Clinically validated line of therapy (LoT) algorithm for patients with metastatic Non-Small Cell Lung Cancer (mNSCLC) can be implemented using systemic anti-cancer therapy (SACT) in Observational Medical Outcomes Partnership (OMOP) database.

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Background:

An approach to group treatments into LoT is crucial in cancer observational studies given treatment plans often include multiple oncological therapies delivered concurrently or sequentially in complex clinical pathways. An accurate assignment of LoT received is important to assess response to therapy and prognosis, for clinical audits and to assess patient suitability for interventional trials.[1] However, there is no common definition of LoT between hospitals and research groups which is straightforward to code, since clinical supervision is often locally exploited to define treatment switches if there is a lack of coded procedures. Some critical points, which can be difficult to standardize, are the inclusion of treatment modalities (systemic treatment, radiotherapy, surgery), treatment intents and their allocation, identification of maintenance phases, and treatment holidays or breaks.[2]

The Digital Oncology Network for Europe (DigiONE) aims to increase the speed of precision oncology real world evidence by transforming a core dataset into OMOP databases for federated analysis. To analyze the management and outcomes of patients with mNSCLC across multiple centres, a LoT algorithm applied consistently to each OMOP database was required. Here, we introduce the approach to developing DigiONE's clinically validated LoT algorithm specifically for mNSCLC and its key principles. The fundamental concept of the LoT algorithm is that LoT advances when there is clinical progression of disease. However, since date of progression is typically manually inputted, which can vary in consistency across hospitals, this LoT algorithm infers disease progression based on drug-level data. The LoT algorithm developed considers SACT prescribed for the management of mNSCLC with palliative intent in the real-world, including the use of any trial drugs. The aim of our preliminary experience is to design a transversal LoT algorithm that could be applied to international coded databases for real-world cancer research.

Methods:

The DigiONE mNSCLC LoT algorithm development and validation involved four steps:

- **Step 1**: A group of 15 participants from 7 European hospitals developed the LoT rules at an in-person "study-a-thon" event. Clinicians from across Europe convened to share care management plans at each country in effort to build a LoT algorithm that reflects real-world clinical practices as widely as possible across Europe. The in-person workshop ensured efficient communication between oncologists, database managers, clinical coders, and data scientists, allowing for real-time adjustments to rules based on dataset applicability. The resulting document describing the rules was sent to other lung oncologists from DigiONE centers for review.
- **Step 2**: A statistician coded the rules using R and tested them on IQVIA's US oncology electronic medical record (oncoEMR) database in OMOP.
- **Step 3**: A search for patients in the US oncoEMR identified edge patient cases whose treatment data may raise potential issues with the defined LoT rules. For example (non-exhaustive list), finding patients who initiated treatment prior to mNSCLC diagnosis date (index date), finding patients receiving concurrently prescribed drugs who initiate the drugs months apart, and finding patients who had extended treatment breaks. The index date, treatment start and stop dates, treatment received, and LoT assignment of 20 patients were sent to lung oncologists from the DigiONE centers for review. This resulted in agreement of LoT assignment for 12 patients and disagreement of LoT assignment in 8 patients. Following rounds of resolution meeting, the algorithm rules were revised, and the R script was updated accordingly. This step was repeated with 20 new patients' treatment data until all clinicians agree on the LoT assignment.

  Step 4 (Ongoing): The LoT algorithm was validated at one of DigiONE's OMOP databases in the UK, where the distribution of patients by LoT was reviewed by lung oncologists on-site to ensure reflection of their routine care. Further validation of this algorithm in other DigiONE European centers' OMOP databases is planned to confirm its generalizability.

