A methodology for determining dosing recommendations for anticancer drugs in patients with reduced kidney function

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Summary

Reduced kidney function (or kidney dysfunction) is commonly an exclusion criterion for randomised controlled trials (RCTs) in cancer. Consequently, high quality evidence for anticancer drug dosing in reduced kidney function is limited and no internationally agreed guidelines exist to inform prescribing decisions in this population. A methodology for guideline development was applied which did not require availability of RCTs but used critical appraisal of existing observational literature and group consensus. An international multidisciplinary working group (n = 38) established consensus recommendations in two parts to form the International Consensus Guideline on Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD). The approach enabled virtual participation worldwide. In Part 1 we developed a standardised approach for assessment and classification of kidney function in patients with cancer using global nephrology standards and working group expertise. Part 2 involved a comprehensive literature search of 59 anticancer drugs followed by a critical appraisal of the evidence certainty through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process and development of dosing recommendations in reduced kidney function. Key external stakeholders (n = 9) invited expert contributors (n = 25), and the working group participated in virtual interactive workshops to vote on the acceptability of these recommendations. The participants were provided with evaluation of the literature, and they engaged in several rounds of virtual discussion (involving robustness of the evidence behind recommendations and their real-world application) and anonymous consensus voting. Adapting the ADDIKD guideline development process to a virtual format enabled engagement with a very broad base of specialised international experts especially during the global pandemic. Combining GRADE meth-

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odology with consensus-building approaches was an effective method of producing recommendations (in an area lacking RCTs) by merging critical review of the literature with expert opinion and clinical practice.

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Keywords: Chemotherapy; Drug dosing; Kidney dysfunction; Renal; Oncology; Haematology; Pharmacokinetics

Research in context

Evidence before this study

The evidence base for dose adjustments of anticancer medications in reduced kidney function is limited, often relying on empirical dose modifications based on clinical experience.

Added value of this study

The development of the International Consensus Guideline on Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) used a combination of online consensus-building techniques and gold-standard evidence evaluation. This approach facilitated agreement in areas lacking high-level evidence by focusing on two main aspects: standardizing kidney function assessment and providing dosing recommendations. The process clarified how consensus was reached and incorporated a wide range of opinions, leading to international standardization in the complex field of anticancer drug dosing for patients with reduced kidney function.

Implications of all the available evidence

The novel, multistep process used to develop ADDIKD provides a template for developing guidelines in settings where there is limited high-level evidence.

Introduction

Reduced kidney function (or kidney dysfunction) is common in patients with cancer.[1–13] The kidneys are the predominant elimination pathway for many anticancer drugs, and nephrotoxic anticancer drugs are integral to many treatment regimens. Recent decades have seen a rapid introduction of new medications. Unfortunately, the evidence base for dose adjustments in reduced kidney function is very limited. Firstly, most clinical trials base their drug dose adjustments on outdated or theoretical data.[14] Secondly, these trials often exclude patients with reduced kidney function from participation.[14] Therefore, in present day practice, dose-adjustment of anticancer drugs continues to rely on clinical experience, at times drawing on data from case reports or small cohort studies.[14] Further limitations is that dosing recommendations[15–18] are based on kidney function estimations (i.e., Cockcroft–Gault equation) developed from creatinine prior to the global standardisation of the creatinine assay,[19–21] and lack consistency with the globally accepted kidney function classifications by Kidney Disease Improving Global Outcomes (KDIGO).[22,23]

Grading of Recommendations, Development and Evaluation (GRADE),[24] is the method of assessment of the certainty of evidence and recommendation development preferred by the Cochrane Collaboration,[25] National Institute for Health and Care Excellence,[26] National Health and Medical Research Council Guidelines for Guidelines Handbook,[27] and World Health Organisation's Handbook for Guideline Development.[28] However, guideline developers have experienced problems with GRADE especially when evaluating non-randomised controlled trials (RCTs) that result in 'low' levels of evidence certainty, and where the interventions are complex.[29–33]

For these reasons, previous attempts at providing guidance in anticancer drug dosing in reduced kidney function have eschewed approaches like GRADE, relying on pharmacokinetic studies (without linkage to pharmacodynamic outcomes) or small case studies.[17,34] These approaches have not taken into account real-life clinical experience, creating the challenge of filling the gaps in published evidence with expert opinion instead. Hybridisation of various consensus building techniques (such as Delphi method,[35,36] RAND/UCLA Appropriateness Methodology (RAM),[37] Nominal Group Technique[38,39]) using real-life experience and robust review of RCTs have successfully been used to build clinical guidelines,[40–42] in other topics within medicine, and may be applicable to our current challenge.[40–42]

Cancer Institute NSW's web-based government program, eviQ (www.eviq.org), being the leading provider of point of care information for cancer health professionals in Australia and widely used internationally (202 countries),[43] was ideally placed to initiate the development of and host the finalised International Consensus Guideline on Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).[44] Here we describe a novel hybrid methodology to combine evidence and

consensus-based recommendations provided within ADDIKD.

