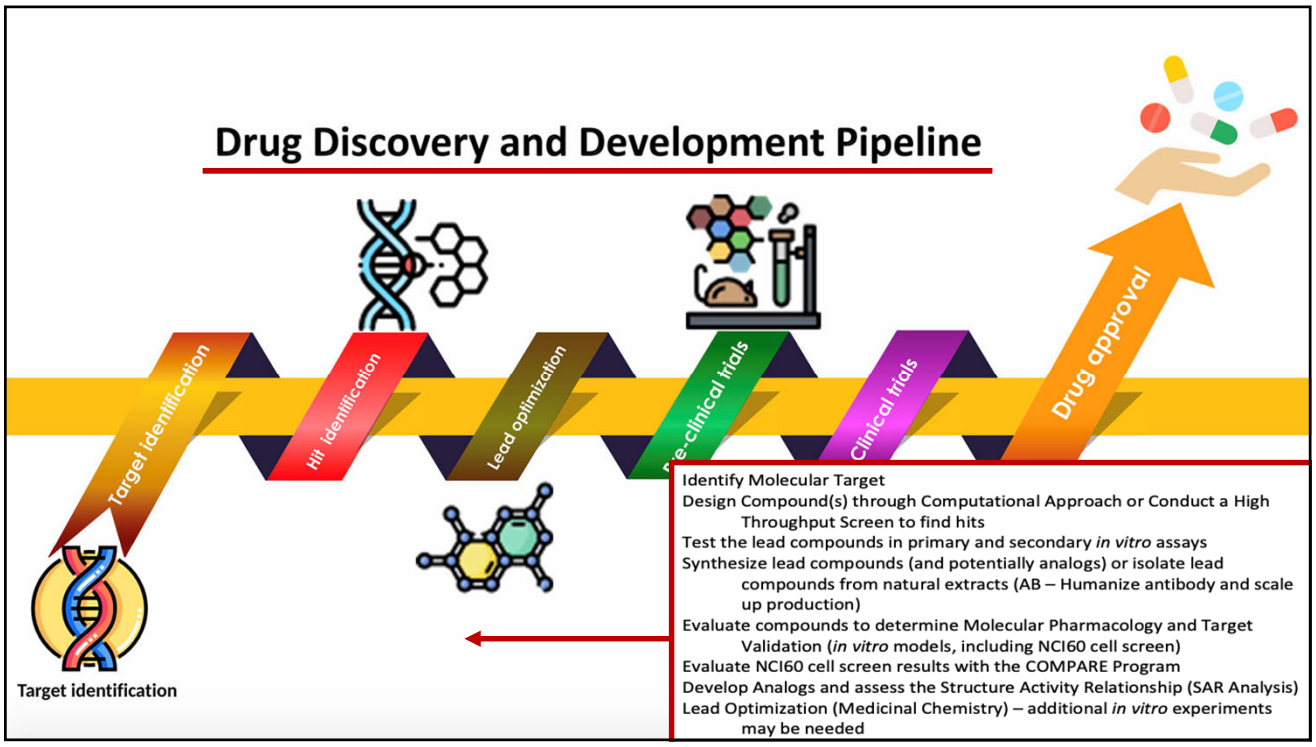
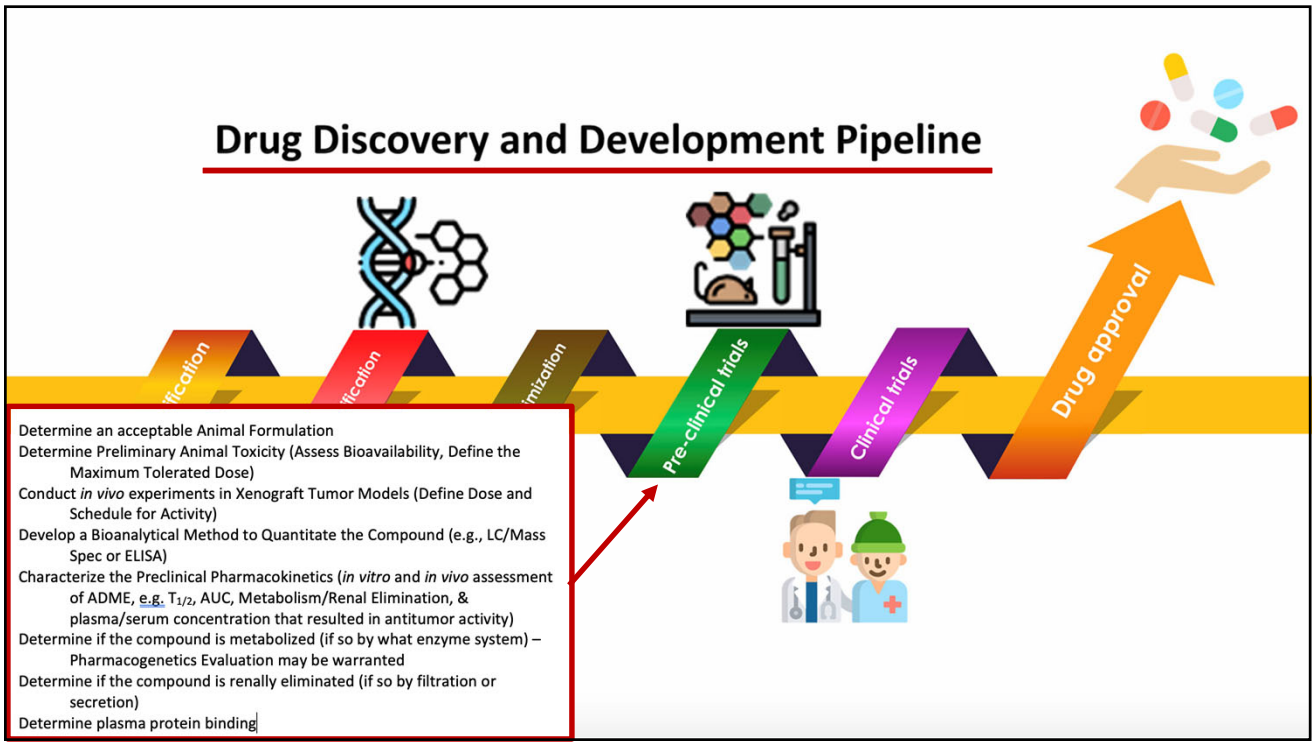
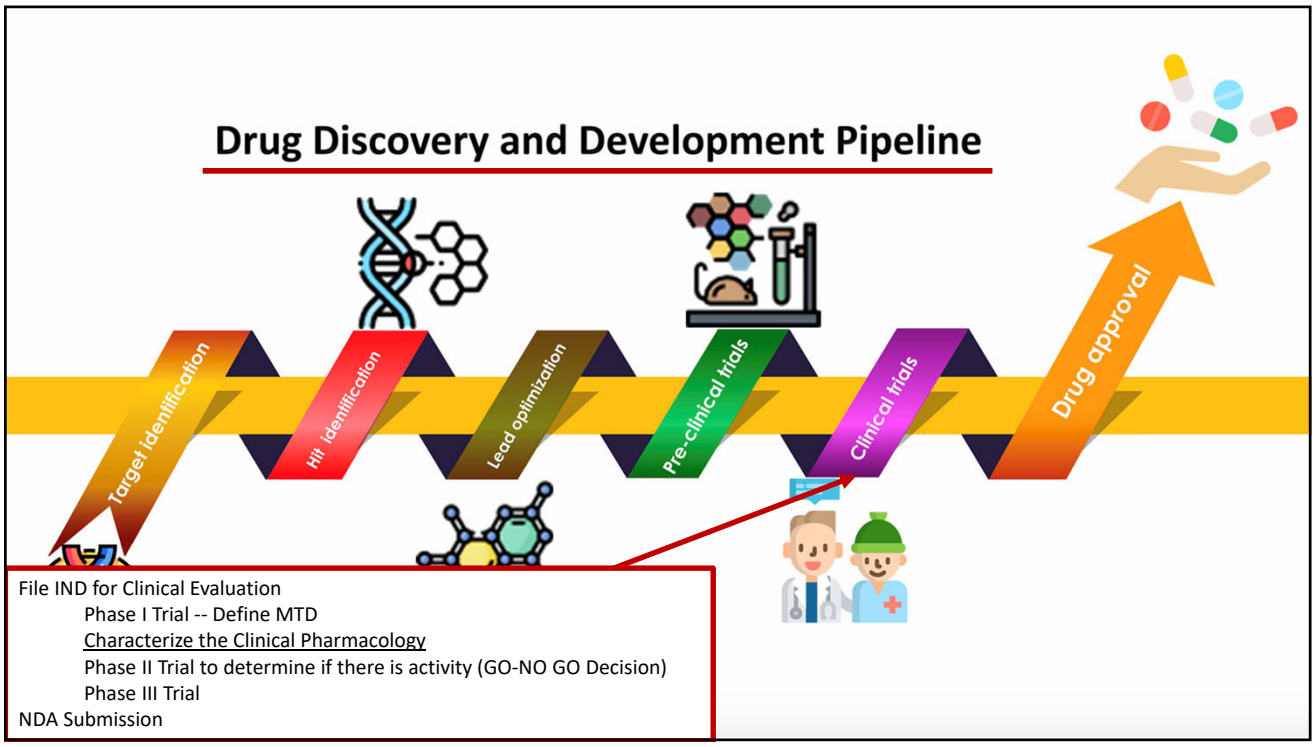

