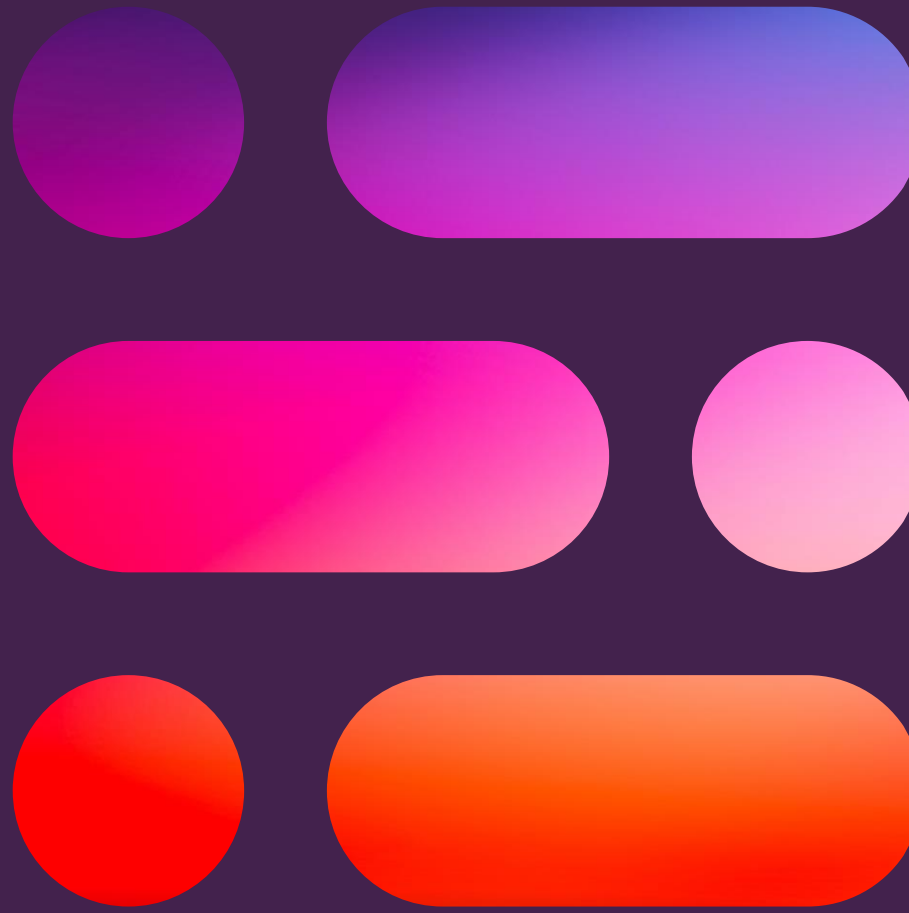
EVALUESERVE

ASCO 2022

Post-conference overview

Prepared by: Evalueserve



ASCO - 2022

Key presentations in Lung cancer, Breast cancer and Acute Myeloid Leukemia

Lung Cancer

- **KRYSTAL-1 (Ph1/2)**: CNS metastases from KRASG12C-mutant NSCLC are common and are associated with a poor prognosis
  - Adagrasib demonstrated encouraging CNS-specific activity in KRASG12C-mutant NSCLC pts with active untreated CNS metastases
- **Neoadjuvant therapy**: ICI are being evaluated as neoadjuvant therapy in resectable NSCLC
  - OS data from NADIM-2 (Ph2) trial expected to be released in next year
  - This data will potentially strengthen the nivo + chemo combo as Neoadjuvant SoC

Breast Cancer

- **DESTINY-Breast04** (Ph3) study results found to be the most significant findings presented this year in terms of management of mBC
- **Sacituzumab govitecan** was another highlighted product in ASCO 2022 with significant clinical benefit data shown in TROPiCS-02 (Ph3) study for HR+/HER- mBC and extended ASCENT study data for mTNBC
- Many studies of potential therapies included **biomarker analysis** with one on alpelisib for patients with PIK3CA-mut, HR+/HER2+ advanced breast cancer, drawing high attention
- **Novel MoAs** including ADCs, PI3K inhibitors, beyond immune checkpoint inhibitors are emerging as potential therapies in breast cancer

Acute Myeloid Leukemia

- **Ph1b 5F9005: magrolimab + azacitidine** elicited moderate efficacy in TP53m AML patients
- Gilead puts the spotlight on magro's CR/MRD-CR results, TP53m inclusion and blast reduction in Ph1b 5F9005 trial
- Declining efficacy compared to previous read-outs coupled with high rates of TEAE-led discontinuations remain concerning
- Gilead stands by the firm confidence in magro's risk-benefit profile despite latest setbacks
- Registrational path in the TP53m AML setting relies on the Ph3 ENHANCE-2 study (magro+aza vs ven+aza); data readout expected in H2'24