Guideline development process

A flow chart of the process for development of ADDIKD is presented in Fig. 1.

Participants

Content development working group

An expert international multidisciplinary working group was established from Australia, New Zealand, Europe, and North America and included oncologists (n = 9), haematologists (n = 3), nephrologists (n = 4), clinical pharmacologists (n = 4), cancer pharmacists (n = 12), renal pharmacists (n = 3) and a nephrology guideline development expert (n = 1) through recognised expertise in their area of practice and interest in the topic. These individuals were invited to participate, ensuring a heterogenous mix of countries, clinical specialities and regional/metropolitan location of practice was represented. Members provided independent, expert review of ADDIKD recommendations as they were developed and participated in various iterations of consensus building (including voting). A Chair and Deputy Chair were appointed from the working group to provide additional strategic leadership. A consumer representative was invited to participate in reviewing of guideline content, ensuring ADDIKD recommendations adequately considered the patient's perspective (See Supplementary Material 1 for full list of ADDIKD participants).

Methodology development working group

Two expert guideline development methodologists independently appraised the guideline development methodology and assisted the *Guideline Development Team* in understanding how to implement the methodology processes.

Invited expert contributors

Key clinicians with expert knowledge (nephrology, n = 4; clinical pharmacology, n = 1; haematology, n = 9; oncology, n = 4; cancer pharmacy, n = 3; kidney health pharmacy, n = 1; clinical pathology, n = 1) were invited to provide additional guidance and participate in consensus building during specific recommendation development workshops because of their expertise and/research in certain areas of clinical practice and/or particular anticancer drugs. These individuals were not involved in initial evidence judgement or the final rounds of working group consensus voting.

Key external stakeholders

Representatives from professional groups of cancer care (e.g., Clinical Oncology Society of Australia, Haematology Society of Australia, Medical Oncology Group of Australia, International Society of Oncology Pharmacy Practitioners), nephrology (e.g., KDIGO, Renal Cochrane Group, Kidney Health Australia, Australian and New Zealand Society of Nephrology), clinical pharmacology and pharmacy (Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, Advanced Pharmacy Australia), geriatric medicine (e.g., International Society of Geriatric Oncology), academia (e.g., Therapeutic Guidelines), government (e.g., Therapeutic Goods Administration), and the pharmaceutical industry were invited to participate in a national consensus workshop (see Supplementary Material 1 for full participant representation from external stakeholder groups).

Guideline development team

Four eviQ pharmacists coordinated and undertook the various components of the guideline development and drafted and edited the guideline content. An independent third-party moderator was utilised to host the workshops and panel discussions.

All participants declared any potential conflict of interests.

Part 1—assessment and classification of kidney function in patients with cancer and its application to drug dosing

Panel discussion—development of preliminary recommendations

Based on KDIGO recommendations[22] and critical appraisal of the literature, 26 panel discussion participants (selected members of *Content Development Working Group*, along with *Invited Expert Contributors* in nephrology, pharmacometrics, clinical pharmacology, and clinical pathology), discussed proposed recommendations for:

1. A standardised approach to assessing kidney function in patients with cancer
2. The application of this standardised approach to anticancer drug dosing
3. Using KDIGO's Chronic Kidney Disease categories[22,23] to guide anticancer drug dosing and monitoring in reduced kidney function

Real-time electronic voting during the 90-min online panel discussion (in November 2020) highlighted the need for further refinement or elaboration of recommendations by the *Guideline Development Team*. Using Nominal Group Technique for consensus building,[38,39] the panel discussion identified that although participants agreed standardisation was important, cancer clinicians and pharmacists were generally unfamiliar with the application of assessing and classifying kidney function using estimated glomerular filtration rate (eGFR), unlike their nephrology counterparts.

