Dose–Response Relationship in Phase I Clinical Trials: A European Drug Development Network (EDDN) Collaboration Study

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Abstract

Introduction: Because a dose–response relationship is characteristic of conventional chemotherapy, this concept is widely used for the development of novel cytotoxic (CTX) drugs. However, the need to reach the MTD to obtain optimal benefit with molecularly targeted agents (MTA) is controversial. In this study, we evaluated the relationship between dose and efficacy in a large cohort of phase I patients with solid tumors.

Experimental Design: We collected data on 1,182 consecutive patients treated in phase I trials in 14 European institutions in 2005–2007. Inclusion criteria were: (i) patients treated within completed single-agent studies in which a maximum-administered dose was defined and (ii) RECIST/survival data available.

Results: Seventy-two percent of patients were included in trials with MTA (N = 854) and 28% in trials with CTX (N = 328). The objective response (OR) rate was 3% and disease control at 6 months was 11%. OR for CTX was associated with higher doses (median 92% of MTD); this was not the case for MTA, where patients achieving OR received a median of 50% of MTD. For trials with MTA, patients treated at intermediate doses (40%–80%) had better survival compared with those receiving low or high doses (P = 0.038). On the contrary, there was a direct association between higher dose and better OS for CTX agents (P = 0.003).

Conclusion: Although these results support the development of novel CTX based on MTD, we found no direct relationship between higher doses and response with MTA in unselected patients. However, the longest OS was seen in patients treated with MTA at intermediate doses (40%–80% of MTD). Clin Cancer Res; 20(22); 5663–71. ©2014 AACR.

Introduction

Phase I trials aim at defining the recommended phase II dose (RP2D) of novel therapeutic agents. This is usually achieved through dose-escalation designs where successive cohorts of patients are treated with increasing doses of the medication until the pharmacologically active, yet tolerable, dose is reached. Although these studies are in most diseases performed in healthy volunteers, phase I
Phase I clinical trials for molecularly targeted agents (MTA) have been designed following the dose–response paradigm inherited from chemotherapy. However, the need to reach the MTD to obtain benefit from these agents is controversial. In this study, we reviewed data from 1,182 patients treated within single-agent phase I clinical trials including new MTA and chemotherapeutic agents. We found that patients treated with chemotherapeutic agents do benefit from higher doses. However, patients treated with MTA have better survival with intermediate doses not close to the MTD. These findings support the current view that phase I trials should try not only to define the MTD but also to prove that the drug is tolerable at a biologically active dose.

Trials of antineoplastic agents are performed in patients with advanced disease because of the potentially toxic nature of anticancer drugs (1). Another feature of oncology trials is that the RP2D is generally estimated by defining the MTD because this has been traditionally considered to be the most relevant surrogate for pharmacologically active dose. This paradigm stems from the observation that alkylating agents (one of the first class of antineoplastic agents) have a steep dose–response curve; this was supported by data from a meta-analysis of phase I trials of cytotoxic agents and studies in breast cancer showing that dose intensity of chemotherapeutic agents correlated with response rates and survival (2, 3). These concepts eventually culminated with the use of high-dose chemotherapy and autologous stem cell support. However, the relevance of MTD in the definition of the RP2D is questioned in the era of newer molecularly targeted agents (MTA) have been designed following the dose–response paradigm as a gold standard for the dose nor-

Materials and Methods

Study design and patient eligibility

This study considered patients included in the European Drug Development Network (EDDN) database, an international consortium involving 14 oncology drug development units (7). This database included a total of 2,182 patients, consecutively treated in phase I trials from January 2005 to December 2007. As can be seen in Supplementary Fig. S1, for this study, 860 patients were excluded because of combination trials and another 140 patients were excluded because of missing information. The primary aim of this study was to determine the relationship between dose (expressed as a percentage of the MTD) and objective response (OR; complete and partial response) by RECIST (8) in single-agent phase I trials with MTA. Secondary aims were to determine the relationship between dose and (i) nonprogression rates [NPR; OR + stable disease (SD)] at 3 and 6 months; (ii) PFS and overall survival (OS); and (iii) to compare these results with the reference group treated with CIX agents.