Drug Discovery and Development Pipeline
Target identification
Hit identification
Lead optimization
Pre-clinical trials
Clinical trials
Drug approval
Target identification
Identify Molecular Target
Design Compound(s) through Computational Approach or Conduct a High Throughput Screen to find hits
Test the lead compounds in primary and secondary *in vitro* assays
Synthesize lead compounds (and potentially analogs) or isolate lead compounds from natural extracts (AB – Humanize antibody and scale up production)
Evaluate compounds to determine Molecular Pharmacology and Target Validation (*in vitro* models, including NCI60 cell screen)
Evaluate NCI60 cell screen results with the COMPARE Program
Develop Analogs and assess the Structure Activity Relationship (SAR Analysis)
Lead Optimization (Medicinal Chemistry) – additional *in vitro* experiments may be needed

9


Drug Discovery and Development Pipeline
Pre-clinical trials
Clinical trials
Drug approval
Determine an acceptable Animal Formulation
Determine Preliminary Animal Toxicity (Assess Bioavailability, Define the Maximum Tolerated Dose)
Conduct *in vivo* experiments in Xenograft Tumor Models (Define Dose and Schedule for Activity)
Develop a Bioanalytical Method to Quantitate the Compound (e.g., LC/Mass Spec or ELISA)
Characterize the Preclinical Pharmacokinetics (*in vitro* and *in vivo* assessment of ADME, e.g. $T_{1/2}$, AUC, Metabolism/Renal Elimination, & plasma/serum concentration that resulted in antitumor activity)
Determine if the compound is metabolized (if so by what enzyme system) – Pharmacogenetics Evaluation may be warranted
Determine if the compound is renally eliminated (if so by filtration or secretion)
Determine plasma protein binding

10



11

Data from CPP for FDA/EMA Approvals

PK Data

Delcath's filter for HCC
Thalidomide for MM
Lenalidomide for MM
Pomalidomide for KS
Selumetinib for NF1
Romidepsin for peripheral T-cell lymphoma
Phenylbutyrate for UCD
*Abiraterone for PC

PG Data

Belinostat for peripheral T-cell lymphoma
Sorafenib for RCC

* NCCN Dosing Guidelines

12

Clinical Pharmacology Program: Projects

- Biospecimen Processing Core
- Use Clinical Pharmacology Principles to Develop New Anticancer Therapies
- Utilize Pharmacogenetics Knowledge to Optimize Drug Development
-

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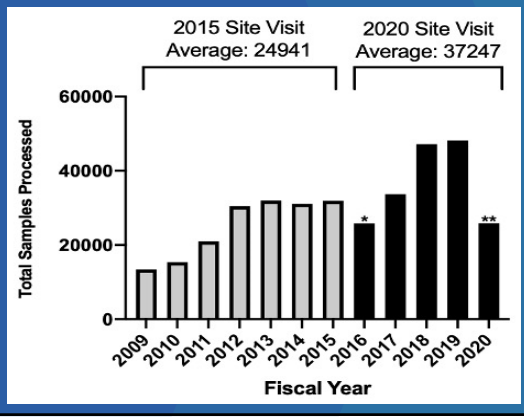
13

Biospecimen Processing Core (BPC)

Since 1992, the BPC has supported over 375 clinical trials (a large part of the clinical treatment protocols within the CCR)

In 2018 and 2019 the core processes >50,000/yr



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14

Clinical Pharmacology Program: Projects

- Biospecimen Processing Core
- **Use Clinical Pharmacology Principles to Develop New Anticancer Therapies**
- Utilize Pharmacogenetics Knowledge to Optimize Drug Development
-

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15

Development of Selumetinib for Plexiform Neurofibromas in NF1

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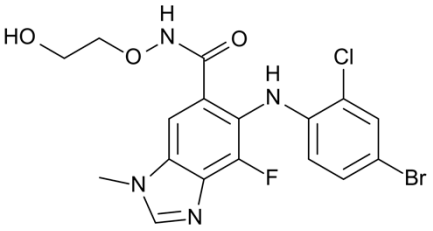
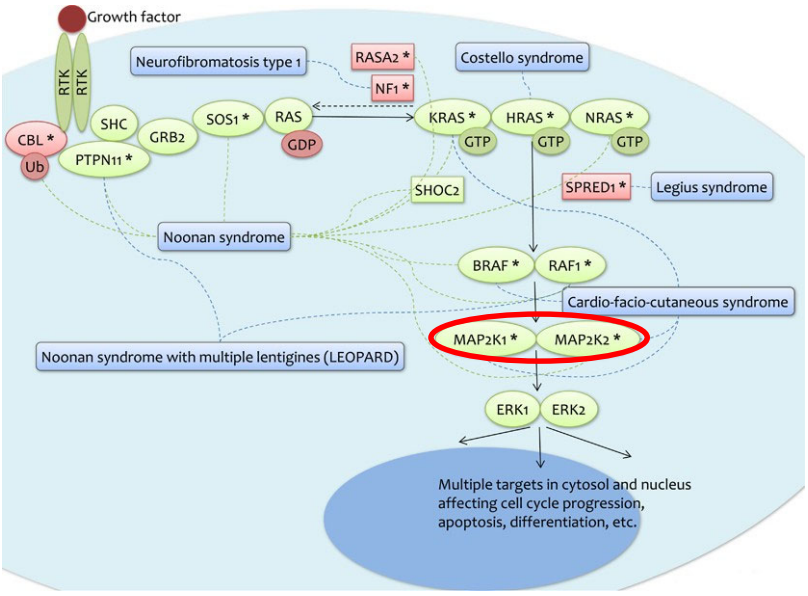
16

Selumetinib



MAP2K1/2 Inhibitor



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Kiuru et al. *Laboratory Investigation* 2017

17

17

Neurofibromatosis Type 1 (NF1)

- Single gene disorder (1:3500)
  - Neurofibromin,17q11.2, RAS pathway activation
- Tumor development:
  - Plexiform neurofibromas (PN)
  - Atypical neurofibromas (AN)
  - Malignant peripheral nerve sheath tumors (MPNST)
  - Optic pathway and low-grade gliomas
  - Leukemias (JMML)
- Organ manifestations:
  - Skin, CNS, peripheral nerves, cardiovascular, gastrointestinal, endocrine, skeletal, growth, hematological

18

Plexiform Neurofibromas in NF1

- Occur in 20-50% of patients with NF1 (Schwann cells)
- Congenital, slow growth, large size, complex shape
- Unknown natural history
- Disfigurement, pain, functional impairment, life-threatening
- Transformation to malignant peripheral nerve sheath tumor (10-15%)
- No effective medical therapy

19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Selumetinib in Children with Inoperable Plexiform Neurofibromas

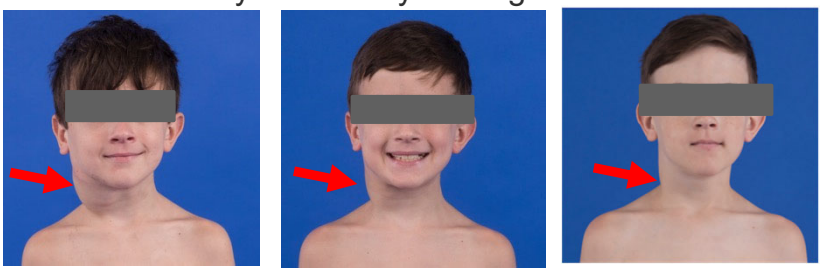
A.M. Gross, P.L. Wolters, E. Dombi, A. Baldwin, P. Whitcomb, M.J. Fisher, B. Weiss, A.R. Kim, M. Bornhorst, A.C. Shah, S. Martin, M.C. Roderick, D.C. Pichard, A. Carbonell, S.M. Paul, J. Therrien, O. Kapustina, K. Heisey, D.W. Clapp, C. Zhang, C.J. Peer, W.D. Figg, M. Smith, J. Glod, J.O. Blakeley, S.M. Steinberg, D.J. Venzon, L.A. Doyle, and B.C. Widemann

3/9/2021

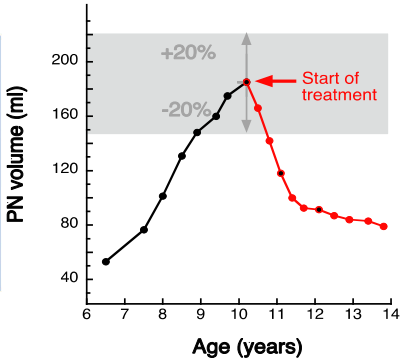
20

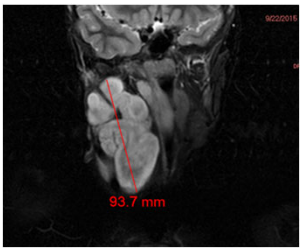
10 y/o with Improvement on Selumetinib

10 year-old boy with right neck PN



Baseline | Pre-Cycle 13 | Pre-Cycle 37





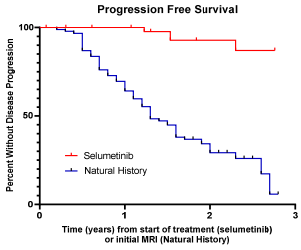
Prevention of morbidity: Airway compromise

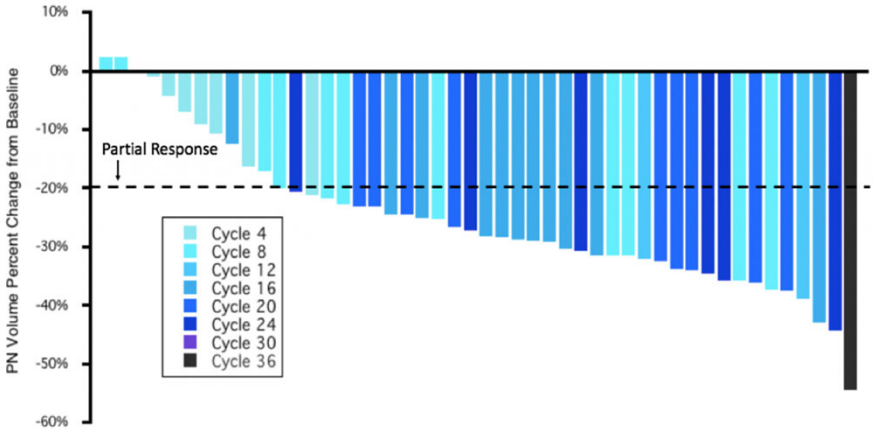
Gross A, et. al. (Figg)…Widemann B: NEJM 2020