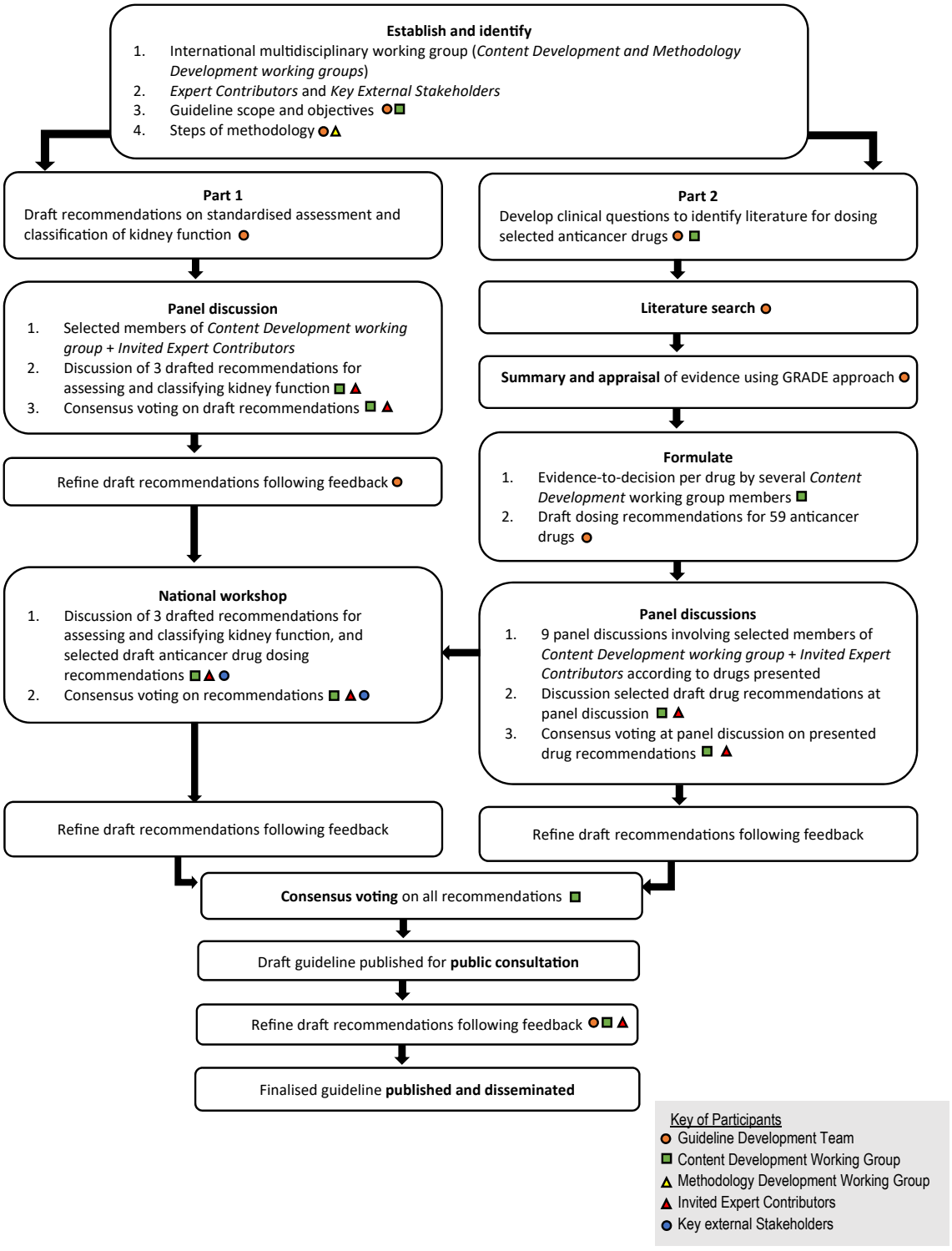

Fig. 1: Summary of ADDIKD guideline development.

National workshop

Following the initial revision of the key recommendations, a virtual workshop was conducted over several hours, inviting *Key External Stakeholders*, *Invited Expert Contributors*, and the *Content Development Working Group* with the objective of attaining wider agreement on these refined recommendations on kidney function assessment and classification by using principles of the Nominal Group Technique.[38,39] The initial plan for a face-to-face workshop was adapted to an online format to accommodate the emergence of COVID-19 pandemic restrictions in December 2020.

Highlighted in the preliminary panel discussion, cancer clinicians and pharmacists were less experienced with using the automatically reported eGFR derived from Chronic Kidney Disease—Epidemiology Collaboration equation ($eGFR_{CKD\text{-}EPI}$),[45] and therefore more reluctant to accept this as the standardised approach to guide drug dosing. To improve the understanding around using $eGFR_{CKD\text{-}EPI}$ to assess and classify kidney function, the consensus workshop, hosted by an experienced external facilitator, was designed to guide participants through the three key recommendations. The workshop engaged selected experts from nephrology, clinical pharmacology, and cancer medicine to provide interactive education at strategic points. Participants were encouraged to discuss their apprehension and obstacles in adopting the recommendations, which allowed the nephrology and clinical pharmacology experts to educate and respond to questions about $eGFR_{CKD\text{-}EPI}$. Based on Delphi consensus technique,[35,36] anonymous real-time voting on the acceptance of the key recommendations was conducted pre- and post-education. Post-education voting resulted in >95% consensus, demonstrating the success of peer-led academic detailing within the workshop.

Participant feedback allowed further refinement of key recommendations incorporating principles of the RAM approach.[37] The acceptance of the key recommendations underpinned the foundational blocks of ADDIKD and the concurrent progression of Part 2.

Part 2—anticancer drug dosing in reduced kidney function

Defining the clinical questions

The key clinical questions and the drugs to be addressed in Part 2 were prioritised by the *Content Development Working Group* and the *Guideline Development Team*. Three questions were formulated according to the PI/ECO (Patient/Problem, Intervention/Exposure, Comparison or Control, Outcome) approach[46] to aid in the development of specific recommendations:

1. Should elimination by the kidney versus no elimination by the kidney be used to direct dosing of this anticancer drug? This question was answered in the affirmative for drugs with >30% elimination by the kidney, or where the drug had nephrotoxic potential and/or altered pharmacokinetics/pharmacodynamics in reduced kidney function.
2. Should the KDIGO Chronic Kidney Disease categories be used in the dose adjustment of this anticancer drug in reduced kidney function?
3. Should full dose versus reduced dose of this anticancer drug be used in patients with reduced kidney function?

