ADHERENCIA Y MONITORIZACIÓN FARMACOCINÉTICA EN LOS TRATAMIENTOS ONCOHEMATOLÓGICOS ORALES

MONITORIZACIÓN FARMACOCINÉTICA DE ANTINEOPLÁSICOS ORALES

Mª DOLORES BELLÉS MEDALL

Hospital General Universitario Castellón/ Grupo PKGen

Review Article

Precision dosing of targeted anticancer drugs—challenges in the real world

Hannah Yejin Kim[1], Jennifer H. Martin[2], Andrew J. Mclachlan[1,3], Alan V. Boddy[1]

[1]Faculty of Pharmacy, University of Sydney, NSW, Australia; [2]Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle, NSW, Australia; [3]Centre for Education and Research on Ageing, Concord Hospital, NSW, Australia

Contributions: (I) Conception and design: AV Boddy, JH Martin, AJ Mclachlan; (II) Administrative support: HY Kim, AV Boddy; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alan V. Boddy. Faculty of Pharmacy, University of Sydney, NSW, Australia. Email: alan.boddy@sydney.edu.au.

Transl Cancer Res 2017;6(Suppl 10):S1500-S1511

http://dx.doi.org/10.21037/tcr.2017.10.30

TDM fármacos Citostáticos

Carboplatino	Calvert Formula Total Carboplatin Dose (mg) = (target AUC) X (GFR + 25)
MTX	dosis rescate folínico
Isotretionina	Cp>10 mcM/L: toxicidad
Busulfán	Cp>900-1025 ng/mL: toxicidad
5-FU	AUC= 20-30 mg.h/L

Problemas logísticos

- Optimización *vs* desarrollo nuevas terapias
- Falta financiación validación métodos analíticos y tiempos respuesta rápidos
- Modelos PK/PD ayuda toma de decisiones
- Matrices biológicas pequeño volumen (gotas sangre seca)
- Desarrollo en farmacometría: tiempos óptimos de muestreo, software

Desafíos metodológicos

- Relación PK/PD: ECA dosis según FT vs dosis según TDM
- PK/PD según tipo tumor
- Definición respuesta terapéutica: biomarcadores
- Elevada variabilidad intraindividual: comida, interacciones, adherencia terapéutica

REVIEW

Therapeutic drug monitoring of oral targeted antineoplastic drugs

Anna Mueller-Schoell[1,2] · Stefanie L. Groenland[3] · Oliver Scherf-Clavel[4] · Madelé van Dyk[5] · Wilhelm Huisinga[6] · Robin Michelet[1] · Ulrich Jaehde[7] · Neeltje Steeghs[3] · Alwin D.R. Huitema[8,9] · Charlotte Kloft[1]

European Journal of Clinical Pharmacology (2021) 77:441–464
https://doi.org/10.1007/s00228-020-03014-8

✉ Charlotte Kloft
charlotte.kloft@fu-berlin.de

[1] Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Berlin, Germany

[2] Graduate Research Training Program, PharMetrX, Berlin/Potsdam, Germany

[3] Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

[4] Institute of Pharmacy and Food Chemistry, Julius-Maximilians-Universität Würzburg, Würzburg, Germany

[5] College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia

[6] Institute of Mathematics, University of Potsdam, Potsdam, Germany

[7] Department of Clinical Pharmacy, Institute of Pharmacy, University of Bonn, Bonn, Germany

[8] Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek, Amsterdam, The Netherlands

[9] Department of Clinical Pharmacy, University Medical Center, Utrecht University, Utrecht, The Netherlands

Fármacos antineoplásicos orales (OADs)

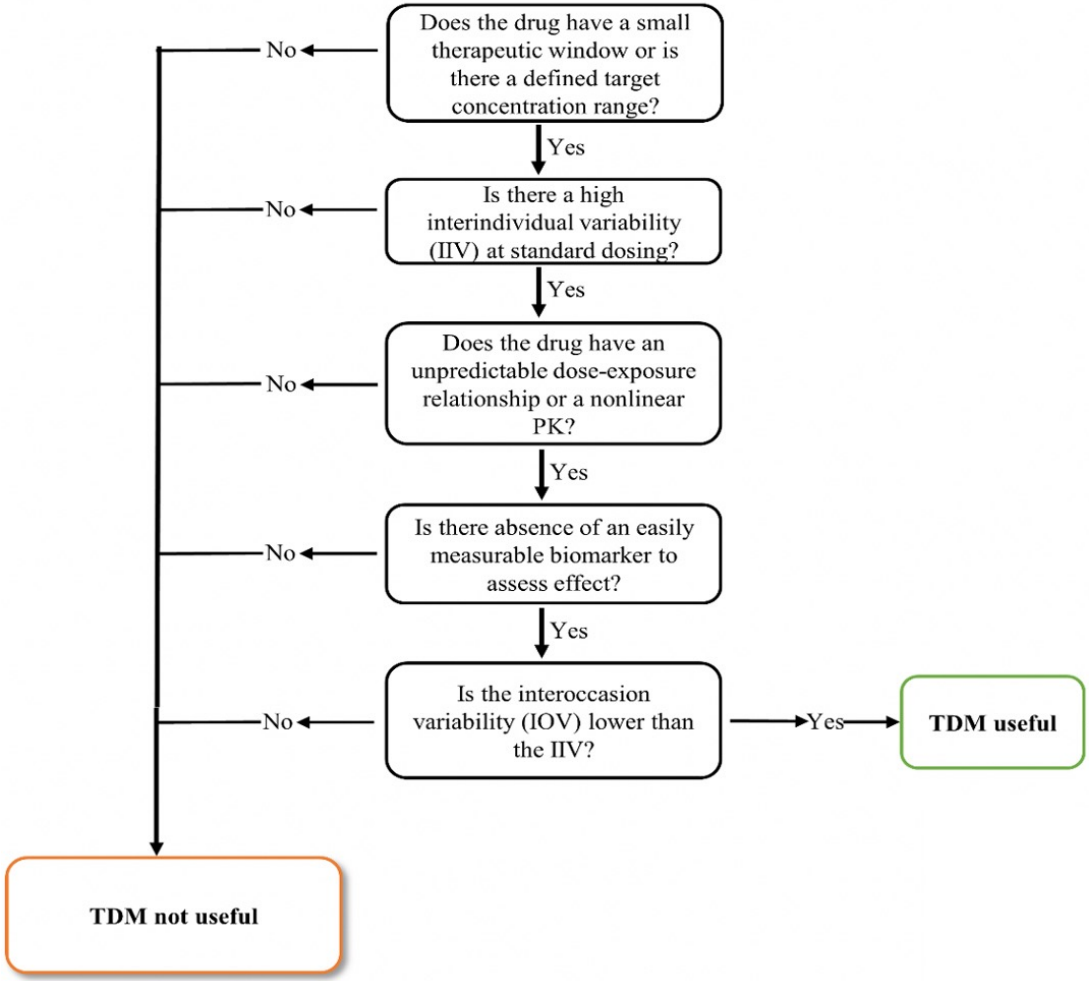
* Nivel de independencia
* Reducción costes asistencia sanitaria
* Corresponsabilidad del paciente:
  - Motivación y entrenamiento toma adecuada de la medicación
  - Conocimiento de la frecuencia y gravedad RAM
* Dosis orales fijas c/24h
  - Dosis máxima tolerada (Fase I, n pequeña)
  - Tiempo de muestreo para *TDM* C_{min}
* Pocos biomarcadores disponibles (Ca próstata, LMC)
* Valoración de la eficacia: SG / SLP a largo plazo

