Targeted therapies in solid oncology: what are the challenges for market access in France?

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Context & Objectives

Targeted therapies aims at targeting molecular alterations to block tumor growth or spread.
All medicinal products are assessed by the French HTA body (TC) to obtain their reimbursement. The clinical trials supporting MA application of targeted therapies are often non-comparative trials with a limited number of patients. These levels of evidence diverge from the methodological standards required by the TC doctrine. However, particularities of targeted approaches in solid oncology must be highlighted:

- Short-term life-threatening pathologies
- Partially or not covered medical need
- Small target population

Then, prices are negotiated between CEPS and pharmaceutical companies. Negotiations are partly based on the TC opinions.
On the one hand, in France, more than 50% of cancer drug reimbursement expenses are targeted therapies. On the other hand, there is an increase of cancer patients due to a diversification of targeted molecular alterations and to the efficacy of treatments (cancers tend to become chronic diseases).
Therefore, there is an increase in the budgetary impact on society. The need to develop actions on the price levels of targeted therapies and the need to promote transparency in price negotiation has then become essential.

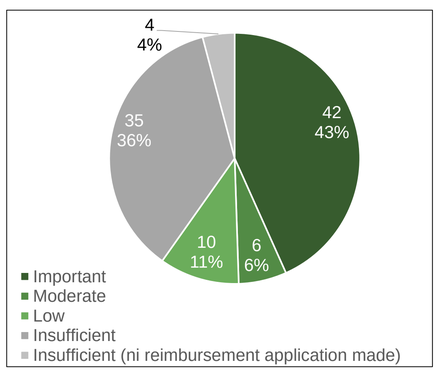
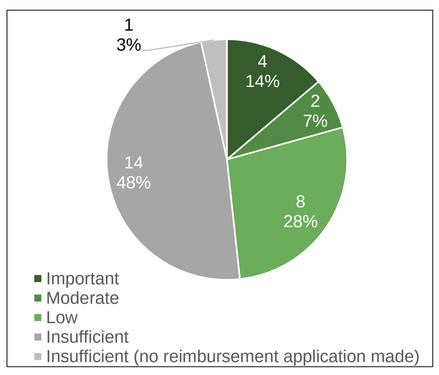
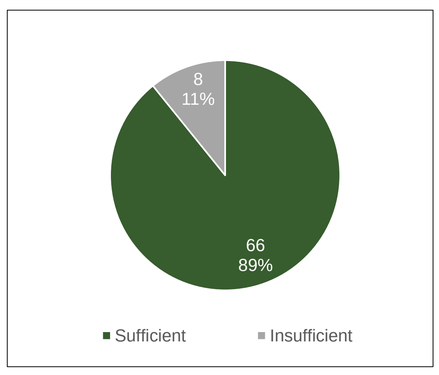
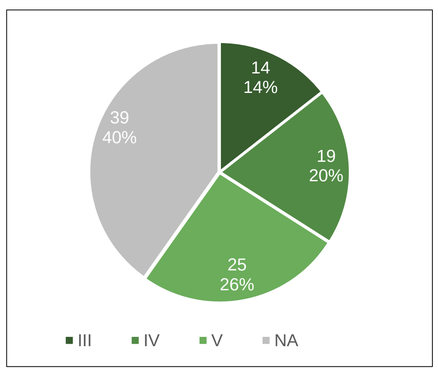
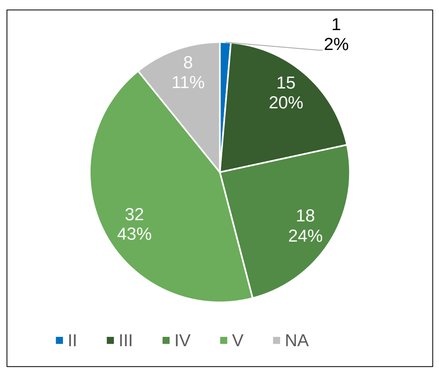
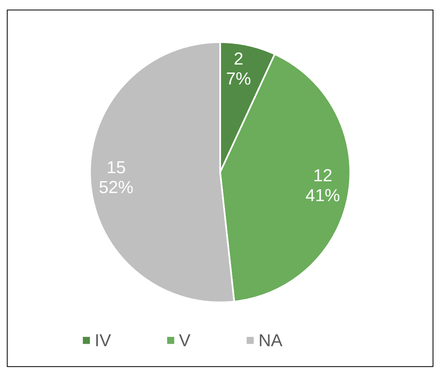
This research aims at identifying challenges of market access for targeted therapies in solid oncology, at assessing the management of uncertain data by the TC, and the impact on health products pricing.

Methods

All TC opinions of targeted therapies in solid oncology from 2018 to February 2024 were extracted. Approvals and extensions were the only TC opinions taken into account. Generic and biosimilar products were excluded from the analysis. Therapies that submitted phases I, I/II or II clinical trials and for which the TC assessment considered that there was no or low added value (ASMR IV, V or SMR insufficient) were selected for a further analysis of transcripts of TC debates and levels of prices.

Results

Among the 97 indications of targeted therapies extracted, 29 had submitted early phases clinical trials and demonstrated no progress or low added value. 15/29 had an insufficient SMR which is **16 times higher** than the proportion of all indications assessed by the TC in 2022, whereas 12/29 had an ASMR V which is **twice as large** as the proportion of indications assessed in 2022. The median time for the TC evaluation was 156 days, **49 days longer** than the median time of standard indications in 2022.
The mean time for the prices negotiation was 505 days, **287 days longer** than the mean time for all indications evaluated in 2022. The DOT was very variable with a maximum range of 437,30 €.

	97 indications of targeted therapies	29 indications of targeted therapies with early phases clinical trials	74 indications assessed in 2022
Level of SMR			
Level of ASMR			
TC assessment period	151 days	156 days	107 days

	Period between TC opinion and price publication (in days)	
	Approvals	Approvals except products under negociation
Mean	594	506
Median	571	328
Min	106	134
Max	1121	1121

DCI	Spécialité	Aire thérapeutique	Price publication	DOT (€)
Brigatinib	ALUNBRIG	NSCLC	12/03/2020	132,67
			22/02/2022	126,04
Lorlatinib	LORVIQUA	NSCLC	21/07/2020	132,67
			15/04/2023	120,00
Larotrectinib	VITRAKVI	Tumors that have a NTRK gene fusion	20/11/2020	548,86
Vandetanib	CAPRELSA	Thyroid gland tumor	21/01/2022	119,00
Pemigatinib	PEMAZYRE	Bile duct cancer	25/10/2022	294,55
Crizotinib	XALKORI	Inflammatory myofibroblastic tumor	06/06/2023	119,56
			12/12/2023	113,58
Trastuzumab deruxtecan	ENHERTU	gastric or gastro-oesophageal junction cancer	23/02/2024	341,33
Trastuzumab deruxtecan	ENHERTU	Metastatic breast cancer	23/02/2024	288,00
Avapritinib	AYVAKYT	Gastrointestinal stromal tumour	04/04/2024	556,30

CONCLUSION

Efficacy/adverse events ratio is poorly established in view of methodological weaknesses of early phase trials. Therefore, these trials can lead to deteriorated assessments, lack of reimbursement or complex negotiations of the prices of targeted therapies in solid oncology. Since France is an international price reference, a decision not to market these drugs can be made. Thus, promoting access to targeted therapies seems necessary to offer treatment alternatives to patients.

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