See Supplementary Material 2 for details on each PI/ECO question.

Identifying evidence

The key clinical questions provided the strategy for a comprehensive literature search using PubMed, Cochrane Library and EMBASE databases, along with a grey literature search and investigation of registered drug product information (Australian, North American, and European) for 59 anticancer drugs (Supplementary Material 3 [literature search strategy]). The searches were limited to studies in humans, with laboratory and animal studies excluded. Identified records were screened for eligibility and assessed against the defined clinical questions by two independent reviewers within the *Guideline Development Team* (Fig. 2).

Judgement about the certainty of the evidence

The GRADE approach was used to critically appraise the certainty and strength of evidence from the identified literature.[24] Evidence profiles for each anticancer drug per clinical question were constructed assessing the certainty of evidence of the included studies (Supplementary Material 4) using the GRADEpro Guideline Development Tool.[24,47] Where the first clinical question was answered in the negative (i.e., not > 30% of the drug is eliminated by the kidney, no nephrotoxic potential and/or altered pharmacokinetics/pharmacodynamics in reduced kidney function), the remaining clinical questions did not require evidence profiles. Thirty-three anticancer drugs required assessment against all three clinical questions, whilst 26 did not proceed beyond the first clinical question.

A final review of 1616 published articles and 177 registered product information monographs enabled 125 GRADE evidence profiles to be developed by the *Guideline Development Team*, addressing the clinical questions for the 59 anticancer drugs. These profiles were independently reviewed by two members of the *Guideline Development Team*.

Formulation of recommendations

Evidence-to-decision framework. At least two members of the *Content Development Working Group* (including at least one with clinical experience with the specific anticancer drug) independently reviewed evidence profiles and summary of findings tables relevant to the

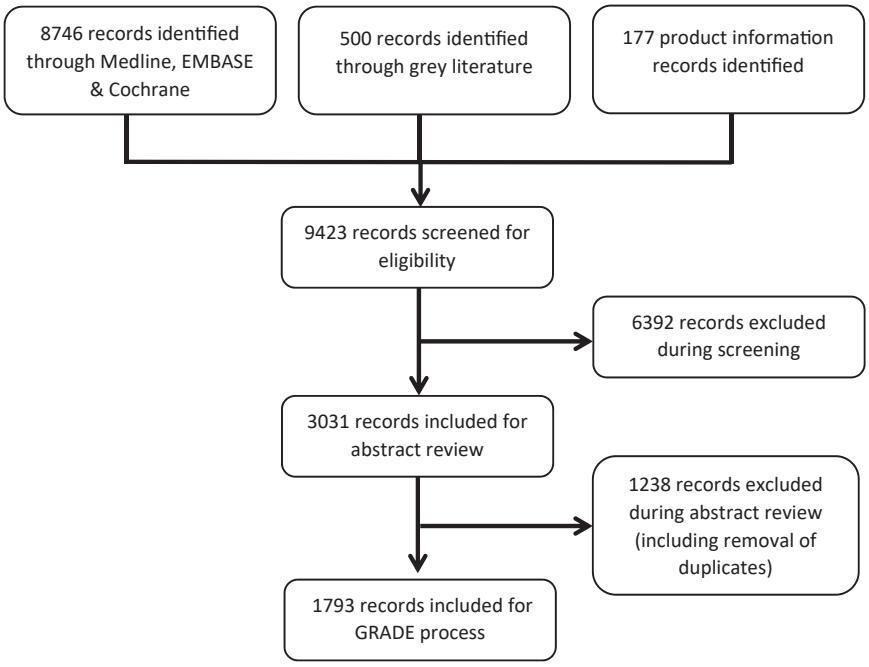

Fig. 2: PRISMA diagram of studies included from the literature search.

clinical questions for each anticancer drug before providing their guidance on the formation of draft recommendations according to the evidence-to-decision framework in the GRADEpro Guideline Development Tool (Supplementary Material 5).[24,47]

As this subject area contained many small observational studies (lower certainty of the evidence) rather than RCTs (higher certainty of the evidence), the GRADE approach categorised the certainty of evidence to be low in most circumstances (Table 1). The certainty of the evidence for observational studies may be rated up to moderate to high if there is a large effect, dose–response relationship evident, or all plausible confounding have been adjusted for.[48] When no studies existed, this was reflected in the certainty of the evidence for the recommendation.

Certainty	Definition
High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.
Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.
Low	This research provides some indication of the likely effect, however, the likelihood that it will be substantially different (a large enough difference that it might have an effect on a decision) is high.
Very low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different (a large enough difference that it might have an effect on a decision) is very high.

