Threshold of Credibility: A New Approach to Product Development for Metastatic Melanoma Therapy

Ke Liu MD PhD & Steven Hirschfeld, MD PhD
Office of Cellular, Tissue and Gene Therapy
Center for Biologics Evaluation and Research
FDA

The Challenge

- Metastatic melanoma is a disease with an invariably fatal outcome in the absence of effective treatment. Only two therapies have been licensed by the FDA-dacarbazine and IL-2. To foster development of new therapeutics for metastatic melanoma, we have reviewed the data submitted for licensure with the intention of suggesting efficient models for pre-trial planning and trial design and to create model pathways for product development.

Patients in Clinical Trials that supported approval of IL-2 for melanoma

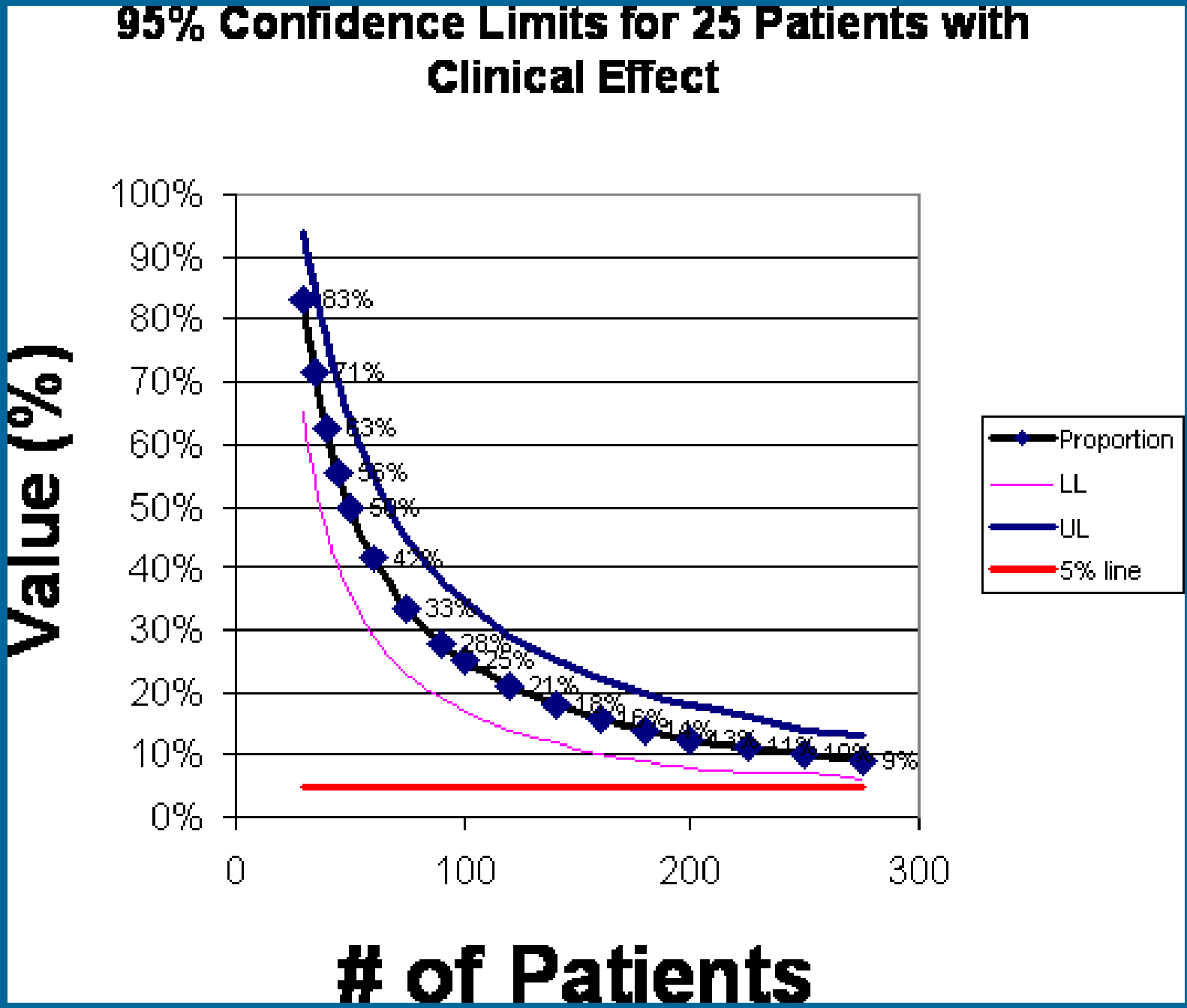
Trial number	**0524**	**0097**	**0053**	**0094**	**0063**	**70002**	**0170**	**29106**	***Total***
Number in study	28	**84**	32	3	9	**45**	64	5	*270*
# CR	2	**6**	2	0	0	**5**	1	1	*17*
# PR	2	**8**	3	0	1	**6**	5	1	*26*
CR in % (95% CI)	7 (0.8–23.5)	**7 (2.7–14.9)**	6.4 (0.8-20.8)	0 (0 – 70.8)	0 (0 – 33.6)	**11 (2.6 – 17.3)**	2 (0.06-11.7)	20 (0.06 – 11.8)	*6 (3.9 – 9.8)*
PR in % (95% CI)	7 (0.8–23.5)	**10 (4.2–17.9)**	9.6 (2–25)	0 (0–70.8)	11 (0.3-48.3)	**13 (3.5-19.3)**	8 (3.7-24)	20 (3.7-24.1)	*10 (6.7-13.7)*
OR in % (95% CI)	14	**17**	16	0	11	**17**	13	40	*16 (12- 20.1)*

The Observation

- Both empiric evidence and statistical analysis of pivotal trials leading to oncology product approvals have shown that, to obtain licensure, the intended clinical effect should be achieved in a minimum of 20 -30 experimental subjects. We term this number the threshold of credibility.

