Clinical efficacy of computational reasoning for personalized treatment planning in a pan-cancer cohort discussed by a French multidisciplinary tumor board: a real-world experience-based analysis

AACR 2026
LB129

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INTRODUCTION

Digital Drug Assignment (DDA) is a computational reasoning model that lists cancer therapies based on the complete individual molecular tumor profiles and ranks them by their DDA scores. Prior analysis of the SHIVA01 cohort linked higher DDA scores to improved outcomes (1). Here, we evaluated predefined DDA tiers in a broad, real-world cohort from Institut Curie's Molecular Tumor Board (MTB).

METHODS

We retrospectively analyzed **394 MTB cases** (2018–2022, adults w solid tumors) with NGS or WES/WGS data, treatment records, and outcomes. Patients receiving molecularly targeted agents (MTAs; n=134) or chemotherapy (n=177) were included. Administered MTAs (including immune checkpoint inhibitors) were assigned DDA scores and stratified into low (<0), intermediate, and high (≥1000) tiers. PFS, OS, ORR, DCR, and survival rates were compared across DDA-score tiers and in relation to chemotherapy.

Cohort characteristics (MTA)

Organic system	n(%)
breast	42 (31%)
gastrointestinal tract	32 (24%)
gynecologic	15 (11%)
sarcoma	9 (7%)
endocrine	7 (5%)
head-neck	7 (5%)
genitourinary tract	7 (5%)
CNS	6 (4%)
lung	4 (3%)
eye	3 (2%)
CUP	2 (1%)

Cohort characteristics (MTA)

Target	n	%
ICI (± ICI)	24	18%
PARPi (±ATRi)	20	15%
TKi	16	12%
HER2i +(±HER2/3i)	14	11%
TROP-2i (±ICI)	12	9%
mTORi (± hormone)	12	9%
FGFRi	6	4%
BRAFi + MEKi (±TKI)	6	4%
CDKi	4	3%
PI3Ki + hormone	3	2%
MEKi (±ICI)	4	3%
Nectin-4i	2	1%
PARPi + ICI	2	1%
RETi / SMOi / EGFRi	1-1-1	1-1-1%
ImmTAC / VEGFi	1-1	1-1%
HER2i + ICI	1	1%
TKi + HER2i	1	1%
EGFR/LGR5i	1	1%
KRASi + EGFRi	1	1%

RESULTS

1. Response stratification

A significant positive trend in response rates was observed with increasing DDA tiers. Chemotherapy showed comparable ORR and DCR to the intermediate tier, while the DDA-high group demonstrated superior outcomes.

	Low	IM	High	Sum^{MTA}	Chemo	x^2 for trend, Low-IM-High
ORR	8%	19%	33%	23%	16%	p = 0.0283
DCR	31%	45%	64%	50%	41%	p = 0.0148
n	13	77	42	132	177	

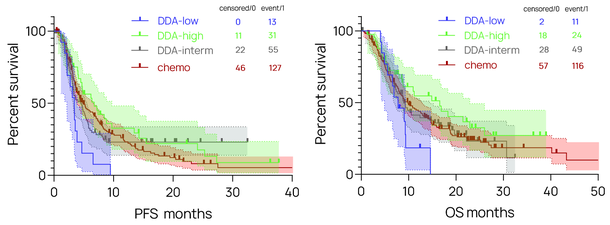
2. PFS and OS stratification

mPFS was 3.4 months in the DDA-low group, significantly shorter than the 6.8 months observed in the DDA-high group (HR: 0.35). The intermediate group had a mPFS of 4.5 months, while chemotherapies achieved a mPFS of 4.9 months. Chemotherapies were superior to DDA-low therapies (HR: 0.44, p=0.0034).

mOS showed the same trend, with significantly shorter survival in the DDA-low group than in the DDA-high group (7.8 vs. 16.6 months, HR: 0.45).

Cases with no molecular–drug link (n=5) had the poorest outcomes (mPFS and mOS: 2.6 and 6.5 months).

Both **6-month PFS and 24-month OS rates** showed positive trends across DDA tiers: 6-month PFSr were 15%, 29%, and 47%, while 24-month OSr were 0%, 5%, and 16% in the DDA-low, intermediate, and DDA-high groups, respectively. Chemotherapy showed rates of 33% and 10%.



	Low	IM	High	Chemo	HR, CI, p (Low vs High)
mPFS (months)	3.4	4.5	6.8	4.9	HR=0.35, 95% CI 0.15-0.85, p=0.0006
mOS (months)	7.8	9.0	16.6	9.8	HR=0.45, 95% CI 0.19-1.08, p=0.0190
n	13	77	42	173	

3. Potential efficacy gain

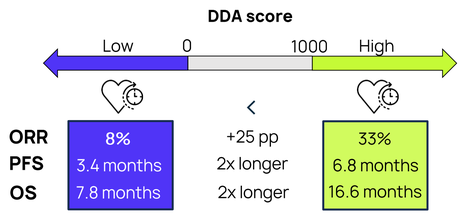
58% of patients had DDA-high therapy options, but only 32% received DDA-high treatment. Eliminating DDA-low therapies and prioritizing DDA-high treatments could result in a +4 percentage point ORR and a +6 pp DCR increase in the MTA cohort.

100 cases	Label	Non-DDA-High	DDA-High	All	
Original	ORR	18 (68%)	33 (32%)	23	
	DCR	43 (68%)	64 (32%)	50	
DDA-optimized	ORR	19 (42%)	33 (58%)	**27**	4 pp gain in ORR, 6 pp gain DCR
	DCR	45 (42%)	64 (58%)	**56**	

CONCLUSIONS

Take-home messages:

- ✓ **~10% of patients receive low-efficacy targeted therapies** (even in a tumor board setting) underperforming compared with chemotherapy due to the underlying molecular complexity unlocked by DDA.
- ✓ **Computational reasoning using DDA can be used to improve precision in decision-making by stratifying cases:**
  - ✓ according to predicted response
  - ✓ using routine NGS results
  - ✓ across multiple therapies
  - ✓ in a pan-cancer population
  - ✓ to avoid ineffective therapies.
- ✓ This can result in **4% ORR and 6% DCR gain.**



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