Características PK - OADs

* F elevada variabilidad: 14-34% Dasatinib, 98% Imatinib
* Elevada unión a PP
* Metabolismo hepático: polimorfismos CYP3A4, CYP2D6, CYP2C9, CYP2C19
* Polimorfismos transportadores (axatinib, dasatinib y sorafenib)
* Tratamiento concomitante con inductores/inhibidores enzimáticos
* Tabaco
* Elevada variabilidad II (gefitinib IIV: 19-100%)

Flat-fixed dosing

TDM guided personalized dose


Does the drug have a small therapeutic window or is there a defined target concentration range?
No
Yes
Is there a high interindividual variability (IIV) at standard dosing?
No
Yes
Does the drug have an unpredictable dose-exposure relationship or a nonlinear PK?
No
Yes
Is there absence of an easily measurable biomarker to assess effect?
No
Yes
Is the interoccasion variability (IOV) lower than the IIV?
No
Yes
TDM useful
TDM not useful

Evidence level	Recommendation	Description
1	Strongly recommended	Randomised, prospective studies demonstrated positive effect of routine TDM with regards to efficacy and/or safety.
2	Recommended	There is an established exposure-response relationship using standard dosage from retrospective studies, a target is established **and** a feasibility study has been performed.
3	Potentially useful	An exposure-response or exposure-safety relationship using standard dosage has been identified and a potential target has been reported.
4	Exploratory	An exposure-response or exposure-safety relationship using standard dosage has been identified but no target has been reported.
5	Not recommended	No exposure-response or exposure-safety relationship using standard dosage has been identified **and/or** - there is very few data on pharmacokinetics of the drug; - there are more useful targets than plasma concentration (PD); - there is evidence that TDM is not useful

European Journal of Clinical Pharmacology (2021) 77:441–464
https://doi.org/10.1007/s00228-020-03014-8

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV[a])	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Abiraterone	Recommended	$C_{SS,min}$ ≥ 8.4 [62,63]	35[62]-42[63]	9.3 (70%)[63]	Yes (PFS)[62,63]	No[63]	Yes[99]	• TDM with food intervention has been proven feasible and cost-efficient[40,100]
Axitinib	Recommended	AUC ≥ 300[b][101] $C_{SS,min}$ ≥5[102]	38[101]	AUC: 367[b] (77%)[103]	Yes (PFS, PR, OS)[101,102]	Yes (hypertension, proteinuria, fatigue, diarrhoea)[104]	Yes[101]	• Diastolic blood pressure (dBP) has additionally been related to efficacy[105] • A placebo-controlled randomised dose titration trial was successfully performed[106] • An integrated approach using both PK and dBP might be the most promising option • Exposure-response relationship only evaluated for axitinib monotherapy but not for combination therapy with an immune checkpoint inhibitor
Everolimus	Recommended	$C_{SS,min}$ ≥10 [64]	37[64]	15.65 (90% CI: 14.79-16.55)[64]	Yes (PFS)[64,107]	Yes (pulmonary events, stomatitis)[64,108]	Yes[109]	• 5 mg BID instead of 10 mg QD decreases C_{max} (potentially decreased risk for toxicity)[65] • PK-guided dosing has been proven feasible[110] • TDM-guided everolimus dosing already SoC in transplantation medicine[111]

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV[a])	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Gefitinib	Recommended	$C_{SS,min}$≥ 200 [4]	30[4]	266 (41%)[4]	Yes (OS)[4]	Yes (skin toxicity, diarrhoea, hepato-toxicity)[4,112]	No	• Treatment at increased doses has been proven feasible[113] • Gefitinib has lost most of its relevance in the treatment of EGFR mutated lung cancer
Imatinib	Recommended	CML: $C_{SS,min}$ ≥1000 [45,67,114] GIST: $C_{SS,min}$ ≥ 1100 [46]	73[115]	979 (54%)[45] 926 (52%) [115]	Yes (MMR, CcyR) [45,67,114] Yes (TTP)[46,69]	Yes (neutropenia, rash, diarrhoea, arthralgia, oedema) [67,116,117]	Yes[70]	• Feasibility of TDM has been proven in a cohort study[44] and a RCT[18] • An alternative threshold of 760 ng/mL has been proposed for GIST [69]
Pazopanib	Recommended	$C_{SS,min}$ ≥ 20500 [61,75,76]	16[76]-20[61]	28100 (40%)[76]	Yes (PFS) [61,75,76]	Yes (fatigue, anorexia, hypertension) [77]	Yes[78]	• PK-guided dosing has been proven feasible[48] • 400 mg BID instead of 800 mg QD as cost-neutral strategy to increase exposure[43] • Concomitant intake with food as cost-neutral strategy to increase exposure[42,118]
Sunitinib	Recommended	Inter-mittent dosing: $C_{SS,min}$ ≥ 50[c] [60] Continuous dosing:	49[115]-52[119]	51.6 (39%)[115]	Yes (TTP, OS)[60]	Yes (hypertension, fatigue, anorexia, myelosuppression, HFSR, altered taste, mucositis) [79,80,120,121]	Yes[81]	• PK-guided dosing has been proven feasible[119]