21

SPRINT Phase II: Response on Selumetinib

- Enrollment: 50 patients 8/2015-8/2016
- Median Age: 10.3 years (3.5-17.4)





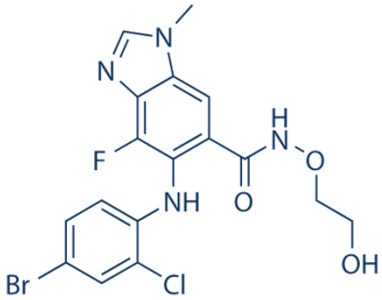
Partial Response (PR):
- 37/50 (74%)

Progressive Disease (PD)
- 4 (8%)

Gross A, et. al. (Figg)…Widemann B: NEJM 2020

22

Selumetinib uHPLC-MS/MS Assay



- Add 3x volume ACN to plasma to deproteinize
- Vortex, centrifuge, dilute supernatant 20-fold
- Inject 2 uL of diluted supernatant onto a C18 column
  - Selumetinib elutes column at 0.94 min
  - Enters a triple quadrupole mass spectrometer operated with positive electrospray ionization
- Assay calibration range is 10 – 5,000 ng/mL

Note – we developed the original assay for non-human primate PK, but for the SPRINT trial all samples were analyzed by AZ

23

Pharmacokinetics of Selumetinib

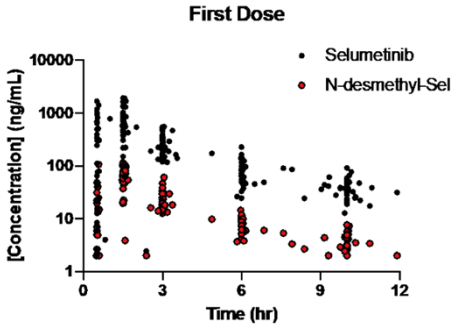
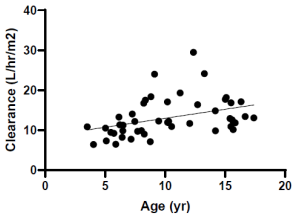


Figure T4. Significant Relationship Between BSA-Adjusted Clearance and Age.



Dose: 25 mg/m^2 q12h

	Selumetinib	
	First Dose*	Steady State
C_{MAX}[1] (ng/mL/mg)	25.96 ± 24.87 (n=50)	28.64 ± 22.59 (n=47)
T_{MAX} (hr)	1.48 ± 0.90 (n=50)	1.45 ± 0.82 (n=47)
AUC (hr*ng/mL/mg)	75.29 ± 47.97 (n=48)	84.82 ± 51.08 (n=43)
$T_{1/2}$ (hr)	2.55 ± 0.64 (n=48)	---
Vz/F (L)	48.86 ± 33.52 (n=48)	---
CL/F[2] (L/hr/m^2)	12.39 ± 4.80 (n=48)	10.79 ± 4.09 (n=43)

Gross A, et. al. (Figg)…Widemann B: NEJM 2020

24

FDA Approval of Selumetinib (Koselugo™) – April 2020

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / Resources for Information | Approved Drugs / FDA approves selumetinib for neurofibromatosis type 1 with symptomatic, inoperable plexiform neurofibromas

FDA approves selumetinib for neurofibromatosis type 1 with symptomatic, inoperable plexiform neurofibromas

---------- **INDICATIONS AND USAGE** ----------

KOSELUGO is a kinase inhibitor indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). (1)

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25

25

Clinical Pharmacology Program: Projects

- Biospecimen Processing Core
- Use Clinical Pharmacology Principles to Develop New Anticancer Therapies
- **Utilize Pharmacogenetics Knowledge to Optimize Drug Development**
-

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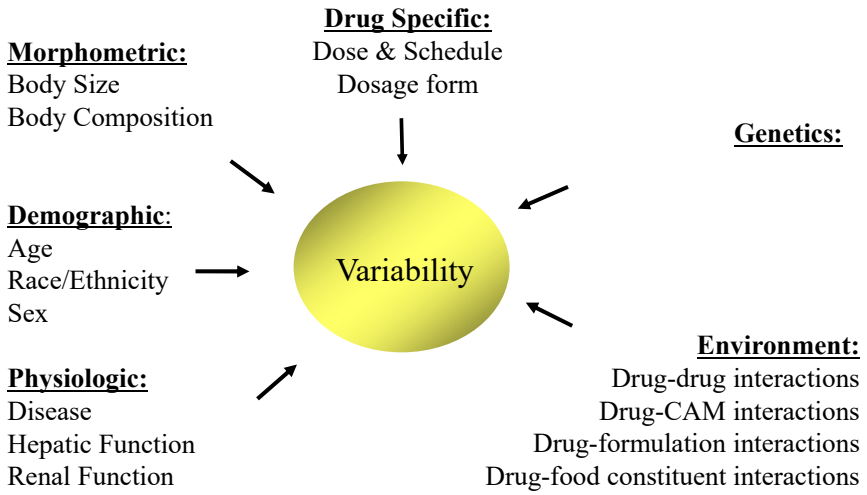
26

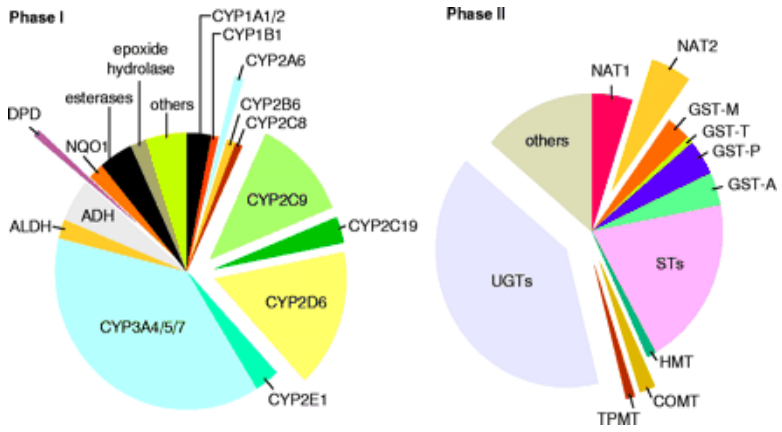
26

Sources of Pharmacokinetic Variability



27

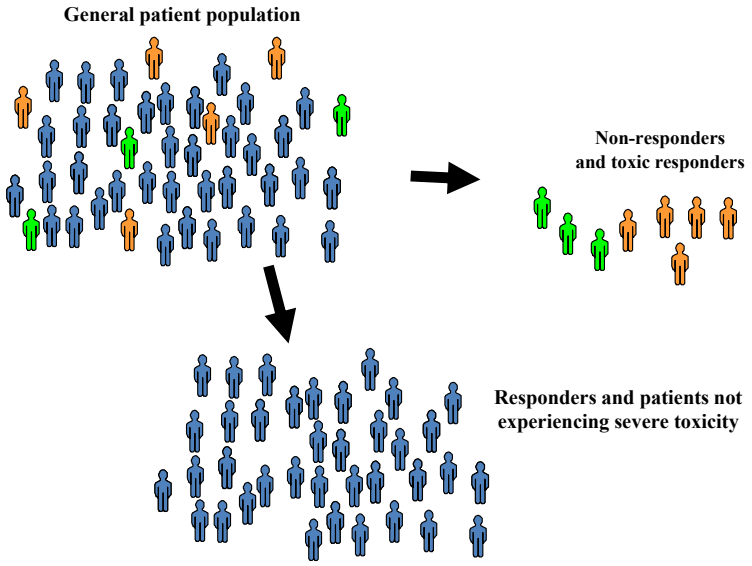
Drug metabolizing enzymes



(Evans and Relling, *Science* 286: 487-91, 1999)

28

The Goal of Pharmacogenetics



29

Pharmacogenetics

Implications of Polymorphisms on Pharmacokinetics

- Drug Absorption
- Drug Distribution
- Drug Metabolism
- Drug Elimination
- Drug Activation

Implications of Polymorphisms on Drug Effect (Response and Toxicity)

- Receptors
- Target Proteins
- Resistant
- Toxicity

30

Pharmacogenomics and Oncology

Pharmacogenomic Strategies Most Relevant When:

- **Narrow therapeutic indices**
- **High degree of inter-individual variability in response**
- **Little or no available methods to monitor safety or efficacy**
- **Few alternative treatment options**

Flowers and Veenstra 2004

31

Pharmacogenomics and Oncology

Pharmacogenomic Strategies Most Relevant When:

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- **Few alternative treatment options**

Flowers and Veenstra 2004

Anticancer agents meet all of these criteria

32

Genotyping Strategies in Medical Oncology

Example of Anticancer Drug Metabolism by Polymorphic Enzymes

Drug	Elimination Pathway	Variability in CL
Amonafide	N-acetyl transferase (NAT)	>3-fold
Busulfan	Glutathione S-transferase (GST)	10-fold
Docetaxel	Cytochrome P-450 (CYP) 3A4 and 3A5	4 to 9-fold
5-Fluorouracil	Dihydropyrimidine dehydrogenase (DPD)	10-fold
Irinotecan	UDP glucuronosyltransferase (UGT)	50-fold
6-Mercaptopurine	Thiopurine methyltransferase (TPMT)	>30-fold