The Concept

- The design and size of studies required to establish the threshold of credibility depend upon the endpoint selected and the activity of the regimen. To demonstrate clinical benefit, a sponsor should plan to show that at least 20-30 subjects in the same treatment arm of a clinical trial achieve a clinically meaningful endpoint.

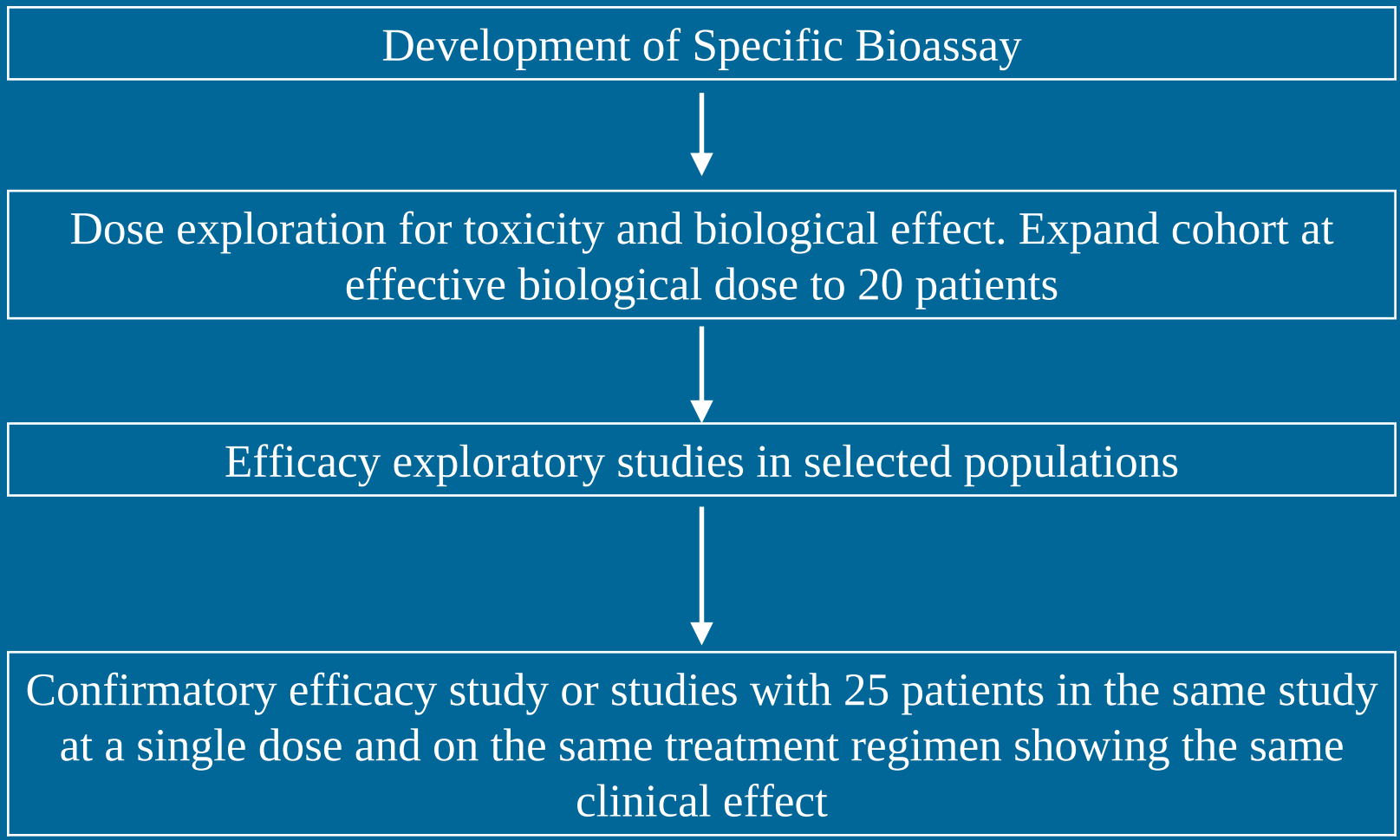

95% Confidence Limits for 25 Patients with Clinical Effect
Value (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
100
200
300
# of Patients
83%
71%
63%
56%
50%
42%
33%
28%
25%
21%
18%
16%
14%
13%
11%
10%
9%
Proportion
LL
UL
5% line

Hypothetical Staged Analyses of a Confirmatory Efficacy Study

Melanoma Proposal

- Resolution of cutaneous lesions could be considered clinical benefit
- Progression free survival and overall survival could be sequential endpoints in the same study

General Development Schema



The Possibility

- Rapid development leading to a “go or no go” decision and recognition of potential based on accepted methodologies will not only conserve resources and reduce ambiguity, but also will provide a credible response to the urgency required by the current state of treatment for metastatic melanoma and the needs of melanoma patients and their care providers.

The Result

- Use of an integrated development plan and a threshold approach to trial design could shorten development time and conserve resources in addressing the urgent need for new therapies.