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV[a])	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
		$C_{SS,min} \geq$ 37.5[c][12]						
Tamoxifen	Recommended	$C_{SS} \geq$ 5.97[d] [83]	20[83]	9.72 [d] <1.73-30.8> [d] [122]	Yes (RR)[83]	No[89]	Yes[92]	• TDM-guided dosing has been proven feasible[20] • Genotype-guided dose escalations have been proven safe[87–89]
Trametinib	Recommended	$C_{SS,min} \geq$ 10.6 [50]	27[123]	12.1 <6-34>[124]	Yes (PFS)[50]	No[124]	Yes[50]	• Exposure-response relationship only evaluated for trametinib monotherapy but not for combination therapy with dabrafenib

Alectinib	Potentially useful	$C_{SS,min}$ ≥ 435 [49,125]	33[125]	572 (48%)[126]	Yes (tumour size, PFS)[49,125]	No[127]	Yes[126]	
Crizotinib	Potentially useful	$C_{SS,min}$ ≥ 235 [49,128]	48[49]	244 (45%) [49]	Yes (PFS, ORR) [49,128]	Yes (neutropenia, AST elevation)[129]	Yes[130]	
Erlotinib	Potentially useful	$C_{SS,min}$> 500 [131]	11[115]	1011 (69%)[115]	Yes (preclinical efficacy, PFS, OS)[131,132]	Yes (skin toxicity) [133,134]	Yes[135]	
Substance	**Evidence level for TDM**	**Proposed TDM target [ng/mL]**	**Patients below TDM target at standard dose (%)**	**Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV[a])**	**Exposure-response relationship [yes/no] (associated parameter(s))**	**Exposure-safety relationship [yes/no] (associated parameter(s))**	**NLME model available**	**Comments**
Gilteritinib	Potentially useful	$C_{SS,min}$>100 [136]	0.6[136]	456 (NA) [136]	Yes (CR)[136]	Yes (CK, AST, ALT, ALB)[136]	Yes[136]	
Letrozole	Potentially useful	$C_{SS,min}$> 85.6 [137]	NA	88.4 <0-349.2>[138]	Yes (TTP)[137]	Not reported	Yes[139]	
Nilotinib	Potentially useful	$C_{SS,min}$ ≥469 [140]	25[140]	1123 (64%) (300 mg BID)[141] 1239 (52%) (400 mg BID)[141]	Yes (TTP, trend for MMR) [140,141]	Yes (bilirubin and liver enzyme elevations) [140–142]	Yes[140]	• Feasibility of TDM has been reported in a case study [143] • Dose selection with respect to UGT1A1 genotype could prevent elevation of bilirubin levels[142]
Vemurafenib	Potentially useful	$C_{SS,min}$≥420 00[51–53]	39[144]-52[145]	61000(41%)[144]	Yes (PFS, OS) [51–54]	Yes (QTc prolongation, rash)[53,146]	Yes[147]	• An alternative threshold of $C_{SS,min}$>50 mg/L has been proposed [54]

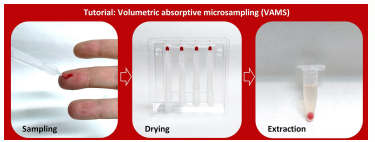
Pocos targets PK definidos (9/>80)

Experiencias en práctica clínica

- Instituto para el cáncer Holanda: DPOG-TDM (35 OADs)
- Australia

Nuevas matrices biológicas: gota sangre seca, VAMS

- Comodidad y fácil obtener
- Identificar factores de corrección respecto [Cp]



Therapeutic Drug Monitoring of Oral Anticancer Drugs: The Dutch Pharmacology Oncology Group–Therapeutic Drug Monitoring Protocol for a Prospective Study

Stefanie L. Groenland, MD, Ruben A. G. van Eerden, BSc,† Remy B. Verheijen, PharmD, PhD,‡ Stijn L. W. Koolen, PharmD, PhD,†§ Dirk Jan A. R. Moes, PharmD, PhD,¶ Ingrid M. E. Desar, MD, PhD,‖ Anna K. L. Reyners, MD, PhD,** Hans J. Gelderblom, MD, PhD,†† Nielka P. van Erp, PharmD, PhD,‡‡ Ron H. J. Mathijssen, MD, PhD,† Alwin D. R. Huitema, PharmD, PhD,‡§§ and Neeltje Steeghs, MD, PhD,* on behalf of the Dutch Pharmacology Oncology Group (DPOG)*

Ther Drug Monit • Volume 41, Number 5, October 2019

www.trialregister.nl;NL6695

TABLE 2. Historical Data of the Percentage of Patients Below TDM Target per Oral Anticancer Drug

Drug	Patients Below TDM Target at Standard Dose (%)	Reference
Abiraterone	35	25
Alectinib	33	26
Axitinib	38	27
Bosutinib	50	28
Cobimetinib	50	29
Crizotinib	25	30
Dasatinib	50	31
Enzalutamide	2	32
Erlotinib	11	3
Everolimus	37	33
Gefitinib	26	34
Imatinib	73	3
Nilotinib	25	35
Olaparib	50	36
Palbociclib	50	37
Pazopanib	16–20	38,39
Regorafenib	50	40
Sorafenib	50	41
Sunitinib	49	3
Tamoxifen	20	42
Trametinib*	27	43
Vemurafenib	52	44
Vismodegib	50	45

*Data reported only for trametinib, as for dabrafenib, no dose adjustments will be recommended because little evidence for an exposure–response relationship for dabrafenib is available.

