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## **Title**

Clinical efficacy of the optimal biological dose in early phase trials of anti-cancer targeted therapies

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## **Abstract**

**BACKGROUND:** Determining the optimal biological dose (OBD) has been described as an alternative strategy to the maximum tolerated doses (MTDs) for the identifying the recommended phase II trial doses (RP2Ds) of phase I anti-cancer therapies. However, the clinical relevance is still unknown. An extensive review was performed to assess if the OBDs defined in early phase trials were useful for subsequent drug development and approvals.

**METHODS:** All the molecular targeted therapies approved by the Food and Drug Administration in solid oncology or in hematological malignancies before July 2018 were listed through the National Cancer Institute Database. The early phase trial publications investigating these drugs as single agents were retrieved and analyzed to identify the drugs for which OBDs were reported. The publications of subsequent pivotal efficacy clinical trials leading to the approvals were retrieved and OBDs compared with the final labeled doses and dosing schedules.

**RESULTS:** A total of 87 early phase trial publications were analyzed, corresponding to 81 FDA approved targeted therapies. OBDs were reported for 40% (32/81) of these drugs (19 small molecules, 13 monoclonal antibodies). MTDs were not identified for 59% (19/32) of molecules. When the OBDs were selected as the RP2Ds (18/32 molecules), the final FDA approved doses were consistent with the OBDs for 83% of the drugs, which is much higher than the previously reported 58% rate when MTDs were chosen as the RP2Ds.

**CONCLUSION:** Although still poorly investigated, the OBD may be a relevant and complementary endpoint for early phase trials of targeted therapies.

**Keywords:**

Dose-Response Relationship, Drug

Antibodies, Monoclonal

Antineoplastic Agents

Maximum Tolerated Dose

## **Manuscript**

### **Introduction**

Since the early 2000s, many molecular targeted therapies have been approved in hematology and solid oncology, including small molecules or monoclonal antibodies (mAbs). New questions were raised about the optimal strategy for defining the best doses and dosing schedules. Indeed, the approach traditionally implemented for conventional chemotherapy agents, relies on dose-escalation trials meant to identify the maximal tolerated doses (MTD) and the recommended phase II trial doses (RP2D). However, this strategy may not be adequate for novel targeted drugs, for which the dose–efficacy and dose–toxicity curves may not be correlated [1–3], and efficacy may occur at doses that do not induce clinically significant toxicity [4].

As a consequence, novel drug development strategies meant to identify the best doses and dosing schedules of novel targeted agents have been proposed [5,6]. Among them, determination of the “optimal biological dose” (OBD), also called “biologically effective dose” appears promising [7]. Indeed, identification of the minimal dose associated with an optimal predefined biological effect, through measurement of target inhibition and pharmacokinetics analyses, might be a good complementary approach for defining the RP2Ds of targeted therapies [4, 7]. However, there are no data about the actual relevance of this endpoint, in terms of clinical efficacy. The present review study aimed at assessing the clinical relevance of OBDs, defined during early phase trials, for further approvals.

### **Materials and methods**

#### **Study design**

This systematic review study was conducted in three consecutive steps.

- 1) Identification of the FDA approved targeted agents, for which early phase trials defined OBDs:

All the molecular targeted therapies approved before July 2018 by the FDA for hematological or solid malignancies were collected through the National Cancer Institute Database (<https://www.cancer.gov/about-cancer/treatment/drugs>). The compilation of all early phase trials publications was performed using MEDLINE via PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>), and using the American Society of Clinical Oncology (ASCO) website, with the search terms “compound name” or “compound code”, “phase I” and “early phase trial”. Identifications of OBDs, doses/dosing schedules and biological effects, were tracked in the article bodies. OBD was defined as the lowest dose shown to inhibit a drug target reliably, or to achieve a target plasma concentration [8], and was reported as the biologically effective dose by authors. The following elements were collected for all considered drugs: name of the first author; date of publication; studied tumor types; maximum tolerated dose if any; RP2D if any; reported OBD; OBD-related biological effects; OBD as the primary endpoint of the trial (yes vs no); structure of the drug (small molecules, or mAbs).

