

**Circulating tumor cells (CTC's) and association
with death in molecular subtypes (MST)
of metastatic breast cancer (MBC)**

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Measurement of CTC's in the Waverly Practice: Goals of an Observational Study

- We measured CTC's longitudinally in all patients in our community oncology practice with MBC to assist in their management.
- As we have measured the CTC's, we have performed an observational study to determine:
 - a.** If recognized MST's of MBC:
 - ER +, HER2 -
 - Triple Negative (TN)
 - HER2 +, ER + / -have different patterns of CTC behavior; and
 - b.** If the highest level of CTC's measured at any time in long term followup (0-4, 5-9*, 10-99*, ≥ 100 CTC's) can define the biologic character of a tumor, and in turn predict survival, independent of the MST.

* Survival data similar for 5-9 and 10-99 CTC's; combined (5-99) in all analyses.

Measurement of CTC's in 96 patients

- We measured CTC's, an FDA-approved test, by the **CellSearch[®]** Method, (Veridex, Raritan NJ) at three commercial laboratories.
- **Timing** of CTC blood draws: On any ChemoRx day, we drew CTC's **before any treatments** had been given, and as much as possible **without premedications** (e.g. steroids) that might in theory change the level of CTC's.
- We performed **859 tests** for CTC's in 96 pts from 11/20/06 - 5/31/09. Average: **8.9 tests** per pt. Range: **1 – 28 tests** per pt.
- The median time of potential f/u from 1st CTC for an individual patient was **18.9 mo.** (Range 1 - 30 mo.)
- At the time of analysis, **23 of the 96 patients had died** of MBC

Distribution of the 96 patients by Molecular Subtype

- **51** had ER+, HER2/neu negative MBC
- **14** had Triple Negative (TN) MBC
- **31** had HER2/neu + MBC, either ER+ or ER-

Distribution of the 96 patients by timing of first measurement of CTC's

- **51** had CTC's measured at 1st presentation of MBC (Survival for this group shown separately later)
- **30** had CTC's measured after 1st presentation of MBC, but later had progression
- **15** had CTC's measured after 1st presentation of MBC but did not have progression in the period of observation.

Strategy of treatment and measurement of CTC's:

