Late phase 1 studies: concepts and outcomes of a new clinical trial design

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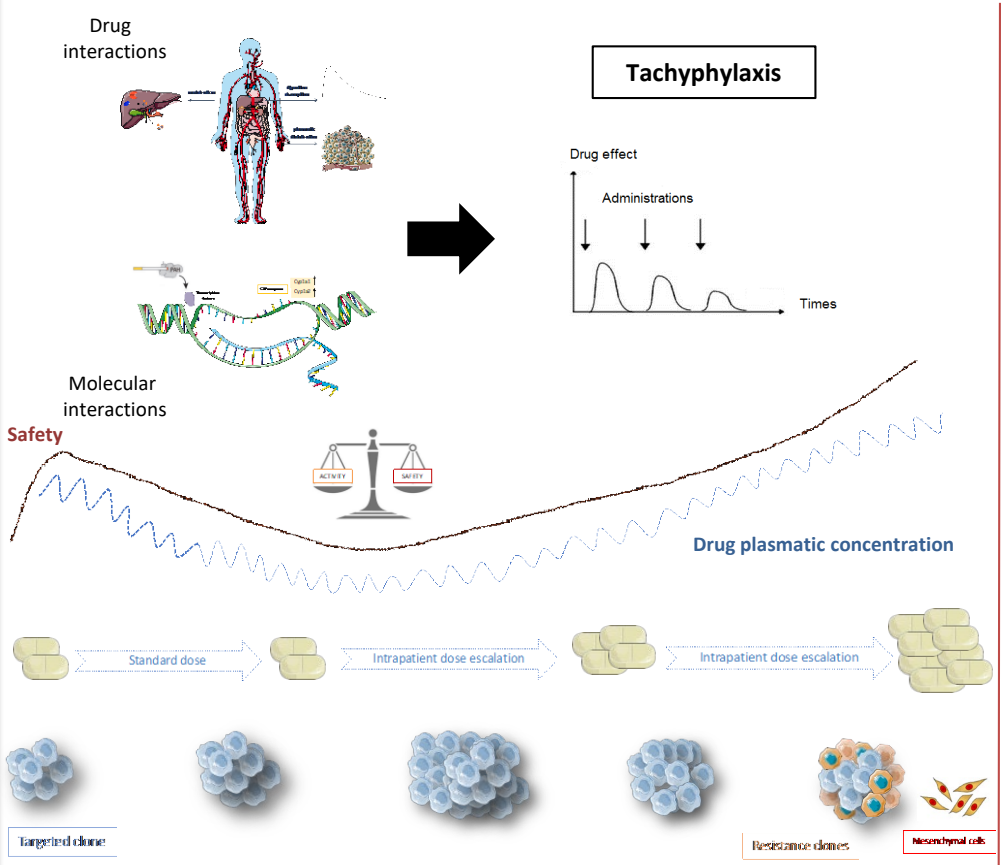
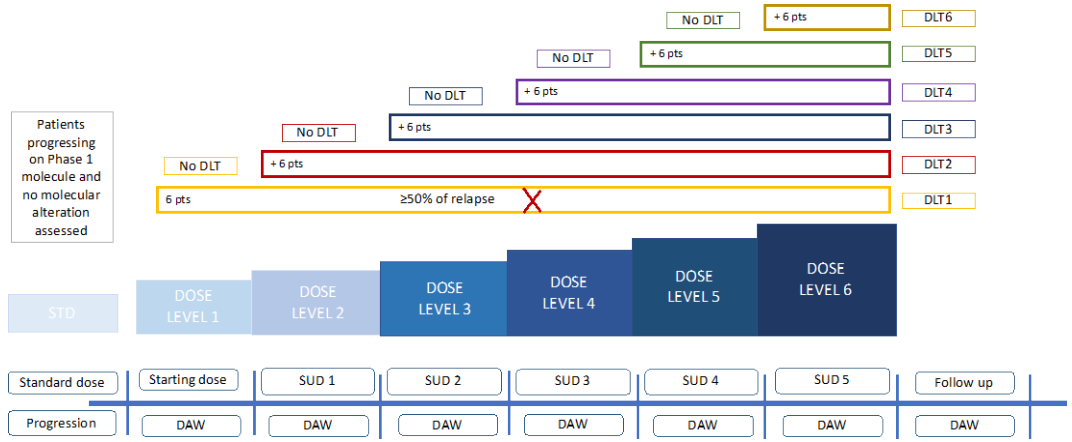