Early phase trials investigating more than one investigational molecular targeted agents, or those focusing on specific populations or ethnicities were excluded, as were those involving active immunotherapies, such as vaccines or Chimeric antigen receptor T cell (CAR T cell) therapies, due to their specific and complex mechanisms of action.

- 2) Identification of the clinically effective doses in subsequent pivotal efficacy trials leading to FDA approvals:

We identified the subsequent efficacy clinical trials leading to the first FDA approvals and the dose/dosing schedules that had been tested, through the “clinical studies” section of the

structured product labeling (SPL) document of every compound, using the website <https://nctr-crs.fda.gov/fdalabel/ui/search>. The corresponding publications were then retrieved using the following keywords on PubMed: “compound name” or “code” and “phase III trial” (“phase II trial” or “phase I trial” when appropriate). The following elements were collected for every selected article: name of the first author; date of publication; studied tumor types; dose and dosing schedule tested; estimated value of the treatment effect on the primary endpoint. Moreover, the following data were collected in the first FDA approvals: approval year; type of approval (accelerated or full), labelled dose/dosing schedules; and tumor indications, using the website <https://www.accessdata.fda.gov/scripts/cder/daf/>.

### 3) Comparison of OBDs and clinically effective doses:

The consistency in between the OBDs reported in the early phase trials, the clinically effective doses reported in efficacy trials leading to FDA approval, and the FDA labelled doses/dosing schedules was finally assessed for each selected drug.

The data extraction was performed by two authors (PC and MEM). They were verified by all coauthors.

### **Statistical analysis**

All analyses were descriptive. Qualitative data were described by percentages.

### **Results**

As of July 2018, total 83 molecular targeted therapies were FDA approved for hematological or solid malignancies. Two of them were excluded, because they were active T cell immunotherapies. For the remaining 81 therapies, 87 early phase trials were identified (Figure 1). The concept of OBD was mentioned in the early phase trials of 50/81 of these FDA approved molecules (62%). Actual OBDs were reported in 32 early phase trials,

corresponding to 32 molecular targeted therapies (40%) (Appendix). One trial was a pilot biological study of lapatinib, while all others were phase I trials. All assessed trials were published between 1999 and 2017. The median year of publication was 2010. As shown in Table 1, 19/32 were small molecules (59%), while 13/32 were mAbs (41%). OBD identifications were clearly reported as the primary objectives of the early phase trials for 7 drugs (22%). The clinical studies that led to the first FDA approvals of small molecules were phase III efficacy trials for 12/19 of them (63%) and phase II trials for 7/19 of them (37%). For monoclonal antibodies, these numbers were phase III trials for 10/13 (77%), phase II trials for 2/13 (15%) and phase I trial (cohort expansion) 1/13 (8%).

For 19 of the 32 studied agents (59%), no MTDs were found during the early phase trials despite dose escalations, including 9 small molecules and 10 mAbs, and corresponding to 47% and 77% of all tested small molecules and mAbs, respectively. Among the 13 drugs with reported MTDs, the OBDs were lower than the MTDs for 10 of them (77%), and similar for 3 of them (23%).

For 18/32 drugs (56%), the OBDs were chosen as the RP2Ds, including 10 small molecules (corresponding to 53% of all small molecules) and 8 mAbs (corresponding to 62% of all mAbs). Of note, no MTD had been found for most of these drugs (11/18, 61%, including 5 small molecules and 6 mAbs). The 14 remaining drugs, for which RP2Ds were not the OBDs (44%), comprised 9 small molecules, and 5 mAbs. These RP2Ds were superior to the reported OBDs for 13/14 of these drugs (93%); cetuximab being the only exception. Among these 14 drugs, MTD had been found for 6 of them, of which 5 were chosen as RP2Ds (36% of drugs for which OBDs were not chosen as RP2Ds). For the 9 remaining drugs (64%), the rationale sustaining the RP2D selection was not clearly reported.