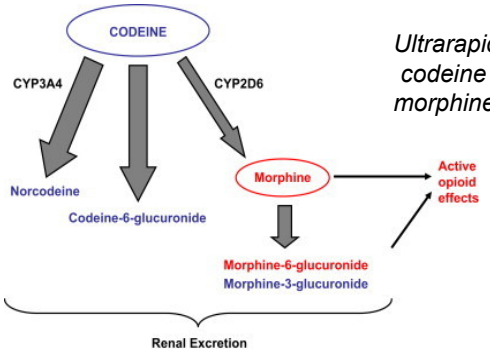
Evans and Relling, *Science* 286: 487-91, 1999

33

The NEW ENGLAND JOURNAL of MEDICINE Volume 361:827-828; August 20, 2009

Case report: Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

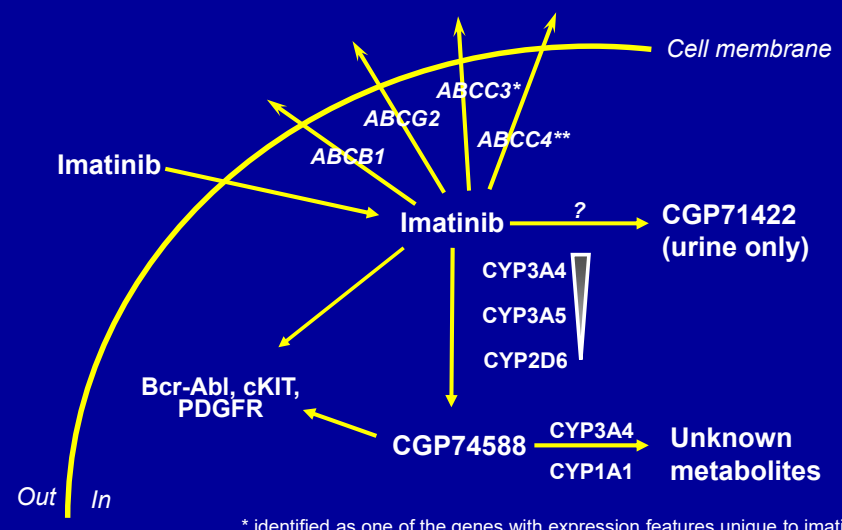
Healthy 2-yo boy, underwent outpatient elective adenotonsillectomy;
After surgery, instructions to take 10-12.5mg of codeine + 120 mg APAP q 4-6 hr prn; 2 days post surgery, child died
Autopsy results: Codeine (0.70 mg/L) & morphine (32 ng/ml) → toxic levels
CYP2D6 genotyping → 3 copies of *CYP2D6* allele → ultrarapid-metabolizer phenotype



Ultrarapid metabolizers may metabolize codeine too efficiently leading to morphine intoxication

34

Selection of Appropriate Genes



* identified as one of the genes with expression features unique to imatinib relapsers in CML (Radich et al, *PNAS* 2006); ** S Hu et al, *CCR* 2008

35

One ultimate goal of pharmacogenetics is to provide a patient with individualized therapy ("getting the dose right")

Using candidate gene approach - It will be virtually impossible to assign a patient to an unequivocal phenotype and especially to an unequivocal genotype

36

DMET Genotyping Array (Affymetrix)

- ***Phase I enzymes:*** *CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2B7, CYP2B7P1, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2S1, CYP3A4, CYP3A5, CYP3A7, CYP3A43, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4Z1, CYP7A1, CYP7B1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP20A1, CYP21A2, CYP24A1, CYP26A1, CYP27A1, CYP27B1, CYP39A1, CYP46A1, CYP51A1*
- ***Phase II enzymes:*** *ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7, ALDH1A1, ALDH2, ALDH3A1, ALDH3A2, CHST1, CHST2, CHST3, CHST4, CHST5, CHST6, CHST7, CHST8, CHST9, CHST10, CHST11, CHST13, COMT, DPYD, FMO1, FMO2, FMO3, FMO4, FMO5, FMO6, GSTA1, GSTA2, GSTA3, GSTA4, GSTA5, GSTM1, GSTM2, GSTM3, GSTM4, GSTM5, GSTO1, GSTP1, GSTT1, GSTT2, GSTZ1, MAOA, MAOB, NAT1, NAT2, NNMT, NQO1, SULT1A1, SULT1A2, SULT1A3, SULT1B1, SULT1C1, SULT1C2, SULT1E1, SULT2A1, SULT2B1, SULT4A1, TPMT, UGT1A1, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2A1, UGT2B4, UGT2B7, UGT2B11, UGT2B15, UGT2B17, UGT2B28, UGT8*
- ***Transporters:*** *ABCB1, ABCB4, ABCB7, ABCB11, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC6, ABCC8, ABCC9, ABCG1, ABCG2, ATP7A, ATP7B, SLCA13, SLC10A1, SLC10A2, SLC13A1, SLC15A1, SLC15A2, SLC16A1, SLC19A1, SLC22A1, SLC22A11, SLC22A12, SLC22A14, SLC22A2, SLC22A3, SLC22A4, SLC22A5, SLC22A6, SLC22A7, SLC22A8, SLC28A1, SLC28A2, SLC28A3, SLC29A1, SLC29A2, SLC5A6, SLC6A6, SLC7A5, SLC7A7, SLC7A8, SLCO1A2, SLCO1B1, SLCO1B3, SLCO2B1, SLCO3A1, SLCO4A1, SLCO5A1*
- ***Other:*** *ABP1, AHR, AKAP9, ALB, AOX1, ARNT, ARSA, CBR1, CBR3, CDA, CES2, CROT, DCK, EPHX1, EPHX2, FAAH, G6PD, HMGCR, HNMT, MAT1A, METTL1, NR1I2, NR1I3, NR3C1, ORM1, ORM2, PNMT, PON1, PON2, PON3, POR, PPARD, PPARG, PTGIS, RALBP1, RPL13, RXRA, SEC15L1, SERPINA7, SETD4, SPG7, TBXAS1, TPSG1, TYMS, VKORC1, XDH*

37

Future Trial

A *UGT1A1* Genotype-Directed Study of Belinostat Pharmacokinetics and Toxicity

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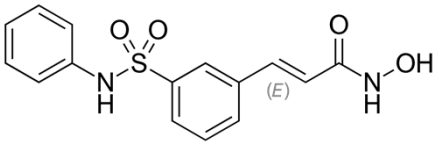
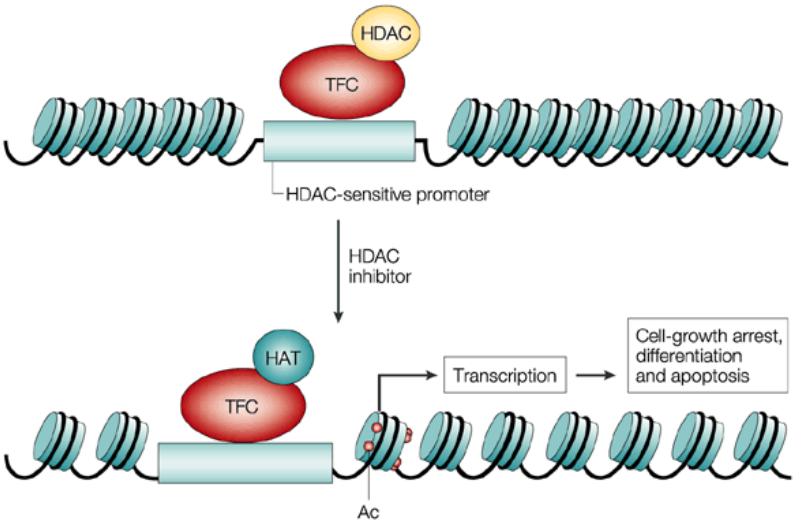
38

38

Belinostat



Histone Deacetylase (HDAC) Inhibitor approved for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL)



Marks et al. *Nature Reviews Cancer* 2001

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39

39

UGT1A1 Genotype-Dependent Dose Adjustment of Belinostat in Patients With Advanced Cancers Using Population Pharmacokinetic Modeling and Simulation

Cody J. Peer, MS, PhD[1], Andrew K. L. Goey, PharmD, PhD[1], Tristan M. Sissung, MS, PhD[1], Sheryl Erlich, MA[1], Min-Jung Lee, PhD[2], Yusuke Tomita, MD[2], Jane B. Trepel[2], Richard Piekarz, MD, PhD[3], Sanjeeve Balasubramaniam, MD[2], Susan E. Bates, MD[2], and William D. Figg, PharmD, FCP[1,4]

The Journal of Clinical Pharmacology 2016;56:450-460

Effects of *UGT1A1* Genotype on the Pharmacokinetics, Pharmacodynamics, and Toxicities of Belinostat Administered by 48-Hour Continuous Infusion in Patients With Cancer

Andrew K. L. Goey, PharmD, PhD[1], Tristan M. Sissung, PhD, MS[2], Cody J. Peer, PhD, MS[1], Jane B. Trepel[3], Min-Jung Lee, PhD[3], Yusuke Tomita, MD, PhD[3], Sheryl Ehrlich, MA[2], Christine Bryla, RN, MSN[4], Sanjeeve Balasubramaniam, MD, MPH[4], Richard Piekarz, MD, PhD[5], Seth M. Steinberg, PhD[6], Susan E. Bates, MD[4], and William D. Figg, PharmD (FCP)[1]

The Journal of Clinical Pharmacology 2016;56:461-473

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40

40

UGT1A1 Genotype-Dependent Dose Adjustment of Belinostat in Patients With Advanced Cancers Using Population Pharmacokinetic Modeling and Simulation