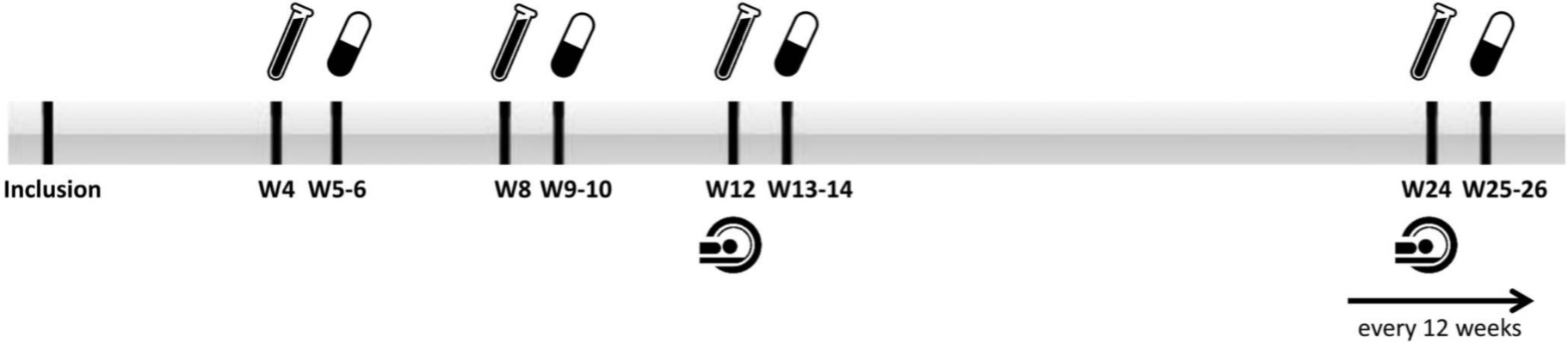
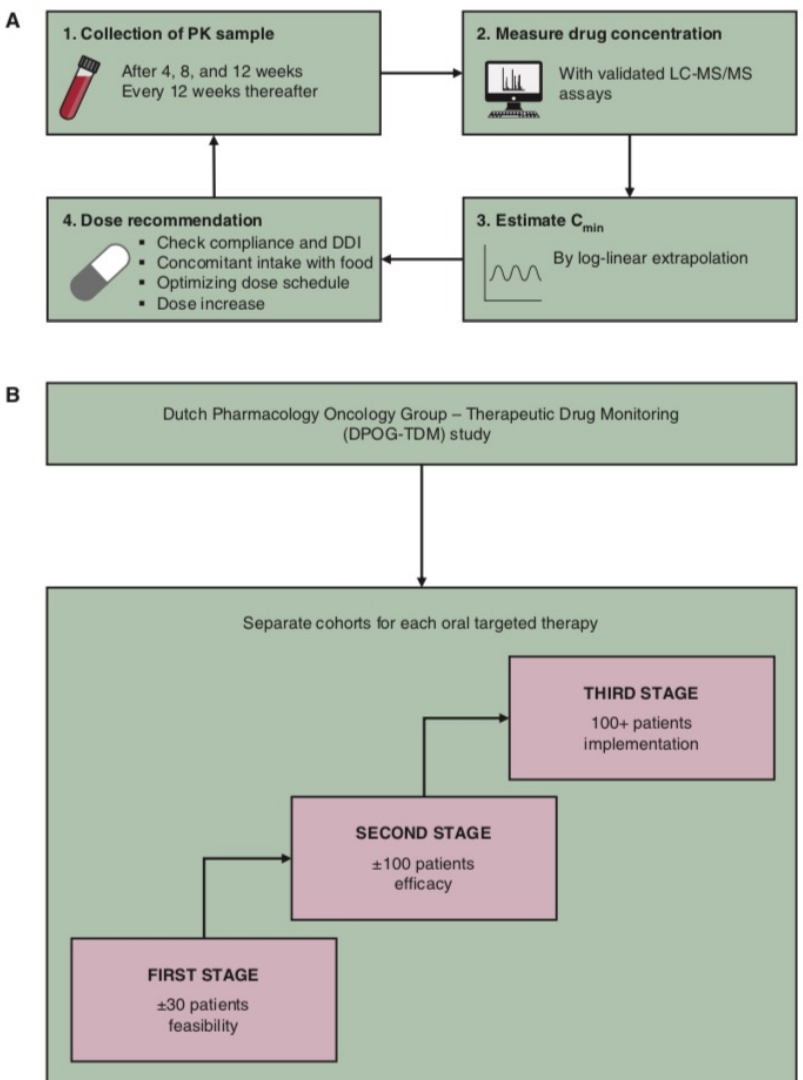


FIGURE 1. Study schedule. PK, pharmacokinetic; W, week.

Therapeutic drug monitoring-based precision dosing of oral targeted therapies in oncology: a prospective multicenter study☆

S. L. Groenland[1*†], R. A. G. van Eerden[2†], K. Westerdijk[3], M. Meertens[4], S. L. W. Koolen[2,5], D. J. A. R. Moes[6], N. de Vries[4], H. Rosing[4], H. Otten[7], A. J. E. Vulink[8], I. M. E. Desar[3], A. L. T. Imholz[9], H. Gelderblom[10], N. P. van Erp[11], J. H. Beijnen[4,12], R. H. J. Mathijssen[2], A. D. R. Huitema[4,13,14] & N. Steeghs[1*], on behalf of the Dutch Pharmacology Oncology Group (DPOG)

doi.org/10.1016/j.annonc.2022.06.010


A
1. Collection of PK sample
After 4, 8, and 12 weeks
Every 12 weeks thereafter
2. Measure drug concentration
With validated LC-MS/MS assays
3. Estimate C_{min}
By log-linear extrapolation
4. Dose recommendation
Check compliance and DDI
Concomitant intake with food
Optimizing dose schedule
Dose increase
B
Dutch Pharmacology Oncology Group – Therapeutic Drug Monitoring (DPOG-TDM) study
Separate cohorts for each oral targeted therapy
THIRD STAGE
100+ patients
implementation
SECOND STAGE
±100 patients
efficacy
FIRST STAGE
±30 patients
feasibility