Table 1: **Levels of evidence certainty.**[23]

Results from the evidence-to-decision framework guided the *Guideline Development Team* in the drafting recommendations based on the clinical question analysed for individual anticancer drugs. A total of 125 individual recommendations were drafted—59 addressing Clinical Question 1 (supporting the development of Recommendation 1 for each drug), and the remaining 66 for Clinical Questions 2 and 3 (supporting the development of Recommendations 2 and 3 for 33 drugs).

Panel discussions. Between December 2020–July 2021 individual anticancer drugs were presented across nine, online, 90 min facilitated panel discussions (involving selected members from the *Content Development Working Group* and *Invited Expert Contributors*), where draft recommendations were reviewed, discussed, and refined for clinical practicality based on the Nominal Group Technique.[38,39]

Panellists were provided with GRADE profiles, initial evidence-to-decision outcomes, and draft recommendations prior to panel discussions to familiarise themselves with the anticancer drugs and issues being discussed. When interpreting the certainty of the evidence and strength of the recommendations, the panellists were asked to consider:

- The quantity and confidence of the evidence (Table 1)
- The balance between benefits and harms associated with the anticancer drug in reduced kidney function

- Whether there were data on critical outcomes (i.e., overall survival, grade ≥ 3 adverse events), with or without dose adjustment.
- The magnitude of effect, feasibility, and accessibility of any dose adjustment

The strength of each recommendation was reflected in its wording (either conditional or strong [Table 2]).[24] Where published evidence was conflicting or absent, expert opinion was sought for strengthening recommendations to 'conditional' by achieving clinical consensus (Table 3). Examples where this occurred were for more recently registered anticancer drugs (i.e., venetoclax, nivolumab, pembrolizumab, obinutuzumab [see online version of ADDIKD for full details: https://www.eviq.org.au/clinical-resources/addikd-guideline/4185-quick-reference-tool-anticancer-drug-dosing]).[44]

Panellists suggested the inclusion of 'practice points' for certain anticancer drugs as additional considerations within individual recommendations when administering the drug in reduced kidney function (e.g., preventative, and supportive care measures). For each cancer drug, a 'Quick reference' dosing table was produced using a traffic light system (clinical risk assessment concept)[49] summarising dosing recommendations and comments i.e., additional monitoring, precautions in special populations (Fig. 3).

Amendments were actioned following each panel discussion and revised recommendations were circulated amongst the panellists for unanimous agreement before the drug recommendations could proceed to working group consensus voting (based on the Delphi consensus technique[35,36] and the RAM approach[37]) (Table 3). During refinement of recommendations, additional reference articles (not originally included in a GRADE profile) identified by the working group were occasionally added to strengthen the justification of certain drug recommendations or to reflect merging evidence.

Working group consensus

Based on the Delphi consensus technique,[35,36] anonymous online voting on the finalised key recommendations and the drug recommendations was conducted involving all members of the *Content Development Working Group*. Due to the large volume of recommendations, consensus voting using SurveyMonkey[50] was divided over four parts (for an example of the online consensus voting process see Supplementary Material 6).

Following a round of voting ADDIKD's key recommendations were unanimously accepted. A median of 95% (range 73–100%) consensus was achieved for the finalised drug-specific recommendations and dosing tables.

External review

The draft guideline was available for public comment on the eviQ website for over one month. The public consultation process was communicated via email, social media and key medical/scientific groups, patient/carer advocacy groups and government agencies. Specific external stakeholders (medical professional organisations, government regulatory authorities) were engaged directly to provide feedback, disseminate, and endorse ADDIKD.

Comments received during this process were documented via an online survey, collated, and presented back to the working group for discussion for any major revisions. The acceptance of amendments followed the processes used in prior steps of guideline development. The only major revisions requiring the working group input were an addition to ifosfamide's dosing options and inclusion of a caution about the potential unreliability of $eGFR_{CKD\text{-}EPI}$ in transgender individuals.

The finalised and endorsed version of ADDIKD was published online with the ability for users to provide eviQ with feedback on the guideline content at any time.

Discussion

Developing ADDIKD required an amalgamation of several consensus building techniques and the gold-standard GRADE approach for critical appraisal of the evidence. This approach was necessary as the available evidence was limited to mostly case reports or small observational studies and hence, we needed to apply a methodology which evaluated the certainty of the evidence and incorporated expert opinion and clinical experience. Our approach enabled us to consolidate existing literature and strengthen the support for a harmonised, practical- and evidence-based approach to the assessment and classification of kidney function,

Strength	Implications	
	Patients	Clinicians
Strong "*We recommend*"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.
Conditional "*We suggest*"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.