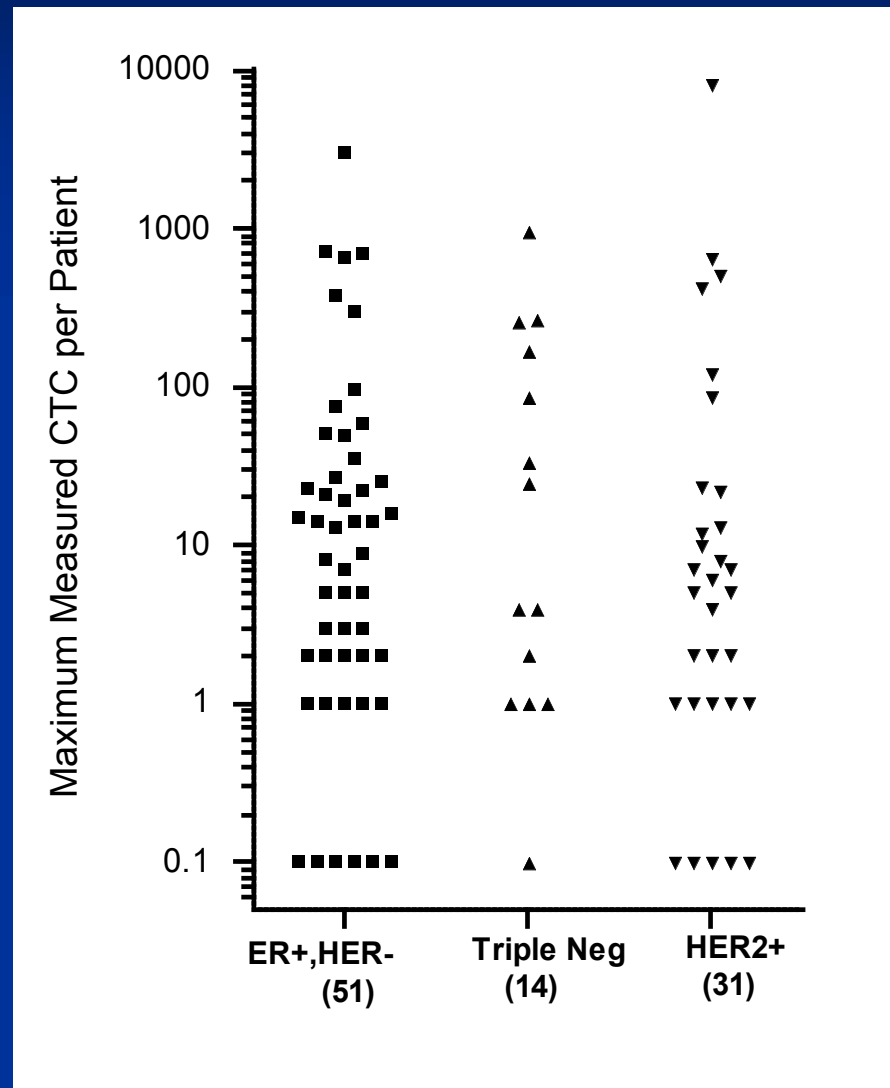
- For patients with elevated CTC 5 or higher, we used optimal chemoRx +/- biologic therapy to bring the CTC's down as quickly as possible.
- If pts with elevated CTC's improved to < 5 for a sustained 2-3 mo. period, we sought lower morbidity therapies:
 - Hormonal if ER+; or
 - ChemoRx +/- biologics if ER- or hormone refractory
- Frequency of CTC measurement in an individual patient:
We measured CTC's at a **time interval** inversely proportional to the highest measured CTC, i.e. the higher the CTC level, the shorter the interval between CTC tests, every 1-2 cycles in patients with CTC's > 5 .

