CASE STUDIES

MAY 2023

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MASSIVE BIO BEST PRACTICES IN PATIENT ENROLLMENT

- Working with Sponsor in a platform basis across portfolio (disease, biomarker, investigational drug) was able to enroll patients much more cost-efficiently, allowing discounts, efficiencies, ease of startup, procurement and expansion into all available markets.
- Direct patient acquisition was three times more successful than provider provider-based approaches despite significant work.
- Getting involved early enough to be able to optimize site selection process: Involving Massive Bio was beneficial as it shortened the due diligence upon activation, and optimized the ability of those sites to enroll, and prevented overlapping competitive trials on site and within the catchment population area.
- SYNERGY-AI site selection, network identification, competitive landscape analysis and heat maps were key to success.
- Activation of targeted social media groups and development of targeted communities and Google leads helped to reduce screen failures although community formation takes time.
- Educating sites in referral network to increase awareness was essential, in one study, out of 338 referral sites, zero site was aware of the study before Massive Bio education.
- Providing value added services to referral sites (e.g., free pre-screening on specific cancers) and simple online referral process increases referral volumes three times.
- Active engagement with site PI, refinement and expansion of their own referral networks and sites were typically very appreciative that the Sponsor understands their issues and provides subsidized support.
- Care coordination to identify satellite sites within referral networks was very helpful for fast and easy referrals.
- 24-hour referral after clinical eligibility and concierge support have tremendously reduced logistical barriers for patients and sites.
- Payer and specialty pharmacy approach will generate material success over time but especially working with payers are significantly time consuming.

Massive Bio: Customized, data-driven and proven approach to BRAF-driven clinical trials

Overall Proposal and Pricing (Cohort A-C)

- Scenario 1 (12 months): Randomize (first dose in) between 12 and 24 patients globally
- Scenario 2 (24 months): Randomize (first dose in) between 18 and 36 patients globally
- Median cost per randomized patient: $27K + Due diligence fixed costs
- Return on Investment: ~25%

- **Prior BRAF targeted trial experience:**
- Estimated Mean Optimization: From 0.07 p/s/m to 0.12 p/s/m
- MB performance: 0.8 patients/month
- 40% identified after MB facilitated NGS
- Gained 8 months of time cumulative/trial
- - NCI-MATCH - ASCO TAPUR
- - My Pathway

Key differentiators

1. **Massive Bio's relationship of enrolling in NCI sponsored trials as their official vendor for "Cancer Clinical Trials Recruitment and Retention Tools for Participant Engagement"**
2. **Massive Bio's SYNERGY-AI registry**
3. **BRAF mutations part of existing machine learning matching algorithms in DLCTMS**
4. **Use of BRAF completed trial sites and investigators (SYNERGY-AI analytics)**
5. **OCR and NLP of Foundation Medicine, Guardant Health, NeoGenomics, and CARIS**
6. **Review J codes, Q codes, CPT codes for genomic testing and cancer-specific treatments, ICD 10 codes for Just-In-Time**
7. **We will exclude competitor sites for TAPISTRY and MyTACTIC**
8. **Concierge enrollment services (logistics, travel, appointments, "last-mile" issues, etc)**
9. **Major partnership with one of the largest specialty pharmacy network in the US**
10. **Major partnership with one of the largest insurance companies in the US to prescreen tens of thousands of patients**
11. **Dedicated oncology nurses and advocates facilitate ordering and completion of comprehensive genomic testing**
12. **Federalwide Assurance (FWA), Privacy Shield, HIPAA, GDPR, and SOC 2 certified, FADP, EDPB, FDA compliant, approach and ICF IRB approved**