Table 2: **Strength of evidence and the implications of the recommendation.**[23]

PI/ECO Question	Should elimination by the kidney be used to direct dosing? (Recommendation 1)		Should the KDIGO categories be used? (Recommendation 2)		Should full dose be used in the setting of reduced kidney function? (Recommendation 3)		Changes post panel discussion
Drug	Evidence certainty	Strength	Evidence certainty	Strength	Evidence certainty	Strength	
Azacitidine	⊕○○○	conditional	⊕○○○	conditional	⊕⊕○○	conditional	minor
Bendamustine	⊕⊕○○	strong	⊕⊕○○	conditional	⊕⊕○○	conditional	nil
Bevacizumab	⊕⊕⊕⊕	conditional	n/a		n/a		minor
Bleomycin	⊕⊕○○	strong	no studies	conditional	⊕⊕○○	strong	nil
Bortezomib	⊕⊕⊕○	conditional	⊕⊕○○	conditional	⊕⊕⊕○	conditional	nil
Cabazitaxel	⊕○○○	strong	n/a		n/a		nil
Capecitabine	⊕⊕⊕○	strong	no studies	conditional	⊕⊕⊕○	strong	minor
Carboplatin	⊕⊕⊕○	strong	no studies	strong	⊕⊕○○	conditional	minor
Cetuximab	⊕⊕○○	strong	n/a		n/a		minor
Chlorambucil	⊕⊕⊕○	strong	n/a		n/a		nil
Cisplatin	⊕⊕⊕○	strong	⊕⊕⊕○	conditional	⊕⊕⊕○	strong	major
Cyclophosphamide	⊕⊕○○	strong	⊕⊕○○	conditional	⊕⊕○○	conditional	minor
Cytarabine	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	major
Dabrafenib	⊕⊕○○	strong	n/a		n/a		major
Dacarbazine	⊕○○○	conditional	no studies	conditional	⊕○○○	conditional	major
Dactinomycin	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	minor
Daunorubicin (including *liposomal* daunorubicin)	⊕○○○	conditional	no studies	conditional	⊕○○○	conditional	major
Docetaxel	⊕⊕○○	strong	n/a		n/a		nil
Doxorubicin	⊕⊕○○	strong	n/a		n/a		nil
Doxorubicin (*pegylated liposomal*)	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	nil
Durvalumab	⊕⊕○○	conditional	n/a		n/a		minor
Epirubicin	⊕○○○	strong	n/a		n/a		nil
Etoposide (including etoposide *phosphate*)	⊕⊕⊕○	strong	no studies	conditional	⊕⊕⊕○	strong	minor
Everolimus	⊕⊕○○	conditional	n/a		n/a		minor
Fludarabine	⊕⊕⊕○	strong	no studies	conditional	⊕⊕⊕○	strong	major
Fluorouracil	⊕○○○	conditional	no studies	conditional	⊕⊕○○	conditional	minor
Gemcitabine	⊕⊕○○	strong	no studies	conditional	⊕⊕○○	conditional	minor
Idarubicin	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	minor
Ifosfamide	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	minor
Irinotecan	⊕⊕⊕○	conditional	no studies	conditional	⊕⊕○○	conditional	major
Lenalidomide	⊕⊕○○	strong	⊕⊕○○	conditional	⊕⊕○○	strong	minor
Melphalan	⊕⊕○○	conditional	⊕⊕○○	conditional	⊕⊕○○	conditional	minor
Mercaptopurine	⊕○○○	conditional	no studies	conditional	⊕○○○	conditional	minor
Methotrexate	⊕⊕○○	strong	⊕⊕○○	conditional	⊕⊕○○	strong	major
Mitomycin	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	nil
Nivolumab	⊕○○○	strong	n/a		n/a		minor
Obinutuzumab	⊕⊕○○	strong	n/a		n/a		major
Oxaliplatin	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	major
Paclitaxel	⊕⊕○○	strong	n/a		n/a		nil
Paclitaxel (nab)	⊕⊕○○	conditional	no studies	conditional	⊕⊕○○	conditional	minor
Panitumumab	⊕⊕○○	strong	n/a		n/a		minor
Pembrolizumab	⊕⊕○○	strong	n/a		n/a		minor
Pemetrexed	⊕⊕○○	conditional	⊕⊕○○	conditional	⊕⊕○○	conditional	nil
Pertuzumab	⊕⊕○○	conditional	n/a		n/a		nil
Procarbazine	⊕○○○	conditional	no studies	conditional	⊕○○○	conditional	minor
Raltitrexed	⊕⊕⊕○	strong	no studies	conditional	⊕⊕⊕○	strong	major
Rituximab	⊕⊕○○	conditional	n/a		n/a		minor
Temozolomide	⊕⊕○○	conditional	no studies	conditional	⊕○○○	conditional	minor
Thalidomide	⊕⊕○○	strong	n/a		n/a		nil
Thiotepa	⊕○○○	conditional	n/a		n/a		nil
Topotecan	⊕⊕○○	strong	no studies	conditional	⊕⊕○○	strong	major
Trastuzumab	⊕⊕⊕○	conditional	n/a		n/a		minor

(Table 3 continues on next page)

