Clinical Application of Routine Comprehensive Tumor Molecular Profiling in the Management of Cancer Patients

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BACKGROUND

- Along with the extension of the FDA approved molecular matched therapies, the evidence is building to support molecular profile-based off-label drug prescription or inclusion in a clinical trial.
- Though clinical laboratories are increasingly deploying NGS tests for CMTP, true clinical utility of mutation profiling diverse among different cancer types and remains unclear for many thereof.
- Here we report the findings from the real-world comprehensive molecular tumor profiling (CMTP) practice to test how comprehensive molecular profiling extends treatment options within and beyond standards of care.

METHODS

- Patients with a confirmed diagnosis of cancers were eligible.
- DNA was extracted from either tumor samples or plasma if the tumor sample was unavailable.
- CMTP included NGS panel. Extent of NGS panel varied (from 17 to 409 genes) based on CMTP recommendations. Additional tests (IHC, FISH, MSI testing) were performed if recommended by a molecular tumor board.

RESULTS

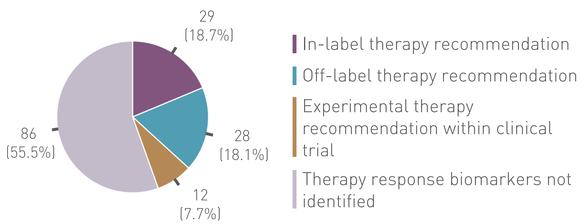
Table 1. Patient characteristics

Total patients	155
Age, Mean ± SD	56.0 ± 15.0
Sex, Female, n (%)	97 (62.5)
Tumor state at the moment of testing, n (%)	
Distant met recurrence/progression	43 (63,2)
Loco-regional recurrence/progression	16 (23,5)
With tumor, non specified	9 (13,2)
Non-informative/Missing	87 (127,9)
Tumor type, n (%)	
Gynecological	30 (19.4)
Bowel	28 (18.1)
Lung	22 (14.2)
Pancreatic	15 (9.7)
Breast	14 (9.0)
Stomach	8 (5.2)
Soft tissue	6 (3.9)
prostate	5 (3.2)
Bladder/Urinary	5 (3.2)
Other*	22 (14.2)

*Other tumor sites included: biliary (n=4), skin melanoma (4), thyroid (3), kidney (2), bone (1), head and neck (1), eye (1), uterus (1), liver (1), ampulla of vater (1) and cancer of unknown primary (2).

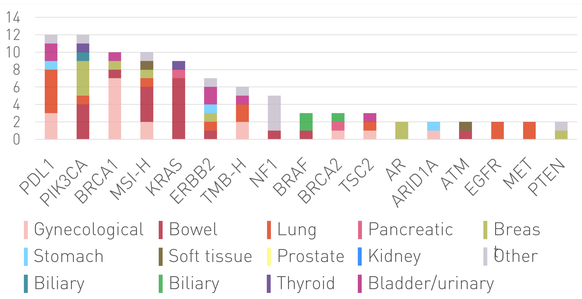
- A total of 94 Actionable Biomarkers associated with potential benefit from approved therapy were identified across 68 (44%) pts.
- Across all patients with identified 49 (72%) pts had only one Actionable Biomarker while 19 had 2 or more AB (up to 5).

Figure 1. Therapy recommendation results



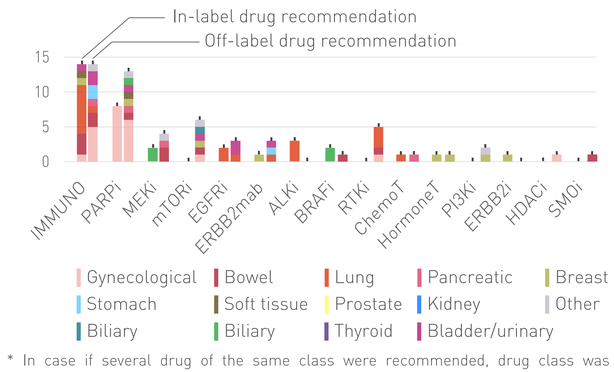
- 29/155 (19%) pts received in-label therapy recommendations (TR) (38% pts - lung, 31% pts – gynecological, 10% pts - colorectal).
- 28/126 (23%) pts without in-label TR received off-label TR (18% pts – gynecological, 18% pts colorectal, 14% pts – pancreatic, 10% pts – stomach) with a total of 56 TR (20% immunotherapy, 13% PARPi, 7% MEKi, 5% ERBB2i).
- 12/98 (12%) pts without in-label or off-label TR received profile-matched TR within a clinical trial.
- Across 19/155 (12%) identified biomarkers associated with the resistance to standard therapy were identified.