Cody J. Peer, MS, PhD[1], Andrew K. L. Goey, PharmD, PhD[1], Tristan M. Sissung, MS, PhD[1], Sheryl Erlich, MA[1], Min-Jung Lee, PhD[2], Yusuke Tomita, MD[2], Jane B. Trepel[2], Richard Piekarz, MD, PhD[3], Sanjeeve Balasubramaniam, MD[2], Susan E. Bates, MD[2], and William D. Figg, PharmD, FCP[1,4]

The Journal of Clinical Pharmacology
2016;56:450-460

Simulation
EM: Extensive Metabolizer
IM: Intermediate Metabolizer

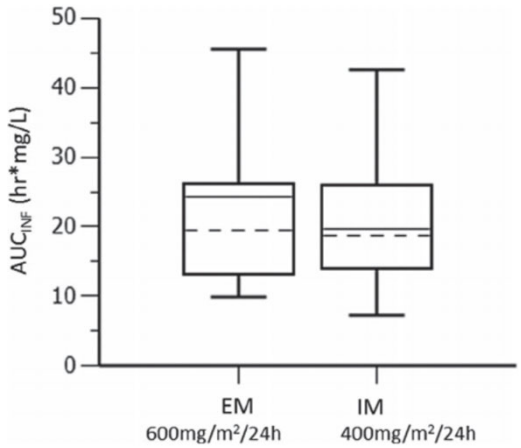

Figure 4. Simulations for optimal belinostat doses to predict equivalent exposures. Simulated AUC_{inf} from EM given 600 mg/m²/24 h versus IM given 400 mg/mg²/24 h from a single 48-hour intravenous infusion.

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41

41

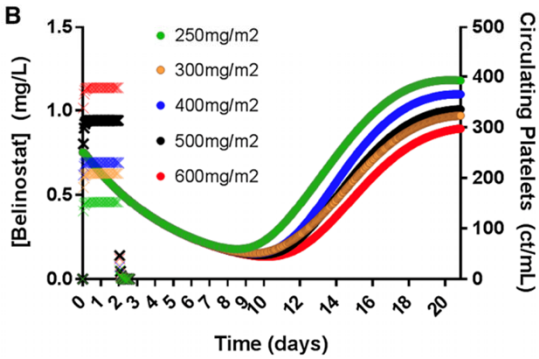
SHORT COMMUNICATION

CrossMark

A population pharmacokinetic/toxicity model for the reduction of platelets during a 48-h continuous intravenous infusion of the histone deacetylase inhibitor belinostat

Cody J. Peer[1] · Oliver M. Hall[1] · Tristan M. Sissung[1] · Richard Piekarz[2] · Sanjeeve Balasubramaniam[3] · Susan E. Bates[4] · William D. Figg[1,5]

Cancer Chemotherapy and Pharmacology
2018;82:566-570



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42

42

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BELEODAQ safely and effectively. See full prescribing information for BELEODAQ.

BELEODAQ® (belinostat) for injection, for intravenous administration
Initial U.S. Approval

----------INDICATIONS AND USAGE----------
Beleodaq is a histone deacetylase inhibitor indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. (1)

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43

Reduce the starting dose of Beleodaq in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities is recommended.

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44

Phase I trial of belinostat with cisplatin and etoposide in advanced solid tumors, with a focus on neuroendocrine and small cell cancers of the lung

Sanjeeve Balasubramaniam[a], Christophe E. Redon[b], Cody J. Peer[c], Christine Bryla[b], Min-Jung Lee[b], Jane B. Trepel[b], Yusuke Tomita[b], Arun Rajan[d], Giuseppe Giaccone[f], William M. Bonner[b], William D. Figg[a,c], Tito Fojo[g,h], Richard L. Piekarz[e] and Susan E. Bates[g,h]

The standard-of-care for advanced small cell lung cancer (SCLC) is chemotherapy with cisplatin + etoposide (C + E). Most patients have chemosensitive disease at the outset, but disease frequently relapses and limits survival. Efforts to improve therapeutic outcomes in SCLC and other neuroendocrine cancers have focused on epigenetic agents, including the histone deacetylase inhibitor belinostat. The primary objective was to determine the maximum tolerated dose of the combination of belinostat (B) with C + E. Belinostat was administered as a 48-h continuous intravenous infusion on days 1–2; cisplatin was administered as a 1-h intravenous infusion on day 2; and etoposide was administered as a 1-h intravenous infusion on days 2, 3, and 4. Twenty-eight patients were recruited in this single-center study. The maximum tolerated dose was belinostat 500 mg/m^2/24 h, cisplatin 60 mg/m^2, and etoposide 80 mg/m^2. The combination was safe, although some patients were more susceptible to adverse events. Hematologic toxicities were most commonly observed. Objective responses were observed in 11 (39%) of 28 patients and seven (47%) of 15 patients with neuroendocrine tumors (including SCLC). Patients carrying more than three copies of variant *UGT1A1* (**28* and **60*) had higher serum levels of belinostat because of slower clearance. DNA damage peaked at 36 h after the initiation of belinostat, as did global lysine acetylation, but returned to baseline 12 h after the end of infusion. The combination of B + C + E is safe and active in SCLC and other neuroendocrine cancers. Future phase II studies should consider genotyping patients for *UGT1A1*28* and *UGT1A1*60* and to identify patients at an increased risk of adverse events. *Anti-Cancer Drugs* 29:457–465 Copyright
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Anti-Cancer Drugs 2018, **29**:457–465

Keywords: advanced carcinomas, histone deacetylase inhibitors, phase I, small cell lung cancer

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Received 22 November 2017 **Revised form accepted** 27 December 2017

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45

45

Phase I trial of belinostat with cisplatin and etoposide in advanced solid tumors, with a focus on neuroendocrine and small cell cancers of the lung

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Received 22 November 2017 **Revised form accepted** 27 December 2017

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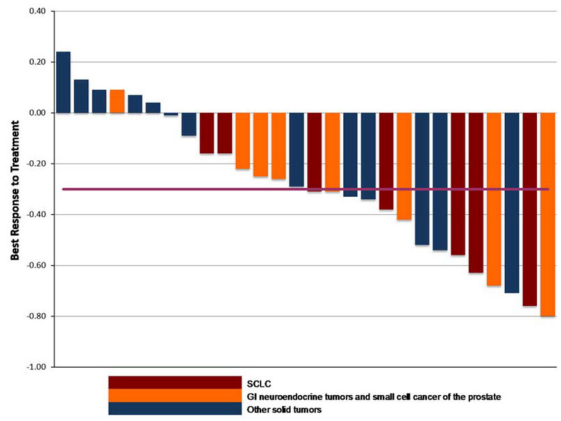
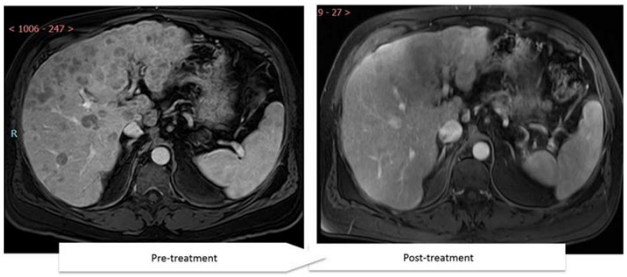
46

46

Response to Belinostat, Cisplatin and Etoposide





Balasubramaniam S, et al (Figg) Anti-Cancer Drugs 2018

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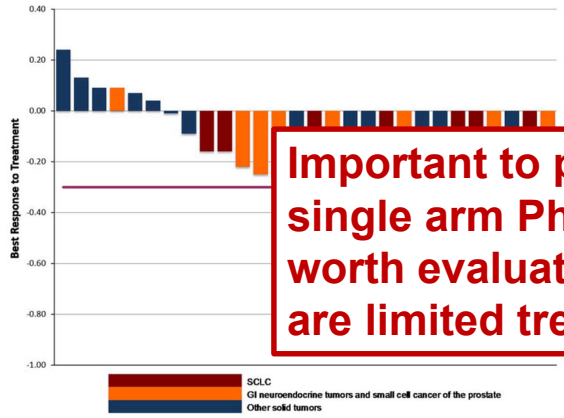
47

47

Response to Belinostat, Cisplatin and Etoposide



Important to point out - this is a single arm Phase 1 study, but is worth evaluating in NEC, as there are limited treatment options

Balasubramaniam S, et al (Figg) Anti-Cancer Drugs 2018

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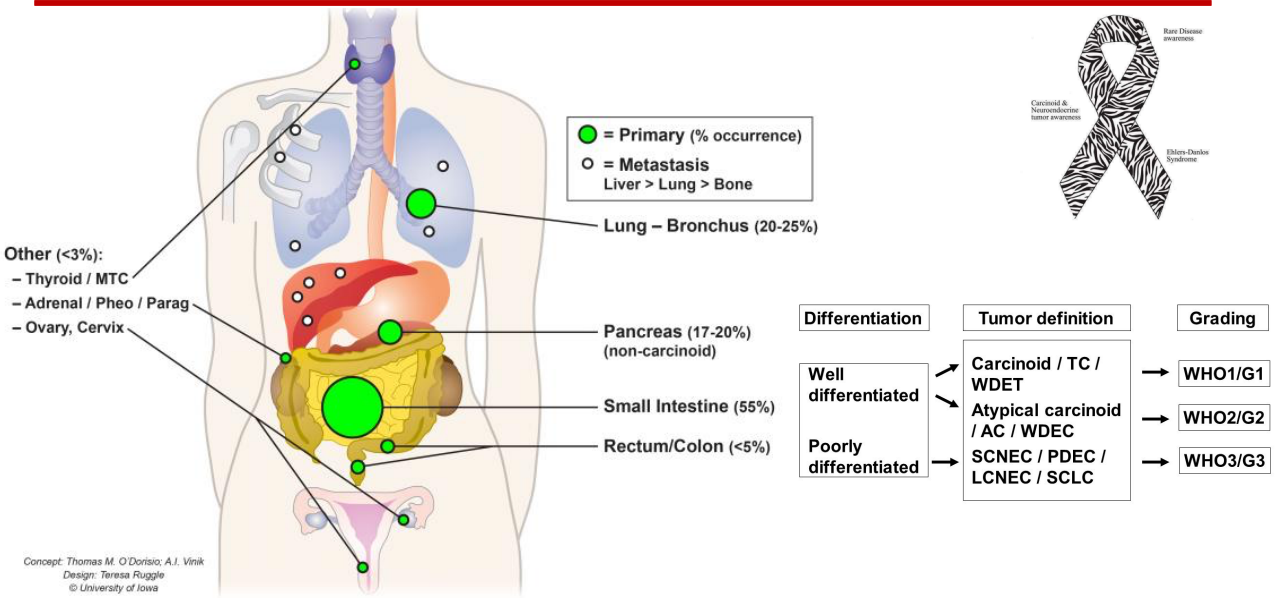
48