SOC: standard of care; ICI: Immune checkpoint inhibitors

Post-conference analysis across key themes

- Lung cancer
- Breast cancer
- Acute Myeloid Leukemia

Lung Cancer

Key presentations by products

Key products in lung cancer

Key Products	Summary	Analyst Views
Adagrasib ***(Mirati)***	**KRYSTAL-1 (Ph1/2):** Intracranial ORR – 33.3%, DoR – 11.2 months; adagrasib was well tolerated and "demonstrated promising efficacy" for patients with the KRAS G12C mutation	• Measured CNS penetration of adagrasib compares favorably with other CNS active compounds from other settings. But impressively, the median duration of intracranial response and PFS wasn't reached
Ramucirumab/ pembrolizumab ***(Eli Lilly/Merck)***	**Lung-MAP study (Ph2):** Pembrolizumab and ramucirumab in the second line after immune therapy failures; overall survival benefit observed as compared to standard chemotherapy	• There have been so many trials trying to show benefit of immunotherapy combinations after relapse on prior immunotherapy. And this looks exciting • The data seems to suggest that pembro plus ramucirumab may be better tolerated than the SoC, as the experimental regimen had fewer SAEs
Atezolizumab ***(Genentech)***	**ATEZO-BRAIN (Ph2)**: 40% patients had confirmed intracranial response based on RANO-BM (12 PR, 4 CR) and 47.5% pts achieved systemic response (all PR)	• KOLs supported emerging data stating patients with NSCLC and brain metastases should not be excluded from clinical trials or from treatment with an immune checkpoint inhibitor, adding. "This is a very good regimen."
PD-(L)1 Tx ***(FDA)***	**FDA pooled analysis (Ph 2)**: Outcomes of anti–PD-(L)1 therapy with or without chemo for 1L Tx of advanced NSCLC with PD-L1 score ≥ 50%. Patients with PD-L1 over 50% need to add chemotherapy to that group or not	• It was great to see the FDA asking a scientific question that only they could uniquely ask, showing that for patients who have PD-L1 over 50%, don't have to give them chemo
Opdivo ***(BMS)***	**NADIM II (Ph2):** Pathological complete response rates overall were 36% versus 7%, favoring the nivolumab arm, but even higher pCR rates occurred in patients with PD-L1 over 50%.	• Neoadjuvant data is very appealing because it's only 3 cycles of chemoimmunotherapy, the challenge though, is most of the pts don't have a CR, or a significant proportion of the patients have an ongoing response or significant residual disease at the time of surgery
Amivantamab/ Lazertinib ***(Janssen)***	**CHRYSALLIS-2 (Ph1)**: ORR by BICR was 36% with 1 CR and 17 PRs, and the clinical benefit rate (CBR) was 58% for amivantamab and lazertinib arm	• Updated efficacy of adding the EGFR-MET bispecific antibody Amivantamab to EGFR TKI therapy upon disease progression, supporting the availability of an important tx option in a setting where there are no approved targeted therapies

BICR: Blinded independent central review

Treatment for brain mets and immunotherapy in neoadjuvant setting are major highlights in lung cancer

Treatment Advances in Lung Cancer: ASCO 2022

Hope in patients with CNS metastases

- Encouraging data from KRYSTAL-1 trial that included a cohort of patients with CNS metastases. Results depicted that the measured CNS penetration of adagrasib is comparable to other CNS active therapies

Immunotherapy as Neoadjuvant treatment

- The recent trials and data (Checkmate 816 ; (Ph3) and NADIM 2) have demonstrated that neo-adjuvant use of immunotherapy presents a new paradigm of treatment option for patients. However, target patient pool with optimum risk/benefit ratio is yet to be determined

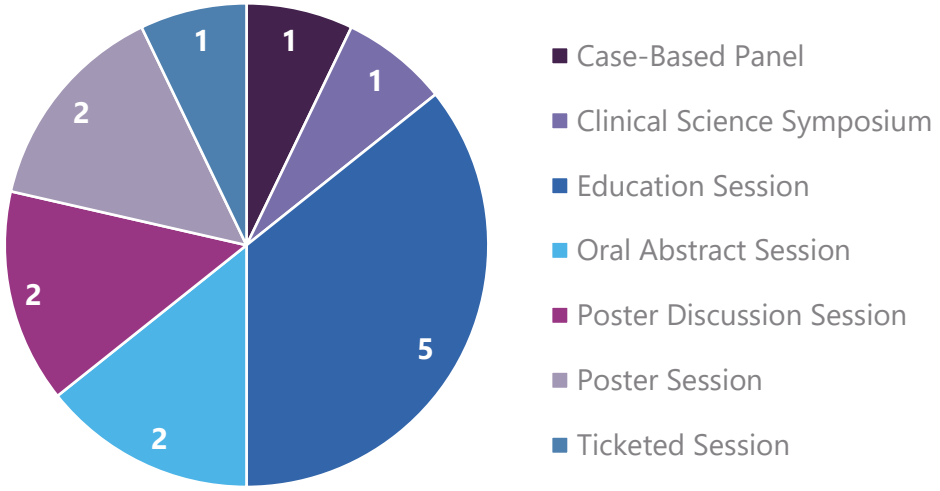
Better Stratification required in KRAS Mutant pts

- There is data to prove that KRAS-directed therapies are promising agents and therefore the need to push these as 1L therapies, however better characterization is required for precision treatment in this patient pool