Overall Direct-to-Patient Approach

- Patients On-boarded from MB Patient Contact Center:
  - Provider Call Center Referral Activation
  - Online Marketing Channel Activation
  - Social Media Group Activation
  - Patient Advocacy Group Activation
- Patients On-boarded from Provider Partners:
  - Referral Network Activation:
    - 50 miles coverage (flexible) and 50 VIP sites
  - Provider Network Activation:
    - 225 sites to review patients for our Sponsored studies, 75 sites we are working more than one study
- **Real-time cluster identification of eligible patients via specialty pharmacy**
- **We pre-screen potentially eligible patients at JIT active sites to facilitate enrollment once first patient is found and enrolled**

Massive Bio: Navigating the Competition to Achieve Enrollment Goals With AI-driven Access to Patients and Referring Oncologists

Background and Goals

Therapeutic Area: Oncology

Indication: Solid tumors; refractory tumors, ERBB2 mutated or EGFR exon 18 mutated, no prior targeted therapy

Number of sites: 65 global, 32 US

Study duration: 100 months

Estimated enrollment: ~400 patients

Total cost reduction: $952,000

Return on investment: 32%

Operational simplification:

- 12% site reduction
- 42% fewer screenings
- Gained six months of time

Goals and Approach

- Goals:
  - US: 8-15 patients, required 33 patients screened for one enrollment.
  - Ex-US: 7-10 patients, required 38 patients screened for one enrollment.
  - Global: 15-25 patients.
- Activated: Provider referral network (338 referral sites within 50-mile radius of US sites; 39 VIP sites engaged daily), online marketing channels (new domain, landing pages, SEO optimization, two Facebook and two Google ads), social media groups, mobile patient engagement with SYNERGY AI and Cancer Quiz App and patient advocacy groups (13 groups; 45,000 members and followers).
- Coordinated NGS testing for patients to optimize the workup of patients under-genotyped for advanced solid tumors.
- Worked with NGS vendor network in US, Europe, and South Korea to determine accurate population densities and how to optimize screening.

Lessons Learned

- Involving Massive Bio from the site selection process shortened the due diligence upon activation, allowed sites to enroll and prevented overlapping competitive trials.
- Direct patient acquisition was more successful than provider provider-based approaches.
- Social media activation reduced screen failures.
- Increase awareness as no referral site (out of 338) was aware of the study before Massive Bio education.
- Provided value-added services to referral sites (e.g., free pre-screening on pancreatic cancer) and simple online referral process.
- Sites appreciated reduced enrollment workload through active engagement with site PI to refine and expand their referral networks.
- Onboarding first-line patients and continuously tracking them increased our ability to rapidly bring patients to sites.
- 24-hour referrals after clinical eligibility and concierge support reduced logistical barriers for patients and sites.