Table 1: Distribution of CTC's in Molecular Subtypes of MBC

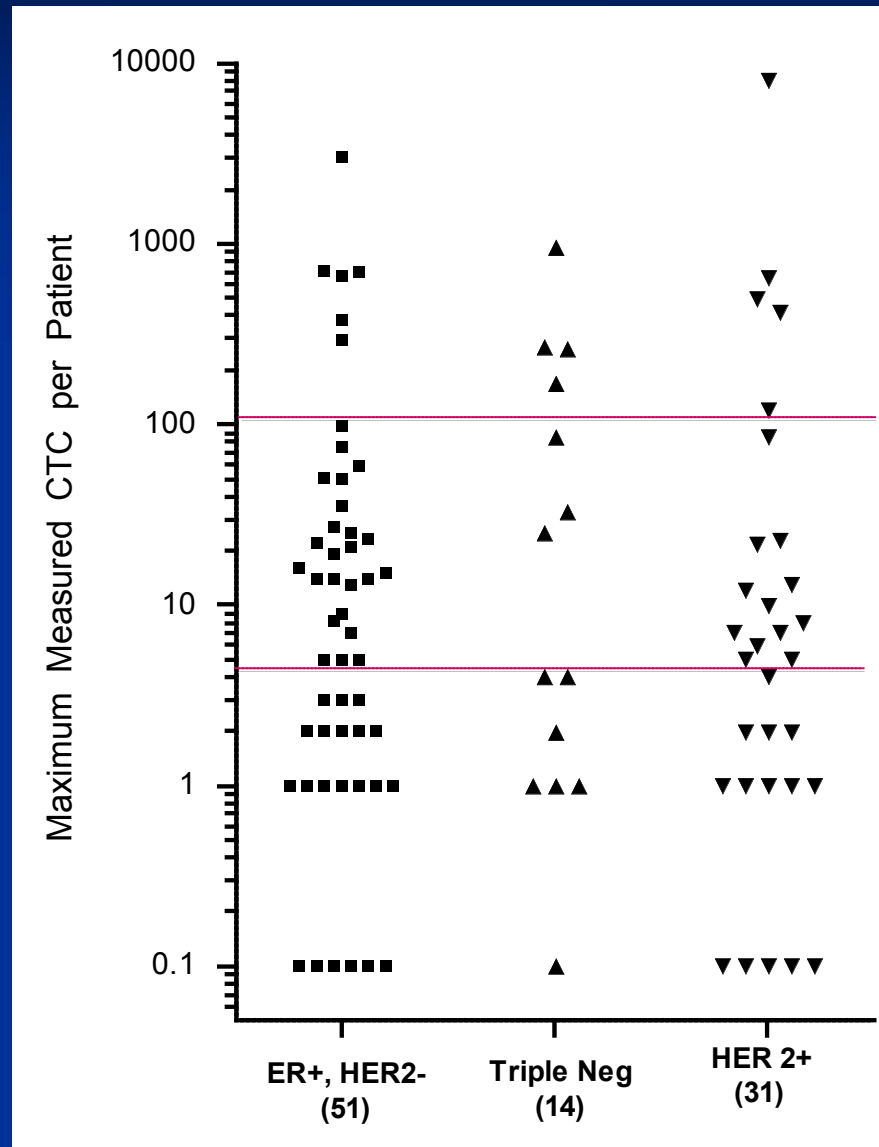
Highest CTC:	< 5	5 - 99	≥ 100
ER+, H2- (n=51)	21 (41%)	24 (47%)	6 (12%)
TN (n=14)	7 (50%)	3 (21%)	4 (29%)
H2+ (n=31)	14 (45%)	12 (39%)	5 (16%)
Totals (n=96)	42 (44%)	39 (41%)	15 (16%)

With 19 mo. median followup, each molecular subtype of MBC has a substantial portion with very low CTC's, (orange) and a smaller set with very high CTC's (blue)