48

Anatomic Distribution of Neuroendocrine Neoplasia (NEN)



Differentiation	Tumor definition	Grading
Well differentiated	Carcinoid / TC / WDET	WHO1/G1
	Atypical carcinoid / AC / WDEC	WHO2/G2
Poorly differentiated	SCNEC / PDEC / LCNEC / SCLC	WHO3/G3

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Classification and Grading of Neuroendocrine Neoplasms

Grade of Progression

Well-Differentiated NET Grade 1, 2			Well-Differentiated NET Grade 3			Neuroendocrine Carcinoma (NEC)		
Small Bowel	Lung NET	Pan NET	Pan NET	Lung	Other	SCLC	LCNEC	EP-NEC
Mutations uncommon CNV common LOH 18q in 80% CDKN1B in 8%	Typical Chromatin remodeling genes (MEN1, SW1/SNF, ARIDIA, PSIP1	Atypical	ATRX, DAXX, MEN1, mTOR	SETD2 (20-30%)	????	????	TP53, Rb + other (High NE, Medium, Low NE	2 types	P53, Rb + Other (depending on site of primary) NEC-low, NEC high Ki67%
Ki 67%	<3	3-20%		>20%			>20%	

DOTA-PET (+)

FDG-PET (+)

50

New Pharmacogenetic Guided Trial

- FDA's recommendation is based on our retrospective data and simulation. They requested prospective data; thus, we will see if we can avoid side effects (esp. platelet change and QTc prolongation) and achieve similar AUC by dosing based on *UGT1A1* genotypes.

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51

51

Study Design (B + C + E)

- Parallel design in which the starting dose of belinostat is administered at two possible doses based on genotype:

  1) 400 mg/m^2/day for *UGT1A1*28/*28* or at least one *UGT1A1*60* allele *UGT1A1*28* and *UGT1A1*60* genotypes

  or

  2) 600 mg/m^2/day for wild-type patients and those carrying *UGT1A1*1/*28* in the absence of other variant alleles

- All patients will also receive cisplatin at 60 mg/m^2 IV on day 2, and etoposide at 80 mg/m^2 IV daily x 3 on days 2 - 4

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52

52

Pharmacogenetic Guided Trials (Since the 2015)

- Mithramycin
- Gemcitabine
- PEN-866 (i.e., HSP90 targeting ligand linked to SN-38)
- MM-398 (i.e., nanoliposomal irinotecan)
- Belinostat

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53

53

Dose De-Escalation of Cancer Therapies using Population-Level Pharmacokinetic Modeling & Simulation

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14 Jan 2021

54

Pharmaceutical Market

- Worldwide pharma market: 1.25 trillion USD/year
- North American pharma market accounts for 48.7%
- The top 10 selling drugs worldwide had $87 billion in annual sales in 2019
- Oncology drugs had $168 billion in annual sales in 2019
  - ~10% increase per year from 2015
  - Projected to be $285 billion annually by 2023

LONDON, Oct. 06, 2020 (GLOBE NEWSWIRE) -- ***(Oncology Drugs Companies Included: F. Hoffmann-La Roche AG, Novartis AG, Bristol-Myers Squibb Company, Merck & Co., Inc., Johnson & Johnson)***

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55

Pharmaceutical Market

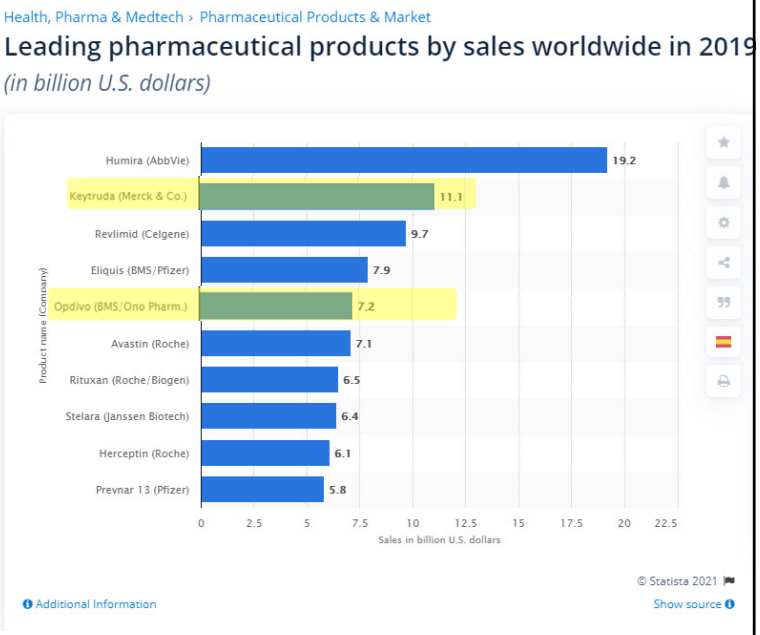
- Two of the top 5 drugs worldwide in all therapeutic classes are:

  # 2 Keytruda® (pembrolizumab)

  $11.1 billion/year

  #5 Opdivo® (nivolumab)

  $ 7.2 billion/year



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56

Spiraling Drug Prices

- Half of generic drugs increased in price last year alone
  - Median increase of 11.8% (4x that of inflation)
- ≥100% price increases for 222 generic drugs in 2019
- In extreme cases (17 drugs), price increased by >1000%
- In Q1 2019, 2862 agents went up in price (mean 8.6%), defying "political pressure to slow rise in prescription drug cost…", *Financial Times* said
- Market forces have not controlled drug prices; a new approach is needed

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Source: Elsevier. (2015). The Impact of Rising Generic Drug Prices on the U.S. Drug Supply Chain. Retrieved from http://www.ncpa.co/pdf/elsevier_wp_genericdrug.pdf

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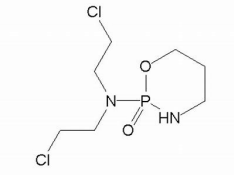
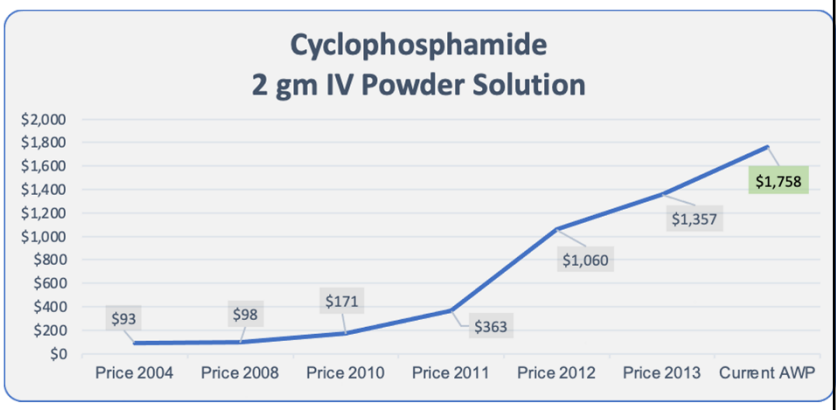
57

Example: Cyclophosphamide



- First approved in 1959
- In last **16 years**, price increased **almost 20-fold** from $93 - $1758
- A **3-fold** increase just from 2011-2012



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Manufacturer AWP: Baxter Healthcare Corporation
AWP = Average Wholesale Price, although most CC/Hospitals pay about 50% the AWP – it is a reference price

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58

Strategies to combat spiraling drug prices

1. **Therapeutic substitution**

2. **Lower dose**
   - Ex: abiraterone: 250mg fed vs 1000mg fast (75% dose reduction and cost savings)

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59

Lowering Abiraterone Dose

VOLUME 36 · NUMBER 14 · MAY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

- In 2019, NCCN guidelines for Prostate Cancer (NCCN v1.2019) for abiraterone dosing were changed from 1000 mg QD fasted to 250 mg QD with a meal* based on a collaborative **noninferiority** study between NCI (Figg Lab) and U Chicago
  - * Low-fat breakfast
- Applicable for all Zytiga® indications

Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer

Russell Z. Szmulewitz, Cody J. Peer, Abiola Ibraheem, Elia Martinez, Mark F. Kozloff, Bradley Carthon, R. Donald Harvey, Paul Fishkin, Wei Peng Yong, Edmund Chiong, Chadi Nabhan, Theodore Karrison, William D. Figg, Walter M. Stadler, and Mark J. Ratain