Lung cancer in ASCO 2022 by numbers

185+	30+	13	5	1
NSCLC	SCLC	Neoadjuvant therapy	Brain met	Symposium

Conference track by subject / issue



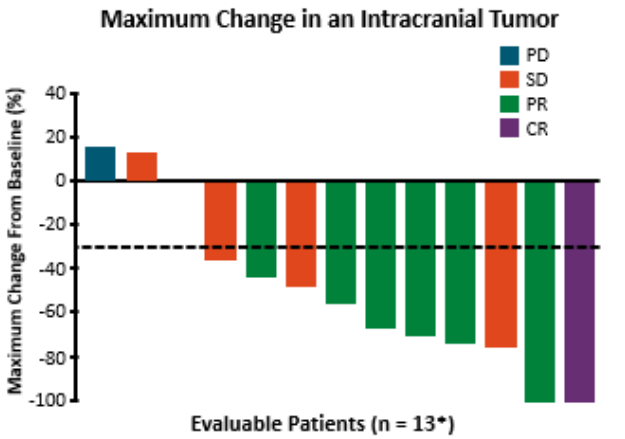
Adagrasib demonstrated durable CNS-specific response in KRYSTAL-1 with a new ray of hope in KRASG12 C NSCLC pts

Patients with active central nervous system (CNS) metastases represent a population of unmet medical need who are often excluded from clinical trials. So, it is a credit to the investigators for including this cohort

KRYSTAL-1

Outcome	Radiographically Evaluable Patients (n = 33)
Intracranial confirmed ORR, % (95% CI)	33.3 (18.0-51.8)
Median duration of intracranial response, mo (95% CI)	11.2 (2.99 to not evaluable)
Median intracranial PFS,* mo (95% CI)	5.4 (3.3-11.6)

*Among n = 42 patients with CNS metastases at baseline.



*Data not shown for those with only nontarget lesions at baseline (n = 19) or not evaluable because postbaseline scan was too early (n = 1).

Expert PoV

- While adagrasib had higher response rate and DOR (vs. Lumakras), lack of difference in mPFS, mOS and subgroup analyses made it less compelling
- Also, adagrasib's IC ORR was lower than systemic ORR, ~30% ORR would suggest a real CNS activity. Furthermore, generally less frequent MRI scanning would inflate IC mPFS, where assessment would be ~6-8 wks for systemic PFS vs ~3 mon for IC mPFS
- Successful combo with PD-1 could provide a major differentiation from Lumakras on top of brain met activity. KOL expected ~65/35% split between adagrasib and Lumakras

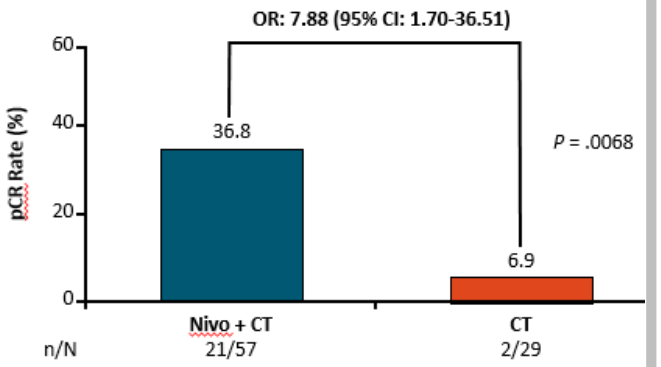
The presenter emphasized that measured CNS penetration of adagrasib compared favorably with other CNS active compounds from other settings. The overall response rate was 35%, with a disease control rate of 80%. But impressively, the median duration of intracranial response and progression-free survival (PFS) wasn't reached. Head-to-head randomized data is still lacking

Promising data from NADIM II suggests that nivolumab plus chemo could become a new SoC for neo-adjuvant NSCLC patients

Outcomes for patients with stage III NSCLC are poor, and multimodal therapy is often necessary. Neoadjuvant CT has been shown to significantly improve overall survival in resectable stage IB-IIIA NSCLC

NADIM II

Patients, n (%)	Nivo + CT (n = 57)	CT (n = 29)	Total
Definitive surgery	53 (93.0)	20 (69.0)	73
Definitive surgery cancelled	4 (7.0)	9 (31.0)	13
Reason for cancelled definitive surgery			
▪ Due to AE	1 (1.7)	0	1
▪ Due to PD	0	4 (13.7)	4
▪ Not fit for surgery	3 (5.2)	5 (17.2)	8



Expert PoV

- The NADIM II study results provide important, practice-changing data
- Neoadjuvant chemo-immunotherapy is likely to be the new SoC for operable stage IIIA NSCLC, based on the significant improvement in pCR without impeding the feasibility of surgical resection
- The optimal duration with adjuvant immunotherapy following neoadjuvant chemo- immunotherapy and optimal chemotherapy backbone with nivolumab remains unclear
- Older adults are often excluded, and the optimal SoC for this age group is unclear