PI/ECO Question	Should elimination by the kidney be used to direct dosing? (Recommendation 1)		Should the KDIGO categories be used? (Recommendation 2)		Should full dose be used in the setting of reduced kidney function? (Recommendation 3)		Changes post panel discussion
Drug	Evidence certainty	Strength	Evidence certainty	Strength	Evidence certainty	Strength	
(Continued from previous page)							
Trastuzumab emtansine	⊕⊕⊕◯	conditional	n/a		n/a		minor
Venetoclax	⊕⊕◯◯	strong	n/a		n/a		major
Vinblastine	⊕⊕⊕◯	strong	n/a		n/a		nil
Vincristine	⊕⊕⊕◯	strong	n/a		n/a		nil
Vindesine	⊕◯◯◯	strong	n/a		n/a		nil
Vinflunine	⊕⊕◯◯	conditional	no studies	conditional	⊕⊕◯◯	conditional	minor
Vinorelbine	⊕⊕◯◯	strong	n/a		n/a		nil

Key: evidence certainty/quality—very low = ⊕◯◯◯, low = ⊕⊕◯◯, medium = ⊕⊕⊕◯, high = ⊕⊕⊕⊕. The recommendations were categorised as strong or conditional based on the response to the three questions shown in the table.

Table 3: **Evidence certainty and recommendation strength for specific drugs.**

and dose adjustment for each drug. Several consensus building methods were successfully hybridised through the guideline development process.

The Delphi consensus technique supported the use of at least two rounds of ratings to find convergence among individuals.[35,36] A similar iterative concept was

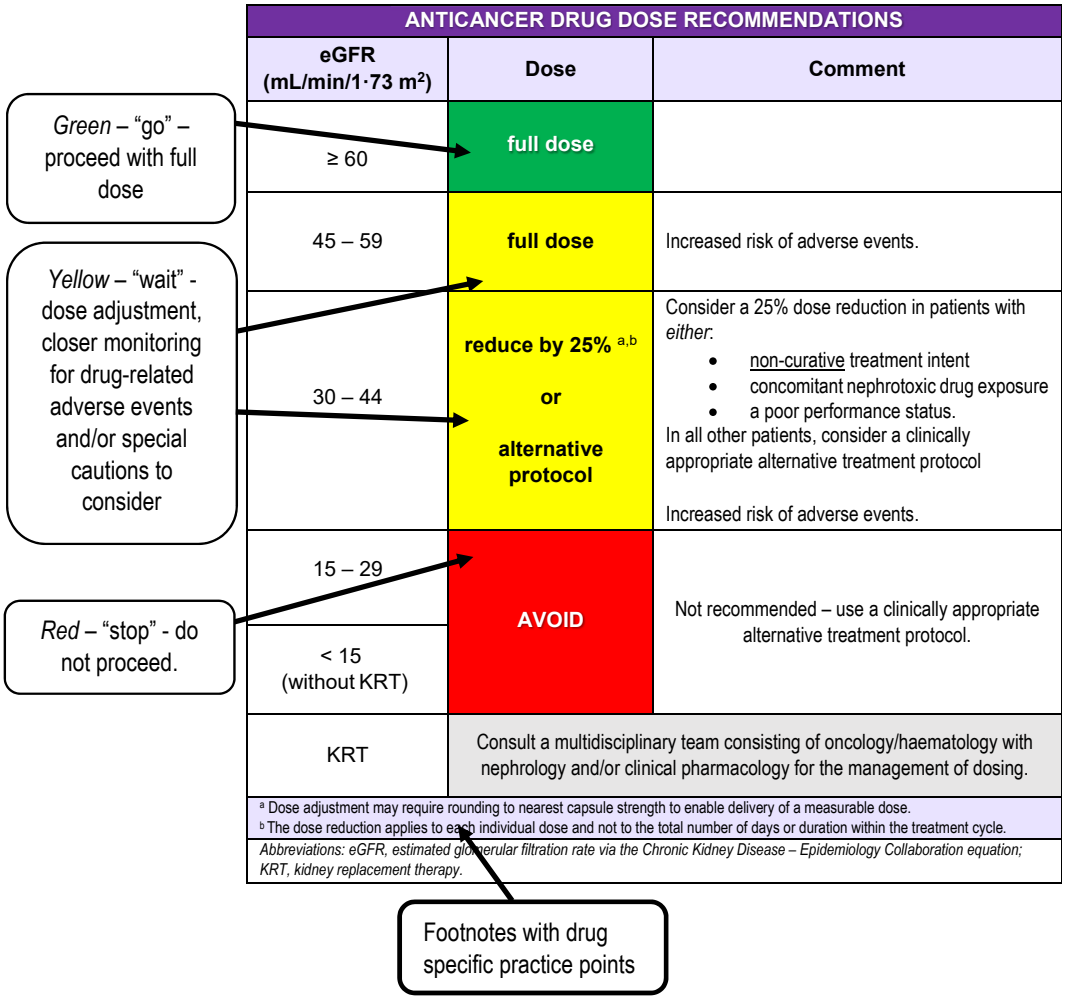

Fig. 3: Example of a dose recommendations table according to kidney function.

used with ADDIKD, where the consensus workshop and drug panel discussions achieved almost 100% acceptance of draft recommendations prior to voting by the wider working group. Fine-tuning recommendations initially with smaller panel discussions reduced the likelihood of disparity during final consensus voting. It also allowed the development of the quick-reference, colour-coded dosing tables and drug practice points, which improved ADDIKD's usability in the clinical setting by tailoring to pertinent, real-world information at the point of prescribing.