Distribution of Highest Measured CTC in Molecular Subtypes of MBC



Distribution of Highest Measured CTC in Molecular Subtypes of MBC



≥ 100

5 - 99

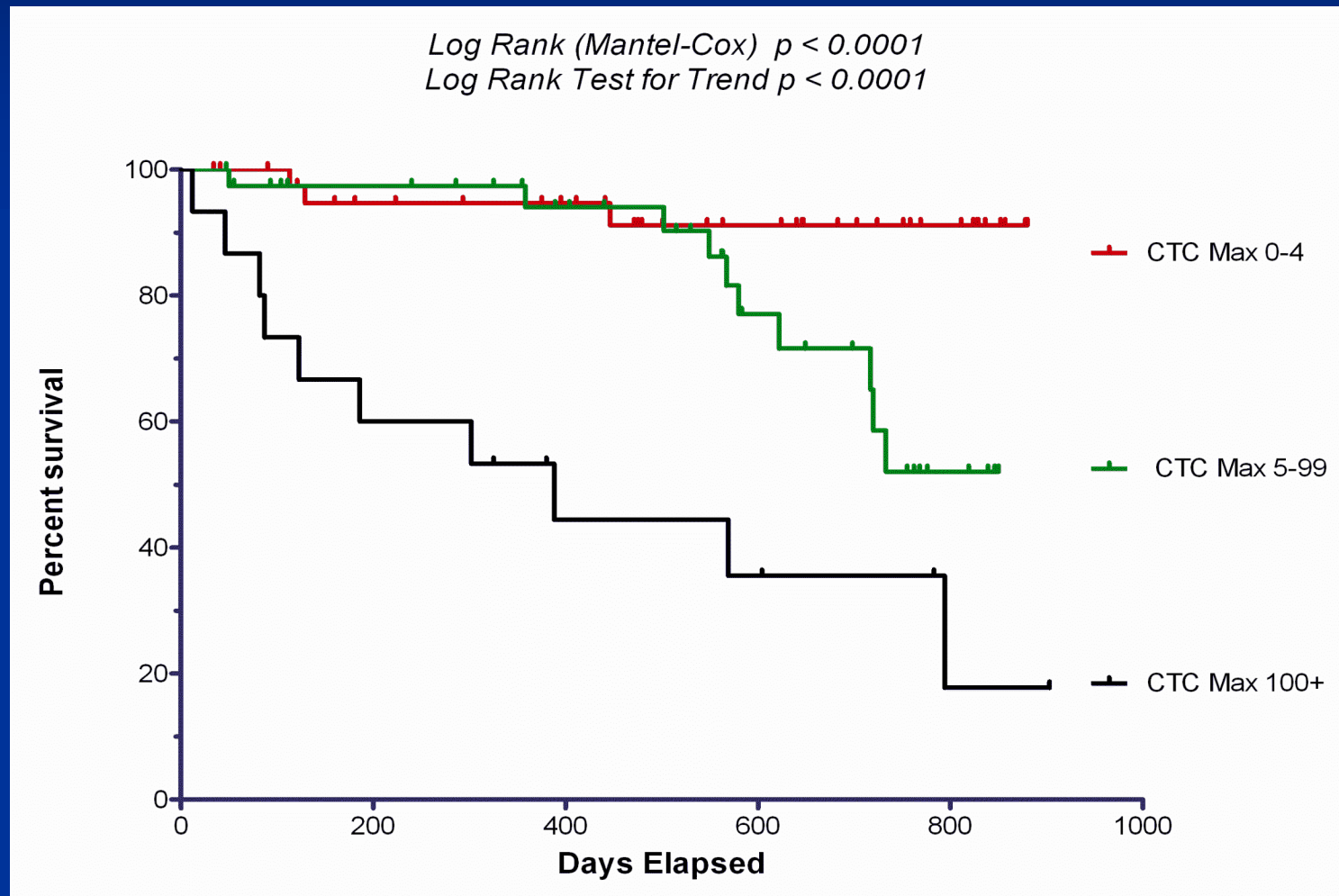
0 - 4

Table 2: Distribution of Deaths by Highest CTC in MST's of MBC

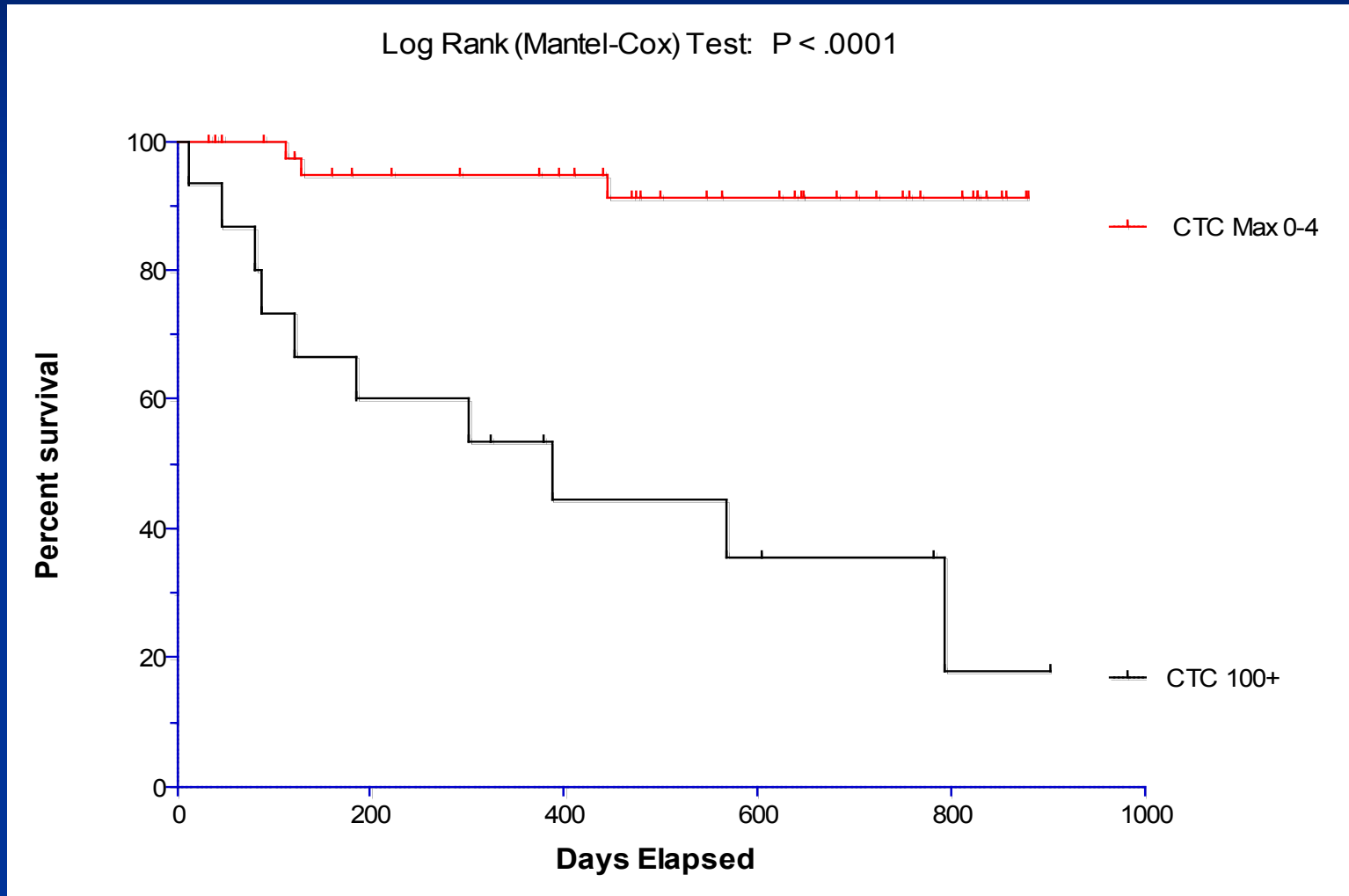
Highest CTC:	< 5	5 – 99	≥100
ER+, H2- (10 / 51; 20%)	1 / 21 (5%)	4 / 24 (17%)	5 / 6 (83%)
TN (5 / 14; 36%)	1 / 7 (14%)	2 / 3 (67%)	2 / 4 (50%)
H2+ (8 / 31; 26%)	1 / 14 (7%)	4 / 12 (33%)	3 / 5 (60%)
Br Ca Deaths (23 / 96; 24%)	3 / 42 (7%)	10 / 39 (26%)	10 / 15 (67%)

43% of deaths (10 of 23) occurred in the 16% of pts with ≥ 100 CTC's; 67% of pts w/ ≥ 100 CTC's died in 19 mo. of f/u. These are early deaths. Only 3 pts (7%) died in the 42 pts with CTC's < 5. ($p < 0.0001$)