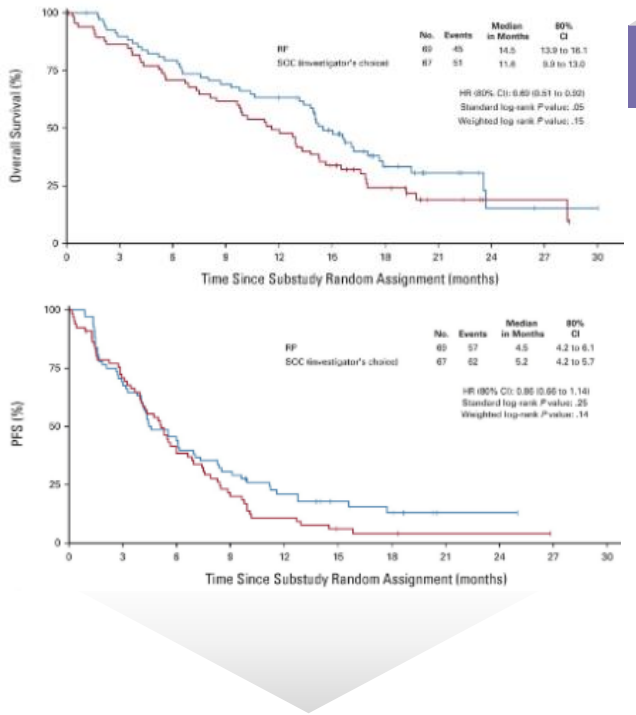
NADIM 2, employs 2:1 versus 1:1 randomization, in Checkmate 816. Another important difference was that NADIM 2 required adjuvant nivolumab for 6 months in the study arm, whereas Checkmate 816 didn't include any immunotherapy in the adjuvant setting, but they allowed for a standard of care chemotherapy

Ramucirumab plus pembro combination is likely to change the t/t paradigm with promising OS in ICI-ref lung cancer patients

Resistance to immunotherapy develops in most advanced NSCLC pts treated with immune checkpoint inhibition (ICI). Therapeutic strategies prospective clinical studies to demonstrate treatment strategies following progression on IO therapy are still lacking

Lung-MAP substudy S1800A

- At the time of analysis, 96 deaths had been reported, and the median (range) of follow-up among those still alive (n = 40) was 17.9 months (1-30)
- RP reduced the risk of death by 31% (HR: 0.69 [80% CI, 0.51 to 0.92], and the median OS (80% CI) was 14.5 (13.9 to 16.1) months in this arm versus 11.6 (9.9 to 13.0) months in the SOC arm
- 119 PFS events had been reported at the time of analysis, PFS was not significantly longer with RP
- The median PFS (80% CI) was 4.5 (4.2 to 6.1) months for RP and 5.2 (4.2 to 5.7) months in the SOC arm. Subgroup analyses were consistent with those for OS



Expert PoV

- S1800A evaluated RP in pts who experienced disease progression at least 84 days after start of ICI
- A standardized definition of resistance has not been established yet
- Definitions of acquired resistance are further complicated for ICI + chemo regimens in frontline setting, where the component contributing to efficacy and resistance is not easily discerned
- The post-progression survival benefit is likely to be responsible for OS findings, especially since pts who were progressing immediately on ICI-achieved OS improvement similar to the overall population

ICI is beneficial in squamous NSCLC and contrary to non-squamous type, independent of PD-L1 status for 2L. Thus, the squamous population should be evaluated further as ramucirumab is not restricted to non-squamous histology. The randomized Ph2 design and smaller sample size suggest that the study results may not be definitive and limits interpretation of subgroup effects

RP: Ramucirumab + Pembrolizumab

Breast Cancer

Key presentations by products

Key products in breast cancer

Key Products	Summary	Analyst Views
Enhertu ***(Daiichi Sankyo/AZ)***	**DESTINY-Breast04 (Ph3):** improved median PFS by 4.8 months and mOS by 6.6 months vs chemo in heavily pre-treated population	• Standing ovation in the conference for DESTINY-Breast04 • Expressions like a beautiful, powerful moment, that will remain in the history of breast oncology, gamechanger were used by various KOLs
	Destiny-Breast03 (Ph3): Improved safety data in HER2+ mBC	
Trodelvy ***(Gilead)***	**TROPiCS-02 (Ph3)**: reduced the risk of disease progression by 34% vs physicians' choice treatment	• Addressing high unmet need patient segment, HR+/HER2-, which accounts for ~70% of mBC • Already approved for TNBC and may provide treatment option for HR+ mBC
	NeoSTAR (Ph2): Demonstrated positive interim data in neoadjuvant TNBC	• NeoSTAR is the first trial of an ADC in TNBC and demonstrated single-agent efficacy in localized TNBC
Keytruda ***(Merck)***	**KEYNOTE-522 (Ph3)**: Positive interim data in neoadjuvant TNBC	• First immunotherapy in early-stage TNBC • With the significantly improved pCR in the adjuvant setting, current data demonstrated it also improves long-term outcome such as EFS
Ribociclib ***(Novartis)***	**MAINTAIN trial (Ph2)** is the first randomized trial to show the benefit of ribociclib and switching endocrine therapy after progression on a CDK4/6 inhibitor in HR-positive/HER2-negative	• Open new potential line of therapy in HR-positive/HER2-negative
	MONALEESA-2 (Ph3) maintained an OS benefit for HR+/HER2- 1L patients who required dose modification of ribociclib	• HR+/HER2- mBC patients may reduce ribociclib dose without jeopardizing outcomes • Neither length of treatment nor timing of dose reduction changed these results
Palbociclib ***(Pfizer)***	**PALOMA-2 (Ph3)** met its primary endpoint (PE) to improve PFS but not the secondary endpoint of OS and was limited by the high rate of patients whose survival information was not available	• Not to conclude that the treatment is failed because trial did not aim to include OS as PE, missed survival data from large proportions of patients • Expressions like shaky OS have been used by the analysts
Alpelisib ***(Novartis)***	**SOLAR-1 (Ph3)**: Combo demonstrated alpelisib and fulvestrant demonstrated improved PFS of 5.3 months	• PIK3CA encodes for a subunit of PI3K • Poor prognosis of HR+, HER2- adv BC is attributed to PI3K pathway alterations being associated with endocrine therapy resistance