Objetivo 1º: ↓50% los pacientes con subexposición comparado con los datos históricos tras 3ª *TDM*

Table 2. Percentage of patients below the TDM target and C_{min} levels at the first three pharmacokinetic measurements

Oral targeted therapy	Number of enrolled patients	Number of assessable patients	C_{min} PK #1 (ng/ml)	PK #1 below target	C_{min} PK #2 (ng/ml)	PK #2 below target	C_{min} PK #3 (ng/ml)	PK #3 below target	Historical comparison[a]	*P* value[b]
Abiraterone	105	79	21.9 (95.9%)	15 (19.0%)	26.1 (88.9%)	11 (13.9%)	24.5 (91.4%)	12 (15.2%)	38.5%[33,34]	< 0.001
Alectinib	18	14	647.4 (24.3%)	2 (14.3%)	579.6 (33.6%)	3 (21.4%)	524.9 (33.5%)	4 (28.6%)	35.1%[35,36]	—
Axitinib	2	2	5.2 (100%)	1 (50.0%)	5.4 (61.1%)	1 (50.0%)	6.0 (95%)	1 (50.0%)	38%[37]	—
Cabozantinib	7	6	1,050 (39.3%)	1 (16.7%)	947.5 (43.2%)	2 (33.3%)	631.3 (38.7%)	4 (66.7%)	50%[38]	—
Crizotinib	2	1	458 (NA)	0	554 (NA)	0	516 (NA)	0	32.4%[36,39]	—
Dabrafenib/ trametinib[c]	68	44	16.4 (34.1%)	6 (13.6%)	16.0 (35.6%)	8 (18.2%)	17.2 (40.1%)	4 (9.1%)	27%[40]	—
Enzalutamide	43	37	11 100 (24.3%)	1 (2.7%)	11 100 (23.4%)	1 (2.7%)	10,800 (28.7%)	2 (5.4%)	1.6%[24,41]	—
Erlotinib	3	2	1863 (26.1%)	0	1975 (7.6%)	0	2024 (32.0%)	0	11%[42]	—
Everolimus	9	4	10.2 (37.3%)	2 (50.0%)	10.1 (81.2%)	2 (50.0%)	10.3 (84.5%)	3 (75.0%)	37%[43]	—
Imatinib	104	91	1290 (52.2%)	38 (41.8%)	1309 (53.8%)	45 (49.5%)	1256 (37.1%)	36 (39.6%)	70.4%[10,30,42]	< 0.001
Lapatinib[d]	1	0	—	—	—	—	—	—	50%[44]	—
Olaparib	21	20	2173 (96.1%)	11 (55.0%)	1869 (78.6%)	7 (35.0%)	1777 (62.8%)	8 (40.0%)	50%[45]	—
Palbociclib	22	15	58.7 (29.6%)	7 (46.7%)	50.2 (36.3%)	10 (66.7%)	65.6 (46.3%)	5 (33.3%)	50%[46]	—
Pazopanib	49	36	31 700 (57.4%)	9 (25.0%)	2800 (44.6%)	9 (25.0%)	29 700 (38.7%)	6 (16.7%)	26.7%[12,47-49]	—
Regorafenib	16	2	701.5 (43.0%)	2 (100%)	989.0 (87.4)	1 (50.0%)	1355 (62.6)	1 (50.0%)	50%[50]	—
Sorafenib[e]	39	17	3911 (55.7%)	11 (64.7%)	4284 (70.4%)	8 (47.1%)	3610 (78.9%)	12 (70.6%)	50%[51]	—
Sunitinib[f]	50	35	74.0 (37.8%)	5 (14.3%)	75.4 (40.8%)	4 (11.4%)	66.0 (44.4%)	5 (14.3%)	44.3%[10,42,52]	< 0.001
Tamoxifen[g]	24	14	10.1 (52.5%)	4 (28.6%)	11.4 (38.6%)	1 (7.1%)	10.6 (38.7%)	1 (7.1%)	21.9%[53-55]	—
Vemurafenib/ cobimetinib	12	6/5	47 700 (41.3%)/ 188.1 (24.6%)	2 (33.0%)/1 (20.0%)	41 900 (48.0%)/ 167.5 (84.1%)	3 (50.0%)/ 3 (60.0%)	48 900 (36.5%)/ 106.8 (63.5%)	4 (67.0%)/ 4 (80.0%)	52%[56]/50%[57]	—
Vismodegib	5	1	12 900 (NA)	0	10 500 (NA)	1 (100%)	12 000 (NA)	0	50%[58]	
All patients	600	426	—	118 (27.7%)	—	119 (27.9%)	—	110 (25.8%)	42.2%	< 0.001