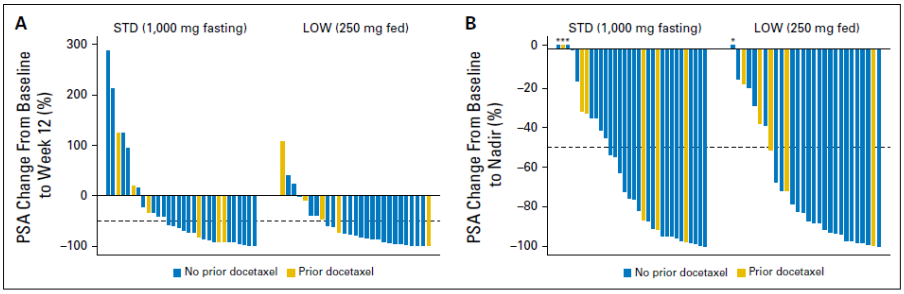

Fig 2. Decrease in prostate-specific antigen (PSA) while receiving treatment. Waterfall plot showing percent reduction in PSA at (A) landmark 12-week time point and (B) maximum nadir. Patients whose best PSA response was progression are denoted with (*). LOW, 250 mg abiraterone acetate with a low-fat meal; STD, 1,000 mg abiraterone acetate fasting

3/9/2021

60

Strategies to combat spiraling drug prices

1. **Therapeutic substitution**
2. **Lower dose**
   - Ex: abiraterone: 250mg fed vs 1000mg fast (75% dose reduction and cost savings)
3. **Shorter duration**
   - 6 vs 12 mo adjuvant trastuzumab
4. **Lower frequency**
   - Zoledronic acid (1 vs 3 months)

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61

PD-1 Inhibitors

Nivolumab & Pembrolizumab

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62

Background: PD-1 inhibitors

- Nivolumab (Opdivo®) and pembrolizumab (Keytruda®) are both IgG4-based mAbs that target and bind PD-1, blocking its ability to bind PD-L1
- FDA approval history for dosing:

Pembrolizumab

- **Sept 2014** – initial approval @ 2 mg/kg q3wk
- **Aug 2016**– 200 mg q3wk
- **April 2020** – 400 mg q6wk

Nivolumab

- **Dec 2014** – initial approval @ 3 mg/kg q2wk
- **Sept 2016** – 240 mg q2wk
- **March 2018** – 480 mg q4wk

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63

Background: PD-1 inhibitors

- There's evidence that lower doses demonstrate comparable activity (ORR) relative to higher doses

Nivolumab

- Topalian et al, *NEJM*, 2012 (in melanoma)

0.1 mg/kg q2wk: **ORR 29% (95%CI: 8-58%)**

10 mg/kg q2wk: **ORR 20% (95%CI: 6-44%)**

- Motzer et al, *JCO*, 2015 (in RCC)

0.3 mg/kg q3wk: **ORR 20% (80%CI: 13.4-28.2%)**

10 mg/kg q3wk: **ORR 20% (80%CI: 13.4-29.1%)**

HR for 10 vs 0.3 mg/kg q3wk: **1.0** (80%CI: 0.8 -1.3)

- FDA CDER review (March 2018; NSCLC)

Squamous (3 vs 1 mg/kg q2wk): HR 2.08 (95%CI 0.87-5)*

Non-Squamous (3 vs 1 mg/kg q2wk): HR 1.02 (95%CI 0.82-4.5)*

Pembrolizumab

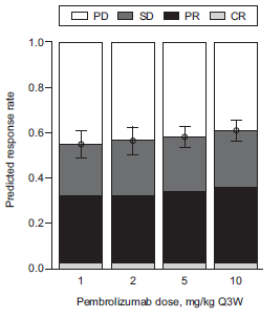
- Patnaik et al, *CCR*, 2015 (in advanced solid tumors)

RO saturated at 1 mg/kg q3wk

- Chatterjee et al, *CPT:PSP*, 2017 (PK simulations)

Simulated 1000 trials, each w/ 10,000 sim patients: predicted median RR at week28

- no difference btw/ 1 mg/kg q3wk and 2 mg/kg q3wk



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*Once adjusted for small sample size and study effects when comparing across studies and study populations

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64

Identify a target C_{SERUM}

- Based on Motzer et al, 0.3 mg/kg q3wk had comparable efficacy to 10 mg/kg q3wk
- Activity observed *as early as week 6 (after second dose)*
- **1.5 ug/mL selected as target to maintain**

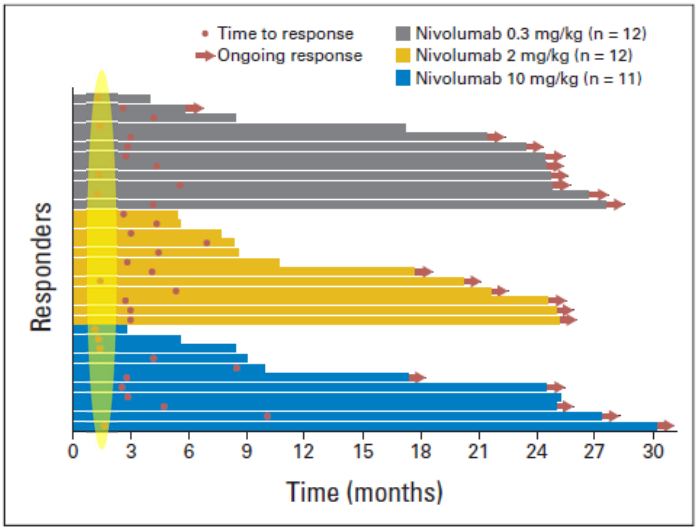

Fig 3. Duration of response in patients who achieved objective response by dose treatment arm. Based on data cutoff date of March 5, 2014.

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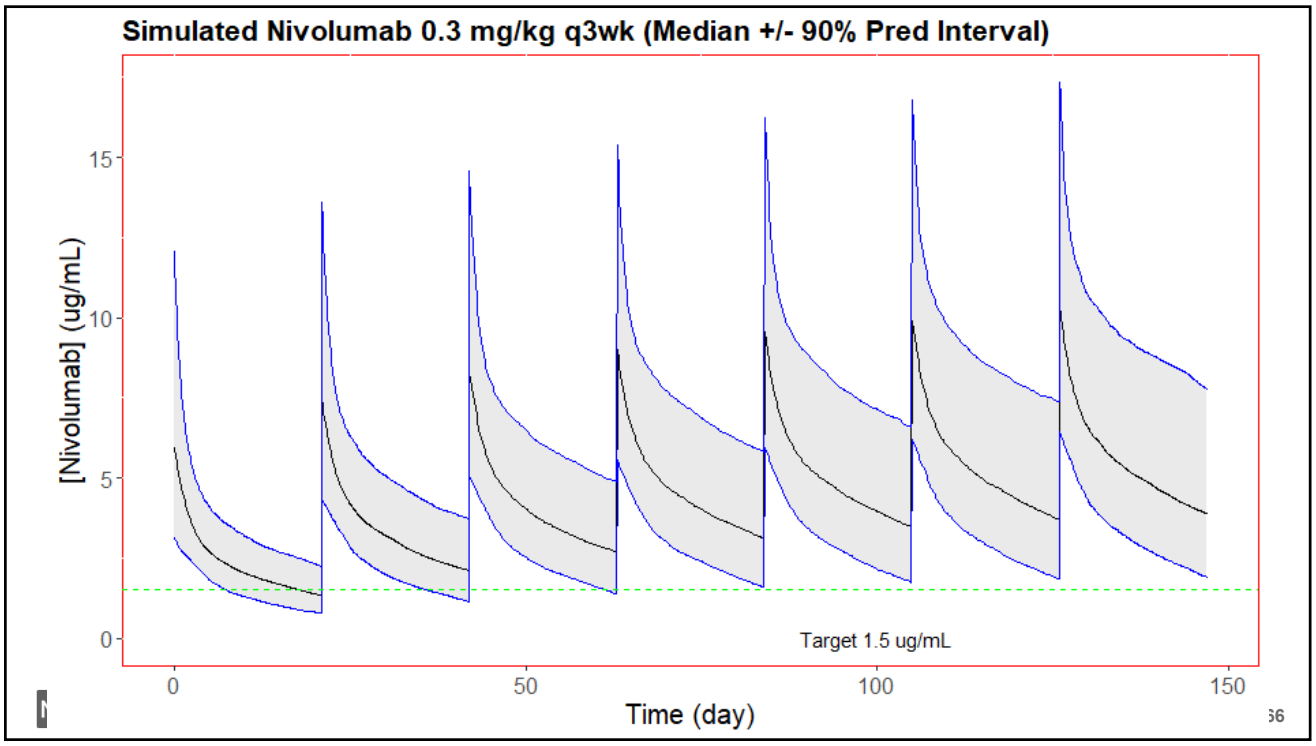
65



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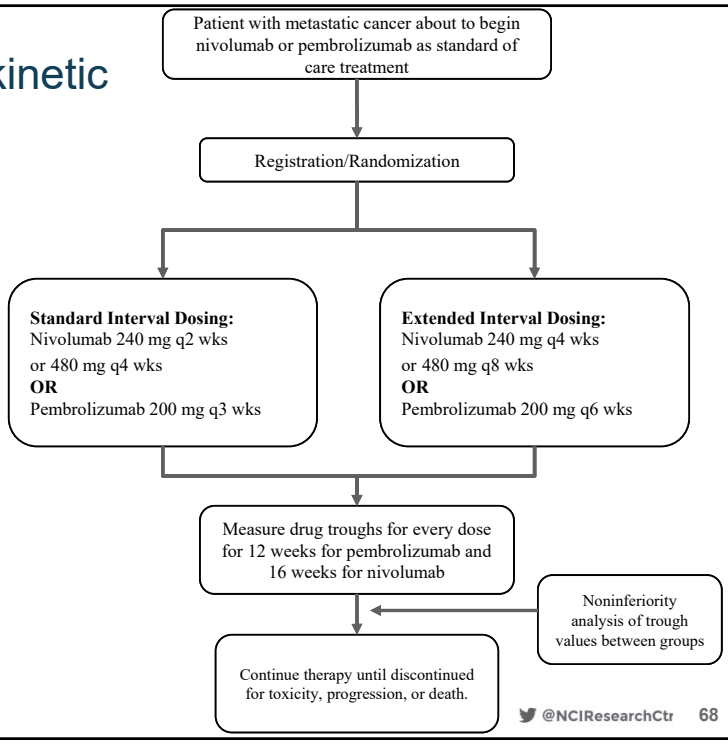
Summarized Pembrolizumab Steady-State Trough ($C_{MIN,SS}$) Statistics