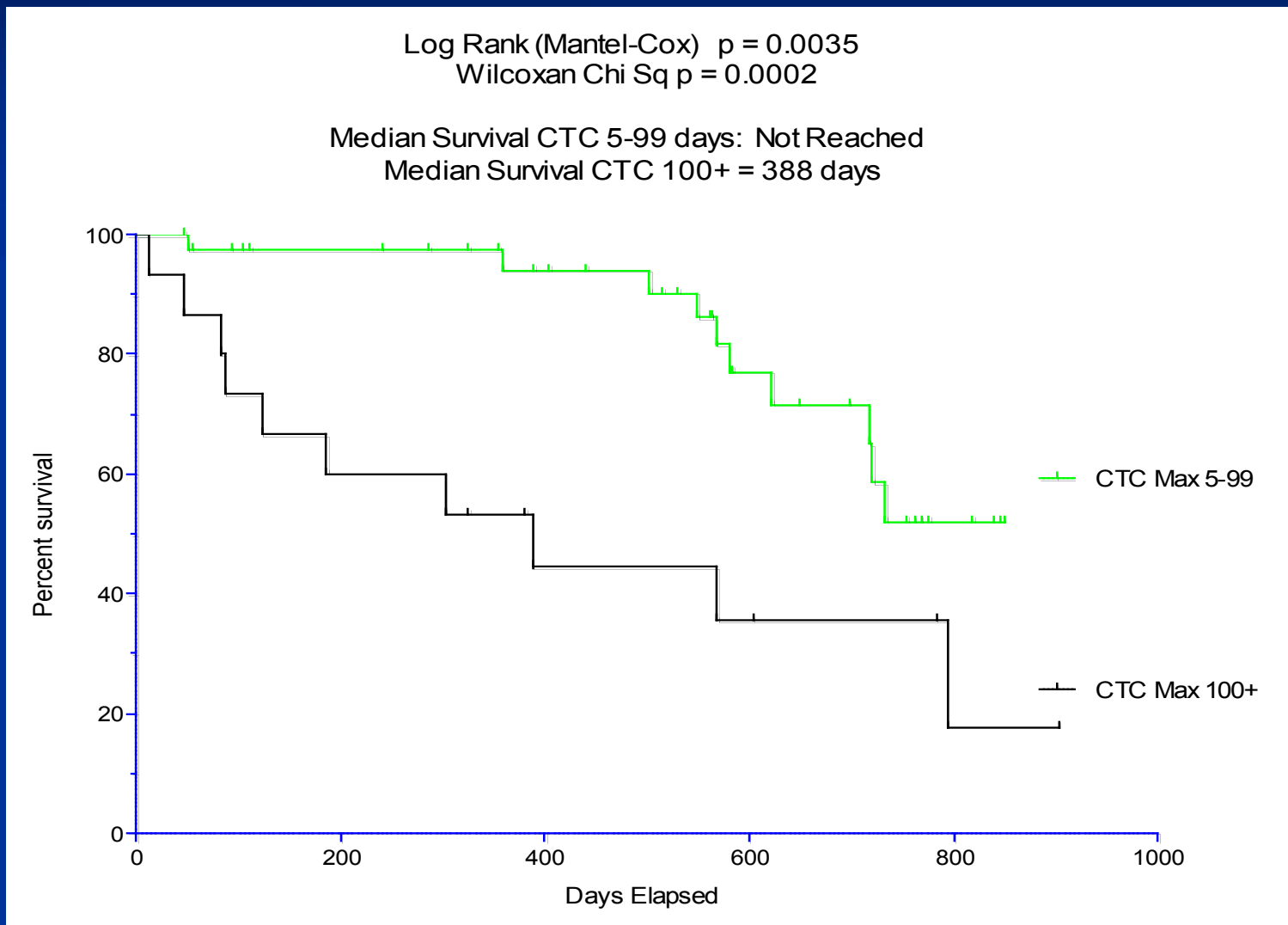
Survival vs. time since first CTC by highest measured CTC: All patients: 0-4 vs. 5-99 vs. 100 or more CTC's