Figure 1. Targeted therapies have become cornerstone treatments for many cancers harboring oncogenic addictions. The emergence of tumor-resistant mechanisms paved the way for next generation inhibitors. Insufficient concentrations of targeted therapies is a frequent but poorly explored mechanism of treatment failure. In some series, a 51% of suboptimal drug blood concentration have been found (26/51 pts). Some drugs such as alectinib, osimertinib or sotorasib did not reported a maximal tolerate dose in their respective phase I trials. A new dose escalation in a pts chronically exposed is possible because of tachyphylaxis. It allows to dose escalade higher than in pts never exposed and increase drug diffusion in sanctuary sites, such as brain. We propose a new concept in clinical development, the late phase 1 trials, to restore drug efficacy at the time of failure at the standard dose. The primary goal of these studies is to define a new maximal tolerated dose (MTD) of a drug in chronically-exposed patients (MTDc) and restore activity. Eligible patients (pts) must be still on treatment with the standard dose of the drug, experienced initial benefit and subsequently progressed without an identified resistance alteration.



* STD: Standard dose; SUD: Step-up dose; pts: patients; DAW: DLT assessment window; DLT: dose limiting toxicity; MTD: maximum tolerated dose ; RP2D: recommended phase 2 dose; MTDc: chronic maximum tolerated dose; LED: late effective dose.

Model	Design	Objectives	MTDc	LED	OBD	Late DLT	Recommended dose	Advantages	Limitations	Possible applications
Late dose-escalation phase 1	Multiple-entry late phase 1	MTDc/LED/ DLT groups	DEL dose below late DLT	DEL dose below MTDc	---	DEL with >33% DLT events	LED	DLT estimation/ Multiple assessment of MTDc-LED-DLT	Number of patients/ Complex design	CT/TKI/ICI/ ADC/ BsAb/ combination
Biological dose-guided escalation late phase 1	---	MTDc/LED	DEL dose below late DLT	Biological proved activity dose assed by PK/PD with no late DLT	PK/PD/ biological activity	DEL with >33% DLT events	OBD	Real biological dose	Technique/ Cost	TKI/ICI/ADC/ BsAb/ combination
Genomic-guided dose-escalation late phase 1	ctDNA monitoring	MTDc/LED/ OBD	DEL dose below late DLT	Biological proved activity dose assed by ctDNA with no late DLT	Negative ctDNA	DEL with >33% DLT events	OBD	Biological response/Targeted monitoring/FU biomarker	Technique/ Cost	TKI/ICI/ADC/ BsAb/ combination
	Allele frequency monitoring	MTDc/LED/ OBD	DEL dose below late DLT	Biological proved activity dose assed by VAF% with no late DLT	VAF>20% reduction	DEL with >33% DLT events	OBD	Biological response/Targeted monitoring/FU biomarker	Technique/ Cost	TKI/ICI/ADC/ BsAb/ combination

* MTD: maximum tolerated dose; LED: late effective dose; OBD: objective biological dose; DEL: dose escalation level; DLT: dose limiting toxicity; VAF: variability of allele frequency; PK: pharmacokinetics; PD: pharmacodynamics; FU: follow up; TKI: tyrosine kinase inhibitor; ADC: anti-drug conjugated; BsAb: bispecific antibody; ICI: immune checkpoint inhibitor.

Figure 2. *Late phase 1 studies multiple-entry design.* Groups composed of six pts will assess the best MTDc as a new late phase 1 recommended standard dose. The first group will initially be treated with a 'dose level 1', corresponding to the standard approved dose by regulatory agencies plus a predetermined dose increase. If no dose limiting toxicity (DLT) is reported after one DLT assessment window (DAW), these first six pts will move forward to dose level 2, and an additional new cohort will be directly included at the second dose escalation level; these cohorts will move forward to dose level 3 (dose level 2 dose plus predetermined increase dose) after one DAW without reporting any DLTs. Groups of six pts will start the study from sequentially established dose levels until the maximal late dose, determined by the dose level with unacceptable toxicity.
If two of six patients in a cohort have DLTs, six additional patients will be included at the same dose level. Each cohort will stop at a dose level reporting ≥33% of DLT events included patients. Unique DLTcs will be described for each subgroup. Cohorts of patients reporting disease recurrence higher than 50% within the trial will be excluded from the analysis.

Table. *Late phase 1 models characteristics.* Along with the definition of MTDc, these trials will determine a late effective dose (LED) in pts, defining the optimal scheme for a rapid intrapatient dose escalation and hopefully reverse drug resistance.

We proposed two new models of late phase 1 based on biological characteristics and evolution of the tumor. These designs will assess the variability of the ctDNA and allele frequency during the monitoring to define the optimal MTDc.

Conclusions

- Late phase 1 trials could be a new approach to restore the activity of a drug by intra-patient dose escalation in cases of relapse without evidence of resistance mutations.