Use of ADC in ER+ mBC with an overall survival benefit is a major advancement in breast cancer

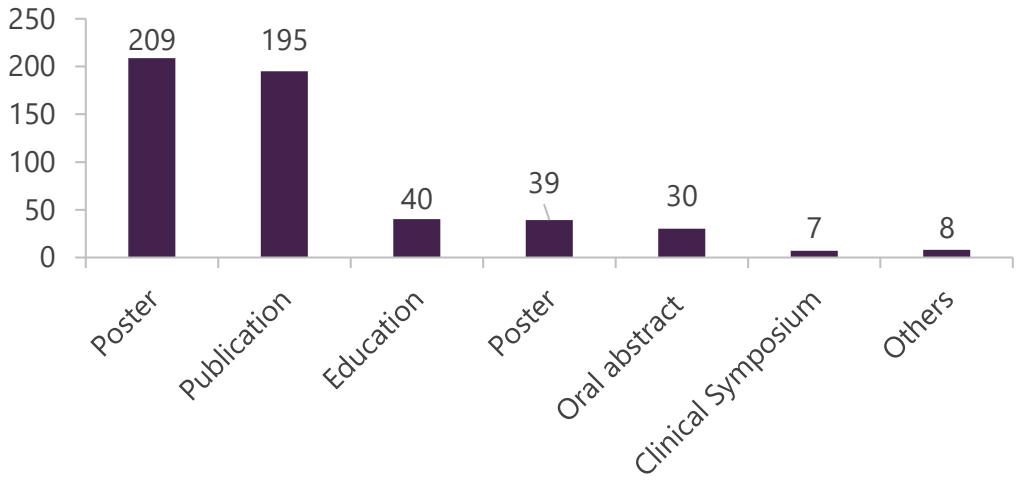
Treatment Advances in mBC: ASCO 2022

ADCs
- Effective use represent a major advance that may also benefit patients with other cancers that express HER2 such as biliary tract cancer, non-small-cell lung cancer, colorectal cancer, and endometrial cancer

Need for healthcare systems
- Research suggests that there is a need of health care systems to invest in areas of low socioeconomic status to improve breast cancer treatment outcomes through better access to care.

Beyond Immune Checkpoint inhibitors
- Apart from approved or pipeline immune checkpoint inhibitors, many other emerging immune manipulators may play a role in the treatment of metastatic breast cancer

Breast cancer tracks in ASCO 2022



>500 presentations featured across breast cancer in ASCO 2022
- Majority of the assets being evaluated belong to CDK inhibitors or ADCs
- DESTINY-Breast04, LUMINA and TROPiCS-02 were the interesting and most talked about presentations

Aza: azacitidine; Ven: Venetoclax; SOC: standard of care

Enhertu emerged as a showstopper in ASCO 2022, aims to address ~50% of breast cancer patients with HER2-low expression

Enhertu (T-DXd) demonstrated clinically meaningful benefits for patients with HER2-low metastatic breast cancer (mBC); With latest data from T-DXd HER2-low may emerge as a new therapeutic target category for mBC

DESTINY Breast-04

Regimen	mPFS(months)	mOS (months)
T-DXd (HR+) (n = 331)	10.1	23.9
TPC (HR+) (n = 163)	5.4	17.5
T-DXd (FAS) (n = 373)	9.9	23.4
TPC (FAS) (n = 184)	5.1	16.8
T-DXd (HR−) (n = 42)	6.6	16.6
TPC (HR−) (n = 21)	2.9	10.3

DESTINY-Breast04

Expert PoV

- Received standing ovation in ASCO 2022
- This kind of reaction was noted when adjuvant trastuzumab was presented
- Expressions like a beautiful, powerful moment, that will remain in the history of breast oncology, gamechanger were used by various KOLs
- HER2-low is identified as a targetable subset which will help redefining treatment for more than half of the HER2- mBC
- Mentioned 654 times by health care practitioners

Doubles progression-free survival in HER2-low breast cancer in heavily pre-treated population; Based on historically poor responses to HER2-targeted therapies, this group of patients gets bucketed into the larger HER2-negative category