All patients included in the database met the eligibility criteria for each study. Specific criteria for this study included: (i) patients treated in single-agent dose-escalation phase I trials and (ii) a maximum administered dose (MAD) was established in the drug schedule in which each patient was treated. All patients included in this analysis gave informed consent to take part in each phase I trial approved by local Institutional Review Boards (IRB). IRBs also granted their approval for this analysis.

The MTD in this study was defined as ‘the highest administered dose level below that dose which ≥33% of patients experience a DLT,’ independently of the original definition established by particular studies. The dose received by each patient was normalized by the ratio: [(dose received/MTD or MAD) × 100]. We also calculated the time per treatment index (TPTi): a ratio of the time interval between diagnosis of advanced/metastatic cancer and phase I trial entry, over the number of lines of systemic treatment [log (time + 1/treatments + 1)]; its aim is to reflect baseline tumor kinetics at study entry (7).

Statistical analysis

Traditional dose-escalation methods usually considered a minimum of 25% change for dose increase and/or reduction during dose escalation (9). Thus for our primary aim, we considered that to detect a true difference in mean dose (%) of at least 25% between responders (patients with OR) and nonresponders (NR), with an α- and a β-errors of 0.10, we will need approximately 900 patients in a two-tailed Student t test [base in our previous data (6, 7) an OR rate for single-agent trials ≥3%, unequal σ values for both groups ≤0.4]. Differences in mean dose between other response groups were explored using Student t test for independent groups.
Nonparametric statistics, that is, Mann–Whitney U test, were used to compare doses in different response groups treated with CTX. In addition, we divided our patients according to received dose in three different cohorts: low doses (<40% of MTD), medium doses (40%–80% of MTD), and high doses, (>80% MTD). Categorical variables were compared with a χ² test. When a significant association with dose and response was found, its independent value was studied in a multivariate stepwise logistic regression model considering all variables with a P value <0.10. Censored data for this endpoint were considered missing and not considered for the analyses. Median survival times for each dose-cohort (low, medium, and high doses) were estimated using the Kaplan–Meier method, and the survival curves generated for each group were compared using the log-rank test. If a significant association between survival and dose was found, the independent association of dose with survival was studied using a multivariate stepwise Cox regression in which all variables with a P value < 0.10 in the univariate analysis were included. The survival analysis was on intention-to-treat. All significant P values (<0.05) were two sided. The SPSS program (Version 19.0, SPSS Inc.) was used for statistical analysis.

Results
A total of 1,182 patients were eligible for this study. Eight hundred and fifty-four patients (72%) were included in trials of MTA and 328 patients (28%) were treated in trials with novel cytotoxics (CTX). Baseline characteristics of the eligible patients are summarized in Table 1.

Patient dose
Median dose received for patients treated with MTA was 73% of the MTD (range 0.3%–240.0%) and distribution according to dose levels was: 235 patients (27.0%) in low doses (<40% of the MTD), 224 (26.0%) in medium doses (40%–80% of the MTD), and 395 (46.0%) in high doses (>80% of the MTD). Median dose for patients treated with CTX was 64% of MTD (range 1.5%–200%) and distribution according to dose levels was: 88 patients (27.0%) in low doses, 141 (43.0%) in medium doses, and 99 (30.0%) in high doses. Prognostic factors were well balanced in the three groups of patients as can be seen in Supplementary Table S1.

Responses and outcomes
Median time on treatment was 18.8 weeks (0.1–192.0). The best response was complete response (CR) for 2 patients treated with MTA and partial response (PR) for 32 patients [(3.0%; 26 (3%) in MTA and 8 (2.0%) in CTX (P = 0.7)], SD in 422 patients [36.0%; 334 (39%) in MTA and 88 (27.0%) in CTX (P < 0.001)], and progressive disease (PD) in 726 [(61.0%; 494 (58%) in MTA and 232 (71%) in CTX (P < 0.001)]. There were significantly more patients with clinical benefit at 3 and 6 months (OR + SD) in the MTA group (P < 0.01 for both; Table 2). However, as can be seen in Table 1, there were significantly more patients with short TPTi (<24 weeks-per-treatment) in trials with CTX: 62.0% versus 53.0% (P = 0.006).