CASE STUDY – MYELOPROLIFERATIVE NEOPLASM TRIAL

Background	Outcome
Myelofibrosis (Myeloproliferative Neoplasm) Criteria: Phase 3, randomized, double blind study of the combination of the PI3Kδ inhibitor or matching placebo and JAK1/2 inhibitor in participants with PMF or secondary MF (PPV-MF or PET-MF) with suboptimal response on JAK inhibitor monotherapy. Participants randomized on Day 1 with stratification for platelet count (≥ 100 × 109/L versus 50 to < 100 × 109/L inclusive) and DIPSS risk category (high vs intermediate-2 vs intermediate-1). The objective measurement of spleen volume at 24 weeks was the primary endpoint. Location: United States (main scope), out of 30 countries we diligenced 10 countries. Australia, Canada, France, Greece, Hungary, Poland, Romania, South Korea, Spain, Switzerland, Taiwan, Turkey. After the due diligence, we recommended 5 countries. Number of sites: 20 US sites; 100 sites planned globally. Estimated enrollment: 212 participants. Number of estimated total patients enrolled per site: 40 patients in US; 2 patients per site per protocol. Massive Bio involvement duration = 18 months; 2 months due diligence and 16 months of patient enrollment; 1.6 patient per month planned (16 months average 26 patients); ongoing Massive Bio pricing = $505k ($100k set-up +$405 recruitment); 15% discount given as referred by our internal network; no BD effort Competition = High; 3 directly competing studies, overall, 25 studies and deficit of ~2,000 slots **Goals** US: Between 12-20 patients, required on average 25 patients to be screened for 1 enrollment, we were managing last mile issues, referral, financial considerations.. Ex-US: Between 8-12 patients, required on average 30 patients to be screened for 1 enrollment. It is also important to note that during the execution phase we only cover a fraction of these countries based on your country of coverage and based on our detailed due diligence. We provided all countries that we can potentially support at the time of SOW submission. Global: Between 20 and 32 patients. Our screen failure at the site after patient was referred almost non-existent as we only refer the patients that are clinically and operationally “ready”	Number of months into the study = 5 months (2 months due diligence and 3 months patient recruitment) Number of patients pre-screened first 3 months = 129 patients: ~43 patients per month Number of patients enrolled first 3 months = 5 patients: ~1.6 patients per month; we are currently on target and we anticipate delivering at least the maximum number of patients because we have been able to deliver these numbers with less than 25% site capacity. Screening cost reduction US planned screening cost per patient = 35X$750 = $26.25k US Massive Bio’s screening cost per patient = 25X$750 = $18.75k US screening cost reduction per patient = $7.5k US screening cost reduction for 12 patients = $90k Outside US planned screening cost per patient = 35X$750 = $26.25k Outside US Massive Bio’s screening cost per patient = 30X$750 = $22.5k Outside US screening cost reduction per patient = $4.0k Outside US screening cost reduction for 8 patients = $32k Total screening cost reduction for 20 patients = $122k Site cost reduction 6 sites saved projection in US. 4 sites saved projection in Outside US. 10 sites saved Globally. Annual cost per site = Activation ($35k) + Ops ($15k) = $50k and 18 months cost per site = $57.5k Site cost reduction = $575k Total cost reduction = $697k ROI = 38%. In addition, significant operational simplification (10% site reduction + 120 less screenings in US + 40 less screening in Outside US) and time gain (twice faster and earlier than planned enrollment timeline) **Key improvements:** Using specialty pharmacy channels to identify patients on JAK inhibitor; providing value added services to referral sites (e.g., free pre-screening on PMF) and simple online referral process increased sites receptivity and further reduced screen failures.

CASE STUDY – METASTATIC ESOPHAGOGASTRIC CANCER TRIAL

Background	Outcome
Metastatic non squamous Esophageal and GE Junction Cancer Criteria: Phase 3, randomized. 2+ line, novel agent added to regimen, required sites with biomarker testing capabilities including PD-L1 testing, ECOG 0-1, MSI-low, Her-2 negative, previous tissue or new biopsy (not FNA), Hemoglobin ≥9 g/dL; PD-L1 > 1%; Serum albumin ≥3.0 g/dL; prior CPI; no neuropathy. Location: United States, France, United Kingdom, Italy, Poland • Number of sites: 15 US sites; 25 sites planned. • Number of estimated total patients enrolled per site: 60-70 patients in US; 4 patients per site per protocol. • Massive Bio involvement duration = 14 months; 2 months due diligence and 12 months of patient enrollment; November 2020, last patient enrollment • Massive Bio pricing = $350k ($75k set-up +$275 recruitment); 15% discount given as referred by our internal network; no BD effort • Competition = High; 3 directly competing studies	Number of patients pre-screened = 368 patients: 31 per month Number of patients enrolled = 16 patients: 1.3 per month Screening cost reduction Planned screening cost per patient = 40X$750 = $30k Massive Bio's screening cost per patient = 23X$750 = $17.25k Screening cost reduction = $480k- $276k = $204k Site cost reduction 4 sites saved. Annual cost per site = Activation ($35k) + Ops (15k) = $50k Site cost reduction = $200k Total cost reduction = $404k **ROI** = 15% in addition significant operational simplification (20% site reduction + 272 less screenings) and time gain (4 months earlier than planned enrollment deadline) **Key improvements:** Using payer partners prior authorization units; Leveraged patients progressing while on first line Esophageal and GE Junction clinical trials on CPI and real-time patient activation using SYNERGY-AI registry; identifying sites that used PD-L1 more often compared to peer sites