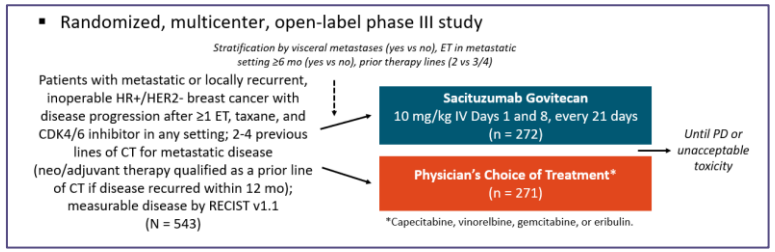
Trodelvy aims to target the high unmet need patient segment, HR+/HER2-, that accounts for ~70% of metastatic breast cancer

Trodelvy (Sacituzumab govitecan) reduced the risk of disease progression by 34% vs TPC; Already approved for mTNBC and metastatic urothelial cancer, may provide a treatment option for HR+ mBC

TROPiCS-02

Regimen	mPFS (months)	mOS* (months)
Sacituzumab govitecan (N=272)	5.5	13.9
Physician's choice of treatment (N=271)	4	12.3

*OS data not mature, follow-up is ongoing



BICR Analysis	Sacituzumab govitecan (n = 272)	Physician's Choice (n = 271)
ORR, n (%)	57 (21)	38 (14)
▪ OR (nominal P value)	1.63 (.03)	
Best overall response, n (%)		
▪ CR	2 (1)	0
▪ PR	55 (20)	38 (14)
▪ SD	142 (52)	106 (39)
– SD ≥6 mo	35 (13)	21 (8)
▪ PD	58 (21)	76 (28)
▪ NE	15 (6)	51 (19)
CBR, n (%)	92 (34)	59 (22)
▪ OR (nominal P value)	1.84 (.002)	
Median DoR, mo (95% CI)	7.4 (6.5-8.6)	5.6 (3.8-7.9)

TROPiCS-02 Breast Cancer

Expert PoV

- Surpasses investors' low bar but faces a commercial climb- (overshadowed by Enhertu's results)
- All the enthusiasm for Trodelvy had evaporated after Enhertu's results were announced
- 1.5-month mPFS benefit might be statistically significant, but it will be tough to argue that this represents a real breakthrough for these breast cancer patients
- For this patient segment, current treatment guidelines recommend to start the treatment with 1L endocrine therapy+CDK4/6i and patients will be given chemo on progression which is associated with declining efficacy and increased toxicity

Significant improvement in clinical benefit and a manageable safety profile compared with standard chemotherapy in patients with heavily pretreated, endocrine-resistant HR+/HER2- advanced breast cancer and should be considered a potential treatment option in this patient population

Acute Myeloid Leukemia

Rise of triplet therapies in AML Tx landscape

Ongoing debate over doublet vs triplet therapies in AML concluded that more mature data needed to determine if triplets represent the future of AML

Potential advantages associated with triplets

Efficacy outcomes

- IDH1/2 and NPM1 co-mutation patients have reported favorable outcomes with HMA + ven in the 1L setting, but triplet therapy has demonstrated better associated outcomes in this segment

Elderly untreated AMLsegment

- In this segment, triplet combination like cusatuzumab + ven + aza has proven to deliver added advantage of controllable infusion-related reaction (IRRs), other than providing similar tolerability and safety profile to that of ven + aza

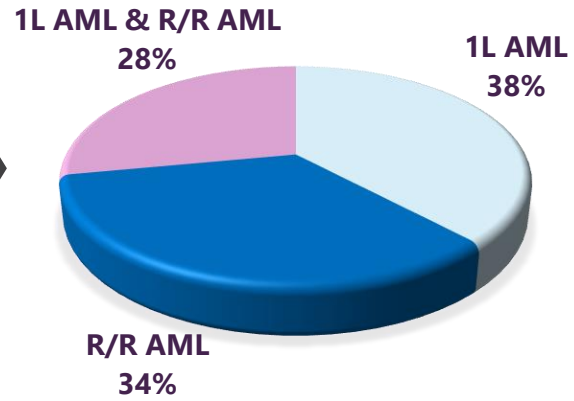
Progression/relapse related outcome

- Current SOC ven + aza is associated with relatively short remission durations driven by FLT3 relapses, triplet therapy of gilteritinib +ven+aza generated 100% of response rate with no relapses in the R/R or ND FLT3m AML

Ven+aza triplet landscape in AML

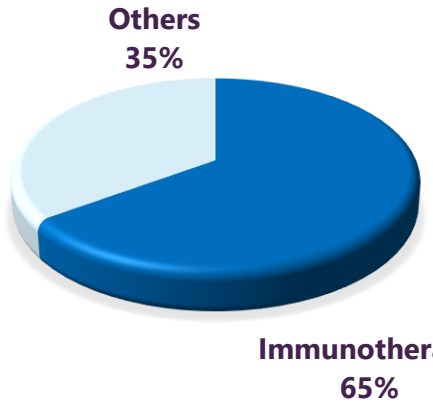
~30 triplet trials exploring ven and aza combo are currently ongoing across varied AML segments

- Majority of the trials are being evaluated in the frontline setting



~25 different assets are being evaluated in triplet combinations with ven and aza for AML treatment

- Majority of the assets being evaluated belong are immunotherapies (CD47 being the most common target)