Scenario	Dose	Week	Geometric Mean (95% CI)	5th Percentile	10th Percentile	Approx Cost Savings
200 mg q3wk	1st	3	10.4 (10.2 – 10.7)	5.2	6.5	n/a
	10th	30	25.9 (25.2 – 26.7)	11.7	14.3	
1 mg/kg q3wk	1st	3	3.91 (3.82 – 4.00)	2.0	2.4	50%
	10th	30	9.74 (9.46 – 10.0)	4.4	5.3	
200 mg q6wk	1st	6	4.12 (3.95 – 4.29)	1.3	1.8	50%
	10th	60	8.49 (8.16 – 8.83)	2.9	3.8	
400 mg q6wk	1st	6	8.23 (7.89 – 8.58)	2.5	3.5	0%
	10th	60	16.9 (16.3 – 17.7)	5.9	7.6	

67

1. Noninferiority Pharmacokinetic Clinical Trial Design

- **Study Design**: A randomized study investigating the pharmacokinetics of **standard interval dosing** compared to **extended interval dosing** of nivolumab (Opdivo®) or pembrolizumab (Keytruda®) in locally advanced or metastatic cancers.



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68

1. Noninferiority Pharmacokinetic Clinical Trial

- **Eligible Patients**: Patients (18yr+) with a diagnosis of locally advanced or metastatic cancer who are to begin either nivolumab or pembrolizumab and *have not received previous immune checkpoint inhibitor therapy*
- **Primary Objective**
  - Evaluable patients categorized as success (trough > 1.5 ug/mL) or failure (< 1.5 ug/mL)
    - Evaluable if received at least one dose
  - Assess NI of PK success (trough >1.5 µg/mL)
- **Secondary Objectives**
  1. Compare time to treatment discontinuation (TTD) in evaluable patients between std vs extended dosing
  2. Compare OS in evaluable patients between std vs extended dosing
- Together, objectives will determine if 1.5 ug/mL is a legitimate MEC

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Planned max accrual n=264 (1:1 randomization)

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69

Future Directions

- IF the nivo/pembro trial DOES demonstrate noninferiority of extended-dosing with standard dosing in the percentage of patients maintaining 1.5 ug/mL, THEN, need to **confirm** efficacy (i.e. 1.5 ug/mL as MEC) in **a second trial** w/ extended dosing and efficacy as primary endpoint

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70

Potential Cost Savings

Drug	Vial Size/Cost	Standard Regimen	Extended Regimen	Cost Savings
Nivolumab	40mg 100mg 240mg 240mg = $6,679	480mg q4wk $13,358/dose (2 vials of 240mg)	240mg q4wk or 480mg q8wk $6,679	50%
Pembrolizumab 200mg vials only	200 mg only $9,870	400mg q6wk $19,740/dose (2 vials of 200mg)	200mg q6wk $9,870	50%

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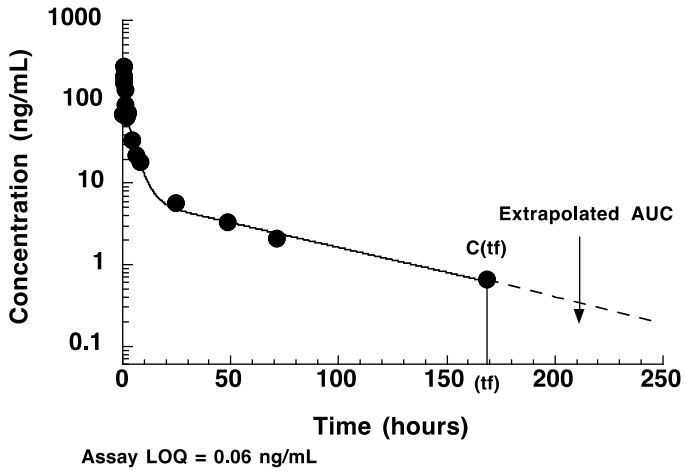
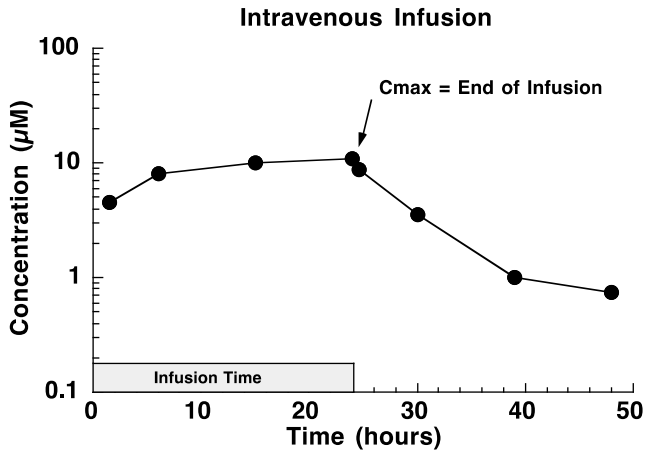
71

Graphical Presentation of AUC

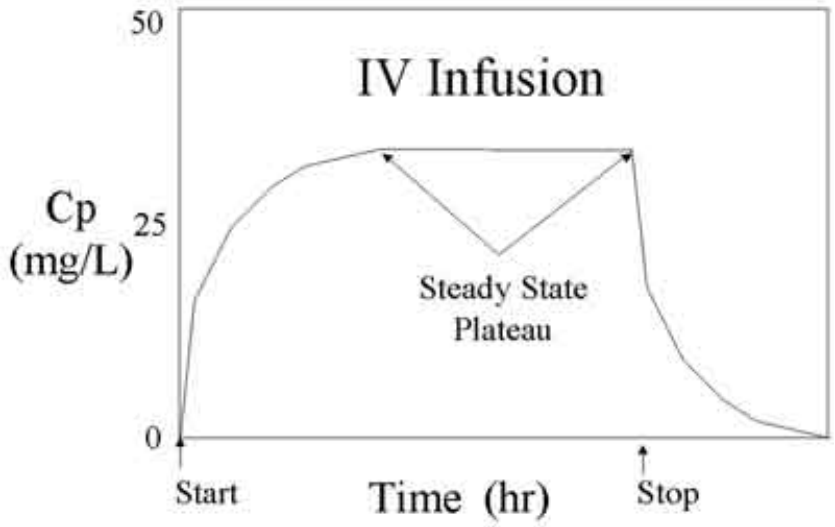


72

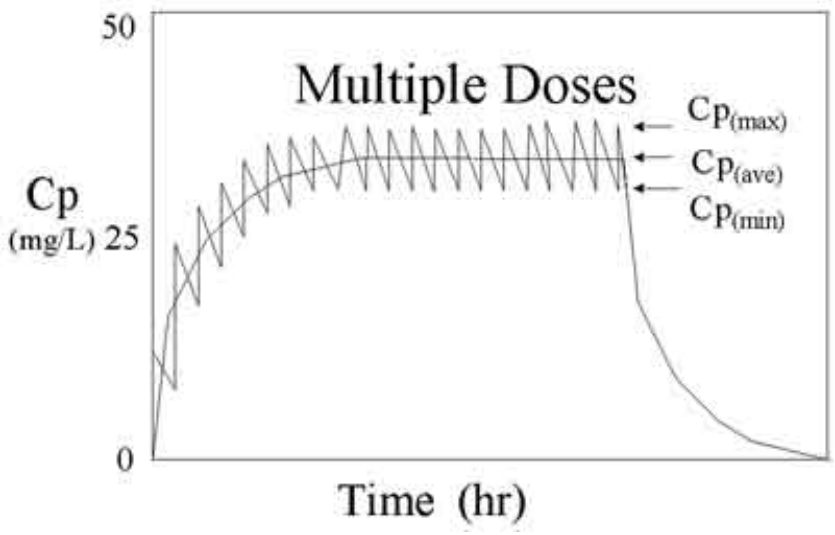
Graphical Presentation of Cmax



73



74



75

Acknowledgements

Figg Laboratory, NCI
Cody Peer
Tristan Sissung
Keith Schmidt
Lisa Cordes
Andrew Goey
Sheryl Erlich
Oliver Hall
Tyler Yin
Ryan Nguyen
Jennie Goodell
Sara Zimmerman

Statistics Sect, NCI
Seth Steinberg
David Venzon

Selumetinib-Clinical
Brigitte Widemann
Andrea Gross
John Glod

Belinostat-Clinical
Jaydira del Rivero
Anish Thomas
Beppe Giaccone
Susan Bates
Richard Piekarz
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Tito Fojo

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76

76

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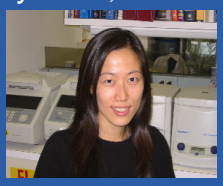

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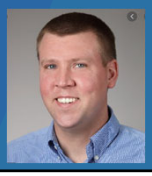

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77

Thank you!!

Questions

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78