Results:

The current DigiONE mNSCLC LoT algorithm rules (principles described in **Table 1**) were applied to oncoEMR in OMOP. In oncoEMR, there were 2,302 eligible patients of which 52% received a 1st LoT and 14% received a 2nd LoT for mNSCLC (**Table 2**). Reasons a patient may not initiate SACT for mNSCLC include that they are deemed too unfit for SACT and therefore receive best supportive care, patient refuses treatment plan, or the patient dies before treatment is initiated.[3] This finding that approximately half of patients receive SACT for mNSCLC is aligned to clinical expectations.[4]

Table 1: Principles of the DigiONE mNSCLC LoT algorithm

Categories	Summary of the rules
Start date of LoT	Earliest drug start date in the LoT. LoT may start before mNSCLC diagnosis due to early SACT initiation based on suspected metastases prior to confirmation from biopsy results.
Grouping SACT into LoT	A LoT can consist of one or multiple regimens, and regimens may include one or multiple drugs with different start dates. Drugs that share the same start date are considered as a 'protocol'.
Treatment changes that do not advance the LoT	If one or more drugs are stopped while other concurrently prescribed drugs continue
	If the dose is changed or the route of administration is changed however the drug continues to be prescribed
	Switching between certain drugs which are presumed to be for toxicity reasons and not for clinical progression of disease. Examples include: • Carboplatin and cisplatin • Paclitaxel and Nab-paclitaxel • Pemetrexed, gemcitabine and vinorelbine, when prescribed with platinum-based therapy • PD1 and PDL1 inhibitors • First and second-generation EGFR TKIs • Targeted therapy for a. EGFR exon20 mutation b. ALK translocation c. ROS1 translocation d. RET translocation e. KRAS G12C mutation f. NTRK translocation g. MET exon14 skipping mutation
	Stopping a drug for any duration if the same drug is initiated after the break.
Treatment changes that do advance the LoT	Addition of a new drug that is not concurrently prescribed with other drugs, unless the drug is in the list of allowable switches due to changes for toxicity reasons.
End of LoT	The latest end date of drugs prescribed within the LoT. If a patient has a date of death prior to the end date of the treatment in the database, the date of death is used as LoT end.

Table 2: Number of patients by LoT and drug class in US oncoEMR database according to the DigiONE LoT algorithm

Criteria	Number of patients	Proportion (%)
Diagnosis of mNSCLC between 1 Nov 2018 and 2 Dec 2021	**2,302**	**100**
Receive 1st LoT for mNSCLC	**1,211**	**52.6**
Immunotherapy with chemotherapy (+/- targeted therapy)	489	40.4
Chemotherapy mono or combo	361	29.8
Immunotherapy without chemotherapy (+/- targeted therapy)	291	24.0
Targeted therapy for EGFR mutations	43	3.6
Other targeted therapy not for EGFR mutations	27	2.2
Receive 2nd LoT for mNSCLC	**333**	**14.5**
Chemotherapy mono or combo	149	44.7
Immunotherapy without chemotherapy (+/- targeted therapy)	107	32.1
Immunotherapy with chemotherapy (+/- targeted therapy)	63	18.9
Targeted agents for EGFR mutations	9	2.7
Other targeted agents not for EGFR mutations	5	1.5

Conclusion:

In multi-centre cancer research, a LoT algorithm applied consistently across the databases is crucial to describe treatment and prognosis by LoT. The algorithm should be tailored to the cancer type and stage of disease. DigiONE presented a clinician developed LoT algorithm to group SACT prescribed for mNSCLC and tested it on OMOP databases in the US and in the UK. Its further clinical validation in other DigiONE European OMOP databases is ongoing. The algorithm is most applicable within Europe where patients are managed similarly, and EMA approvals are practised.

Developing and implementing a LoT algorithm is challenging given i) clinical practice differs by country, ii) clinicians think in regimens, whereas data is often at the drug level, iii) some useful variables to assign LoT (including planned course of treatment, date of progression, reason for treatment change) are often missing from structured databases and therefore clinicians' inferences on the clinical context ought to be required. The DigiONE mNSCLC LoT algorithm can be shared with researchers in the OHDSI community once finalized.

References

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