Regarding FDA approvals, the labelled doses were similar to the OBDs for 19 of the 32 drugs with reported OBDs (59%), corresponding to 47% of small molecules and to 77% of



mAbs, respectively. Regarding the 18 molecules for which OBDs were chosen as the RP2Ds, the final FDA labelled doses were consistent with the OBDs for 15 of them (83%), including 8/10 small molecules (80%), and 7/8 mAbs (88%). The three remaining molecules approved at doses different from OBDs were lapatinib, midostaurin and siltuximab. Their labelled doses were lower than the reported OBDs, and than their RP2Ds. Two of them (lapatinib and midostaurin) were actually approved in combination with chemotherapy at lower doses. Siltuximab was approved at 11 mg/kg every three weeks, instead of 12 mg/kg every three weeks, that was the OBD and defined as the RP2D.

Interestingly, 4 drugs for which RP2Ds were not similar to the OBDs, were finally approved at the OBDs: abemaciclib, cetuximab, obinutuzumab and necitumumab. Cetuximab was approved at intravenous 400 mg/m<sup>2</sup> loading dose followed by weekly 250 mg/m<sup>2</sup>, although the reported RP2D was intravenous weekly 200 mg/m<sup>2</sup>. Abemaciclib was approved at 150 mg orally twice a day, which is inferior to the MTD RP2D, that was set up at 250 mg orally twice a day. As for obinutuzumab and necitumumab, the approved dosing schedules were adjusted for chemotherapy combinations at doses that were similar to OBDs.

Overall, 19/81 (23%) assessed molecular targeted therapies approved by the FDA were approved at their OBDs.

The impact of the type of approval (accelerated versus full) on the results were explored. FDA granted accelerated approval to 11/32 (34%) molecules, including 6 small molecules and 5 mAbs. OBDs were selected as the RP2Ds for 4 of them (36%), and the approved doses were similar to the OBDs for 5 of them (45%). When OBDs were chosen as the RP2Ds, the accelerated FDA approved doses were consistent with the OBDs for all of them (100%), against 11/14 (79%) for the drugs that were directly fully approved.

Regarding the biological effects of small molecules, OBDs mainly relied on indirect effects on elements of the involved signaling pathways (11/19, 58%). For example, OBDs of

imatinib and ponatinib, two BCR-ABL inhibitors, were based on the inhibitions of CRK-like protein (CRKL) phosphorylation, a substrate of BCR-ABL. Otherwise, the biological effects relied on direct inhibition of the target (6/19, 32%) (i.e. diminution of the formation of poly ADP ribose (PAR) for olaparib, a Poly ADP-Ribose Polymerase (PARP) inhibitor), or receptor occupancy (2/19, 10%). For mAbs, the assessed biological effects involved receptor occupancy (6/13, 46%), followed by direct inhibition of the target activity (4/13, 31%), or indirect effects on components of the signaling pathways (2/13, 15%), and finally on target concentration associated with biological effects based on pharmacokinetic study outcomes (1/13, 8%) (Table 2).

Of note, in the early phase trials of 18 other drugs, representing 22% of all approved targeted molecular therapies, no OBDs were finally reported although the concept of OBD was mentioned in the articles. Most of time, the authors failed to determine the OBDs due to the lacks of correlation between drug doses and the assessed biological effects [9–26].

The time intervals from the publications of early phase trials reporting OBD to the first FDA approvals were relatively short (median, 1 year, range: less than one year to 16 years for midostaurin), with no differences in between small molecules and mAbs.

## **Discussion:**

In 2014, Fontes Jardim et al. showed that the RP2Ds had been used as the labelled doses for 97% of cytotoxic chemotherapy agents, against 58% of targeted agents approved in between 1990 and 2011, thereby suggesting the limitations of traditional toxicity-based trials for defining the optimal clinically effective doses of these novel drugs [27].

The first reason relates to the lack of direct dose-toxicity relationships for many of these drugs. In a review study of 201 phase I trials, DLTs were less frequently identified with targeted therapies (48%) than with cytotoxic drugs (89%) [28]. Consistently, in a review of

82 articles about mAb phase I trials, MTDs had been found in 16% of early phase trials only [29]. In the present study, MTDs were reported for 53% and 23 % of assessed small molecules and mAbs, respectively, corroborating these data.