Dose and response
There was no direct relationship between higher doses and response in patients treated with MTA. As can be seen in Fig. 1A, patients that achieved an OR (CR + PR), received a median dose of 50.0%, whereas patients with SD or PD received a median dose of 73.0% and 80.0%, respectively (P = 0.6). However, in trials of CTX agents, there was a trend toward higher doses received by responder patients: those with OR received a median dose of 92.0% and patients with SD and PD 60.0% and 64.0%, respectively (P = 0.08 and P = 0.05; Fig. 1B). When OR was grouped with prolonged stabilization (NPR at 3 and 6 months), we did not find any differences in doses received between "responders" and "nonresponders" (Fig. 1C–F).

When patients were divided into three groups according to dose received, the results were similar. We found a slightly higher response rate for patients in the medium doses for trials with MTA [4.1% vs. 3.0% (low) and 2.6% (high) dose] and for patients treated at high doses with CTX, although results were not statistically significant (Fig. 2). In line with this, the NPRs at 3 and 6 months for patients treated with MTA in the medium doses were higher than those treated at low or high doses (Table 3).

Dose and survival outcomes
After a median follow-up of 43.0 weeks (range 0.4–229), median PFS for the entire cohort was 8.0 weeks [95% confidence interval (CI), 7.6–8.4]; median PFS for patients treated with MTA was 8.0 weeks (95% CI, 7.3–8.7) and 7.1 weeks (95% CI, 5.8–8.4; P < 0.001) for patients treated with CTX. The median OS was 34.9 weeks (95% CI, 32.1–37.7), 34 weeks (95% CI, 30.9–37.1) for patients treated with MTA, and 37.3 (95% CI, 32–42.6) for patients treated with CTX (P = 0.61).

In patients treated with MTA, there was a higher PFS for patients treated at intermediate dose (median 9.9 weeks) compared with 7.9 and 8.0 weeks for patients treated at high and low doses, respectively (P = 0.008; Fig. 3A). Similarly, the OS was worse for patients treated at high doses (median 30.4 weeks) than those treated at intermediate (34.1 weeks) and low dose (35.0 weeks; P = 0.038; Fig. 3B). In patients treated with CTX agents, there was a trend toward better PFS at high doses (median 8.6 weeks) compared with 6.4 and 6.1 weeks for patients treated at intermediate and low doses, respectively (P = 0.07; Fig. 3C). The OS was also better for patients treated at high doses (Fig. 3D).

