A regulatory view on the role of registries for generating data on cancer therapies

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What are potential regulatory uses of registries in oncology?

- **Describing the prevalence and prognosis of biomarker-selected populations**
- **Defining comparator cohorts for single arm trials**
- **Use as post-authorisation efficacy studies: Informing on outcomes achieved overall / outcomes in subgroups or special populations**
- **Use as post-authorisation safety studies: addressing drug-specific safety issues, or safety in special populations**

Describing the prognosis of biomarker-selected populations

- **It is not uncommon that the prognostic impact of a biomarker, proposed to define an indication, is not known.**
- **This hampers both the interpretation of Duration of Response (DoR) as well as any comparison with non-biomarker selected populations**
- **From the withdrawal AR for Opdivo MSI-H CRC:**

"*The MAH argues that patients with MSI have a worse prognosis and that response to therapy is lower than that in non-MSI (MSS) mCRC patients. However, current knowledge in the field is limited and no sound evidence has been provided to substantiate that this general statement is true across the different lines of treatment*."

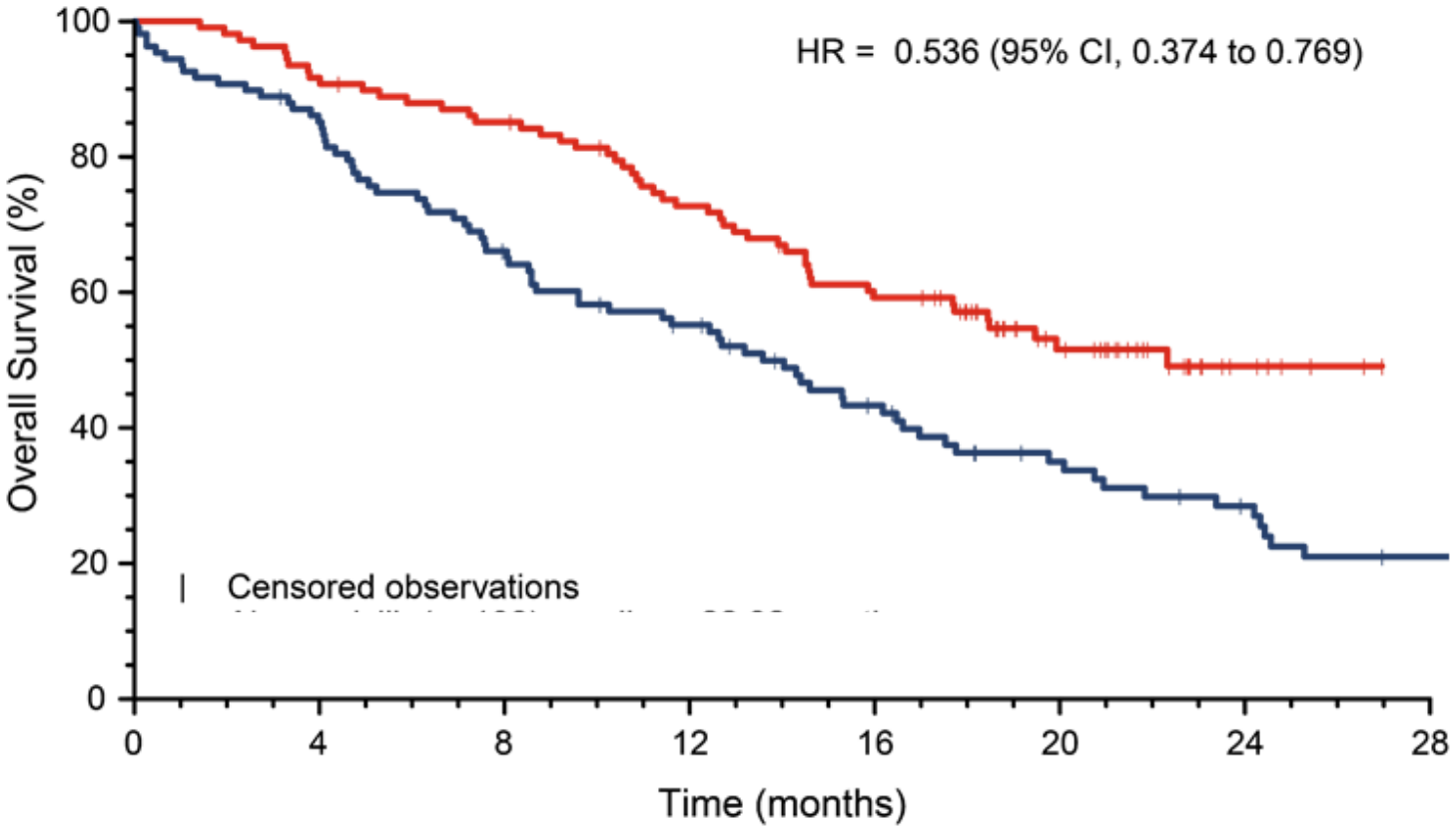
Defining comparator cohorts for single arm trial

Concerning the matching of study patients and external controls

- **What is the source of the external controls and how were they selected?**
- **Was the use of external controls pre-planned, including the method of data analysis and the hypothesis described in the statistical analysis plan?**
- **If controls are matched, what is the matching procedure and how are key prognostic variables represented by these criteria?**
- **Are important prognostic variables missing and not captured indirectly by those used?**
- **Are the populations adequately matched on the selected criteria?**
- **Are missing data (e.g., outcomes, censoring) managed similarly in the study and in the external controls?**

Is there a conflict between pre-specification and efficiency of matching?