Survival vs. time since first CTC: 0-4 CTC's vs. 100 or more CTC's

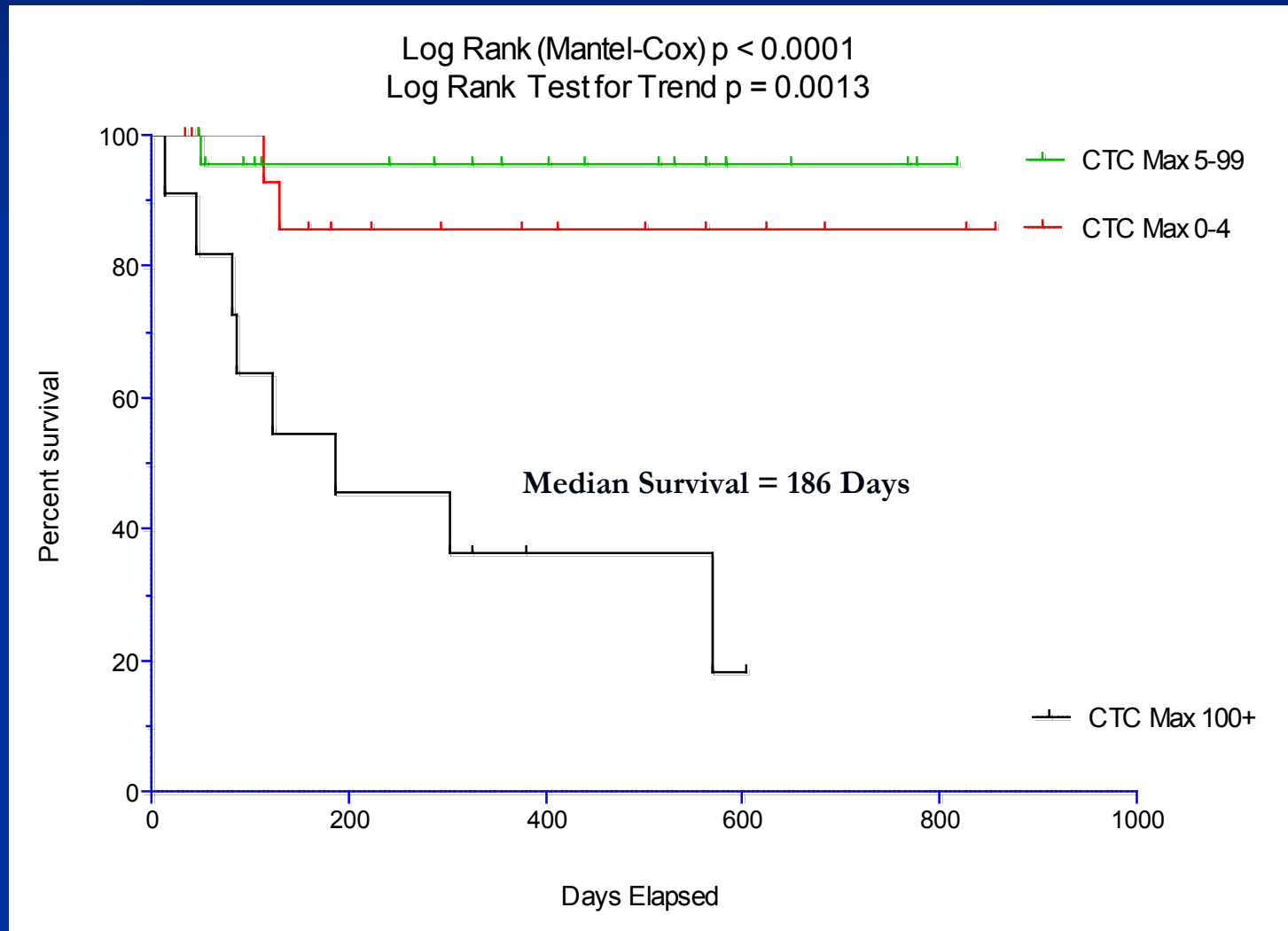


Survival vs. time since first CTC: 5-99 vs. 100 or more CTC's



Survival vs. time since first CTC:

For the three groups in the 51 patients with CTC's measured at 1st presentation of MBC



CTC's in a Community Practice: Conclusions

- CTC's give independent and complementary data to the Molecular Subtypes in MBC
- Very high levels of CTC's ≥ 100 are an **Oncologic Emergency.**
- CTC's should be considered as a stratification factor for Phase 2 and 3 clinical trials.