The second reason is the frequent lack of direct dose-efficacy relationships, meaning that the highest tolerable doses are not necessarily the most effective doses, contrarily to what is accepted with most of cytotoxic chemotherapy agents.

To solve this issue, identification of the optimal biologically effective dose is frequently described as a relevant approach [1]. Indeed, the knowledge of the mechanisms of actions of these new targeted agents offers the opportunity to assess the biological effect magnitude induced by the novel drugs, and thus to define the lowest dose associated with the expected pharmacodynamic effects. It was reported that OBDs were indeed frequently identified at lower doses compared to MTDs, thereby suggesting that this strategy could potentially reduce the toxicity profiles, and the costs of anti-cancer treatments [7].

The present study first suggests that OBDs are still rarely assessed, reported in less than 40 % of early phase trials of recent FDA approved targeted agents. When reported, they were chosen as the RP2Ds in 56% of cases. Our work suggests that the search for OBDs may be a relevant strategy, since 83% of the final approved doses were consistent with the OBDs, when they were selected as the RP2Ds. This percentage is much higher than the previously reported 58% with MTD [27]. Moreover, when both MTDs and OBDs had been defined, the OBDs were lower for most of studied agents (77%), hence corroborating the assumption that the OBD identification strategy could improve the safety of anti-cancer treatments.

Niraparib, a recently approved PARP inhibitor, is an illustrative example. The MTD at 300 mg/day was defined as the RP2D, although the lower 80 mg/day dose was identified as the minimum biologically effective dose, based on PARP inhibition effects in peripheral blood mononuclear cells [30]. In 2017, niraparib was approved as a maintenance treatment for

recurrent epithelial ovarian cancer at the MTD (300 mg/day), based on the positive NOVA trial outcomes [31]. However, this dose has subsequently been recognized as too high and toxic, and dose reductions based on patient weight and platelet count are now advised for prescriptions of niraparib in the majority of patients, and for on-going clinical trials [32, 33]. If these data about the clinical efficacy of OBDs are encouraging, they also raise issues. The selection and measurement of the adequate biological effects required for OBD identification are not easy, especially for mAbs [7]. We noticed that the measured biological effects associated with OBDs were heterogeneous among small molecules and mAbs, but also among some molecules of the same classes. For example, the OBDs of pembrolizumab and nivolumab, two Programmed cell Death protein 1 (PD-1) inhibitors, relied on IL2 stimulation, and on PD-L1 occupancy, respectively [34,35]. The lack of validated biomarkers and thresholds for novel study agents contributes to this inconsistency. Such a complexity may explain why OBDs frequently rely on indirect effects on the involved signaling pathway components for small molecules, and on receptor occupancy or saturation for the majority of mAbs, as already reported [29]. It may also explain why, actual OBDs could not be found for about a quarter of drugs, despite the mention of biological effective dose in the articles. For example, the authors demonstrated some pharmacodynamic effect-dose relationships as proofs of concepts, and set up the RP2Ds of bortezomib [9], sonidegib [10], and vorinostat [11], based on other criteria, without defining OBDs. This observation is consistent with Sweis et al. who reported that despite their increased uses, the impact of biopsy-derived pharmacodynamic biomarkers in phase I oncology studies remains uncertain on subsequent drug development, as no effects on subsequent dose or schedule were demonstrated [36]. Another difficulty relates to the impact of the trial designs on the relevance of identified OBDs. For example, the number of assessed dose levels restricts the search in a dose-window, as illustrated by nilotinib for which only two doses were evaluated

[37]. Of note, the rationale sustaining the selection of the RP2Ds was not clear in more than 60% of drugs, for which the RP2Ds were not based on OBDs or MTDs.