↓39%

$C_{min} < C_{target}$

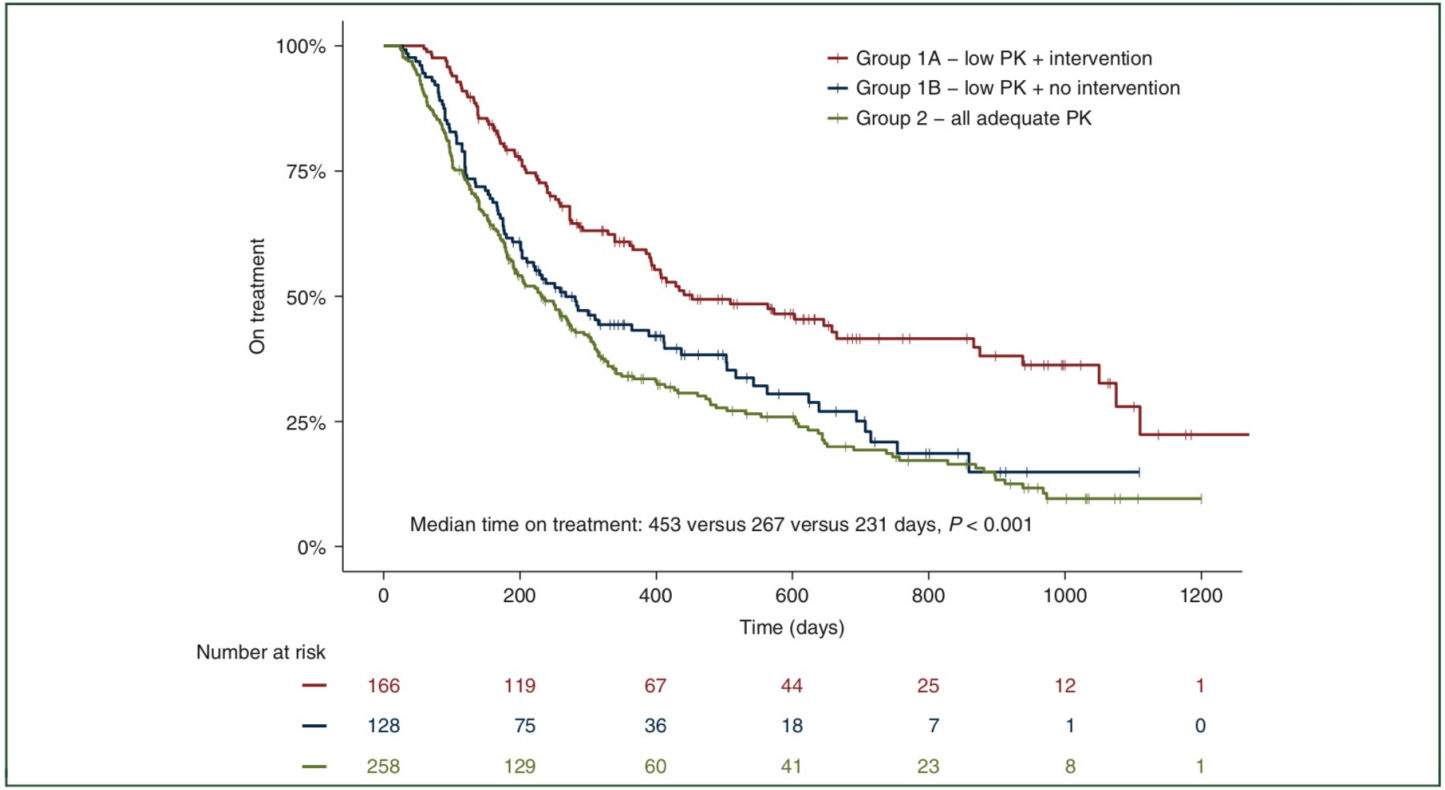


Figure 5. Kaplan–Meier curve of time on treatment.
Group 1A are patients with one or more PK samples below the target who received a pharmacokinetically guided intervention. Group 1B are patients with one or more PK samples below the target who did not receive a pharmacokinetically guided intervention due to various reasons (i.e. toxicity, physician adherence, treatment discontinuation). Group 2 are patients with all PK samples above the target.
PK, pharmacokinetic.

TDM: efecto HAWTHORNE

$C_{min} < C_{target}$:

27.7% estudio (1ª *TDM*)

vs

42.2% datos históricos

Evaluation of Extrapolation Methods to Predict Trough Concentrations to Guide Therapeutic Drug Monitoring of Oral Anticancer Drugs

Julie M. Janssen, PhD, Thomas P.C. Dorlo, PhD,* Jos H. Beijnen, PhD,*†*
and Alwin D.R. Huitema, PhD‡*

(*Ther Drug Monit* 2020;42:532–539)

TABLE 1. Summary of the Identified Population PK Models and Parameter Estimates Used in the Simulations for the Evaluation of the Four Extrapolation Methods

	Base Model Structure	Parameter Estimates	Interindividual Variability (CV%)	Covariate Relationships*	References
Abiraterone	Two-compartment, transit compartments, and sequential zero-order and first-order absorption	K_a = 1.91 h^{-1} D1 = 0.267 h F = 1.24† V_c = 5620 L Q = 1360 L/h V_p = 17,400 L CL = 1550 L/h	K_a = 58.0% D1 = 144% F = 61.1% CL = 28.2%	mCRPC/healthy subjects and food effect	15
Dabrafenib	Two-compartment, first-order absorption, lag time, and dose-dependent clearance	K_a = 1.8 h^{-1} T_{lag} = 0.482 h V_c/F = 69.1 L Q/F = 3.44 L/h V_p/F = 149 L CL/F = 98.8 L/h	K_a = 160% V_c/F = 54.1% Q/F = 102% CL/F = 60.8%	Weight, sex, drug formulation, and last administered dose	16
Imatinib	One-compartment, zero-order absorption, and linear elimination	D1 = 1.7 h V_c/F = 284 L CL/F = 10.2 L/h	V_c/F = 35.8% CL/F = 34.6%	Albumin and WBC	17
Pazopanib	Two-compartment, fast and slow first-order absorption, and dose-dependent bioavailability	$K_{a,fast}$ = 0.40 h^{-1} $K_{a,slow}$ = 0.12 h^{-1} $T_{lag,\ slow}$ = 0.98 h V_c = 2.43 L Q = 0.99 L/h V_p/F = 25.1 L CL/F = 0.27 L/h	K_a = 140% F = 35.6% V_p/F = 98.2% CL/F = 30.9%	Dose	18

Métodos para estimar C_{min}

- Método 1: Estimación bayesiana
- Método 2: ratio de concentraciones

$$C_{min,\ pred} = C_t / C_{t,sim} \times C_{min,sim}$$

- Método 3: extrapolación log-lineal

$$C_{min,\ pred} = C_{t,\ sim} \times 0.5^{\left(\frac{\tau - TAD}{t_{1/2}}\right)}$$