CASE STUDY – FOLLICULAR LYMPHOMA TRIAL

Background	Outcome
CRO was seeking to accelerate patient enrollment of Sponsor's Multicenter, Randomized, Double-Blind, Placebo-Controlled, Two-Arm, Phase 2 Study of [compound x] in Subjects with Follicular Lymphoma After Failure of Two or More Prior Systemic Therapies CRO has engaged Massive Bio for the purpose of having Massive Bio to provide patent identification and clinical trial matching services to the SPONSOR TRIAL protocol using CRO' existing sites. 50% of the sites were activated when Massive Bio was involved, and Massive Bio's participation has also enabled less site openings due to Massive Bio's acceleration and expansion of enrollment for an already opened site. • Study Start Date: March 2019 • Estimated Primary Completion Date: September 2021 • Study Duration Between First and Last Patient In: 24 months • Estimated Enrollment: 150 participants • Average Number of Patients Per Site: 1.4 (based on 107 sites) • Number of Enrolled Patients by Massive Bio at the end of February 2021: 20 • Number of Enrolled Patients by Massive Bio at the end of September 2021 (planned enrollment based on current rates): 25 • Based on our estimates and initial due diligence, Massive Bio planned enrolling 25 patients to the study, equivalent to 18 regular active enrollment sites and 17% of total enrollment. • Countries: United States, Spain, Italy, United Kingdom, South Korea, France, Germany, Poland, Belgium, Taiwan, Australia, New Zealand, Canada, Austria, Switzerland	**How many patients were screened and recruited by Massive Bio?** – Massive Bio pre-screened 625 patients at the end of September 2021. **Number of Screened Patients:** Screenings Needed without Massive Bio to Randomize 25 Patients: 1,250, CRO projected the need to screen approximately 50 patients to enroll 1 on the Sponsor studies, 50% will be eligible, 10% will ultimately enroll on study Number of Screenings with Massive Bio to Randomize 25 Patients: 625, Massive Bio needed to profile 25 patients to enroll 1 on the Sponsor study Number of Screenings Saved by Involving Massive Bio: 625 screenings Cost to Pre-screen 1 patient = $750Screening Savings to Randomize 25 Patients, (1,250X$750) - (25X25X$750) = $468k **Number of Sites:** Number of Sites Needed without Massive Bio: 107 Number of Sites with Massive Bio: 89 Number of Sites Saved by Involving Massive Bio: 18 Annual Cost to Activate 1 Site: $40K, cost savings, 18x$40k = $720k Annual Cost to Operate 1 Site 2 Years: $30K, cost savings, 18x$30k = $540k Total Savings Due to Reduced Number of Site Openings: $1,260k **ROI:** Total Savings: Screening saving ($468k) + Site activation saving ($1,260) which is $1,728k Total Investment, i.e. Massive Bio engagement price: $600k **CRO ROI:** 188% ($1,728-$600k/$600k).In addition, Massive Bio has reached 32% of its enrollment targets (7/22) in 6 months, which enables IQVIA to focus on other trials and generate additional revenues **Key improvements:** Using SYNERGY-AI data to select areas to target based on competitive landscape, KOL engagement, country-specific referrals due diligence and advocates

CASE STUDY – MYELODYSPLASTIC SYNDROME TRIAL

Background	Outcome

Phase III multi-center, randomized, two-arm parallel-group, double-blind, placebo controlled study of [Compound X] (a high-affinity, humanized IgG4 monoclonal antibody which blocks the binding of a to b target) or placebo added to azacitidine in adult subjects with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R, or Chronic Myelomonocytic Leukemia-2 (CMML-2). The randomization was stratified into 4 groups: intermediate risk MDS, high risk MDS, very high risk MDS and CMML-2. These subjects would have an indication for treatment with azacitidine in first line setting and are not eligible for intensive chemotherapy or hematopoietic stem cell transplantation (HSCT) according to medical judgment by the investigator.
 	