The present study has several limitations that are important to notice. First, we chose to restrain our analysis to single agent studies for avoiding the effects of pharmacodynamic interactions. In addition, we assumed that approved doses were clinically effective, but this is debatable. Although clinical efficacy cannot be reduced to drug approvals, the FDA labeled dose appeared as the most objective and assessable endpoint for the present analysis. In particular, our research did not focus on unpublished early phase trials for feasibility reasons, which did not allow us to assess the number of negative efficacy trials testing the OBDs, thereby leading to drug abandons before approvals.

### **Conclusions:**

While being insufficiently investigated, OBD may be a relevant and complementary endpoint to toxicity endpoints traditionally assessed in oncologic phase I trials. Indeed the reported OBDs were found to be consistent with subsequent doses approved by FDA for the large majority of oncology and hematology targeted therapies, when developed at these doses. The design of future early phase trials should be adjusted to integrate systematic assessment of the biological effective dose, as a way of reducing the high attrition rate and costs in oncology drug development, and improving the quality of life of patients.

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**Conflict of interest statement**

The authors have declared no conflicts of interest.

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## Tables

**Table 1:** Characteristics of the considered drugs and associated trials

<b>MTD reached in early phase trials</b>	Yes	13/32 (41%)	Small molecules	10/13 (77%)
			mAbs	3/13 (23%)
	No	19/32 (59%)	Small molecules	9/19 (47%)
			mAbs	10/19 (53%)
<b>OBDs selected as RP2Ds</b>	Yes	18/32 (56%)	Small molecules	10/18 (56%)
			mAbs	8/18 (44%)
			MTD reached	7/18 (39%)
			Molecules granted under accelerated approvals	4/18 (22%)
	No	14/32 (44%)	Small molecules	9/14 (64%)
			mAbs	5/14 (36%)
			MTD reached	6/14 (43%)
			Molecules granted under accelerated approvals	7/14 (50%)
<b>OBDs = FDA approved doses</b>	Yes	19/32 (59%)	Small molecules	9/19 (47%)
			mAbs	10/19 (53%)
			Molecules granted under accelerated approvals	5/19 (26%)
<b>OBD selected as RP2Ds and FDA approved doses</b>	Yes	15/18 (83%)	Small molecules	8/15 (53%)
			mAbs	7/15 (47%)
			Molecules granted under accelerated approvals	4/15 (27%)

Abbreviations: MTD, Maximum Tolerated Dose; OBD, Optimal Biologic Dose; FDA, Food and Drug Administration; RP2D, Recommended Phase II trial Dose

**Table 2:** Biological effects selected for the determination of the optimal biologic doses

<b>Type of targeted therapy</b>	Direct target inhibition	Indirect target inhibition	Target receptor occupancy or saturation	Target concentration of the drug associated with biological effects based on pharmacokinetic studies
<b>Small molecules (<i>n</i> = 19)</b>	6/19 (32%)	11/19 (58%)	2/19 (10%)	0/10 (0%)
<b>mAbs (<i>n</i> = 13)</b>	4/13 (31%)	2/13 (15%)	6/13 (46%)	1/13 (8%)