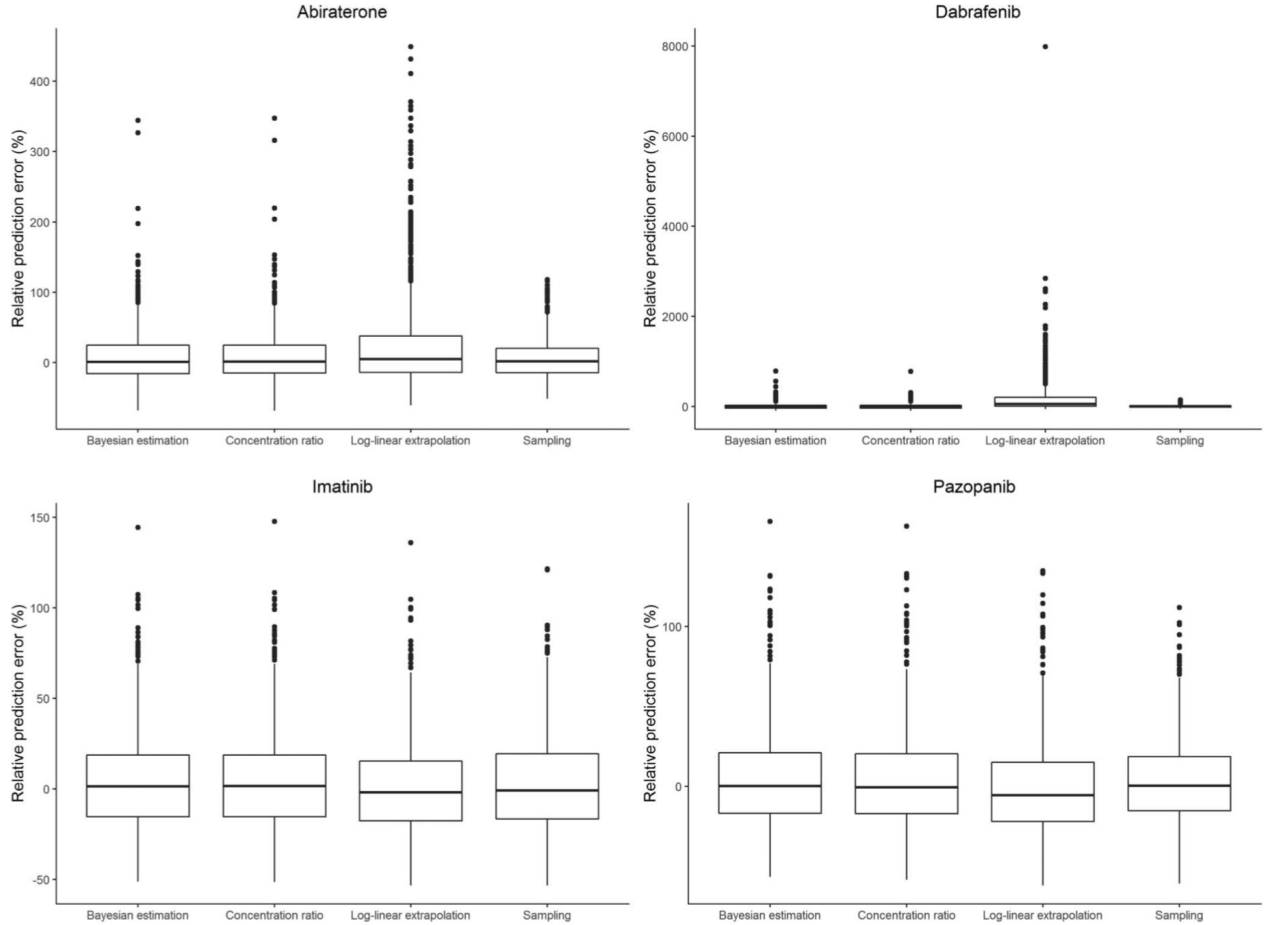


FIGURE 1. RPE of $C_{min,pred}$ of the 3 extrapolation methods for abiraterone, dabrafenib, imatinib, and pazopanib for samples collected after T_{max} compared with that for samples collected at the end of the dosing interval (scenario A).

Present and Future of Therapeutic Drug Monitoring in New Fields

Review

Dose Individualization of Oral Multi-Kinase Inhibitors for the Implementation of Therapeutic Drug Monitoring

Satoshi Noda,*[a] Shin-va Morita,[a] and Tomohiro Terada[a,b]

Biol. Pharm. Bull. **45**, 814–823 (2022)

☆ Sunitinib

Pazopanib

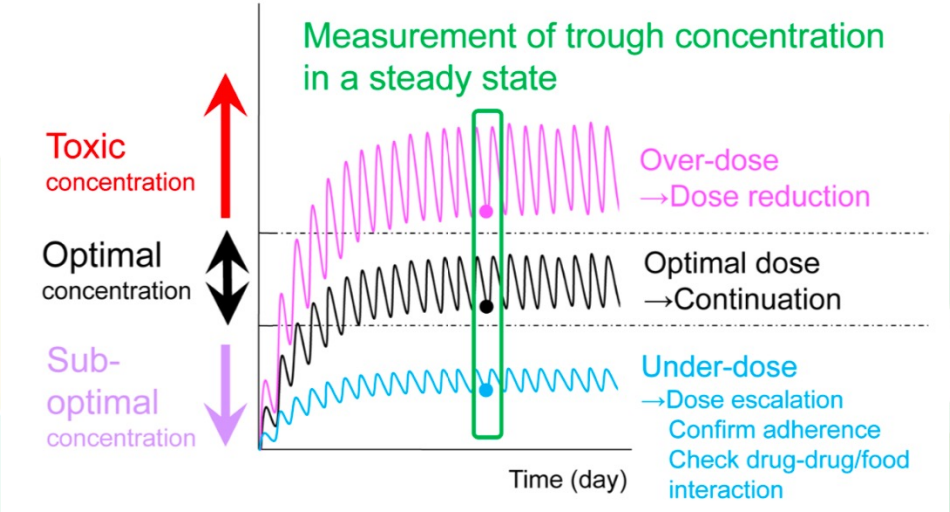
Sorafenib

Lenvatinib

Table 1. Current Doses, and Target Concentration of Sunitinib, Pazopanib, Sorafenib, and Lenvatinib