In the multivariate model adjusted for clinical and demographic variables, the dose (continuous) was not predictive of OS for patients treated with either CTX (HR = 0.7, P = 0.3) or MTA (HR = 1.1, P = 0.4). Because the OR and NPR at 3 and 6 months consistently pointed to a nonlinear relationship between dose and clinical benefit from MTA, we analyzed the multivariate model for OS with dose as a
Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All N (%)</th>
<th>MTA N (%)</th>
<th>CTX N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1,182</td>
<td>854</td>
<td>328</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>677 (57)</td>
<td>503 (59)</td>
<td>174 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>505 (43)</td>
<td>351 (41)</td>
<td>154 (47)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
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</tr>
<tr>
<td>Median (range)</td>
<td>58.4 (18.5–85.5)</td>
<td>58.4 (18.5–85.5)</td>
<td>58.1 (18.5–82.3)</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
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<tr>
<td>ECOG 0</td>
<td>424 (36)</td>
<td>286 (34)</td>
<td>138 (42)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>713 (60)</td>
<td>535 (63)</td>
<td>178 (53)</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>45 (4)</td>
<td>33 (4)</td>
<td>12 (4)</td>
</tr>
<tr>
<td><strong>Number of previous systemic treatments</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (0–11)</td>
<td>2 (0–9)</td>
<td>3 (0–11)</td>
</tr>
<tr>
<td><strong>Time from advanced disease to phase I (mo)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>17.8 (0–302)</td>
<td>18.9 (0–193)</td>
<td>15.1 (0–302)</td>
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<tr>
<td><strong>Number of metastatic sites</strong></td>
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</tr>
<tr>
<td>Median (range)</td>
<td>2 (0–6)</td>
<td>2 (0–6)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td><strong>Site of metastases</strong></td>
<td></td>
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<tr>
<td>Liver metastases</td>
<td>588 (50)</td>
<td>439 (51)</td>
<td>149 (45)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>547 (46)</td>
<td>435 (51)</td>
<td>112 (34)</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>564 (48)</td>
<td>406 (47)</td>
<td>158 (48)</td>
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<tr>
<td>Bone metastases</td>
<td>191 (16)</td>
<td>158 (18)</td>
<td>33 (10)</td>
</tr>
<tr>
<td><strong>Tumor type</strong></td>
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<tr>
<td>Colorectal</td>
<td>227 (19)</td>
<td>160 (19)</td>
<td>67 (20)</td>
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<tr>
<td>Upper gastrointestinal</td>
<td>143 (12)</td>
<td>105 (12)</td>
<td>38 (12)</td>
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<tr>
<td>Gynecological</td>
<td>144 (12)</td>
<td>103 (12)</td>
<td>41 (12)</td>
</tr>
<tr>
<td>Sarcomas and connective tissue</td>
<td>140 (12)</td>
<td>101 (12)</td>
<td>39 (12)</td>
</tr>
<tr>
<td>Lung and mesothelioma</td>
<td>104 (8)</td>
<td>74 (9)</td>
<td>30 (9)</td>
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<tr>
<td>Melanoma</td>
<td>93 (8)</td>
<td>65 (8)</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Genitouriological (nonprostate)</td>
<td>75 (6)</td>
<td>63 (7)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>65 (5)</td>
<td>59 (7)</td>
<td>6 (2)</td>
</tr>
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<td>Breast cancer</td>
<td>64 (5)</td>
<td>40 (5)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>45 (4)</td>
<td>31 (4)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>82 (7)</td>
<td>53 (6)</td>
<td>29 (9)</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>52 (4)</td>
<td>52 (6)</td>
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<tr>
<td>Apoptosis</td>
<td>40 (3)</td>
<td>40 (5)</td>
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</tr>
<tr>
<td>Cell adhesion/migration</td>
<td>29 (3)</td>
<td>29 (3)</td>
<td></td>
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<tr>
<td>Cell cycle/mitosis</td>
<td>93 (8)</td>
<td>54 (6)</td>
<td>39 (12)</td>
</tr>
<tr>
<td>DNA repair</td>
<td>59 (5)</td>
<td>47 (5)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>DNA</td>
<td>163 (14)</td>
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<tr>
<td>Downstream signaling</td>
<td>95 (8)</td>
<td>95 (11)</td>
<td></td>
</tr>
<tr>
<td>Epigenetics and transcription</td>
<td>65 (6)</td>
<td>65 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>75 (6)</td>
<td>53 (6)</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Protein degradation</td>
<td>10 (1)</td>
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<tr>
<td>Tyrosine kinase receptor</td>
<td>339 (29)</td>
<td>339 (40)</td>
<td></td>
</tr>
<tr>
<td>Steroid synthesis</td>
<td>17 (1)</td>
<td>17 (2)</td>
<td></td>
</tr>
<tr>
<td>Stress response</td>
<td>19 (2)</td>
<td>19 (2)</td>
<td></td>
</tr>
<tr>
<td>Tissue remodeling</td>
<td>15 (1)</td>
<td>15 (2)</td>
<td></td>
</tr>
<tr>
<td>Tubulin</td>
<td>111 (10)</td>
<td>19 (2)</td>
<td>92 (28)</td>
</tr>
<tr>
<td><strong>TPTi</strong></td>
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<td></td>
</tr>
<tr>
<td>Slow growing (&gt;24 w/treatment)</td>
<td>517 (45)</td>
<td>399 (47)</td>
<td>118 (38)</td>
</tr>
<tr>
<td>Fast growing (&lt;24 w/treatment)</td>
<td>643 (55)</td>
<td>450 (53)</td>
<td>193 (62)</td>
</tr>
</tbody>
</table>

