Tumour-specific randomized controlled trials in rare oncogene-driven cancers: asking for the impossible?

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BACKGROUND

- Randomized controlled trials (RCTs) remain the gold standard for evaluating the efficacy and safety of new interventions.
- Development of oncologic therapies that target specific gene mutations ("targeted therapies") has led to an important shift in how these new therapies are evaluated in clinical trials, particularly when targeting rare genomic alterations.
- Factors that influence the feasibility of RCTs of targeted therapies include the prevalence of the target genomic alteration, the number of potential tumours indicated, number of trials competing for the same pool of patients, and unmet need.
- NTRK fusion positive tumours can be considered as a case example: numerous different tumours have been associated with NTRK fusion positivity, multiple tumour-specific RCTs would be required to investigate NTRK-targeted therapies across all potential settings
- However, given NTRK positivity's very low prevalence (0.27%), ensuring well powered RCTs at the tumour level can be challenging.
- Furthermore, these RCTs would have to compete for patient enrollment across multiple NTRK targeted therapies.
- "Basket trials" which refer to those that enroll patients with a specific genomic alteration into a single trial across multiple tumour types have emerged to address feasibility issues in these settings. While randomized basket trials could potentially be considered, these trials would share most of the limitations of histology-specific RCTs. Given small patient populations and high unmet need, basket trials are often single-arm in nature.
- While basket trials overcome several of the before mentioned challenges, they are associated with analytic challenges.
- We developed a decision tool to assess the feasibility of conducting tumour-specific RCTs as an alternative to single-arm basket trials, based on features of disease and mutation prevalence. NTRK fusion positive was the case example.

METHODS

- A feasibility tool was built in Microsoft Excel according to the schematic presented in **Figure 2.** The tool was built to evaluate the feasibility of conducting an NTRK RCT program that considers 12 tumours observed in the clinical trials of entrectinib in NTRK fusion-positive tumours.[1]

Sample size - related parameters

- The assumed primary outcome of interest was progression-free survival (PFS). The required sample size was estimated for each tumour based on the assumption of SoC PFS as reported for relevant SoC therapies (**Table 1**), and a clinically-meaningful difference of 30% reduction in PFS hazard associated with targeted therapy (1:1 allocation; alpha = 0.05; beta = 0.2).[2]
- Estimates of PFS at the tumour level were obtained from the literature from clinical trials of therapies prescribed in Canada for the management of patients with similar treatment experience in the STARTRK trial (NTRK+ patients).[1]

Enrollment rate - related parameters

- Enrollment rate in each tumour-specific trial was dependent on the enrollment rate in the clinical trial program of NTRK mutations (STARTRK-2 2018 average; 4.25 patients per month over 150 sites).
- Patient enrollment across tumour-specific trials was assumed to follow the same distribution as observed in the STARTRK trial program (**Table 1**).
- The time required to enroll patients into each tumour-specific RCT was estimated based on the tumour-specific enrollment rate and the estimated sample size.

Feasibility - related parameters

- Time to reporting of study results was estimated as the time to enroll the target sample size for the tumour-specific trial plus time to reach median PFS in the intervention arm plus six months from date of data lock up to readout of results.
- An individual RCT was deemed to be feasible if time to generation of interim study results was less than an arbitrary threshold of 5 years. The minimum required study duration for the conduct of the trial program was estimated as the maximum study duration across all tumour-specific RCTs.
- Two sensitivity analyses were conducted: 1) fixed enrollment of 2 patients per month across trial program (average STARTRK-2 recruitment), and 2) enrollment rate was assumed homogeneous across tumours (**Table 1**).