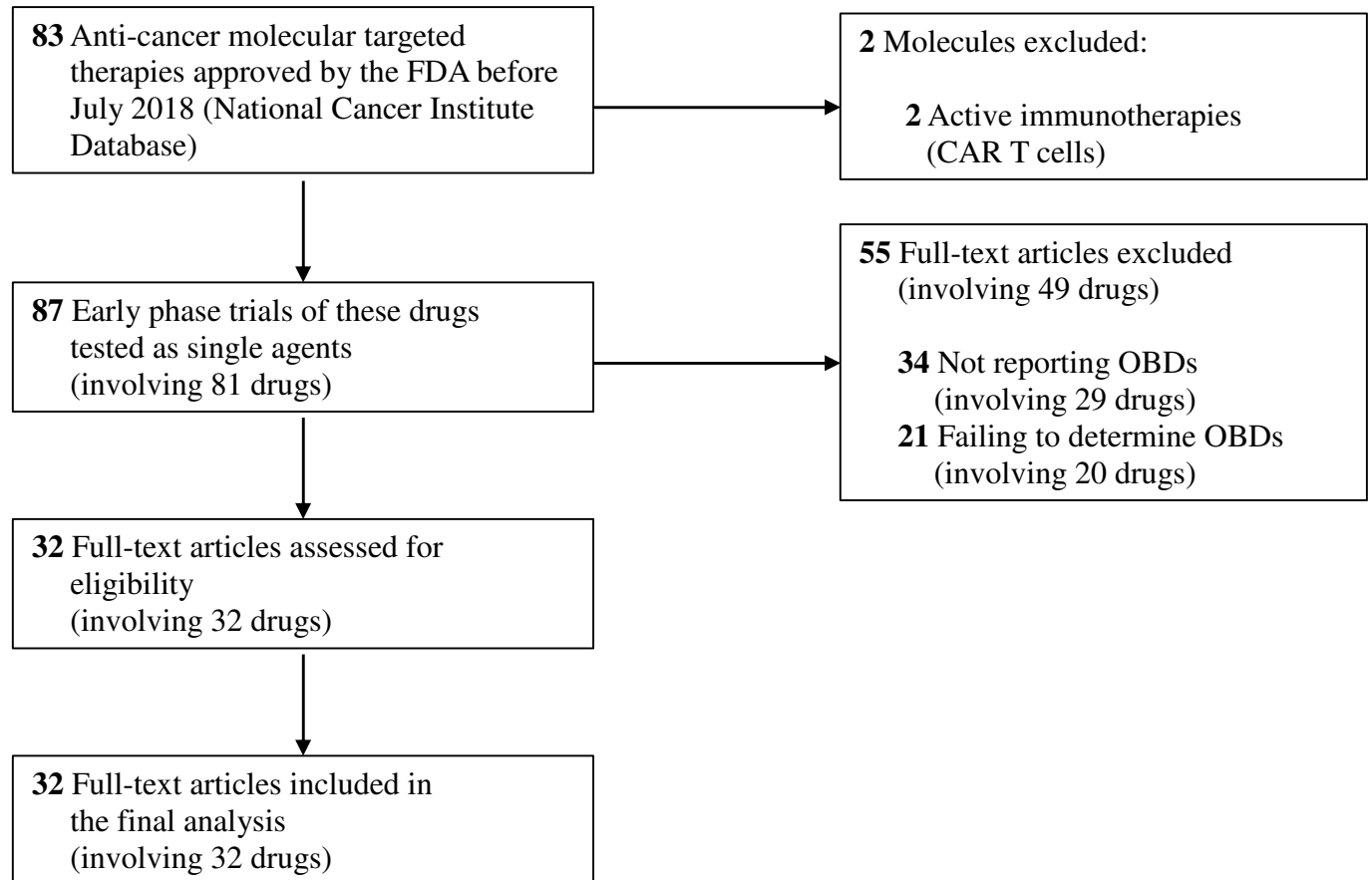
Abbreviations: mAbs, Monoclonal antibodies; OBD, Optimal Biological Dose

## **Appendix**

Early phase trials of FDA approved anti-cancer targeted agents with reported optimal biological dose, clinical effective doses and FDA approved doses

## Figures

**Figure 1:**



Abbreviations: CAR T cells, chimeric antigen receptor T cells; FDA, Food and Drug Administration.

Color is not needed.

**81 anti-cancer molecular targeted therapies**  
approved by the FDA before July 2018

52 small molecules	29 mAbs
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**32 drugs (40%)**  
with optimal biological doses reported in the early phase trial articles (as monotherapy agents)

19 small molecules	13 mAbs
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**19 drugs (59%)**  
with no maximum tolerated doses reached

9 small molecules	10 mAbs
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**18 drugs (56%)**  
with optimal biological doses selected as the RP2Ds

10 small molecules	8 mAbs
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**15 drugs (83%)**  
with FDA approved doses consistent with the optimal biological doses

8 small molecules	7 mAbs
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FDA = Food and Drug Administration;  
mAbs = monoclonal antibodies;  
RP2Ds = recommended phase II trial doses