Aza: azacitidine; Ven: Venetoclax; SOC: standard of care

Magrolimab + azacitidine (1L) showed moderate efficacy and durable response in TP53m AML pts with dismal prognosis

Ph1b data informs the ongoing registration-enabling Ph3 ENHANCE-2 study

Magrolimab Backgrounder

GILEAD

- **First-in-class** CD47 targeted immune checkpoint inhibitor
- Development ongoing in **hematological indications** - AML, MDS, MM, DLBCL, **as well solid tumors** – HNSCC, TNBC, CRC
- Gilead strategizes to establish magrolimab as a **backbone for potential combinations** across multiple tumor types including AML
- In Jan 2022, Gilead faced **clinical setback** with FDA's partial hold on **magrolimab & azacitidine combination studies** in AML & MDS, due to an apparent imbalance in investigator reported SUSAR
- The **hold was lifted** in April, following comprehensive review of safety data
- Ongoing Ph3 ENHANCE-2 (magro + aza) study in 1L TP53m AML intends to leapfrog the current SoC
- Another ongoing Ph3 ENHANCE-3 study in ND IC IE AML evaluates a paradigm shifting triplet (magro + ven+ aza) regimen

Targets addressable population of ~4K TP53m & ~14K 1L unfit AML patients

H2H competition with venetoclax, newly evolved SoC

Potentially the first immunotherapy to make inroads in AML; close competition with Novartis' sabatolimab (TIM3)

Clinical Highlights from ASCO & EHA 2022

Abs S132 (EHA) & #7020 (ASCO): Ph1b (5F9005) results of magro + aza in frontline TP53m AML patients

Study Design

Untreated AML pts ineligible for IC

Dose Evaluation	Dose Expansion	TP53m AML Expansion
Magrolimab (Q2W) + AZA	Magrolimab (Q1W) + AZA	Magrolimab (Q2W) + AZA

Magrolimab IV 1 mg/kg priming dose D1, 4, then ramp up to 30 mg/kg Q2W + Azacitidine SC 75 mg/m2 D1-7

Efficacy

Outcome	TP53m AML (N = 72)
ORR	48.6%
CR	33.3%
MRD-(-ve) CR	50.0%
CR/CRi	41.7%
mDoR	8.7 months
mPFS	7.3 months
mOS	10.8 months

- RBC transfusion independence: 29.7%
- Platelet transfusion independence: 45.8%
- Encouraging transplant outcomes in magro+aza treated pts

Safety

- TEAEs led to discontinuation of magro in 30.6% and of aza in 29.2% pts; **none discontinued for magro-related anemia**
- No dose-reduction with magro
- TEAEs:
  - G3: neutropenia, pneumonia and anemia
  - G4: thrombocytopenia & anemia
  - G5: pneumonia & neutropenia
- **Anemia: G3 in 26.4% pts & G4 in 2.8%**
- TEAEs led to death in 21 pts; none were magro related

SUSAR: Suspected Unexpected Serious Adverse Reaction; Aza: azacitidine; Magro: Magrolimab; ND ICE IE: Newly diagnosed Induction/Intensive Chemotherapy Ineligible; H2H: Head-to-head

Magrolimab's data has stirred mixed reactions among clinicians & KOLs

Gilead remains optimistic despite mounting pressure on diminishing efficacy and safety profile