• Patient Population: The target sample size was approximately 500 adult subjects at multiple sites including but not limited to North America, the EU and Asia.
• Countries: United States, China, Japan, South Korea, India, Germany, Italy, Spain, France, UK.
• Sponsor looking for Massive Bio to provide the following 3 components of digital outreach:
  • Patient, Caregiver, HCP targeting / outreach
  • Landing page(s) for patients and caregivers
  • Study support center – call-center – for last mile handover
 	
Based on our estimates and initial due diligence, Massive Bio planned to enroll 35 patients for the duration of the study; i.e. Massive Bio replaced up to 17 sites. To accomplish this, Massive Bio required screening approximately between 525 and 1,225 patients over the study period (calculated 27 months of enrollment per protocol)
	Number of months into the study = 20 months (2 months due diligence and 18 months patient recruitment)
	Number of patients pre-screened first 3 months = 129 patients: ~43 patients per month
	Number of patients enrolled= 35 patients (28 US and 7 ex-US)
	<u>Screening cost reduction</u>
	US planned screening cost per patient = 35X$750 = $26.25k
	US Massive Bio's screening cost per patient = 22X$750 = $16.5k
	US screening cost reduction per patient = $10k
	US screening cost reduction for 22 patients = $220k
	Outside US planned screening cost per patient = 35X$750 = $26.25k
	Outside US Massive Bio's screening cost per patient = 30X$750 = $22.5k
	Outside US screening cost reduction per patient = $4.0k
	Outside US screening cost reduction for 7 patients = $28k
	Total screening cost reduction for 35 patients = $248k
	<u>Site cost reduction</u>
	11 sites saved projection in US.
	6 sites saved projection in Outside US.
	17 sites saved Globally.
	Annual cost per site = Activation ($35k) + Ops ($15k) = $50k and 18 months cost per site = $57.5k
	Site cost reduction = $977.5k
	Total cost reduction = $1.225M
	In addition, significant operational simplification and time gain (twice faster and earlier than planned enrollment timeline)
	
	Key improvements: Using payer partners prior authorization units; activating relationship with specialty pharmacy networks; concierge services to promote early referral to trial patients at the country level; analysis of claims-based data.

CASE STUDY – $160B MARKET CAP PHARMA COMPANY HIRED MASSIVE BIO FOR A GLOBAL PROSTATE CANCER STUDY

- Trial: Chemotherapy-naïve for metastatic castration-resistant prostate cancer (mCRPC), 984 participants, 340 sites
- Original scope: US patient recruitment support.
- Current scope (went through 6 additions to scope with 9 more countries): US and OUS patient recruitment support (Brazil, France, Germany, Israel, Italy, Spain, Romania, Poland, Turkey).
- Recruitment challenge: 1) Past medical history that is excluded, 2) Treating oncologist not agreeing with chemotherapy as next line and 3) Country specific lack of fit to standard of care covered by government.
- Massive Bio's enrollment contribution per month: 1,000 pre-pre-screening, 150 pre-screening, 5-10 enrolled; important consideration, these are not patients that were at sites, these are patients that were found outside.
- Massive Bio's value proposition
    - Time reduction: Our contribution has reduced 2 months (out of 24 months) from the volume that we have generated but since the enrollment at sites have been significantly lower, they are still following original LPI.
    - Site reduction or utilization: We would eliminate 10% of sites if we have been hired prior to site openings instead we have provided patients in 40 sites that they have not been able to activate by themselves.
    - Urologist referrals: Prior to Massive Bio, pharmaceutical company doesn't have a way to activate urologists as a referral channel which is key for the success of this trial despite country level differences.
    - Country level nuances due diligence: Before Massive Bio's due diligence, pharmaceutical company was not aware that some prior treatments were not covered by government (the insurer in the country) as standard of care and thus their projections were much higher than what they can enroll.