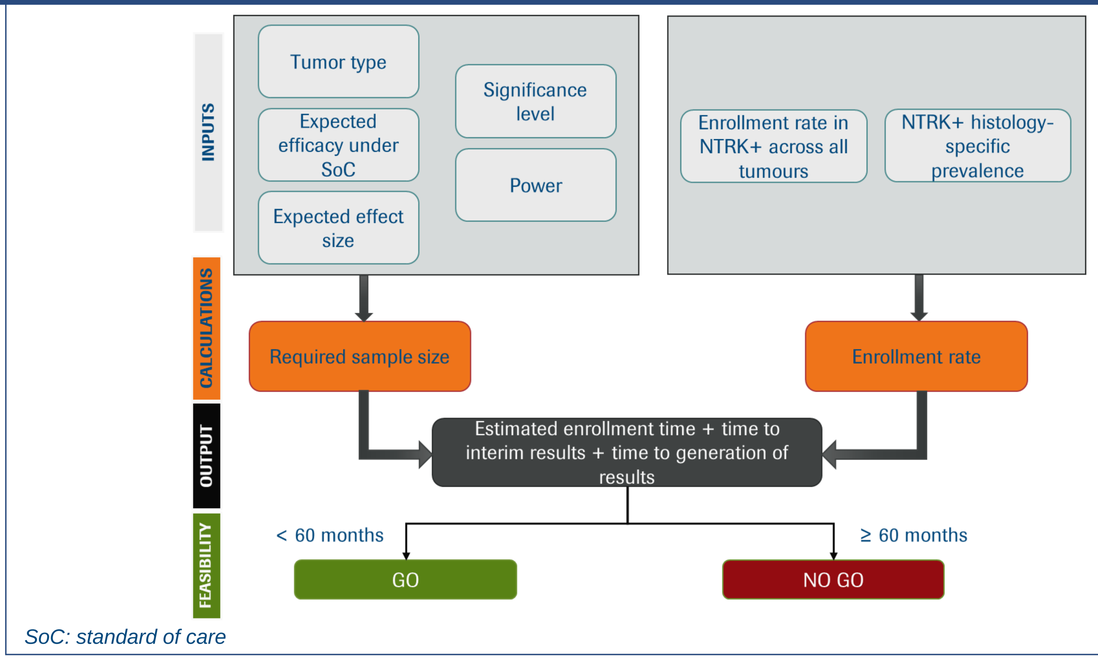
Table 1. Feasibility tool model inputs

Cancer type	Median PFS (months)	STARTRK trial patient enrollment	Enrollment rate / month		
			4.25 patients per month[a]	2 patients per month[a]	Homogeneous enrollment (4.25 pts/m)[b]
Colorectal cancer	7.8	4	0.33	0.16	0.39
MASC	4.5	7	0.58	0.27	0.39
Papillary thyroid	15.8	3	0.25	0.12	0.39
Anaplastic thyroid	3.0	2	0.17	0.08	0.39
Squamous NSCLC	3.6	2	0.17	0.08	0.39
Non-squamous NSCLC	3.3	8	0.67	0.31	0.39
Pancreatic cancer	4.1	3	0.25	0.12	0.39
Sarcoma	5.6	13	1.08	0.51	0.39
Neuroendocrine	9.7	3	0.25	0.12	0.39
Secretory breast cancer	4.3	4	0.33	0.16	0.39
Non-secretory breast cancer	4.5	2	0.17	0.08	0.39

MASC: Mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer; pts/m: patients per month.

[a] Distribution across tumours based on STARTRK trial patient enrolment; [b] 4.25 patients evenly distributed across tumours.