The Nominal Group Technique for consensus was partly utilised for the national consensus workshop and panel discussions. This technique involves a facilitated meeting with a small group to formulate ideas and agree on a group opinion based on viewpoints of each participant, followed by anonymous ranking of the group opinion.[38,39] It also allows for non-consensus to be addressed in the earlier steps, such as the panel discussions for Part 1 and 2 of ADDIKD's development. Cancer clinician and pharmacist inexperience with $eGFR_{CKD\text{-}EPI}$ was uncovered in the preliminary panel discussion in Part 1, identifying the need to provide informed expert opinion to address this during the national consensus workshop to facilitate agreement. Similarly in Part 2, the small drug panel discussions allowed for deliberations on recommendations where there were either differing opinions for certain drugs or where large gaps in evidence existed with the objective of achieving consensus.

The RAM is another consensus building approach that ADDIKD partially integrated into its recommendation development process.[37] Like the Delphi process, RAM involves iterations of voting, as incorporated into ADDIKD's Parts 1 and 2. However, unlike Delphi, RAM enables feedback and discussion where voting outcomes diverge,[37] which was also used in ADDIKD's Part 1 for the key recommendations and at various stages of small panel discussions in Part 2.

The online format of ADDIKD's development supported international engagement despite COVID-19 pandemic restrictions, reduced travel times for participants, cut the associated costs of face-to-face meetings, increased overall participation due to flexibility of meeting arrangements and improved the efficiency of administrative tasks e.g., collating results of consensus voting and feedback. It provided anonymity with consensus voting, and the chat function during online panel discussions enabled participation without the peer pressure of face-to-face meetings.

Although utilising the consensus-based approach potentially reinforces existing clinical practice patterns without compelling evidence to justify their use, potential biases can be reduced. ADDIKD's development process did this by ensuring the working group members and selected experts provided a heterogenous clinical and geographical representation (i.e., various countries, rural versus metropolitan), participants declared conflict of interests and voting was anonymous.

Other challenges with ADDIKD's hybridised method included attaining consensus on anticancer drugs that were primarily eliminated by the kidney, dosed across large ranges, and/or used in multiple solid and haematological malignancies i.e., cisplatin, methotrexate, ifosfamide.[44] These drugs required debate at several drug panel discussions, often with major iterations to the dose adjustments recommendations to reflect the varied use of these drugs in clinical practice. Newer immunotherapy agents (e.g., pembrolizumab, nivolumab), although not reliant on elimination by the kidney, also required deliberation at several panel discussions. This was due to limited published evidence on their potential nephrotoxicity and recent introduction to real-life patient populations with multiple comorbidities outside of a clinical trial.[44]

The traditional method of guideline development requires high-level evidence, and therefore if ADDIKD's development had followed this, high powered studies linking drug pharmacokinetics with pharmacodynamics with treatment outcomes would be needed. Bevacizumab was the only drug that had high certainty of evidence in ADDIKD and, interestingly, resulted in a conditional recommendation through the consensus process rather than a strong recommendation.[44] Despite the published literature, real-life experience, and case reports on the potential kidney-related adverse events in reduced kidney function with bevacizumab remain a concern for clinicians, consequently leading to a conditional strength of the recommendation. Many anticancer drugs had no published studies applicable to Recommendation 2 however unanimous agreement was always achieved amongst the working group and experts as it was strongly believed that the standardisation of kidney function classification across medicine would improve safety and decision-making.[44]

The novel, multistep process developed for ADDIKD's methodology incorporating the rigor of GRADE and several consensus building techniques will hopefully provide a template for other groups when developing guidelines in patient populations with limited high-level evidence. We envisage with such methodology in place, the guidance will be considered gold standard and endorsed by international cancer groups and adopted in regulatory drug processes within government and the pharmaceutical industry.

Outstanding questions

Despite the existence of many consensus building methodology approaches, ADDIKD in the time of the COVID-19 pandemic difficulties, successfully integrated the gold-standard of evidence evaluation using GRADE with modified online applications of Delphi, RAM and Nominal Group Technique to facilitate agreement

where high-level evidence was non-existent. This novel method provided clarity on how consensus was achieved and accommodated a broad range of opinions leading to international standardisation of practices in the complex area of anticancer drug dosing in reduced kidney function.

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All authors provided critical revision of the manuscript for important intellectual content and gave approval of the submission of the manuscript for publication. GS, RLW and JA verified data in the study for publication, and GS and RLW had final responsibility for the decision to submit for publication.

Data sharing statement

None.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103101.

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