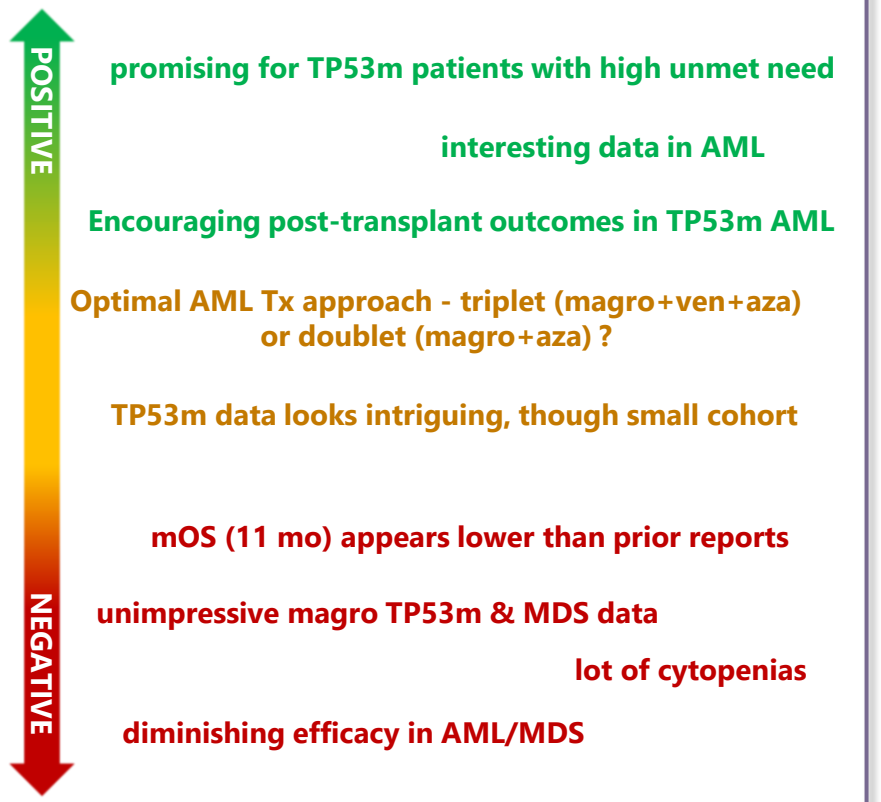
Gilead's Views

- **Gilead remains confident** with breakthrough potential of magrolimab, amid safety concerns
- Focuses on the fact that they came off the hold without any change in trial design or study endpoints
- Views **magrolimab as one of the three growth assets** (lenacapavir in HIV and Trodelvy in breast cancer being the other two)
- **CR rate** in AML (33%) & MDS (31%) population from Ph1b (5F9005) being **positively viewed**, with **spotlight** drawn **on TP53m pts inclusion** (26% & 76% TP53m pts in MDS and AML respectively) and **blast reduction** numbers
- **CR-MRD negativity** in 50% pts signals **deeper molecular remissions**; MRD response may inform Tx decisions, enable early intervention, refine outcome predictions

KOL & Analyst's Views

- **Slight dip in efficacy compared to ASH'20** readout, that showed 71% ORR (48% CR, 19% CRi, 5% MLFS, 24% SD and 5% PD)
- KOLs believe that **magro+aza looks "better than any other treatment" in TP53m pts** and the progress likely to considered favorably by regulators
- Analyst expressed **concerns on "best-in-class" potential**, given the recent hold and mixed opinions from medical community on ASCO/EHA22 readout
- **Tx discontinuation rates** due to TEAEs could become **barrier to adoption**; ~40% of magro's Ph1/2 studies demonstrated anemia as a TEAE in a mixed MDS/AML population so far
- Magro associated **anemia** is early and transient and overall **appears to be manageable** with no cumulative toxicity

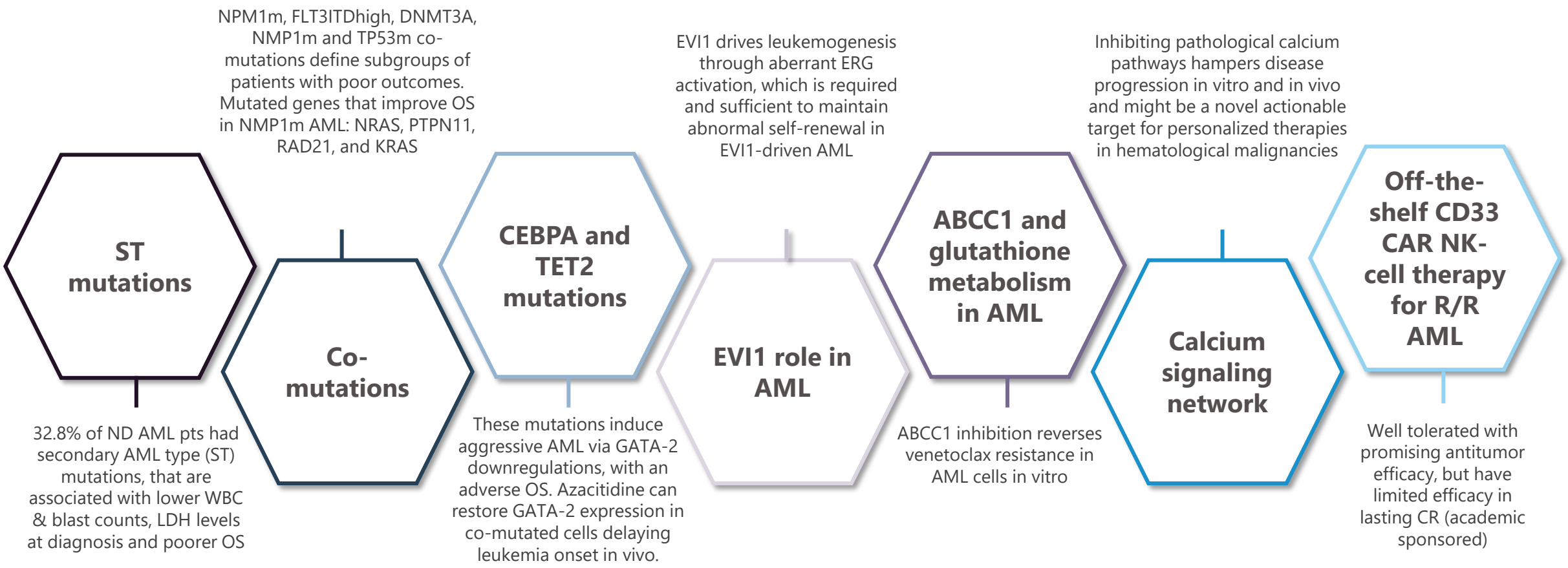
Twitter Sentiment Analysis



Aza: azacitidine; Magro: Magrolimab

Array of highlights from educational sessions

Core themes of discussion revolved around novel mutations & co-mutations for prognosis, emerging targets in Tx landscape, and progress of CAR-NK therapies



Aza: azacitidine; Magro: Magrolimab

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Thank You