NOTE: Slow versus fast growing tumor is defined as TPTi ≥ 24 weeks per treatment.
*aData available for 1,137 patients.*
categorical variable in three groups. As expected, patients treated with MTA at intermediate doses had a better survival (HR = 0.8 P = 0.037) than patients treated at low or high doses (Supplementary Table S2). The model also confirmed the results for CTX agents were patients treated at higher doses had better survival than patients treated at doses below 80% (HR = 1.29 and HR = 2.1 for low and medium doses, respectively; Supplementary Table S3).

Trials with no MTD
In six trials of MTA [146 patients (12%)], the MTD was not reached and the dose selection was based on pharmacokinetic/pharmacodynamic data. The results in this subgroup were similar to the entire cohort of patients treated with MTA. Seven patients achieved a PR (4.8%) with median dose received of 25% of the MAD (range 12.5%–50%), whereas nonresponding patients received a median dose of 50% (0.3%–125%; P = 0.236). Six of the responders were treated in the low-dose cohort and the other one in the intermediate dose group. PFS and OS were similar for the three groups of low, medium, and high dose (PFS: 8, 8.3, and 8.7 weeks, respectively, P = 0.9 and OS: 37.4, 37, and 62 weeks; P = 0.29).

Discussion
Our analysis evaluate the dose-effect relationship for both novel cytotoxic drugs and MTA in a large European multi-institutional oncology phase I trials cancer population. Our results confirm the impact of higher doses of experimental cytotoxic drugs in OR, OS, and toxicity as well as the utility of current development design based on MTD. For MTAs, our findings support the observation of others (3, 6, 10) that higher doses do not correlate with an increase in response or survival in unselected patients. The relationship between dose and response with cytotoxic drugs has not been addressed since the early trials which established the dose–response paradigm (2, 3). Our results with novel cytotoxics are in line with these observations with classic chemotherapy as patients receiving >80% of the MTD have higher response rates and longer OS than patients at <80% MTD (52 vs. 34 weeks) with a trend toward longer PFS (8.6 vs. 6.8 weeks). Interestingly, dose level was not predictive of OS in the multivariate model adjusted to clinical and demographic data, suggesting that other variables such as performance status and TPTI have much greater impact on survival.

Postel-Vinay and colleagues (6) and Jain and colleagues (5) have already addressed the question about the correlation between clinical benefit and dose in MTA phase I clinical trials with similar results. Postel-Vinay and colleagues showed, with a cohort of 135 patients treated at the Royal Marsden Hospital (London, United Kingdom) that patients with 0% to 33%, 34% to 66%, or 67% to 100% of the MTD have the same percentage of NPR (combining CR + PR + SD at 3 and 6 months), concluding that potential clinical benefit is not confined to patients treated at the higher doses. Jain and colleagues showed that in 683 patients treated at the MD Anderson Cancer Center (Houston, TX), time to treatment failure was not significantly different between patients treated at lower or higher doses, with a trend for longer time in the lower doses. Our results support these conclusions and add the value of a reference group using a similar cohort of phase I trial patients treated with cytotoxic agents in clinical development. A recently published meta-analysis by Gupta and colleagues (11) suggested that patients treated with doses >60% MTD (in a model controlling prognostic demographic variables as PS, LDH, albumin, and others) had a better overall response rate (CR + PR) and OS. Their dataset includes dose information from 1,262 patients with solid tumors treated across 6 dose levels (<20%, 20%–40%, 40%–60%, 60%–80%, 80%–100%, and >100%). However, it is difficult to directly compare our results because there is no specific mention about the exact contribution of each dose level to the final result (more patients could be in the “high-dose group” while receiving a dose of 60%–80% which would fall into the intermediate dose level that we found to be more active).