Drug	Approved starting dose (Indications)	PK-related PD markers		Proposed target trough concentration
		PK-related efficacy	PK-related toxicity	
Sunitinib	50 mg (RCC, GIST)	Tumor shrinkage[18] TTF,[29] PFS[29]	Neutropenia,[18] Thrombocytopenia,[29] Anorexia,[29] Fatigue[29]	50–100 ng/mL (RCC)[10,29–32,38]
Pazopanib	800 mg (RCC, STS)	Tumor shrinkage,[51] PFS[51,52,56]	Anorexia,[54] Fatigue,[54] Hypertension[53,54]	20–50 μg/mL (RCC, STS)[51,52,54,56]
Sorafenib	800 mg (HCC, DTC)	Tumor shrinkage[72] PFS[75]	Hand-foot syndrome,[72,74] Fatigue,[72] Diarrhea,[72] Rash[72]	1.40–3.45 μg/mL (HCC)[72]
Lenvatinib	24 mg (DTC) 12 mg for body weight ≥60 kg or 8 mg for body weight <60 kg (HCC)	Tumor shrinkage[86,87]	Adverse events of any cause of grade ≥3*.[86]	42–88 ng/mL (DTC)[88] 40–70 ng/mL (HCC)[82,86,87]

PK, pharmacokinetics; PD, pharmacodynamics; RCC, renal cell carcinoma; GIST, gastrointestinal stromal tumor; TTF, treatment to failure; PFS, progression-free survival; STS, soft tissue sarcoma; HCC, hepatocellular carcinoma; DTC, differentiated thyroid cancer. * grade ≥3 anorexia, grade ≥3 fatigue, grade ≥3 hypertension, grade ≥3 edema, grade ≥3 hand-foot syndrome, grade ≥3 stomatitis, and grade ≥3 proteinuria.



68 CONGRESO NACIONAL SEFH BILBAO 5-7 de OCT 2023

On precision dosing of oral small molecule drugs in oncology

Alex K. Lyashchenko[1], **Serge Cremers**[1,2]

[1]Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY, USA

[2]Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA.

Br J Clin Pharmacol. 2021 February ; 87(2): 263–270. doi:10.1111/bcp.14454.

Stage 1:
Assess variability in drug exposure (e.g. C_{min})

↓

Stage 2:
Correlate drug exposure with drug efficacy and toxicity

↓

Stage 3:
Test feasibility of TDM:
Primary outcome = prevalence of therapeutic exposure

↓

Stage 4:
RCT of TDM vs no TDM:
Primary outcome = overall survival, PFS, etc.

On precision dosing of oral small molecule drugs in oncology

Alex K. Lyashchenko[1], **Serge Cremers**[1,2]

[1]Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY, USA

[2]Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA.

Br J Clin Pharmacol. 2021 February ; 87(2): 263–270. doi:10.1111/bcp.14454.

Stage 4:
RCT of TDM vs no TDM:
Primary outcome = overall survival, PFS, etc.

- Dificultad obtención datos preliminares para ayudas
- Alta heterogeneidad tasas crecimiento tumoral previas y en niveles biomarcadores: ↑↑ n
- Estudios larga duración : relaciones temporales exposición-eficacia/toxicidad
- Seleccionar pacientes con falta eficacia o toxicidad
- OPTIM (Rousselot *et al.* Imatinib: *TDM* aumenta tasas de respuesta molecular LMC, doi:10.3390/pharmaceutics14081676)

MODALIDAD DE FOMENTO DE ACCIONES PREPARATORIAS (AP)
PARA LA EXPLORACIÓN Y FORMULACIÓN DE FUTUROS PROYECTOS DE INVESTIGACIÓN /INNOVACIÓN 2022

MEMORIA CIENTÍFICO-TÉCNICA AP

TÍTULO DE LA ACCIÓN PREPARATORIA: Antineoplásicos orales a dosis fijas: variabilidad en oncología clínica asistencial.

ACRÓNIMO: AOVAR

SUBPROGRAMA: UJISABIO - Programa de colaboración UJI-FISABIO

Investigador/a Principal UNIVERSIDAD	**Investigador/a Principal HOSPITAL**
Nombre: María Ibáñez Martínez Centro: Universitat Jaume I Grupo/Estructura de Investigación: Química Analítica en Salud Pública y Medio Ambiente	Nombre: Mª Dolores Bellés Medall DS/Centro: Hospital General Universitario Castellón Grupo/Servicio: Farmacia Clínica, terapias innovadoras y tecnología del medicamento/ Servicio Farmacia Hospitalaria Hospital General Universitario Castellón.

MODALIDAD DE APOYO PARA EL DESARROLLO DE PROYECTOS DE INNOVACIÓN (PI) 2023

MEMORIA CIENTÍFICO-TÉCNICA PI

TÍTULO DEL PROYECTO DE INNOVACIÓN: AGENTES DIRIGIDOS AL RECEPTOR DE ANDRÓGENOS (ARTA) ORALES A DOSIS FIJAS: VARIABILIDAD EN ONCOLOGÍA CLÍNICA ASISTENCIAL

ACRÓNIMO: ARTA-VAR

SUBPROGRAMA: UJISABIO - Programa de colaboración UJI-FISABIO

Investigador/a Principal UNIVERSIDAD	**Investigador/a Principal HOSPITAL**
Nombre: María Ibáñez Martínez Departamento/Centro/Instituto: Química Analítica en Salud Pública y Medio Ambiente/ Universitat Jaume I	Nombre: Mª Dolores Bellés Medall DS/centro: Farmacia Clínica, terapias innovadoras y tecnología del medicamento/ Servicio Farmacia Hospitalaria Hospital General Universitario Castellón

Proyecto ARTA-VAR

Objetivo principal:

- Identificar si la implementación de la monitorización farmacocinética de ARTA, en nuestra población, contribuye a mejorar la seguridad y eficacia de estos fármacos

Objetivos secundarios:

- Relacionar las concentraciones plasmáticas del fármaco y su metabolito con variables clínicas (tiempo libre de progresión), variables bioquímicas (antígeno prostático específico-PSA), variables farmacológicas (ingesta con o sin alimentos, tratamiento concomitante con inductores y/o inhibidores enzimáticos) y variables fisiopatológicas (edad, peso, función hepática y función renal).

sefh
Sociedad Española de Farmacia Hospitalaria

I ♥ TDM

68 CONGRESO NACIONAL SEFH
BILBAO
5-7 de OCT
2023