Figure 2. Identified clinically actionable biomarkers*,**



*Presented only clinically actionable markers, i.e. reported in association with potential drug efficiency. Cases were
**Presented only markers identified in two or more cases. The rest identified markers include: AKT1 (breast); ALK (ling); BAP1 (other); ER (breast); ERBB3 (stomach); FBXW7 (bowel); FGFR1 (breast); FLT3 (bowel); HRAS (other); PBRM1 (pancreatic); PTCH1 (bowel); RB1 (pancreatic); RET (lung); SMAD4 (lung); TS1 (bladder/urinary)

Figure 3. Spectrum of drugs reported to have potential benefit*,**

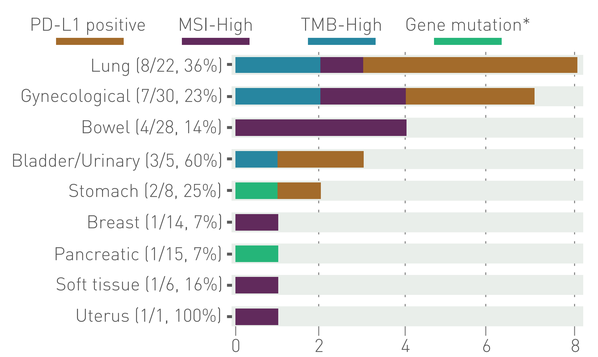


* In case if several drug of the same class were recommended, drug class was accounted only one time per patient case.

**In some cases after off-label drug therapy recommendation, drug was approved in this indications. All such cases are noted as 'off-label' as at the moment of report.
In case if drug scheme recommended, each drug was counted one time. Drug schemes included: Vemurafenib + Cobimetinib (2 melanoma cases), Dabrafenib + Trametinib (2 melanoma, 1 bowel case) and Nivolumab + Ipilimumab (2 melanoma, 2 bowel cases). Drug classes included: Immunotherapy (Pembrolizumab, Atezolizumab, Nivolumab, Darvalumab, Avelumab); PARPi (Olaparib, Rucaparib, Niraparib); MEKi (Cobimetinib, Trametinib); mTORi (Everolimus, Temsirolimus, Sirolimus); EGFRi (Erlotinig, Dacomitinib, Osimertinib, Afatinib, Gefitinib); ERBB2mab (Cetuximab, Panitumumab); ALKi (crizotinib, Ceritinib, Alectinib); BRAFi (Dabrafenib, Vemurafenib); RTKi (Dasatinib, Regorafenib, Sorafenib, Vandetanib, Cabozantinib); ChemoT (Cisplatine, Oxaliplatine, Etoposide); HormoneT (breast and prostate cancer hormone therapy); PI3Ki (Alpelisib); ERBB2i (Lapatinib); HDACi (Vorinostat) and SMOi (Vismodegib, Sonidegib)

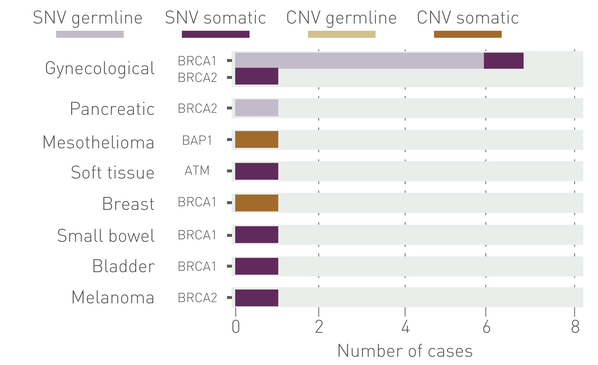
- Across a total of 152 drug recommendations for in-label or off-label use 40 (26%) were PARP inhibitors and 47 (30%) were immunotherapy, recommended in total for 15 (22% of patients with therapy recommendations) and 27 (40%) patients respectively.
- Apart from gynecological cancers, PARP inhibitors recommendations were given in 7 cases (6% of non-gynecological cancers): bladder cancer (n=1), small bowel cancer (1), breast cancer (1), melanoma (1), pancreatic cancer (1), mesothelioma (1) and angiosarcoma (1).
- Across 57 patients with in-label or off-label therapy recommendations, for 31 (54%) only immunotherapy or PARP inhibitors were among drugs associated with potential benefit, thus these tumor agnostic markers provides highest information yield .

Figure 4. Identified biomarkers of immunotherapy response



*Gene mutations included PBRM1 mutation (Arg876His) and ARID1A mutation (Phe2141fs*59) identified in pancreatic and gastric cancers respectively

Figure 5. Identified biomarkers of PARP inhibitors response



Authors disclosure

IM, VE, RE, KA, SM and MV are employees of Atlas Oncology Diagnostics, Ltd. IE declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

CONCLUSIONS

- In this series of 155 patients, CMTP was informative for 72/155 (46%) pts while 69/155(44%) pts received therapy recommendations proving the reasonability of further development of affordable molecular treatment.
- Across tumor types least % of patients received therapy recommendations were prostate (0/5, 0%), pancreatic (4/15, 26%) and breast (5/14, 36%) , suggesting the need to define patients population who may benefit from CMTP as well as the optimal extent of clinically meaningful list of targets screened for each tumor type.
- Immunotherapy and PARP inhibitors sensitivity testing constitute the most into CMTP providing the highest information yield. That should be considered when planning CMTP for the particular patient as the most likely outcome of testing