Example: SAT results compared with matched controls from Flatiron database



Clinical trials often have inclusion criteria such as:

- ***Likely to survive 3 months***
- ***ECOG performance status 0-1***
- ***No serious comorbidities***
- ***Adequate end-organ functions***

How are such selection criteria represented in the selection of the external controls?

Are relevant data available from the registry?

How is a common baseline established for time dependent endpoints?

- **Are all patients in the study and in the external control dataset in progression at the time of initiation of therapy (for instance, the availability of a clinical trial may prompt initiation or switching of therapy)?**
- **Is the time from progression to initiation of new therapy similar in the study and among external controls?**
- **Beware of immortal time bias**

Are methods of evaluation similar in the study and the external controls?

- **Are the methods of evaluation of baseline variables and study endpoints similar between the SAT and the external controls (e.g., use of RECIST criteria)?**
- **Are the same testing schedules and timetables used in the SAT and the external control?**
- **Are key measurements liable to be impacted by centre and setting (e.g., the use of symptom scores, rating scales or measures requiring the training of investigator and/or study subject)?**

Is the background standard of care similar in the study and in the external controls?

- **Are background treatment interventions, post-progression therapies and supportive care adequately captured in both datasets?**
- **Are post baseline treatment decisions made on the same basis and according to the same rules**
- **How similar or different is the healthcare visit schedule in the trial and the external control setting?**
- **Are secular or geographic trends in management and outcome or differences in concomitant therapies and supportive care understood and handled as potential sources of bias?**

Non-interventional studies and registries to meet specific obligations to corroborate efficacy and safety – The Vitrakvi case

- **Larotrectinib is an inhibitor of TRK-A, -B and -C**

VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,

- ***who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and***
- ***who have no satisfactory treatment options (see sections 4.4 and 5.1).***

Conditional marketing authorisation based on pooled single arm trial data

Table 6: Overall response rate and duration of response by tumour type

Tumour type	Patients (n=102)	ORR		DOR	
		%	95% CI	≥ 12 months	Range (months)
Soft tissue sarcoma[a]	21	81%	58%, 95%	78%	1.9+, 38.7+
Salivary gland[a]	17	88%	64%, 99%	91%	3.7+, 33.7+
Infantile fibrosarcoma[a]	13	92%	64%, 100%	60%	1.6+, 17.3+
Thyroid[a]	10	70%	35%, 93%	86%	3.7, 29.8+
Primary CNS[b]	9	11%	0%, 48%	NR	2.0+
Lung[a]	7	71%	29%, 96%	75%	7.4+, 25.8+
Melanoma[a]	7	43%	10%, 82%	50%	1.9+, 23.2+
Colon[a]	6	33%	4%, 78%	NR	5.6, 9.2+
Gastrointestinal stromal tumour[a]	4	100%	40%, 100%	67%	7.4+, 20.0+
Bone sarcoma[a]	2	50%	1%, 99%	0%	9.5
Cholangiocarcinoma[a]	2	SD, NE	NA	NA	NA
Congenital mesoblastic nephroma[a]	1	100%	3%, 100%	NR	9.8+
Appendix[a]	1	SD	NA	NA	NA
Breast[a, c]	1	PD	NA	NA	NA
Pancreas[a]	1	SD	NA	NA	NA

Tissue of tumour origin and concomitant genetic alterations are likely effect modifiers

- **In patients with rare tumour types where NTRK-fusions are common, ORR was higher than in patients with common tumour types where NTRK-fusions are rare**
- **The ORR in 48 patients who had other genomic alterations in addition to *NTRK* gene fusion was 58%, and in 37 patients without other genomic alterations ORR was 84%.**
- **There are no reliable estimates of the impact on PFS and OS in different target histologies and lines of therapy**
- **An RCT in a NTRK-positive target population was not considered feasible**

Key objectives of the specific obligations (SOB)

- **To provide more precise effect estimates (ORR, DoR)**
- **To further characterise tissue of tumor origin as an effect modifier (corroborate the assumption of ”histology independent” activity) – endpoint ORR**
- **To identify potential tissues of origin where larotrectinib does not have clinically relevant activity – endpoint ORR**
- **To provide further PK data in small children**
- **To provide long term safety outcomes (particularly in children)**

The applicant proposed as key SOB

- **A prospective non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib**
- **The purpose of this study is to evaluate, under real-world conditions, the safety and effectiveness of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrollment.**

Evaluation of the proposed non-interventional SOB

- **The planned non-interventional real-world design was not considered to be able to provide an unbiased (in relation to the criteria used in the SAT) and precise measure of the size of the treatment benefit on ORR, DoR and time-dependent outcome measures**
- **This is since tumour assessments will not be performed at pre-defined time intervals, and will generally not be evaluated according to RECIST criteria.**
- **Long term safety in pediatric patients better studied in an interventional protocol**
- **"*An interventional single arm study to address the non-comprehensive data should be proposed as specific obligation (SOB) for a CMA*."**

EURACAN

- **The Marketing Authorisation Holder will support a European adult registry through the European Reference Network (ERN)-EURACAN, a European network focusing on rare adult solid cancers**
- **The EURACAN Genomic registry will be set up to collect genomic, clinical and safety data.**
- **Bayer will receive annual summary results (efficacy and safety) in counterpart of its support to the EURACAN registry.**

Conclusions

- **The most evident regulatory use of cancer registries presently is to define the prevalence and the prognostic impact of biomarker-defined populations**
- **The use of registries to select external populations as ”formal” control groups in inferential/pivotal clinical trials in oncology is presently not appropriate, because the impact of unmeasured confounders in comparisons is not sufficiently understood**
- **The appropriateness of registries for post-authorisation commitments depend on the nature of the concerns and the corresponding ability of the study to capture key data**