Figure 2. Feasibility tool schematic



SoC: standard of care

RESULTS

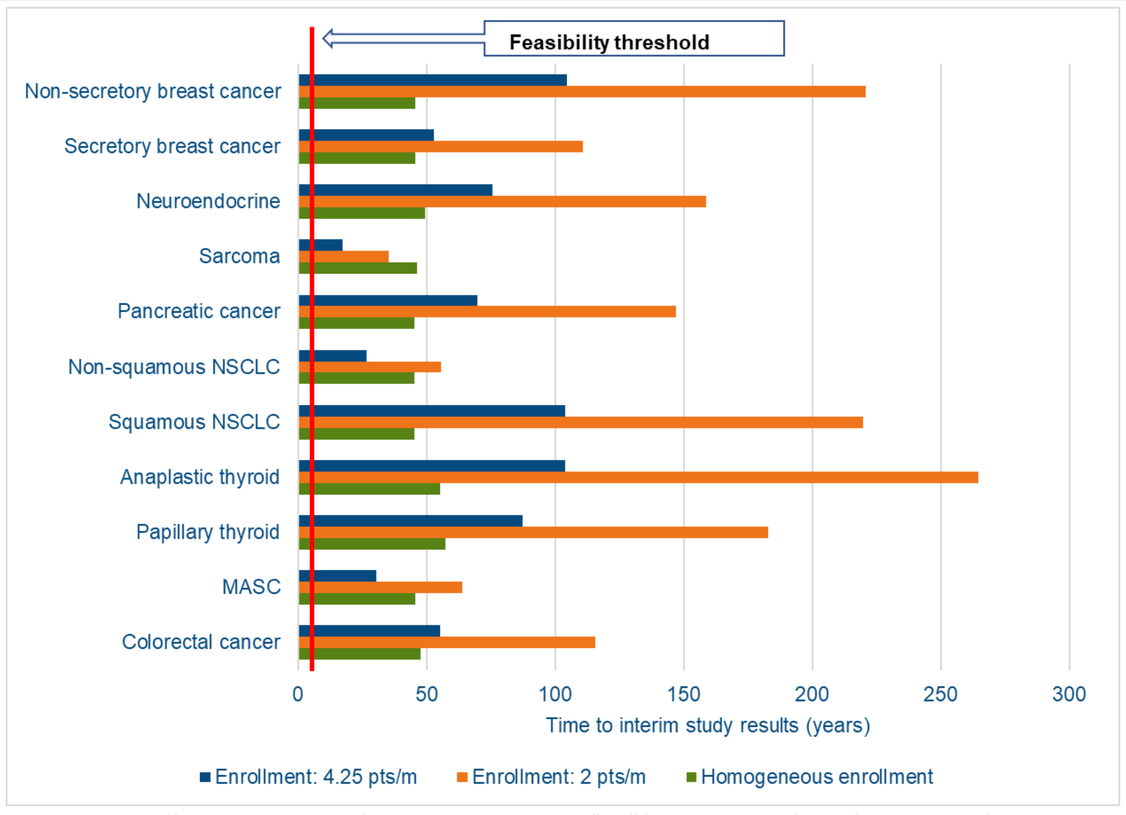
- Across all tumours, sample sizes per tumour type required to achieve sufficient power ranged from 206 to 255 (trial program N=2,387).
- Under base case assumptions, the time to study results ranged from 17 to 105 years, which led to all individual RCTs being deemed infeasible at the a priori threshold of 5 years (**Table 2**).
- The RCT trial program remained infeasible across all scenario analyses considered (**Figure 3**).

Table 2. Assessment of feasibility for tumour-specific RCTs in NTRK positive cancers

	Minimum sample size	Time to study results (years)	Feasible?
Colorectal cancer	215	55	✗
MASC	207	31	✗
Papillary thyroid	255	87	✗
Anaplastic thyroid	206	104	✗
Squamous NSCLC	206	104	✗
Non-squamous NSCLC	206	27	✗
Pancreatic cancer	206	70	✗
Sarcoma	209	17	✗
Neuroendocrine	222	76	✗
Secretory breast cancer	207	53	✗
Non-secretory breast cancer	207	105	✗

MASC: Mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer.

Figure 3. Feasibility assessment in the base case and scenario analyses



MASC: Mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer; pts/m: patients per month.

CONCLUSIONS

- Conducting tumour-specific RCTs can be infeasible for targeted therapies aimed at low prevalence mutations, based on consideration of time and resources needed for the conduct of the RCT program
- This analysis found tumour-specific RCTs to be infeasible in the case of NTRK fusions; this is focusing on an outcome of PFS – overall survival, which is of higher relevance to payers, would lead to even longer trial durations.
- Based on these findings it was concluded that in the case example of NTRK fusion positive tumours, basket trials are the only feasible approach to assess efficacy. Use of basket trials allows for quicker access to novel therapies targeting patients with rare diseases.

REFERENCES

1. Drilon A, Liu SV, Cho BC, et al. 2017. ACR Annual Meeting 2017; April 1–5, 2017, 2017; Washington, DC
2. Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman & Hall/CRC Biostatistics Series