Our finding that patients treated with MTA receiving 40% to 80% of the MTD showed a significant increase in PFS and OS compared with the higher doses is not surprising. It has already been observed that higher doses do not necessarily mean increase in clinical benefit, especially in those tumors with predictive biomarkers of response (12, 13). It is well known that higher doses of MTA might be tolerable during the short dose-limiting toxicity (DLT) period (usually 3–4 weeks), but
**Complete/partial response (N = 26)**

PD + SD <3 months (N = 616) OR + SD <3 months (N = 238) PD + SD <3 months (N = 272) OR + SD <3 months (N = 56)

**Medians**

- Molecularly targeted agents: Median = 50%
- Cytotoxic agents: Median = 73%
- Molecularly targeted agents: Median = 80%
- Cytotoxic agents: Median = 67%

**Best response**

- Molecularly targeted agents: Median = 50%
- Cytotoxic agents: Median = 73%

**PD (N = 494)**

- Molecularly targeted agents: Median = 80%
- Cytotoxic agents: Median = 67%

**SD (N = 364)**

- Molecularly targeted agents: Median = 73%
- Cytotoxic agents: Median = 63%

**Median = 67%**

**SD (N = 494)**

- Molecularly targeted agents: Median = 80%
- Cytotoxic agents: Median = 64%

**Best response**

- Molecularly targeted agents: Median = 80%
- Cytotoxic agents: Median = 80%

**PD (N = 232)**

- Molecularly targeted agents: Median = 64%
- Cytotoxic agents: Median = 63%

**Median = 80%**

**PD + SD <3 months (N = 238)**

- Molecularly targeted agents: Median = 80%
- Cytotoxic agents: Median = 63%

**Median = 80%**

**PD + SD <3 months (N = 238)**

- Molecularly targeted agents: Median = 80%
- Cytotoxic agents: Median = 64%
chronic toxicity can limit the long-term tolerance. In fact, a publication by Postel-Vinay and colleagues shows that in a cohort of 445 phase I trial patients, 30% patients interrupted temporarily or definitively experimental treatment and 10% reduced the administered dose, in most cases after cycle 2 (14). There are other examples of an increase in clinical benefit with lower-than-MTD doses as with temsirolimus (15) or cediranib (16). Despite this, phase I trial design for MTA still favors classical MTD evaluation rather than the association of pharmacokinetic or pharmacodynamic endpoints and/or ORs (17).

Our study has some limitations. In the era of MTA, not only OR, but also prolonged SD may be of clinical benefit in patients with cancer. Because of the inherent characteristics of phase I trials, in which patients with excellent performance status and optimal organ function are accepted, there is a selection bias toward patients with slow growing tumors. In our cohort, 44% of patients presented with “slow growing” tumors as defined by TPTi ≥ 24 weeks per treatment, and in the group of patients treated with MTAs, 59% fell into this category. This highlights the fact that PFS or time-to-progression in non-randomized phase I trial patients with SD as best response could be misleading as markers of efficacy. We conclude that not only RECIST, but also complementary tumor response evaluation techniques such as circulating tumor cells or DNA, PET scans, or dynamic evaluation of tumor growth before and during experimental treatment should be implemented to better characterize potential tumor response in these patients (18).

Our results do support the current concept of biomarker-driven phase I clinical trials. Furthermore, to define a RPD2 for a MTA based only on the MTD in unselected population could be detrimental to candidate patients. Using the classic definition of MTD (<33% of patients with DLT during the first cycle) many patients who could benefit from the treatment, may not be able to tolerate it due to excessive toxicity, whereas lower doses could achieve equivalent antitumor activity. Thus, the primary objective of the phase I trial should be not just to define the MTD but rather to prove that the drug is tolerable at a biologically active dose. In many new anticancer agents not only toxicity, but also mostly efficacy will determine the RPD2, and potential treatment benefit will depend more on the presence of a particular mutation and target modulation rather than the dose (19).

Figure 2. Relationship between mean percentage of MTD received and OR for MTAs (A) and CTX agents (B).
In conclusion, these results support the development of novel CTX agents based on MTD. We also found that patients treated at intermediate dose levels (40%-80% of the MTD) obtained greater clinical benefit from phase I trials of MTA. We did not find a benefit for utilizing doses close to the MTD in unselected patients.
treated with MTA, and this should be borne in mind in the clinical development plans of these agents.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
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